Systemic therapies - nonbiologic

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So many choices
Treatment options

• **TOPICALS**
  - Glucocorticosteroids
    - Topical
    - Intraleisonal
  - Calcipotriol
  - Tar
  - Dithranol
  - Tazarotene
  - Keratolytics
  - Ascomycin derivatives / calcineurin inhibitors
Treatment options

- **PHOTOTHERAPY**
  - Narrowband UVB
    - Whole body
    - Localised
  - PUVA
    - Oral
    - Bath
    - Topical
  - Excimer laser
Phototherapy

- Broadband and narrowband UVB phototherapy
  - Effective treatments for guttate or plaque psoriasis resistant to topical therapy
  - Combination with other anti-psoriasis treatments (tars, topical calcipotriol, oral retinoids) have proved effective

- Photochemotherapy (PUVA)
  - Combination with other anti-psoriasis treatments (vitamin D analogue preparations, retinoids) have proved effective.

- Phototherapy requires good metering, equipment monitoring and maintenance of patient records to track UV exposure
Phototherapy

- Phototherapy incorporates the use of ultraviolet radiation as a treatment for psoriasis.
- The two main forms of phototherapy are narrow-band ultraviolet B (UVB) and psoralen plus ultraviolet A (PUVA).
- While UVB is effective alone, UVA requires a photosensitising agent.
- Psoralens, either topically or systemically, are used.
Phototherapy

• Both phototherapy modalities cause a depletion of dermal and epidermal inflammatory cells, including lymphocytes, macrophages and dendritic cells.
• They may also have a role in decreasing keratinocyte hyperproliferation.
Phototherapy

• Most effective when undertaken three times a week.
• Less than this makes dosage increments low to avoid burning, hence prolonging treatment.
• More frequent visits do not seem to lessen the total dose and treatment number required.
• Most patients require 6-8 weeks of therapy.
• Requirement to visit clinic may limit use for some patients.
Phototherapy

- If patients receive too much ultraviolet radiation in one visit they may develop a 'sunburn'.
- Narrow-band UVB phototherapy may result in some tanning or freckling of the skin.
- Eye protection is important to avoid the types of damage that can also be produced by sunlight.
- There is at least a theoretical concern of photocarcinogenesis. The increased risk tends to be predominantly non-melanoma skin cancer.
Phototherapy

- Narrow-band UVB has largely replaced PUVA because of the increased risk of SCC and possibly both Merkel cell carcinoma and melanoma associated with systemic PUVA therapy.
- PUVA is administered 2-3 times a week. A 48-hour gap between therapies is recommended, as any ‘burn’ may take up to 48 hours to appear.
Phototherapy

• For oral PUVA, in Australia 8-methoxypsoralen is taken two hours before UVA exposure.
• From the time the psoralen capsules are taken, eye protection is required. This needs to be continued until sundown on the day that this medication is taken.
• In addition to generalised photosensitivity, psoralens may cause nausea, flushing and headaches.
Evaluation of PUVA using PASI in a randomized, double-blind, placebo (UVA)-controlled trial

PASI 75 response*
- PUVA: 63%
- UVA + placebo: 0%
- p<0.0001

*ITT LOCF analysis

UVA + methoxsalen (n=30) vs UVA + placebo (n=10)

Phototherapy

- Side effects associated with PUVA therapy include burning, photosensitivity, pruritus, hypertrichosis, tanning and freckling, nausea, headache and hepatotoxicity.
- Prolonged use results in skin aging, increased risk of cataracts (eye protection required for 24 hours post therapy) and the probable increased risk of skin cancer.
- More than three-quarters of patients seem to respond to PUVA therapy, which can induce remissions of six months or more.
Excimer laser

- XeCl laser
- 308 nm
- Ablates rather than burns or cuts
- LASIK = laser eye surgery - refractive surgery for myopia, hypermetropia and astigmatism
- Twice weekly treatments
- Can use erythemogenic doses
- Targets lesions
- Spares ‘non-involved’ skin
Treatment options

• **SYSTEMIC AGENTS**
  - Methotrexate
  - Acitretin
  - Cyclosporin

• Second line
  - Mycophenolate
  - Hydroxyurea
  - Thioguanine
  - Fumaric acid esters
Indications for systemic therapy

- Failure of adequate trial of topical therapy
- Repeated hospital admissions for topical therapy
- Extensive chronic plaque psoriasis in the elderly or infirm
- Generalised pustular or erythrodermic psoriasis
- Severe psoriatic arthropathy
- Rule of tens
  - Body surface area affected (BSA) >10%, or
  - PASI score >10, or
  - DLQI >10
Non-biologic systemic therapies for moderate to severe psoriasis

