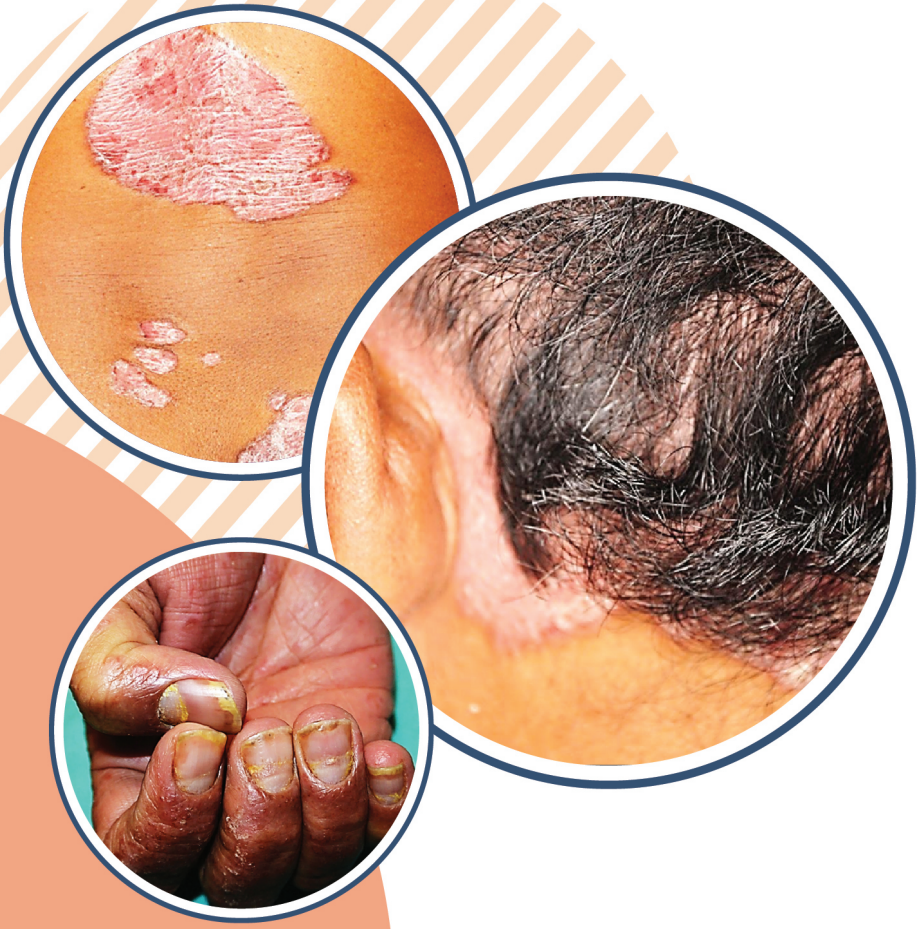
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF PSORIASIS

2024 SECOND EDITION MOH/P/PAK/568.24(GU)-e



Ministry of Health Malaysia Dermatological Society of Malaysia Academy of Medicine Malaysia

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STATEMENT OF INTENT

The clinical practice guideline (CPG) is meant to be a guide for clinical practice based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2024 and will be reviewed in a minimum period of four years (2028) or sooner if there is an urgent need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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TABLE OF CONTENTS

LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG development group (DG).
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "**should**" being considered. Otherwise, weak recommendations use the word "**may**" in proposing an action to be made.
- In the CPG, a yellow box ☐ highlights important message(s) in the management while a blue box ☐ contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

CO-MORBIDITIES

- All patients with psoriasis should be screened for cardio-metabolic disorders, psychiatric disorders and other co-morbidities as indicated.

ASSESSMENT

- All psoriasis patients should be assessed on the disease severity and quality of life before treatment is initiated.
  - Disease severity assessment may be measured using Body Surface Area, Psoriasis Area and Severity Index or Physician's Global Assessment.
  - Quality of life may be measured using Dermatology Life Quality Index or Children Dermatology Life Quality Index.

TREATMENT

a) Topical Treatment

- Moisturisers should be used regularly to maintain the skin barrier in psoriasis.
- Topical corticosteroids should be used as the first-line topical treatment in psoriasis.
  - The potent and very potent corticosteroids should be used as a short-term therapy to gain rapid control. These preparations should be avoided on the face, genitalia and body folds.
- Topical tar-based preparations may be used in the treatment of psoriasis.
- Topical vitamin D analogue with or without corticosteroids may be used in the treatment of psoriasis.
- Topical salicylic acid may be used in combination with other topical treatment in psoriasis.
- Topical calcineurin inhibitors may be used for facial and flexural psoriasis.
- Topical dithranol may be used as short-contact therapy for recalcitrant thick plaques in psoriasis.

b) Phototherapy

- Phototherapy 2 - 3 sessions/week should be offered to patients with moderate to severe psoriasis.
  - Narrowband ultraviolet B (NBUVB) should be considered as the first-line phototherapy.
- Skin cancer should be screened in psoriasis patients receiving treatment sessions >200 psoralen plus ultraviolet A (PUVA) and >500 NBUVB treatments.

c) Conventional Systemic Therapy

- Methotrexate (MTX) should be used as the first-line conventional systemic therapy for moderate to severe psoriasis.
  - Folic acid supplementation may be given either 5 mg daily except for MTX therapy day or 5 mg once a week after the day of MTX.
  - Full blood count and liver function test should be closely monitored.
- Acitretin may be offered for the treatment of moderate to severe psoriasis.
  - It should be avoided in women of childbearing age without reliable contraception and in those who are planning pregnancy.
  - Liver function test and fasting lipid profile should be closely monitored.
- Ciclosporin therapy in psoriasis:
  - may be offered as short-term treatment for rapid disease clearance in moderate to severe disease
  - should not be used for more than two years
  - should not be used with previous history of psoralen plus ultraviolet A (PUVA) exposure
  - should not be used concurrently with phototherapy (NBUVB and PUVA)
  - blood pressure, renal function and lipid profile should be closely monitored

d) Biological Therapy

- Biological therapy:
  - should be offered to patients with moderate to severe psoriasis who have intolerance/contraindication or failed phototherapy and conventional systemic therapy
  - may be considered as a first-line treatment in severe disease based on clinical judgement where sufficient treatment success cannot be expected with a conventional therapy
- Careful evaluation for contraindications should be performed prior to initiation of biological therapy for psoriasis patients.
- Response and adverse events should be monitored during biological therapy.

e) Oral Small Molecules Therapy

- Oral small molecules may be offered to patients with moderate to severe psoriasis.

f) Combination Therapy

- Combination therapy may be considered when monotherapy fails in the treatment of psoriasis.

SPECIAL GROUP

a) Psoriatic Arthritis

- In psoriasis patients, regular assessment should be performed at least annually for early detection of psoriatic arthritis i.e. joint swelling, dactylitis, enthesitis, inflammatory back pain and prolonged early morning stiffness.
  - Various screening tools may be used to screen for psoriatic arthritis.

b) Paediatrics

- The following topical treatments may be used as monotherapy or in combination for children with psoriasis:
  - moisturisers (as adjunct therapy)
  - corticosteroids (first-line treatment)
  - calcineurin inhibitors (preferred choice for lesions on the face, flexures and genitalia)
  - vitamin D analogues
  - salicylic acid
  - tar-based preparations
  - dithranol
- Narrowband ultraviolet B (NBUVB) may be considered for moderate to severe psoriasis in children prior to systemic/biological therapy.
- Methotrexate (MTX) should be considered as first-line conventional systemic therapy for moderate to severe psoriasis in children.
- Ciclosporin may be used for rapid control of psoriasis while acitretin may be used in immunosuppressed children.
- Biological therapy may be prescribed in children with moderate to severe psoriasis who have intolerance/contraindication or failed phototherapy and conventional systemic therapy.

c) Pregnancy and Lactation

- Topical moisturisers and low- to mid-potent corticosteroids may be used in pregnant and lactating women with psoriasis.
- Pregnant patients with moderate to severe psoriasis may be offered:
  - narrowband ultraviolet B phototherapy in those who fail to respond to topical treatments
  - ciclosporin if its potential benefits outweigh the risks

d) Others

- Psoriasis patients with hepatitis B virus, hepatitis C virus or human immunodeficiency virus infection should be co-managed with the respective specialties.
- Patients with psoriasis on biological / conventional systemic therapies undergoing:
  - low-risk surgery may continue the treatment
  - moderate- to high-risk surgery may need treatment withdrawal based on risk assessment and discussion with the surgeon
- Vaccination status should be checked and completed if possible before initiating a systemic therapy in psoriasis.

GUIDELINES DEVELOPMENT AND OBJECTIVES
GUIDELINES DEVELOPMENT

The members of the DG for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Higher Education and private sector. There was active involvement from a multidisciplinary Review Committee (RC) during the process of the CPG development.

This is the second edition of an evidence-based CPG on the Management of Psoriasis. Literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published on humans, publication from year "2013 to Current" and English language. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed. All searches were conducted from 7 March 2023 to 14 April 2023. Literature searches were repeated for all clinical questions at the end of the CPG development process, allowing any relevant papers published before 13 August 2024 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines on psoriasis as listed below:

- EuroGuiDerm Guideline on the systemic treatment of psoriasis vulgaris - Part 1: treatment and monitoring recommendations (2020)
- EuroGuiDerm Guideline on the systemic treatment of psoriasis vulgaris - Part 2: specific clinical and comorbid situations (2021)
- Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures (2021)
- Joint AAD-NPF Guidelines of care for the management of psoriasis with systemic nonbiologic therapies (2020)
- Joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines of care for the management and treatment of psoriasis in pediatric patients (2020)

A total of sixteen clinical questions were developed under six sections (assessment and diagnosis, co-morbidities, principles of treatment, treatment, special conditions and referral/follow-up). Members of the DG were assigned individual questions within the sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 48 times throughout the development of these guidelines. All literature retrieved

were appraised by at least two DG members using Critical Appraisal Skill Programme checklist when applicable, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2015), while the grading of recommendation was done using the principles of GRADE as much as possible (refer to the preceding page). The writing of the CPG strictly followed the requirements of Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Upon completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the Health Technology Assessment and Clinical Practice Guidelines Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from the Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

OBJECTIVES

The objective of this CPG is to provide evidence-based recommendations on the management of psoriasis on the following aspects:

a) diagnosis
b) assessment
c) treatment including principles of treatment
d) referral and follow-up

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- Patients with plaque psoriasis

Exclusion criteria

- Erythrodermic psoriasis
- Pustular psoriasis including generalised and localised pustular psoriasis
- Nail psoriasis

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of psoriasis including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policymakers
v. patients and their advocates
vi. professional societies

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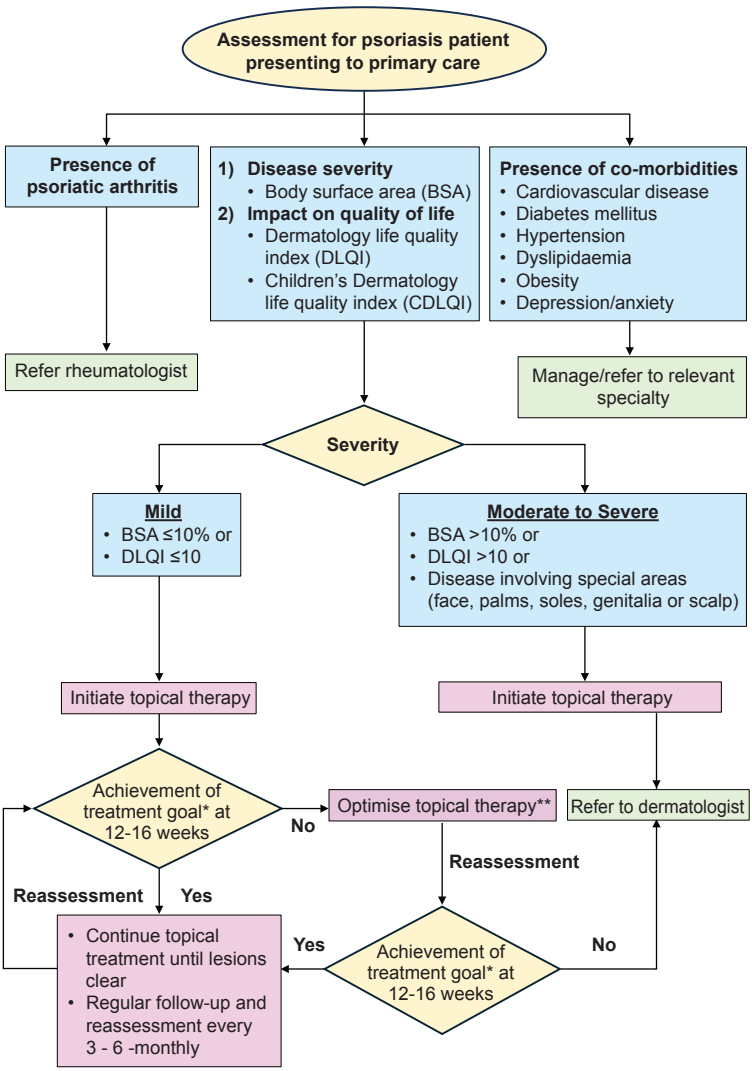
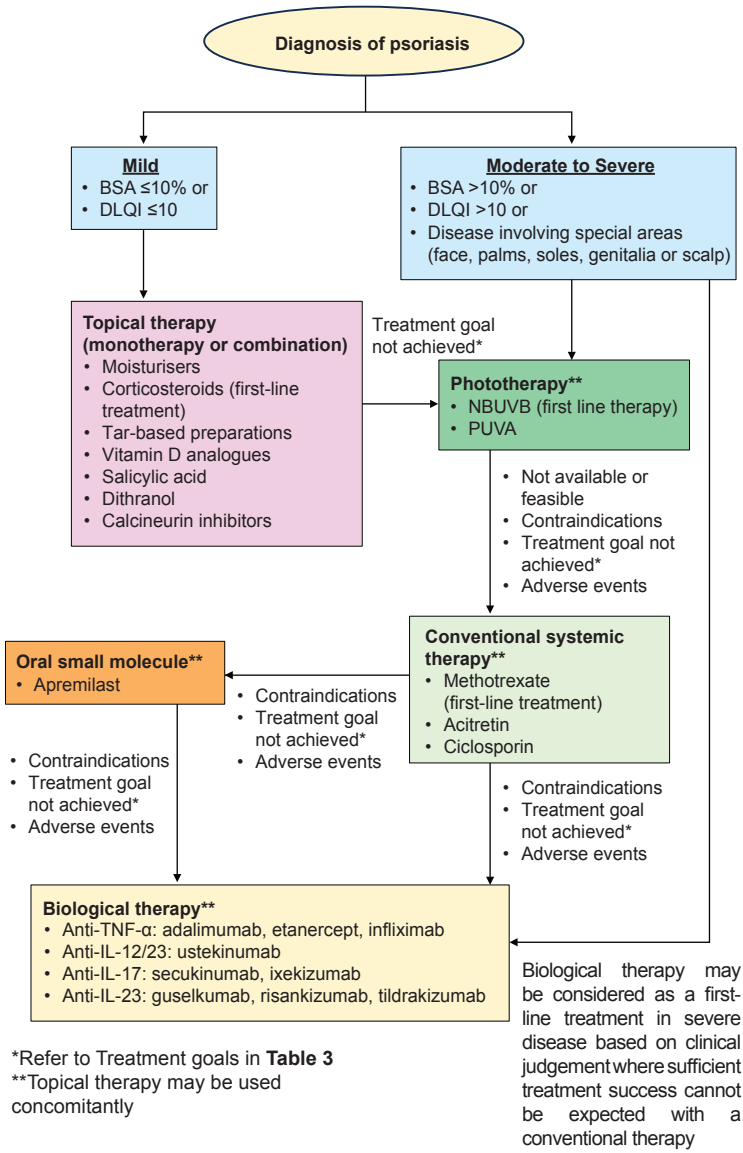
ALGORITHM 1: MANAGEMENT OF PSORIASIS IN PRIMARY CARE



*Treatment goal: BSA ≤3% AND DLQI ≤5

**This may be optimised by increasing the potency of the topical steroid or in combination with another topical agent

ALGORITHM 2: TREATMENT MODALITIES IN PSORIASIS



*Refer to Treatment goals in **Table 3**
**Topical therapy may be used concomitantly

1. INTRODUCTION

Psoriasis is a chronic inflammatory disease that affects primarily the skin and joints. The understanding of the psoriasis immunopathogenesis has evolved remarkably over the past few decades, leading to a transformation in the conceptualisation of the disease. Initially viewed as a disorder primarily affecting the skin, psoriasis is now recognised as a complex, genetically determined and immune-mediated systemic inflammatory condition.[1, level III] Immunological and genetic studies have identified interleukin-23 (IL-23)/Th17 pathway as key drivers of psoriasis pathogenesis in individuals with genetic susceptibility.[2, level III] Risk factors e.g. streptococcal infection, stress, smoking, obesity and alcohol consumption are pivotal in triggering or exacerbating the disease.[3, level III]

Psoriasis is associated with high disease burden. The marked visible appearance of the lesion has negative impact on body image and leads to decreased self-esteem, hence compromising the patient's quality of life (QoL). Psoriasis patients also need to endure physical discomfort e.g. pain, bleeding and itch. There are strong evidences linking psoriasis with various co-morbidities particularly cardiometabolic disorders. The link between psoriasis and cardiometabolic diseases is likely due to the systemic inflammation driven by proinflammatory cytokines [e.g. tumour necrosis factor-alpha (TNF-α), interleukin-17 (IL-17) and IL-23].[4, level III] Regular screening and monitoring for these co-morbidities, along with effective psoriasis intervention is crucial for improving overall health outcomes in the patients.

While there is currently no cure for psoriasis, effective treatment can lead to substantial skin clearance and improvement in the symptoms. However, many patients may experience suboptimal care or remain on ineffective treatments for extended periods which can impact their overall management including QoL.

Treatment options encompass a range of approaches which is tailored to severity of the disease and individual patient's needs. Topical agents, phototherapy and conventional systemic agents have traditionally been the cornerstone of psoriasis management for many years. However, advances in understanding the immunopathogenesis of psoriasis have led to the development of new targeted therapies, e.g. biological therapy and small molecule agents. These innovations have transformed the treatment landscape, providing more effective and personalised options that enhance therapeutic outcomes and QoL for the patients.

In view of the chronic nature of the disease, treatment of psoriasis and its complication is associated with high direct and indirect costs which can lead to a significant economic burden, both for individuals

and the healthcare system. In this context, newer targeted therapies, despite their high cost, may provide favorable cost-benefit ratios and lead to cost offsets in the treatment of psoriasis.[5, level II-2] Hence, there is a need for guidelines that emphasize the importance of cost-effective and sustainable approaches within the treatment armamentarium for psoriasis.

The first Clinical Practice Guideline (CPG) on the Management of Psoriasis Vulgaris in Malaysia was published in 2013. This second edition will update recommendations for managing psoriasis based on the best and latest evidence available to provide evidence-based guidance to all healthcare providers involved in caring for patients with psoriasis. The goal of the document is to ensure that every patient receives appropriate, effective and safe care by clearly outlining treatment goals and recommendations.

1.1. Epidemiology

Psoriasis is a common disease with a higher prevalence in higher income countries. The prevalence of psoriasis varies from 0.11% in East Asia, 1.58% in Australasia to 1.52% in West Europe. The prevalence rates increase with age up to 60 - 70 years and then declines.[6, level II-2] The incidence of psoriasis ranges from 31.4/100,000 person-year in East Europe to 521.1/100,000 person-year in West Europe.[7, level II-2] In Malaysia, the prevalence of psoriasis is estimated to be 0.34% with an incidence of 34.2/100,000 person-year. Indians (0.54%) have a higher prevalence rate of psoriasis compared with Malays (0.38%) and Chinese (0.29%).[8, level II-2]

The age for psoriasis onset exhibits a bimodal pattern with the first peak occurring at 30 to 39 years and the second peak at 60 to 69 years. Women tend to present with psoriasis earlier compared with men.[6, level II-2] The Malaysian Psoriasis Registry recorded a slightly higher proportion of males (53.6%) and reported the mean age of psoriasis onset at 34.1 ± 16.3 years for adults and 10.3 ± 4.5 years for the paediatric group. Familial psoriasis was noted to be 24.7% in the psoriasis population.[9, level III] This percentage varies from the one quoted in China (15.3%)[10, level III] and in Colombia (32%).[11, level III]

2. CLINICAL FEATURES AND DIAGNOSIS

2.1. Clinical Features

Psoriasis is a heterogenous disease with five known phenotypes i.e. plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis and erythrodermic psoriasis (refer to **Figure 1, 2, 3, 4, 5** and **6**). Plaque psoriasis is the most common form seen in 80 - 90% of patients.[12, level III] Different phenotypes may present together in a patient at any time point. Patients with plaque psoriasis present with symmetrical well-defined thick erythematous scaly plaques.[13, level III]

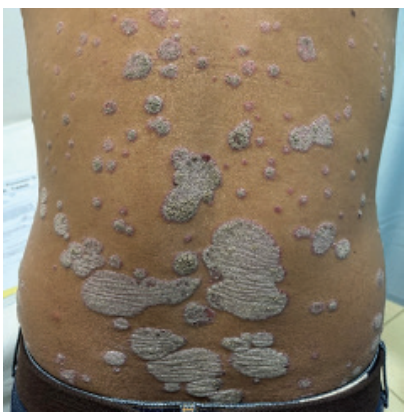


Figure 1: Plaque psoriasis

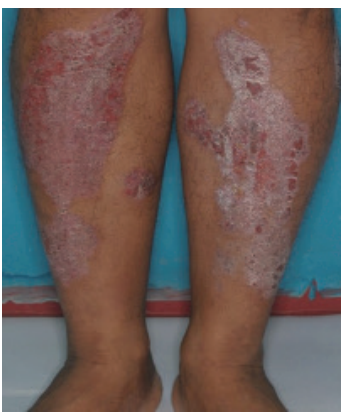


Figure 2: Plaque psoriasis

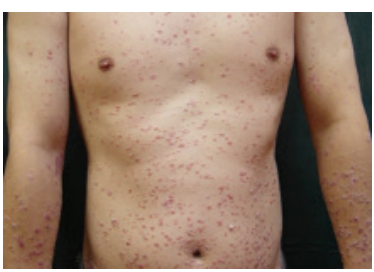


Figure 3: Guttate psoriasis

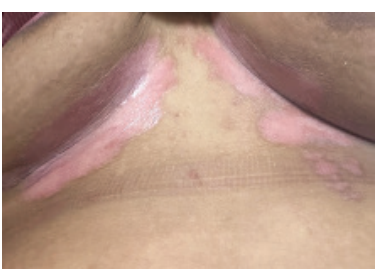


Figure 4: Flexural psoriasis

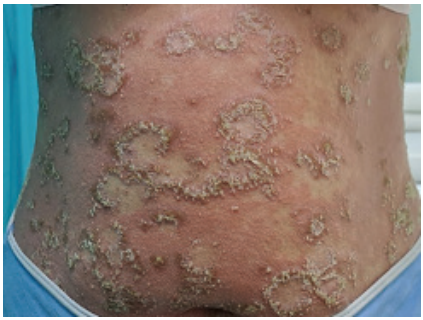


Figure 5: Pustular psoriasis

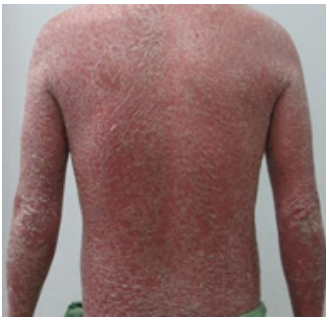


Figure 6: Erythrodermic psoriasis

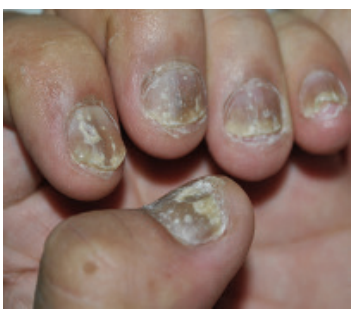


Figure 7: Nail psoriasis: Onycholysis

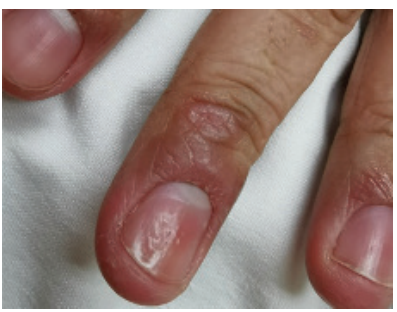


Figure 8: Nail pitting

However, the plaques can be hyperpigmented or violaceous in skin of colour.[14, level III] These lesions usually arise on the scalp, trunk, gluteal fold and extensor surfaces e.g. elbows and knees. Pinpoint bleeding may result on removal of scales or scratching known as Auspitz's sign.[15, level III] Based on the Malaysian Psoriasis Registry, the common symptoms are itch (77.5%) and pain (13.8%).[9, level III] Psoriasis can affect the nail in 40 - 50%[16, level III] and the joint in 20% of patients.[17, level II-2] Nail matrix involvement manifests as pitting, leuconychia, crumbling and/or erythematous dots in the lunula. Whereas nail bed signs appear as oil drop or salmon patch, onycholysis, nail-bed hyperkeratosis and/or splinter haemorrhages.[18, level III] Refer to **Figure 7** and **8**.

2.2. Diagnosis

The diagnosis of psoriasis is mainly based on history and clinical examination. A skin biopsy may be performed in non-classical/atypical cases to confirm the diagnosis.

3. RISK AND AGGRAVATING FACTORS

Various risk factors have been identified to contribute to the onset and exacerbation of psoriasis. Therefore, clinicians need to be aware of these risks and aggravating factors as they might provide insight into the management of psoriasis.

The risk and aggravating factors of psoriasis are discussed below.

