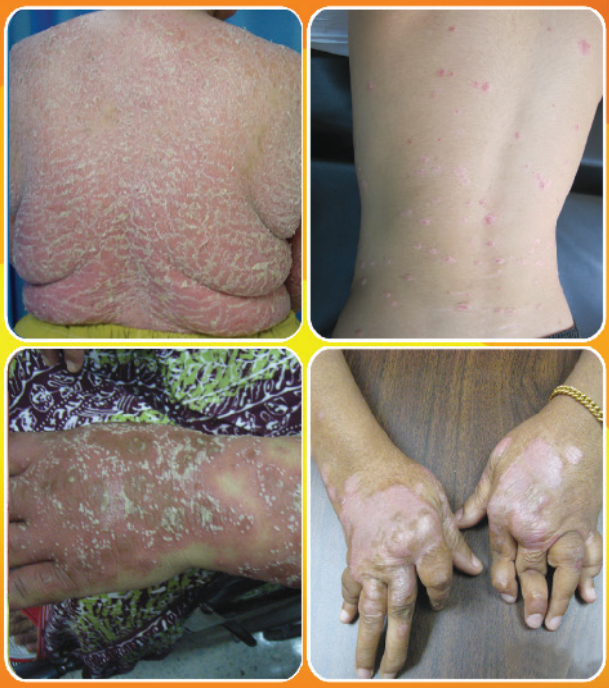
CLINICAL PRACTICE GUIDELINES

JUNE 2013

MOH/P/PAK/266.13(GU)

MANAGEMENT OF PSORIASIS VULGARIS



Ministry of Health Malaysia

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Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2013 and will be reviewed in 2017 or sooner if new evidence becomes available.

TABLE OF CONTENTS

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MOH) and Ministry of Higher Education. There was active involvement of a multidisciplinary review committee (RC) during the process of development of this CPG.

A systematic literature search was carried out using the following databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed, Cochrane Database of Systemic Reviews (CDSR) and International Health Technology Assessment websites. A search strategy to cover all aspects on management of psoriasis was developed in the Medline database and adapted to other databases. Search strategies were a combination of MeSH and keyword searches including abbreviations (refer to **Appendix 1** on an example of **Search Strategy**). Search was restricted to human studies; literature published in English language and the last ten years. If the evidence was insufficient, the period of publication was extended for another ten years. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. All searches were conducted from August 2011 till December 2012. Literature searches were repeated for all clinical questions at the end of the CPG development process. The aim was to identify any further relevant papers published before 28 February 2013 to be included. Future CPG update will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPGs on Psoriasis such as i) Guidelines on the treatment of psoriasis vulgaris by the German Society of Dermatology (2012), ii) The assessment and management of psoriasis by the National Institute for Health and Clinical Excellence (NICE 2012), iii) Canadian Guidelines for the Management of Plaque Psoriasis by the Canadian Dermatology Association (2012), iv) Diagnosis and management of psoriasis and psoriatic arthritis in adults by the Scottish Intercollegiate Guidelines Network (2010) and v) Guidelines of care for the management of psoriasis and psoriatic arthritis by the American Academy of Dermatology (2009).

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references. The Ministry of Health had published a Protocol for Biologic Intervention for Psoriasis (2011) and a Technology Review on Biologic for Psoriasis (2011). This CPG incorporated recommendations from these two publications.

A total of 25 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to Appendix 2) The DG members had met 21 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme

checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The evidence used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network.

On completion, the draft guidelines was sent for review 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, the HTA and CPG Council MOH Malaysia for review and approval.

OBJECTIVES

The aims of this CPG are

- Assist clinicians and other healthcare providers in making evidence-based decisions on the management of psoriasis.
- Implement treatment goals to improve outcome of patients living with psoriasis.

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Adult patients with psoriasis

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in all healthcare settings including:

i. Doctors
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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The draft of these guidelines was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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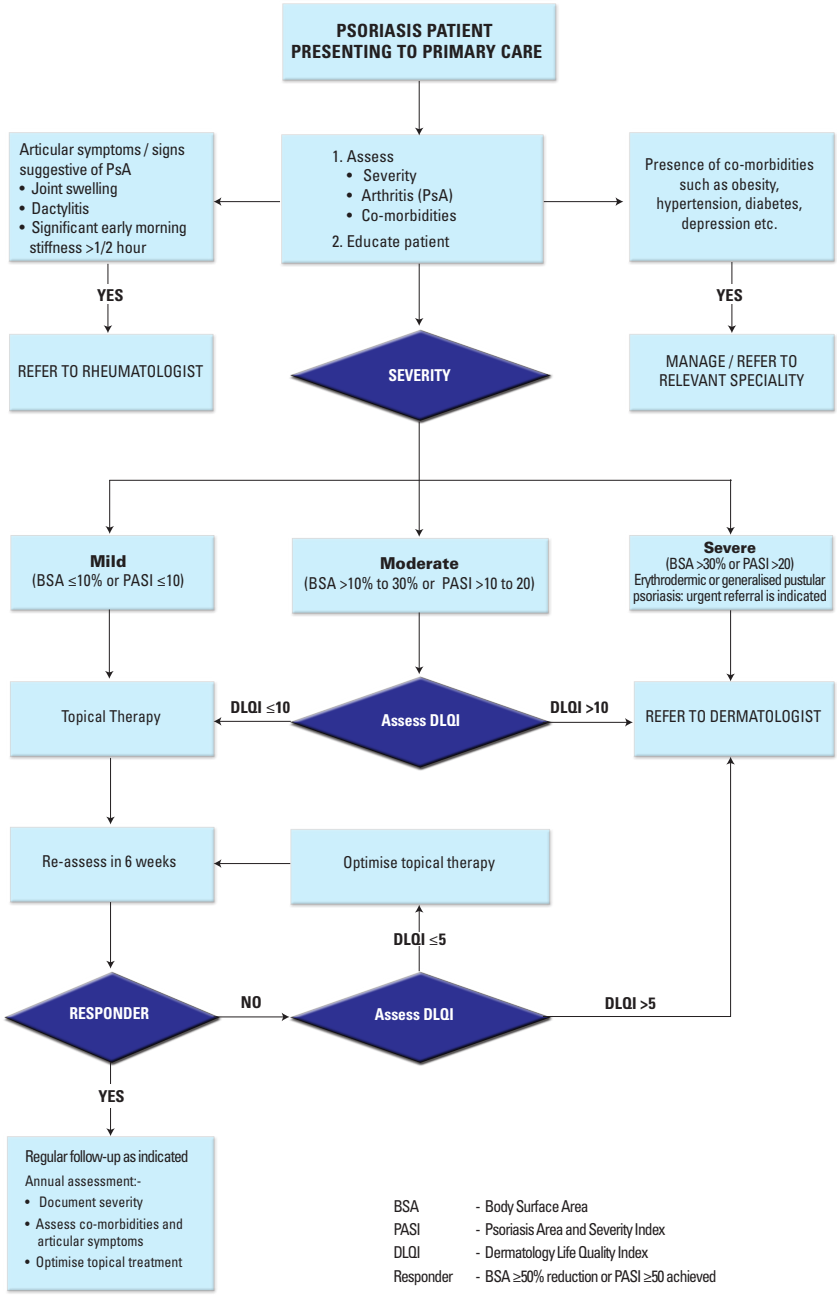
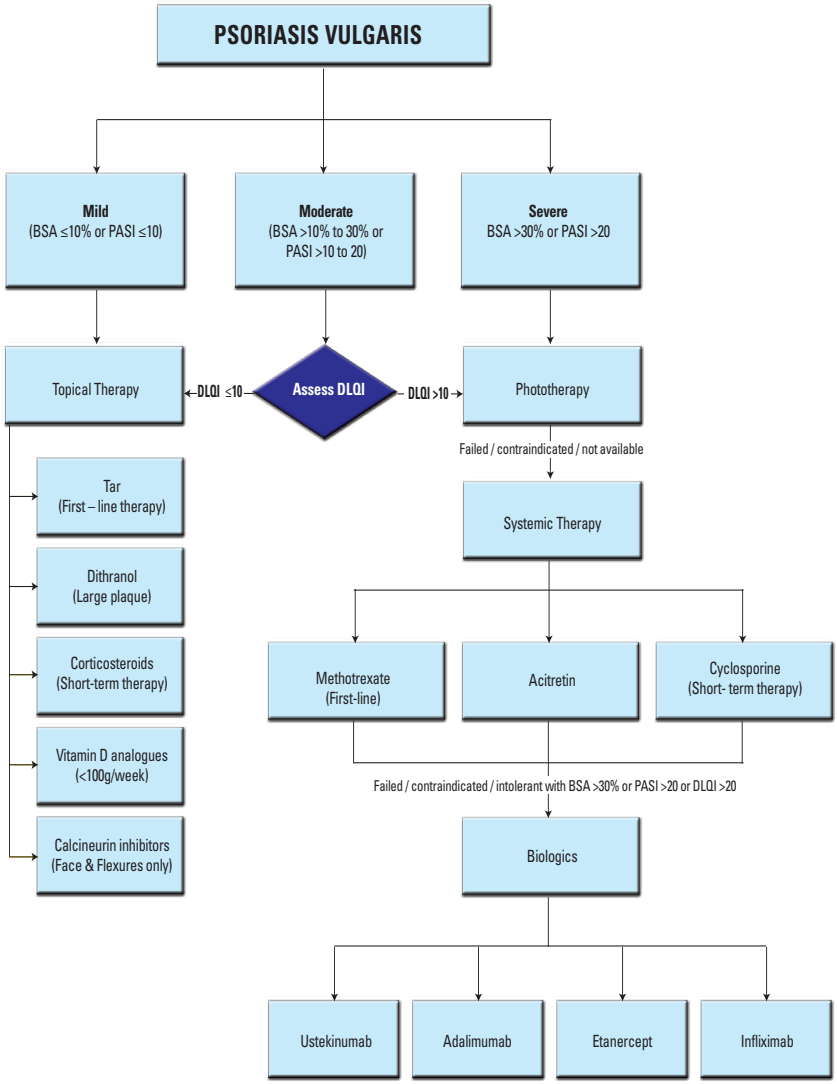
ALGORITHM 1: MANAGEMENT OF PSORIASIS VULGARIS IN PRIMARY CARE

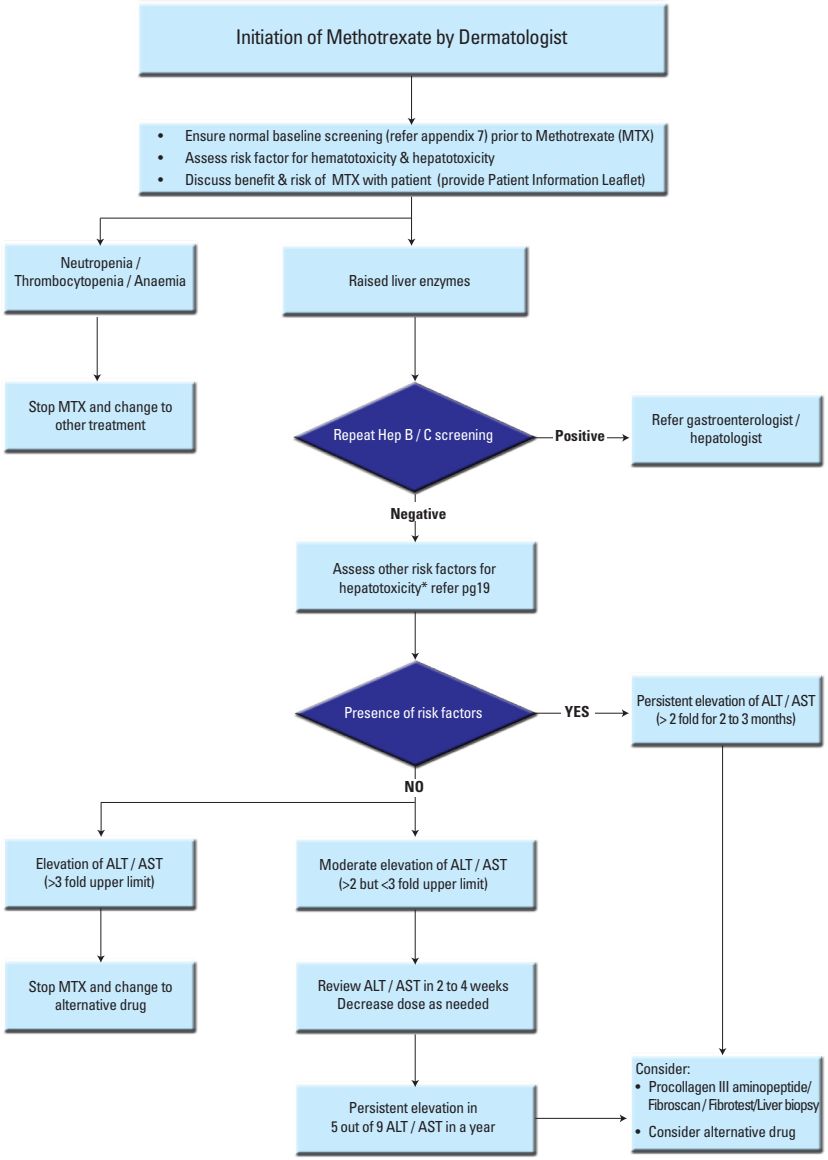


BSA	- Body Surface Area
PASI	- Psoriasis Area and Severity Index
DLQI	- Dermatology Life Quality Index
Responder	- BSA ≥50% reduction or PASI ≥50 achieved

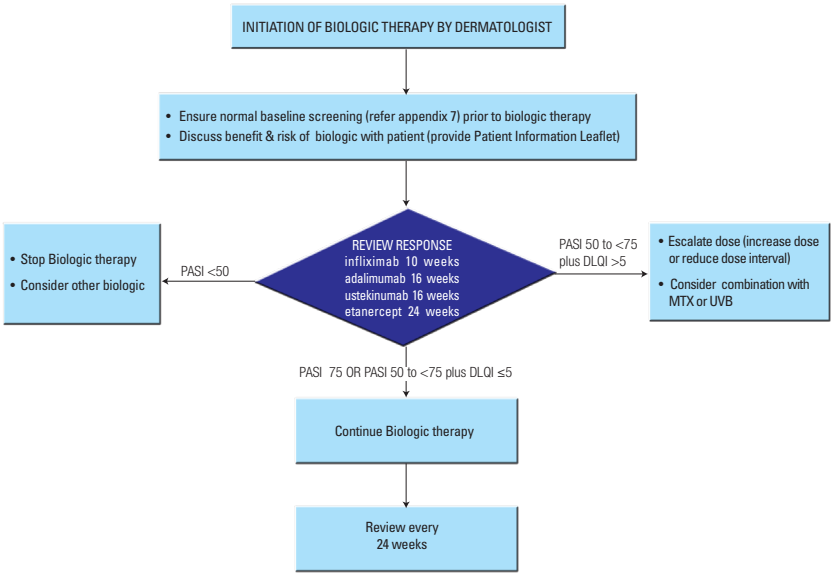
ALGORITHM 2: TREATMENT OF PSORIASIS VULGARIS



ALGORITHM 3: MONITORING OF METHOTREXATE INDUCED HEMATOTOXICITY AND HEPATOTOXICITY



ALGORITHM 4: BIOLOGIC THERAPY



1. INTRODUCTION

Psoriasis is a genetically determined, systemic immune-mediated chronic inflammatory disease that affects primarily the skin and joints. It has been estimated to affect 1 - 3% of the general population worldwide.

Plaque psoriasis, the most common form, seen in 80 - 90% of patients, is characterized by sharply demarcated erythematous plaques.[1- 5, level III; 6, level II-2] Psoriatic arthritis (PsA) occurs in up to 50% of patients with psoriasis.[7, level II-2] Although not usually life-threatening, psoriasis can be mentally and physically disabling. Patients not only have to deal with their highly visible skin disease, they also endure physical discomfort such as tightness, pain, bleeding and itch. Studies have shown that psoriasis causes as much disability as other major medical diseases such as cancer, heart disease, diabetes, hypertension, arthritis and depression.[8- 9, level III]

Furthermore, several studies have shown that patients with psoriasis are more prone to cardiovascular disease, stroke, lymphoma and non-melanoma skin cancers.[10 - 15, level II-2] The risk of developing these important co-morbidities such as myocardial infarction (MI) appears to correlate with severity of skin lesions. Young adults with severe psoriasis have a 3-fold increased risk of developing MI and a reduction of 3 - 4 years in life expectancy.[10-11, level II-2; 14, level II-2] There is also increasing evidence that controlling chronic inflammation of psoriasis with systemic agents or biologics may reduce cardiovascular co-morbidity.[12, level II-2; 15, level II-2, 16]

Although cure is not available, skin clearance can occur with appropriate treatment. Unfortunately, surveys showed that patients frequently received suboptimal care or were on ineffective treatment for longer than neccessary.[17-18, level III] Hence, these guidelines are developed to provide an evidence-based guidance to all health care providers involved in the care of adults with chronic plaque psoriasis. To ensure that all patients receive appropriate and adequate care, treatment goals and recommendations are clearly stated.

1.1 EPIDEMIOLOGY

Psoriasis occurs worldwide. Its prevalence varies greatly among different countries and ranges from 0.2% in China to 4.8% in Norway.[19, level II-2] A recent study using a national health insurance database documented a prevalence of 0.24% in Taiwan with a male: female ratio of 1.59:1.[20, level II-2] There is no local population-based epidemiological study on psoriasis. However, prevalence of psoriasis among Malaysian dermatology clinic attendees ranges from 2% to 6%.[21, level III; 5, level III] Studies on incidence of psoriasis are very rare. One study reported an annual incidence of 78.9 (95% CI 75.0 to 82.9) per 100,000 population in the United States of America (US) population and incidence is higher in males (p=0.003).[22, level III] Another study reported an incidence rate of 14 per 10,000 person-years in United Kingdom (UK) with a slightly higher rate in males after 30 years old.[23, level II-2] Psoriasis was first diagnosed before the age of 40 in 40% of patients.[22, level II-2]

Male preponderance was also seen in a Malaysian study with a male: female ratio of 1.7:1 ($p<0.001$).[5, level III] Males accounted for 56.4% of 4445 patients registered in the Malaysian national psoriasis registry.[2, level III] The mean age of onset for psoriasis in Malaysia was 33 years,[21, level III; 2, level III, 5, level III] which was lower than that observed in other countries (41 years in Sweden,[4, level III] 43 years in US [22, level III] and 46 years in Taiwan.[19, level II-2]).

