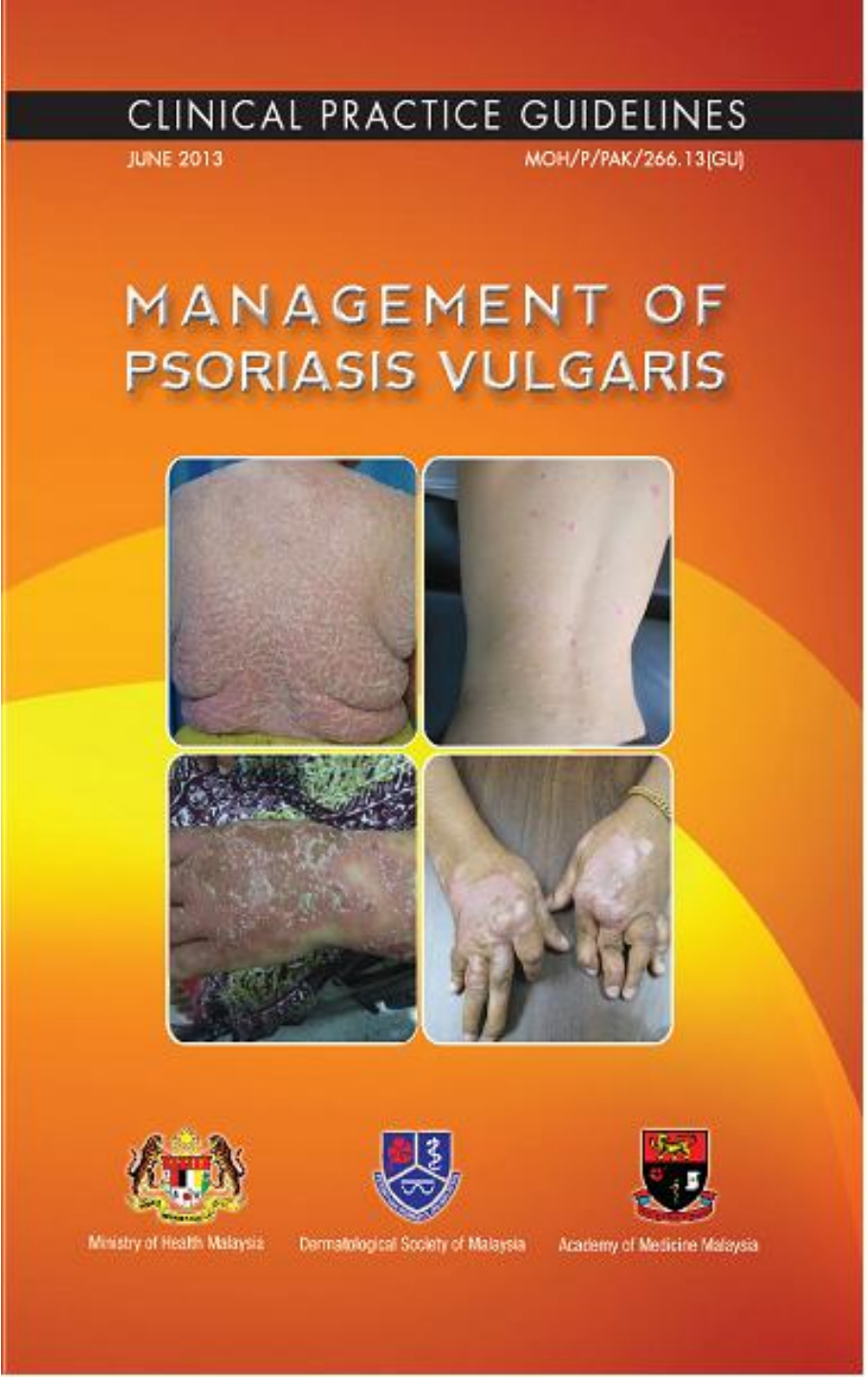

Biologics

Clinical Practice Guidelines Management of Psoriasis Development Group

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Learning Objectives

- To know the indications and eligibility criteria of biologics in treating moderate to severe psoriasis
- To know the contraindications of biologics before initiating this treatment
- To know the efficacy of biologics in treating moderate to severe psoriasis
- To know the side effect of biologics during and after the treatment
- To know the cost effectiveness of different type of biologics

Biologics Therapy

- Biologics are bioengineered protein designed to block specific molecular steps important in the pathogenesis of psoriasis
- It can be divided into:

1) T cell modulator
   - Alefecept (Amevive®)
   - Efalizumab (Raptiva®)-withdrawn in 4/2009

