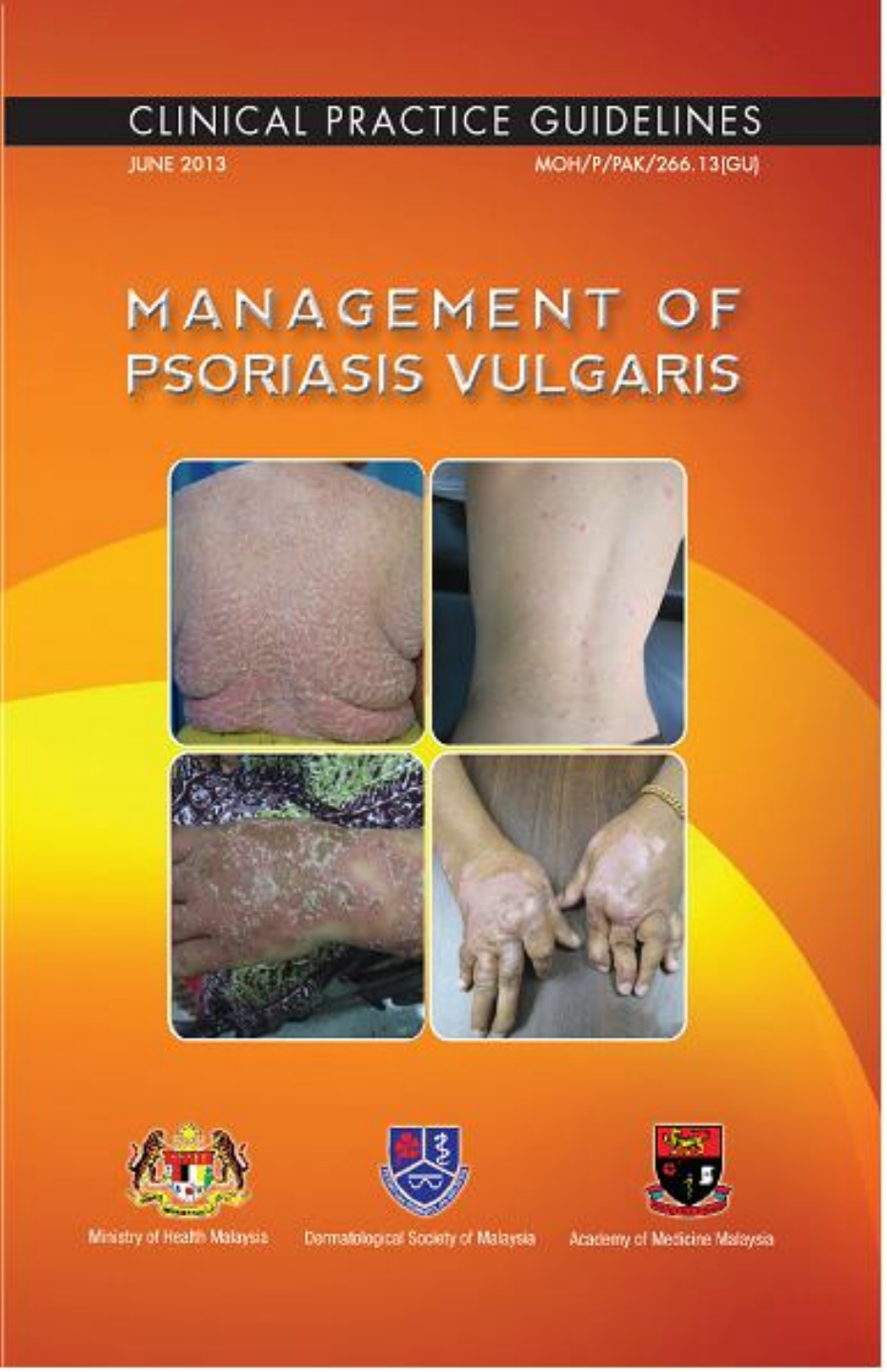

Systemic Therapy

Clinical Practice Guidelines Management of Psoriasis Development Group

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Systemic Therapy

•Moderate to severe psoriasis frequently require **systemic or biologic therapy.**

•Systemic agents :

- **methotrexate**
- **acitretin**
- **cyclosporine**

have significant side-effects and cumulative toxicity

- **Pretreatment** assessment
  - •to identify risk of developing toxicity.

