Systemic Agents in Psoriasis

Dr Sushil Tahiliani
Introduction

- Pso is a systemic disease
- 30% pts need systemic drugs*
- Many pts feel:
  - Dissatisfied with treatment
  - Feel under-treated
  - Desire more complete control of disease

Indications

- Severe plaque disease (BSA > 10 or PASI > 10)
- Gen pustular PSO
- Erythroderma
- Significant PSA
- Cases refractory to topicals/Phototherapy
- Limited disease with significant physical /psychosocial disability
Conventional systemic agents:

Advantages

- Ease of administration
- Lower cost
- Vast experience in use with longer term follow-up
Systemic agents

Commonly used
- Methotrexate (MTX)
- Cyclosporin (CsA)
- Acitretin

Uncommonly used
- Fumaric Acid esters
- Hydroxyurea
- Azathioprine
- Leflunomide
- Mycophenolate mofetil
MTX

- Gold standard systemic drug
- First used in PSO > 50 yrs ago
- Approved by FDA in 1972 for PSO and in late ‘80s for RA
- Monotherapy / as one of molecules in combination/ sequential therapy
- Clinical experience >> efficacy thro’ clinical studies
- Available as tab & Injection for SC/IM/IV use
Controversies & confusions

- Criteria for selection of patients
- Method of lab evaluation
- Need for liver biopsies in surveillance
**MTX: MOA**

**Inhibits dihydrofolate reductase within 1 hour**
- Also inhibits thymidylate synthetase
  - less rapidly

**Decreased synthesis of tetrahydrofolate needed for DNA & RNA synth**
- Works on S phase of cell cycle

**Significant inhibition of lymphoid cell proliferation & ↓ CLA & e-Selectin**
- Little or no effect on proliferation of epidermal cells
  - Effect on lymphoid cells 1000 times more
MTX: MOA - New Concepts

- Inhibits AICAR transformylase
- Accumulation of AICAR*
- ↑ tissue accumulation of Adenosine
- Anti-inflammatory action

*a-aminooimidazole-4-carbonucleotide riboxamide
SIG Psoriasis Antipsoriatics Systemic
25/03/18
MTX- dosing

- Test dose: +/-
- 0.3-0.5mg/kg/wk
- Oral vs. IM vs. SC
- Build up vs. fulldose initially
- Folic acid supplementation
Subcutaneous Methotrexate

- Higher intracellular level of Mtx-PG
- Higher absorption rates & bioavailability
- Fewer adverse events

Increased efficacy of Subcutaneous Methotrexate
MTX has been the standard systemic therapy for psoriasis for more than five decades and still continues to be gold standard in era of biologics.

Single weekly oral dose of MTX has a favourable side-effect profile compared to intermittent oral schedule.

**Dose of 0.3-0.5 mg/kg/week (25-30 mg)**, continue till PASI 75 is achieved, then gradually taper it. Good and rapid control of disease in majority of the patients.

Concomitant administration of folic acid (1 to 5 mg/day) reduces side effects.
Methotrexate 25mg is an effective dose as monotherapy for the treatment of severe psoriasis, whereas the 10mg dose is slow to act and less effective, but has a less severe side-effect profile.”
Monitoring

Baseline:

- History & clinical examn
- CBC, Platelet count
- BUN, Sr Creatinine, LFT
- Pregnancy test*
- Test for HIV*
- PPD, X-ray chest*
- Liver biopsy*

*in select cases
Monitoring

Follow up:

1. CBC, Platelet count, LFT (esp Tranaminases):
   5-6 days after test dose
   1-2 wks after each dose escalation
   Every 3 mths long term (while on treatment)

2. Renal function tests:
   Twice yearly
### Dls

| Drugs that increase MTX levels | Salicylates  
|                              | NSAID  
|                              | Sulfonamides  
|                              | Dipyrimadole  
|                              | Phenothiazines  
|                              | Chloramphenicol, Tetracyclines  
|                              | Phenytoin  
|                              | Probenecid  
| Drugs that increase hematologic toxicity | Sulfonamides, DDS  
|                              | Trimethoprim  
| Drugs that may increase hepatotoxicity | Systemic Retinoids  
|                              | Alcohol  

**SIG Psoriasis**  
**Antipsoriatics**  
**Systemic**  
25/03/18
Contra-indications

**Absolute**
- Pregnancy
- Lactation
- Alcoholic liver disease
- Other chr liver diseases
- Immunodeficiency syndr
- Bone marrow hypoplasia
- Hypersensitivity to MTX

**Relative**
- Abnormal LFT, RFT
- Active infection
- Obesity
- DM
- Concomitant use of hepatotoxic drug
- Recent administration of live vaccine
- Unreliable pt
Indications for liver biopsy

**Low risk group**
- No baseline biopsy
- Done after cumulative dose of 3.5-4g
- Earlier if >5 SGPT values (out of 9 tests done in 12 mths) elevated
- If Sr albumin values fall to less than normal

**High risk group**
- After 2-6 mths of initiation of therapy
- Repeated after every additional 1-1.5 g of MTX
PIIINP

- Measures fibrogenic activity in liver
- If levels remain stable, liver biopsy can be avoided
- Not organ specific
- Measures ongoing fibrogenic activity only
Pso pts on MTX: Diagnostic accuracy of non-invasive markers of liver fibrosis

- Maybury CM et al
- British Journal of Dermatology (2014) 170, pp1237–1247
- Systematic Review
MTX induced liver fibrosis

- MTX is the ‘primary’ systemic drug for Pso
- It is also effective in recalcitrant LP, AD etc.
- There is a risk of liver fibrosis in pts on MTX
- Liver biopsy is a reference standard for diagnosis
- Evaluation of non-invasive methods of diagnosis is done (17 studies included)
## Comparison