2) Tumour necrosis factor-α inhibitor
   - *Etanercept (Enbrel®)*
   - *Infliximab (Remicade®)*
   - *Adalimumab (Humira®)*

3) Cytokine inhibitor
   - *Ustekinumab (Stelara®)*

Drug name	Trade name	Mechanism	FDA approval for psoriasis
T-cell modulator			
Alefacept	Amevive®	Dimeric fusion protein of CD2/LFA3 linked to Fc portion of human IgG1	2003
Efalizumab	Raptiva®	Recombinant humanized monoclonal antibody against LFA-1	Withdrawn in 4/2009
TNF-α inhibitor			
Etanercept	Enbrel®	Dimeric fusion protein linked to Fc portion of human IgG1	2004
Infliximab	Remicade®	Chimeric human IgG1 monoclonal antibody	2006
Adalimumab	Humira®	Recombinant human IgG1 monoclonal antibody	2008
Cytokine inhibitor			
Ustekinumab	Stelara®	IL-12 and IL-23 blocker	2009

Types of Biologics available in Malaysia for psoriasis

Adalimumab

Infliximab

Etanercept

Ustekinumab

Eligibility and Indication

- Patients with psoriasis may be considered for biologics 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)

Pretreatment Assessment

- All potential patients for biologics intervention should undergo

1. General pretreatment assessment
   - Detailed history and examination to exclude conditions that are contraindicated for biologics
2. Laboratory investigations
3. Intensive counseling and be given adequate information about the medication, after which they sign the informed consent form

Investigations

1. FBC
2. ESR
3. CRP
4. UFEME
5. LFT
6. FLP
7. FBS
8. RP
9. HepBsAg
10. HCV Ab
11. HIV
12. ANA
13. CXR
14. Mantoux test
15. Interferon gamma release assay (if indicated)
16. Urine pregnancy test (UPT)

Efficacy

There are strong and consistent evidences on the efficacy of biologics in the treatment of moderate to severe plaque psoriasis

Types of Biologics	Dosing Schedule	Expected Onset of Clinical Effect (week)	Review of response (week)	Efficacy at week 10 to 16 (PASI 75)	Efficacy at week 48 - 52 (PASI 75)
Infliximab[104,level I; 77,level I; 105, level I; 113, level I	Intravenous 5 mg/kg at week 0,2,6 and then every 8 weeks	2	10	75.5 to 87.9	80
Ustekinumab[114, level I, 115, level I;116	BW<100kg: Subcutaneous 45 mg at week 0,4 and then every 12 weeks	2	12	69	71
	BW≥100kg: Subcutaneous 90 mg at week 0,4 and then every 12 weeks	2	12	74	79
Adalimumab[104,level I; 77,level I, 107, level I;117, level 1	Subcutaneous 80 mg at week 0 then 40 mg every 2 weeks	4	16	58 to 71	84
Etanercept[104,level I; 77,level I; 105, level I	Subcutaneous 25 mg or 50 mg biweekly up to 24 weeks	12	12	30 to 39 (25 mg) 47 to 54 (50 mg)	63 (week 48)

Side Effect

Common adverse effects (≥1 to 10 per 100 patients)

Adverse effect	Infliximab	Etanercept	Adalimumab	Ustekinumab
Upper respiratory tract infection	√	√	√	√
Injection site reactions	√ (acute infusion reactions with fever, chills, nausea)	√	√	√
Headache	√	NA	√	√
Pruritus	√	√	NA	NA
Urticaria	√	NA	NA	NA
Elevated Transaminases	√	NA	NA	√

Side Effect

Uncommon but severe adverse effects requiring hospital admission

Adverse effect	Infliximab	Etanercept	Adalimumab	Ustekinumab
Severe infections	√	√	√	√
Reactivation of latent TB	√	√	√	√
New onset or exacerbation of demyelinating disorders*	√	√	√	NA
Possible increased risk of malignancy*	√	√	√	√
Drug-induced lupus	√	√	√	NA
Exacerbation of congestive heart failure	√	√	√	√
Vasculitis	√	√	√	√
Haematologic events (Pancytopaenia)	√	√	√	√
HBV reactivation	√	√	√	√
Liver failure	√	√	NA	NA

Side effect

- Cochrane systematic review by Singh et al (2011)
  - Adverse effects of nine biologics including infliximab, etanercept, and adalimumab were pooled
  - When compared to control, biologics were associated with higher rate of
    - TAEs (OR = 1.2, 95%CI 1.1 to1.3)
    - Withdrawals due to AEs (OR = 1.3, 95% CI 1.1 to1.6)
    - Tuberculosis reactivation (OR = 4.7, 95% CI 1.2 to 18.6)
  - No significant difference in terms of
    - SAEs,
    - Serious infection,
    - Lymphoma
    - Congestive cardiac failure