- Baseline laboratory/ imaging tests
  - regularly to monitor side effects/ toxicity

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Pre-treatment assessment

RECOMMENDATION

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

Methotrexate

- Methotrexate
  - analogue of folic acid
  - inhibits dihydrofolate reductase
- Methotrexate is efficacious in treating moderate to severe plaque psoriasis
- Bansback et al meta analysis on efficacy of systemic therapy
  - 42% of patients on methotrexate 15 to 22.5 mg/week
    - PASI 75 at week 16
    - RR of 9.8 (95% CI 6.08 to 13.19)
    - NNT=3
- In a separate study
  - 70% of patients taking methotrexate 15 to 20mg/week
    - PASI 75 at week 12
- No benefit in increasing methotrexate from 20 to 25 mg/week in patients who failed to achieve PASI 50 at week 12

Methotrexate

- No signifiicant difference in patients taking methotrexate 15 to 22.5 mg/week compared to cyclosporine (60.5% vs 71.4%) (p=0.09)
- Methotrexate was comparable to mycophenalate mofetil with 73.3% vs. 58.8% of patients achieving PASI 75 at week 12 (p>0.05)
- Methotrexate was superior to hydroxycarbamid

Methotrexate

- Adverse events:
  - hepatotoxicity
  - myelosuppression
  - gastrointestinal manifestation
    - nausea
    - vomiting
    - mouth sores
    - loss of appetite
  - hair loss and malaise
- Most serious side effects are
  - hepatotoxicity
  - myelosuppression

- Identify the risk factors before initiation of methotrexate

Methotrexate

- Severity of side-effects is dose dependant

- Most common cause of withdrawal : hepatic adverse events
- Common gastrointestinal side effects
  - were nausea
  - diarrhoea
  - abdominal pain
- Incidence of liver fibrosis ranged from 5.7% to 71.8%
- risk factors for liver fibrosis:
  - type 2 diabetes mellitus (OR=7.7, 95%CI 2.7 to 21.7)
  - obesity (OR=2.4, 95% CI 1.1 to 5.4)

  - Alcohol consumption and viral hepatitis were not significant risk factors

Methotrexate

- Data on myelosuppression with methotrexate were derived from patients with rheumatoid arthritis

- The risk of myelosuppression in psoriasis patients is unknown

Risk factors for methotrexate induced hematotoxicity

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

Methotrexate

- Monitoring of hepatoxicity varies in different centres.
  - regular serum liver function test to liver biopsy.
- Routine to do liver biopsy after a cumulative methotrexate dose of 1.5 gm ---→1.0 to 1.5 gm interval to monitor methotrexate-induced hepatotoxicity.

- Recent data : risk of developing liver fibrosis is less than 2.6% in low risk patients taking a cumulative methotrexate dose of more than 4g.

- Liver biopsy deferred till a cumulative dose of ≥4 gm
  - in low risk patients taking low dose (<20 mg) methotrexate.

Methotrexate

- Non-invasive methods to monitor hepatoxicity such as
  - Serum Procollagen III aminopeptide
    - (sensitivity : 77.3%, specificity : 91.5%)
  - fibrotest
    - (sensitivity : 83% , specificity : 61 %)
  - Fibroscan
    - (sensitivity : 50%, specificity : 88%)

NOT widely available in Malaysia.