PASI 75 responses at primary endpoints

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients achieving PASI75 (%)</th>
<th>Mean dose or regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin¹</td>
<td>52</td>
<td>0.54 mg/kg/day (n=127)</td>
</tr>
<tr>
<td>Methotrexate²</td>
<td>60</td>
<td>15-22.5 mg/wk (n=43)</td>
</tr>
<tr>
<td>PUVA³</td>
<td>63</td>
<td>3 times weekly (n=30)</td>
</tr>
<tr>
<td>Ciclosporin²</td>
<td>71</td>
<td>3-5 mg/kg/d (n=42)</td>
</tr>
<tr>
<td>NB-UVB⁴</td>
<td>70</td>
<td>16 weeks (n=20)</td>
</tr>
</tbody>
</table>

Immunosuppression and infection

• With immunosuppression potential for:
  - New-onset infections
  - Re-activation of latent infections
  - Opportunistic infections
Malignancy and psoriasis

• Increased risk of:
  - Cutaneous malignancy
    • Nonmelanoma skin cancer
  - Lymphoproliferative disease
    • Non-Hodgkin’s lymphoma
    • Hodgkin’s disease

Mycophenolate mofetil

- Immunosuppressant
- Prodrug of mycophenolic acid
- Inhibits inosine monophosphate dehydrogenase in purine (guanine) biosynthesis
  - Needed for growth of T cells and B cells
- Up to 1.5 g BD
- No randomised trials in psoriasis
Fumaric acid esters

- Not available in Australia
- **Germany, Austria, Switzerland**
- Dimethyl fumarate + Ca, Mg, and Zn salts of monoethyl hydrogen fumarate
- Thought to shift $T_{h-1}$ cytokine response to a $T_{h-2}$ type pattern - IL-10 inhibits IL-2, IL-12, IFN$\gamma$
- Inhibit translocation of NF-$\kappa$B
- GI upset 60%, flushing 30%
- 120 mg tabs - up to 6 daily
Hydroxyurea

- Hydroxycarbamide
- Antineoplastic
- Inhibits ribonucleotide reductase
  - Decreases production of deoxyribonucleotides
- Slows down division of skin cells
- 500mg up to TDS
- Drowsiness, nausea, GI upset, bone marrow toxicity, alopecia
Thioguanine

- Thioguanine = 6-TG
- Thiopurine antimetabolite
- Purine analogue of guanine
- 40 mg tab – up to 120 mg/d
- Bone marrow toxicity, hepatotoxicity, GI upset, hyperuricaemia
Oral methotrexate (MTX)

- Methotrexate is one of the most commonly used oral systemic agents for psoriasis
- Potential for adverse effects necessitates careful selection and monitoring of patients

<table>
<thead>
<tr>
<th>Dosing</th>
<th>7.5-22.5 mg per week</th>
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<tr>
<td>Efficacy</td>
<td>&gt; 60% PASI 75 response</td>
</tr>
<tr>
<td>Major toxic effects</td>
<td>Foetal death or abnormalities, myelosuppression, hepatotoxicity, pneumonitis, stomatitis</td>
</tr>
<tr>
<td>Monitoring required</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Methotrexate

Proposed mechanisms of action

• Immunomodulatory effects
  - Inhibition of proliferating lymphoid tissue
  - Inhibition of IL-1 activity and IL-6 production

• Anti-inflammatory effects
  - Reduced neutrophil and monocyte chemotaxis
  - Inhibition of leucocyte accumulation at sites of inflammation

• Inhibition of epidermal proliferation
  - Interference with cell kinetics via temporary reduction on DNA synthesis
Methotrexate and ciclosporin

PASI 75 responses at Week 12


Methotrexate 7.5-15 mg/week (n=37) vs. Ciclosporin 3-5 mg/kg/day (n=31)

Patients (%)

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate 7.5-15 mg/week (n=37)</th>
<th>Ciclosporin 3-5 mg/kg/day (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>24%</td>
<td>58%</td>
</tr>
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</table>

p=0.0094
Oral systemic agents can be highly effective in the treatment of moderate to severe psoriasis.