Malays accounted for 48.5% of registered psoriasis patients, Chinese 24.3% and Indians 17.8%,[2, level III] suggesting a higher prevalence of psoriasis in Indians when compared to the ethnic distribution of Malaysia (67.4% Malays, 24.8% Chinese and Indian 7.3%) based on 2010 population census. A similar finding was observed among Malaysian Indians in another study ($p<0.001$).[5, level III]

The majority of patients (66.3%) in the Malaysian psoriasis registry had Type 1 psoriasis which is defined as onset of psoriasis by age 40.[2, level III] A positive family history of 17.1% to 29.0 % was observed in Malaysian patients with psoriasis.[21, level III; 2-3, level III; 5, level III]

2. CLINICAL CHARACTERISTICS AND RISK FACTORS

2.1 Clinical Characteristics

Psoriasis is a common skin disease with several distinct clinical phenotypes. Besides the presence of skin lesions, most patients (80%) also have associated symptom such as skin pain (41.7%, 95% CI 31.8 to 50) and skin discomfort (36.7%, 95% CI 29.1 to 45).[24, level II-2; 1, level III] The most common symptom is desquamation (68%), followed by pruritus (41%),[1, level III; 4, level III] dry skin (40%) and erythema (30%).[1, level III] Although embarrassment from excessive desquamation and pruritus are common complaints, there is no study documenting the extent of physical discomfort suffered by psoriasis patients in Malaysia.

Consistent with studies from other countries,[1, level III; 24, level II-2; 25, level III] plaque psoriasis is the commonest type of psoriasis accounting for 85.3% of the 4445 patients registered in Malaysian Psoriasis Registry. Other phenotypes include guttate psoriasis (4.7%), erythrodermic psoriasis (2.6%), pustular (1.5%) and flexural/inverse psoriasis (0.5%). Lower limbs (81.1%) is the commonest site affected, followed by scalp (80.4%), upper limbs (76.8%), trunk (73.9%), nail (59.8%) and face/neck (50.1%). The commonest nail abnormality is pitting (71.5%).[2, level III]

The majority of Malaysian patients (76.4%) have mild psoriasis (Body Surface Area [BSA] ≤10%) while 23.6% have moderate-severe psoriasis (BSA >10%). PsA is present in 16%. The commonest clinical pattern is oligo/monoarthropathy, followed by rheumatoid-like symmetrical polyarthropathy, distal hand joints arthropathy, spondylitis and arthritis mutilans.[2, level III]

2.2 Assessment of Severity

Various instruments are available to measure the severity of psoriasis. BSA involvement is widely used in daily clinical practice but it has not been validated.[26, level III] Psoriasis Area and Severity Index (PASI) is the gold standard to assess the physical severity of plaque-type psoriasis because it is the best validated tool with good internal consistency, good intraobserver variation and acceptable interobserver variation.[26-27, level III; 28, level II-2; Physician Global Assessment (PGA) is another validated tool to assess physical severity with good intraobserver and acceptable interobserver variation.[27, level III]

PASI, PGA and BSA do not reflect the psychosocial impact of mild psoriasis located on critical areas such as face, hands and genitalia. Short Form 36 (SF36), Dermatology Life Quality Index (DLQI) and Psoriasis Disability Index (PDI) are commonly used to measure the impact of psoriasis on patient's quality of life (QoL). Dermatology Life Quality Index (DLQI) is validated, concise and simple to use in clinical practice.[28-29, level III] Hence, assessing the severity of psoriasis should include an objective evaluation of the disease extent and its impact on the patient's health-related quality of life. Description of the assessment tools and grading of disease severity are shown in **Table 1** and **Table 2** respectively.

PGA or PASI is a sufficient tool for assessing the physical severity in patients with moderate to severe psoriasis.

Table 1: Assessment Tools for Measuring Psoriasis Severity

TOOLS	DESCRIPTION
PGA	Measures severity based on induration, erythema and scaling (refer appendix 4)
BSA	Measures percentage of body surface affected by psoriasis based on "rule of 9" or taking patient's one palm-size (flat hand with thumb and fingers) as 1% ↓ BSA 75=75% reduction in BSA after treatment ↓ BSA 50=50% reduction in BSA after treatment
PASI	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 appendix 5) • PASI 75=75% reduction in PASI score after treatment • PASI 50=50% reduction in PASI score after treatment
DLQI	Questionnaire to assess impact of psoriasis on quality of life. Score ranges from 0 to 30. (refer appendix 6) • 0 to1 - no effect at all • 2 to 5 - small effect • 6 to 10- moderate effect • 11 to 20 - very large effect • 21 to 30- extremely large effect

Source: Langley RG and Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index; Psoriasis Global Assessment and Lattice System Physician's Global Assessment. J Am Acad Dermatol. 2004; 51(4):563-569

Table 2: Definition of Psoriasis Severity

GRADE OF SEVERITY	MEASUREMENT TOOLS	INTERPRETATION
Mild	• BSA ≤ 10 % • PGA mild • PASI ≤ 10 • DLQI ≤ 10	Disease with a minimal impact on the patient's QoL and patient can achieve acceptable symptom control by standard topical therapy
Moderate	• BSA >10% to 30% • PGA moderate • PASI >10 to 20 • DLQI >10 to 20	Disease that cannot be, or would not be expected to be controlled to an acceptable degree by standard topical therapy, and/or disease that moderately affects the patient's QoL
Severe	• BSA >30% • PGA severe or very severe • PASI >20 • DLQI >20	Disease that cannot be, or would not be expected to be controlled by topical therapy and that severely affects patient's QoL (this includes erythrodermic psoriasis, pustular psoriasis and psoriatic arthritis)

Source: 1) National Protocol for management of Psoriasis in Tele Primary Care;
2) Ministry of Health Malaysia, Protocol for Biologics Intervention for psoriasis, 2011

RECOMMENDATION 1

- Psoriasis Area and Severity Index (PASI) or percentage of Body Surface Area (BSA) involvement should be used to assess the physical severity of psoriasis. **(Grade C)**
- Dermatology Life Quality Index (DLQI) should be used to measure the impact of psoriasis on the quality of life of patients. **(Grade C)**

2.3 Risk and Aggravating Factors

It is difficult to differentiate between risk and aggravating factors in psoriasis. Retrievable studies discussed these factors interchangeably. The following have been identified as significant risk factors for the condition:-

2.3.1 Family History

A positive family history is a significant risk factor for psoriasis (OR ranging from 5.4 to 34).[30, level II-2; 31, level II-2, 32, level II-2] Patients with a positive family history have their first symptoms of psoriasis 9.5 years earlier than those without (p=0.008).[21, level III]

2.3.2 Alcohol Consumption

Alcohol consumption of >5 drinks/month (OR=3.4, 95% CI 1.4 to 8.1) is a risk factor in men for psoriasis.[33, level II-2] However, its role as a risk factor in women is inconclusive.[34, level II-2; 33, level II-2]

2.3.3 Obesity

Obesity is a risk factor for psoriasis (Body Mass Index [BMI] >30, RR=1.5, 95% CI 1.2 to1.9; BMI >35, RR=2.7, 95% CI 2.1 to 3.4).[35, level II-2]

2.3.4 Smoking

A significant risk factor for psoriasis is current smoking with OR ranging from 1.7 to 1.9.[33, II-2, 23 , level II-2, 36, level II-2] The risk is dose dependent (11 - 20 pack-years, RR=1.6, 95% CI 1.3 to 2.0; >20 pack-years, RR=2.1, 95% CI 1.7 to 2.5) The risk remains significant in past smokers, except in those who have quit more than 20 years.[37, level II-2] Environment tobacco exposure is also a significant risk factor (OR=2.3, 95% CI 1.1 to 4.7).[30, level II-2]

2.3.5 Psychological Factors

Significant psychological risk factors for psoriasis are stressful life event (OR=2.2, 95% CI 1.4 to 3.4),[36, level II-2] divorce (OR=5.7, 95% CI 2.3 to 14.3) and change in work condition (OR=8.3, 95% CI 1.9 to 37.4).[38, level II-2]

2.3.6 History of Skin Disorders

Having a skin disorder within the past year is a risk factor for psoriasis (OR=3.6, 95% CI 3.2 to 4.1).[23, level II-2]

2.3.7 Recent Infections

A study using the United Kingdom General Practice Research Database showed that having an episode of infectious disease in the last year increased the risk of psoriasis (OR=1.6, 95%CI, 1.5 to 1.9). Risk of having psoriasis doubled in patients with infectious skin disorders (OR=2.1, 95% CI, 1.8 to 2.4) and in patients aged 21 to 40 years who had upper respiratory tract Infection in the past month.[23, level II-2] Acute pharyngitis as a risk factor was confirmed by an Italian study (OR=7.8 95% CI 1.8 to 32.5).[32, level II-2]

2.3.8 Koebner Phenomenon

Skin injury is a known risk factor for psoriasis (OR=1.6, $p<0.01$);[39, level III] Koebner phenomenon (development of skin lesions at the site of injury) was observed in 5% of early onset guttatte psoriasis in a Swedish study.[4, level III]

2.3.9 Physical Activity

Vigorous physical activity is associated with a reduced risk of psoriasis (RR=0.66, 95% CI 0.54 to 0.81).[40, level II-2]

2.3.10 Drugs

Several drugs such as beta blockers, NSAIDs and lithium have been associated with psoriasis based on anecdoctal reports. However, two population-based case-control studies showed no significant association of psoriasis, with the use of antihypertensive agents (beta blockers, angiotension-converting enzyme inhibitors and calcium channel blockers), non-steroidal anti-inflammatory drugs, acetaminophen, acetylsalicylic acid or central nervous system drugs.[31, level II-2; 23, level II-2]

2.4 Diagnosis and Investigation

Psoriasis is diagnosed clinically; however biopsy may occasionally be needed to confirm cases with atypical presentations.[41, level III]

Chronic plaque psoriasis, the most common type of psoriasis, is characterised by well demarcated erythematous plaques with silvery scales (Fig 1).

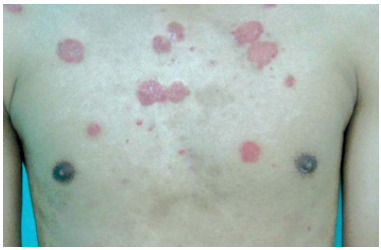


Fig.1: **Erythematous scaly plaques**

However erythema may be difficult to appreciate on darker skin (Fig 2). Sites of predilection are on extensor prominences (Fig 3-4) and lumbosacral region (Fig 5). Scalp (Fig 6) and nail involvements (Fig 7) are useful clues to diagnosis.

Guttate psoriasis is usually seen in children and adolescents after an upper respiratory tract infection and is characterised by multiple small plaques of psoriasis (Fig 8). Erythrodermic psoriasis (Fig 9) which is extensive psoriasis affecting more than 80 % body suface area and generalised pustular psoriasis (Fig 10) which is characterised by widespread erythema studded with superficial pustules should be referred urgently to a dermatologist.

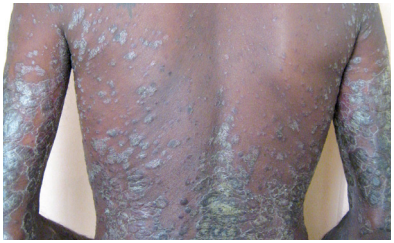


Fig 2: **Erythema may be difficult to appreciate on darker skin**

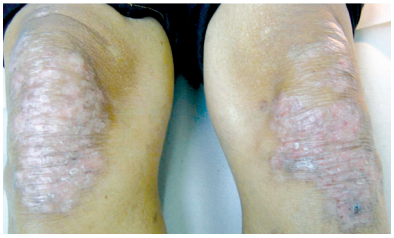


Fig 3: **Erythematous scaly plaques on both knees**

3. CO-MORBIDITIES

There is increasing evidence that psoriasis is associated with multiple co-morbidities especially metabolic syndrome.

3.1. Metabolic Syndrome and Its Components

There are various definitions of metabolic syndrome. Definition based on NCEP-ATP III criteria (original and revised), modified Asian NCEP-ATP III criteria and WHO clinical criteria were used in the following evidence in this section.[42, level II-2; 43, level II-2; 44, level III]

Prevalence of metabolic syndrome is increased in psoriasis patients with significant OR ranging from 1.3 to 5.9.[45-46, level II-2] A population-based study done in United Kingdom also showed that psoriasis was associated with metabolic syndrome (OR=1.41, 95% CI 1.31 to 1.51), and

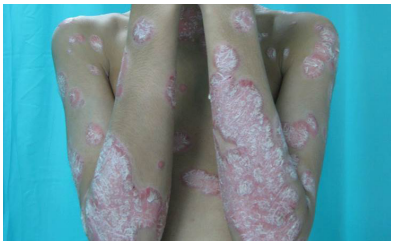


Fig 4: **Erythematous scaly plaques on elbows**

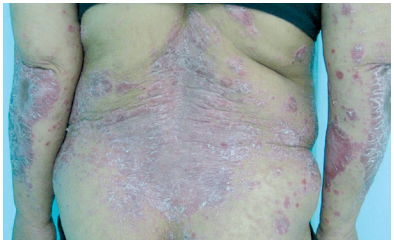


Fig 5: **Well-demarcated erythematous plaque on lumbosacral region**

the association increased with increasing disease severity, from mild (OR= 1.22, 95% CI 1.11 to1.35) to severe psoriasis (OR=1.98, 95% CI 1.62 to 2.43).[42, level II-2] The prevalence of metabolic syndrome among 212 psoriasis patients seen at a local tertiary referral public hospital was 55.7%, higher when compared with normal Malaysian population (OR=3.56, 95% CI 2.60 to 4.88).[43, level II-2]

Patients with psoriasis have increased risk of diabetes, hypertension, hyperlipidemia, obesity and smoking. Risk of diabetes mellitus and obesity were higher in moderate-severe compared to mild psoriasis (diabetes: OR=1.4, 95% CI 1.2 to1.6; obesity: OR=1.5 95% CI 1.3 to1.6).[14, level II-2] Similarly an Asian study also showed that increasing BMI was associated with increasing severity of psoriasis (p=0.004) particularly in men (p=0.002).[47, level II-2]

Metabolic abnormalities associated with psoriasis include:-

- Abdominal obesity (OR=1.72, 95% CI 1.03 to 2.86).[45, level II-2]
- Hypertriglyceridaemia (OR=2.08, 95% CI 1.39 to 3.11[45, level II-2] and RR=1.6, 95% CI 1.5 to 1.7[20, level II-2]).
- Hypertension (OR ranging from 1.03 to 1.49 [46, level II-2; 48, level II-2; 16, level II-2; 13, level II-2] and RR=1.51 (95% CI 1.47 to 1.56[20, level II-2]).
- Diabetes mellitus (OR ranging from 1.13 to 1.42[20, level II-2; 46, level II-2; 16, level II-2; 13, level II-2] and RR=1.64,95% CI 1.58 to 1.70[20, level II-2]).

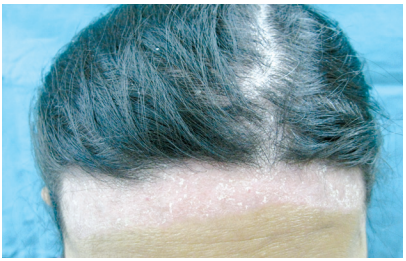


Fig 6: **Scalp lesions may extends 1-2cm beyond hairline**

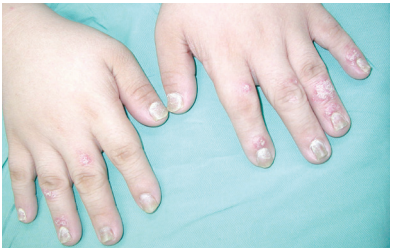


Fig 7: **Nail changes in psoriasis**

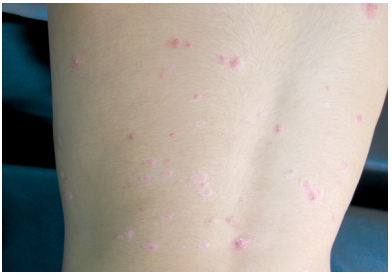


Fig 8: **Guttate psoriasis**

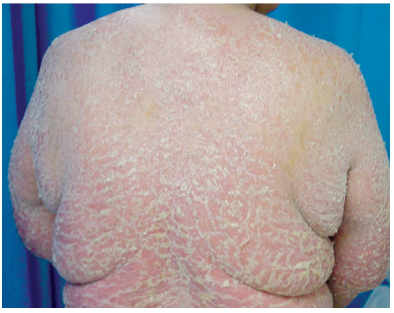


Fig 9: **Erythrodermic psoriasis**

3.2 Atherosclerosis and Related Diseases

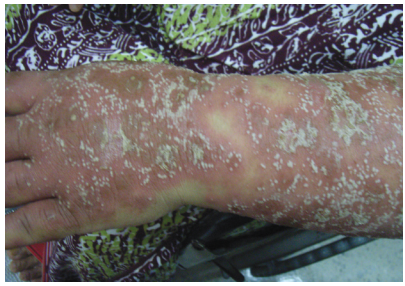


Fig 10: **Erythematous plaques studded with superficial pustules**

Psoriasis patients have higher risk of atherosclerosis with OR of 2.2 (95% CI 1.6 to 3.0), and atherosclerosis-related diseases like ischaemic heart disease (OR=1.8, 95% CI 1.5 to 2.1), cerebrovascular disease (OR=1.7, 95% CI 1.3 to 2.2) and peripheral vascular disease (OR=2.0, 95% CI 1.4 to 2.8).[12, level II-2] Severe psoriasis is a risk factor for major cardiovascular (CV) events like non-fatal myocardial infarct, non-fatal stroke or death (HR=1.5, 95% CI 1.3 to 1.9). It confers an additional 6.2% absolute risk of 10-year major CV events compared with the general population.[10, level II-2] Patients with severe psoriasis also have a significant 1.6-fold increase risk of CV mortality and the risk is higher in younger patients (RR of 2.7 and 1.9 for a 40-year-old and a 60-year-old respectively).[11, level II-2] Psoriasis is an independent predictor for non-fatal cardiovascular disease among women, particularly those diagnosed with psoriasis at <40 years of age (HR=3.26, 95% CI 1.2 to 8.8) and those with longer duration of psoriasis (≥9 years, HR=3.09, 95% CI 1.2 to 8.3) and concomitant psoriatic arthritis (HR=3.47, 95% CI 1.9 to 6.6).[49, level II-2]

3.3 Malignancy

Patients with psoriasis have an elevated risk of malignancies (HR=1.7, 95% CI 1.4 to 2.0) especially male patients (HR=1.9, 95% CI 1.5 to 2.3).[50, level II-2] The associated malignancies are cancer of the lips, oropharynx, larynx, liver, gallbladder, colon, peritoneum, rectum, urinary bladder and malignant melanoma.[20, level II-2; 50, level II-2]

3.4. Psychiatric co-morbidity

Patients with psoriasis have higher risk of depression (HR=1.39, 95% CI 1.37 to 1.41), anxiety (HR=1.31, 95% CI 1.29 to 1.34) and suicidality (HR=1.4, 95% CI 1.3 to 1.6) especially in severe disease.[51, level II-2]

3.5 Inflammatory Bowel Diseases (Ulcerative Colitis and Crohn's Disease)

Psoriasis is associated with increased risk of ulcerative colitis (OR=1.6, 95% CI 1.2 to 2.3).[52, level II-2] The risk of Crohn's disease however varies between countries probably due to genetic influence. The risk is not observed in Taiwan (RR=0.7, 95% CI 0.5 to 0.9),[20, level II-2] but is high in Israel (OR=2.5, 95% CI 1.7 to 3.6).[52, level II-2]

RECOMMENDATION 2

- Assessment of patients with psoriasis should include psychosocial measures and patients should be referred to mental health services if necessary. **(Grade C)**
- Psoriasis patients should be regularly screened for metabolic syndrome and risk factors of artherosclerosis-related diseases. **(Grade C)**
- Patients with psoriasis or psoriatic arthritis should be encouraged to adopt a healthy lifestyle (regular exercise, maintain healthy body weight [Body Mass Index 18.5 – 24.9], stop smoking, avoid alcohol or drink alcohol in moderation). **(Grade C)**

4. TREATMENT

4.1 Principles of Care

The treatment of psoriasis should be based on shared decision between patients and their healthcare providers (HCPs). Patients should be given adequate information regarding their disease and current available treatment options. This information should be reinforced by supplying them with evidence-based patient information leaflets in appropriate languages to enable them to make informed decision regarding their care. The goal of treatment is to improve and maintain patients' health-related quality of life through control of symptoms and signs of psoriasis. Implementing and regular monitoring of treatment goals based on disease severity and patients' preferences are necessary to ensure long-term effective treatment and to prevent complications from uncontrolled disease activity. The choice of treatment should be individualised based on patient's disease severity, patient's preference, availlability of treatment and the risk-benefit of treatment (refer Appendix 3).