- A liver biopsy can be deferred if the level of procollagen type III remains within the normal limits

Methotrexate

- Supplementation with folic acid or folinic acid is an effective measure to reduce hepatic adverse effects

- No significant reduction in side effects of
  - Gastrointestinal (ARR= -0.09, 95% CI -0.2 to 0.02)
  - Mucocutaneous (ARR= -0.07, 95% CI -0.2 to 0.04)
  - Haematological (ARR=0.004, 95% CI -0.02 to 0.03)

Methotrexate

- Data on risk of pulmonary fibrosis in long term MTX is limited
- A study on 27 psoriatic arthritis patients on low dose MTX (5 - 15 mg/week for 52 months showed no association with pulmonary fibrosis
- Systematic review reported 84 cases of lung related adverse event in 3463 patients with rheumatoid arthritis on methotrexate
  - Only 15 of which were felt to be directly caused by methotrexate (incidence 0.43%).

Treatment regime and monitoring of Methotrexate in patients with psoriasis

Initial therapy

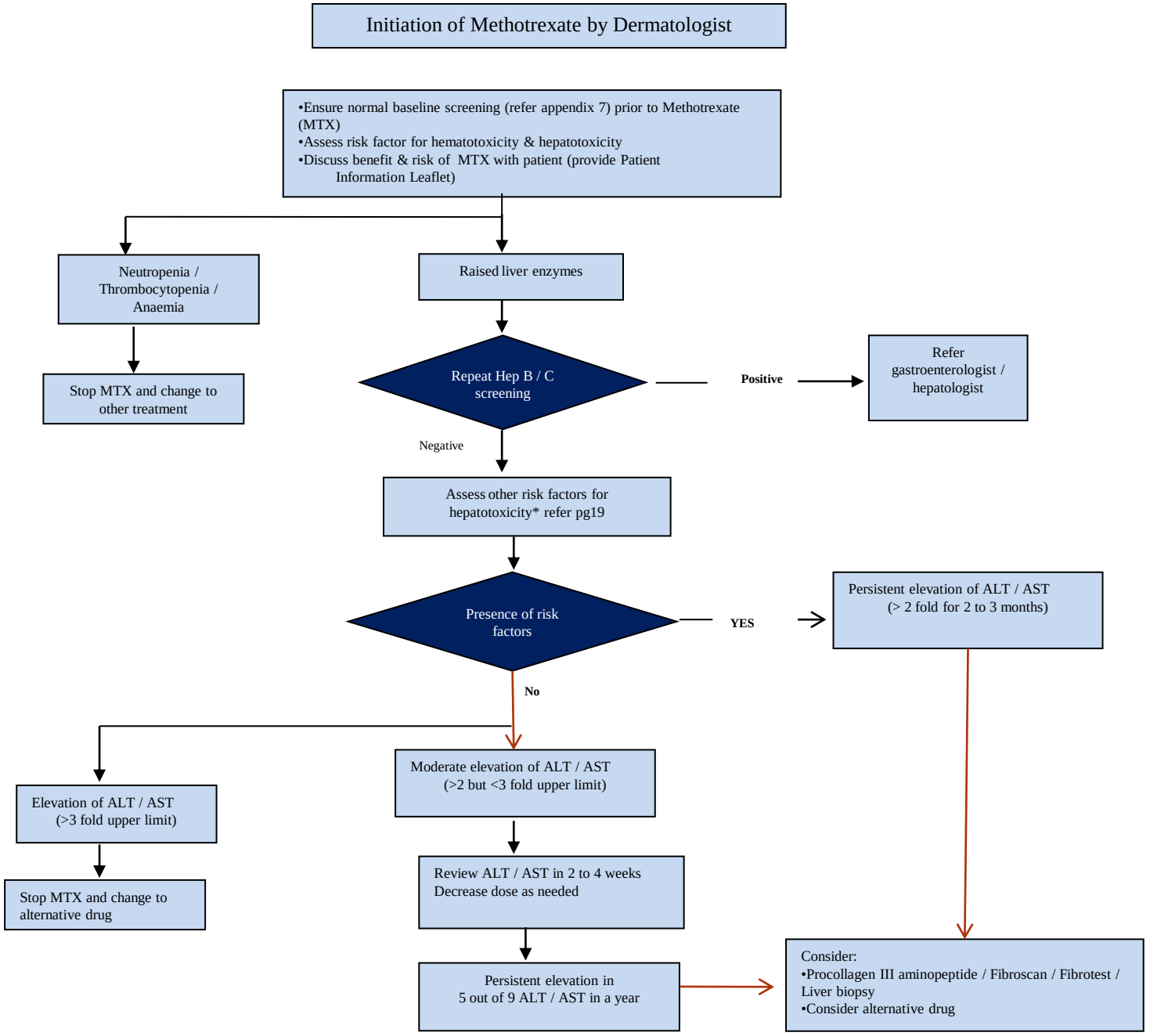
- oral test dose of 5.0 - 7.5 mg /week
- Supplement with Folic acid 5mg od (except the day of methotrexate) or 5mg once a week (the day after methotrexate)
- Repeat FBC, LFT and RP within 2 weeks