Subjects achieving PASI 75 (%)

PASI 75 at week 16 in patients treated with MTX or CsA for psoriasis

<table>
<thead>
<tr>
<th>Subjects achieving PASI 75 (%)</th>
<th>Methotrexate 15 mg/week</th>
<th>Ciclosporin 3 mg/kg/day</th>
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Adalimumab
PASI 75 in the comparative CHAMPION trial vs methotrexate¹


*p<0.001 vs. placebo; †p<0.001 vs. MTX; ‡p=0.001 vs. placebo; Intention to treat (ITT), patients with missing PASI scores were considered non-responders.
Methotrexate

- The most commonly used systemic agent for psoriasis is methotrexate.
- This agent has been available for more than 50 years.
- It works by competitively inhibiting folate biosynthesis, specifically the enzyme dihydrofolate reductase.
- This impairs nucleic acid production and hence impairs DNA replication.
Methotrexate

- Originally, MTX was thought to exert its effect primarily on hyperproliferating epidermal keratinocyte replication.
- However, it is now believed that the main action of MTX is anti-inflammatory, by inhibiting proliferation of lymphocytes.
- MTX is most commonly prescribed as a once-weekly dosage. The dose may be divided into two or three doses, taken 12 hours apart.
- Typically patients will be started on 5-10mg/week after baseline screening with FBC, renal function and LFTs.
Methotrexate

- MTX is metabolised by the liver but excreted by the kidneys.
- Renal impairment increases the risk of toxicity.
- It is recommended that LFTs and FBC be undertaken monthly until the dose is stable for three months, and then three monthly.
- Patients are typically assessed after 6-8 weeks of therapy and the dose increased at 2.5-5mg increments.
- Once the psoriasis is under control, the patient remains on a stable dose for a number of months before the dose is gradually reduced.
- MTX may also be administered SC or IM at weekly intervals. Maintenance doses of MTX typically range from 7.5mg/week to 25mg/week for patients with psoriasis.
Methotrexate

- The most common side effects of MTX are nausea, anorexia and fatigue.
- Mouth ulcers may develop, particularly if neutropenia occurs.
- Of particular concern with MTX is the potential for bone marrow suppression, especially if there is renal impairment, or if the drug is given on a daily basis.
- The risk for haematological toxicity is also increased with advanced age, hypo-albuminaemia and drug interactions, including with agents such as cotrimoxazole, aspirin and NSAIDs.
- Pulmonary fibrosis.
How to use MTX

- Test dose?
- Frequency of review
- Rapid escalation
- Addition of topicals
- SC
- Monitoring
- Folate
- Alcohol
Methotrexate

• Hepatotoxicity.
• Liver impairment is more common in patients who consume alcohol, have diabetes or have hyperlipidaemia.
• Non-alcoholic steatohepatitis is more common in patients with psoriasis than the general population, perhaps explaining why hepatotoxicity is more common in dermatology patients than rheumatology patients.
• American guidelines suggest that patients on methotrexate should undergo a liver biopsy after cumulative lifetime doses of 3.5-4.5g.
• This is rarely performed in Australia. Most experts would suggest that monitoring of liver function is sufficient to detect any liver impairment. In Europe, serial measurements of amino-terminal procollagen 3 peptide is used as a method of detecting increased fibrosis.
• Hepatitis, reactivation of tuberculosis and lymphoma have all been reported but have not been confirmed.

Copyright
Oral ciclosporin

- Ciclosporin is an effective drug for short-term management of moderate-to-severe psoriasis
- Ciclosporin is associated with a range of adverse effects including nephrotoxicity

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<th>Dosing</th>
<th>2.5-5 mg/kg/day</th>
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<tr>
<td>Efficacy</td>
<td>&gt; 60% PASI 75 response</td>
</tr>
<tr>
<td>Major toxic effects</td>
<td>Nephrotoxicity, hypertension, immunosuppression (increased risk of infection or malignancy)</td>
</tr>
<tr>
<td>Monitoring required</td>
<td>Yes (creatinine, blood pressure)</td>
</tr>
</tbody>
</table>
Ciclosporin

Proposed mechanism of action

1. Ciclosporin forms complex with cyclophilin (isomerase)
2. Complex inhibits calcineurin
3. Signal transduction from T cell receptor to cytokine promoters is blocked
4. Inhibition of IL-2, IL-3, IL-4, IL-5, GM-CSF and TNF-α

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Cyclosporin

- Cyclosporin is a calcineurin inhibitor.
- It is used as an immunosuppressive agent, particularly in solid-organ transplant recipients.
- Prolonged use of cyclosporin is associated with an increased risk of skin cancer, particularly SCC.
  - The risk of skin cancer with cyclosporin is dramatically increased with prior phototherapy.
- It is currently recommended that cyclosporin not be used for more than 2 years in dermatology patients.
Cyclosporin

- Prolonged use also results in the development or exacerbation of hypertension and renal impairment.
- Hypertriglyceridaemia has also been detected in rare cases, and rebound has been seen with sudden discontinuation of cyclosporin.
- The typical dose of cyclosporin is 2.5-5mg/kg/day in two divided doses.
Cyclosporin

• There are two approaches in terms of starting dose.
• The usual initial dose of cyclosporin is 2.5-3.0 mg/kg/day, although in patients with severe psoriasis where a rapid response is warranted, 3.0-5.0 mg/kg/day can be used.
Cyclosporin