- Management should start with patient education.
- Treatment should be a combined decision between patients and their healthcare providers.
- Treatment goals achieved should be monitored regularly to detect loss of response which may necessitate modification of therapy.

4.2 Treatment Goals

The ideal treatment goal would be complete clearance of skin lesions but this is currently not achievable in most patients. Thus, it is necessary to set a minimal target to allow modification of therapy if target is not achieved within a set time. (Refer to Table 3).

Treatment goal and minimal target set should be based on disease severity and patient's preference.

Table 3: Treatment Goals of Various Modalities

Treatment	Minimal targets	Time for Evaluation (weeks)	Subsequent Evaluation (months)
Topical therapy	↓ BSA ≥ 50 or PASI ≥ 50 or DLQI ≤5	6	6 - 12
Phototherapy Methotrexate Cyclosporine Acitretin	↓ BSA ≥ 75 or PASI ≥75 or DLQI ≤5	6 16 16 12	6
Infliximab Adalimumab Ustekinumab Etanercept	PASI ≥ 75 OR PASI 50 to <75 plus DLQI ≤5	10 16 16 24	6

BSA - Body surface area; PASI - Psoriasis Area and Severity Index; PGA - Psoriasis Global Assessment; DLQI- Dermatology Life Quality Index

4.3 Topical therapy

Success of topical therapy is highly dependent on patients' compliance to treatment. Compliance is usually better during the early phase of treatment and more likely when treatment is once daily. It is generally accepted that patients with less than 5% body surface involvement can be treated adequately with topical agents alone. However, even patients with extensive psoriasis can be effectively treated with topical therapies provided adequate time for education is given to patient to enhance compliance and appropriate use.

4.3.1 Emollients

Emollients either as soap substitutes or moisturizers are routinely used in the management of psoriasis although there is no evidence-based data on its benefits. However, one study demonstrated its steroid-sparing effect when used in combination with betamethasone dipropionate where control is achieved with less steroid used.[53, level I] This steroid-sparing effect is probably due to the ability of emollients to restore normal hydration and epidermal barrier function.

RECOMMENDATION 3

- Emollients should be used regularly in psoriasis. **(Grade C)**

4.3.2 Tar- based preparation

There is a lack of good quality evidence on the efficacy of coal tar. In Mason's Cochrane review, coal tar was shown to be as efficacious as placebo (SMD= -0.5, 95% CI -1.2 to 0.2 and less efficacious than calcipotriol (SMD= -1.1; 95% CI -1.6 to -0.7).[54, level I] However, another systematic review (SR) supported the use of coal tar preparations whereby 5% liquor carbonis distillate (LCD) showed 48.7% improvement in total severity score based on erythema, scaling, induration and pruritus at week 4 compared to 35.3 % improvement in placebo arm.[55, level I] A new topical LCD 15% solution was more efficacious than calcipotriene after 12 weeks of treatment [PASI 75: 41% vs 0% ($p<0.05$)].[56, level I]

Coal tar is well tolerated and has no significant differences in withdrawals due to adverse events (RD=0.03, 95% CI -0.05 to 0.12) or treatment failure (RD=0.00; 95% CI -0.06 to 0.06) when compared to calcipotriol.[54, level I] Although occupational exposure to coal tar is associated with lung, scrotal and skin cancer, risk of carcinogenicity following therapeutic use is unknown.[57, level III; 58, level II-2] A recent large cohort study of 13,200 patients with psoriasis and eczema treated with coal tar for a median duration of six months demonstrated no increased risk of cancer with a HR of 1.1 (95% CI 0.7 to 1.7) for skin cancer and 0.9 (95% CI 0. 8 to 1.1) for non-skin cancer.[58, level II-2]

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

Recommendation 4

- Tar-based preparations may be used as a first-line topical therapy for mild psoriasis. **(Grade A)**

4.3.3 Topical corticosteroids

Topical corticosteroids are the most widely used agent for treatment of psoriasis and they are available in a variety of formulations including ointment, cream, gel, lotion, spray and solution. A Cochrane review demonstrated the efficacy of topical corticosteroids compared to placebo whereby the standardized mean difference (SMD) for potent corticosteroids was -0.95 (95% CI -1.11 to -0.80) and very potent corticosteroids was -1.29 (95% CI -1.45 to -1.13). There were no significant adverse local and systemic events documented for both potent and very potent corticosteroids. However, duration of therapy in the included studies was short (2 - 3 weeks for very potent corticosteroids and 3 - 12 weeks for potent corticosteroids).[54, level I] Short-term use of topical potent and very potent corticosteroids had also been demonstrated to be safe in another systematic review.[59, level I]

Good quality evidence on the efficacy of medium and low potency corticosteroids in psoriasis is lacking. Evidence on the choice of formulations or frequency of application for topical corticosteroid is also scanty but most guidelines recommend once or twice daily application with tapering of frequency after disease control is achieved.

When topical corticosteroid was used with hydrocolloid dressing, disease clearance increased by 44% compared to corticosteroids monotherapy. However, combining corticosteroids and salicylic acid therapy did not increase disease clearance (RD=0.03, 95% CI -0.00 to 0.07). Combining corticosteroids with UVB treatment also did not increase disease clearance compared to UVB monotherapy (RD= -0.06, 95% CI -0.24 to 0.12).[60, level I]

Short-term use of potent or very potent topical corticosteroid is efficacious and safe for the treatment of plaque psoriasis. However, use on extensive lesions or long-term continuous use may result in skin atrophy and systemic absorption.

RECOMMENDATION 5

- Short-term therapy with potent and very potent topical corticosteroids may be used to gain rapid clearance in psoriasis patients with limited plaques. **(Grade A)**
  - These preparations should be avoided on the face, genitalia and body folds. **(Grade C)**
  - Limit use of super potent corticosteroids to less than 30g/week. **(Grade C)**
  - Limit use of potent corticosteroids to less than 60g/week. **(Grade C)**
- Continuous use of potent corticosteroids should not exceed four weeks. **(Grade C)**
- Continuous use of super potent corticosteroids should not exceed two weeks. **(Grade C)**
- Mild potency corticosteroids may be used for face, genitalia and body folds. **(Grade C)**

4.3.4 Dithranol Preparations

Dithranol is more efficacious than placebo (SMD= -1.1, 95% CI -1.7 to -0.5) and as efficacious as Vitamin D analogues (SMD=0.04, 95% CI -0.53 to 0.61). There was no significant difference in local or systemic adverse events compared to placebo.[54, level I] However, it may irritate surrounding normal skin, causing burning and staining. It has to be applied accurately to affected plaques to prevent irritation. Hence, it is more suitable for psoriasis patients with few large chronic thick plaques.

RECOMMENDATION 6

- Dithranol may be used for psoriasis patients with a few large thick plaques. **(Grade A)**

4.3.5 Topical Vitamin D Analogues

Calcipotriol is the only topical vitamin D analogue available in Malaysia. The Cochrane review by Mason et al, showed that vitamin D analogue was:[54, level I]

- more efficacious than placebo [SMD ranging from -0.8 (95% CI -1.3 to -0.3) to -1.9 (95% CI -2.1 to -1.7)], coal tar (SMD=-1.1, 95% CI -1.6 to -0.7) and tacrolimus (SMD= -0.95, 95% CI -1.55 to -0.34).
- as efficacious as potent corticosteroids (SMD=0.08, 95% CI -0.07 to 0.24), very potent corticosteroids (SMD=0.1, 95% CI - 0.6 to 0.8) and dithranol (SMD=0.04, 95% CI -0.53 to 0.61).

There is no difference in systemic adverse events when compared with placebo, potent or very potent corticosteroids, coal tar and dithranol. Calcipotriol causes more local adverse events mainly irritation and pruritus compared to potent corticosteroids (RD=0.09, 95% CI 0.04 to 0.14). It is better tolerated than dithranol (RD= -0.3, 95% CI -0.5 to -0.1) but this needs to be interpreted with caution due to significant heterogeneity among the studies. Twice daily calcipotriol was more efficacious than once daily dosing (SMD=-0.19, 95% CI -0.37 to -0.02).[54, level I]

The two-compound preparation containing calcipotriol and potent corticosteroids is more efficacious than either constituent alone (SMD vs corticosteroids alone was -0.44, 95% CI -0.54 to -0.35 and vs calcipotriol alone was 0.5, 95% CI 0.4 to 0.6). It causes less local adverse event compared to calcipotriol alone (RD=0.07, 95% CI 0.05 to 0.09). Although the studies included in this systematic review are of short duration (2 - 3 weeks),[54, level I] its safety when used on a “as-needed basis” has been demonstrated in a 52 week study.[61, level I]

Bailey et al, also showed a similar result whereby topical vitamin D analogue and corticosteroid combinations resulted in increased disease clearance compared to topical vitamin D analogue monotherapy (RD=0.2, 95% CI 0.1 to 0.3) or corticosteroid monotherapy (RD=0.20, 95% CI 0.15 to 0.24). However, this effect was dependent on the potency of the corticosteroids used. There was an increased likelihood of disease clearance using a potency group 1 corticosteroid combination (RD=0.3, 95% CI 0.2 to 0.4) and a potency group 2 corticosteroid combination (RD of 0.14, 95% CI 0.05 to 0.22) compared to topical vitamin D analogue monotherapy. Use of a potency group 3 corticosteroid combination did not lead to increased disease clearance in similar comparison.[60, level I]

- Total amount of calcipotriol used should not exceed 100g/week to avoid hypercalcemia.
- Potent corticosteroid used in vitamin D analogue and corticosteroid fixed dose combination may cause local and systemic side-effects.

Recommendation 7

- Fixed dose combination of topical vitamin D analogue and corticosteroid may be used for short-term treatment of psoriasis. **(Grade A)**
- Topical Vitamin D analogue may be used for treatment of psoriasis. **(Grade A)**

4.3.6 Calcineurin inhibitors

Pimecrolimus 1% cream is efficacious and well-tolerated when used for the treatment of facial and flexural psoriasis. In the Cochrane review by Mason et al, Pimecrolimus 1% cream is more efficacious than placebo in treating flexural psoriasis (SMD=1.1, 95% CI -1.7 to -0.5).[54, level I] Another study documented a 74.3% improvement ($p<0.005$) in total symptom score after 8-week treatment with pimecrolimus twice daily.[62, level II-3] Both studies showed no significant differences in term of local or systemic side-effects.[54, level I; 62, level II-3]

A multicentre, double-blind vehicle-controlled study demonstrated that tacrolimus 0.1% ointment is efficacious and well-tolerated when used for flexural and facial psoriasis. Excellent improvement in PGA score was achieved in 66.7% in tacrolimus group and only 36.8% in the vehicle ($p=0.002$).[63, level I] However, tacrolimus has limited efficacy for the rest of body (SMD=0.1, 95% CI -0.5 to 0.6),[54, level I] unless when used in combination with 6% salicylic acid leading to significant improvement in erythema, scale, and pruritus but not thickness score.[64, level I]

Topical tacrolimus and pimecrolimus are efficacious for face and flexures psoriasis but not licensed for the treatment of psoriasis.

4.3.7 Topical Salicylic Acid

The same Cochrane review as above showed that 2% salicylic acid alone (SMD= -0.96, 95% CI -1.89 to -0.02) or in combination with betamethasone diproprionate (SMD= -1.7, 95% CI -2.7 to -0.6) or with betamethasone valerate and tretinoin (SMD= -0.76, 95% CI -1.21 to -0.31) is more efficacious than placebo. Combination of 6% salicylic acid with betamethasone diproprionate is as efficacious as calcipotriol (SMD= -0.05, 95%CI -0.26 to 0.15).[54, level I]

RECOMMENDATION 8

- Topical salicylic acid may be used for plaque psoriasis. **(Grade A)**

4.4 Phototherapy

Phototherapy is indicated for patients with moderate to severe chronic plaque psoriasis. It includes ultraviolet A (UVA), ultraviolet B (UVB), red light, blue light and excimer laser. UVA is delivered in combination with a photosensitizing agent (psoralen) in oral, topical or bath form. Different wavelengths of UVB may be used eg narrowband (NBUVB), broad band (BBUVB) or selective band (SELUVB).

The efficacy of NBUVB is comparable to SELUVB, complete clearance is achieved in 56% vs 40% of patients. NBUVB is more effective than BBUVB, whereby PASI 60 was achieved in 84% patients treated with NBUVB compared to 38% (p<0.01) treated with BBUVB.[65, level I] The predictors of good response to NBUVB therapy are lower baseline PASI, a previous course of NBUVB, higher minimal erythema dose (MED) and lower body weight. Longer duration of remission is observed in patients who require fewer numbers of exposures to achieve clearance.[66, level II-2] High dose (70% MED) and low dose (35% MED) NBUVB are both efficacious, but lower dose requires more treatment sessions (20.6±6.9 vs 24.1±6.1 sessions, p<0.05).[67, level I] NBUVB treatment given twice a week or thrice a week has the same efficacy, however twice a week therapy requires longer treatment duration (PASI reduction 11.1±4.1 vs 11.9±3.6, p=0.29, duration of treatment 88 (48 - 150) days vs 58 (32 - 112) days, p<0.00).[68, level I] Topical psoralen combined with NBUVB has greater efficacy than NBUVB alone (PASI reduction of 58.6% vs 37.7%, p=0.043).[69, level I] Oral PUVA has greater clinical response than NBUVB (complete clearance: OR=3.04, 95% CI 1.18 to 7.84,[65, level I] and clearance rate: OR=2.79, 95% CI 1.40 to 5.55,[70, level I]). The number of sessions and cumulative dose are lower with oral PUVA compared to NBUVB (16.7 - 19.0 vs 25.3 - 28.5 sessions, p<0.05,[65, level I] 12.7 vs 16.4 sessions, p<0.05,[71, level II-1] and cumulative dose of 70.1 - 126.0 vs 35.0 - 41.3 J/cm^2, p<0. 001,[65, level I] 7.4 vs 1.1 J/cm^2, p<0.05).[71, level II-1] Oral PUVA provides better remission rate at 6 months (OR=2.73; 95% CI 1.18 to 6.27) and a longer duration of remission than NBUVB.[70, level I]

NBUVB is superior to bath PUVA (PASI score, 17.5 vs 20.0, p=0.044), number of treatment required for clearance (19.0 vs 24.5, p=0.014) and the duration for clearance (p=0.0014).[72, level I] The efficacy of cream PUVA is similar to NBUVB.[65, level I]

A meta-analysis of 3 studies showed no significant difference in efficacy between initial PUVA dose according to minimal phototoxic dose compared to initial PUVA dose according to skin-type. PUVA therapy twice per week compared with thrice per week is equally efficacious, but number of sessions required for clearance is significantly less with thrice per week regime (p<0.0001) and cumulative dose for clearance is also significantly less (p<0.001).[70, level I]

There is no evidence on the practice of maintenance phototherapy.

PUVA is associated with an increased risk of photoaging, lentigines and skin cancer. Squamous cell carcinoma (SCC) is the most common skin cancer encountered and the risk increases with higher number of exposures. The risk for basal cell carcinoma (BCC) is only seen with very high number of PUVA exposures. A significant risk for melanoma is only seen 15 years after first exposure to PUVA and the risk is also dose dependent. Among patients treated with PUVA, the risk for invasive scrotal and penile SCC is high (RR= 81.7, 95% CI 52.1 to 122.6).[73, level I] There is an increased incidence of cataract in patients exposed to PUVA compared to the population but the relationship to the level of PUVA exposure is conflicting.[74, level I]

Excimer laser is efficacious in limited plaque psoriasis (PASI 75 ranging from 54 to 84%) although studies are done on small number of patients.[75, level II-2; 76, level II-3] Blisters (45.2 - 92.3%), hyperpigmentation (37.9 - 100%), erythema (50.8 - 69.2%) and pruritus (84.6%) are the common side effects.[75, level II-2] There is no good evidence for blue and red light therapy in psoriasis.

RECOMMENDATION 9

- Phototherapy 2 - 3 sessions/week may be offered to patients with moderate to severe plaque psoriasis. **(Grade A)**
- Phototherapy should not exceed >200 sessions for PUVA or >350 sessions for UVB. **(Grade C)**

4.5 Systemic Therapy

The majority of patients with psoriasis have mild disease which can be adequately controlled with topical therapy. However patients with moderate to severe psoriasis frequently require systemic or biologic therapy. Systemic agents such as methotrexate, acitretin and cyclosporine have significant side-effects and cumulative toxicity while long-term safety data on biologics is still limited. Therefore, pre-treatment assessment of patients for systemic / biologic is important to identify those at risk of developing toxicity. Laboratory / imaging tests should be done at baseline and regularly, to monitor for side effects / toxicity.

RECOMMENDATION 10

- All patients for systemic / biologic therapy should have a pre-treatment assessment including laboratory / imaging tests and regular monitoring for side effects / toxicity*. **(Grade C)**

*Refer to Appendix 7

4.5.1 Methotrexate

Methotrexate is an analogue of folic acid which inhibits dihydrofolate reductase. It is a frequently used systemic agent for moderate to severe plaque psoriasis.