Reactivation of tuberculosis

- Based on British Society for Rheumatology Biologics Registry, monoclonal antibodies was associated with higher risk of tuberculosis was higher than fusion protein in patients with rheumatoid arthritis
  - Adalimumab [144 events per 100 000 person-years(pyrs)]
  - Infliximab (136 per 100 000 pyrs)
  - Etanercept (39 per 100 000 pyrs)
- Based on Spanish Society of Rheumatology Database on Biologic Products , 9 months isoniazid prophylactic therapy is effective in preventing reactivation of latent TB infection for patients receiving TNF antagonists
  - Active TB rates decrease by 78% following this recommendation with incidence risk ratio was 0.22 (95% CI 0.03 to 0.88)

Reactivation of Hepatitis B

- A small case series found that anti-TNF alpha (infliximab more than etanercept and adalimumab) may induced
  - reactivation of hepatitis B in psoriasis patients with positive hepatitis B surface antigen (HbsAg +ve)
  - less frequently in patient with an isolated positive Hepatitis B core antibody (anti-Hbc +ve)
- Reactivation can be prevented with appropriate anti-virus therapy
- Presence of hepatitis B in psoriasis is not an absolute contraindication to the use of anti -TNF alpha

Monitoring

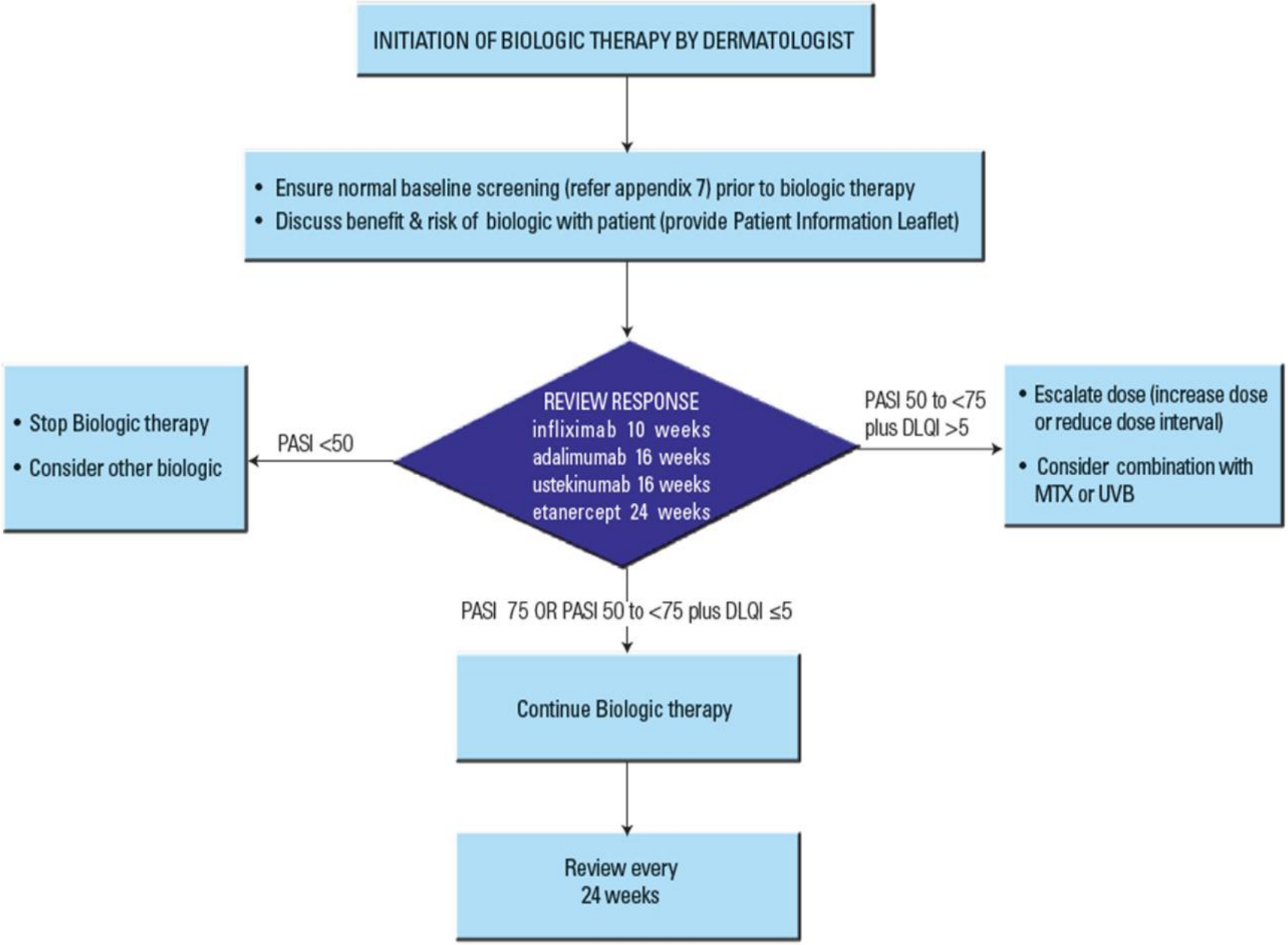
- Patient education and counseling
  - 6 monthly update on safety profile and reminder of potential risk of malignancy
  - Weighing at every visit – to look for loss of weight associated with tuberculosis/malignancy
- Blood investigations
  - 3 monthly FBC, ESR, CRP, LFT, RP, FLP, HBsAg, HCV Ab, HIV, ANA
- Assessment for tuberculosis
  - Yearly CXR/Mantoux test
- ***Patients must be fully assessed if symptomatic**