- The speed at which clinical improvement appears depends upon the intensity of the starting dose.
- There is usually clinical improvement of psoriasis within four weeks or less, but the optimal response is not usually seen till 8-10 weeks after commencing cyclosporin.
- If a patient does not respond satisfactorily to an initial starting dose of 2.5-3.0 mg/kg/day after 4 weeks the dose can be increased stepwise, at regular intervals, to a maximum of 5.0 mg/kg/day.
- This of course depends on any adverse side effects experienced, and regular monitoring of the patient's blood parameters.
- If there is no response after 12 weeks at maximal dose, then cyclosporin should be discontinued.
Cyclosporin

- Before starting therapy, patients need to have their renal function, liver function and lipids measured.
- They also need to have their blood pressure checked and monitored.
- Cyclosporin is one of the more potent agents available for the treatment of psoriasis and has a very rapid onset of action.
- However, its use has been limited because of concerns with its side-effect profile.
Cyclosporin

- Common nuisance but non-serious side effects include:
  - Headache.
  - Tremor.
  - Nausea.
  - Paraesthesia.
  - Hypertrichosis.
  - Gingival hyperplasia, particularly with poor gum hygiene.
  - Lethargy.
Cyclosporin

- There is an increased risk of infection in people using cyclosporin, as well as at least a theoretical risk of cancer.
- Occasionally hypomagnesaemia and hyperkalaemia may develop.
- Multiple agents may interact with cyclosporin, and care needs to be taken when introducing any additional therapeutic agent in patients using this medication.
Cyclosporin and infection

• In psoriasis:
  - Influenza-like symptoms 9.9%
  - URTI 7.7%

• In liver transplants:
  - Bacterial infection 40%
  - Sepsis 20%
  - CMV 15-20%

Cyclosporin

- It is recommended that patients have blood pressure, renal function, liver function, FBC and lipid profile measured regularly.
- Blood pressure and renal function should be monitored fortnightly for the first three months. The other measurements should be performed monthly.
Acitretin

- Acitretin is an oral retinoid effective in treating psoriasis.
- The recommended daily dose is 1mg/kg/day for maximal efficacy. However, most patients do not tolerate this, so dosages of 10-50mg/day are more commonly seen.
- Acitretin works as a pro-differentiating factor and may have some immunomodulatory activity.
Acitretin

- The efficacy and side effects of acitretin appear to be dose related.

- Patients are at risk of developing hyperlipidaemia, particularly hypertriglyceridaemia, on acitretin.
  - In rare instances, associated with hypertriglyceridaemia, pancreatitis may develop.
  - The risk of hypertriglyceridaemia appears more common in patients with diabetes, obesity and excessive alcohol intake.

- Occasionally patients will develop abnormal LFTs.
Acitretin

• The most common side effects seen with acitretin are mucocutaneous.
• Cheilitis (inflammation and cracking of the skin of the lips) occurs in most patients.
• Patients may also experience dryness of the eyes, nose & oral mucosa.
• Epistaxis may occur.
• Serositis, nail fragility, dry hair and alopecia, and burning or sticky skin may also be seen.
• Occasionally patients develop exuberant granulation tissue adjacent to nails, or periungual pyogenic granulomas.
Acitretin

• Patients may also develop musculoskeletal side effects.
• Benign intracranial hypertension/pseudotumour cerebri can occasionally occur if patients are using tetracycline antibiotics.
• Impaired night vision has been reported.
Acitretin

- Because it is relatively poorly tolerated in higher doses, low-dose acitretin is often used in combination with phototherapy.
  - This results in lower doses of both modalities being required.

- Acitretin is also used to treat disorders of keratinisation and has been used as a skin cancer prophylactic agent.
Acitretin

- Patients taking acitretin require monitoring of lipids and liver function.
- Acitretin is a pregnancy category X drug.
  - It is a potent teratogen and hence usually avoided in women of childbearing age.
  - Because of its half-life and reverse metabolism to etretinate, it is recommended that any woman who has taken acitretin not consider conception for at least two years after completion of a course of therapy.
ACITRETIN

- Hyperlipidaemia
- Skeletal effects
- Teratogenicity
- Mucocutaneous
- Alopecia
- Hepatotoxicity
METHOTREXATE

- Hepatotoxicity
- Lymphoproliferative disorders
- Bone marrow suppression
- Pulmonary fibrosis
- Opportunistic infection
- Foetal death/abnormalities
- GI disorders
CICLOSPORIN

• Hypertension
• Nephrotoxicity
• Hyperlipidaemia
• Increased risk of malignancy
  – Cutaneous malignancy
• Increased risk of infection
• Hypomagnesaeemia
QUESTIONS?