Methotrexate is efficacious in treating moderate to severe plaque psoriasis. In a meta-analysis on efficacy of systemic therapy by Bansback et al, PASI 75 at week 16 was achieved in 42% of patients on methotrexate (15 - 22.5mg/week) with a RR of 9.8 (95% CI 6.08 to 13.19) and NNT of 3.[77, level I] In a separate study, 70% of patients taking methotrexate 15 to 20mg/week achieved PASI 75 at week 12. There was no benefit in increasing the dose of methotrexate from 20 to 25mg/week in patients who failed to achieve PASI 50 at week 12.[78, level I] A lower percentage of patients taking methotrexate (15 - 22.5mg/week) achieved PASI 75 at week 16 compared to cyclosporine (60.5% vs 71.4%) but the difference was not significant (p=0.09).[79, level I] Methotrexate was comparable to mycophenolate mofetil (73.3% vs. 58.8% of patients achieved PASI 75 at week 12, $p>0.05$). However, this open-label study involved only 32 patients.[80, level I] Methotrexate was superior to hydroxycarbamide as shown in a RCT with PASI 75 at week 12 of 66.7% and 13.3% respectively ($p<0.05$).[81, level I]

Methotrexate is associated with adverse events such as hepatotoxicity, myelosuppression, gastrointestinal symptoms (nausea, vomiting, mouth sores, loss of appetite), hair loss and malaise.[82, level I] The prevalence and severity of side-effects is dependent on dosing regime. In Schmitt's meta-analysis on safety and tolerability of biologic and non-biologic, adverse events were found in 17.7% of patients taking methotrexate but none were serious. However, withdrawal due to adverse events was seen in 7.3% of patients. The most common cause of withdrawal was hepatic adverse events.[83, level I] In a separate study, common gastrointestinal side effects were nausea (8%), diarrhoea (6%) and abdominal pain (3%).[84, level I] Documented incidence of liver fibrosis ranged from 5.7% to 71.8%. Significant risk factors for liver fibrosis are type 2 diabetes mellitus (OR=7.7, 95%CI 2.7 to 21.7) and obesity (OR=2.4, 95% CI 1.1 to 5.4). Alcohol consumption (OR=1.7, 95% CI 0.9 to 3.5) and viral hepatitis (OR=5.6, 95% CI 0.9 to 33.5) were not significant risk factors.[85, level I]

Most data on myelosuppression with methotrexate are derived from patients with rheumatoid arthritis. The real risk of myelosuppression in psoriasis patients is unknown even though literature suggested that the risk is relatively low in appropriately monitored patients without risk factors.

Risk factors for methotrexate induced hematotoxicity

- Renal insufficiency
- Advanced age
- Lack of folate supplementation
- Medication errors
- Drug interactions
- Hypoalbuminemia
- Excessive alcohol intake

Monitoring of hepatotoxicity in patients taking methotrexate vary in different centres. These methods range from regular serum liver function test to liver biopsy. It has been a routine to do liver biopsy after a cumulative methotrexate dose of 1.5g and therafter at 1.0 to 1.5g interval to monitor methotrexate-induced hepatotoxicity. Recent data showed that the risk of developing liver fibrosis is less than 2.6% in low risk patients taking a cumulative methotrexate dose of >4g. Hence liver biopsy may be deferred till a cumulative dose of ≥4g.[86, level II-3; 87, level II-3]

Non-invasive methods to monitor hepatotoxicity such as serum procollagen III aminopeptide (sensitivity 77.3%, specificity 91.5%), fibrotest (sensitivity 83%, specificity 61%) and fibroscan (sensitivity 50%, specificity 88%) are not widely available in Malaysia. A liver biopsy can be deferred if the level of procollagen III aminopeptide remains within the normal limits.[85, level I]

Risk factors for methotrexate-induced hepatotoxicity

- Diabetes mellitus
- 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
- Hyperlipidemia

Supplementation with folic acid or folinic acid is an effective measure to reduce hepatic adverse effects (ARR= -0.4, 95% CI -0.5 to -0.2). However there is no significant reduction in gastrointestinal (ARR= -0.09, 95% CI -0.2 to 0.02), mucosal and cutaneous (ARR= -0.07,95% CI -0.2 to 0.04) or haematological side effects (ARR=0.004, 95% CI -0.02 to 0.03).[82, level I]

Data on the risk of pulmonary fibrosis in psoriasis patients on long-term methotrexate is limited. Pulmonary fibrosis was not documented in a study of 27 psoriatic arthritis patients on low dose methotrexate (5 -15mg/week) with average treatment period of 52 months (3 - 240 months).[88, level II-2] However, a systematic review reported 84 cases of lung related adverse event (AEs) in 3463 patients with rheumatoid arthritis on methotrexate, but only 15 of which were felt to be directly caused by methotrexate (incidence 0.43%). It is prudent to look for pulmonary fibrosis in psoriasis patients on long-term methotrexate.[89, level I]

Methotrexate treatment regime and monitoring in patients with psoriasis

Initial therapy

- Start with oral test dose of 5.0 - 7.5mg /week
- Supplement with folic acid 5mg od (except the day of methotrexate) or 5mg once a week (the day after methotrexate)
- Repeat full blood count (FBC), liver function test (LFT) and renal profile (RP) within 2 weeks

Maintenance therapy

- Escalate dose from 7.5mg/week till clinical response (maximum 20mg/week) [administered as a single dose or divided into 3 doses and administered at 12-h intervals over 2 consecutive days]
- Monitor FBC/LFT/RP
    - o Every 1 to 2 weeks during dose escalation
    - o Monthly for the first 3 months
    - o Subsequently every 1 to 3 month
- Do blood test 5 - 7 days after last dose of methotrexate
- Monitor cumulative dose of methotrexate
    - o Consider procollagen III aminopeptide / fibroscan / fibrotest / liver biopsy when total cumulative dose reach 3.5 to 4.0g in patients without risk factors for hepatotoxicity or 1.0 to 1.5g for those with risk factors for hepatotoxicity*

*Refer to yellow box on "Risk factors for methotrexate-induced hepatotoxicity"

RECOMMENDATION 11

- Methotrexate should be used as first-line systemic treatment for moderate to severe plaque psoriasis. **(Grade A)**
- Neutropaenia and hepatotoxicity should be closely monitored. **(Grade C)**

4.5.2 Retinoids (Acitretin)

Retinoids are vitamin A analogues which modulate epidermal proliferation and differentiation. Oral retinoids have been used for a very long time for the treatment of psoriasis. The first published study on etretinate was in 1984. No good RCTs assessing efficacy of oral retinoids were available. A study in 1989 comparing etretinate and acitretin documented mean PASI improvement of 70.8% vs 75.8%.[90, level I]

A study on adverse effects of acitretin by Pearce et al, showed low dose acitretin (<25mg/day) had less adverse effects compared to high dose acitretin (>25mg/day). The side-effects were chelitis, skin peeling, pruritus, alopecia, dry mouth, xerophtalmia, and raised alanine transaminase, aspartate aminotransferase and triglycerides.[91, level I]

When phototherapy is not an option, acitretin is an appropriate alternative treatment for HIV patients with psoriasis as it does not cause immunosuppression.[92, level III]

Acitretin treatment regime and monitoring in patients with psoriasis

Initial therapy

- Baseline lipid profile and LFTs
- Start with 0.5 – 1mg/kg/day for 2 - 4 weeks

Maintenance therapy

- Adjust dose according to response, usually within range of 25 - 50mg daily (maximum 75mg daily).
- Repeat lipid profile and LFTs every 4 - 8 weeks during dose escalation, then every 12 weeks

**in rare cases of use in women of childbearing age, a baseline pregnancy test should be done and repeated monthly*

RECOMMENDATION 12

- Acitretin may be offered for the treatment of moderate to severe plaque psoriasis. **(Grade A)**
- Acitretin should be avoided in women of childbearing age without reliable contraception and in those who are planning pregnancy. However, it is safe for men who are planning to have a child. **(Grade C)**

4.5.3 Cyclosporine

Cyclosporine is an oral calcineurin inhibitor. Efficacy of cyclosporine in treating moderate to severe plaque psoriasis had been demonstrated by Schmitt et al, (PASI 75= 28% to 97% at week 8 to16, RD=0.3, 95% CI 0.1 to 0.5).[83, level I] In another meta-analysis, PASI 75 was achieved in 33% of patients on cyclosporine 3mg/kg/day (RR=7.6, 95% CI 3.7 to 11.7, NNT=4).[77, level I]

Adverse events (16.1%), serious adverse events (2.3%) and withdrawal due to adverse events (1.2%) were documented in patients taking cyclosporine.[83, level I] In a 5-year cohort study on the risk of malignancy in psoriasis patients on cyclosporine, risk of non-melanoma skin malignancies was higher among patients treated for more than 2 years (SIR >2 years=11.4, 95% CI 5.2 to 21.7 vs SIR <2 years=4.6, 95% CI 2.4 to 8.1). Previous exposure to PUVA increased the risk of non-melanoma skin cancer (RR=7.3, 95% CI 1.3 to 134.5).[93, level III; 28, level II-2,]

Cyclosporine treatment regime and monitoring in patients with psoriasis

Initial therapy

- Ensure normal baseline investigation (refer appendix 7) prior to cyclosporine
- Discuss benefit & risk of cyclosporine with patient
- Starting dose of 2.5mg/kg/d divided twice a day

Maintenance therapy

- Escalate dose every 4 to 6 weeks till clinical response (maximum 5mg/kg/day)
- Monitoring while on therapy:
  - Blood pressure, RP, FBC, lipids, LFT, serum bilirubin,and magnesium monitored monthly

RECOMMENDATION 14

- Cyclosporine may be offered as short-term treatment for rapid disease clearance in moderate to severe psoriasis. **(Grade A)**
- Cyclosporine may be offered as second-line systemic agent to psoriasis patients who fail, intolerant or have contraindications to methotrexate. **(Grade A)**
  - Cyclosporine should **NOT** be used for more than 2 years. **(Grade B)**
  - Cyclosporine should be avoided in patient with previous PUVA exposure. **(Grade B)**
- Blood pressure, renal function, lipid profile should be monitored closely in psoriasis patients on cyclosporine**. (Grade C)**

4.5.4 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immune modulator which inhibits inositol monophosphate dehydrogenase. MMF (2g daily) is less efficacious than cyclosporine (2.5mg/kg body weight/day) with PASI 75 at week 12 of 12% and 29% respectively (p=0.01).[94, level I] Mean PASI improvement is also lower in MMF (30mg/kg/day) compared to cyclosporine (4mg/kg/day) (p=0.04). The tolerability and adverse events between the two drugs are similar.[95, level I]

4.5.5 Antibiotics

There is no good evidence to support the use of antibiotics in treating plaque psoriasis.[95, level I; 96, level I]

4.5.6 Hydroxyurea

Hydroxyurea is an anti-metabolite agent which inhibits deoxyribonucleic acid. There are no good quality studies to determine the efficacy and safety of hydroxyurea. In a prospective observational study, hydroxyurea 500mg twice daily was an efficacious alternative treatment for patients with chronic plaque psoriasis where 76% of patients achieved PASI 75 at week 10 to 12. Adverse events reported were leukopenia, thrombocytopenia, skin infection, dry skin, diffuse reversible alopecia and anaemia. Post-inflammatory lesional and nail hyperpigmentation were seen in all patients taking hydroxyurea.[97, level I]

4.5.7 Salozopyrin (Sulfasalazine)

Salazopyrin is a 5-lipoxygenase inhibitor which has anti-inflammatory and immunomodulatory effect. Its efficacy in treating psoriatic arthritis had been shown in several RCTs conducted in 1990s.[98, level I] However the evidence on the use of salazopyrin in treating plaque psoriasis is limited. In a small double-blind RCT, salazopyrin (1.5g to 4.0g) was shown to be more efficacious than placebo [psoriatic severity: marked improvement 41% vs 0%, moderate improvement 41% vs 4%]. There was a 26% drop out rate at the end of week 8 in salazopyrin arm due to rash or nausea.[99, level I]

4.5.8 Leflunomide

Leflunomide is a dihydro-orotate dehydrogenase inhibitor which is a key enzyme in the de novo synthesis of pyrimidine. There is limited RCT on the efficacy of leflunomide although several small, uncontrolled studies suggested its efficacy in treating patients with psoriasis and psoriatic arthritis.[98, level I, 100-101, level I; 102; level II-1] In a double blind placebo controlled RCT, leflunomide was more efficacious than placebo (PASI 75 17.4% vs 7.8%, p=0.048, Psoriatic Arthritis Response Criteria (PsARC) 58.9% vs 9.7%, p<0.0001) at week 24. In the same study, leflunomide was associated with higher incidences of diarrhea (24%), increased alanine transaminase level (12.5%) and lethargy (6.3%).[103, level I]

4.6 Biologic Therapy

Biologics are bioengineered proteins designed to block specific molecular steps important in the pathogenesis of psoriasis.

Eligibility and Indication

Patients with psoriasis may be considered for biologic intervention if they have severe disease as defined in Criteria A and fulfill at least one of the clinical categories in Criteria B.

Criteria A

Severe Disease

1. PASI >20 OR
2. BSA >30 OR
3. DLQI >20

AND

Criteria B

Clinical Categories

1. Contraindications to phototherapy and standard systemic therapies AND/OR
2. Intolerance/inaccessibility to phototherapy and standard systemic therapies AND/OR
3. Failed phototherapy and standard systemic therapies

Contraindication

Absolute

- Active infection including current tuberculosis
- Current history of malignancy
- Congestive cardiac failure class 3 or 4
- Demyelinating diseases

Relative

- Previous history of tuberculosis
- HIV infection
- Hepatitis B/C
- Previous history of malignancy
- Congestive cardiac failure class 1 or 2
- Pregnancy or breast-feeding
- Intention to get pregnant
- Patient who have had prior PUVA (>200 sessions) and UVB (>350 sessions)

Source: Ministry of Health Malaysia, Protocol for Biologics Intervention for Psoriasis (refer appendix), 2011; MOH Technology Review Biologic for Psoriasis, 2011.

4.6.1 Efficacy

There are strong and consistent evidences on the efficacy of biologics in the treatment of moderate to severe plaque psoriasis.[104, level I; 77, level I, 83, level I, 105, level I] Summary of the dosing schedule and efficacy of various biologics available in Malaysia is in Table 4.

a. Infliximab

Efficacy is demonstrated in three meta-analyses for infliximab (5mg/kg) versus placebo with 75.5% to 87.9% patients achieving PASI 75 at week 10 and significant RR of 17.4 to 22.6.[104, level I; 77, level I; 105, level I] Another meta-analysis reported a RD of 0.8 (95% CI 0.7 to 0.8) between infliximab and placebo at week 10.[83, level I] Two studies reported NNT of 1 in achieving PASI 75.[106,level I, 77, level I] In RESTORE-1 trial, infliximab 5mg/kg was more efficacious than methotrexate 15mg/week (PASI 75 at week 16, 77.8% vs 41.9%, $p<0.001$).[84, level I] However, loss of efficacy was observed at week 50 (PASI 75=61%). Efficacy is better sustained in patients on continuous compared to intermittent therapy (PASI 75 at week 50 was 54.5% vs 38.1%).[107, level I] It took an average of 14 - 16 weeks to achieve PASI 50 from baseline on re-starting treatment in patients on intermittent therapy.[108, level I]

b. Ustekinumab

Ustekinumab either 45mg [for body weight (BW) ≤100kg] or 90mg (for BW >100kg) is significantly more efficacious than placebo with 69% (RR=19.5) and 74% (RR=20.9) of patients achieving PASI 75 at week 12 respectively.[104, level I] In ACCEPT trial, ustekinumab 45mg or 90mg was significantly more efficacious than etanercept 50mg twice a week with PASI 75 achievement at week 12 was 67.5%, 73.8% and 56.8% respectively.[109, level I]

c. Adalimumab

Two meta-analyses showed adalimumab 40mg is more efficacious than placebo with 58% (RR=16.5) and 71% (RR=16.7) of patients achieving PASI 75 at week 12 to 16.[104, level I; 77, level I] It is supported by another meta-analysis which demonstrated a RD of 0.64 (95% CI 0.61 to 0.68) at week 16.[83, level I] Two studies reported NNT of 1 to achieve PASI 75.[110, level I; 77, level I] In CHAMPION trial, adalimumab 40mg had been shown to be more efficacious than methotrexate (7.5 to 25mg/week) and placebo in achieving PASI 75 at week 16 (79.6% vs 35.5% vs 18.9%; $p<0.001$).[78, level I] Open-label extension study for patients from REVEAL demonstrated that continuous adalimumab up to 3 years was still safe and efficacious with PASI 75 achievement at week 16 of 76% among the initial responders.[79, level I]

d. Etanercept

Efficacy of etanercept had been demonstrated in three meta-analysis and the response was dose related. Etanercept 50mg twice a week showed better efficacy than etanercept 25mg twice a week with PASI 75 achievement at week 12 of 47% to 54% (RR of 11.7 to 14.7) and 30% to 39% (RR of 10.2 to 10.9) respectively when compared with placebo.[104, level I; 77, level I; 105, level I] Another meta-analysis reported RD of 0.30 (95% CI 0.25 to 0.35) for etanercept 25mg twice a week and 0.44 (95% CI 0.40 to 0.48) for etanercept 50mg twice a week when compared with placebo at week 12.[83, level I] Two studies reported NNT of 2 for etanercept 50mg twice weekly and NNT of 3 for etanercept 25mg twice a week in achieving PASI 75.[110, level I; 77, level I] There is a further increase in the efficacy of etanercept after the induction phase of 16 weeks with maximal efficacy to be reached after 18 to 24 weeks. It was demonstrated that etanercept 25mg twice a week resulted in PASI 75 of 34% at week 12 and 44% at week 24 whereas etanercept 50mg twice a week showed PASI 75 of 49% at week 12 and 59% at week 24.[111, level I]

The above findings on efficacy of biologics had been confirmed by a recent meta-analysis in 2012 by Lucka TC et al.[112, level I]

Table 4: Dosing schedule and efficacy of available biologics for Psoriasis

Types of Biologics	Dosing Schedule	Expected Onset of Clinical Effect (week)	Review of response (week)	Efficacy at week 10 to 16 (PASI 75)	Long- term Efficacy (PASI 75)
Infliximab [104, 112, level I; 77, level I;105, level I]	Intravenous 5mg/kg at week 0,2,6 and then every 8 weeks	2	10	75.5 to 87.9	54.5% (week 50) 62.5% (week 46) 71.9% (week 42)
Ustekinumab [112, level I;104, level I]	BW<100kg: Subcutaneous 45mg at week 0,4 and then every 12 weeks	2	16	69	71.2% (>week 28) 69.5% (week 28) 68.8% (week 52)
	BW≥100kg: Subcutaneous 90mg at week 0,4 and then every 12 weeks	2	16	74	78.6% (>week 28) 78.5% (week 28)
Adalimumab [112, level I; 104, level I; 77, level I]	Subcutaneous 80mg at week 0, then 40mg every other week beginning 1 week after initial dose	4	16	58 to 71	56% to 64% (week 60)
Etanercept [112, level I, 104, level I; 77, level I; 105, level I]	Subcutaneous 25mg biweekly Subcutaneous 50mg biweekly	12	24	30 to 39 (25mg) 47 to 54 (50mg)	51% (week 96) 55% (week 72) 63% (week 48)

4.6.2 Safety

Biologics are associated with adverse events of which some are serious and life threatening. These include opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, hematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction.