Risk and aggravating factors	Evidence
Genetic and family history	• Genetic susceptibility to psoriasis is polygenic with 109 loci identified.[19, level II-2] • PSORS1, encompassing HLA-Cw6 allele, is the loci of importance that accounts for 35 - 50% of psoriasis heritability. Genome Wide Association Study (GWAS) identified the following genes implicated in the pathogenesis of psoriasis:[20, level III] o antigen presentation (HLA-C, ERAP1) o T17 cell activation (IL-23R, IL-23A, IL-12B, TYK2, TRAF3IP2) o innate antiviral immunity/ type I interferon signalling (RNF114, IFIH1) o skin barrier function (LCE3B/3D) • Positive family history is a significant risk factor for psoriasis (OR ranging from 5.4 to 34).[21] • Maternal only psoriasis and paternal only psoriasis are risk factors for developing psoriasis with HR of 5.70 (95% CI 2.71 to 11.99) and 3.69 (95% CI 1.65 to 8.26) respectively.[22, level II-2]
Smoking	• In a systematic review, smokers had an increased risk of psoriasis compared with non-smokers:[23, level II-2] o history of smoking (OR=1.39, 95% CI 1.27 to 1.52) o current smokers (OR=1.94, 95% CI 1.64 to 2.28) o 1 - 14 cigarettes/day (OR=1.81, 95% CI 1.38 to 2.36) o ≥25 cigarettes/day (OR=2.29, 95% CI 1.74 to 3.01) o smoking ≥30 years (OR=1.99, 95% CI 1.75 to 2.25)

Risk and aggravating factors	Evidence
	• A systematic review on Mendelian randomisation studies showed that smoking consistently predicted psoriasis incidence and associated with over two-fold odds of developing the disease.[24, level II-2]
Obesity	• A meta-analysis of seven prospective cohort studies showed that body mass index (BMI), weight gain and waist circumference increased the risk of psoriasis with the increment of every:[25, level II-2] o 5 units in BMI (RR=1.19 95% CI 1.10 to 1.28) o 5 kg in weight (RR=1.11 95% CI 1.07 to 1.16) o 10 cm in waist circumference (RR=1.24 95% CI 1.17 to 1.31) o 0.1 unit in waist-to-hip ratio (RR=1.37 95% CI 1.23 to 1.53) • A systematic review on Mendelian randomisation studies showed that increased BMI and adiposity were associated with increased risk for psoriasis and PsA.[24, level II-2]
Alcohol	• Alcohol consumption is a risk factor for psoriasis.[26, level II-2] • High alcohol consumption (high consumption as >224 g/week) has an increased risk of incident psoriasis (HR=1.30, 95% CI 1.05 to 1.60).[27, level II-2]
Stress and depression	• A systematic review showed that the prevalence of stress-related psoriasis ranged from 27 to 71% and patients experiencing higher levels of perceived stress reported greater psoriasis severity.[28, level II-2] • In a large prospective cohort study, depression was independently associated with an increased risk of psoriasis:[29, level II-2] o patients with the most severe depressive symptomatology [Mental Health Index (MHI) <52] but not on anti-depressants (RR=1.59, 95% CI 1.21 to 2.08)

Risk and aggravating factors	Evidence
	○ patients with severe depressive symptomatology and on anti-depressants (RR=1.91, 95% CI 1.30 to 2.81)
Skin trauma/Koebner phenomenon	• Skin injury is a known risk factor for psoriasis (OR=1.6, p<0.01). Koebner phenomenon (development of skin lesions at the site of injury) is observed in 5% of early onset guttate psoriasis.[21]
Infection	• Infectious skin disorders and upper respiratory tract infection in the past month have been shown to be risk factors for psoriasis.[21] • Infections e.g. *Streptococcus pyogenes*, *Staphylococcus aureus, Malassezia spp., Candida spp, Epstein-Barr virus* (EBV), Varicella zoster virus (VZV), Cytomegalovirus (CMV), human immunodeficiency virus (HIV) are associated with onset and flare of psoriasis.[3, level III] • A large prospective long-term cohort study showed that HIV infection was an independent risk factor for incident psoriasis (HR=1.80, 95% CI 1.38 to 2.36).[30, level II-2] • In a recent meta-analysis, periodontitis increased the odds of developing psoriasis compared with good periodontal health (OR=1.61, 95% CI 1.23 to 2.11).[31, level II-2]
Drugs	• Drugs that have been associated with psoriasis in some cases are: ○ non-steroidal anti-inflammatory drugs (NSAIDs)[21] ○ anti-TNF-α (paradoxical reactions)[32, level III] ○ lithium, beta-blockers, synthetic antimalarial drugs, antibiotics (especially tetracyclines), angiotensin-converting enzyme inhibitors and interferons[3, level III]
Physical activity and exercise	• In a systematic review, low cardiorespiratory fitness or <1 hour of exercise/week was associated with increased incidence of psoriasis whereas vigorous or regular physical activity reduced the risk of psoriasis.[33, level I]

Risk and aggravating factors	Evidence
Environmental factors	• A cross-sectional study showed that short-term air pollution exposure in 60 days before assessment was associated with increased psoriasis activity and likelihood of having a psoriasis flare with a higher risk of absolute Ppsoriasis Area and Severity Index (PASI) 5 or greater point worsening.[34, level III] • In a prospective cohort study, long-term exposure to air pollution [nitrogen dioxide, fine particulate matter (diameter <2.5 μm) and particulate matter (diameter <10 μm) was associated with increased psoriasis risk.[35, level II-2]

4. CO-MORBIDITIES

Psoriasis is known to be associated with multiple co-morbidities due to shared immunological mechanism and the list of associated conditions continues to grow with emerging evidence. It is important to recognise these co-morbidities to provide holistic care. In a meta-analysis, patients with psoriasis had higher risks of single and multiple organ-based co-morbidities with a relative risk (RR) ranging from 1.09 (95% CI 1.01 to 1.18) to 1.75 (95% CI 1.33 to 2.29) compared to general population.[36, level II-2]

a. Cardio-metabolic disorders

Based on the previous edition of CPG, it was well established that psoriasis patients had a higher risk for cardiovascular diseases (CVD).[21]

In a meta-analysis of 14 cohort studies, myocardial infarction and stroke were associated with psoriasis [RR of 1.40 (95% CI 1.03 to 1.89) and 1.13 (95% CI 1.01 to 1.26) respectively].[37, level II-2] These findings were supported by a more recent meta-analysis of 31 cohort studies where psoriasis was found to be associated with an increased risk of cardiovascular events:[38, level II-2]

- ischaemic heart disease (RR=1.17, 95% CI 1.02 to 1.34)
- myocardial infarction (RR=1.17, 95% CI 1.11 to1.24)
- arrhythmia (RR=1.35, 95% CI 1.30 to 1.40)
- thromboembolism (RR=1.36, 95% CI 1.20 to 1.55)
- stroke (RR=1.19, 95% CI 1.11 to 1.27)
- cardiovascular death (RR=1.46, 95% CI 1.26 to1.69)

The association was greater in moderate to severe psoriasis (RR=1.41, 95% CI 1.31 to 1.52) compared with mild psoriasis (RR=1.18, 95% CI 1.13 to 1.24).

In a large cross-sectional study, the prevalence of co-morbidities in psoriasis was 26.1% for hypertension, 27.5% for dyslipidaemia and 11.0% for diabetes mellitus (DM).[39, level III] Another cross-sectional study revealed that individuals with psoriasis were more likely to have metabolic syndrome than those without (OR=1.35, 95% CI 1.17 to 1.56).[40, level III]

The Malaysian Psoriasis Registry reported that obesity (62.9%) was the most common cardio-metabolic co-morbidity among adult psoriasis patients followed by hypertension (28.5%), hyperlipidaemia (22.7%), DM (19.2%) ischaemic heart disease (4.9%), fatty liver (3.4%) and stroke (1.6%).[9, level III]

b. Gastrointestinal disorders

In a meta-analysis on inflammatory bowel diseases (IBDs), patients with psoriasis have an increased risk of Crohn's disease (RR=2.53,

95% CI 1.65 to 3.89) and ulcerative colitis (RR=1.71, 95% CI 1.55 to 1.89).[41, level II-2]

In a systematic review, patients with psoriasis had a two-fold increased risk of non-alcoholic fatty liver disease (NAFLD) compared with controls (OR=2.15, 95% CI 1.57 to 2.94).[42, level II-2]

Based on the Malaysian Psoriasis Registry, 0.8% of psoriasis patients had liver disease of which the most common were viral hepatitis (62.1%), fatty liver (14.4%) and liver cirrhosis (10.9%). Those with liver disease exhibited higher rates of co-morbidities, more severe psoriasis and arthropathy than those without.[43, level III]

c. Psychiatric disorders

In a large cohort study, individuals with psoriasis were shown to have higher risk of various mental health disorders compared with those without as listed below:[44, level II-2]

- depression (HR= 1.72, 95% CI 1.49 to 1.98)
- generalised anxiety disorder (HR=1.88, 95% CI 1.08 to 3.30)
- bipolar disorder (HR=2.33, 95% CI 1.59 to 3.41)
- schizophrenia (HR=1.64, 95% CI 1.01 to 2.65)
- personality disorders (HR=2.06, 95% CI 1.55 to 2.73)
- vascular dementia (HR=1.73, 95% CI 1.21 to 2.47)

The above was supported by recent evidence where patients with psoriasis had higher prevalence of psychiatric disorders compared with the general population which included:[45, level II-2]

- anxiety (OR=1.41, 95% CI 1.36 to 1.46)
- depression (OR=1.35, 95% CI 1.31 to1.41)
- adjustment disorder (OR=1.27, 95% CI 1.18 to 1.36)

d. Malignancies

Psoriasis patients have an increased risk of developing lympho-hematologic malignancies. These include:[34, level III]

- Hodgkin's lymphoma (HR=1.71, 95% CI 1.27 to 2.30)
- non-Hodgkin's lymphoma (HR=1.27, 95% CI 1.08 to 1.50)
- cutaneous T-cell lymphoma/mycosis fungoides (HR=6.22, 95% CI 3.39 to 11.42
- multiple myeloma (HR=1.32, 95% CI 1.03 to 1.69)
- leukaemia (HR=1.28, 95% CI 1.00 to 1.65)

There is higher risk of other malignancies excluding non-melanoma skin cancer in psoriasis patients compared with those without psoriasis with an HR of 1.10 (95% CI 1.08 to 1.12).[46, level II-2]

e. Other disorders

A cohort study demonstrated that patients with psoriasis had higher risk of developing sleep apnoea compared with those without psoriasis. The increased risk was evident in both mild [incidence rate ratio (IRR)=1.30, 95% CI 1.17 to 1.44] and severe (IRR=1.65, 95% CI 1.23 to 2.22) cases of psoriasis.[47, level II-2]

A meta-analysis demonstrated an increased risk of incident chronic kidney disease (RR=1.34, 95% CI 1.14 to 1.57) and end-stage renal disease (RR=1.29, 95% CI 1.05 to 1.60) among patients with psoriasis compared with individuals without it.[48, level II-2]

Another meta-analysis that compared patients with and without psoriasis showed an increased risk of both prevalent (RR=1.97, 95% CI 1.68 to 2.31) and incident (RR=1.23, 95% CI 1.05 to 1.45) uveitis.[49, level II-2]

Recommendation 1

- All patients with psoriasis should be screened for cardio-metabolic disorders, psychiatric disorders and other co-morbidities* as indicated.

*malignancies, inflammatory bowel diseases, etc.

5. ASSESSMENT

5.1. Disease Severity Measurement

Assessment of disease severity in psoriasis is important to determine the appropriate choice of treatment and monitor its effectiveness. Several clinical tools and scoring systems are commonly used to assess psoriasis severity and impact on patients' QoL. These outcome measurements are essential to determine treatment plans and monitor the effectiveness of therapy.

The list of disease severity assessment tools for psoriasis are shown below:[50, level III; 51]

Physician-reported outcomes	Patient-reported outcomes
Most commonly used - • Body Surface Area (BSA) • Psoriasis Area and Severity Index (PASI) • Physician's Global Assessment (PGA)	Most commonly used - • Dermatology Life Quality Index (DLQI) (> 16 years old) • Children's DLQI (CDLQI) (4-16 years old) • VAS of pruritus and pain
Others - • Simplified PASI (SPASI) • Psoriasis Log-based Area and Severity Index (PLASI) • Psoriasis Exact Area and Severity Index (PEASI) • Psoriasis Assessment Severity Score (PASS)	Others - • Short-Form 36 (SF36) • Psoriasis Disability Index (PDI) • Psoriasis Symptoms Inventory (PSI) • Psoriasis Symptoms and Signs Diary (PSSD) • Psoriasis Index of Quality of Life (PSORIQoL)

In a large real world cohort study on patients receiving systemic therapies based on data from BADBIR (British Association of Dermatologists Biologics and Immunomodulators Register) registry, absolute PASI ≤2 was consistent with PASI 90 response and PGA clear or almost clear with Cohen's κ of 0.78 (95% CI 0.77 to 0.79) and 0.79 (95% CI 0.78 to 0.80) respectively.[52, level II-2]

Based on integrated analysis of three UNCOVER trials, Optimal Psoriasis Assessment Tool (OPAT) was a simple tool which can strongly predict a full PASI and QoL assessment. OPAT consisted of BSA assessment and one of the patient-reported outcomes measurement which included itch numeric rating scale (NRS), patient reported skin pain score and patient global assessment (PatGA) of disease severity. The best two-term models were BSA with PatGA

(R2=0.82) and BSA with itch NRS (R2=0.81) for PASI, whereas BSA with itch NRS (R2=0.62) was the best for DLQI.[53, level III]

NICE recommends the following assessment for psoriasis:[54]

- disease severity
  - assess PGA, BSA, involvement of high impact or difficult-to-treat area (face, scalp, palm, soles, flexures and genitals) and patient's global assessment
  - PASI can be used in specialist setting
- impact on psychological and social wellbeing
  - assess impact on daily living, family or carers, coping mechanism, support and mood
  - DLQI can be used in specialist and non-specialist settings if practical
- presence of psoriatic arthritis (PsA) and other co-morbidities (e.g. CVD, DM, hyperlipidaemia, obesity and hypertension)

The first edition of Malaysian CPG on psoriasis advocates the use of PASI or BSA to assess physical severity of psoriasis and DLQI to measure the impact of psoriasis on the QoL of the patients. In local setting, BSA and DLQI are advocated as they are simple tools to be used in clinical practice. Description of assessment tools in measuring psoriasis severity is shown in **Table 1**.[21]

Table 1: Assessment Tools for Measuring Psoriasis Severity and QoL

Tools	Description
BSA	• Measures percentage of body surface area affected by psoriasis based on "rule of 9" or taking patient's one palm-size (flat hand with thumb and fingers) as 1%
PASI	• The best validated tool with good internal consistency, good intraobserver variation and acceptable interobserver variation • Measures severity (erythema, scaling and induration) and extent of involvement based on four regions (head and neck, upper limbs, trunk and lower limbs) with score ranging from 0 - 72 (refer to **Appendix 3**)
PGA	• Validated tool to assess physical severity with good intraobserver and acceptable interobserver variation • Measures severity based on induration, erythema and scaling (refer to **Appendix 4**)
DLQI/CDLQI	• Questionnaire to assess impact of psoriasis on QoL. It consists of ten questions related to symptoms, mental health, impact on daily life, leisure, work and school, personal relationships and burden of psoriasis treatment. Score ranges from 0 to 30 (refer to **Appendix 5**).

Adapted: Ministry of Health, Malaysia. Management of Psoriasis Vulgaris. Putrajaya: MoH; 2013

5.2. Disease Severity Classification

Defining disease severity is important for treatment selection. There are many severity classification systems based on different guidelines but there is no general agreement on the definition of disease severity. Most of the international guidelines classify psoriasis disease severity into two categories which are mild and moderate to severe. The severity of psoriasis can be defined by parameters based on PASI, BSA and DLQI, either individually or in combination.[55, level III]

EuroGuiDerm Guidelines define psoriasis severity as follows:[51]

- mild psoriasis - PASI ≤10 and BSA ≤10% and DLQI ≤10
- moderate to severe psoriasis -

- PASI >10 or BSA >10% and DLQI >10 or
- major involvement of visible areas or
- major involvement of scalp, genitals, onycholysis or onychodystrophy of at least two fingernails or
- presence of itch leading to scratching or
- presence of recalcitrant plaque

A Delphi consensus statement by International Psoriasis Council describes two categories of psoriasis severity:[56, level III]

i. candidates for topical therapy
ii. candidates for systemic therapy (biological and non-biological therapy e.g. phototherapy and older systemic agents) who meet at least one of the following criteria -
   a. BSA >10%
   b. disease involving special areas (hands/feet, face, genitals, scalp)
   c. failure of topical therapy

The CPG DG advocates using the following definition of psoriasis severity grading as shown in **Table 2**.

Table 2: Definition of Psoriasis Severity

Grade of Severity	Definition
Mild	Candidate for topical therapy: • BSA ≤10% or • PASI ≤10 or • DLQI ≤10
Moderate to Severe	Candidate for phototherapy or systemic therapy (non-biologics and biologics): • BSA >10% or • PASI >10 or • DLQI >10 or • disease involving special areas (face, palms, soles, genitalia or scalp) or • failure of topical therapy

Adapted:

1. Strober B, Ryan C, van de Kerkhof P, et al. International Psoriasis Council Board Members and Councilors. Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. J Am Acad Dermatol. 2020;82(1):117-122.
2. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of psoriasis vulgaris - Part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol. 2020;34(11):2461-2498

Recommendation 2

- All psoriasis patients should be assessed on the disease severity and quality of life* before treatment is initiated.
  - Disease severity assessment may be measured using Body Surface Area, Psoriasis Area and Severity Index and Physician's Global Assessment.
  - Quality of life may be measured using Dermatology Life Quality Index.

*refer to **Table 2**

6. TREATMENT

6.1 Principles of Treatment

The goal of psoriasis treatment is to improve and maintain patients' health-related quality of life through control of symptoms and signs. The treatment option should be based on shared decision between patients and healthcare providers. The choice of treatment is individualised based on age, disease severity, co-morbidities, risk-benefit of treatment, cost of treatment and patient's preference.[21] Patients should be given adequate information regarding their disease and the treatment options available. Risks and benefits of treatment options need to be discussed with the patients to enable them to make informed decision regarding their care. Importance of adherence to treatment also need to be emphasised to optimise the treatment outcomes.

6.2. Treatment Goals

Treatment goals for psoriasis aim to raise the quality of care and ensure long-term effective therapy to prevent complications related to uncontrolled disease. The goals should be defined for both the induction and maintenance phases of treatment, and monitored continuously from time to time. The induction phase is typically the initial phase of treatment which focus on rapid reduction of psoriasis symptoms severity during the first 12 to 16 weeks. This is followed by maintenance phase once the symptoms have been controlled to maintain the achieved level of improvement and prevent relapse of severe symptoms. Appropriate modification should be made if treatment goal is not achieved. This treat-to-target strategy should be personalised to each patient to ensure the goals are met.

With emergence of highly effective new biologics e.g. anti-IL-17 and anti-IL-23, higher treatment goals (e.g. PASI 90 or PASI 100) should be aimed for.[51] In addition, the focus has shifted away from percentage reduction of PASI towards a targeted outcome to reflect minimal or no disease activity (e.g. PASI ≤2).[51] This ideal treatment goal, however, is often not realistic due to multiple confounding factors e.g. limited access to biologics, cost of treatment and lack of fundings. Hence setting an acceptable treatment goal is more practical in the daily practice. Below are the treatment goals set by various agencies.

The Medical Board of National Psoriasis Foundation of United States of America recommends the following treatment targets for plaque psoriasis:[57, level III]

- preferred assessment instrument - BSA
- acceptable response after treatment initiation - either BSA ≤3% or BSA improvement ≥75% from baseline at three months after treatment initiation

- target response after treatment initiation - BSA ≤1% at three months after treatment initiation
- target response during maintenance therapy - BSA ≤1% at every 6-monthly assessment interval during maintenance therapy

Definition of treatment goals for plaque psoriasis of EuroGuiDerm guidelines are:[51]

- treatment success - PASI response ≥75
- treatment failure - PASI response <50
- PASI response ≥50 but <75 with -
  - DLQI ≤5: treatment success
  - DLQI >5: treatment failure
  - assess response to systemic therapy after induction phase depending on type of systemic agent (range 6 - 24 weeks) and at regular interval during maintenance phase
- new treatment goal with advancements of new biologics (time till onset of action: 10 - 12 weeks) either -
  - PASI 90/PASI 100
  - PASI ≤2
  - DLQI <2
  - PGA clear or almost clear

Based on the above evidences, the CPG DG has set the following treatment goals as shown in **Table 3**.

Table 3: Treatment Goals for Psoriasis

Treatment	Treatment Goal*		Time for assessment
	Disease severity	Quality of life	
• Topical	BSA ≤3%	DLQI ≤5	Induction Phase 12 - 16 weeks after initiation Maintenance Phase 3 - 6-monthly
• Phototherapy • Systemic therapy • Biologics • Oral small molecules	BSA ≤3% or PASI ≤5 or PASI75** response	DLQI ≤5	

*Treatment goal must include both disease severity and quality of life
**PASI 75 = 75% reduction in PASI score after treatment

Recommendation 3
- Treatment goal should be determined based on shared decision and monitored regularly in the treatment of psoriasis.

6.3. Non-pharmacological Treatment

Non-pharmacological treatments have been used in the management

of psoriasis. They are mainly life-style modifications which include dietary interventions and exercise.

A meta-analysis of six randomised controlled trial (RCT)s on obese patients with psoriasis showed that lifestyle intervention (diet or physical activity) was more effective compared with control in achieving PASI 75 (RR=1.47, 95% CI 1.27 to 1.69) and reduction in mean PASI score (MD= -2.59, 95% CI -4.09 to -1.09). The RCTs had a mixture of risk of bias (RoB).[58, level I]

A systematic review by the National Psoriasis Foundation recommended the following dietary intervention for adults with psoriasis:[59, level I]

- dietary weight reduction in overweight and obese (BMI≥25) patients with duration of intervention ranging from 16 weeks to six months
- gluten-free diets for patients with confirmed coeliac disease while 3-month trial of a gluten-free diet as an adjunct for those who tested positive for serologic markers of gluten sensitivity
- dietary supplements [e.g. ω-3 fatty acids (fish oil), vitamin D, selenium, vitamin B12, micronutrient supplementation] and specific dietary patterns (e.g. mediterranean diet, higher consumption of ω-3 polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids, fibre or complex carbohydrates) were not recommended due to either limited or low-quality evidences

However, adults with PsA who were overweight or obese (BMI ≥25) may benefit from dietary weight reduction and trial of oral vitamin D supplementation (0.5 µg alfacalcidol or 0.5 - 2.0 µg calcitriol daily) as an adjunctive therapy.

In a systematic review, the effect of Mediterranean Diet in psoriasis patients were inconclusive due to poor adherence to the diet. A single arm trial with two phases weight loss programme on overweight or obese psoriasis patients showed that initial 4-week of protein-sparing, very low-calorie ketogenic diet decreased PASI score by a mean of -7.2 (95% CI -8.7 to -5.6) followed by a 6-week of hypocaloric, Mediterranean-like Diet which decreased the score by -10.6 (95% CI -12.8 to -8.4).[60, level I]

A meta-analysis of 10 RCTs assessed the benefit of low-calorie diet modification vs usual care on obese people with psoriasis. The intervention showed higher achievement in PASI 75 (RR=1.66, 95% CI 1.07 to 2.58), greater PASI score reduction (MD= -3.71, 95% CI -6.80 to -0.62) and greater body surface area (BSA) reduction (MD= -6.06, 95% CI -8.56 to -3.56) at week 24. However, the quality of evidences was very low to moderate.[61, level I]

In another systematic review, a large RCT compared a 20-week exercise programme (aerobic exercise for at least 40 minutes, three times a week and dietary intervention with a goal of 5% weight reduction) and control (simple informative counselling). PASI reduction was found to be higher in the intervention group [48% versus (vs) 25.5%, p=0.02].[33, level I]

In a cohort study, former smokers had higher PASI 75 achievement at week eight than current smokers (OR=3.37, 95% CI 1.40 to 8.10). Patients without tobacco smoking had a higher proportion of PASI 75 achievement at week eight compared with current smokers (OR=14.14, 95% CI 8.27 to 24.20) and former smokers (OR=3.05, 95% CI 1.20 to 7.76). However, potential confounding factors e.g. alcohol consumption, lack of physical exercise and high-fat diet were not assessed in the study.[62, level II-2]

The above findings are supported by another cohort study on chronic plaque psoriasis where current and ex-smoking were associated with poorer response in achieving PASI 90 within six months following initiation of first-line biological therapy (adalimumab, etanercept and ustekinumab) compared with non-smoker. However, only half of the patients had PASI measurements at the times required for this analysis.[63, level II-2]

A systematic review on a variety of psychological interventions on patients with psoriasis showed varying degrees of success. The most promising methods included cognitive behavioural therapy (CBT), mindfulness-based therapies, motivational interviewing, and educational and interdisciplinary interventions. However, this review was limited by methodological quality of primary studies i.e. small sample sizes, poor retention rates, short follow-up and lack of standardised outcome assessment.[64, level I]

The above findings were supported in a meta-analysis of eight RCTs where CBT was effective in terms of reducing disease severity of psoriasis (MD of PASI reduction= -1.36, 95% CI -2.52 to -0.19). Subgroup analysis showed that it was significantly effective in moderate to severe psoriasis. JADAD scores of the primary papers were two to three.[65, level I]

Recommendation 4

- The following non-pharmacological interventions should be incorporated in the treatment of psoriasis:
  - achieve and maintain ideal body weight via dietary interventions and exercise
  - smoking cessation
  - psychotherapy, especially cognitive behavioural therapy

6.4. Topical Therapy

Topical therapy is the most common modality used to treat patients with psoriasis. They can be used as monotherapy for mild disease or as an adjunct with phototherapy, systemic or biological therapy. Treatment success is dependent on patient's adherence to the topical treatment. Adherence can be enhanced with adequate education on its appropriate use and simplified treatment regimen.

a. Moisturisers

Moisturisers is an adjunct treatment in plaque psoriasis. It restores epidermal barrier function thus helps to moisturise dry skin and, reduce scaliness and itchiness. Moisturisers also improve penetration of other topical agents.

In an RCT on mild to moderate plaque psoriasis comparing combination of linoleic acid-ceramide-containing moisturiser (LA-Cer) and mometasone furoate (MF) vs MF alone, the combination treatment was more effective in terms of:[66, level I]

- significantly higher proportion of patients achieved PASI 50 (65.06% vs 40.00%) and PASI 75 (28.92% vs 13.33%) at week 8
- significantly lower relapse rate at week 8 (34.94% vs 60.00%) and week 12 (44.58% vs 64.00%)

The medications were well tolerated with no serious adverse events (AEs) observed.

The Joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guidelines recommend the use of moisturisers in conjunction with topical corticosteroids for psoriasis.[67] This is supported by the previous local CPG on psoriasis which recommends moisturisers to be used regularly in psoriasis.[21]

Recommendation 5

- Moisturisers should be used regularly to maintain the skin barrier in psoriasis.

b. Topical corticosteroids

Corticosteroids are the mainstay of topical treatment for plaque psoriasis especially for localised disease. They are classified into four categories based on vasoconstrictive properties with potency ranging from mild, moderate, potent to very potent (refer to **Appendix 6**). They are available in various formulations including ointment, cream, gel, lotion, spray and solution. The choice of corticosteroids potency should be based on disease severity, disease location and age of patient.

A Cochrane systematic review reported that topical corticosteroids was more effective than placebo based on combined end point

[Investigator's Assessment of Overall Global Improvement (IAGI)/ Total Symptom Score (TSS)/PASI/Patient's Assessment of Global Improvement (PAGI)] with:[68, level I]

- SMD= -0.89 (95% CI -1.06 to -0.72) for potent corticosteroids
- SMD= -1.56 (95% CI -1.87 to -1.26) for very potent corticosteroids

In term of safety, there was no significance (NS) difference in local and systemic AE for both potent and very potent corticosteroids. However, duration of treatment in the included studies was short (2 - 3 weeks for very potent corticosteroids and 2 - 12 weeks for potent corticosteroids). The general RoB assessment which included RCTs on corticosteroids was moderate in quality.

The Joint AAD-NPF guidelines recommend the use of moderate to superpotent topical corticosteroids for up to four weeks in the treatment of plaque psoriasis not involving intertriginous areas.[67]

In the first edition of the local CPG on psoriasis, short-term therapy with potent and very potent topical corticosteroids may be used to gain rapid clearance in patients with limited plaque psoriasis. These preparations should be avoided on the face, genitalia and body folds. Apart from these, continuous use should not exceed four weeks for potent corticosteroids and two weeks for superpotent corticosteroids. Mild potency corticosteroids may be used for face, genitalia and body folds.[21]

- Practical guides for topical corticosteroids application,[21; 69]
  - Topical corticosteroids should be used concomitantly with moisturisers.
  - Fingertip unit (FTU) can be used as a guide to the amount of corticosteroids required for an affected area.
  - Choice of vehicle depends on the affected sites (i.e. gel for scalp; cream for face, genital and flexural areas; ointment for palm and sole).
  - Choice of potency depends on the clinical severity of psoriasis, age of the patient and area of application.
  - Short-term therapy with potent and very potent topical corticosteroids may be used to gain rapid clearance. These preparations should be avoided on the face, genitalia and skin folds.
  - Mild potency corticosteroids may be used for face, genitalia and body folds.

Recommendation 6
- Topical corticosteroids should be used as the first-line topical treatment in psoriasis.
  - The potent and very potent corticosteroids should be used as a short-term therapy to gain rapid control. These preparations should be avoided on the face, genitalia and body folds.

c. Tar-based preparations

Tar-based preparation has anti-inflammatory, anti-proliferative and pruritus-reducing properties. It has been widely used in the treatment of psoriasis.

In a Cochrane systematic review, coal tar showed NS difference compared with placebo and calcipotriol for combined end points of IAGI/TSS/PASI/PAGI. Apart from that, coal tar was well tolerated with NS differences in withdrawals due to AE or treatment failure compared with calcipotriol.[68, level I] The general RoB assessment which included RCTs on coal tar was moderate in quality.

Tar-based preparation contains polycyclic aromatic hydrocarbons (PAH) which raises safety concern of carcinogenic potential. A large case-control study showed that topical application of coal tar was not associated with bladder cancer.[70, level II-2]

In the previous local guidelines, tar-based preparations have been recommended to be used as a first-line topical therapy for mild psoriasis.[21] It is also mentioned in the AAD-NPF guidelines where coal tar preparations have also been recommended for the treatment of mild to moderate psoriasis.[67]

- Tar-based preparations may cause staining, irritation and folliculitis and should not be used on body folds, face and genitalia.

Recommendation 7
- Topical tar-based preparations may be used in the treatment of psoriasis.

d. Vitamin D analogue monotherapy/in combination with corticosteroids

Vitamin D analogues exert their effect in psoriasis by binding to vitamin D receptors which leads to inhibition of keratinocyte proliferation and enhancement of keratinocyte differentiation. Calcipotriol is the only topical vitamin D analogue available in Malaysia. It is available as a

single agent in the form of cream or ointment and also as calcipotriol-containing preparations combined with betamethasone dipropionate in the forms of ointment, gel and foam.

In a large Cochrane systematic review on chronic plaque psoriasis, calcipotriol monotherapy:[68, level I]

- was more effective than placebo on combined end points (IAGI/TSS/PASI/PAGI) (SMD= -0.96, 95% CI -1.15 to -0.77)
- had NS difference in effectiveness compared with potent corticosteroids, very potent corticosteroids, coal tar, dithranol and topical calcineurin inhibitors on the same outcome

In terms of safety, there was NS difference in systemic AEs between calcipotriol and placebo, potent or very potent corticosteroids, coal tar and dithranol. However, the rate of local AEs was higher with calcipotriol than betamethasone dipropionate (RD=0.07, 95% CI 0.04 to 0.09).

In the same review, combination therapy was more effective in combined end points (IAGI/TSS/PASI/PAGI) than monotherapy:[68, level I]

- combination of calcipotriol and betamethasone dipropionate vs betamethasone dipropionate (SMD= -0.4, 95% CI -0.52 to -0.27)
- combination of calcipotriol and betamethasone dipropionate vs calcipotriol (SMD=0.66, 95% CI 0.31 to 1.02)

On safety profile, both comparisons showed NS difference in local AEs with no report on systemic AEs. The RoB of primary papers was moderate.

In a phase II RCT comparing calcipotriol plus betamethasone dipropionate aerosol foam vs calcipotriol plus betamethasone dipropionate ointment, both given once daily in plaque psoriasis, the former showed greater improvements in PGA clear or almost clear (OR=1.7, 95% CI 1.1 to 2.8) and PASI 75 (OR=1.7, 95% CI 1.0 to 2.7) after four weeks. Both arms had similar safety and tolerability profile.[71, level I]

A phase III RCT on psoriasis compared calcipotriol plus betamethasone dipropionate aerosol foam and calcipotriol plus betamethasone dipropionate gel demonstrated larger proportion of patients achieving treatment success in the former at the end of treatment (OR=2.55, 95% CI 1.46 to 4.46). Both arms had similar safety profile at 12 weeks treatment period (41.6% vs 45.2%) with mild to moderate AEs.[72, level I]

In a 52-week RCT evaluating long-term maintenance proactive treatment, fixed-dose calcipotriol plus betamethasone dipropionate foam twice-weekly was superior than vehicle foam in adults with plaque psoriasis in the following outcomes:[73, level I]

- longer median time to first relapse by 26 days
- risk of experiencing first relapse was reduced by 43% (HR=0.57,

95% CI 0.47 to 0.69)
- rate of relapse was 46% lower (95% CI 37% to 54%) with smaller predicted number of relapses per year of exposure (3.1 vs 4.8)
- additional 41 days in remission over one year with treatment difference of days in remission at 11% (95% CI 8% to 14%)

The extended treatment period of calcipotriol plus betamethasone dipropionate foam twice weekly was well tolerated with favorable safety profile which was similar to once-daily treatment for four weeks during relapse.

In a large Cochrane systematic review on topical treatment for scalp psoriasis, combination of vitamin D and corticosteroids were more effective than corticosteroids or vitamin D monotherapy with lesser risk of causing harmful side effects:[74, level I]
- clearance (clinician-assessed severity based on IGA)
  - corticosteroids plus vitamin D vs corticosteroids (RR=1.22, 95% CI 1.08 to 1.36)
  - corticosteroids plus vitamin D vs vitamin D (RR=2.28, 95% CI 1.87 to 2.78)
- treatment response (IGA)
  - corticosteroids plus vitamin D vs corticosteroids (RR=1.15, 95% CI 1.06 to 1.25)
  - corticosteroids plus vitamin D vs vitamin D (RR=2.31, 95% CI 1.75 to 3.04)
- treatment response (subjective reduction in severity based on PatGA)
  - corticosteroids plus vitamin D vs corticosteroids (RR=1.13, 95% CI 1.06 to 1.20)
  - corticosteroids plus vitamin D vs vitamin D (RR=1.76, 95% CI 1.46 to 2.12)
- AE
  - corticosteroids plus vitamin D vs corticosteroids (RR=0.88, 95% CI 0.42 to 1.88)
  - corticosteroids plus vitamin D vs vitamin D (RR=0.19, 95% CI 0.11 to 0.36)

RoB showed moderate quality of primary studies in the review.

In the first edition of local guidelines on psoriasis, topical vitamin D analogue is recommended to be used for the treatment of psoriasis. Fixed dose combination of topical vitamin D analogue and corticosteroids may be used for short-term treatment of psoriasis.[21]

AAD-NPF guidelines recommend the long-term use of topical vitamin D analogues (up to 52 weeks) for the treatment of mild to moderate psoriasis. The use of combination calcipotriol and betamethasone dipropionate gel is recommended for 4 - 12 weeks for the treatment of mild to moderate scalp psoriasis.[67]

Recommendation 8
- Topical vitamin D analogue with or without corticosteroids may be used in the treatment of psoriasis.
- Proactive use of twice weekly calcipotriol plus betamethasone dipropionate may be considered for up to 52 weeks to prevent relapse of psoriasis.

e. Salicylic acid

Salicylic acid is a topical keratolytic agent and commonly used in combination with other topical therapies in psoriasis. It reduces binding between keratinocytes and results in decrement of scaling and softening of psoriatic plaques.

In a Cochrane systematic review on chronic plaque psoriasis, salicylic acid 2 - 3% in combination with betamethasone valerate and tretinoin was more effective in combined end point (IAGI/TSS/PASI/PAGI) than placebo (SMD= -0.76, 95% CI -1.21 to -0.31). However, the effectiveness of combination salicylic acid with betamethasone dipropionate was similar to calcipotriol monotherapy. For scalp psoriasis, combination of salicylic acid and betamethasone dipropionate was more effective than placebo (SMD= -1.48, 95% CI -2.5 to -0.47).[68, level I] The RoB of primary papers was moderate.

In an open label RCT comparing topical salicylic acid ointment 3% and betamethasone dipropionate ointment applied once at night for 12 weeks for treatment of limited chronic plaque psoriasis, the latter demonstrated significantly more rapid reduction in mean PASI score at week two (4.4 vs 2.7) and week four (3.5 vs 2.3). However, there was NS difference in the score between groups at treatment completion at week 12 (2 vs 2.59). There was no side effects reported in both groups.[75, level I]

According to AAD-NPF guidelines, topical salicylic acid 3 - 6% may be used for 8 - 16 weeks for mild to moderate psoriasis. On the other hand, combination of topical salicylic acid with topical corticosteroids may be used for moderate to severe psoriasis (BSA<20%).[67]

Recommendation 9
- Topical salicylic acid may be used in combination with other topical treatment in psoriasis.

f. Calcineurin inhibitors

Calcineurin is an intracellular enzyme that regulates the transcription of certain genes. Topical calcineurin inhibitors bind to calcineurin, blocking its phosphorylation and thus, inhibiting T-cell activation and synthesis

of several proinflammatory cytokines in the pathogenesis of psoriasis. Examples of such agents are tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream. Although not Food and Drug Administration (FDA)-approved, both tacrolimus and pimecrolimus have been recognised as valid off-label treatments for psoriasis in sensitive skin areas.

In a Cochrane systematic review, pimecrolimus was more effective than vehicle in combined end point with SMD of -0.86 (95% CI -1.30 to -0.41) in flexural or facial psoriasis. Another comparison on flexural psoriasis showed NS difference in the same end point between calcipotriol and pimecrolimus. RoB of the RCTs was generally low.[68, level I]

The above findings were supported by a large systematic review on facial and genital psoriasis where two RCTs showed that topical calcineurin inhibitors was significantly more effective than vehicle based on Investigator Global Assessment (IGA) (clear or excellent) i.e. 67% vs 37% for tacrolimus and 71% vs 21% for pimecrolimus at eight weeks. The studies also found NS difference or transient AE which included burning/stinging, hyperaesthesia or itching. An RCT from the same systematic review showed that, Total Affected Area reduction was comparable between tacrolimus and mid-potency topical corticosteroids (clobetasone butyrate) at six weeks of treatment (22% vs 18%). In another RCT from the same systematic review also did not find a significant advantage of pimecrolimus compared with vehicle or calcipotriol 0.005% in severe genital psoriasis as measured by Modified Psoriasis Area and Severity Index. The study also found that betamethasone 0.1% was significantly more effective than both pimecrolimus 1% and vehicle. Based on Newcastle-Ottawa Scale (NOS), the evidences were of high quality.[76, level I]

The Joint AAD-NPF guidelines recommend the off-label use of 0.1% tacrolimus for psoriasis involving the face and flexural for up to eight weeks. Off-label use of pimecrolimus for flexural psoriasis for 4 - 8 weeks is also being recommend. Long-term use of tacrolimus or pimecrolimus can be considered for flexural psoriasis treatment.[67]

Recommendation 10

- Topical calcineurin inhibitors may be used for facial and flexural psoriasis.

g. Dithranol

Dithranol (also known as anthralin) works by preventing T-lymphocyte activation and keratinocyte proliferation. It has been utilised as a short-contact therapy for limited, scaly plaques on the body or scalp that have not cleared by other treatment.

In a Cochrane systematic review, dithranol was more effective than placebo (SMD= -1.06, 95% CI -1.66 to -0.46) but had NS in effectiveness compared Vitamin D analogues for combined end point (IAGI/TSS/PASI/PAGI). There was also NS difference in local or systemic AEs between dithranol and placebo. The three old RCTs used had generally mix of RoB.[68, level I]

Dithranol may cause skin irritation e.g. burning and staining. Thus, AAD-NPF guidelines recommend the use of dithranol for treatment of mild to moderate psoriasis for short-contact (up to two hours per day) to limit the AEs.[67] In the previous local guidelines, dithranol has been recommended to be used for psoriasis patients with a few large thick plaques. It requires accurate application on affected plaques in order to prevent irritation on surrounding normal skin.[21]

Recommendation 11
- Topical dithranol may be used as short-contact therapy for recalcitrant thick plaques in psoriasis.

h. Topical small molecules

Topical small molecule is a targeted therapy that modulate proinflammatory cytokines and selectively inhibit intracellular signaling pathways involve in the pathogenesis of psoriasis. It may be used as an alternative treatment for psoriasis patients that do not respond to conventional topical therapy. The agents include:
- phosphodiesterase-4 inhibitors (roflumilast, crisaborole)
- aryl hydrocarbon receptor modulating agent (tapinarof, benvitimod)
- janus kinase inhibitors (ruxolitinib)

Roflumilast and tapinarof are approved by US Food and Drug Administration (USFDA). However, none of these are approved to be used for psoriasis in Malaysia.

In a small RCT on intertriginous, anogenital and facial psoriasis, crisaborole 1% ointment BD demonstrated greater improvement in Target Lesion Severity Scale (TLSS) at week four (66% vs 9%, p=0.0011) compared to vehicle. At week eight crisaborole group showed 81% lesional improvement, and 71% clinical clearance (TLSS ≤1). There were no reports of application site reactions and signs of atrophy or telangiectasias.[77, level I]

Two RCTs (PSOARING 1 and 2) from a Phase 3 trial showed that tapinarof 1% cream OD was superior to vehicle in reducing severity of plaque psoriasis over a period of 12 weeks. PGA response was 35.4% vs 6.0% in PSOARING 1 (RR=5.8, 95% CI 2.9 to 11.6) while it was 40.2% vs 6.3% in PSOARING 2 (RR=6.1, 95% CI 3.3 to 11.4). However, the incidence of AEs was higher with tapinarof 1% cream (50.3% vs

22.4% in PSOARING 1 and 54.5% vs 26.2% in PSOARING 2) with mostly mild AEs e.g. folliculitis, nasopharyngitis, contact dermatitis and headache.[78, level I]

In a recent large network meta-analysis (NMA) of 10 RCTs on multiple regimens of topical small molecule in adults with plaque psoriasis, topical aryl hydrocarbon receptor modulating agent and roflumilast were more effective than vehicle in PGA and PASI 75 response at 12 weeks. There were NS differences between topical JAK-STAT inhibitors and vehicle in PGA and PASI 75 responses except ruxolitinib ointment 1% OD for PGA response. Tofacitinib ointment also demonstrated NS difference in both outcomes of effectiveness. In term of safety, topical aryl hydrocarbon receptor modulating agent had higher risk of AEs while the other small molecules agents showed NS difference in risk compared with vehicle. For SUCRA analysis, the following highest ranking of effectiveness (PGA response and PASI 75) were:[79, level I]

- PGA response:
  - Tapinarof 1% BD - 94.09
  - Tapinarof 1% OD - 87.72
  - Ruxolitinib 1% OD - 86.36
  - Tapinarof 0.5% BD - 79.88
  - Tapinarof 0.5% OD - 68.45
  - Roflumilast 0.3% OD - 60.87
- PASI 75:
  - Tapinarof 1% BD - 91.41
  - Tapinarof 1% OD - 87.95
  - Tapinarof 0.5% OD - 75.16
  - Tapinarof 0.5% BD 75.15
  - Benvitimod 1% BD: 74.64
  - Ruxolitinib 0.5% OD: 61.7
  - Roflumilast 0.3% OD - 48.92

Most of the studies had low RoB.

In a 52-weeks extension study (PSOARING 3) using both study subjects of PSOARING 1 and 2, tapinarof 1% cream demonstrated complete disease clearance (PGA 0) in 40.9% patients with an average duration of remission of 130.1± 89.4 days. The most common AEs reported were folliculitis (22.7%), contact dermatitis (5.5%) and upper respiratory tract infections (4.7%).[80, level I]

- Topical tapinarof 1% and roflumilast 0.3% have been shown to be effective and relatively safe in the treatment of psoriasis.

6.5. Phototherapy

Phototherapy is an energy-based treatment using different wavelengths of ultraviolet light which includes:

- ultraviolet A (UVA) (320 - 400 nm)
- ultraviolet B (UVB):
  - narrowband UVB (NBUVB) (311 - 313 nm)
  - selective band UVB (SELUVB) (305 - 325 nm)
  - broadband UVB (BBUVB) (290 - 320 nm)
- excimer light/laser (308 nm)

UVA is delivered in combination with a photosensitising agent (psoralen) in oral, topical or bath form.[21] Phototherapy is mainly a clinic-based treatment that requires frequent visits to the phototherapy centres. Phototherapy can be administered as monotherapy or combined with other treatment modalities e.g. topical agents or conventional systemic agents (refer to **Chapter 6.8** on **Combination Therapy**).

The starting dose for phototherapy can be based on skin phototype or minimal erythema dose (MED). A frequency of twice or thrice weekly is effective and is therefore recommended. Although both twice-weekly treatment and thrice-weekly treatment eventually achieve clearance in equal proportions, twice-weekly treatments take 1.5 times longer to achieve skin disease clearance.[81]

In a Joint AAD-NPF guidelines, phototherapy is mentioned as a reasonable and effective treatment option for patients who do not respond well to topical medications and in those who are not keen to receive conventional systemic therapy or biological therapy.[81]

A consensus guideline by the British Association of Dermatologists recommends NBUVB to patients with psoriasis who have an inadequate response to topical therapy or when topical therapy is not suitable, prior to offering systemic immunosuppression or immunomodulation therapies, including psoralen plus ultraviolet A (PUVA).[82]

a. Effectiveness

A meta-analysis compared various phototherapy modalities as monotherapy in the treatment of moderate to severe psoriasis and showed:[83, level I]

- oral PUVA monotherapy was more effective than NBUVB [proportion of clearance at 0.79 (95% CI 0.69 to 0.88) vs 0.68 (95% CI 0.57 to 0.78) respectively]
- NBUVB was more effective than BBUVB and bath PUVA [proportion of clearance at 0.68 (95% CI 0.57 to 0.78) vs 0.59 (95% CI 0.44 to 0.72) and 0.47 (95% CI 0.30 to 0.65) respectively].

Based on JADAD score, the quality of the primary studies was moderate.

NBUVB is preferred to PUVA monotherapy in the treatment of psoriasis because of enhanced safety, convenience and cost saving. Targeted UVB treatments e.g. excimer laser, excimer light (308 nm) and targeted NBUVB light are well suited and recommended for treating localised psoriatic lesions.[82] An advantage of targeted phototherapy is that it spares unaffected skin and permits higher doses leading to faster clearance of lesions and less AE experienced by the patients.[84, level III]

A meta-analysis showed that combination of calcipotriene ointment and targeted UVB phototherapy was more effective than UVB monotherapy in treating psoriasis in achieving MD of PASI relative change (MD= -22.68%, 95% CI -37.12 to -8.24). The quality of the primary studies, assessed using JADAD scores ranged between 2 and 3 which indicated moderate quality.[85, level I]

A consensus guideline by the British Association of Dermatologists recommends the following:[82]

- adding NBUVB as a short-term rescue therapy to control flares in patients on systemic treatments (e.g. acitretin, methotrexate (MTX), fumaric acid ester agents (FAEs), apremilast or biological agents)
- avoiding combination therapy of NBUVB and acitretin in individuals of childbearing potential

Home phototherapy is also an option for those who are unable to attend clinic-based treatment. There was NS difference between the effectiveness and safety of clinic-based and home treatments.[67; 82]

b. Safety

According to British Association of Dermatologists, there are no limits to the number of phototherapy sessions in the treatment of psoriasis. However, the treatment sessions of >200 PUVA and >500 NBUVB treatments are thresholds to trigger skin cancer screening review.[86]

The short-term AEs reported in meta-analysis were mild e.g. asymptomatic erythema, symptomatic erythema or blistering, nausea and vomiting.[83, level I] Other short-term AEs include pruritus, phototoxic drug eruption, provocation of previously undiagnosed photodermatoses, risk of triggering lupus erythematosus in any individual with relevant symptoms/family history, and reactivation of herpes simplex virus (HSV) and HSV keratitis. In patients with a history of HSV infection, the use of prophylactic acyclovir and facial shielding during treatment should be considered.[82]

Absolute contraindications to the use of phototherapy include:[82]

1. photogenodermatoses - xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy, Bloom syndrome and Rothmund-Thomson syndrome

2. disorders with a genetic predisposition to skin cancers - Gorlin syndrome and albinism
3. concomitant oral immunosuppressive medication in particular ciclosporin (CsA), azathioprine, mycophenolate mofetil and tacrolimus
4. medically unfit and unable to stand safely (e.g. severe CVD or respiratory disease, and poorly controlled epilepsy)

Phototherapy is not contraindicated in childhood, pregnancy or breastfeeding.

Joint AAD-NPF guidelines on phototherapy outline several AEs and management strategies as stated below:[81]

- On oral PUVA - phototoxicity, nausea, pruritus, photo-onycholysis, melanonychia, lentigines and photocarcinogenesis (primarily squamous cell carcinoma). The risk of squamous cell carcinoma is mainly increased in patients who have received >350 treatments. Non-melanoma skin cancer with oral PUVA is associated with fair-skinned individuals.
- Men exposed to PUVA and BBUVB have higher incidences of genital tumours. Even though no evidence exists separately for NBUVB inducing genital tumours, it is prudent to cover male genitalia during treatment.

- Exposure of the eye to UV radiation can result in acute and chronic ocular damage e.g. photokeratitis, photo-conjunctivitis and cataracts. Therefore, the use of UV-protective goggles during treatment is warranted.

A recent and large Finnish cohort study showed an increased incidence of skin cancers with standardized incidence ratio (SIR) for basal cell carcinoma of 3.1 (95% CI 2.1 to 4.3) and cutaneous melanoma of 4.4 (95% CI 2.1 to 8.1).[87, level II-2]

Recommendation 12

- Phototherapy 2 - 3 sessions/week should be offered to patients with moderate to severe psoriasis.
  - Narrowband ultraviolet B (NBUVB) should be considered as the first-line phototherapy.
- Skin cancer should be screened in psoriasis patients receiving treatment sessions >200 psoralen plus ultraviolet A (PUVA) and >500 NBUVB treatments.

6.6. Conventional Systemic Therapy

Patients with moderate to severe psoriasis frequently require systemic therapy. The main conventional systemic therapy that has been used in patients with moderate to severe psoriasis includes the following:

Systemic treatment	Description and mode of action
Methotrexate	Antimetabolite which acts as an antagonist of folic acid, low doses of MTX has anti-inflammatory and immunomodulatory effects.
Ciclosporin	An oral calcineurin inhibitor that inhibit the activation of CD4+ T cells which blocks the synthesis of IL-2 by the complex cyclophilin-CsA, thus preventing T cell proliferation.
Acitretin	Retinoid that is involved in the growth and differentiation of the skin tissue. It modulates many types of proteins including epidermal structural proteins, metalloproteinases and cytokines.
Fumaric acid ester (FAEs)*	Derived from unsaturated dicarboxylic acid, the oral preparation of FAEs is a combination of dimethyl fumarate (DMF) and salts of monoethyl fumarate (MEF). It induces anti-inflammatory effects by preventing the proliferation of T cells.

*FAEs is not available in Malaysia

a. Effectiveness

A systematic review showed that conventional systemic agents were effective in daily practice for the treatment of psoriasis:[88, level II-3]

- at short-term (12 weeks), PASI 75 was 27% for acitretin, 47% for FAEs, 46% for CsA and 40 - 49% for MTX
- at long-term (one year), PASI 75 was 76% for FAEs and 81% for MTX

In a large living Cochrane systematic review compared the effectiveness and safety of conventional systemic agents for patients with moderate to severe psoriasis showed:[89, level I]

- higher proportion of patients reaching PASI 90 (RR=2.82, 95% CI 1.02 to 7.78) and PASI 75 (RR=2.34 95% CI 1.81 to 3.03) compared to placebo at induction phase
  - MTX - PASI 90 (RR=2.06, 95% CI 0.53 to 7.97) and PASI 75 (RR=2.36, 95% CI 1.19 to 4.68)
  - FAEs - PASI 90 (RR=4.47, 95% CI 2.01 to 9.95) and PASI 75 (RR=2.39, 95% CI 1.78 to 3.21)
  - Acitretin - PASI 75 (RR=1.85 95% CI 0.23 to 14.80)
- head-to-head comparison between conventional systemic agents:
  - CsA and MTX were comparably effective in achieving PASI 90 (RR=1.18 95% CI 0.47 to 2.98) and PASI 75 at induction phase (RR=1.37 95% CI 0.84 to 2.23)

  - MTX was superior than FAEs in PASI 90 (RR=3.82, 95% CI 1.65 to 8.85) but similar in PASI 75
- higher proportion of patients reaching PGA 0/1 (RR=2.35 95% CI 1.79 to 3.08) compared to placebo at induction phase:
  - MTX - (RR=2.22, 95% CI 1.54 to 3.21)
  - FAEs - (RR=3.19, 95% CI 1.66 to 6.16)
- head-to-head comparison between systemic agents:
  - CsA and MTX were comparably effective in achieving PGA 0/1 at induction phase (RR=0.82 95% CI 0.47 to 1.46)
  - MTX was superior than FAEs in in achieving PGA 0/1 (RR=3.86, 95% CI 1.84 to 8.09)

RoB assessment showed that most of the studies were of low risk.