Maintenance therapy

- Escalate dose from 7.5 mg/week till response (maximum 20 mg/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 monthly for the first 3 months and then after every 1 to 3 monthly
- More frequent monitoring is needed with dose escalation
- Do blood test 5 - 7 days after last dose of methotrexate
- Monitor total cumulative dose of methotrexate
    - Consider Procollagen III aminopeptide/ Fibroscan/Fibrotest or Liver biopsy when achieve total cumulative dose of 3.5 to 4.0g (without risk factors for hepatotoxicity) or 1.0 to 1.5g (with risk factors for hepatotoxicity)*

*Refer to yellow box on “Risk factors for methotrexate induced hepatotoxicity”

ALGORITHM 3: MONITORING HEMATOTOXICITY AND HEPATOTOXICITY OF METHOTREXATE



Malaysian CPG on the management of Psoriasis vulgaris
Methotrexate

RECOMMENDATION

- Methotrexate should be used as first-line systemic treatment for moderate to severe plaque psoriasis. **(Grade A)**

- Neutropaenia and hepatotoxicity should be monitored closely. **(Grade C)**

Retinoids (Acitretin)

- Retinoids are vitamin A analogues
  - modulate epidermal proliferation and differentiation.
- First study to be published on acitretin was in 1984
- No recent RCTs after 2000 in assessing efficacy of oral retinoids

Retinoids (Acitretin)

- A study on adverse effects of acitretin by Pearce et al. Showed
  - low dose acitretin (<25 mg/day) had less adverse effects
  - compared to high dose acitretin (>25 mg/day)

- The side-effects were
  - chelitis
  - skin peeling
  - pruritus, alopecia
  - dry mouth
  - xerophtalmia
  - raised alanine transaminase, aspartate aminotransferase and triglycerides

- When phototherapy is not an option, Acitretin is an appropriate alternative treatment for patients with psoriasis

Retinoids (Acitretin)

Initial therapy

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

Maintenance therapy

- Adjust according to response, usually within range of 25 - 50 mg daily (max 75 mg daily).
- Repeat lipid profile and LFTs every 4 - 8 weeks until stable, then every 6-12 weeks

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

Malaysian CPG on the management of Psoriasis vulgaris

Acitretin

RECOMMENDATION

- 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)**

Cyclosporine

- Cyclosporine is an oral calcineurin inhibitor with cyclical peptide composed of 11 aminoacids and strongly hydrophobic

- Cyclosporine is efficacious as shown by Schmitt et al
  - PASI 75, at week 8 to16 ranged from 28% to 97%
  - RD of 0.3 (95% CI 0.1 to 0.5)

- This wide range of efficacy was due to different initial dosage of cyclosporine