In a Cochrane systematic review by Singh et al, in 2011, biologics were associated with higher rate of total adverse events (TAEs) [OR=1.2, 95%CI 1.1 to1.3], withdrawals due to AEs [OR=1.3, 95% CI 1.1 to1.6] and an increased risk of tuberculosis reactivation (OR=4.7, 95% CI 1.2 to 18.6). There was no significant difference in terms of severe adverse events (SAEs), serious infection, lymphoma and congestive cardiac failure.[113, level I] The risk of tuberculosis (TB) was higher with monoclonal antibodies, adalimumab [144 events per 100000 person-years (pyrs)] and infliximab (136 per 100000 pyrs), as compared with etanercept (39 per 100000 pyrs) in patients with rheumatoid arthritis reported to the BSRBR (British Society for Rheumatology Biologics Register).[114, level II-2]

Registry data from BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products) demonstrated effectiveness of 9 months isoniazid prophylactic therapy in preventing reactivation of latent TB infection for patients receiving tumor necrosis factor (TNF) antagonists. Active TB rate in BIOBADASER patients was 20.9-fold higher (95% CI 12.0 to 36.8) than in the background Spanish population before implementation of prophylactic isoniazid therapy as compared to 4.7-fold (95% CI 0.5 to18.9) after implementation of this recommendation. There was a decrease in active TB rates by 78% among the BIOBADASER patients following this recommendation with incidence risk ratio (IRR) of 0.22 (95% CI 0.03 to 0.88).[115, level II-2]

A small case series found that anti-TNF alpha (infliximab more than etanercept and adalimumab) induced reactivation of hepatitis B in psoriasis patients with positive hepatitis B surface antigen (HbsAg +ve) and less frequently in patients with isolated positive hepatitis B core antibody (anti-Hbc +ve). This can be prevented with appropriate anti-viral therapy, thus hepatitis B in psoriasis is not an absolute contraindication to the use of anti -TNF alpha.[116, level III]

a. Infliximab

The meta-analysis by Singh et al, showed that Infliximab was associated with higher risk of TAEs (OR=1.3, 95% CI 1.1 to 1.6) and withdrawals due to AEs (OR=2.0, 95% CI 1.4 to 2.9).[113, level I] Another meta-analysis confirmed that Infliximab was associated with higher AEs (RR=1.2, 95% CI 1.07 to 1.3) but not SAEs (RR=1.3, 95% CI 0.6 to 2.8). Common AEs were acute infusion reaction, upper respiratory tract infection, headache and increased hepatic enzymes.[105, level I]

b. Ustekinumab

In the PHOENIX-1 and 2 trials, the risk of AEs was comparable between ustekinumab 45mg, ustekinumab 90mg and placebo (53.1% to 57.3%, 47.9% to 51.4% and 48.2% to 49.8% respectively). There was no difference in SAEs among the three arms (0.8% to 2.0%, 1.2% to 1.6%, and 0.8% to 2.0% respectively). In general, AEs reported were mild such as upper respiratory tract infection, injection site reaction, nasopharyngitis, headache and arthralgia.[117, level I; 118, level I]

c. Adalimumab

Adalimumab was associated with higher risk of TAEs (OR=1.2, 95% CI 1.03 to 1.6) but without increase in withdrawal (OR=1.02, 95% CI 0.7 to 1.5) when compared to placebo. Common AEs were injection site reaction, infection (e.g. upper respiratory infection), dizziness and headache.[113, level I]

d. Etanercept

Compared to placebo, etanercept showed no significant TAEs (OR=1.2, 95% CI 0.98 to 1.4) or withdrawal due to AEs (OR=1.3, 95% CI 0.9 to 1.8).[113, level I] Common AEs documented were injection site reaction, headache and upper respiratory tract infection.[105, level I]

Monitoring adverse effects of biologics in patients with psoriasis

- Patient education and counseling
  - ❒ Regular update on safety profile and reminder of potential risk of malignancy
  - ❒ Weight monitoring
- Blood investigations
  - ❒ 6 monthly FBC, ESR, CRP, LFT, RP, FLP, HBsAg, HCV Ab, HIV, ANA
- Assessment for tuberculosis
  - ❒ Yearly CXR / Mantoux test

4.6.3 Cost- Effectiveness

The use of biologics in treating psoriasis is limited by its high costs. Hence various studies had been carried out in different countries to investigate the cost-effectiveness of biologics and economic impact of psoriasis. However, there is no local study evaluating the cost effectiveness of different biologics agent in Malaysia.

A retrospective cohort study in Netherlands showed higher mean total direct costs in the biologic period compared to the pre-biologic period [€17712, 95% CI €15004 to €20 421 vs €10146, 95% CI €7614 to €12 678 per patient per year (PPPY)]. This difference was attributed to the cost of biologics. However the use of biologics significantly decreased the direct costs related to day-care admission (pre and post biologic cost: €1167 PPPY vs €60 PPPY) and hospitalization (€6738 PPPY vs €1475 PPPY).[119, level II-2]

Another study in United Kingdom (UK) showed a significant decrease in mean annual hospital care costs by £1682 (p=0.028) even though the mean annual drug cost was increased by £9456 (p<0.001) following commencement of biologics.[120, level II-2]

Adalimumab was the most cost-effective biologic in Swiss healthcare system for PASI 75 at week 12 with lowest incremental cost-effectiveness ratio (ICER) of CHF 14 921 followed by Infliximab (CHF 16 505) and etanercept (CHF 25 748). For ICER per PASI 90 at week 12, Infliximab was most cost effective with lowest ICER of CHF 22995 followed by adalimumab (CHF 34 815) and etanercept (CHF 59 407).[121, level I]

Similar result were demonstrated in the Spanish National Health System, the most cost effective biologics in terms of cost per PASI 75 responder was adalimumab (ICER €8013 at week 16) followed by etanercept 25mg twice a week (ICER €9110 at week 12), usteknumab 45mg (ICER €9627 at week 12), infliximab 5mg/kg (ICER €10 523 at week 10), etanercept 50mg twice a week (ICER €12797 at week 12) and ustekinumab 90mg (ICER €17981 at week 12).[122, level I]

The expected cost and benefit, expressed as quality-adjusted life-years (QALYs), were estimated for biologics from National Health Service (NHS) data. Adalimumab was most cost-effective (ICER £30 000 per QALY) followed by etanercept (£37 000 per QALY) and infliximab (£42 000 per QALY).[123, level I] However, these health economic studies do not measure the cost-benefits derived from the prevention of disease-related morbidity and mortality such as depression, joint deformities and cardiovascular disease.

RECOMMENDATION 14

- Biologic therapy should be offered by a dermatologist to patients with severe plaque psoriasis who fail, have intolerance or contraindication to conventional systemic treatment and phototherapy.* **(Grade A)**
- Careful evaluation for contraindications should be done prior to initiation of biologics for psoriasis patients. **(Grade A)**
- Safety issues should be monitored during and after treatment of biologics. **(Grade A)**
- All patients on biologics should be registered with the National Psoriasis Registry. **(Grade C)**
- Psoriasis patients with latent tuberculosis should be referred to respiratory physician for treatment before biologics initiation. **(Grade A)**

* Refer to yellow box above for the indication and eligibility criteria

4.7 Various Combinations

Combination therapies are frequently used in clinical practice for the treatment of psoriasis.[60, level I] Limited data documented better efficacy, tolerability and fewer adverse events for combination therapies.[124-125, level III] Systemic treatments are sometimes combined for variable time periods to achieve an additive or synergistic effect. Dosages of the individual agents may then be reduced to minimise adverse effects.[124, level III] Evidence on combinations using vitamin D derivatives, vitamin A derivatives (retinoid), UVB and corticosteroid presented in this subchapter are based on the meta-analysis by Bailey et al.[60, level I]

4.7.1 Vitamin D analogues Combination

Combined vitamin D analogues and phototherapy treatment cleared psoriasis better than vitamin D analogues monotherapy (RD=0.3, 95% CI 0.2 to 0.5) but not when compared to UVB monotherapy (RD= 0.07, 95% CI -0.02 to 0.2).[60, level I]

RECOMMENDATION 15

- Topical vitamin D analogue and ultraviolet B phototherapy combination may be used for treatment of psoriasis. **(Grade A)**

4.7.2 Vitamin A analogues (retinoids) Combination

Retinoids and PUVA combinations led to improved disease clearance compared to oral retinoids monotherapy (RD=0.5, 95% CI 0.3 to 0.7) and PUVA monotherapy (RD=0.22, 95% CI 0.07 to 0.38).[60, level I]

Both oral and topical retinoids combination with topical corticosteroid produced better disease clearance when compared to retinoid monotherapy (RD=0.2, 95% CI 0.1 to 0.3). There was insufficient data to compare the efficacy of this combination with topical corticosteroid monotherapy. Retinoids and UVB combination resulted in better disease clearance than UVB monotherapy (RD=0.20, 95% CI 0.05 to 0.36). However, when a study using acitretin was removed from the analysis, this effect lost its statistical significance, suggesting better efficacy only when systemic retinoid and UVB combination is used.[60, level I]

RECOMMENDATION 16

- Acitretin and ultraviolet B phototherapy combination may be offered to patients with inadequate response to ultraviolet B monotherapy in psoriasis. **(Grade A)**
- Acitretin and PUVA combination may be offered to patients with inadequate response to PUVA in psoriasis. **(Grade A)**

4.7.3 Ultraviolet B (UVB) Combination

Based on two small RCTs in the systematic review, the use of UVB-methotrexate combination therapy had better clearance compared to UVB monotherapy (RD=0.4, 95% CI 0.1 to 0.6). However, UVB combinations with balneotherapy, psoralen or tar did not increase the likelihood of achieving disease clearance when compared to UVB monotherapy.[60, level I]

Ultraviolet B phototherapy and tar-based preparation combination has no additional benefit compared with ultraviolet B phototherapy alone.

4.7.4 Etanercept Combination

In a systematic review by Foley et al, two RCTs showed superior PGA ratings for patients on combination of etanercept and methotrexate. The RCT by Zachariae et al, showed that the proportion of patients judged as 'clear' or 'almost clear' according to the PGA at week 24 was superior for etanercept with continued methotrexate treatment compared with etanercept /methotrexate taper (66.7% vs 37.0%, p=0.03). While Moore et al study, the OR of achieving 'clear', 'almost clear', or 'mild' on the PGA scale with concomitant etanercept 50mg biweekly and methotrexate therapy was 2.3 at week 12 (95% CI 1.3 to 4.0) compared with etanercept monotherapy. The HR estimate for AEs was similar for both groups.[126, level I]

PASI 75 was achieved by 45% of patients on etanercept 25mg twice weekly, 30% of patients on acitretin 0.4mg/kg daily and 44% of patients treated with etanercept (25mg once a week) / acitretin (0.4mg/kg/day) combination at week 24 (p=0.001 for both etanercept groups compared with acitretin alone).[126, level I] Although once weekly etanercept/ acitretin daily combination was as efficacious as biweekly etanercept monotherapy, larger trial was required to confirm the finding.

PASI 75 was achieved by 90% of the etanercept 25mg twice a week and narrowband UVB combination group compared to 40% of the etanercept monotherapy group at week 12.[126, level I]

RECOMMENDATION 17

The following combination may be used to improve disease clearance in patients with moderate to severe psoriasis:-

- Etanercept / methotrexate combination. **(Grade A)**
- Etanercept / narrow band Ultraviolet B phototherapy combination.**(Grade A)**

4.8 Adjunctive Therapy

There is no good quality evidence to recommend adjunctive therapy such as traditional Chinese medicine, herbal treatment, psychological intervention or dietary supplement. Although there is no retrievable evidence on the role of anti-histamines in the treatment of psoriasis, anti-histamine is useful in treating associated pruritus.

RECOMMENDATION 18

- Anti-histamines should be offered for the treatment of pruritus in patients with psoriasis. (**Grade C)**

5. SPECIAL CONDITIONS

5.1 Treatment of Psoriasis in Pregnancy

Psoriasis improves in 55%, worsen in 23% and remains static in 21% of patient during pregnancy.[17] Psoriasis frequently flares in the immediate post-partum period. Although there are many modalities of treatment, safety data for the use of these therapies in pregnant and lactating women is limited. Safety data are mainly from case reports, or observational studies and post-marketing surveillance reports.

In managing psoriasis in pregnant and lactating women, drug chosen should confer benefit to the mother and pose minimal risk to the foetus. The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

Category	Interpretation
A	**Controlled human studies show no risk** Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	**No evidence of risk in studies** Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters
C	**Risk cannot be ruled out** Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	**Positive evidence of risk** There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	**Contraindicated in pregnancy** Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
N	FDA has not classified this drug

5.1.1 Topical Agents

a. Emollients

The use of emollients is safe.[127-129, level III]

b. Topical Corticosteroids

A Cochrane review of observational studies on topical corticosteroids of various potencies showed no significant adverse event in pregnancy outcomes. However, high potency corticosteroids particularly on large body surface areas should be used with caution because of the possibility of low birth weight baby.[130, level II-2]

c. Tar-Based preparations and Anthralin

Tar-based preparations are found to be teratogenic in animals at doses that caused maternal toxicity. However there is insufficient data to enable an accurate estimate of teratogenic risk to be made in humans. Short-term use of topical coal tar is probably safe in second and third trimester of pregnancy.[128, level III]

There is no information on the use of anthralin (dithranol) during pregnancy in humans or animals. Since there is no evidence of systemic absorption, dithranol is considered safe in pregnancy.[128-129, level III]

d. Calcipotriol Analogues

Use of calcipotriol is to be avoided in pregnancy because of systemic absorption.[127-128, level III] Animal studies showed increased incidence of skeletal abnormalities, incomplete ossification of pubic bones and forelimb phalanges of foetuses.[131, level III] Nevertheless, use of topical calcipotriol during pregnancy at recommended doses (<100g/week) is unlikely to be associated with a high risk of teratogenicity. Although there is no published data on the reproductive or teratogenic effect on humans, use beyond the recommended doses may be teratogenic.[129, level III]

e. Tacrolimus

Tacrolimus is effective in the treatment of facial and intertriginous psoriasis. Systemic absorption of tacrolimus after topical administration is very low. Blood concentrations of tacrolimus in patients with atopic dermatitis treated topically are 7 to 17 times lower than those observed in transplantation recipients after oral administration. Hence risk of teratogenicity is likely low if tacrolimus is used for limited disease although there is no published human data.[129, level III]

f. Salicylic acid

Topical salicylic acid is not recommended as studies are limited and topical absorption can be substantial.[131, level III]

5.1.2 Phototherapy

Both NBUVB[128-129, level III; 1131-32, level III] and BBUVB[131-132, level IIII] are safe in pregnancy.

Insufficient evidence exists on the safety of PUVA in pregnancy but in view of the mutagenic potential of PUVA, it is not recommended for use in pregnancy.[128, level III; 132, level III] Even though there was no documented increase rate of congenital anomalies, an increase number of low-birth weight infants was noted in patients who are treated with PUVA.[132, level III; 127-128, level III]

5.1.3 Systemic Agents

The availability of systemic therapies for psoriasis in pregnancy is limited. Only two drugs; cyclosporine and corticosteroids are considered to be relatively safe but have to be used with caution.

a. Cyclosporine

Based on studies of pregnant transplant patients who were treated with cyclosporine (C), the rate of congenital anomalies shows no difference from that expected in the general population.[127-129, level III] However increased incidence of prematurity and intrauterine growth restriction (IUGR) had been reported.[129, level III; 131, level III]

b. Systemic Corticosteroids

Systemic corticosteroids are infrequently used for treatment of psoriasis except in pregnancy-induced generalised pustular psoriasis. Long-term effects on growth, neurodevelopment and social-emotional functioning have not been associated with exposure to a single course of corticosteroids during pregnancy. Although long-term effects of multiple courses of prenatal corticosteroids on neurodevelopment and growth in humans are limited, repeated courses of corticosteroids should be used with caution.[129, level III]

A systemic review by Park-Wyllie et al, found a significant association between first-trimester corticosteroids and oral clefts in case control studies (OR=3.4, 95% CI 2.0 to 5.7).[133, level II-2]

c. Acitretin

Acitretin (X), a systemic retinoid, is contraindicated in pregnancy due to high risk of teratogenicity[129, level III, 127, level III] especially in first trimester[128, level III] The risk of fetal malformation in pregnancies exposed to an oral retinoid in early pregnancy is 25.6 times higher than the general population. Acitretin characteristically caused malformation involving craniofacial, cardiac, thymic, and central nervous system structures.[129, level III]

Pregnancy should be avoided in patients who are taking acitretin and for at least 2 years after stopping treatment or longer (up to 3 years) in patients who consumed alcohol. When alcohol is consumed, acitretin is metabolized to etretinate, which has an elimination half-life up to 168 days. The elimination half-life of acitretin ranges from 33 to 96 hours.[129, level III]

Prescribing acitretin to any woman of childbearing potential warrants careful consideration. It is prudent to document two negative urine or serum pregnancy tests before initiating acitretin therapy. Patients should be advised to use two effective forms of contraception simultaneously for at least 1 month before initiation of acitretin therapy, during acitretin therapy, and for at least 2 - 3 years after discontinuing acitretin therapy. Patients should also be advised to abstain from consuming alcohol while taking acitretin and for at least 2 months after acitretin treatment has been discontinued.[129, level III]

d. Methotrexate

Methotrexate (X) is contraindicated in pregnancy as it is associated with increased risk of spontaneous miscarriage, mental retardation and aminopterin / methotrexate syndrome.[129, level III] Features of this syndrome are mainly skeletal abnormalities involving the skull and limbs, microcephaly and hydrocephalus.[134, level III] Data are still insufficient to quantify exact threshold doses. However, based on pregnancy data from women exposed to methotrexate in early pregnancy, it appears that doses greater than 10mg/week are necessary to produce aminopterin/methotrexate syndrome and that the critical exposure period is between 6 and 8 weeks post-conception. The effect of exposure to methotrexate and aminopterin on foetus during the second and third trimesters is not known.[129, level III]

The potential foetal risk when the father is exposed to methotrexate at the time of conception (paternal conception) remains unclear. No congenital malformation was observed in small case series and case reports of pregnancies after paternal exposure to low-dose methotrexate.[134, level III] Nevertheless, because of the mutagenic potential of methotrexate, both men and women are to avoid conception for at least three months after taking methotrexate.[128-129,level III]

5.1.4 Biologics

Tumour necrosis factors (TNF) inhibitors (B) such as adalimumab, etanercept and infliximab should be used cautiously in pregnancy.[128, level III] Animal studies did not report any toxicity or teratogenicity but there is limited human data.[135, level III]

Registry data from 142 pregnancies exposed to infliximab in Crohn's patients did not show any increased adverse outcome compared to the general population. Congenital abnormalities such as Fallot's tetralogy and intestinal malrotation, lower birthweights and prematurity has been occasionally reported in live birth infants from mothers exposed to infliximab.[135, level III] A Dermatology Expert Group reached the consensus that patients who become pregnant while being treated with infliximab should suspend therapy temporarily.[136, level III] Some expert recommend limiting the use of infliximab to the first 30 weeks of pregnancy and resumed treatment 3 - 14 days after delivery since the transplacental transport of immunoglobulin G (Ig G) is poor until late second or early third trimester.[133, level III] The teratogenic risk of adalimumab is unknown. Healthy full-term infants were delivered by patients with Crohn's disease or rheumatoid arthritis treated with adalimumab in 6 case reports.[129, level III]

Most information on etanercept safety comes from patients with rheumatoid arthritis. No congenital malformation was seen among 25 live-born infants exposed to etanercept during the first trimester of pregnancy. However, one case of VATER syndrome (congenital malformation of vertebral anomalies, anal atresia, tracheo-esophageal fistula, esophageal atresia, renal anomalies, radial dysplasia) was seen among 33 infants of women who were on etanercept during the first trimester of pregnancy.[129, level III] There is no clinical data on the use of ustekinumab in pregnancy.[131, level III]

5.2 Treatment in Lactating Women

Topical agents such as emollients, low-moderate potency topical corticosteroids and dithranol are safe and can be used a first-line in treating psoriasis in lactating women. Topical treatment should be applied after breastfeeding, and washed off thoroughly before the next feed. It is also safe to use ultraviolet B phototherapy but PUVA should be avoided.[128, level III]

Systemic therapies like acitretin, methotrexate, cyclosporine and biologics are to be avoided in lactating women.[127-128, level III] Infliximab is probably safe in breast-feeding as it is undetectable in both infants and breast milk. Etanercept is minimally excreted in breast milk, but systemic absorption is highly unlikely as it is a large protein.[133, level III]

Treatment of a pregnant woman with psoriasis should take into consideration the benefit of the therapy to her and her foetus, and the availability of safe and effective alternatives.