A systematic review of cohort studies on moderate to severe psoriasis examined the persistence (duration of treatment) and effectiveness of FAEs and MTX, findings showed:[90, level II-2]

- mean discontinuation duration ranged from 28 to 50 months for FAEs and 7.7 to 22.3 months for MTX.
- at 12 months of follow-up, 76% of patients on FAEs and 53-59% of patients on MTX achieved a PASI 75. Additionally, 76% of patients on FAEs achieved a markedly improved or clear PGA
- two studies reported that 53% and 59% of patients on MTX respectively achieved PASI 75 at one year of treatment

Quality assessment using NOS categorised two studies as high quality, while the remaining six studies were of moderate quality.

A systematic review showed effectiveness ranging between 27% and 53% for conventional systemic therapies (MTX, CsA, acitretin and FAEs) as measured by PASI 75 at 12 to 16 weeks in patients aged ≥65 treated with plaque psoriasis.[91, level I]

In a Cochrane systematic review, pooled analysis of two RCTs demonstrated that FAEs was superior to placebo in the treatment of PP (RR=4.55, 95% CI 2.80 to 7.40). Based on Cochrane RoB, the quality of primary papers were low.[92, level I]

b. Safety

A large Cochrane systematic review on the safety of conventional systemic agents for patients with moderate to severe psoriasis showed:[89, level I]

- in terms of overall AEs at induction phase-
  - MTX and placebo had comparable AEs
  - FAEs had higher risk of AEs compared with placebo (RR=1.40, 95% CI 1.22 to 1.62)
  - MTX had comparable AEs with either CsA or FAEs
- NS difference between all non-biological systemic agents and

placebo on the risk of serious AEs (SAEs) at induction phase. There was also NS difference in the same outcome between MTX and FAEs.

The above findings were supported in another systematic review of patients aged ≥65 with psoriasis which showed that conventional systemic therapies (MTX, CsA, acitretin and FAEs) were safe.[91, level I]

In a case-control study, long-term treatment with MTX in psoriasis was associated with a lower risk of mortality compared with no exposure to it (RR=0.08; 95% CI 0.02 to 0.28).[93, level II-2]

Another systematic review revealed that when compared with no systemic therapies, monotherapy systemic treatment with either MTX, CsA or acitretin did not increase risk of herpes zoster in psoriasis. However, systemic corticosteroids was associated with increased risk of herpes zoster infection (HR=2.4, 95% CI 2.10 to 2.73).[94, level I]

c. Therapeutic Strategy Options

Conventional systemic therapy has been recommended to be administered in intermittent or rotational regimens in psoriasis patient due to the potential cumulative toxicity.[55, level III; 95, level III]

Patients deemed suitable for intermittent therapy include those with good response and without fast relapses. A treatment can be discontinued (either abruptly or by tapering) when the treatment goal has been achieved for a period of ≥6 months. In addition, it is also recommended when a SAE occurs, upon patient request or indicated for other reasons e.g. planning for pregnancy, etc.[55, level III]

However, it is important to note that treatment interruption may lead to recurrence or relapse as demonstrated by a systematic review indicating the median time to relapse of psoriasis after discontinuing CsA and MTX was four weeks.[55, level III; 96, level I]

Treatment re-introduction can be considered if/or PASI ≥5 and/or DLQI ≥5. This decision should be made between the physician and patient.

d. The pre-initiation assessment

The following investigations have been recommended prior to initiation of the conventional systemic therapy (refer to Table 4).[21; 51; 55; 97, level III] Patients with abnormal results should be managed according to the local guidelines prior to starting the medications.

Table 4. Investigations to be Performed Before Initiation of Conventional Systemic Therapy

Investigation	MTX	CsA	Acitretin
Full blood count	✔	✔	X*
Renal profile	✔	✔	✔
Liver function test	✔	✔	✔
Fasting blood glucose	X*	X*	✔
Fasting lipid profile	X*	✔	✔
Hepatitis B serology test	✔	✔	X*
Hepatitis C serology test	✔	✔	X*
HIV screening	✔	✔	X*
Chest x-ray (CXR)/Mantoux test/IGRA	✔	✔	X*
Pregnancy test	✔	X*	✔
Urinalysis	X*	✔	X*
Serum calcium and magnesium	X*	✔	X*

HIV = human immunodeficiency virus
IGRA = interferon-gamma release assay

*Baseline investigations prior to initiation of therapies should be tailored to the individual patient according to their co-morbidities and risk factors for therapeutic side effects.

e. Instructions for use

The conventional systemic therapy should be prescribed only for moderate to severe plaque psoriasis. These are summarised in the following table.[21; 51; 55, level III; 97, level III]

Table 5. Summary of Instructions for Use of Systemic Treatment for Adults

Contraindications and Precautions	Methotrexate	Ciclosporin	Acitretin
Absolute contraindications	• Severe liver disease • Severe infection • Renal failure • Pregnancy/breastfeeding • Alcohol abuse • Bone marrow dysfunction/haematologic changes • Immunodeficiency • Acute peptic ulcer • Reduced lung function	• Impaired renal function • Uncontrolled hypertension • Severe infections • History of malignancy • Current malignancy • Previous PUVA • Simultaneous phototherapy (PUVA and NBUVB therapy) • Extensive previous UV exposure with high risk of cutaneous malignancy • Severe hepatic disease • Breastfeeding	• Severe renal/hepatic dysfunction or hypertriglyceridaemia • Pregnancy (high risk of teratogenicity) • Breastfeeding • Blood donation • History of pancreatitis
Relative contraindications	• Kidney or liver diseases • Old age • Ulcerative colitis • History of hepatitis • Lack of compliance • Actively trying to become pregnant • Gastritis • Obesity • DM • Previous malignancy	None	• Women of child-bearing age

Contraindications and Precautions	Methotrexate	Ciclosporin	Acitretin

Special precaution during use	• Written informed consent form
	• It is important to consider the impact of the following risk factors on liver toxicity in patients who receive MTX:
	  ○ DM
	  ○ Obesity
	  ○ History of or current alcohol consumption
	  ○ Persistent abnormal liver function test (LFT)
	  ○ History of liver disease including chronic hepatitis B or C
	  ○ Family history of inheritable liver disease
	  ○ History of significant exposure to hepatotoxic drugs or chemicals
	  ○ Lack of folate supplementation
	  ○ Hyperlipidaemia
	• Watch out for risk factors of MTX-induced haematotoxicity
	  ○ Renal insufficiency
	  ○ Advanced age
	  ○ Lack of folate supplementation
	  ○ Medication error
	  ○ Drug interaction
	  ○ Hypoalbuminaemia
	  ○ Excessive alcohol intake
	• Reliable contraception in women of child bearing age and in men
	• Avoid alcohol
		• Close BP monitoring
		• Avoid treatment of >2 years
		• Watch out for important drug interactions
		• Avoid progesterone-containing contraception due to drug-drug interaction
		• Regular use of sunscreen and avoidance of excessive sun exposure
			• Written informed consent form
			• For childbearing age - double contraception
			• Contraception must be practised for at least one month prior to and during treatment
			• Start treatment on second or third day of the menstrual cycle
			• Take the capsule with a meal containing some fat or with whole milk
			• Alcohol abstinence and, low-fat and low- carbohydrate diet are advised

Contraindications and Precautions	Methotrexate	Ciclosporin	Acitretin
Dose initiation and titration	• Initial dose: 5 – 7.5 mg/week • Escalate dose every 2 – 4 weeks from 7.5 to maximum 25 mg/week till clinical response • Folic acid supplementation may be given 5 mg daily except for MTX therapy day or 5 mg once a week after the day of MTX • The dose can be administered as a single dose or divided into three doses and administer at 12 hours interval over two consecutive days • Maximum clinical response can be expected within 12 - 20 weeks • If patients do not respond to 25 mg/week of MTX at 16 - 24 weeks, the effect of further increment of dose is unclear • Increased effectiveness and tolerability may be achieved by subcutaneous administration • May be given to patients for as long as it is effective and well tolerated	• Initial dose: 2.5 – 3 mg/kg/day • Escalate dose every 4 – 6 weeks till clinical response (maximum 5 mg/kg/day) • Intermittent short courses over 3 - 6 months can be used for inducing skin clearance • When necessary, it may be given to patients responding to treatment continuously for up to two years	• Initial dose: 0.5 - 1 mg/kg/day • Escalate dose every 4 - 6 weeks till clinical response with a usual dose of 25 - 50 mg daily (maximum 75 mg daily) • May be given to patients for as long as it is effective and well tolerated
Recommended laboratory assessment	• Monitor full blood count (FBC), LFT and renal profile (RP) ○ Two weeks after initiation ○ Subsequently monthly for two months and 3-monthly thereafter • Do blood test 5 - 7 days after last dose of MTX	• Monitor FBC, RP, serum calcium magnesium, LFT and fasting lipid profile (FLP) ○ Monthly for four months ○ Subsequently 2-monthly • Urinalysis at four weeks, then every 4 - 8 weeks	• Monitor FBC, LFT and FLP ○ Monthly for two months ○ Subsequently 3-monthly • Pregnancy test should be performed periodically during treatment and up to three years after discontinuation

Contraindications and Precautions	Methotrexate	Ciclosporin	Acitretin
	• Risk of liver toxicity may increase with cumulative doses of MTX • Procollagen III aminopeptide (PIIINP), if available, to be performed every 3 - 6 monthly to monitor for liver fibrosis; however, PIIINP may be inaccurate in patients with active PsA, lung fibrosis and conditions in which fibroneogenesis occurs • Consult gastrointestinal team when MTX-induced hepatotoxicity, inflammation, fibrosis or cirrhosis are suspected for further investigations (blood serology, vibration controlled transient elastography, magnetic resonance elastography or liver biopsy) • No clear evidence of increased risk of malignancies or serious infections with MTX in psoriasis		
Post-treatment precautions	• Women should be advised not to become pregnant for at least three months after discontinuation of therapy • Men must not father a child for at least three months after discontinuation.	• After discontinuation, patients should be monitored periodically for skin cancer especially in cases with extensive UV exposure (therapeutic or natural)	• Reliable contraception in women of child-bearing age for three years after discontinuation of therapy • Do not donate blood for up to three years after discontinuation of therapy

Recommendation 13

- Methotrexate (MTX) should be used as the first-line conventional systemic therapy for moderate to severe psoriasis.
  - Folic acid supplementation may be given either 5 mg daily except for MTX therapy day or 5 mg once a week after the day of MTX.
  - Full blood count and liver function test should be closely monitored.
- Acitretin may be offered for the treatment of moderate to severe psoriasis.
  - It should be avoided in women of childbearing age without reliable contraception and in those who are planning pregnancy.
  - Liver function test and fasting lipid profile should be closely monitored.
- Ciclosporin therapy in psoriasis:
  - may be offered as short-term treatment for rapid disease clearance in moderate to severe disease
  - should not be used for more than two years
  - should not be used with previous history of psoralen plus ultraviolet A (PUVA) exposure
  - should not be used concurrently with phototherapy (NBUVB and PUVA)
  - blood pressure, renal function and lipid profile should be closely monitored

6.7. Biological Therapy

Biological therapies are bioengineered protein-based drugs which block specific molecular steps (either immune mediators or receptor) in the pathogenesis of psoriasis. A better understanding of psoriasis pathogenesis has led to the identification of multiple new therapeutic targets which have revolutionised the treatment of psoriasis. Biological therapy does not only improve skin symptoms but also alter systemic inflammation, hence influencing long-term outcomes of psoriasis and its co-morbidities. Biological therapy also has been proven to improve QoL of patients.

However, there is no single biological therapy that works for all patients. Each biological therapy has its own advantages and limitations for psoriasis treatment. Psoriasis-related co-morbidities may complicate the choice of the agent. Treatment regimens for patients with psoriasis should be tailored to meet the specific needs based on disease severity, impact on QoL, response to previous treatment and presence of co-morbidities.

Currently, there are four classes of biological therapies approved by the FDA for use in moderate to severe psoriasis:[98; 99]

- anti-TNF-α (adalimumab, certolizumab pegol, etanercept, infliximab)

- anti-IL-12/23 (ustekinumab)
- anti-IL-17 (bimekizumab, brodalumab, ixekizumab, secukinumab)
- anti-IL-23 (guselkumab, risankizumab, tildrakizumab)

a. Effectiveness

Data from clinical studies on the safety and effectiveness of biological therapy provide essential information for a personalised patient care. A recent large Cochrane NMA of 179 studies involving 62,339 participants revealed that biological agents (anti-TNF-α, anti-IL-12/23, anti-IL-17 and anti-IL-23) in adults with moderate to severe plaque psoriasis were more effective than placebo and non-biological systemic agents based on the following results:[89, level I]

i. PASI 75

- Biological agents vs placebo
  - Anti-IL-17, anti-IL-23, anti-IL-12/23 and anti-TNF-α (RR ranging from 9.21 to 14.51)
- Biological agents vs acitretin
  - Etanercept (RR=1.98, 95% CI 1.26 to 3.12)
- Biological agents vs MTX
  - Adalimumab, infliximab, ixekizumab and risankizumab (RR ranging from 1.25 to 2.25)
- Biological agents vs FAEs
  - Brodalumab, guselkumab, ixekizumab, risankizumab and secukinumab (RR ranging from 2.13 to 4.08)
- Biological agents vs CsA
  - Etanercept (RR=1.05, 95% CI 0.89 to 1.23)
- Anti-IL-17, anti-IL-23 and anti-IL-12/23 appeared significantly superior to the small molecule class
- Biological agents vs biological agents
  - Infliximab, anti-IL-17 drugs (ixekizumab, bimekizumab and secukinumab) and risankizumab were significantly more likely to reach PASI 75 than ustekinumab, other anti-TNF-α (adalimumab, certolizumab and etanercept) and small molecules (apremilast).

ii. PASI 90

- Biological agents vs placebo
  - anti-IL-17 (secukinumab, ixekizumab, brodalumab, bimekizumab, netakimab and sonelokimab) with RR of 27.51 (95% CI 19.19 to 39.46)
  - anti-IL-23 (guselkumab, tildrakizumab and risankizumab) with RR of 19.96 (95% CI 13.51 to 29.49)
  - anti-IL-12/23 (ustekinumab) with RR of 18.37 (95% CI 12.56 to 26.85)
  - anti-TNF-α (infliximab, etanercept, adalimumab and certolizumab) with RR of 13.61 (95% CI 10.65 to 17.41)
- Biological agents vs MTX
  - infliximab (RR=2.86, 95% CI 2.15 to 3.80)

- adalimumab (RR=3.73, 95% CI 2.25 to 6.19)
- ixekizumab (RR=2.05, 95% CI 1.43 to 2.94)
- risankizumab (RR=2.37, 95% CI 1.59 to 3.54)

- Biological agents vs FAEs
  - secukinumab (RR=8.31, 95% CI 4.23 to 16.35)
  - ixekizumab (RR=8.60, 95% CI 3.69 to 20.04)
  - guselkumab (RR=6.02, 95% CI 3.13 to 11.60)
  - risankizumab (RR=8.33, 95% CI 3.87 to 17.95)
  - brodalumab (RR=3.00, 95% CI 2.04 to 4.42)

iii. SUCRA analysis on PASI 90

- the ranking of effectiveness compared with placebo (class-level) were:
  - anti-IL-17 (SUCRA=99.5)
  - anti-IL-23 (SUCRA= 83.8)
  - anti-IL-12/23 (SUCRA=66.7)
  - anti-TNF-α (SUCRA=48.7)
- the ranking of effectiveness compared with placebo (drug-level):
  - infliximab (SUCRA=96.8)
  - bimekizumab (SUCRA=92.0)
  - ixekizumab (SUCRA=90.3)
  - risankizumab (SUCRA=85.3).

Clinical effectiveness of these biological therapies was similar when compared against each other.

Early initiation of treatment with guselkumab in psoriasis patients with shorter disease duration (≤2 years) was associated with better clinical response than those with longer disease duration in terms of PASI 90 reduction (80.1% vs 73.2%, p=0.019) and absolute PASI 0 (51.8% vs 39.4%, p<0.001) in an open label clinical trial. Those achieving complete skin clearance at week 20 and week 28 were defined as a super responder. The likelihood of being one was higher in those with the following characteristics:[100, level II-I]

- younger age
- lower BMI
- disease duration of ≤2 years
- biologic naïve

b. Safety

The safety of biological agents has been well-documented through clinical trials and real-world evidence since the introduction of infliximab in 2006 for the treatment of chronic plaque psoriasis. These agents are generally considered safe, with mild AEs being common and SAEs rare.

Common AEs associated with biological agents include:[21]

- injection site reactions
- upper respiratory tract infections

- oropharyngeal pain
- urinary tract infections
- superficial cutaneous fungal infections
- mucocutaneous herpes simplex
- arthralgia
- headache
- diarrhoea
- nausea

Rare SAEs may include:

- severe infections
- CV events
- malignancies

These AEs underscore the importance of careful management including monitoring when using biological agents in clinical practice.

A recent Cochrane NMA on patients with psoriasis compared biological agents vs placebo during induction phase (8 - 24 weeks) and revealed:[89, level I]

- varying low risk of AEs with mixture of significant and NS results
- NS low risk of SAEs for all biological agents

A meta-analysis of 48 RCTs on anti-TNF-α vs placebo in treatment of patients with psoriasis or PsA showed a slightly increased risk of overall infections (RR=1.09, 95% CI 1.02 to 1.15) with etanercept having the highest risk (RR=1.14, 95% CI 1.03 to 1.27). There were no increased risk of upper respiratory tract infections or serious infections.[101, level I]

In a large systematic review of 52 RCTs comparing serious *Candida* infection in patients with moderate to severe psoriasis on various biological agents vs placebo showed increased risk of infections in anti-IL-17 (OR=2.30, 95% CI 1.54 to 3.45) but NS risk for anti-IL-12/23 and anti-TNF-α.[102, level I]

Three meta-analyses of RCTs with study duration ranging from 10 to 36 weeks on psoriasis demonstrated the following findings:

- overall rates of major adverse CV events (MACE) was 0.06% for any biological therapies[103, level I]
- NS differences in risk of MACE or other CVS events between biologics and placebo, and between biologics[103 - 105, level I]

A nationwide cohort study showed that risk of TB was highest in anti-TNF-α (HR=7.82, 95% CI 3.72 to 16.42), followed by anti-IL-12/23 (HR=6.35, 95% CI 3.60 to 11.20) and CsA (HR=1.54, 95% CI 1.14 to 2.08). There was NS risk of TB with MTX and acitretin.[106, level II-2]

In a multicentre cohort that looked into the effectiveness and safety of adalimumab treatment in psoriasis patients with hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and/or TB infections, 42% patients had

latent TB infections. They were given isoniazid at 300 mg/day for one month before starting adalimumab and for an additional five months in co-treatment of anti-TB and adalimumab. No case of reactivation of TB was observed until week 48.[107, level II-2]

An RCT on moderate to severe psoriasis patients with LTBI who received anti-TB treatment prior to biological therapy initiation revealed no active TB being reported among guselkumab-treated patients through week 100 but two new cases were detected in adalimumab-treated patients.[108, level I]

A multicentre retrospective cohort study evaluated the safety profile of secukinumab in psoriasis patients with latent TB infection. All patients who had latent TB and received secukinumab up to 84 weeks had no TB reactivation.[109, level II-2]

There was no good evidence for the risk of herpes zoster in psoriasis patients on biological agents.

A population-based cohort study showed generally NS difference in overall malignancy rates between biological therapy and non-biological therapy users with psoriasis although anti-TNF showed a slight increased risk of squamous cell carcinoma (HR=1.42, 95% CI 1.12 to 1.80).[110, level II-2]

In another retrospective cohort study on effects of different biological agents (anti-TNF, anti-IL-12/23 and anti-IL-17) among psoriasis or PsA patients, there was NS difference in renal function over two years follow-up.[111, level II-2]

Long-term safety of most biological agents had been documented for up to five years duration of exposure. The results were reassuring as the rates of any AEs, SAEs and AEs of interest were generally low and stable/declined over the years. The details of long-term safety is summarised in **Table 7**.[112, level II-2; 113 - 116, level I]

Table 7. Long-term Safety of Biological Therapies

Biological agent	Ustekinumab[116], level I	Ixekizumab[115], level I	Secukinumab[112], level II-2	Guselkumab[113], level I	Risankizuma[114], level I
Study design, study duration and sample size	Post-hoc analysis of RCTs and open labelled extension studies; N=1482 subjects treated for ≥4 years, including 838 subjects treated for ≥5 years; duration of exposure up to five years	Post-hoc analysis of controlled trials; N=6892 subjects; cumulative exposure of 18,025.7 PY	Pooled analysis of clinical trials and post-marketing safety monitoring; N=9561 subjects; duration of exposure up to 5.4 years	Pooled analysis of clinical trials; N=2891 subjects; median duration of exposure 3.5 years	LIMMitless open-label extension study; N=897 subjects enrolled, 706 were still ongoing at the time of data cutoff; median duration of exposure 5.3 years
Incidence rates of any AEs and common AEs (event/100 PY)	• Overall AEs=232.6 • Nasopharyngitis =20.8 • Upper respiratory tract infection (URTI)=16.2 • Headache=7.1 • Arthralgia=4.7	• Any AE=32.5 • Nasopharyngitis =8.8 • URTI=6.2 • Injection site reaction=3.9 • Arthralgia=3.6	• Any AE=212.4 • Nasopharyngitis =19.4 • Upper respiratory tract infection =6.1 • Headache=6.6	• ≥1 AE=169.0 • Nasopharyngitis =21.1 • URTI=11.9	• Any AEs=155.3 • Nasopharyngitis =13.7 • URTI=8.0 • Arthralgia=4.3
Incidence rates of SAEs & AEs of interest (event/100 PY)	• Overall SAEs=7.1 • Infections=1.1 • MACE=0.4 • Malignancy=1.1 ○ Non-melanoma skin cancer (NMSC)=0.5 ○ Other malignancies (excluding NMSC)=0.6	• Overall SAEs=5.4 • Infections, overall=1.3 ○ Candidiasis =1.9 ○ Herpes zoster infection=0.7 ○ Latent TB=0.6 • MACE=0.5 • Malignancy, overall=0.8 ○ NMSC=0.3 ○ Other malignancy (excluding NMSC)=0.5	• Any SAEs=7.1 • Infections, overall=1.5 (mainly localised) ○ Candidiasis =2.7 ○ Herpes infection=2.7 ○ TB-related events=0.04 • MACE=0.4 Malignancy= 0.8	• ≥1 SAEs=5.3 • Infection=0.9 ○ Candidiasis =0.6 • MACE=0.3 Malignancy= 0.7	• SAEs=6.9 • Infections=1.1 ○ Herpes zoster infection=0.4 ○ Active TB=0 ○ Candidiasis =0.6 • MACE=0.4 Malignancy= 0.9

- Biological agents have good short and long-term safety profile.

c. Indications and contraindications

Patients with psoriasis may be considered for biological therapy if they have:[117]

- moderate to severe disease that is contraindicated/intolerant to phototherapy and conventional systemic therapies
- moderate to severe disease that fails to respond to phototherapy and conventional systemic therapies (treatment goal not achieved)
- severe disease if treatment success cannot be expected with conventional systemic therapies

Contraindications for biological therapy are summarised in **Table 8**.[21; 51, 55; 118]

Table 8: Contraindications of Biological Agents

Contraindications	Anti-TNF-α	Anti-IL-12/23	Anti-IL-17	Anti-IL-23
Absolute contraindications	• Active TB • Severe infections • Congestive heart failure (NYHA class III/IV) • Active chronic hepatitis B • History of allergic reaction to therapeutic agent or vehicle	• Active infections • History of allergic reaction to therapeutic agent or vehicle	• Active infections • History of allergic reaction to therapeutic agent or vehicle	• Active infections • History of allergic reaction to therapeutic agent or vehicle
Relative contraindications	• Latent TB • History of recurrent infections • Concomitant systemic lupus erythematosus (SLE) or multiple sclerosis (MS) • PUVA >200 treatments (especially if followed by CsA use) • Malignancies or lymphoproliferative disorders • Hepatobiliary disorders	• Recurrent or chronic infections • Previous history of lymphoreticular malignancies	• IBD • Depression and history of suicidal behaviour (brodalumab)	• Recurrent or chronic infections

d. Pre-initiation assessment

Patients should be counselled and educated for pre-biologic assessment prior to the initiation of biological therapy on the following:[21; 55, level III; 117]

- history and clinical examination focusing on prior exposure to treatments, malignancies (NMSC), infections (TB), IBD, CCF, neurological disease or symptoms and depression and/or suicidal ideation or behaviour
- objective assessment of the disease (e.g. PASI/BSA/DLQI)
- need for reliable contraception
- need for vaccinations
- laboratory/radiological investigations -
  - FBC
  - RP
  - LFT
  - antinuclear antibody (ANA)
  - erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
  - fasting blood sugar (FBS)
  - fasting lipid profile
  - hepatitis B serology test
  - hepatitis C serology test
  - HIV screening
  - CXR
  - Mantoux test or IGRA
  - pregnancy test
  - urinalysis

Not all investigation tests are necessary for all patients. Patient's history, risk exposure and characteristics have to be taken into account in the decision to perform the tests. Further specific testing may be required according to clinical indications. Patients with abnormal results should be managed according to the local guidelines prior to starting the biological therapy. Psoriasis patients with latent TB should be referred to respiratory physician for treatment before biologics initiation.[21]

e. Selection of biological therapy

Clinicians need to take into account effectiveness and safety, onset of treatment response, co-morbidities, individual patient's factors and resources when choosing a biological agent for moderate or severe psoriasis. Each biological agent has its own advantages and limitations in the treatment of psoriasis.[21; 55, level III; 118; 119] Refer to **Table 9** below for selection of biological agent in patients with co-morbidities. It is developed based on evidences discussed in this CPG and EuroGuiDerm Guideline.[119]

Table 9: Selection of Biological Agent in Patients with Co-Morbidities

Co-morbidity	Anti-TNF				Anti-IL-12/23	Anti-IL-17			Anti-IL-23		
	Etanercept	Infliximab	Adalimumab	Certolizumab	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab	Tildrakizumab
PsA	✔✔	✔✔	✔✔	✔✔	✔✔	✔✔	✔✔	✔	✔✔	✔	✔
Crohn's disease	✔	✔✔	✔✔	✔✔	✔✔	×	×	×	✔	✔	✔
Ulcerative Colitis	✔	✔✔	✔✔	✔	✔✔	×	×	×	✔	✔	✔
DM/Metabolic Syndrome/ Dyslipidaemia	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Chronic kidney disease	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Chronic liver disease	✔	✔	✔	✔	✔✔	✔✔	✔✔	✔✔	✔	✔	✔
Advanced heart failure	×	×	×	×	✔	✔	✔	✔	✔	✔	✔
Ischemic heart disease	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
History of malignancy	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Latent/treated TB	×	×	×	×	✔	✔	✔	✔	✔	✔	✔
Hepatitis B#	-	-	-	-	-	-	-	-	✔	✔	✔
Hepatitis C#	-	-	-	-	-	-	-	-	✔	✔	✔
HIV*	✔	✔	✔	-	✔	✔	✔	-	-	✔	-

✔✔	Preferred option
✔	Alternative option
×	Avoid
-	Insufficient or no evidence

#Patients must be co-managed with hepatologist;

*PLHIV with undetectable viral load

f. Monitoring

Monitoring AEs of biological therapy in patients with psoriasis include:[21]

- update on safety profile and reminder of potential risk of malignancy e.g. NMSC/ infection e.g. TB
- patient's body weight
- blood investigations, 3 - 6 monthly or when clinically indicated e.g. FBC, LFT, RP
- assessment for TB yearly or when clinically indicated e.g. CXR, Mantoux test or IGRA

The biological therapy should be prescribed by the dermatologists only for moderate to severe psoriasis.

g. Assessment of treatment response

During maintenance treatment, an assessment of treatment success should be made in intervals in accordance with the safety monitoring recommendations (typically every 8 - 12 weeks). If treatment goals are not met, a number of measures can be applied to increase the effectiveness of the biological agents e.g. increasing the dose, shorten the dosing interval or adding another drug (combination therapy). When dose adjustments are either ineffective or not appropriate, changing the drug is an important step.[21; 55, level III; 117; 118]

h. Treatment optimisation and transitioning

Biological therapy is always used as monotherapy. When clinically required, it may be combined with topical agents e.g. corticosteroids, vitamin D analogues or other systemic conventional therapies to augment the effectiveness or reduce the potential AEs.[55, level III; 95, level III; 118]

i. Titration of dose and discontinuation of biological therapy

During successful maintenance as monotherapy, a dosage reduction in biological agent can be considered to limit drug exposure. However, long-term effectiveness and safety data has only been generated for the approved dosage and there is a theoretical risk of decreased effectiveness when using reduced dosages. In addition, there is some evidence to suggest that a lower dosage of a biological agents may increase the risk of anti-drug antibody formation.