Cyclosporine

- Adverse events of 16.1%
- Smaller percentages with serious adverse events (2.3%)
- Withdrawal due to adverse events (1.2%)
- In a 5-year cohort study on the risk of malignancy
  - 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)

Cyclosporine

Treatment regime and monitoring of cyclosporine in patients with psoriasis

Pre Cyclosporine screening:

- **Ensure normal baseline Investigations (refer appendix 7) prior to cyclosporine**
- **Discuss benefit & risk of cyclosporine with patient**

Initial therapy

- **Starting dose of 2.5 mg/kg/d divided twice a day**
- **If inadequate response to initial dose after 4 to 6 weeks, the dose may be increased to a maximum of 6 mg/kg of body weight.**
- **Treatment for more than 2 years not recommended**
- **Monitoring while on therapy:**
  - **Blood pressure, RP, FBC, uric acid, potassium, lipids, liver enzymes, serum bilirubin and magnesium should be monitored monthly**

Malaysian CPG on the management of Psoriasis vulgaris
Cyclosporine

RECOMMENDATION

- 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, are 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 patient on cyclosporine. **(Grade C)**

Mycophenolate Mofetil

- Mycophenolate mofetil (MMF) is an immune modulator which inhibits inositol monophosphate dehydrogenase.

- MMF (2 gm daily) is less efficacious than cyclosporine (2.5 mg/kg/day) with PASI 75 at week 12 of 12% and 29% respectively (p=0.01)

- Mean PASI improvement is lower in MMF (30 mg/kg/day) compared to cyclosporine (4 mg/kg/day) (p=0.04)

- The tolerability and adverse events are similar between the two drugs

Antibiotics

- There is no good evidence to support the use of antibiotics in treating plaque psoriasis

Hydroxyurea

- Hydroxyurea is an antimetabolite 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 500 mg twice daily was an efficacious alternative treatment for patients with chronic plaque psoriasis
  - 76% of patients had a PASI 75 reduction at week 10 - 12

Hydroxyurea

- Adverse events reported were
  - Leucopenia
  - Thrombocytopenia
  - Skin infection
  - Dry skin
  - Diffuse reversible alopecia
  - Anaemia
  - Post-inflammatory lesional and
  - Nail hyperpigmentation were seen in all patients taking hydroxyurea

Salozopyrin (Sulfasalazine)

- Salazopyrin is a 5-lipoxygenase inhibitor which has anti-inflammatory and immunomodulatory effect
- It had been shown to be efficacious in treating psoriatic arthritis based on several randomized controlled trials in1990s
- Evidence on the use of salazopyrin in treating plaque psoriasis is limited.

Salozopyrin (Sulfasalazine)

- 8 week double-blind randomized controlled trial, salazopyrin (1.5 g to 4.0 g)(n=23) vs placebo(n=27) was more efficacious to achieve improvement
  - marked improvement : 41% vs 0%
  - moderate improvement : 41% vs 4%

- In the salazopyrin arm
  - 26% dropped out at the end of 8 week due to rash or nausea
  - 14 patients who continued for an additional 4 weeks
    - 8 had marked improvement
    - 2 had moderate improvement

Leflunomide

- Leflunomide is a dihydro-orotate dehydrogenase inhibitor which is a key enzyme in the de novo synthesis of pyrimidine

- Limited randomized controlled trial on the efficacy of leflunomide

- In a randomized double blind placebo controlled trial
  - leflunomide 20mg (n=95) vs placebo (n=91)
  - Leflunomide was more efficacious
  - PASI 75 : 17.4% vs 7.8% (p=0.048)

Leflunomide

- In the same study, leflunomide showed higher incidences of
  - diarrhea (24%)
  - increased alanine transaminase level (12.5%)
  - lethargy (6.3%)

  As compared to placebo

Malaysian CPG on the management of Psoriasis vulgaris

Systemic therapy

RECOMMENDATION

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

Systemic therapy

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- 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 patient who fail, intol**erant 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 patient on cyclosporine. (**Grade C)**