RECOMMENDATIONS 19

- First-line treatment of psoriasis in pregnant and lactating patients should be topical emollient and low-mid potent topical corticosteroids. **(Grade C)**
- Ultraviolet B phototherapy may be offered when psoriasis is extensive or not controlled by topical treatments alone during pregnancy. **(Grade C)**
- Cyclosporine may be used in pregnant women with severe psoriasis. **(Grade C**)
- Cyclosporine should not be used in psoriasis patients who are breast-feeding. **(Grade C)**
- Acitretin and methotrexate must not be used in pregnant and lactating women and should be avoided in those planning pregnancy.**(Grade C)**
- Acitretin should be stopped two years before conception in women. **(Grade C)**
- Methotrexate should be stopped three months before conception in both women and men. **(Grade C)**

6. PSORIATIC ARTHRITIS

Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Early recognition and treatment of PsA are essential to prevent joint damage and physical disability.

6.1 Screening Tools

Various screening tools such as the Psoriasis Epidemiology Screening Tool (PEST), Toronto Psoriatic Arthritis Screen (ToPAS) and Psoriatic Arthritis Screening and Evaluation Tool (PASE) have been proposed to help in the early detection of PsA.[137-139, level III] None of these have been validated and are therefore not recommended for routine use in our local setting. However, early detection of arthritis is important.

RECOMMENDATION 20

Regular assessment for early arthritis should be performed at least annually by looking for relevant signs and symptoms **(Grade C)**

- Significant early morning joint stiffness.
- Joint swelling or dactylitis.
- Spinal pain with significant early morning stiffness.

6.2 Signs and Symptoms

Inflammatory joint symptoms include pain (82 - 90%), early morning stiffness more than 30 minutes (71%), swelling (32 - 68%) and peripheral joint deformity (22%).[2, level III; 140, level III]

Up to 17% of patients complained of inflammatory spinal pain, whilst 30 - 40% presented with dactylitis and peripheral enthesitis in recent onset PsA.[89, level III]

Clinical features in favour of PsA include:[89, level III; 140-142, level III]

- Personal or family history of psoriasis (past or present)
- Distal inter-phalangeal joint (DIPJ) arthritis and asymmetrical distribution of the involved peripheral joints
- Dactylitis, enthesitis or axial skeletal involvement (past or present)
- Extra-articular manifestation (uveitis)

6.3 Investigations

There is no laboratory investigation to confirm the diagnosis of PsA. However, inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein may be helpful. Rheumatoid factor antibody and anti-cyclic citrullinated peptide are usually absent in patients with PsA.[2, level III; 89, level III; 143-145, level III]

Radiographs of the hands and wrists (anteroposterior view), feet (anteroposterior and lateral views) and all symptomatic sites (including axial sites) may aid diagnosis. [89, level III; 142, level III; 145, level III] Radiographs in early phase of disease may be normal. Characteristic radiographic features of PsA include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including 'pencil in cup' deformity and acro-osteolysis, ankylosis, spur formation and spondylitis.

New imaging modalities such as ultrasound and magnetic resonance imaging may help to detect early changes in the joints and periarticular tissues.[89, level III]

There is no single diagnostic test for PsA.

RECOMMENDATION 21

- Diagnosis of Psoriatic Arthritis should be based on both clinical and radiological findings. **(Grade C)**

6.4 CASPAR Classification Criteria

The CIASsification criteria for Psoriatic ARthritis (CASPAR- refer Appendix 8) for the classification of PsA amongst psoriatic patients with inflammatory joint disease have been validated in many centres worldwide such as Europe, United States of America, Canada, Australia, New Zealand, South Africa and Morocco, but not in Asia.[142, level III] It has 98.7% specificity and 91.4% sensitivity for established PsA. However, it is less sensitive (77%) in classifying patients with early (less than 12 months) PsA.[146, level III]

6.5 Clinical Patterns

Moll and Wright classified the patterns of PsA into the following:[147, level III]

- DIPJ arthritis
- Asymmetrical oligoarthritis (less than 5 joints involvement)
- Symmetrical polyarthritis (similar to rheumatoid arthritis)
- Arthritis mutilans (deforming and destructive arthritis)
- Spondyloarthritis (including sacroiliitis and spondylitis)

Oligoarthritis or polyarthritis is the commonest pattern seen in PsA from various studies. These patterns may overlap or change over time, as the disease progresses or with the institution of treatment.[2, level III; 7, level III; 148, level III; 141, level III; 145, level III]

7. REFERRAL

Referral criteria are based on existing referral pathway of Ministry of Health Malaysia.

7.1 Dermatology Referral

Indications for referral

- Diagnostic uncertainty
- Erythrodermic or pustular psoriasis should be referred urgently for specialist assessment and treatment
- Patients who have failed adequate trial of topical therapy for 6 - 12 weeks
- Severe psoriasis that requires phototherapy or systemic therapy

7.2 Rheumatology Referral

Indications for referral

- Diagnostic evaluation of patients with suspected PsA.
- Formulate management plan for PsA.

8. IMPLEMENTATION OF GUIDELINES

Implementation of this CPG is the responsibility of each healthcare provider. Mechansim should be in place to review care provided against the guidelines recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guidelines in individual hospital, units and practices.

a. Facilitating and Limiting Factors

The facilitating factors in implementing these CPG are:-

i. Wide dissemination of these CPG to healthcare providers (hard-copy & soft-copy)

ii. Annual dermatology update course for primary care doctors

iii. Tele-primary care

The limiting factors in the implementation are:-

i. Cost and availability of treatment

ii. Variation in treatment practice and preferences

iii. Lack of culture to measure severity of psoriasis

b. Potential Resource Implications

In implementing recommendations in these CPG, the possible resource implication is additional cost and human resource involved in patient care.

To enhance the utilisation of these CPG on Management of Psoriasis, the following clinical audit indicators for quality management are proposed:-

Percentage of patients with psoriasis assessed annually with BSA/PASI/PGA/DLQI	=	$\frac{\text{Number of patients with psoriasis assessed annually with BSA/PASI/PGA/DLQI}}{\text{Total number of patients with psoriasis}}$	X 100%
Percentage of patients on biologics based on criteria*	=	$\frac{\text{Number of patients on biologics based on criteria}}{\text{Total of patients on biologics}}$	X 100%

REFERENCES

1. Rigopoulos D, Gregoriou S, Katrinaki A, et al. Characteristics of psoriasis in Greece: an epidemiological study of a population in a sunny Mediterranean climate. Eur J Dermatol, 2010 20(2):189-195.
2. Chang CC, Noor Addillah S, Asmah J, et al. Annual Report of the Malaysian Psoriasis Registry 2007-2009, National Dermatology Registry (DermReg), Malaysia, and Clinical Research Centre (CRC), Ministry of Health, Malaysia, 2007-2009.Kuala Lumpur, Malaysia 2011. Available from: http:// www.acrm.org.my/dermreg/.
3. Chang CC, Gangaram HB, Hussein SH. Malaysian Psoriasis Registry - Preliminary report of a pilot study using a newly revised registry form. MMJ, 2008. 63:68 -71.
4. Mallbris L, Larsson P, Bergqvist S, et al. Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. J Invest Dermatol, 2005 124(3):499-504.
5. Siow KY, Safdar NA, Chong KH, et al. A clinical appraisal of patients with psoriasis treated in Seremban General Hospital, Malaysia. MJM, 2004 59(3):330 - 334.
6. Kundakci N, Türsen U, Babiker MO, et al. The evaluation of the sociodemographic and clinical features of Turkish psoriasis patients. Int J Dermatol, 2002 41(4):220-224.
7. Nossent J, Gran JT. Epidemiological and clinical characteristics of psoriatic arthritis in northern Norway. Scand J Rheumatol, 2009. 38(4):251-255.
8. Weiss SC, Kimball AB, Liewehr DJ, et al. Quantifying the harmful effect of psoriasis on health-related quality of life. J Am Acad Dermatol, 2002. 47:512-518.
9. Rapp SR, Feldman SR, Exum L, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999. 41:401-407.
10. Mehta NN, Yu Y, Pinnelas R, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med, 2011 124(8775):e1-6.
11. Mehta NN, Azfar RS, Shin DB, et al. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J, 2010 31(8):1000-1006.
12. Prodanovich S, Kirsner RS, Kravetz JD, et al. Association of Psoriasis With Coronary Artery, Cerebrovascular, and Peripheral Vascular Diseases and Mortality. Arch Dermatol, 2009. 145(6):700-703.
13. Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol, 2006 55 (5):829-835.
14. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA 2006. 296:1735-1741.
15. Prodanovich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol 2005. 52:262-267.
16. Wu Y, Mills D, Bala M. Psoriasis: cardiovascular risk factors and other disease comorbidities. J Drugs Dermatol, 2008 7(4):373-377.
17. Horn EJ, Fox KM, Patel V, et al. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. J Am Acad Dermatol 2007. 57:957-962.
18. Nast A, Erdmann R, Hofelich V, et al. Do guidelines change the way we treat? Studying prescription behaviour among private practitioners before and after the publication of the German Psoriasis Guidelines. Arch Dermatol Res, 2009. 301:553-559.
19. Gudjonsson JE, Elder JT. Psoriasis: epidemiology. Clin Dermatol, 2007. 25:535-546.
20. Tsai TF, Wang TS, Hung ST, et al. Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. J Dermatol Sci, 2011 63(1):40-46.
21. Choon SE, Lai NM, Norshaleyna M, et al. Clinical profile, morbidity and outcome of adult-onset Generalised Pustular Psoriasis: Analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. International J Dermatol, 2013: doi: 10.1111/ijd.12070
22. Icen M, Crowson CS, McEvoy MT, et al. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol, 2009 60(3):394-401.

23. Huerta C, Rivero E, Rodríguez LA. Incidence and Risk Factors for Psoriasis in the General Population. Arch Dermatol, 2007. 143(12):1559-1565.
24. Ljosaa TM, Rustoen T, Mörk C, et al. Skin Pain and Discomfort in Psoriasis: An Exploratory Study of Symptom Prevalence and Characteristics. Acta Derm Venereol 2010. 90:39-45.
25. Mallbris L, Wolk K, Sánchez F, et al. HLA-Cw*0602 associates with a twofold higher prevalence of positive streptococcal throat swab at the onset of psoriasis: a case control study. BMC Dermatol, 2009 29(9):5.
26. Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. J Eur Acad Dermatol Venereol, 2010 24 (Suppl 2):10-16.
27. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. J Am Acad Dermatol, 2012 66(3):369-375.
28. Paul C, Gourraud PA, Bronsard V, et al. Evidence-based recommendations to assess psoriasis severity: systematic literature review and expert opinion of a panel of dermatologists. J Eur Acad Dermatol Venereol, 2010 Suppl 2:2-9.
29. Bronsard V, Paul C, Prey S, et al. What are the best outcome measures for assessing quality of life in plaque type psoriasis? A systematic review of the literature. J Eur Acad Dermatol Venereol, 2010 Suppl 2:17-22.
30. Jankovic S, Raznatovic M, Marinkovic J, et al. Risk factors for psoriasis: A case-control study. J Dermatol, 2009 36(6):328-334.
31. Naldi L, Chatenoud L, Belloni A, et al. Medical history, drug exposure and the risk of psoriasis. Evidence from an Italian case-control study. Dermatology, 2008. 216(2):125-130.
32. Naldi L, Peli L, F P. Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: Results of a case-control study. J Am Acad Dermatol, 2001 44(3):433-438.
33. Katrina W, Lotus M, Per L, et al. Excessive Body Weight and Smoking Associates with a High Risk of Onset of Plaque Psoriasis. Acta Derm Venereol, 2009. 89:492-497.
34. Qureshi AA, Dominguez PL, Choi HK, et al. Alcohol Intake and Risk of Incident Psoriasis in US Women. Arch Dermatol, 2010 146(12):1364-1369.
35. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. Arch Intern Med, 2007 167(15):1670-1675.
36. Naldi L, Chatenoud L, Linder D, et al. Cigarette Smoking, Body Mass Index, and Stressful Life Events as Risk Factors for Psoriasis: Results from an Italian Case-Control Study. J Invest Dermatol 2005. 125:61 -67.
37. Setty AR, Curhan G, Choi HK. Smoking and the risk of psoriasis in women: Nurses' Health Study II. Am J Med, 2007 120(11):953-959.
38. Jankovi S, Raznatovi M, Marinkovi J, et al. Relevance of Psychosomatic Factors in Psoriasis: A Case-control Study. Acta Derm Venereol 2009. 89:364-368.
39. Soltani-Arabshahi R, Wong B, Feng BJ, et al. Obesity in Early Adulthood as a Risk Factor for Psoriatic Arthritis. Arch Dermatol, 2010. 146(7):721-726.
40. Frankel HC, Han J, Li T, et al. The association between physical activity and the risk of incident psoriasis. Arch Dermatol, 2012. 148(8):918-924.
41. Nast A, Rosumeck S, Sammain A, et al. S3-guidelines for the treatment of psoriasis vulgaris--methods report. J Dtsch Dermatol Ges, 2011. 9 (Suppl 2):e64-84.
42. Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol, 2012. 132(3 Pt 1):556-562.
43. Tan WC. Risk of metabolic syndrome in multi-ethnic Malaysian psoriasis patients (unplished Thesis). Kuala Lumpur: Universiti Kebangsaan Malaysia; 2013.
44. Tan CE, Ma S, Wai D, et al. Can we apply the national cholesterol education program adult treatment panel definition of the metabolic syndrome to Asians? Diabetes Care, 2004. 27:1182-1186.

45. Love TJ, Qureshi AA, Karlson EW, et al. Prevalence of the metabolic syndrome in psoriasis: results from the National Health and Nutrition Examination Survey 2003-2006. Arch Dermatol, 2011 147(4):419-424.

46. Prey S, Paul C, Bronsard V, et al. Cardiovascular risk factors in patients with plaque psoriasis: a systematic review of epidemiological studies. J Eur Acad Dermatol Venereol, 2010 24 (Suppl 2):23-30.

47. Huang YH, Yang LC, Hui RY, et al. Relationships between obesity and the clinical severity of psoriasis in Taiwan. J Eur Acad Dermatol Venereol, 2010 24(9):1035-1039.

48. Cohen AD, Weitzman D, Dreiher J. Psoriasis and Hypertension : A Case-Control Study. Acta Derm Venereol 2010. 90:23-26.

49. Li WQ, Han JL, Manson JE, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. Br J Dermatol, 2012 166(4):811-818.

50. Chen YJ, Wu CY, Chen JL, et al. The risk of cancer in patients with Psoriasis: A population based cohort study in Taiwan. J Am Acad Dermatol, 2011 65(1):84-91.

51. Kurd SK, Troxel AB, Crits-Christoph P, et al. The Risk Of Depression, Anxiety and suicidality in patients with psoriasis. Arch Dermatol, 2010. 146(8):891-895.

52. Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol, 2009 23(5):561-565.

53. Watsky KL, Freije L, Leneveu MC. Water-in-oil emollients as steroid-sparing adjunctive therapy in the treatment of psoriasis. Cutis, 1992 50(5):383-386.

54. Mason AR, Mason J, Cork M, et al. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev, 2009 15(2):CD00502.

55. Slutsky JB, Clark RA, Remedios AA, et al. An evidence-based review of the efficacy of coal tar preparations in the treatment of psoriasis and atopic dermatitis. J Drugs Dermatol, 2010 9(10):1258-1264.

56. Alora-Palli MB, Perkins AC, Van Cott A, et al. Efficacy and tolerability of a cosmetically acceptable coal tar solution in the treatment of moderate plaque psoriasis: a controlled comparison with calcipotriene (calcipotriol) cream. Am J Clin Dermatol, 2010. 11(4):275-283.

57. Rushton L, Bagga S, Bevan R, et al. Occupation and cancer in Britain. Br J Cancer, 2010 102(9):1428-1437.

58. Roelofzen JH, Aben KK, Oldenhof UT, et al. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. J Invest Dermatol, 2010 130(4):953-961.