Stopping biologic agent is generally not recommended. In patients with moderate to severe psoriasis, significant therapeutic breaks are difficult to achieve without risk of recurrence or an impact on effectiveness following re-initiation of therapy. Thus, biological therapy should generally be administered using a continuous uninterrupted treatment regimen.[55, level III; 95, level III; 118]

j. Biosimilar

The use of biological therapy has significantly improved the treatment outcomes of patients with psoriasis, with the downside of increased healthcare costs. This has limited their wide use and contributed to inequalities of care provided to psoriasis patients. In recent years, the introduction of biosimilars for inflammatory diseases has become a fast-evolving field. They offer substantial cost savings in health care while maintaining effectiveness and safety of the reference product and increasing access to biological therapy for the patients.[51; 118; 120, level III]
Patients and clinicians may be concerned about potential loss of effectiveness, altered immunogenicity or unanticipated differences in AEs when switching to a biosimilar. A systematic review of 14 RCTs

and three cohort studies of moderate quality showed no clinically and statistically significant difference in effectiveness (improvement in PASI 75) and safety (risks of AEs at week 16 and week 52) between biosimilars of adalimumab, etanercept, infliximab and ustekinumab and their originators.[121, level I]

There is no loss of effectiveness in switching from an original biological agent to a biosimilar. However multiple switching of the same biosimilar group is not encouraged.[120, level III; 122, level III]

- Biological agents are preferably prescribed by a dermatologist for the treatment of psoriasis in the local setting.

Recommendation 14
- Biological therapy:
  - should be offered to patients with moderate to severe psoriasis who have intolerance/contraindication or failed phototherapy and conventional systemic therapy
  - may be considered as a first-line treatment in severe disease based on clinical judgement where sufficient treatment success cannot be expected with a conventional therapy
- Careful evaluation for contraindications should be performed prior to initiation of biological therapy for psoriasis patients.
- Response and adverse events should be monitored during biological therapy.

6.8. Oral Small Molecules Therapy

Small molecules [<1 kilodalton (kDa)] target intracellular enzymes to modulate nuclear transcription and cytokines productions compared with biological therapy which are monoclonal antibodies acting extracellularly. Unlike biological therapy which are large molecules requiring subcutaneous or intravenous administration to achieve bioavailability, small-molecules are available in oral form. Currently, apremilast and deucravacitinib are the small molecules approved for the treatment of psoriasis. They are described below.

Small molecules	Description and mode of action
Apremilast	Phosphodiesterase-4 (PDE-4) inhibitor with immunomodulatory effect by suppressing the production of proinflammatory cytokines e.g. TNF-α, IL-17 and IFN-γ
Deucravacitinib	Inhibits tyrosine kinase 2 (TYK2) that mediates signaling of IL-23, IL-12 and type I interferons.

a. Effectiveness and safety profile

A meta-analysis of RCTs on PDE-4 inhibitor showed that apremilast was more effective than placebo in the treatment of psoriasis and PsA especially in difficult-to-treat areas:[123, level I]

- achievement of PASI 75 (RR=3.22, 95% CI 2.59 to 4.01)
- higher percentage of participants with static PGA of 0/1 (RR=3.57, 95% CI 2.58 to 4.93)
- improvement in the difficult-to-treat sites -
  - higher scores in scalp PGA of 0/1 (RR=2.21, 95% CI 1.69 to 2.91)
  - higher scores in palmoplantar PGA of 0/1 (RR=2.33, 95% CI 1.16 to 4.66)
  - lower nail psoriasis severity index (SMD= -0.46, 95% CI -0.58 to -0.33)
- reduction in DLQI (SMD= -0.58, 95% CI -0.65 to -0.50)

The safety analysis showed that apremilast had higher rates of any Treatment-Emergent Adverse Events (TEAEs) (RR=1.22, 95% CI 1.17 to 1.28) and drug-related TEAEs (RR=1.98, 95% CI 1.77 to 2.20). However, there were NS differences in serious TEAEs e.g. opportunistic infections, malignant disease, systemic vasculitis, MACE or death. The included trials in the meta-analysis had low and unclear RoB.

In an RCT on patients with moderate to severe psoriasis, deucravacitinib demonstrated superior effectiveness compared with apremilast and placebo at week 16:[124, level I]

- PASI 75 was achieved in 58.4% in deucravacitinib vs 35.1% in apremilast and 12.7% in placebo ($p<0.0001$)
- PASI 100 was achieved in 14.2% in deucravacitinib vs 3.0% in apremilast and 0.6% in placebo ($p<0.0001$)
- static PGA 0/1 was achieved in 53.6% in deucravacitinib vs 32.1% in apremilast and 7.2% in placebo ($p<0.0001$)

Deucravacitinib was also well tolerated. Overall, AE rates were similar across all three groups. The most frequent AEs in deucravacitinib-treated patients were nasopharyngitis and URTI whereas headache, diarrhoea and nausea were more common with apremilast.

b. Pre-initiation assessment

A few laboratory and radiographic investigations have been recommended prior to initiation of the oral small molecules (OSM) therapy and they are summarised in following table. Patients with abnormal results should be managed according to the local guidelines prior to starting the medications.[51; 125, level III]

Table 10. Investigations to be Performed Before Initiation of Oral Small Molecules

Investigation	Apremilast	Deucravacitinib
Full blood count	✔	✔
Renal profile	✔	✔
Liver function test	✔	✔
Fasting lipid profile	-	✔
Hepatitis B serology test	Optional	✔
Hepatitis C serology test	Optional	✔
HIV screening	Optional	✔
CXR	-	✔
Mantoux test or IGRA	-	✔
Pregnancy test	✔	✔

c. Instructions for use

OSM therapy should be prescribed by dermatologists only for the indication of moderate to severe psoriasis.[51; 125, level III; 126] The instructions of its use are summarised in the following table.

Table 11. Summary of Instructions for Use of Oral Small Molecules

Instructions	Apremilast	Deucravacitinib
Dosage	• Gradual up-titration dose to 30 mg BD to reduce GI symptoms • No dose adjustment for liver impairment • In renal impairment with estimated Glomerular Filtration Rate (eGFR) <30 mL/min, renal adjusted dose is 30 mg OD	• 6 mg OD • No dose adjustment for renal impairment and mild or moderate liver impairment • Avoid in severe liver impairment and viral hepatitis

Instructions	Apremilast	Deucravacitinib
Absolute contraindications	• Pregnancy or breastfeeding • Severe acute infections • Age <18 years old	• Pregnancy or breastfeeding • Active infection e.g. active TB infection • Age <18 years old
Relative contraindications	• Galactose intolerance, lactase deficiency or glucose-galactose malabsorption • Malignancies or lymphoproliferative disorders • Major depression and suicidal ideation • Anorexia	• Galactose intolerance, lactase deficiency or glucose-galactose malabsorption
Special precaution during use	• Adverse drug reaction: ○ Diarrhoea and nausea ○ Weight loss ○ Risk of infection e.g. upper respiratory infections; no reactivations of TB or opportunistic infections reported ○ Depression and suicidal behaviour • Special consideration: ○ Surgery - No evidence that continuous treatment with apremilast will lead to perioperative complications - Can be continued for patient who needs minor surgical treatments - In major surgery, decision of apremilast withdrawal should be individualised based on patient's characteristics, risk of infection and risk of psoriasis worsening ○ Should not be administered together with cytochrome P450 3A4 (CYP3A4) enzyme inducer e.g. rifampicin, phenobarbital, carbamazepine, phenytoin as this will reduce circulating apremilast resulting loss of effectiveness	• Adverse drug reaction: ○ URTI, herpes simplex infection, herpes zoster infection ○ Oral ulcer ○ Acneiform rash, folliculitis ○ Raised creatine kinase ○ Malignancies, including lymphomas and non-melanoma skin cancer ○ Venous thromboembolism ○ MACE • Special consideration - ○ Avoid live vaccines ○ Patients with latent TB should be initiated on anti-TB therapy prior to or concurrent in starting deucravacitinib

Instructions	Apremilast	Deucravacitinib
	○ No significant pharmacokinetic interaction between apremilast with MTX, oral contraceptives and ketoconazole	
Recommended laboratory assessment	FBC, RP, LFT may be tested before and after initiation of apremilast based on patient's characteristics, medical history and risk exposure	Periodic TB evaluation, LFT, fasting lipid profile

Recommendation 15
- Oral small molecules may be offered to patients with moderate to severe psoriasis.

6.9. Combination Therapy

Combination therapies are commonly used to treat psoriasis due to their potential additive or synergistic effect benefits. Furthermore, the possibility of using lower doses of combination can help to minimise cost and toxicity of the treatment.

Various combination therapies can be employed e.g.:
- phototherapy with other therapies
- biological therapy with other therapies
- oral small molecule with other therapies
- combination of systemic therapies

a. Phototherapy with other therapies

A NMA studied ultraviolet (UV) combination therapy regimens as shown below.[127, level I]

cPUVA: • PUVA combined with vitamin A and its derivatives* • PUVA combined with vitamin D and its derivatives#	cUVB: • UVB combined with vitamin A and its derivatives • UVB combined with vitamin D and its derivatives • UVB combined with systemic treatments • UVB combined with skin lubricants

*include oral aromatic retinoids (etretinate), oral acitretin, oral isotretinoin, topical tazarotene gel
#include calcipotriol cream and calcipotriol ointment

It demonstrated that the regimens were safe and effective compared with UV monotherapy in the treatment of plaque psoriasis:

- SUCRA for PASI 75 response were 86.0% for combination PUVA (cPUVA) and 79.0% for combination UVB (cUVB); the combination therapies included are shown above
- among common AE reported was cutaneous erythematous reaction

The primary papers were of high quality.

The combination of NBUVB and MTX are commonly used among patients with moderate to severe psoriasis. In a small RCT, the combination of NBUVB with MTX was significantly more effective than MTX monotherapy in terms of:[128, level I]

- PASI ≥90% reduction (100% vs 83%)
- faster clinical response (mean of 7.4 vs 10.4 weeks)
- lower total cumulative dose of MTX used (89.8 vs 165.5 mg)

Gastritis, erythema and severe itching had been reported. However, there was NS difference in AEs between groups. In this RCT there was no explanation on randomisation and no mention on blinding.

In a cohort study among Taiwanese patients with psoriasis, combination of NBUVB with MTX therapy did not increase the risk of skin cancer in them.[129, level II-2]

b. Biological therapy with other therapies

A meta-analysis compared the effectiveness and safety profile of biological agents plus MTX vs biologic monotherapy in psoriasis. The combination therapy showed greater improvement in the following outcomes at:[130, level I]

- Week 12 - PASI 75 (RR=1.37, 95% CI 1.23 to 1.53)
- Week 24 - PASI 75 (RR=1.25, 95% CI 1.15 to 1.35)
- Week 48 - PASI 75 (RR=1.41, 95% CI 1.09 to 1.82)

There was no increased risk of severe AEs and drug withdrawals; however, combination of anti-TNF-α with MTX showed a significantly higher risk of infection and nausea. Most primary papers based on Cochrane RoB were categorised as low RoB.

In a small RCT on combined 50 mg of etanercept once weekly and NBUVB phototherapy vs etanercept monotherapy in the treatment of obese patients with moderate to severe plaque psoriasis, both arms had similar rates of achieving PASI 75 at week 24 (53.3% vs 46.7% respectively). The combined treatment was well tolerated with no serious AEs.[131, level I]

A systematic review of ten cohort studies did not report occurrence of skin cancers following biologic and NBUVB combination therapy during the short study period (6 - 24 weeks).[132, level II-2]

c. Oral small molecules with other therapies

In a cross-sectional study, apremilast in combination with other therapies (phototherapy, systemic or biologic therapy) was effective where 81% of patient achieved PASI 75 at week 12 for the treatment of chronic plaque psoriasis. The NBUVB/apremilast group had the highest PASI 75 achievement rate at 89% while the acitretin/apremilast group had the lowest at 60%. Nausea and/or diarrhoea were reported in 25% of patients while weight loss was observed in 15% of them.[133, level III]

In a systematic review, two cohort studies showed NS differences between apremilast monotherapy and combination with conventional systemic/biological therapy in PASI 75 or PGA 0/1. These could be due to significant differences in baseline characteristics e.g. higher therapies failure before adding on apremilast and prior conventional systemic and/or biologic therapy use in the combination group. There was also NS difference in safety profile.[134, level II-2]

In carefully selected psoriasis patients, well-chosen combination therapies can enhance effectiveness and minimise side effects.

d. Combination of systemic therapies

A non-blinded RCT assessed the effectiveness and safety of a fixed-dose combination of MTX and CsA at reduced doses vs MTX monotherapy for the treatment of chronic plaque psoriasis. The combination therapy was significantly more effective in achieving PASI 75, PASI 90 and PASI 100 responses. The onset of action, defined by achieving PASI 50 at four weeks was also significantly earlier in the combination group. There was NS difference in both clinical and laboratory AEs between the two groups.[135, level I]

Recommendation 16

- Combination therapy may be considered when monotherapy fails in the treatment of psoriasis.

7. COMPLEMENTARY AND ALTERNATIVE THERAPY

Complementary and alternative medicines are a set of health practices that are not in the conventional medicine practice of a country but used for the management of a disease.[136] Examples are traditional Chinese medicine (TCM), herbal medicine, dietary supplements, climatotherapy and mind/body interventions.

TCM is believed to show some benefits as they are customised to individuals and has multitarget effect in helping to alleviate psoriasis symptoms. In a meta-analysis which compared systemic TCM with various comparisons for the treatment of psoriasis, the findings showed:[137, level I]

- TCM was more effective than placebo in reducing PASI score (MD= -3.49, 95% CI -5.21 to -1.77)
- TCM was equally effective as acitretin in reducing PASI score (MD= -2.66, 95% CI -5.62 to 0.29)
- Combination of TCM and Western medicine was more effective than Western medicine monotherapy in reducing PASI score (MD= -2.86, 95% CI -3.92 to -1.79)
- TCM was as safe as placebo (RR=1.64, 95% CI 0.75 to 3.55)
- TCM-related AEs based on two RCTs were less than Western medicine (RR=0.68, 95% CI 0.56 to 0.82); the most commonly reported AEs was diarrhoea

However, the RCTs used in the review lack of quality. The intervention duration was not long enough to provide long-term effectiveness.

Another systematic review of RCTs evaluating benefits of TCM modalities (e.g. herbal therapies, dietary supplements, climatotherapy and mind/body interventions) demonstrated effectiveness with some interventions. However, limitations in methodology, ingredient contaminations and safety issues were not addressed in the primary studies.[138, level III]

A systematic review of four studies on systemic vitamin D supplementations in patients with psoriasis were inconclusive on PASI improvement.[139, level I]

In a systematic review of multiple study designs, findings of the followings dietary supplements on psoriasis were inconclusive and the evidence was of poor quality:[60, level I]

- ω-3 polyunsaturated fatty acids (fish oil)
- vitamin D
- curcumin

However, probiotic supplementations had shown improvements in inflammatory serum markers and PASI in two RCTs.

The above findings were supported in a latest systematic review where there was no consistent evidence supporting the effectiveness of fish oil supplements in psoriasis with limitation of heterogeneity and lack of high-quality evidence of the primary papers.[140, level I]

- There is insufficient evidence to support the use of complementary and alternative medicines in psoriasis.

8. SPECIAL CONDITIONS

8.1 Psoriatic Arthritis

PsA is a chronic inflammatory arthritis associated with psoriasis. Early recognition and treatment of the condition are essential to prevent permanent joint damage and physical disability.

i. Risk factors

In a systematic review, significant clinical characteristics associated with PsA were:[141, level II-2]

- longer disease duration
- certain psoriatic skin features
  - nail involvement
  - more extensive skin involvement
  - scalp lesions
  - intergluteal/perianal lesions

In a recent systematic review of psoriasis patients with skin and/or nail involvement, severe diseases and obesity were identified as risk factors for PsA.[142, level II-2]

A meta-analysis showed that arthralgia (RR=2.15 95% CI 1.16 to 3.99) and imaging-detected musculoskeletal (MSK) inflammation or imaging-detected structural damage (RR=3.72 95% CI 2.12 to 6.51) were also risk factors for PsA.[142, level II-2] There was no quality assessment done on the primary papers.

ii. Clinical features

Clinical manifestations of PsA are complex and may involve both peripheral and/or axial joints. They are characterised by synovitis, enthesitis (inflammation around the insertion sites of ligaments and tendons), dactylitis as in **Figure 9** [swelling of the entire digit (finger or toe) or termed as “sausage digit”] and sacroiliitis.

Five clinical subtypes of PsA were described by Moll and Wright as below.[143, level III]

- Oligoarticular arthritis is asymmetric and involves <5 small or large joints.
- Polyarticular arthritis is usually symmetric and presents similar to rheumatoid arthritis but may involve the distal interphalangeal (DIP) joint with negative rheumatoid factor.
- DIP joint arthritis is signified by prominent involvement of the DIP joints.
- Arthritis mutilans (refer to **Figure 10**) is characterised by severe destructive joint disease with deformities, especially in the hands and feet.
- Spondyloarthritis is manifested as saroiliitis and spondylitis, occurring with or without peripheral joint disease.

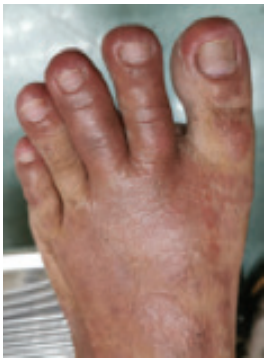


Figure 9: Dactylitis

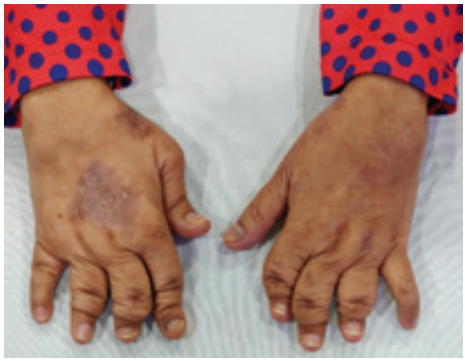


Figure 10: Arthritis Mutilans

The Malaysian National Inflammatory Arthritis Registry (MyNIAR) 2020-2022 reported that Malaysian patients with PsA have the following clinical findings:[144, level III]

- over two-thirds (81.51%) had only peripheral joint disease, 16.16% had both axial and peripheral joint involvement whilst a minority (2.33%) had only axial disease
- among those presented with peripheral joint involvement, the prevalence of synovitis was the highest (76.36%), followed by dactylitis (46.19%) and enthesitis (23.47%)
- polyarticular symmetrical arthritis (56.59%) was the commonest clinical subtype followed by oligoarticular arthritis (33.66%)
- most patients had extra-articular manifestations, of which 88.06% had skin involvement, 1.75% interstitial lung disease and 0.87% uveitis
- approximately seven of 10 patients with skin involvement had skin manifestation prior to joint symptoms, whereas 8.15% had joint symptoms preceding the skin condition and 7.28% presented with simultaneous skin and joint manifestations

iii. Screening tools

Prevalence of undiagnosed PsA in patient with psoriasis is estimated to be 15.5%.[145, level II-2]

There are various validated screening tools to detect PsA in patients with psoriasis. Despite their high sensitivities and specificities, there is a lack of consensus on the most effective tool. Barriers to the implementation of PsA screening tools in clinical practice include time constraints, disease complexity and the availability of diverse screening tools.[146, level II-2]

Screening tools must be simple, homogeneous across primary and secondary care, and exhibit good sensitivity. However experts agree

that selecting a screening tool with high specificity is crucial to prevent over-referral.[146, level II-2]

The following tools are available for screening of PsA with sensitivity and specificity as shown below:[146, level II-2; 147, level III]

Tool	Sensitivity (%)	Specificity (%)
Psoriasis Epidemiology Screening Tool (PEST)	27.5 - 92	37.2 - 98
Psoriatic arthritis UnclutteRed screening Evaluation (PURE-4) questionnaire	85.7	83
Toronto Psoriatic Arthritis Screen (ToPAS)	41 - 95.8	29.7 - 97
Psoriatic Arthritis Screening and Evaluation (PASE)	24 - 100	19.5 - 94
Early Arthritis for Psoriatic Patients (EARP)	78 - 100	34 - 97.2

Refer to **Appendix 7** on details of the specific tools.

Previous local guidelines recommend regular assessment of at least once annually for early detection of arthritis. Patients should be screened for relevant signs and symptoms including joint swelling, dactylitis, inflammatory back pain and significant early morning stiffness.[21]

Recommendation 17

- In psoriasis patients, regular assessment should be performed at least annually for early detection of psoriatic arthritis i.e. joint swelling, dactylitis, enthesitis, inflammatory back pain and prolonged early morning stiffness.
  - Various screening tools may be used to screen for psoriatic arthritis.

iv. Investigations

Various imaging modalities are available to aid in the diagnosis of PsA, with X-ray being the preferred first choice. Characteristic radiographic features of PsA include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis typically 'pencil-in-cup' deformity and acro-osteolysis, ankylosis, spur formation and spondylitis. However, X-rays may be normal in early phase of arthritis.[21] Other imaging modalities such as ultrasound and magnetic resonance imaging (MRI) can aid in detecting early changes indicative of PsA.

A cross-sectional study of 326 subjects showed that the modified classification criteria for PsA (CASPAR) with integration of ultrasound (USG) improved diagnostic utility for PsA when compared with the original CASPAR criteria which was based solely on physical examination (higher specificity 91.4% vs 84.0% but similar sensitivity 95.7% vs 94.5% respectively). Additionally, the presence of tenosynovitis (OR=21.3, 95% CI 6.8 to 66.9, p<0.01) and enthesitis (OR=21.7, 95% CI 7.7 to 61.4, p <0.01) on USG emerged as independent risk factors for predicting the diagnosis of PsA.[148, level III]

In cases of PsA with axial joint involvement, European League Against Rheumatism (EULAR) consensus guidelines recommend the following imaging modalities:[149, level III]

- X-ray of sacroiliac (SI) joints as the first imaging method to diagnose sacroiliitis as part of axial SpA
- MRI of the SI joints if the diagnosis of axial SpA cannot be established especially in young patients and those with short symptom duration.