Special Considerations

- Pregnancy
  - Patients who get pregnant during biologics intervention should have the treatment discontinued and be referred to the obstetrician for detail assessment.
- Surgery
  - Biologics therapy should be discontinued prior to major surgery.
  - Infliximab : 6 weeks before planned surgery
  - Etanercept : 4 weeks before planned surgery
  - Adalimumab : 10 weeks before planned surgery
  - Ustekinumab : 12 weeks before planned surgery
- Vaccination
  - Patients on biologics intervention should not receive live or live attenuated vaccinations < 2 weeks before, during and for 6 months after discontinuation of therapy

Cessation of Biologic Therapy

- Poor response
  - Failure to achieve PASI 75 or 75% reduction in BSA or DLQI ≤5
- Serious adverse event
  - Malignancy
  - Severe drug related toxicity
  - Severe infection
- Pregnancy
- Elective surgical procedures (withhold biologics therapy temporarily)


INITIATION OF BIOLOGIC THERAPY BY DERMATOLOGIST
• Ensure normal baseline screening (refer appendix 7) prior to biologic therapy
• Discuss benefit & risk of biologic with patient (provide Patient Information Leaflet)
REVIEW RESPONSE
infliximab 10 weeks
adalimumab 16 weeks
ustekinumab 16 weeks
etanercept 24 weeks
PASI <50
• Stop Biologic therapy
• Consider other biologic
PASI 50 to <75 plus DLQI >5
• Escalate dose (increase dose or reduce dose interval)
• Consider combination with MTX or UVB
PASI 75 OR PASI 50 to <75 plus DLQI ≤5
Continue Biologic therapy
Review every 24 weeks

Malaysian Psoriasis Registry

- All patients with psoriasis receiving biologic intervention should be registered in the Malaysian Psoriasis Registry

- Aims of the registry:

  1. Providing information on effectiveness of biologics intervention in Malaysia.

  2. Providing information on the long term safety profile of biologics intervention in Malaysia.

Cost Effectiveness

- Swiss healthcare system
  - Cost-effectiveness for PASI 75 at week 12 [assessed by incremental cost-effectiveness ratio (ICER)]:
  - Most cost effective: Adalimumab (CHF 14 921)

  →Infliximab (CHF 16 505)

  →Etanercept (CHF 25 748)
- UK, National Health Service (NHS)
  - Cost and benefit were expressed as quality-adjusted life-years (QALYs)
  - Most cost-effective : Adalimumab (ICER £30 000 per QALY)

  →Etanercept (£37 000 per QALY)

  →Infliximab (£42 000 per QALY)

Cost Effectiveness

- Spanish National Health System
  - Cost effectiveness for PASI 75 [assessed by incremental cost-effectiveness ratio (ICER)]:
  - Most cost effective : Adalimumab (ICER 8013€)

→Etanercept 25mg twice a week (ICER 9110€),

→Usteknumab 45mg (ICER 9627€),

→Infliximab 5 mg/kg (ICER 10 523€)

→Etanercept 50mg twice a week (ICER 12 797€)

→Ustekinumab 90mg (ICER 17 981€)

Malaysian CPG on the management of Psoriasis vulgaris

Biologic therapy

RECOMMENDATIONS

- Biologic should be offered by a dermatologist to patients with moderate to severe plaque psoriasis who fail, have intolerance or contraindication to conventional systemic treatment and phototherapy . **(Grade A)**

- Careful evaluation for contraindication 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 in National Psoriasis Registry. **(Grade C)**

- Psoriasis patients with latent tuberculosis should be referred to respiratory physician for treatment before biologics initiation. **(Grade A)**


Thank you