59. Bruner CR, Feldman SR, Ventrapragada M, et al. A systematic review of adverse effects associated with topical treatments for psoriasis. Jr Dermatol Online J, 2003 9(1):2.

60. Bailey EE, Ference EH, Alikhan A, et al. Combination treatments for psoriasis: a systematic review and meta-analysis. Arch Dermatol, 2012 148(4):511-522.

61. Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product .(Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. Br J Dermatol, 2006. 154(6):1155-1160.

62. Jacobi A, Braeutigam M, Mahler V, et al. Pimecrolimus 1% cream in the treatment of facial psoriasis: a 16-week open-label study. Dermatology 2008. 216(2):133-136.

63. Lebowhl M, Freeman AK, Chapman MS, et al. Tacrolimus ointment is effective for facial and intertriginous psoriasis. J Am Acad Dermatol, 2004. 51(5):723-730.

64. Carroll CL, Clarke J, Camacho F, et al. Topical tacrolimus ointment combined with 6% salicylic acid gel for plaque psoriasis treatment. Arch Dermatol, 2005. 141(1):43-46.

65. Medical Advisory Secretariat. Ultraviolet phototherapy management of moderate-to-severe plaque psoriasis: an evidence-based analysis. Ontario Health Technology Assessment Series, 2009. 9((27).

66. Ryan C, Renfro L, Collins P, et al. Clinical and genetic predictors of response to narrowband ultraviolet B for the treatment of chronic plaque psoriasis. Br J Dermatol, 2010 163(5):1056-1063.

67. Kleinpenning MM, Smits T, Boezeman J, et al. Narrowband ultraviolet B therapy in psoriasis: randomized double-blind comparison of high-dose and low-dose irradiation regimens. Br J Dermatol, 2009 161(6):1351-1356.

68. Cameron H, Dawe RS, Yule S, et al. A randomized, observer-blinded trial of twice vs. three times weekly narrowband ultraviolet B phototherapy for chronic plaque psoriasis. Br J Dermatol, 2002 147(5):973-978.

69. Seckin D, Usta I, Yazici Z, et al. Topical 8-methoxypsoralen increases the efficacy of narrowband ultraviolet B in psoriasis. Photodermatol Photoimmunol Photomed, 2009 25(5):237-241.

70. Archier E, Devaux S, Castela E, et al. Efficacy of psoralen UV-A therapy vs. narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol, 2012 (Suppl 3):11-21.

71. Dayal S, Mayanka, Jain VK. Comparative evaluation of NBUVB phototherapy and PUVA photochemotherapy in chronic plaque psoriasis. Indian J Dermatol Venereol Leprol, 2010 76(5):533-537.

72. Dawe RS, Cameron H, Yule S, et al. A randomized controlled trial of narrowband ultraviolet B vs bath-psoralen plus ultraviolet A photochemotherapy for psoriasis. Br J Dermatol, 2003 148(6):1194-1204.

73. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol, 2012. 26 (Suppl 3)):22 - 31.

74. Archier E, Devaux S, Castela E, et al. Ocular damage in patients with psoriasis treated by psoralen UV-A therapy or narrow band UVB therapy: a systematic literature review. J Eur Acad Dermatol Venereol, 2012. 26 (Suppl 3):32 - 35.

75. Gattu S, Pang ML, Pugashetti R, et al. Pilot evaluation of supra-erythemogenic phototherapy with excimer laser in the treatment of patients with moderate to severe plaque psoriasis. J Dermatolog Treat, 2010 21(1):54-60.

76. Feldman SR, Mellen BG, Housman TS, et al. Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. J Am Acad Dermatol, 2002 46(6):900-906.

77. Bansback N, Sizto S, Sun H, et al. Efficacy of systemic treatment for moderate to severe psoriasis: Systematic Review and Meta-analysis. Dermatology 2009. 219:209-218.

78. Saurat JH, Langley RG, Reich K, et al. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. Br J Dermatol, 2011 165(2):399-406.

79. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med, 2003 349(7):658-665.

80. Akhyani M, Chams-Davatchi C, Hemami MR, et al. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. J Eur Acad Dermatol Venereol, 2010 24(12):1447-1451.

81. Ranjan N, Sharma NL, Shanker V, et al. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study. J Dermatolog Treat, 2007. 18(5):295-300.

82. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. Br J Dermatol, 2009 160(3):622-628.

83. Schmitt J, Zhang Z, Wozel G, et al. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severepsoriasis: meta-analysis of randomized controlled trials. Br J Dermatol, 2008 159(3):513-526.

84. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). Br J Dermatol, 2011 165(5):1109-1117.

85. Montaudié H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol, 2011 25 (Suppl 2):12-18.

86. Thomas JA, Aithal GP. Monitoring liver function during methotrexate therapy for psoriasis: are routine biopsies really necessary? Am J Clin Dermatol, 2005. 6(6):357-363.

87. Aithal GP, Haugk B, Das S, et al. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? Aliment Pharmacol Ther, 2004 19(4):391-399.

88. Belzunegui J, Intxausti JJ, De Dios JR, et al. Absence of pulmonary fibrosis in patients with psoriatic arthritis treated with weekly low-dose methotrexate. Clin Exp Rheumatol, 2001. 19(6):727-730.

89. Salliot C, Dernis E, Lavie F, et al. Diagnosis of peripheral psoriatic arthritis : Recommendations for clinical practice based on data from the literature and experts opinion. Joint Bone Spine, 2009. 76:532-539.

90. Kragballe K, Jansen CT, Geiger JM, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of Nordic multicentre study. Acta Derm Venereol, 1989. 69(1):35-40.

91. Pearce DJ, Klinger S, Ziel KK, et al. Low-dose acitretin is associated with fewer adverse events than high-dose acitretin in the treatment of psoriasis. Arch Dermatol, 2006 142(8):1000-1004.

92. Buccheri L, Katchen BR, Karter AJ, et al. Acitretin Therapy Is Effective for Psoriasis Associated With Human Immunodeficiency Virus Infection. Arch Dermatol, 1997. 133(6):711-715.

93. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. J Am Acad Dermatol, 2010. 63(6):949-972.

94. Beissert S, Pauser S, Sticherling M, et al. A comparison of mycophenolate mofetil with ciclosporine for the treatment of chronic plaque-type psoriasis. Dermatology, 2009. 219(2):126-132.

95. Pedraz J, Daudén E, Delgado-Jiménez Y, et al. Sequential study on the treatment of moderate-to-severe chronic plaque psoriasis with mycophenolate mofetil and cyclosporin. J Eur Acad Dermatol Venereol, 2006 20(6):702-706.

96. Dogan B, Karabudak O, Harmanyeri Y. Antistreptococcal treatment of guttate psoriasis: a controlled study. Int J Dermatol, 2008 47(9):950-952.

97. Sharma VK, Dutta B, Ramam M. Hydroxyurea as an alternative therapy for psoriasis. Indian J Dermatol Venereol Leprol, 2004 70(1):13-17

98. Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum, 2012. 71:319-326.

99. Gupta AK, Ellis CN, Siegel MT, et al. Sulfasalazine improves psoriasis. A double-blind analysis. Arch Dermatol 1990. 126(4):487-493.

100. Reich K, Hummel KM, Beckmann I, et al. Treatment of severe psoriasis and psoriatic arthritis with leflunomide. Br J Dermatol, 2002. 146:335-336.

101. Cuchacovich M, Soto L. Leflunomide decreases joint erosions and induces reparative changes in a patient with psoriatic arthritis. Ann Rheum Dis, 2002. 61:942-943.

102. Tlacuilo-Parra JA, Guevara-Gutierrez E, Rodri-Guezcastellanos MA, et al. Leflunomide in the treatment of psoriasis: results of a phase II open trial. Br J Dermatol, 2004. 150:970-976.

103. Kaltwasser PJ, Nash P, Gladman D, et al. Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis : A Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Arthritis & Rheumatism, 2004. 50(6):1939-1950

104. Reich K, Burden AD, Eaton JN, et al. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. Br J Dermatol, 2012 166(1):179-188.

105. Brimhall AK, King LN, Licciardone JC, et al. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. Br J Dermatol, 2008 159(2):274-285.

106. Langley RG, Strober BE, Gu Y, et al. Benefit-risk assessment of tumour necrosis factor antagonists in the treatment of psoriasis. Br J Dermatol, 2010. 162:1349-1358.

107. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol, 2007. 56(31):e1-31.

108. Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol, 2004. 51:534-542.

109. Griffiths CEM, Strober BE, van de Kerkhof P, et al. Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis. N Engl J Med, 2010. 362(2):118-128.

110. Langley RG, Gupta A, Papp K, et al. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. Dermatology, 2011. 222(2):148-156.

111. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med, 2003 349(21):2014-2022.

112. LuckaTC,PathiranaD,SammainA,etal.EfficacyofsystemictherapiesformoderatetoseverepsoriasisasystematicreviewandmetaanalysisoflongtermtreatmentJEurAcadDermatolVenereol,2012 26(11):1331-1344.

113. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview (Review). Cochrane Database Syst Rev, 2011 16(2):CD008794.

114. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis, 2010 69(3):522-528.

115. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum, 2005 52(6):1766-1772.

116. Abramson A, Menter A, Perrillo R. Psoriasis, hepatitis B, and the tumor necrosis factor-alpha inhibitory agents: a review and recommendations for management. J Am Acad Dermatol, 2012. 67(6):1349-1361.

117. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet, 2008 371(9625):1665-1674.

118. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet, 2008 371(9625):1675-1684.

119. Driessen RJB, Bisschops LA, Adang EMM, et al. The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics. Br J Dermatol, 2010. 162:1324-1329.

120. Fonia A, Jackson K, Lereun C, et al. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol, 2010 163(4):807-816.

121. Greiner RA, Braathen LR. Cost-effectiveness of biologics for moderate-to-severe psoriasis from the perspective of the Swiss healthcare system. Eur J Dermatol, 2009 19(5):494-499.

122. Ferrándiz C, García A, Blasco AJ, et al. Cost-efficacy of adalimumab, etanercept, infliximab and ustekinumab for moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol, 2012 26(6):768-777.

123. Sizto S, Bansback N, Feldman SR, et al. Economic evaluation of systemic therapies for moderate to severe psoriasis. Br J Dermatol, 2009 160(6):1264-1272.

124. Jensen P, Skov L, Zachariae C. Systemic combination treatment for psoriasis: a review. Acta Derm Venereol, 2010 90(4):341-349.

125. Koo JY. Using topical multimodal strategies for patients with psoriasis. Cutis, 2007 79(1 Suppl 2):11-17.

126. Foley PA, Quirk C, Sullivan JR, et al. Combining etanercept with traditional agents in the treatment of psoriasis: a review of the clinical evidence. J Eur Acad Dermatol Venereol, 2010 24(10):1135-1143.

127. Hale EK, MK P. Dermatologic agents during pregnancy and lactation: an update and clinical review. Int J Dermatol, 2002 41(4):197-203.

128. Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. BMJ 2007. 334:1218-1220.

129. Lam J, Polifka JE, MA D. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. J Am Acad Dermatol, 2008. 59:295-315.

130. Chi CC, Lee CW, Wojnarowska F, et al. Safety of topical corticosteroids in pregnancy. Cochrane Database Syst Rev, 2009 (3):CD007346.

131. Bae YS, Van Voorhees AS, Hsu S, et al. Review of treatme nt options for psoriasis in pregnant or lactating women: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol, 2012 67(3):459-477.

132. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J Am Acad Dermatol, 2010 62(1):114-135.

133. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology, 2000 62(6):385-392.

134. Beghin D, Cournot MP, Vauzelle C, et al. Paternal exposure to methotrexate and pregnancy outcomes. J Rheumatol, 2011 38(4):628-632.

135. Puig L, Barco D, Alomar A. Treatment of psoriasis with anti-TNF drugs during pregnancy: case report and review of the literature. Dermatology, 2010. 220(1):71-76.

136. Reich K, Griffiths C, Barker J, et al. Recommendations for the long-term treatment of psoriasis with infliximab: a dermatology expert group consensus. Dermatology, 2008. 217(3):268-275.

137. Khraishi M, Landells I, G M. The self-administered Psoriasis and Arthritis Screening Questionnaire (PASQ): A sensitive and specific tool for the diagnosis of early and established psoriatic arthritis. Psoriasis Forum, 2010. 16(2):9-16.

138. Gladman DD, Schentag CT, Tom BD, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto Psoriatic Arthritis Screen (ToPAS). Ann Rheum Dis, 2009. 69(497-501).

139. Dominguez PL, Husni ME, Holt EW, et al. Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire. Arch Dermatol Res, 2009 301(8):573-579.

140. Gisondi P, Girolomoni G, Sampogna F, et al. Prevalence of psoriatic arthritis and joint complaints in a large population of Italian patients hospitalised for psoriasis. Eur J Dermatol 2005. 15(4):279-283.

141. Lindqvist URC, Alenius GM, Husmark T, et al. The Swedish early psoriatic arthritis register - 2 year follow-up: a comparison with early rheumatoid arthritis. J Rheumatol, 2008. 35(4):668-673.

142. 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):2665-2673.

143. Alenius GM, Berglin E, Dahlqvist SR. Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without inflammation. Ann of Rheum Dis, 2006. 65:398-400.

144. Bogliolo L, Alpini C, Caporali R, et al. Antibodies to cyclic citrullinated peptides in psoriatic arthritis. J Rheum 2005. 32(3):511-515.

145. Alenius GM, Stenberg B, Stenlund H, et al. Inflammatory joint manifestations are prevalent in psoriasis: prevalence study of joint and axial involvement in psoriatic patients, and evaluation of a psoriatic and arthritic questionnaire. J Rheumatol, 2002. 29(12):2577-2582.

146. D'Angelo S, Mennillo GA, Cutro MS, et al. Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. J Rheumatol, 2009 36(2):368-370.

147. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum, 1973. 3(1):55-78.

148. Chembalingam G, Gun SC, D'Souza , et al. Pattern of joint involvement in psoriatic arthropathy (PsA) in Hospital Tuanku Jaafar Seremban, Negeri Sembilan, Malaysia Int J Rheum Dis, 2008. 11(suppl 1):A361.

APPENDIX 1

EXAMPLE OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limit to english, human and 2001 to current

Cal tar

1. Psoriasis/
2. psorias$.tw.
3. 1 or 2
4. coal tar/
5. (coal adj1 tar).tw.
6. 4 or 5
7. 3 and 6
8. Limit 7

Topical corticosteroids

1. Psoriasis/
2. psorias$.tw.
3. 1 or 2
4. glucocorticoids/ or fluocinolone acetonide/ or administration, topical/ or betamethasone/
5. corticoids.tw.
6. corticosteroids.tw.
7. fluocinolone acetonide.tw.
8. synalar.tw.
9. betamethasone.tw.
10. clobetasone.tw.
11. hydrocortisone.tw.
12. (topical adj1 administration).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13
15. limit 14

Phototherapy

1. Psoriasis/ 2.Psorias$.tw.
3. 1 or 2
4. Phototherapy/
5. Phototherap$.tw.

Salicylic Acid

1. Psoriasis/
2. psorias*.tw.
3. 1 or 2
4. Salicylic Acids/
5. (salicyclic adj1 acid).tw.
6. 4 or 5
7. 3 and 6
8. limit 7
6. Light therap$.tw.
7. 4 or 5 or 6
8. 3 and 7

Vitamin D analogues

1. psoriasis/
2. psorias$.tw.
3. 1 and 2
4. calcitriol/
5. calcitriol.tw.
6. 1,25 dihydroxyvitamin d3.tw.
7. silkis.tw.
8. calcipotriol.tw.
9. vitamin D analogue$.tw.
10. tacalcitol.tw.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. Limit 12

Combination Treatment

1. Psoriasis/
2. psorias$.tw.
3. 1 or 2
4. Drug Therapy, Combination/
5. polytherap$ drug$.tw.
6. 4 or 5
7. 3 AND 6

Dithranol

1. Psoriasis/
2. psorias*.tw.
3. 1 or 2
4. Anthralin/
5. anthralin.tw.
6. dithranol.tw.
7. 4 or 5 or 6
8. 3 and 7
9. limit 8

Tacrolimus or pimecrolimus

1 Psoriasis/
2 psorias*.tw.
3 1 or 2
4 Tacrolimus/
5 tacrolimus.tw.
6 pimecrolimus.tw.
7 4 or 5 or 6
8 3 and 7
9. limit 8

Biologic

1. Psoriasis/
2. psorias$.tw.
3. 1 or 2
4. adalimumab.tw.
5. alefacept.tw.
6. etanercept.tw.
7. ustekinumab.tw.
8. golimumab.tw.
9. infliximab.tw.
10. biologic.tw.
11. t cell modulator.tw.
12. tumour necrosis factor alpha inhibitor.tw.
13. cytokine inhibitor.tw.
14. certolizumab.tw.
15. tocilizumab.tw.
16. or 4-15
17. 3 and 16
18. limit 17

Systemic Treatment

1. Psoriasis/
2. psorias$.tw.
3. 1 or 2
4. Methotrexate/
5. methotrexate.tw.
6. Retinoids/
7. Retinoids.tw.
8. cyclosporin$ a.tw.
9. neoral.tw.
10. c#closporin$.tw.
11. Cyclosporine/12. Steroids/
13. Prednisolone/
14. Prednisone/
15. steroid.tw.
16. prednisolone.tw.
17. prednisone.tw.
18. Hydrocortisone/
19. hydrocortisone.tw.
20. Methylprednisolone/
21. Methylprednisolone.tw.
22. Triamcinolone/
23. Triamcinolone.tw.
24. Dexamethasone/
25. Dexamethasone.tw.
26. Sulfasalazine/
27. salazopyrin.tw.
28. Hydroxyurea/
29. hydroxyurea.tw.
30. hydroxycarbamid$.tw.
31. Mycophenolic Acid/
32. (mycophenolic adj1 acid).tw.
33. Mycophenolate mofetil.tw.
34. Acitretin/
35. sulphasalazine.tw.
36. sulfasalazine.tw.
37. acitretin.tw.
38. 13-cis-acitretin.tw.
39. Neotigason.tw.
40. Azathioprine/
41. Azathioprine.tw.
42. Imuran.tw.
43. Fumarates/
44. (fumaric acid adj1 esters).tw.
45. fumarates.tw.
46. Antistreptococcal.tw.
47. Anti-Bacterial Agents/
48. Antibacterial.tw.
49. Streptococcal Infections/
50. Antibiotic.tw.
51. Antistreptococcal.tw.
52. or/4-51
53. 3 and 52
54. limit 53

APPENDIX 2

CLINICAL QUESTIONS

1. INTRODUCTION

- What is the epidemiology of psoriasis?

2. ASSESSMENT AND DIAGNOSIS

- What are the clinical characteristics?
- How is severity being assessed?
- What are the risk and aggravating factors?
- What are the investigations?