There is no laboratory investigation to confirm the diagnosis of PsA. However, inflammatory markers such as ESR and C-reactive protein may be helpful. Rheumatoid factor antibody and anti-cyclic citrullinated peptide (anti-CCP) are usually absent in patients with PsA.[21] Anti-CCP antibodies if present, are associated with polyarticular phenotypes and structural lesions, and are markers of severity rather than aiding in diagnosis.[150, level II-2]

A systematic review and meta-analysis of novel biomarkers such as Cartilage Oligometrix Metallo Proteinase (COMP), Matrix MetalloProteinase-3 (MMP3), Receptor Activator of Nuclear Kappa-B Ligand (RANK-L) and Osteoprotegerin (OPG) levels did not identify any specific diagnostic biomarkers for PsA.[150, level II-2]

v. Classification criteria

The most accepted and validated classification criteria for PsA is the CASPAR criteria which have been widely used since 2006.[151, level II-2; 152, level III] The criteria have high sensitivity and specificity in established PsA (91.4% and 98.7% respectively) but were less sensitive (77%) in classifying patients with early (<12 months) PsA.[153, level III]

These criteria were established to provide a standardized and reliable way to diagnose PsA, ensuring consistency across studies and clinical practices. Refer to **Appendix 8**.

vi. Treatment

The principles of management in PsA require:

- assessment of all disease domains including peripheral arthritis,

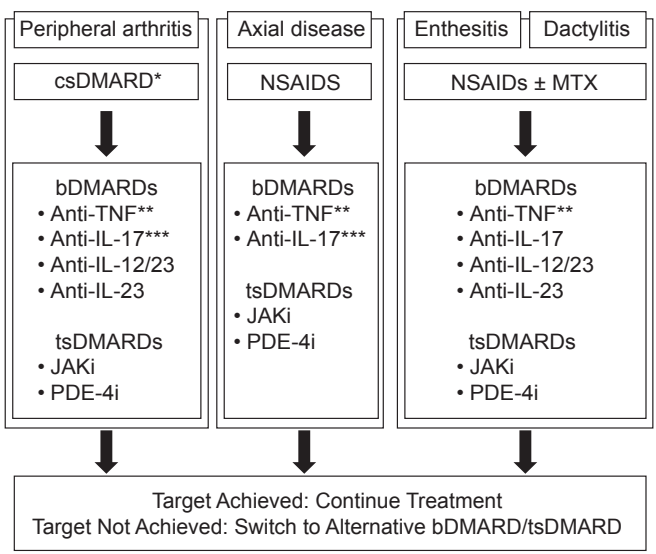
axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, uveitis and IBD
- examining the impact of disease on pain, function, QoL and structural damage
- clinical assessment including a comprehensive history-taking, physical examination and patient-reported measures, supplemented by laboratory and imaging tests

Common treatment agents used in PsA include:[154]

a. conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) e.g. MTX, sulfasalazine, leflunomide
b. biological therapy (bDMARDs)
c. targeted synthetic DMARDs (tsDMARDs)
d. corticosteroids
e. NSAIDs for pain relief

Apremilast, although widely used for psoriasis, is not commonly used in the treatment of PsA mainly due to the availability of other effective treatment options.

The choice of therapy should address domain involvement, patient preference and previous/concomitant therapies. This is summarised in **Figure 11**.



*The preferred csDMARDs: MTX, SSZ, LEF
**If concomitant uveitis/IBD: anti-TNF (except etanercept) is preferred
***Anti-IL-17 is preferred in PsA with severe skin involvement

- biological disease-modifying anti-rheumatic drugs (bDMARDs); conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs); targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs); sulfasalazine (SSZ); leflunomide (LEF); anti-interleukin-17 (Anti-IL-17); anti-interleukin-12/23 (Anti-IL-12/23); anti-interleukin-23 (Anti-IL-23); janus kinase inhibitors (JAKi); phosphodiesterase-4 inhibitor (PDE-4i)

Figure 11: Treatment Algorithm for Psoriatic Arthritis

Adapted: Malaysian Society of Rheumatology (MSR). Consensus on Advanced Therapy for Inflammatory Arthritis. Petaling Jaya. MSR; 2023

8.2. Paediatrics

Psoriasis has been found to affect 0.5 - 1.5% of the paediatric population in certain regions with plaque psoriasis being the most common phenotype and onset is most common during adolescence. One-third of psoriasis cases begin in the paediatric ages.[155] Early onset is more frequently associated with a positive family history and predicts a graver prognosis. In general, the clinical features, diagnosis and disease severity assessment are similar to the adults (refer to **Chapter 2** and **5**). The most commonly affected body site in children is the scalp, followed by the limbs and trunk. Pruritus is a frequent symptom in children.[156]

i. Risk factors

Similar to the common risk factors seen in adults with psoriasis, paediatric psoriasis is associated with emotional stress, increased BMI, second-hand cigarette smoke, pharyngeal and perianal group A β-haemolytic Streptococcus infection, Kawasaki disease, withdrawal of systemic corticosteroids and paradoxically, anti-TNF-α medications.[155]

ii. Co-morbidities

In a retrospective cohort study among paediatric population, children with psoriasis were at higher risk of any co-morbidities compared with children without (IRR=1.86, 95% CI 1.63 to 2.13). The specific risks identified were as follows:[157, level II-2]

- obesity (IRR=1.64, 95% CI 1.32 to 2.05)
- serious infections (IRR=1.73, 95% 1.38 to 2.16)
- juvenile idiopathic arthritis (IRR=9.03, 95% CI 4.94 to 16.31)
- hyperlipidaemia (IRR=2.11, 95% CI 1.31 to 3.34)
- IBD (IRR=2.75, 95% CI 1.46 to 5.17)
- any psychiatric co-morbidity (IRR=1.16, 95% CI 1.02 to 1.33)
- depression (IRR=1.17 95% CI 1.01 to 1.36)
- suicidal ideation (IRR=1.70, 95% CI 1.29 to 2.25)

A large cross-sectional study of inpatient children showed that paediatric psoriasis was associated with multiple cardiovascular co-morbidities:[158, level III]

- obesity (OR=3.15, 95% CI 2.46 to 4.05)
- hypertension (OR=2.63, 95% CI 1.93 to 3.59)
- DM (OR=2.90, 95% CI 1.0 to 4.42)
- arrhythmia (OR=1.39, 95% CI 1.02 to 1.88)
- valvular heart disease (OR=1.90, 95% CI 1.07 to 3.37)

iii. Topical treatments

a) Topical treatments

As in adults, moisturiser is an adjunct treatment in paediatric plaque psoriasis and are used in combination with other topical treatments.

The following topical treatment may be used in children with psoriasis:[155]

- corticosteroids - off-label but mainstay of treatment especially for localised disease; selection of treatment regime (potency, delivery vehicle and frequency of application) should be tailored to individual based on age, sites of involvement, anticipated occlusion and disease severity
- calcineurin inhibitors - off-label but preferred first-line therapy for psoriasis involving the face, genitalia and body folds
- vitamin D analogues - used alone or in combination with other topical therapies to enhance effectiveness and limit possible AEs; an important advantage is its corticosteroid-sparing function. On safety profile -
  - caution must be taken regarding quantities used, given the theoretical risk of hypercalcaemia and hypovitaminosis D from systemic absorption; should be avoided in children with hypercalcemia or renal disease[155]
  - once-daily application of a combined calcipotriol and betamethasone dipropionate foam in children aged 12 to 16 years has shown good tolerability with no clinically significant dysregulation of the hypothalamic-pituitary-adrenal axis nor calcium homeostasis[159, level II-3]
- salicylic acid 2 - 10% - is effective when combined with other topical agents including TCS, TCIs and vitamin D analogues
- coal tar - is effective when combined with other topicals (TCS or TCIs) or in conjunction with phototherapy but its use may be limited by the theoretical long-term risk of carcinogenesis
- dithranol - can be an alternative treatment for localised areas, especially in patients who have failed other topical treatments and given to patients prior to systemic or phototherapy
- combination topical therapy - rotational therapy with TCS, TCIs, topical vitamin D analogues and tar-based therapies should be considered as corticosteroid-sparing regimens to reduce potential AEs

b) Phototherapy

Phototherapy has been used as an alternative treatment in moderate to severe psoriasis in older children, before starting systemic therapy or biologics. The Joint AAD-NPF guidelines recommend NBUVB phototherapy as a treatment for paediatric psoriasis. AEs are similar to those of adults.[155]

A meta-analysis on NBUVB in paediatric psoriasis showed that it was an effective therapeutic option (80% achieved ≥75% clearance, 95% CI 70 to 80) with a good short-term safety profile (erythema was the most common AE).[160, level II-2] There was no report on quality assessment of the primary studies.

Oral PUVA should be avoided in children younger than twelve years old due to the risk of cutaneous carcinogenesis and PUVA induced cataract.[161, level III]

c) Non-biologic systemic therapy

Conventional systemic therapies, e.g. MTX, acitretin and CsA, have been used off label to treat moderate to severe paediatric psoriasis. The aim of these therapies used in children is to control the disease. Absolute contraindications, pre-initiation assessment, monitoring and AEs of treatment are generally similar to those in adults.

According to Joint AAD-NPF guidelines, the following systemic treatments may be used in children with psoriasis.[155]

- MTX is the most commonly used systemic agent for moderate to severe psoriasis and may be used as monotherapy or in combination with other systemic agents. Folic acid supplementation six times weekly during treatment with MTX is recommended.
- Acitretin is the preferred option in immunosuppressed or very young children. Its use is discouraged in female patients of childbearing age due to the risk of teratogenicity.
- CsA is generally well tolerated in children and may be an option for the rapid control of severe, unstable plaque psoriasis. Oral absorption may be less and clearance may be faster in children than adults; therefore, children may require higher weight-based doses.
- FAEs have been used with good outcomes in moderate to severe paediatric psoriasis. However, they are not available locally.

A cohort study of paediatric patients with psoriasis showed that patients responded well to MTX treatment without significant side-effects during a 2-year follow-up.[162, level II-2]

- At week 24, 29.4% (95% CI 20.8 to 39.9%) of patients achieved a PASI 75 response and 30.4% (95% CI 21.7 to 40.3%) achieved an absolute PASI ≤2.0 without any persistent AEs, with 22.5% (95% CI 14.9 to 31.9%) maintaining PASI ≤2.0 up to two years.

- There was NS difference of occurrence of GI AEs with folic acid six times per week vs once weekly.
- Most frequently reported AEs were nausea, abdominal pain, fatigue and increased transaminase levels.

A systematic review on systemic therapy for psoriasis in children concluded that MTX was the first treatment of choice and the most extensively used conventional systemic treatment. The most frequently reported AEs were nausea, vomiting and transient elevation of liver enzymes. In patients where MTX was ineffective or contraindicated, FAEs could be considered before proceeding to biologics.[163, level I] Most of the primary papers were case report and case series.

In a cohort study on oral systemic agents in paediatric psoriasis, acitretin, MTX and CsA were safe and well-tolerated. Most common AEs were:[164, level II-2]

- acitretin - mucocutaneous dryness (25.9%), hyperlipidaemia (1.7%) and GI symptoms, mainly nausea (1.7%)
- MTX - nausea and vomiting (8%) and abnormal LFTs (1.1%)
- CsA - hyperlipidaemia (3.8%), elevated serum creatinine, GI upset and cytopaenia (1.3%)

An RCT revealed that FAEs was more effective than placebo in treating moderate to severe psoriasis in children and adolescents aged 10 to 17 years. 55% of patients achieved PASI 75 with FAEs compared to 19% with placebo, resulting in an absolute difference in responder rates of 35% (95% CI 0.20 to 0.53; $p<0.001$). Additionally, at week 20, 42% of patients achieved a Physician's Global Assessment (PGA) score of 0 or 1 with FAEs compared to 7% with placebo, yielding an absolute difference in responder rates of 36% (95% CI 0.21 to 0.49, $p<0.001$).[165, level I]

d) Oral small molecule therapy

A pre-post study of weight-based apremilast dosing regimen showed that it was safe in children and adolescents with moderate to severe psoriasis. Most frequently reported AEs were nausea (52.4%), headache (45.2%), abdominal pain (42.9%) and nasopharyngitis (38.1%).[166, level II-3]

e) Biological therapy

Biological agents e.g. etanercept, adalimumab, ustekinumab, ixekizumab and secukinumab can be considered as an alternative systemic therapy in moderate to severe chronic psoriasis in children. Absolute contraindications, pre-initiation assessment and monitoring while on treatment are similar to adults. Refer to **Subchapter 6.6.** on Biological Therapy.

In a meta-analysis on moderate to severe psoriasis in paediatric patients, biological therapy (etanercept, adalimumab ustekinumab, ixekizumab and secukinumab) was more effective than placebo or non-biologic agents in improving burden of disease and had a good safety profile at initial follow-up of 12 - 16 weeks as shown below:[167, level I]

- PASI 75 (OR=12.37, 95% CI 6.23 to 24.55)
- PGA 0/1 (OR=12.65, 95% CI 4.85 to 32.96)
- CDLQI 0/1 (OR=5.26, 95% CI 3.58 to 7.72)
- NS difference for any AEs including serious AE, any infection and serious infection

There was low RoB of the primary papers.

A NMA revealed that biological agents (ustekinumab, secukinumab, ixekizumab, adalimumab and etanercept) were effective and safe in the treatment of paediatric psoriasis:[168, level I]

- high dose ustekinumab was the most effective with low incidence of AEs
- SUCRA for effectiveness of high dose ustekinumab was 72.5%, low dose ustekinumab 71.6% and secukinumab 56.6%

The RCTs used were of high quality.

In an RCT comparing high dose (HD) and low dose (LD) secukinumab* in the treatment of moderate to severe psoriasis in paediatric patients, a high proportion of patients responded to both dosing regimens of secukinumab and maintained clinical responses through 52 weeks of treatment. There was no difference observed in effectiveness of secukinumab across the paediatric subgroups. Safety events were consistent with the established safety profile of secukinumab. The details of the findings were:[169, level I]

- PASI 75 and IGA 0/1 were similar between LD and HD groups (92.8% vs 93.3% and 88.9% vs 84.7% respectively) at week 52
- Mean absolute PASI change from baseline at week 52 was -17.3 ± 5.0 and -18.2 ± 7.0 for LD and HD groups
- More than 70% of patients achieved CDLQI 0/1 at week 52 (LD of 70.7% and HD 70.3%)

*HD and LD secukinumab were based on weight category (<25, 25 to <50 and ≥50 kg): patients weighing <25 kg received secukinumab 75 mg (both LD and HD groups), patients weighing 25 to <50 kg received 75 mg (LD group) or 150 mg (HD group) and patients weighing ≥50 kg received 150 mg (LD group) or 300 mg (HD group).

A cohort study showed that serious infections were infrequent in children with psoriasis treated with immunomodulating agents. There was no increase in risk of outpatient infections in those treated with ustekinumab compared with etanercept or MTX:[170, level II-2]

- rate of serious infection was 18.4 per 1000 person-years for ustekinumab, 25.6 for etanercept and 14.9 for MTX

- rate of outpatient infection was 254.9 per 1000 person-years for ustekinumab, 435.7 for etanercept and 433.6 for MTX
- risk of outpatient infection was consistently lower for ustekinumab compared with the comparators -
  - ustekinumab vs etanercept (RR=0.58, 95% CI 0.41 to 0.83)
  - ustekinumab vs methotrexate (RR=0.66, 95% CI 0.48 to 0.91) NS between etanercept and MTX.
- overall, most frequently occurring outpatient infections were skin and soft tissue infections, sinusitis, streptococcal pharyngitis and acute otitis media. Skin infections and acute otitis media were most frequent with ustekinumab, while sinusitis was most frequent with etanercept and MTX

In a Cochrane systematic review on anti-TNF agents, a high quality RCT showed that etanercept was more effective than placebo and safe (at least in short-term i.e. 12 weeks) for the treatment of moderate to severe paediatric psoriasis:[171, level I]

- PASI 75 with RR of 4.95 (95% CI 2.83 to 8.65) and NNT of 2 (95% CI 1.77 to 2.95)
- PGA 0/1 with RR of 3.96 (95% CI 2.36 to 6.66)
- Three serious AEs were reported but they resolved without sequelae while deaths or other events e.g. malignant tumours, opportunistic infections, tuberculosis or demyelination were not reported

An RCT on children with severe psoriasis where initial treatment (IT) of adalimumab (ADA) 0.4 mg/kg, ADA 0.8 mg/kg and MTX were continued with either ADA 0.4 or 0.8 mg/kg in long-term extension (LTE) until 52 weeks showed:[172, level I]

- effectiveness based on PASI 75 was maintained or improved from entry to end of LTE
  - MTX(IT)/ADA 0.8 (LTE) from 31% to 86% of patients
  - ADA 0.4(IT)/0.4 or 0.8(LTE) from 28% to 47% of patients
  - ADA 0.8(IT)/0.8(LTE) from 50% to 72% of patients
- no serious infections occurred in LTE and most common AEs were nasopharyngitis and upper respiratory tract infections

- In local setting, biological agents can only be prescribed by dermatologist in the treatment of psoriasis in children.

Recommendation 18

- The following topical treatments may be used as monotherapy or in combination for children with psoriasis:
  - moisturisers (as adjunct therapy)
  - corticosteroids (first-line treatment)
  - calcineurin inhibitors (preferred choice for lesions on the face, flexures and genitalia)
  - vitamin D analogues
  - salicylic acid
  - tar-based preparations
  - dithranol
- Narrowband ultraviolet B (NBUVB) may be considered for moderate to severe psoriasis in children prior to systemic/biological therapy.
- Methotrexate (MTX) should be considered as first-line conventional systemic therapy for moderate to severe psoriasis in children.
  - Folic acid supplementation should be given daily except for MTX therapy day.
- Ciclosporin may be used for rapid control in severe or unstable psoriasis.
- Acitretin may be used in combination with other systemic therapy or phototherapy in immunosuppressed children with extensive or moderate to severe psoriasis.
- Apremilast may be used as an alternative to conventional systemic therapy in moderate to severe psoriasis in children.
- Biological therapy may be prescribed in children with moderate to severe psoriasis who have intolerance/contraindication or failed phototherapy and conventional systemic therapy.

8.3. Pregnancy and Lactation

i. Treatment in pregnancy

Pregnancy poses an unpredictable effect on psoriasis. Majority of the patients (55%) have their psoriasis improve during pregnancy. However, psoriasis is more likely to flare during postpartum period at a rate of 65%. It is important to consider maternal and foetal health outcomes when deciding on the best treatment for those patients who are planning conception or are pregnant. Although data are limited and not always consistent across studies, untreated severe maternal psoriasis may lead to adverse pregnancy outcomes. Therefore, the risk of untreated maternal psoriasis must be weighed against any potential harm due to drug exposure to the foetus.[119]

a. Topical agents

- **Moisturisers and topical corticosteroids**

Topical moisturisers and low- to mid-potent topical corticosteroids should be the first-line treatment of psoriasis in pregnancy.[21]

- **Vitamin D analogues**

As there is no data on the effect on pregnancy outcomes, Vitamin D analogues is not recommended to be used during pregnancy unless the potential benefit outweighs the risk to the foetus.[173, level III]

- **Tar-based preparation**

Coal tar preparation is not recommended to be used during pregnancy although there is lack of data to suggest teratogenicity or poor pregnancy outcome in humans.[173, level III]

- **Salicylic acid**

Topical salicylic acid can be absorbed systemically (approximately 9 - 25%). In view of the associated increased risk of gastroschisis during the first trimester, it is not recommended during pregnancy.[173, level III]

- **Calcineurin inhibitors**

In view of lacking data on the effect on pregnancy outcomes, calcineurin inhibitors are not recommended to be used during pregnancy, except when the potential benefit outweighs the potential risk for the foetus.[173, level III]

- **Dithranol**

Topical anthralin should be discontinued in the treatment of psoriasis once pregnancy is confirmed due to its teratogenic potential.[173, level III]

b. Phototherapy

UVB phototherapy, used alone or in combination with topical treatments, may be offered when psoriasis is extensive or not controlled by topical treatments alone during pregnancy.[21; 173, level III]

c. Systemic agents

The availability of systemic therapies for psoriasis in pregnancy is limited.

- **Ciclosporin**

CsA appears to cross the placenta although no evidence for teratogenicity has been reported. It should not be initiated during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.[174, level III]

- **Acitretin**

Acitretin must not be used in pregnant women and should be avoided in women planning for pregnancy. It should be stopped two to three years before a conception is planned.[21; 119]

- **Methotrexate**

MTX is contraindicated in pregnancy as it is teratogenic in humans and associated with increased risk of adverse foetal outcomes. In terms

of fertility, high dose of MTX may influence oogenesis and reduce fertility. However, this effect of MTX appears to be reversible after discontinuation of the medications.[119] MTX should be stopped three months before conception in both women and men.[21] However, recent guidelines state that paternal exposure to low-dose MTX (<25 mg/ week) is compatible with pregnancy.[175]

- **Apremilast**

There is limited data on the use of apremilast during pregnancy although there are reported dose-related foetal loss and reduced birth weight. Therefore, it is contraindicated during pregnancy. It is also important to emphasise on the use of effective contraception and this should be continued until at least four weeks after discontinuation of apremilast treatment.[119]

d. Biological therapy

TNF-α inhibitors appear to be the safest option for treating psoriasis in pregnancy with evidence demonstrating lack of teratogenicity. Certolizumab pegol is the safest alternative due to non-existent or minimal placental permeability compared with others.[174, level III] All biological therapy currently licensed to be used for psoriasis (with the exception of certolizumab pegol) cross placenta during the second and third trimester. The effects and risks of infections to both mother and newborn babies are not known. On the other hand, due to its almost non-existent placental permeability, certolizumab pegol can be used throughout the entire pregnancy.[174, level III] It is the first-line agent when biological therapy is to be initiated in women planning conception and when it is necessary to start a biological therapy during the second or third trimester.[119]

Due to limited published data, other biological agents are recommended to be used during the first trimester only.[174, level III] The risk of continuing biologics and its benefits need to be evaluated and discussed with patients. The use of live or live attenuated vaccines in infants whose mothers received biological therapy beyond 16 weeks gestation is contraindicated up to six months of age.[119]

ii. Treatment in lactating women

Breastfeeding is not contraindicated in psoriasis although some of the prescribed medications might be contraindicated in breastfeeding.[119]

Topical agents e.g. moisturisers and low-moderate potency topical corticosteroids can be used as first-line treatment of psoriasis in lactating women.[21]

Systemic corticosteroids are reported to be excreted in low amounts in breast milk. As there is no report of AEs in infants born to the mothers,

systemic corticosteroids can be used during breastfeeding as long as the benefits outweigh the risks. In addition, it should be administered at minimum doses and shortest possible duration in achieving good control of psoriasis.[173, level III] MTX, CsA and acitretin should not be used in lactating women.[21]

As for biological therapy, only certolizumab pegol has been approved for use in breastfeeding mother with psoriasis. The need to start and use other biological agent requires discussion with patients.[119]

Recommendation 19
- Topical moisturisers and low- to mid-potent corticosteroids may be used in pregnant and lactating women with psoriasis.
- Pregnant patients with moderate to severe psoriasis may be offered:
  - narrowband ultraviolet B phototherapy in those who fail to respond to topical treatments
  - ciclosporin if its potential benefits outweigh the risks

8.4 Other Special Conditions

a. Tuberculosis

Treatment options for psoriasis patients with previous TB, latent TB or active TB infection should be carefully weighed based on the risk of TB reactivation/progression, potential contraindications and AEs associated with TB chemoprophylaxis.

Systemic treatments e.g. MTX and CsA with immunosuppressive activity are associated with risk of TB reactivation and thus contraindicated in active TB infection. Phototherapy and/or acitretin may be used together with anti-TB treatment among psoriasis patients with active TB infection because these are not associated with increased risk of TB reactivation.[176, level III]

Based on consensus guidelines, the risk of TB reactivation in patients with LTBI treated with anti-IL-17, anti-IL-23 or PDE4 inhibitors is deemed to be lower compared with anti-TNF-α, anti-IL-12/23 or TYK2 inhibitors. The following are recommended:[177, level III]
- all patients starting with biologic and non-biologic targeted therapies should be screened for latent TB or TB infection which includes CXR, IGRA or Mantoux test
- psoriasis patients with positive LTBI
  - should undergo at least one month of chemoprophylaxis before starting targeted therapies
  - if contraindicated/intolerant to TB chemoprophylaxis, may preferentially be treated with anti-IL-17, IL-23 or PDE4 inhibitors
- psoriasis patients with previously treated TB disease or LTBI who have completed anti-TB treatment

- anti-IL17, anti-IL23 or PDE4 inhibitors are preferable psoriasis treatment with periodic TB surveillance
- psoriasis patients being treated with targeted therapies who develop TB disease
  - anti-TNF-α, anti-IL-12/23 or TYK2 should be discontinued
  - anti-IL17, anti-IL23 or PDE4 inhibitors may be continued after discussion with relevant specialists*
  - anti-TB treatment should be immediately initiated

  *in local setting, referral to a respiratory physician is done

b. Viral hepatitis and chronic liver disease

Treatment for psoriasis patient with liver disease is challenging due to potential hepatotoxic and immunosuppressive effects of most medications. Thus, the choice of treatment should be carefully selected and appropriate monitoring is required. The hepatotoxicity effects of various systemic agents and biological therapy in psoriasis are summarised as follow:[125, level III; 178, level III]

Drugs	Hepatotoxic/immunosuppressive effects
MTX	As MTX is immunosuppressive and potentially hepatotoxic, it is preferably avoided in NAFLD.
CsA	CsA is immunosuppressive and may increase serum bilirubin and liver enzymes, worsen NAFLD by increasing serum lipid levels and blood pressure. Thus, close monitoring of LFT and lipid profile is recommended as abnormal values may necessitate dose reductions.
Acitretin	Acitretin is associated with transient increases in liver enzymes but hepatotoxicity is rare. Its use in patients with or at high risk of NAFLD is preferably avoided due to hyperlipidaemia.
Apremilast	There have been no documented hepatotoxic effects for apremilast.
Deucravacitinib	Deucravacitinib is immunosuppressive and potentially hepatoxic with risk of elevation of liver enzymes and triglycerides. It is not recommended in severe hepatic impairment or chronic HBV or HCV infection.
Anti-TNF-α	There is evidence of hepatotoxic risk with TNF-α inhibitors e.g. infliximab, adalimumab, certolizumab

Drugs	Hepatotoxic/immunosuppressive effects
	and etanercept. Monitoring liver enzymes during treatment is advocated. TNF-α inhibitors should be used cautiously in patients with or at high risk of NAFLD.
Ustekinumab	Ustekinumab has been less widely investigated but have generally exhibited minimal hepatotoxicity.
Anti-IL-17	Brodalumab, ixekizumab and secukinumab are minimally hepatotoxic.
Anti-IL-23	There is no evidence of acute liver injury or reactivation of hepatitis B or worsening of hepatitis C with the use of guselkumab, risankizumab and tildrakizumab.

Clinical data are scarce for any direct hepatoprotective effects of systemic psoriasis treatments. Fumarates have immunomodulatory and anti-inflammatory effects that are potentially advantageous in psoriatic patients with NAFLD.

Evidence had shown that biological therapies were generally safe to be given in psoriasis patients with HBV and HCV:

- Patients with different states of HBV and HCV infection ± antiviral treatment according to indications and on adalimumab had no reactivation of HBV or HCV.[179, level II-3] On the other hand, those treated with secukinumab did not develop reactivation except one (concomitant HBV and HCV reactivation).[109, level II-3]
- Patients with concurrent chronic inactive HBV or HCV infections and treated with TNF-α, IL-12/23, IL-17 and anti-IL-23, mainly risankizumab, without antiviral prophylaxis showed no hepatitis reactivation.[180, level II-2]
- Patients had decreased risk of HBV reactivation (HR=0.24, 95% CI 0.12 to 0.47) while on anti-IL-23 compared with anti-TNF-α. Those on anti-IL-17 had reduced HBV (HR=0.59, 95% CI 0.46 to 0.76) and HCV (HR=0.71, 95% CI 0.57 to 0.88) reactivation compared with anti-TNF-α.[181, level II-2]
- Among psoriasis patients with chronic HBV infection (HBsAg positive, HBsAb negative) treated with guselkumab, HBV reactivation developed in 10% of patients without antiviral prophylaxis. No HBV reactivation was observed in those with occult and resolved HBV infection without antiviral prophylaxis.[182, level II-2]
- None of the psoriasis patients with HBV or HCV infection ± antiviral treatment according to indications treated with risankizumab experienced viral reactivation.[183, level II-2]

EuroGuiDerm Guideline recommends referral to a hepatologist for cases of psoriasis with HBV or HCV infection. In term of treatment, the preferred systemic treatment options include acitretin, apremilast, fumarates, ustekinumab, anti-IL-17 and anti-IL-23.

In local setting, all psoriasis patients with HBV or HCV infection are referred to the gastroenterologist/hepatologist for further co-management.

c. Human immunodeficiency virus infection

Psoriasis may be the presenting feature of HIV infection. People living with HIV (PLHIV) tend to have more severe psoriasis with atypical presentations.[184, level III] Psoriasis with concomitant HIV infection is a challenge to be managed especially with the scarce high-level evidence on effective and safe treatment. A multidisciplinary collaboration with an infectious disease specialist is crucial in the complex management of these patients.

Antiretroviral therapy (ART) as a standard treatment for PLHIV may be used as monotherapy or in combination with other treatment modalities to treat psoriasis. Topical therapy including moisturisers, topical corticosteroids, keratolytics, vitamin D3 analogue, calcineurin inhibitors, dithranol and various tar preparations may be used to treat this group of patients.[185, level III]

Phototherapy including NBUVB and PUVA may be used for the PLHIV with moderate to severe psoriasis except those with Kaposi sarcoma.[185, level III; 186, level III]

For systemic treatment, the following are recommended.

- Oral retinoids and apremilast may be used in moderate to severe disease.[184 - 185, level III; 187 - 188, level III]
- Other systemic immunosuppressive agents e.g. CsA, MTX and FAEs are only reserved for the most refractory psoriasis in PLHIV with undetectable viral load.[187, level III]
- Drug-drug interactions between ART and oral systemic treatment should also be checked carefully especially with CYP3A4 inducers.[187, level III]

Biological agents may be used in PLHIV with undetectable viral load and psoriasis who do not respond to acitretin and apremilast.[187, level III] In a systematic review on small sample size of PLHIV with psoriasis, biological agents i.e. anti-IL-17 (secukinumab and ixekizumab), anti-IL-12/23 (ustekinumab), anti-IL-23 (risankizumab) and anti-TNF-α (etanercept, adalimumab, infliximab) were found to be effective. The CD4+ cell counts improved or remained stable in 75% of patients. SAE was reported in 14.4% of patients with 9.8% were serious infections. Most serious AE and treatment-emergent deaths were related to anti-

TNF-α.[189, level III] However, there was no report on quality assessment conducted on the primary studies.

d. Cancer

The treatment of psoriasis in patients with a personal history of cancer is debated and the available evidence to guide clinicians on it is limited. The use of immunomodulatory therapies for psoriasis theoretically has the potential to impact the course of malignant disease and thus making their safety in this context uncertain. However, recent studies indicate that there is little evidence of association between non-cutaneous malignancies and psoriasis treatments, regardless of a prior history of cancer.[190 - 191, level III]

Treatment decisions should be individualised, involving discussions with oncology specialists. The discussions should consider patient's preferences, the severity of psoriasis and potential treatment risks as well as the need for compliance with national cancer screening programmes.

According to the EuroGuiDerm guidelines, for patients with a current cancer diagnosis or a cancer diagnosis within the previous five years, the following treatment recommendations are provided:[119]

- strong recommendation - topical treatment, NBUVB phototherapy and/or acitretin
- weak recommendation - methotrexate, apremilast and biological therapies, including anti-TNF, IL-12/IL-23, IL-17 and anti-IL-23
- contraindicated - CsA
- no specific recommendation - dimethyl fumarate

These recommendations aim to balance the effective management of psoriasis with the safety considerations necessary for patients with a history of cancer.

The Psoriasis Group of the Spanish Academy of Dermatology and Venereology Recommendations also state that active cancer does not contraindicate with the use of biological therapy.[192, level III]

A cross-sectional study on dermatology patients (mainly psoriasis) with a diagnosis of malignancy while on biological therapy showed:[190, level III]

- where biological therapies were discontinued, all patients developed flares of their dermatological disease
- many patients required multiple consecutive therapies in an effort to control their disease
- there were cases where decision was made to restart biological therapy when other measures failed
- patient education and long-standing pharmacovigilance were needed for clarification of patient safety and long-term AEs

In a multicentre observational study looking at secukinumab treatment in patients with psoriasis and a personal history of cancer:[193, level II-2]

- no tumour recurrence nor progression occurred in 42 patients over a mean of 56±31.7 weeks of treatment
- PASI 75, 90 and 100 were achieved by 64%, 28.6%, and 14.3% of patients at week 12, by 88.1%, 52.4% and 37.2% at week 24, and by 91.2%, 64.7% and 38.2% at week 48 respectively
- mean DLQI, itch and pain Visual Analogue Score (VAS) scores significantly improved during treatment

A case series looking at patients with moderate to severe psoriasis who had cancer prior to or concurrent with biological therapy showed that therapy (anti-TNF-α, anti-IL-12/23, anti-IL-23 and anti-IL-17) was considered safe and not contraindicated.[194, level III]

e. Heart failure

Systemic therapies of MTX, acitretin and apremilast are considered safe to be used in psoriasis patients with heart failure.

Studies among psoriasis and PsA patients showed NS difference in the incidence of CCF and overall CV events between biological agents (anti-TNF, anti-IL-12/23, anti-IL-23 and anti-IL-17) and placebo.[104 - 105, level I]

EuroGuiDerm guidelines suggest against the use of CsA in psoriasis with advanced CCF. This is because it may increase blood pressure, reduce kidney function in the patients and causes drug-drug interaction in the treatment of CCF. The guidelines also recommend against using anti-TNFs in the same group of patients.

f. Chronic kidney disease

CsA is an absolute contraindication in patients with renal impairment. MTX, acitretin and apremilast should only be used with caution in patients with mild chronic kidney disease (CKD). However, MTX and acitretin are absolutely contraindicated in those with severe renal impairment.[119]

A retrospective cohort study on the effects of biological agents (anti-TNF, anti-IL-12/23 and anti-IL-17) in psoriasis patients with and without PsA found NS differences in change of eGFR over a period of two years. The baseline CKD stages of the study population were 72.2% with stage 1, 23.5% stage 2, 3.6% stage 3 and 0.7% stage 4.[111, level II-2]

g. Surgery

There is a concern of surgical site infection and delayed wound healing in psoriasis patients on biological therapy and small molecule therapy. Therefore, there is a need to determine if and when these treatments need to be stopped and re-commenced.

In a cross-sectional study of psoriasis patients on biological therapy who had surgery, only 2.3% of them developed wound infections or delayed wound healing.[195, level III]

In another cross-sectional study of psoriasis patients on biological therapy who underwent surgery, there was no association between the development of complications and biological therapy interruption. The median duration of treatment interruption was three weeks (IQR, 2 - 14.3 weeks). There was no wound infection or delayed healing for patients whose biological therapy was continued.[196, level III]

The Joint AAD-NPF guidelines recommend the following:[118]

- all biological therapy can be continued through low-risk surgical procedures in patients with psoriasis; low-risk surgical procedures are defined as procedures without a break in sterile technique and no entry to the respiratory, GI and genitourinary tracts
- moderate- and high-risk surgical procedures require an individualised approach and discussion with the surgeon/medical team -
    - risk assessment should consider each patient's individual risk factors and co-morbidities
    - if considered necessary, the biological agent may be discontinued approximately 3 - 4 half-lives before and until 1 - 2 weeks after elective surgery if there are no post-operative complications

On the other hand, the EuroGuiDerm Guideline recommends the discontinuation of systemic and biological therapy prior to surgery as below:[51]

- acitretin - no need to discontinue
- CsA - consider discontinuing one week prior to elective surgery
- biological agents and small molecule (apremilast) -
    - minor surgery - may continue
    - major surgery - withdrawal may be considered case-by-case after consulting the surgeon and taking into account the patients' characteristics, risk of infection and risk of worsening psoriasis
    - elective surgery - may discontinue treatment prior to procedure 3 - 5 half-lives, especially in patients with diabetes or other conditions with increased risk of infection
    - if treatment to be continued, the procedure is best placed between two doses

In a most recent publication, The Medical Board of the National Psoriasis Foundation suggests the following recommendations regarding systemic, biological and small molecule therapy preceding surgery.[197]

- Acitretin can be continued for any type of procedure.
- For low-risk procedures, MTX, CsA, anti-TNF-α, anti-IL-17, anti-

IL-23, ustekinumab, abatacept and apremilast can be continued.
- For intermediate- and high-risk procedures, MTX, CsA, anti-IL-17, anti-IL-23, ustekinumab, abatacept and apremilast may be continued with caution based on risk assessment of each case.
- For total knee or total hip arthroplasties, anti-TNF-α may be stopped for one dosing interval

h. Vaccination

Vaccination is essential in the management of psoriasis patients on immunomodulatory or immunosuppressive therapies because they are at increased risk of infection. The EuroGuiDerm Guidelines on the systemic treatment of psoriasis recommends the following statements regarding vaccinations.[119]

- Before initiating a systemic treatment, vaccination status should be checked and completed if possible.
- Vaccination against influenza and pneumococci is particularly recommended for patients aged >60 years. National recommendations for vaccination should be followed.
- It is recommended to use inactivated vaccines two weeks prior to initiation of systemic therapy.
- For patients receiving systemic or immunosuppressive therapy, inactivated vaccines should be given without treatment interruption.
- Live vaccines (including measles-mumps-rubella, varicella) can be used in patients on acitretin, apremilast and fumarates.
- Live vaccines are contraindicated in psoriasis patients treated with CsA, MTX, anti-TNF-α (e.g. adalimumab, certolizumab, etanercept, infliximab), anti-IL-17A (e.g. ixekizumab, secukinumab) and anti-IL-17RA (e.g. brodalumab).
- Administration of a live vaccine after discontinuation of immunosuppressive therapy should be determined on factors including its half-life (i.e. 5 half-lives) or mechanism of action.
  - Guselkumab: Wait two weeks after live vaccine, start vaccination 12 weeks after last dose
  - Risankizumab: Wait four weeks after live vaccine, start vaccination 21 weeks after last dose
  - Ustekinumab: Wait two weeks after live vaccine, start vaccination 15 weeks after last dose
  - Tildrakizumab: Wait four weeks after live vaccine, start vaccination 17 weeks after last dose

Recommendation 20

- Psoriasis patients with hepatitis B virus, hepatitis C virus or human immunodeficiency virus infection should be co-managed with respective specialties.
- Patients with psoriasis on biological/conventional systemic therapies undergoing:
  - low-risk surgery may continue the treatment
  - moderate- to high-risk surgery may need treatment withdrawal based on risk assessment and discussion with the surgeon
- Vaccination status should be checked and completed if possible before initiating a systemic therapy in psoriasis.

9. REFERRAL

Existing guidelines mentioned that psoriasis can be managed in the primary care, however cases can be referred in the following conditions:

- Dermatology -
  - diagnostic uncertainty[21; 198, level III]
  - erythrodermic and generalised pustular psoriasis should be referred urgently for assessment and treatment[21]
  - severe or extensive psoriasis e.g. more than 10% BSA affected[21; 198, level III]
  - any type of psoriasis that cannot be controlled with topical therapy within 12 weeks[21; 198, level III]
  - special site of psoriasis (scalp, face, nail, hands/feet, genital) that has a major functional or cosmetic impact[56, level III; 198, level III]
  - any type of psoriasis that has a major impact on a person's physical, psychological or social well-being[198, level III]
- Rheumatology -
  - suspicion of PsA for evaluation and assessment[21; 198, level III]
  - care plan and management of PsA[21; 198, level III]

10. IMPLEMENTING THE GUIDELINES

The management of psoriasis should be guided by an evidence-based approach in order to provide quality care to the patients. Several factors may affect the implementation of recommendations in the CPG.

10.1. Facilitating and Limiting Factors

Existing facilitating factors for application of the recommendations in the CPG include:

- online dissemination of the CPG to healthcare providers nationwide
- regular dermatology scientific meetings/congress and trainings nationally where updates on psoriasis management are delivered
- Malaysian Psoriasis Registry Steering Committee that oversees the psoriasis registry
- Medication Therapy Adherence Clinic Protocol developed by the Task Force psoriasis MTAC, Pharmacy Practice and Development Division. Clinical Pharmacy Working Committee (Dermatology Subspecialty) of MoH to optimise pharmacists' management of psoriasis in hospitals and clinics
- World Psoriasis Day celebration and educational activities at various hospitals across the country to raise awareness on psoriasis and its management
- Annual psoriasis masterclass organised by Malaysian Dermatological Society
- Patient's Support Group e.g. Psoriasis Association of Malaysia (https://www.psoriasismalaysia.org/), Persatuan Penyayang Pesakit Psoriasis Pulau Pinang and Pertubuhan Psoriasis Johor (Psoriasis Association of Johor)

Existing barriers for application of the recommendations of the CPG are:

- insufficient knowledge on psoriasis assessment and its treatment among healthcare providers
- inadequate accessibility to psoriasis training at all levels of healthcare
- inadequate resources e.g. various topical agents to manage mild psoriasis at primary care level
- unavailability of phototherapy service in certain tertiary dermatology centres
- inadequate resources to initiate biological therapy due to high cost of drug at tertiary dermatology centres
- lack of post-basic training in psoriasis for allied healthcare
- lack of awareness, knowledge and understanding on psoriasis among patients and caregivers

10.2. Potential Resource Implications

The recommendations in this CPG require additional resources in terms of funds, healthcare infrastructures and human resources/expertise for their successful implementation as discussed below.

Training programmes for healthcare providers are needed to ensure they are equipped with the latest knowledge and skills in psoriasis management. These include ongoing education and certification programmes to keep healthcare providers updated on best practices and emerging treatments. Apart from that, educational resources in multiple languages and platforms should be made available and accessible to patients, caregivers and the public. These will improve psoriasis management which includes treatment adherence and will prevent disease deterioration and frequent relapses.

Limited availability of various topical agents for psoriasis at the primary care level can hinder effective disease management. This can be due to restricted drug options or limited budgets available for these agents at the primary care. Besides that, initiating biological therapy for patients with moderate to severe psoriasis in secondary/tertiary dermatology centres can be challenging in resource-limited healthcare settings due to the high cost of such treatments. These often lead to restricted access and delay in initiation of biological therapy for patients who require them. Indirectly, these may subject the patients to unwanted side effects of systemic agents which are unable to control the disease effectively. Hence a higher biologic budget is essential to ensure timely initiation of biological therapies in patients with moderate to severe psoriasis when clinically indicated.

Several key performance indexes on psoriasis management monitored by MOH is in line with the CPG recommendations. Thus, the following are proposed as clinical audit indicators for the CPG:

$$\text{Percentage of psoriasis patients assessed for BSA} = \frac{\text{Number of psoriasis patients assessed for BSA in a period}}{\text{Number of psoriasis patients seen in the same period}} \times 100\%$$

Target 90%

$$\text{Percentage of newly diagnosed psoriasis patients assessed for DLQI} = \frac{\text{Number of newly diagnosed psoriasis patients assessed for DLQI in a period}}{\text{Number of newly diagnosed psoriasis patients seen in the same period}} \times 100\%$$

Target 90%

$$\text{Percentage of moderate to severe psoriasis patients treated with biological therapy} = \frac{\text{Number of moderate to severe patients treated with biological therapy in a period}}{\text{Number of moderate to severe psoriasis patients requiring* biological therapy in the same period}} \times 100\%$$

Target 70%
*Patients who failed/intolerant or contraindicated to conventional systemic therapy/ phototherapy

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the effective and safe treatment (biological therapy) in psoriasis vulgaris patients with cancer?

1. PSORIASIS/
2. Psorias#s.tw.
3. (Plaque adj1 psoriasis).tw.
4. 1 or 2 or 3
5. TUMOR NECROSIS FACTOR INHIBITORS/
6. (tnf adj1 (antagonist* or blocker* or inhibitor*)).tw.
7. (tumo?r necrosis factor adj3 (blocker* or inhibitor* or antagonist*)).tw.
8. tumo?r necrosis factor-a antagonist*.tw.
9. tumo?r necrosis factor-a blocker*.tw.
10. tumo?r necrosis factor-a inhibitor*.tw.
11. ADALIMUMAB/
12. adalimumab.tw.
13. adalimumab-adbm.tw.
14. adalimumab-atto.tw.
15. humira.tw.
16. ustekinumab.tw.
17. secukinumab.tw.
18. ixekizumab.tw.
19. brodalumab.tw.
20. bimekizumab.tw.
21. sonelokimab.tw.
22. guselkumab.tw.
23. risankizumab.tw.
24. tildrakizumab.tw.
25. mirikizumab.tw.
26. BIOSIMILAR PHARMACEUTICALS/
27. biosimilar*.tw.
28. (biosimilar adj1 pharmaceutical*).tw.
29. or/5- 28
30. NEOPLASMS/
31. ((benign or malignant) adj1 neoplasm*).tw.
32. cancer*.tw.
33. malignanc*.tw.
34. neoplas*.tw.
35. tumo?r*.tw.
36. 30 or 31 or 32 or 33 or 34 or 35
37. 4 and 36
38. 29 and 37
39. limit 38 to (english language and humans and yr=”2013 -Current”)

Appendix 2

CLINICAL QUESTIONS

1. What are the risk and aggravating factors for psoriasis?
2. What are the co-morbidities associated with psoriasis?
3. How is disease severity being measured for psoriasis?
4. What is the definition of mild, moderate and severe psoriasis?
5. What are the treatment goals for psoriasis?
6. Is non-pharmacological treatment safe & effective in psoriasis?
7. Is topical treatment safe and effective in psoriasis?
8. Is phototherapy safe and effective in psoriasis?
9. Is systemic treatment safe and effective in psoriasis?
10. Is biologics treatment safe and effective in psoriasis?
11. Is small molecule treatment safe and effective in psoriasis?
12. Is combination therapy safe and effective in psoriasis?
13. What are the safe and effective complementary and alternatives medicines for psoriasis?
14. Special Conditions

    Psoriatic arthritis

    a) What are the risk factors for psoriatic arthritis?
    b) What are the clinical patterns in psoriatic arthritis?
    c) What are the investigations (laboratory tests, radiological studies) in psoriatic arthritis?
    d) What are the accurate screening tools in psoriatic arthritis?
    e) What are the classification/diagnostic criteria in psoriatic arthritis?
    f) What are the effective and safe treatment in psoriatic arthritis?

    Other special groups with psoriasis

    What are the effective and safe treatment in psoriasis patients with the following conditions?

    a) paediatrics
    b) pregnant and lactating mother
    c) tuberculosis
    d) viral hepatitis B & C
    e) heart failure
    f) chronic kidney disease
    g) HIV
    h) cancer
15. What are the special considerations in psoriasis patient on systemic/biologics treatment requiring surgery or vaccination?
16. What are the criteria to refer patients with psoriasis to dermatological or rheumatological service?

Appendix 3

PSORIASIS AREA AND SEVERITY INDEX (PASI)

Symptom Score

Score	0	1	2	3	4
Erythema	None	Mild	Moderate	Severe	Very Severe
Induration					
Scaling					

Area Score

Score	0	1	2	3	4	5	6
Area	<1%	1% - <10%	10% - <30%	30% - <50%	50% - <70%	70% - <90%	90% - 100%

Area Score

Lesion score	Head (H)	Trunk (T)	Upper limbs (UL)	Lower limbs (LL) including buttock
Erythema (E)				
Induration (I) (thickness)				
Scaling (S)				
Sum=E + I + S				
Percentage of affected area				
Area Score				
SUBTOTAL: Sum x Area Score				
Body Area: Subtotal x amount indicated	x 0.1	x 0.3	x 0.2	x 0.4
TOTALS	H	T	UL	LL

PASI Score: H + T + UL + LL	

Adapted: Ministry of Health, Malaysia. Management of Psoriasis Vulgaris. Putrajaya: MoH; 2013

Appendix 4

LATTICE PSORIASIS PHYSICIAN GLOBAL ASSESSMENT (PGA)

Score	Definition	Morphological Description
0 = Clear	Clear, except for residual discolouration	• 0 (induration) = no evidence of plaque elevation • 0 (erythema) = no evidence of erythema, hyperpigmentation may be present • 0 (scaling) = no evidence of scaling
1 = Minimal disease	Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 1	• 1 (induration) = minimal plaque elevation, ~0.5 mm • 1 (erythema) = faint erythema • 1 (scaling) = minimal; occasional fine scale over <5% of the lesion
2 = Minimal disease	Majority of lesions have individual scores for IES that average 2	• 2 (induration) = mild plaque elevation, ~1 mm • 2 (erythema) = light red colouration • 2 (scaling) = mild, fine scale predominates
3 = Moderate disease	Majority of lesions have individual scores for IES that average 3	• 3 (induration) = moderate plaque elevation, ~1.5 mm • 3 (erythema) = moderate red coloration • 3 (scaling) =moderate; coarse scale predominates
4 = Severe disease	Majority of lesions have individual scores for IES that average 4	• 4 (induration) = marked plaque elevation, ~2 mm • 4 (erythema) = bright red coloration • 4 (scaling) = marked; thick, non-tenacious scale predominates
5 = Very severe disease	Majority of lesions have individual scores for IES that average 5	• 5 (induration) = severe plaque elevation, ~2.5 mm or more • 5 (erythema) = dusky to deep red colouration • 5 (scaling) = very thick tenacious scale predominates

Adapted: Ministry of Health, Malaysia. Management of Psoriasis Vulgaris. Putrajaya: MoH; 2013

Appendix 5

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX (for adults) DLQI

Hospital No.: Date: Score:
Name: Diagnosis:
Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, **how itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure activities**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If “No”, over the last week how much has your skin been a problem at **work** or **studying**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

8.	Over the last week, how much has your skin created problems with your **partner** or any of **your close friends** or **relatives**?	Very much		Not relevant ☐
		A lot		
		A little		
		Not at all		
9.	Over the last week, how much has your skin caused any sexual **difficulties?**	Very much		Not relevant ☐
		A lot		
		A little		
		Not at all		
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy or by taking up time?	Very much		Not relevant ☐
		A lot		
		A little		
		Not at all		

Please check you have answered EVERY question. Thank you.

Instructions For Use

The DLQI questionnaire is designed for use in adults i.e. patients over the age of 16. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes.

Scoring

The scoring of each question is as follows:

Very much	Scored 3
A lot	Scored 2
A little	Scored 1
Not at all	Scored 0
Not relevant	Scored 0
Question unanswered:	Scored 0
Question 7: “prevented work or studying”	Scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

DLQI Scores Interpretation

Score	Interpretation
0 - 1	No effect at all on patient's life
2 - 5	Small effect on patient's life
6 - 10	Moderate effect on patient's life
11 - 20	Very large effect on patient's life
21 - 30	Extremely large effect on patient's life

Detailed Analysis of DLQI

The DLQI can be analysed under six headings as follows:

Section	Question	Score
Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and schooling	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Interpretation of incorrectly completed questionnaires

There is a very high success rate of accurate completion of the DLQI. However, sometimes subjects do make mistakes.

1. If one question is left unanswered, this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered, the questionnaire is not scored.
3. If question 7 is answered 'yes', this is scored 3. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
4. If two or more response options are ticked, the response option with the highest score should be recorded.
5. If there is a response between two tick boxes, the lower of the two score options should be recorded.
6. If one item is missing from a two-item subscale, that subscale should not be scored.

For children DLQI, patients can fill it themselves or with the assistance of their parents or guardians as necessary.

CHILDREN DERMATOLOGY LIFE QUALITY INDEX (for children 4 - 16 years old) CDLQI

Hospital No.: Date: Score:
Name: Diagnosis:
Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how itchy, "scratchy", sore or painful has your skin been?	Very much	
		A lot	
		A little	
		Not at all	
2.	Over the last week, how embarrassed or self-conscious, upset or sad have you been because of your skin?	Very much	
		A lot	
		A little	
		Not at all	
3.	Over the last week, how much has your skin affected your friendships?	Very much	
		A lot	
		A little	
		Not at all	
4.	Over the last week, how much have you changed or worn different or special clothes/shoes because of your skin?	Very much	
		A lot	
		A little	
		Not at all	
5.	Over the last week, how much has your skin trouble affected going out, playing or doing hobbies?	Very much	
		A lot	
		A little	
		Not at all	
6.	Over the last week, how much have you avoided swimming or other sports because of your skin trouble?	Very much	
		A lot	
		A little	
		Not at all	
7.	Last week, was it school time or not? If school time: Over the last week, how much did your skin problem affect your school work? ❑ Prevented school ❑ Very much ❑ Quite a lot ❑ Only a little ❑ Not at all OR was it holiday time? If holiday time: How much over the last week, has your skin problem interfered with your enjoyment of the holiday?	Very much	
		A lot	
		A little	
		Not at all	
8.	Over the last week, how much trouble have you had because of your skin with other people calling you names, teasing, bullying, asking questions or avoiding you?	Very much	
		A lot	
		A little	
		Not at all	

9.	Over the last week, how much has your sleep been affected by your skin problem?	Very much	
		A lot	
		A little	
		Not at all	
10.	Over the last week, how much of a problem has the treatment for your skin been?	Very much	
		A lot	
		A little	
		Not at all	

Please check you have answered EVERY question. Thank you.