3. CO-MORBIDITIES

- What are the co-morbidities associated with psoriasis?

4. TREATMENT

- Is coal tar effective and safe in the treatment of psoriasis?
- Are topical corticosteroids effective and safe in the treatment of psoriasis?
- Are topical vitamin D analogues effective and safe for the treatment of psoriasis?
- Is salicylic acid effective and safe in the treatment of psoriasis?
- Is dithranol effective and safe in the treatment of psoriasis?
- Is tacrolimus or pimecrolimus effective and safe for the treatment of psoriasis?
- Is systemic treatment (Methotrexate, Cyclosporin, Retinoids / Acitretin, Hydroxyurea Fumaric acid ester / Fumarates, Corticosteroid, Azathioprine, Mycophenolic mofetil, Leflunomide, Sulfasalazine / Salazopyrine, Antibiotic / Antistreptococcal) safe and effective in treatment of plaque psoriasis?
- Are Biological Agents (Alefacept, Infliximab, Adalimumab, Etanercept, Golimumab, Ustekinumab) safe and effective in treatment of psoriasis?
- Is phototherapy safe and effective in treatment of psoriasis?
- Is combination treatment safe and effective in the treatment of psoriasis?

5. SPECIAL CONDITIONS

- What are the treatments for pregnant and lactating patients with psoriasis?

6. PSORIATIC ARTHRITIS

- What are the clinical patterns in psoriatic arthritis?
- What are the investigations in psoriatic arthritis (laboratory tests; radiological studies)?
- What are the screening tools in psoriatic arthritis?
- What are the signs and symptoms in psoriatic arthritis?

7. REFFERRAL AND FOLLOW-UP

- What are the criteria to refer patients with psoriasis to Dermatologist or Rheumatologist?

Recommended Medication Dosing, Side Effects and Contraindications

DRUG	RECOMMENDED DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTION	DRUG INTERACTION	PREGNANCY CATEGORY
TOPICAL COSTICOSTEROIDS						
Mild Hydrocortisone 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 lesions, in rosacea, and in perioral dermatitis	Avoid prolonged use on the face		C
Moderate Betamethasone 17-Valerate 0.025% Cream / Ointment						
Clobetasone Butyrate 0.05% Cream / Ointment						
Potent Betamethasone 17- Valerate 0.1% Cream / Ointment				Avoid use on face and body folds Limit continuous use to <4 weeks Limit to 60g/week		
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 Limit to 30 g/week		
TAR–BASED PREPARATIONS		Dermatitis, folliculitis, irritation, photosensitivity	Avoid in acutely inflammed lesions, and pustular psoriasis	Avoid contact with eyes, genital / rectal areas Avoid use in 1st trimester		

DRUG	RECOMMENDED DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTION	DRUG INTERACTION	PREGNANCY CATEGORY
TOPICAL VITAMIN D ANALOGUE Calcipotriol 50 mcg/g Cream / Ointment	Twice daily	Itching, erythema, burning, paraesthesia, dermatitis, photosensitivity	Hypercalcemia or evidence of vitamin D toxicity;	Avoid use on face; avoid excessive exposure to sunlight and sunlamps; pregnancy; breast feeding		**C**
Calcipotriol 50 mcg/ml Scalp Solution						
Calcipotriol Hydrate 50 mcg/g & Betamethasone Dipropionate 0.5 mg/g Ointment / Gel	Once daily	Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity				
DITHRANOL PREPARATIONS	0.1-0.5% suitable for overnight treatment for skin 1-2% short contact therapy 30 min -1 hour	Local burning sensation and irritation; stains skin, hair and fabrics	Acutely inflammed and pustular psoriasis	Avoid use near eyes and sensitive areas of skin		**C**
SALICYCLIC ACID 2-10% CREAM / OINTMENT	Twice daily	Sensitivity, drying, irritation, salicylism with excessive use		Avoid broken or inflamed skin		**C**

DRUG	RECOMMENDED DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTION	DRUG INTERACTION	PREGNANCY CATEGORY
SYSTEMIC AGENTS						
Acitretin	0.5 to 1 mg/kg body wt/day Max: 75 mg/day	Cheilitis, xerosis, alopecia, skin peeling, stickiness, paronychia, periungual pyogenic granuloma pruritus, hyperlipidemia, transaminitis, hyperaesthesia	Pregnancy or intention to become pregnant, breast feeding, hypersensitivity, severe hepatic or renal dysfunction, concomitant use with methotrexate or tetracyclines	Avoid pregnancy for at least 1 month before, during, and for at least 3 years after treatment	Alcohol, methotrexate, tetracyclines, tigecycline, vitamin A, contraceptives	**X**
Cyclosporine	2.5mg- 5 mg/kg body wt/day divided twice daily	Hypertension, hyperuricaemia, hyperkalaemia, hypomagnesaemia, hyperlipidaemia, oedema, headache, hypertrichosis, nausea, diarrhoea, tremor, renal dysfunction, infections	Hypersensitivity, abnormal renal function, uncontrolled hypertension, malignancies, concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, or radiation therapy	Limit use to 2 years, monitor renal function closely, liver function, blood pressure, hyperuricaemia, serum magnesium; pregnancy and breast feeding, acute porphyria, avoid excessive exposure to UV light, including sunlight	ACE inhibitors, aliskiren, allopurinol, BCG, bosentan, calcium channel blockers, ivabradine, statins, methotrexate, mifepristone, phenytoin, potassium-sparing diuretics, live vaccines, vincristine	**C**

DRUG	RECOMMENDED DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTION	DRUG INTERACTION	PREGNANCY CATEGORY
Methotrexate	Oral, IM or SC: 10-20mg/ dose once weekly	Nausea & vomiting, malaise, headache, hepatoxicity, mucositis, myelosuppression, lung fibrosis, immunosuppression	Hypersensitivity, pregnancy, pre- existing liver disease or blood dyscrasias	Chronic alcoholism, obesity, diabetes, Hep B & C, renal insufficiency	Acitretin, BCG, clozapine, cyclosporine, loop diuretics, NSAIDs sulfonamides, trimethoprim	**X**
BIOLOGICS						
Adalimumab	Loading dose: 80mg Maintenance dose: 40mg every other week beginning 1 week after initial dose	Opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, haematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction	**Absolute** Active infection including tuberculosis, malignancy, congestive cardiac failure class 3 or 4, demyelinating diseases **Relative** History of tuberculosis/ malignancy, HIV infection, Hepatitis B/C, congestive cardiac failure class 1 or 2, pregnancy or breast feeding, prior PUVA (>200 sessions) and UVB (>350 sessions) exposure	Biologics should be discontinued: ❍ in pregnancy ❍ prior to major surgery (6 weeks for infliximab; 4 weeks entanercept; 10 weeks adalimumab and 12 weeks ustekinumab) Patient should not receive live or live attenuated vaccine <2 weeks before, during and 6 months after biologics discontinuation	Abatacept, anakinra, BCG, leflunomide, live vaccines	**B**
Etanercept	25-50mg twice weekly					

DRUG	RECOMMENDED DOSAGE	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL PRECAUTION	DRUG INTERACTION	PREGNANCY CATEGORY
Infliximab	5mg/kg at 0, 2 and 6 weeks followed by 5mg/kg every 8 weeks thereafter	Opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, haematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction	**Absolute** Active infection including tuberculosis, malignancy, congestive cardiac failure class 3 or 4, demyelinating diseases **Relative** History of tuberculosis/ malignancy, HIV infection, Hepatitis B/C, congestive cardiac failure class 1 or 2, pregnancy or breast feeding, prior PUVA (>200 sessions) and UVB (>350 sessions) exposure	Biologics should be discontinued: ❍ in pregnancy ❍ prior to major surgery (6 weeks for infliximab; 4 weeks entanercept; 10 weeks adalimumab and 12 weeks ustekinumab) Patient should not receive live or live attenuated vaccine <2 weeks before, during and 6 months after biologics discontinuation	Abatacept, anakinra, BCG, leflunomide, live vaccines	**B**
Ustekinumab	45mg for patients weighing ≤100kg and 90mg for patients weighing >100kg given at weeks 0 and 4 then every 12 weeks					

Source: (1)Thomson Reuters. Micromedex®1.0 (Healthcare Series). Greenwood Village Thomson Reuters; 2011; (2) British National Formulary 61March 2011, http://filepost.com/files/832f2e13/British_National_Formulary_61.pdf; (3) Product Pack

APPENDIX 4

PSORIASIS PHYSICIAN GLOBAL ASSESSMENT (PGA)

Score	Definition	Morphological Description
0=Clear	Clear, except for residual discoloration	• 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 less than 5% of the lesion
2 = Mild disease	Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 2	• 2 (induration)=mild plaque elevation, ~1 mm • 2 (erythema)=light red coloration • 2 (scaling)=mild, fine scale predominates
3 = Moderate disease	Majority of lesions have individual scores for induration, erythema and scaling (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 induration, erythema and scaling (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 induration, erythema and scaling (IES) that average 5	• 5 (induration)=severe plaque elevation, ~2.5 mm or more • 5 (erythema)=dusky to deep red coloration • 5 (scaling)=very thick tenacious scale predominates

Source: Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System physician's Global Assessment. J Am Acad Dermatol. 2004 Oct; 51(4):563-569

APPENDIX 5

PSORIASIS AREA AND SEVERITY INDEX (PASI)

Symptom Score

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

Area Score

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

Area Score

Symptom Score	Head (H)	Trunk (T)	Upper Limbs (UL)	Lower Limbs (LL)
Erythema (E)				
Induration (I)				
Scaling (S)				
Sum=E + I + S				
Area Score				
Sum x Area=				
Constant factor	0.1	0.3	0.2	0.4

PASI Score	

APPENDIX 6

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**?	A lot A little Not at all	☐ ☐ ☐	
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 A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
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 A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

DERMATOLOGY LIFE QUALITY INDEX

INSTRUCTIONS FOR USE

The Dermatology Life Quality Index 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

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 the DLQI

The DLQI can be analysed under six headings as follows:

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 School	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.

APPENDIX 7

PRETREATMENT ASSESSMENT

History and examination to exclude the following:

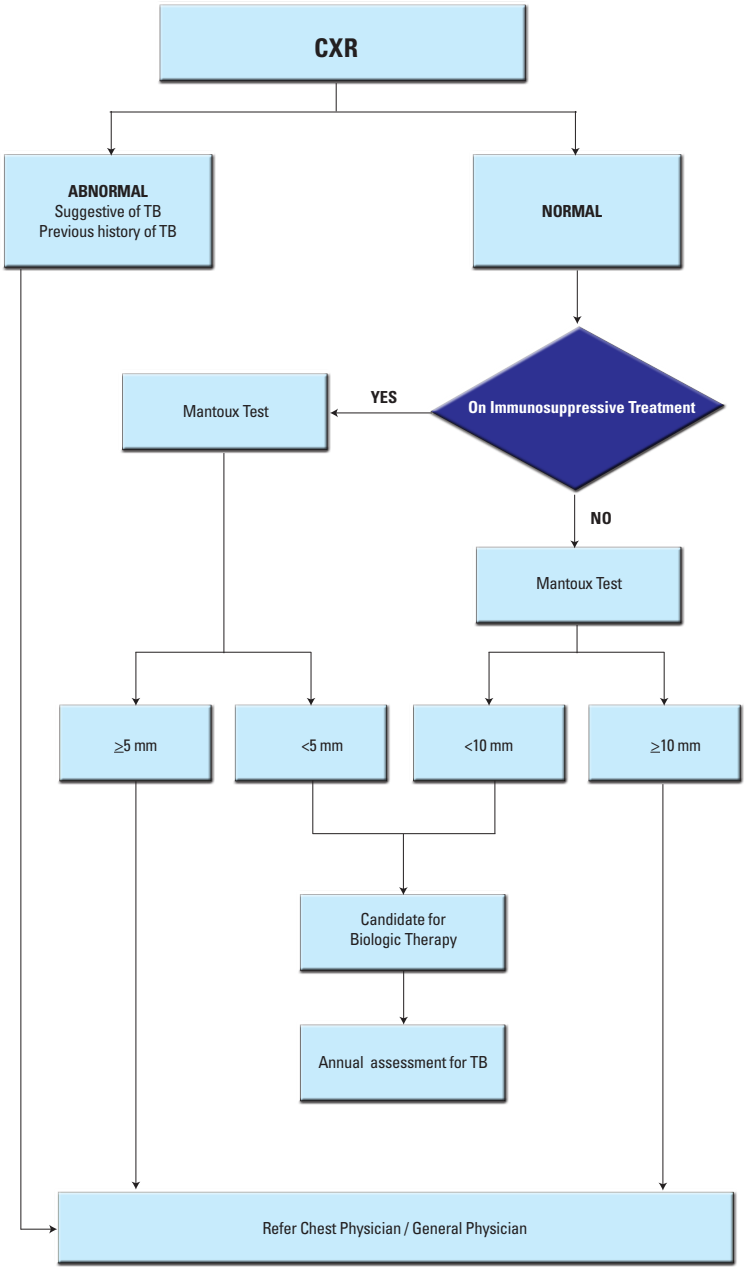
- Current and previous history of TB infection
- Current and previous history of malignancy
- Active infection
- HIV infection
- Hepatitis B/C
- Congestive heart failure
- Demyelinating disease
- Pregnancy
- Intention to get pregnant
- Breast-feeding

Investigations

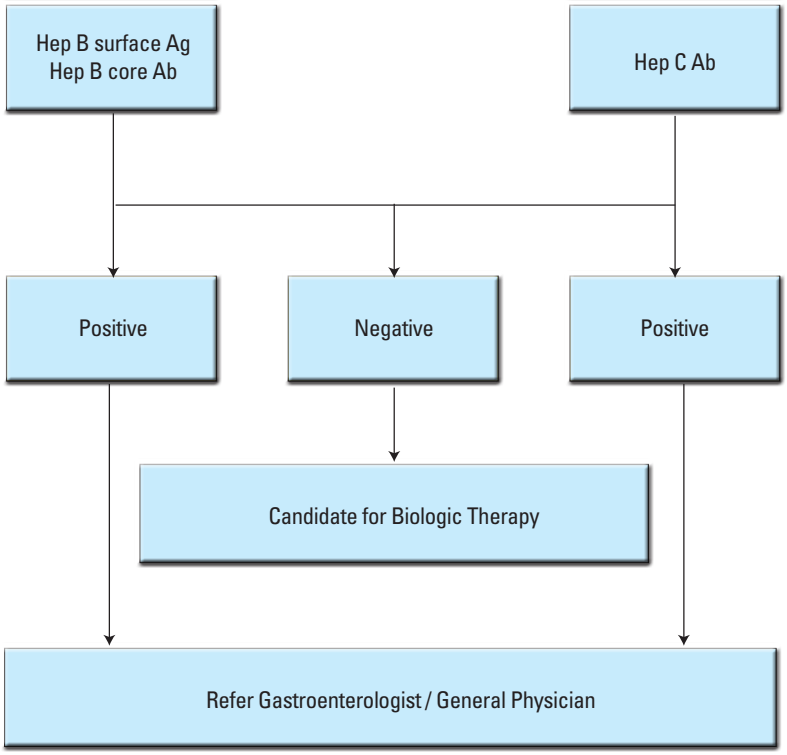
- FBC
- ESR
- CRP
- UFEME
- LFT
- FLP
- FBS
- RP
- HBsAg – If positive refer Gastroenterologist/General Physician
- Hepatitis B core antibody- If positive refer Gastroenterologist/General Physician
- HCV Ab - If positive refer Gastroenterologist/General Physician
- HIV antibody
- ANA – If positive to refer Rheumatologist/General Physician
- CXR
- Mantoux test
- Interferon gamma release assay if indicated
- Urine pregnancy test (UPT)

Patient education and counseling

ALGORITHM FOR PRETREATMENT ASSESSEMENT OF TUBERCULOSIS



ALGORITHM FOR PRETREATMENT ASSESSMENT OF HEPATITIS B AND C INFECTION



APPENDIX 8

The CASPAR Criteria*

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories:

1. Evidence of current psoriasis*, a personal history of psoriasis**, or a family history of psoriasis***.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

*The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

- Current psoriasis is assigned a score of 2
- All other features are assigned a score of 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.

LIST OF ABBREVIATIONS

ACCEPT	Efficacy and Safety of Ustekinumab Compared to Etanercept in the Treatment of Subjects with Moderate to Severe Plaque Psoriasis
AEs	Adverse Events
ANA	Antinuclear Antibody
ARR	Absolute Risk Reductions
BCC	Basal Cell Carcinoma
BIOBADASER	Spanish Society of Rheumatology Database on Biologic Producta
BMI	Body Mass Index
BSA	Body Surface Area
BSRBR	British Society for Rheumatology Biologics Registry
bw	Body Weight
CI	Confidence Interval
CHAMPION	Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis
CHF	France currency
cm	Centimeter
CPG	Clinical Practice Guidelines
CV	Cardiovascular
DIPJ	Distal Inter-Phalangeal Joint
DG	Development Group
DLQI	Dermatology Life Quality Index
g	Gram
HDL	High-Density Lipoprotein
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
IRR	Incidence Rate Ratio
LCD	Liquor carbonis distillate
LFT	Liver function test
MaHTAS	Malaysian Health Technology Assessment Section
MED	Minimal Erythema Dose
mg	Milligrams
MI	Myocardiac Infarction
mmol/L	Millimoles per Litre
mmHg	Millimeter of Mercury
MOH	Ministry of Health Malaysia
NBUVB	Narrow Band Ultraviolet B
NHS	National Health Service

NNT	Number Needed to Treat
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
OR	Odd Ratio
P	P Value
PASI	Psoriasis Area and Severity Index
PDI	Psoriasis Disability Index
PPPY	Per patient per year
PGA	Psoriasis Global Assessment
PHOENIX-1	Efficacy and safety of Ustekinumab, a human interleukin 12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial
PHOENIX-2	Efficacy and safety of Ustekinumab, a human interleukin 12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial
PsA	Psoriatic Arthritis
PUVA	psoralen plus Ultraviolet A
pys	Person-years
QALYs	Quality Adjusted Life Years
QoL	Quality of Life
RC	Review Committee
RCT	Randomised Control Trial
RD	Risk Difference
RESTORE-1	Efficacy and safety of infliximab vs methotrexate in patients with moderate-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial
REVEAL	Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III tria
RR	Risk Ratio
SAEs	Seriou Adverse Events
SELUVB	Selective Band Ultraviolet B
SCC	Squamous cell carcinoma
SF 36	Short Form 36
SIR	Standardized Incidence Ratios
SMD	Standardized Mean Difference
SR	Systematic Review
TAEs	Total Adverse Events
US	United States of America
UK	United Kingdom
UVA	Ultraviolet A
UVB	Ultraviolet B
vs	Versus

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