Adapted: Ministry of Health, Malaysia. Management of Psoriasis Vulgaris. Putrajaya: MoH; 2013

Appendix 6

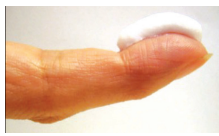
TOPICAL CORTICOSTEROIDS CLASS AND POTENCY (UK CLASSIFICATION)

Potency	Drug (Generic Name)
Mild	• Betamethasone valerate 1 in 8 dilution (0.0125%) cream/ointment • Betamethasone valerate 1 in 10 dilution (0.01%) cream/ointment • Desonide 0.05% lotion • Hydrocortisone acetate 1% cream/ointment
Moderate	• Betamethasone valerate 1 in 2 dilution (0.05%) cream/ointment • Betamethasone valerate 1 in 4 dilution (0.025%) cream/ointment • Clobetasone butyrate 0.05% cream/ointment
Potent	• Beclomethasone dipropionate 0.025% cream/lotion • Betamethasone valerate 0.1% cream/lotion/ointment • Betamethasone dipropionate 0.05% cream/gel/ointment/foam • Diflucortolone valerate 0.1% cream • Fluocinolone acetonide 0.025% cream • Fluticasone propionate 0.05% cream • Hydrocortisone aceponate 0.127% cream/lipocream • Mometasone furoate 0.1% cream/ointment • Triamcinolone acetonide 0.1% cream
Very Potent	• Clobetasol propionate 0.05% cream/ointment

Adapted: Joint Formulary Committee. British National Formulary (online) London: BMJ and Pharmaceutical Press (Available at: http://www.medicinescomplete.com)

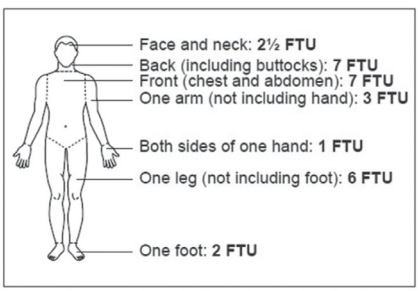
FINGERTIP UNIT

Fingertip Unit (FTU) can be used as a guide to the amount of topical required for affected area.



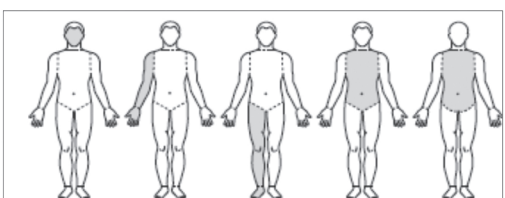
One fingertip unit = the amount of medication dispensed from a standard 5-mm nozzle over a distance from the tip of the index finger of an adult to the crease of the distal interphalangeal joint.

- 1 FTU = 0.5g (cover approximately 2% of the BSA on an adult)
- an adult palm = 1% of BSA



Amount of FTUs for different body parts in adults (general guide only)

Amount of FTUs for different body parts in children (general guide only)



	Face and neck	Arm and hand	Leg and foot	Front	Back
Age	**Number of FTU**				
3-6 months	1	1	1½	1	1½
1-2 years	1½	1½	2	2	3
3-5 years	1½	2	2	3	3½
6-10 years	2	2½	4½	3½	5

Adapted:

1. Ministry of Health, Malaysia. Topical Preparations Counselling Guide for Pharmacist. Pharmaceutical Service Programme 1st Edition. Putrajaya: MoH; 2018
2. Ministry of Health, Malaysia. Management of Atopic Eczema. Putrajaya: MoH; 2018
3. Aung T, Aung ST. Selection of an effective topical corticosteroid. Aust J Gen Pract. 2021;50(9):651-655.

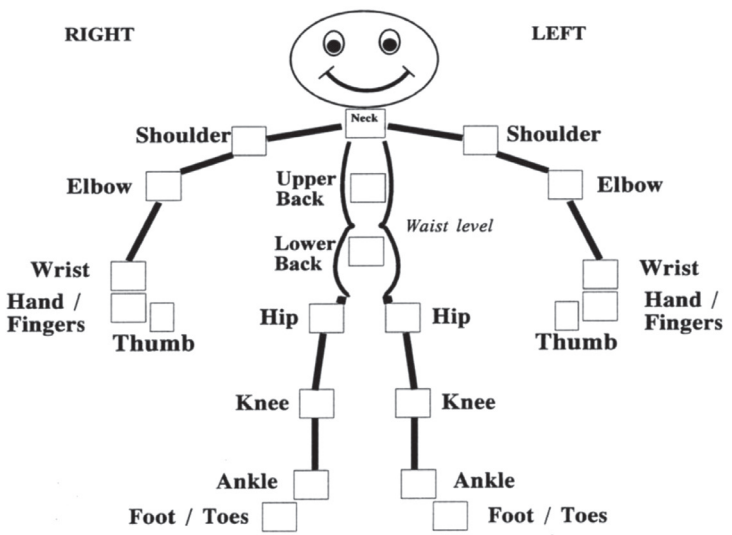
Appendix 7

SCREENING TOOLS OF PSORIATIC ARTHRITIS

1. Psoriasis Epidemiology Screening Tool (PEST) Questionnaire

	NO	YES
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your finger nails or toe nails have holes or pits?		
Have you had pain in your heel?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints)



PEST Questionnaire for psoriatic arthritis. Score 1 point for each question answered. A total score of 3 or more indicates psoriatic arthritis.

Adapted: Ibrahim GH, Buch MH, Lawson C, et al. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clinical & Experimental Rheumatology. 2009;27(3):469.

2. Psoriatic arthritis UnclutteRed screening Evaluation (PURE-4)

1. Evocative signs of dactylitis Have you ever had a globally swollen and painful finger or toe? □ Yes □ No
2. Inflammatory heel pain Have you ever had heel pain as soon as you stand up in the morning? □ Yes □ No
3. Bilateral buttock pain Have you ever had left and right buttock pain, at the same time or not? □ Yes □ No
4. Peripheral joint pain with swelling, aged <50 Have you ever had a swollen and painful joint? □ Yes □ No

At the threshold of ≥1 positive item, the resulting instrument (PURE-4) yields both excellent sensitivity (85.7%) and specificity (83.6%)

Source: Audureau E, Roux F, Lons Danic D, et al. psoriatic arthritis screening by the dermatologist: development and first validation of the 'PURE-4 scale'. J Eur Acad Dermatol Venereol. 2018;32(11):1950-1953.

Appendix 8

CASPAR (ClASsification criteria for Psoriatic ARthritis) Criteria (2006)

PsA is considered present in patients with inflammatory articular disease (joint, spine or entheseal) who have at least three points from the following five categories;

Category	Points
1. Skin psoriasis: Current psoriasis* or Personal history of psoriasis** or Family history of psoriasis (patient not affected)***	 2 or 1 or 1
2. Typical nail dystrophy (onycholysis, pitting, hyperkeratosis)	1
3. Current or history of dactylitis, recorded by a rheumatologist	1
4. Negative rheumatoid factor (by any method except for latex)	1
5. Evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margin (excluding osteophytes) on plain radiographs of the hand or foot	1

*Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist

**A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist or other qualified health care provider

***A family history of psoriasis is defined as a history of psoriasis in a first or second-degree relative according to patient report

Adapted: Taylor W, Gladman D, Helliwell P, et al. CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73

RECOMMENDED MEDICATION DOSING, ADVERSE EFFECTS AND CONTRAINDICATIONS FOR COMMONLY USED MEDICATIONS IN PSORIASIS

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
TOPICAL CORTICOSTEROIDS				
Mild • Betamethasone valerate 1 in 8 dilution (0.0125%) cream/ointment • Betamethasone valerate 1 in 10 dilution (0.01%) cream/ointment • Desonide 0.05% lotion • Hydrocortisone acetate 1% cream/ointment	1 - 2 times daily	• Worsening of untreated infection • Contact dermatitis • Perioral dermatitis • Acne • Depigmentation • Dryness • Hypertrichosis • Secondary infection • Skin atrophy • Pruritus • Tingling/stinging • Rosacea • Folliculitis • Photosensitivity	• Untreated bacterial, fungal, or viral skin lesion • Rosacea • Perioral dermatitis	Avoid prolonged use on face
Moderate • Betamethasone valerate 1 in 2 dilution (0.05%) cream/ointment • Betamethasone valerate 1 in 4 dilution (0.025%) cream/ointment • Clobetasone butyrate 0.05% cream/ointment	1 - 2 times daily			
Potent • Beclomethasone dipropionate 0.025% cream/lotion • Betamethasone valerate 0.1% cream/lotion/ointment • Betamethasone dipropionate 0.05% cream/gel/ointment/foam • Diflucortolone valerate 0.1% cream • Fluocinolone acetonide 0.025% cream • Fluticasone propionate 0.05% cream	1 - 2 times daily			• Avoid use on face and body folds • Limit continuous use to <4 weeks

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
• Hydrocortisone aceponate 0.127% cream/lipocream • Triamcinolone acetonide 0.1% cream				
• Mometasone furoate 0.1% cream/ointment	Once daily			Avoid prolonged use on face
Very Potent • Clobetasol propionate 0.05% cream/ointment	1 - 2 times daily			• Avoid use on face and body folds • Limit continuous use to <2 weeks
TOPICAL VITAMIN D ANALOGUES				
Calcipotriol 50 µg/g cream/ointment	Twice daily	• Itching • Erythema • Burning • Paraesthesia • Dermatitis • Photosensitivity	• Hypercalcaemia • Evidence of Vitamin D toxicity	• Avoid use on face • Avoid excessive exposure to sunlight and sunlamps • Pregnancy • Breastfeeding • Maximum dose: 15 g/day • BSA <30%
Calcipotriol 50 µg/g scalp solution				
Calcipotriol 50 µg/g and Betamethasone dipropionate 0.5 mg/g ointment/gel/foam	Once daily	• Worsening of untreated infection • Contact dermatitis • Perioral dermatitis • Acne • Depigmentation • Dryness • Hypertrichosis • Secondary infection • Skin atrophy • Pruritus • Tingling/stinging • Rosacea • Folliculitis • Photosensitivity		
TOPICAL CALCINEURIN INHIBITORS				
Tacrolimus 0.03 - 0.1% ointment	Twice daily	• Burning/stinging	Acutely inflamed lesion	

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
	Paediatric 0.03%: ≥2 years 0.1%: ≥16 years	• Pruritus		
Pimecrolimus 1% cream	Twice daily Paediatric 3 months and above			
TOPICAL SMALL MOLECULES				
Phosphodiesterase-4 Inhibitors Roflumilast 0.3%*	Once daily	• Application site pain irritation • Upper respiratory tract infection		Avoid apply to unaffected areas
Aryl Hydrocarbon Receptor Modulating Agent Tapinarof 1%* Benvitimod*	Once daily	• Folliculitis • Contact dermatitis • Nasopharyngitis		
OTHER TOPICAL TREATMENT				
Tar-based Preparations	1 - 2 times daily	• Dermatitis • Folliculitis • Irritation • Photosensitivity	Acutely inflammed lesion and pustular psoriasis	• Avoid contact with eyes, genital/rectal areas • Avoid use in first trimester
Dithranol	0.1 - 0.5% suitable overnight treatment for skin 1 - 2% short contact therapy 30 minutes - 1 hour	• Local burning sensation and irritation • Staining of skin, hair and fabrics	Acutely inflammed lesion and pustular psoriasis	Avoid use near eyes and sensitive areas of skin
Salicylic Acid 2 - 10% cream/ointment	Twice daily	• Sensitivity • Drying • Irritation • Salicylism with excessive use (limit up to BSA 20%)		Avoid broken or inflammed skin

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
CONVENTIONAL SYSTEMIC AGENTS				
Acitretin	Adults 0.5 - 1 mg/kg body weight/day (Max: 75 mg/day) Paediatric 0.1 - 1 mg/kg body weight/day (Max: 35 mg/day)	• Cheilitis • Xerosis • Alopecia • Skin peeling • Stickiness • Paronychia • Periungual pyogenic granuloma pruritis • Hyperlipidaemia • Transaminitis • Hyperaesthesia	Absolute • Severe renal/hepatic dysfunction • Hypertriglyceridaemia • Pregnancy (high risk of teratogenicity) • Breastfeeding • Blood donation • History of pancreatitis Relative • Women of child-bearing age	Pregnancy Avoid pregnancy for at least 1 month before, during and for at least 3 years after treatment
Ciclosporin	Adults 2.5 - 5 mg/kg body weight/day in 2 divided doses Paediatric 2 - 5 mg/kg body weight/day in 2 divided doses	• Hypertension • Hyperuricaemia • Hyperkalaemia • Hypomagnesaemia • Hyperlipidaemia • Oedema • Headache • Hypertrichosis • Nausea • Diarrhoea • Tremor • Renal dysfunction • Infections	Absolute • Impaired renal function • Uncontrolled hypertension • Severe infections • History of malignancy • Current malignancy • Previous PUVA • Simultaneous phototherapy (PUVA and NBUVB therapy) • Extensive previous UV exposure with high risk of cutaneous malignancy • Severe hepatic disease • Breastfeeding	• Limit use to 2 years • Avoid excessive exposure to UV light including sunlight
Methotrexate	Adults Oral, IM or SC: 5 - 25 mg/dose once weekly Paediatric 0.2 - 0.7 mg/kg body weight/dose once weekly	• Nausea • Vomiting • Malaise • Headache • Hepatotoxicity • Mucositis • Myelosuppression • Lung fibrosis • Immunosuppression	Absolute • Severe liver disease • Severe infection • Renal failure • Pregnancy • Breastfeeding • Alcohol abuse • Bone marrow dysfunction/ haematologic changes	• Pregnancy: stop at least 3 months prior to conception • Tablet folic acid 5 mg daily except MTX day • Risk factors on liver toxicity in patients who receive MTX including diabetes mellitus,

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
	(Max:25 mg/week)		• Immunodeficiency • Acute peptic ulcer • Reduced lung function Relative • Kidney or liver diseases • Old age • Ulcerative colitis • History of hepatitis • Lack of compliance • Actively trying to become pregnant • Gastritis • Obesity • Diabetes mellitus • Previous malignancy	obesity, history of or current alcohol consumption, persistent abnormal liver function test, history of liver disease including chronic hepatitis B or C, family history of inheritable liver disease, history of significant exposure to hepatotoxic drugs or chemicals, lack of folate supplementation, hyperlipidaemia • Risk factors of MTX-induced haematotoxicity include renal insufficiency, advanced age, lack of folate supplementation, hypoalbuminaemia, excessive alcohol intake
ORAL SMALL MOLECULES				
Phosphodiesterase-4 (PDE-4) Apremilast	Adults Day 1: 10 mg OM Day 2: 10 mg BD Day 3: 10 mg AM 20 mg PM Day 4: 20 mg BD Day 5: 20mg AM 30mg PM Day 6 and thereafter: 30 mg BD	• Diarrhoea • Nausea • Weight loss • Risk of infection e.g. upper respiratory infections with apremilast; no reactivations of tuberculosis or opportunistic infections reported	Absolute • Pregnancy • Breastfeeding • Severe acute infections • Age <18 years old Relative: • Galactose intolerance, lactase deficiency or glucose-galactose malabsorption	• Should not be administered together with cytochrome P450 3A4 (CYP3A4) enzyme inducer e.g. rifampicin, phenobarbital, carbamazepine, phenytoin as this will reduce circulating

DRUG	RECOMMENDED DOSAGE	POSSIBLE ADVERSE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTIONS
		• Depression and suicidal behaviour	• Malignancies or lymphoproliferative disorders • Severe impairment of renal function (eGFR <30 mL/min) • Major depression and suicidal ideation • Anorexia	apremilast resulting in loss of effectiveness
Tyrosine Kinase 2 (TYK2) Deucravacitinib	Adults 6 mg OD	• Upper respiratory tract infection, herpes simplex infection, herpes zoster infection • Oral ulcer • Acneform rash • Folliculitis • Raised creatine kinase • Malignancies, including lymphomas and non-melanoma skin cancer • Venous thromboembolism • Major adverse cardiac event	Absolute: • Pregnancy • Breastfeeding • Active infection e.g. active tuberculosis infection • Age <18 years old Relative: • Galactose intolerance, lactase deficiency or glucose-galactose malabsorption	• Avoid live vaccines • Patients with latent tuberculosisshould be initiated on anti-tuberculosis therapy prior to or concurrent in starting deucravacitinib
BIOLOGICAL AGENTS				
Anti-TNF-α				
Adalimumab	Adults Loading dose: Subcutaneously 80 mg at week 0, then followed by 40 mg 1 week later Maintenance dose: Subcutaneously 40 mg every 2 weeks thereafter Paediatric Age: ≥4 years Dose range: 0.8 mg/kg given at weeks 0 and 1	• Infections • Injection site reactions • Infusion reactions • Hepatotoxicity, (infliximab) • Congestive heart failure • Drug-induced systemic lupus erythematosus • Cytopaenia • Multiple sclerosis	Absolute • Active tuberculosis • Severe infections • Congestive heart failure (NYHA class III/IV) • Active chronic hepatitis B • History of allergic reaction to therapeutic agent or vehicle Relative • Latent tuberculosis • History of recurrent infections	Pregnancy • Foetal risk cannot be ruled out • The risk and benefit of continuing biological agents beyond the first trimester need to be evaluated and discussed with patients. Lactation Infant risk cannot be ruled out

	and then every other week to a maximum dose of 40 mg		• Concomitant systemic lupus erythematosus or multiple sclerosis • PUVA >200 treatments (especially if followed by CsA use) • Malignancies or lymphoproliferative disorders • Hepatobiliary disorders	
Certolizumab*	Adults Subcutaneously 400 mg every other week OR Weight ≤90 kg Loading dose: Subcutaneously 400 mg at week 0, 2 and 4 initially Maintenance dose: Subcutaneously 200 mg every other week			Pregnancy • Foetal risk cannot be ruled out • Certolizumab pegol is the preferred agent and can be used throughout the entire pregnancy Lactation Infant risk cannot be ruled out
Etanercept	Adults Loading dose: Subcutaneously 50 mg twice per week for 12 weeks Maintenance dose: 50 mg/week (50 mg twice/week may be required in some patients) Paediatric ≥6 yr 0.8 mg/kg once weekly for up to 24 week Max: 50 mg weekly Discontinue if no response after 12 week			Pregnancy • Foetal risk cannot be ruled out • The risk and benefit of continuing biological agents beyond the first trimester need to be evaluated and discussed with patients Lactation Infant risk cannot be ruled out
Infliximab	Adults Loading dose: Intravenously at a			Pregnancy • May cause foetal harm • The risk and benefit of continuing biological

	dose of 5 mg/kg at weeks 0, 2 and 6 Maintenance dose: Intravenously at a dose of 5 mg/kg every 8 weeks			agents beyond the first trimester need to be evaluated and discussed with patients Lactation Infant risk cannot be ruled out
ANTI-IL-12/IL-23				
Ustekinumab	Adults Loading dose: - weight ≤100 kg, 45 mg administered subcutaneously initially and 4 weeks later - weight >100 kg, dosage is 90 mg administered subcutaneously initially and 4 weeks later Maintenance dose: - weight ≤100 kg, 45 mg administered subcutaneously every 12 weeks - weight >100 kg, 90 mg administered subcutaneously every 12 weeks Paediatric Age: ≥6 years Weight-based dosing: - ≤60 kg, 0.75 mg/kg - >60 kg to ≤100 kg, 45 mg - >100 kg, 90 mg given at weeks 0 and 4 and then every 12 weeks	• Hypersensitivity reactions • Infections	Absolute • Active infections • History of allergic reaction to therapeutic agent or vehicle Relative • Recurrent or chronic infections • Previous history of lymphoreticular malignancies	Pregnancy May cause foetal harm Lactation Infant risk cannot be ruled out

ANTI-IL-17				
Bimekizumab*	Adults Loading dose: 320 mg subcutaneously at weeks 0, 4, 8, 12 and 16 Maintenance dose: 320 mg subcutaneously every 8 weeks Weight ≥120 kg, a dose of 320 mg every 4 weeks after week 16 may be considered	• Hepatotoxicity • Inflammatory bowel disease • Neutropaenia • Infections - mucocutaneous candidiasis • Suicidal ideation (brodalumab) • Injection site reaction	Absolute • Active infections • History of allergic reaction to therapeutic agent or vehicle Relative • Inflammatory bowel disease • Depression and history of suicidal behaviour (brodalumab)	Pregnancy May cause foetal harm Lactation Infant risk cannot be ruled out
Brodalumab*	Adults Loading dose: 210 mg subcutaneously at weeks 0, 1 and 2 Maintenance dose: 210 mg subcutaneously every 2 weeks			Pregnancy Foetal risk cannot be ruled out Lactation Infant risk cannot be ruled out
Ixekizumab	Adults Loading dose: 160 mg subcutaneously at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12 Maintenance dose: 80 mg subcutaneously every 4 weeks Some patients may require an 80 mg dose every 2 weeks to maintain response to treatment			Pregnancy Foetal risk cannot be ruled out Lactation Infant risk cannot be ruled out

	Paediatric Age: ≥6 years Weight-based dosing; - <25 kg, 40 mg at week 0 and then 20 mg every 4 weeks - 25 to 50 kg, 80 mg at week 0 and then 40 mg every 4 weeks - >50 kg, 160 mg at week 0 and then 80 mg every 4 weeks			
Secukinumab	Adults Loading dose: 300 mg subcutaneously at weeks 0, 1, 2, 3 and 4 Maintenance dose: 300 mg subcutaneously every 4 weeks Paediatric Age: ≥6 years Weight-based dosing; - <50 kg, 75 mg - ≥50 kg, 150 mg Given at weeks 0, 1, 2, 3, and 4 and then every 4 weeks			Pregnancy May cause foetal harm Lactation Infant risk cannot be ruled out
ANTI-IL-23				
Guselkumab	Adults Loading dose: 100 mg subcutaneously at week 0 and 4 Maintenance dose:	• Infection	Absolute • Active infections • History of allergic reaction to therapeutic agent or vehicle Relative • Recurrent or chronic infections	Pregnancy Foetal risk cannot be ruled out Lactation Infant risk cannot be ruled out

	100 mg subcutaneously every 8 weeks			
Risankizumab	Adults Loading dose: 150 mg subcutaneously at week 0 and 4 Maintenance dose: 150 mg subcutaneously every 12 weeks			Pregnancy Foetal risk cannot be ruled out Lactation Infant risk cannot be ruled out
Tildrakizumab	Adults Loading dose: 100 mg subcutaneously at week 0 and 4 Maintenance dose: 100 mg subcutaneously every 12 weeks			Pregnancy There are limited data available about tildrakizumab use of during pregnancy Lactation Infant risk cannot be ruled out

*Not available in Malaysia

Sources:

1. Truven Health Analytics Micromedex® Solutions 2024 at MIMS Gateway (Available at: https://online1.mimsgateway.com.my/)
2. Joint Formulary Committee. British National Formulary. 85. London: BMJ Publishing and the Pharmaceutical Press; 2023
3. Joint Formulary Committee. British National Formulary for Children. London: BMJ Publishing and the Pharmaceutical Press; 2023

LIST OF ABBREVIATIONS

µg	microgramme
µm	micrometre
AAD-NPF	American Academy of Dermatology-National Psoriasis Foundation
AE(s)	adverse event(s)
anti-CCP	anti-cyclic citrullinated peptide
ART	antiretroviral therapy
BBUVB	broad band ultraviolet B
BD	bis in die (twice a day)
BMI	body mass index
BSA	body surface area
CASPAR	classification criteria for psoriatic arthritis
CCF	congestive cardiac failure
CDLQI	children dermatology life quality index
CI	confidence interval
CKD	chronic kidney disease
CPG	clinical practice guidelines
cPUVA	combination PUVA
CsA	ciclosporin
cUVB	combination UVB
CV	cardiovascular
CVD	cardiovascular diseases
CXR	chest x-ray
DIP	distal interphalangeal
DLQI	dermatology life quality index
DM	diabetes mellitus
DMARDs	disease-modifying antirheumatic drugs
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAEs	fumaric acid esters
FBC	full blood count
FDA	Food and Drug Administration
GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HIV	human immunodeficiency virus
HR	hazard ratio
HSV	herpes simplex virus
IAGI	Investigator's Assessment of Overall Global Improvement
IBDs	inflammatory bowel diseases
IGA	investigator Global Assessment
IGRA	interferon-gamma release assay
IL	interleukin
IRR	incidence rate ratio
IT	initial treatment
LD	low dose
LFT	liver function test
LTBI	latent TB infection

LTE	long-term extension
MACE	major adverse cardiovascular events
MF	mometasone furoate
mg	milligramme
MoH	ministry of health
MRI	magnetic resonance imaging
MTX	methotrexate
NAFLD	non-alcoholic fatty liver disease
NBUVB	narrowband ultraviolet B
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMSC	non-melanoma skin cancer
NOS	Newcastle-Ottawa Scale
NRS	Numeric Rating Scale
NS	no significance
NSAIDs	non-steroidal anti-inflammatory drugs
OD	once daily
OPAT	Optimal Psoriasis Assessment Tool
OR	odd ratio
OSM	oral small molecules
p	*p* value
PAGI	Patient's Assessment of Global Improvement
PASI	Psoriasis Area and Severity Index
PatGA	Patient Global Assessment
PDE-4	phosphodiesterase-4
PGA	Physician's Global Assessment
PIIINP	procollagen III aminopeptide
PLHIV	people living with HIV
PsA	Psoriatic arthritis
PUFAs	polyunsaturated fatty acids
PURE-4	Psoriatic arthritis UnclutteRed screening Evaluation
PUVA	psoralen plus ultraviolet A
QoL	quality of life
RANK-L	receptor activator of nuclear kappa-B ligand
RCT(s)	randomised controlled trial(s)
RC	review committee
RoB	risk of bias
RP	renal profile
RR(s)	risk ratio(s)
SAEs	serious AEs
SMD	standardised mean difference
SUCRA	surface under the cumulative ranking analysis
TB	tuberculosis
TCM	traditional Chinese medicine
TEAEs	treatment-emergent adverse events
TLSS	Target Lesion Severity Scale
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-alpha
TSS	Total Symptom Score
TYK2	Tyrosine kinase 2
URTI	upper respiratory tract infection
USFDA	US food and drug administration

USG	ultrasound
UV	ultra violet
UVA	ultra violet A
UVB	ultra violet B
vs	versus
WHO	World Health Organization

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