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT</td>
<td>38%</td>
<td>83%</td>
</tr>
<tr>
<td>P3NP</td>
<td>74%</td>
<td>77%</td>
</tr>
<tr>
<td>Fibroscan</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>USG</td>
<td>55%</td>
<td>49%</td>
</tr>
</tbody>
</table>

**Clinical utility limited**

**Low quality data**

**Small sample size**

*If done in isolation, significant number of cases may remain unidentified*
ADR

Minor

- Nausea
- Anorexia
- Stomatitis
- Fatigue

Major

- Myelosuppression
- Hepatotoxicity
- Pulmonary fibrosis
- Reactivation of TB
- Lymphoma
Mechanisms of Methotrexate Resistance

- Di-hydrofolate reductase gene polymorphism
- Impaired transport of MTX into cells
- Decreased ability to synthesize MTX polyglutamate
- Increased expression of drug efflux transporters of the multidrug resistance protein class
I'm being unable to sleep during the meetings.
Systemic agents

Cyclosporine
Cyclosporine

Syn. - Cyclosporin A, Ciclosporin, CsA

History:

- Isolated from soil fungus Tolypocladium inflatum gams in 1970
- Also isolated from Cyclindocarpon lucidum
- Identified as immunosuppressive in 1976
- 1979-discovered to be effective in psoriasis
Formulation

- Soft gelatin cap.-25,50,100 mg.
- Oral soln.-100 mg/ml
- Inj.-5 ml vial ( 50 mg/ml )

Drug is dissolved in ethanol & olive oil. It forms a microemulsion in contact with aqueous fluids.

Oral soln. should be diluted with orange or apple juice just before intake

Dose: 3-5mg/kg initial 2-4mg/kg maintenance
Mechanism of action

- Ag on APC $\rightarrow$ T cells $\rightarrow$ transcription of IL2 $\rightarrow$ mitogenesis of Ag specific helper T cells $\rightarrow$ secretion of cytokines $\rightarrow$ activation of cellular & immune response
- CsA binds to cyclophilins. This complex binds to & inactivates calcineurin.
- This leads to blockage of signal transduction of events leading to IL2 gene transcription
Mechanism of Action of Cyclosporine
CsA in psoriasis

4 regimens:
1) Crisis intervention
2) Short intermittent (as a bridge to other therapies)
3) Six month ‘block’
4) Continuous long-term (in unresponsive cases) - should not be used for more than 2 yrs
CsA

ADR-
• Renal
• Hypertension
• GI
• Neurologic
• Metabolic
• Hematologic
• Neoplastic
• Musculoskeletal
• Mucocutaneous
CsA-C.I.

- Renal insufficiency
- Uncontrolled HTN
- Hypersensitivity to CsA
- h/o systemic malignancy
- Prior treatment with PUVA
- Uncontrolled infections
CsA-usage guidelines

- Benefit-to-risk analysis: efficacy, toxicity, economic effect, acceptability, alternative options
- Thorough history & clinical examn
- Lab.: Sr creatinine, BUN, urinalysis
  CBC, LFT
  Lipid profile
  Sr magnesium, K, uric acid
CsA

**Advantages**

- Selective action on T helper cells
- Rapid therapeutic action
- Weak myelotoxicity
- Safety in pregnancy (category C)

**Drawbacks**

- Nephrotoxicity
- Risk of hypertension
- High rates of relapse
- High cost
- Not very effective in PSA
Systemic agents

Acitretin
Historical aspects

- 1972 - Bollag discovered Acitretin, Etretinate
- 1986 - Etretinate introduced for treating Pso
- 1988 - Etretinate replaced by Acitretin
- 2005 - Acitretin introduced in India
Mechanism of Action

- Decreases the thickness of stratum corneum and the inflammation
- Promotes epidermal accumulation of mucus-like material
- Inhibition of neutrophil migration from dermal capillaries
- Reduction in epidermal concentrations of polyamines which regulate cell growth, proliferation, and differentiation.
MOA

Affects pathways involved in-

- Inflammation
- Cellular differentiation
- Apoptosis
- Sebaceous gland activity
- Broad effect on multiple tissues apart from skin
Mechanism of Action of Retinoid (Acitretin)

- Normalization of abnormal keratinocyte differentiation
- Reduction in keratinocyte proliferation
- Reduction in inflammation
Retinoids: Channeling to Cell Nucleus

- Retinoid
- CRABP-II
- RAR-α,β,γ

Epidermal Cell

Nucleus
Dose

- 0.5 – 1.5 mg / kg body weight
- Usually 25 – 75 mg / day
- Maintenance dose – 10 mg / day or 25mg on alternate day
- 0.3 mg / kg in combination therapy
Indications

► Pustular psoriasis - gen. / local.

► Erythrodermic psoriasis

► Moderate to severe plaque psoriasis

► In immunosuppressed patients
Use in chr. plaque psoriasis

- Combination therapy
- Sequential therapy
- Rotational therapy
- Monotherapy
# Dose-ranging studies - Acitretin

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients(n), disease type</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lassus et al</td>
<td>n = 80 Plaque (70), pustular (4),</td>
<td>10,25 or 50 mg /d x 8 weeks</td>
<td>Average ↓ in PASI 61%, 79%, &amp; 86% in 10, 25 &amp; 50 mg group respectively, side effects &gt;50 mg/d</td>
</tr>
<tr>
<td></td>
<td>erythrodermic(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldfarb et al</td>
<td>38</td>
<td>10,25, 50 or 75 mg/d x 8 weeks followed by open</td>
<td>51-75% ↓ in PASI score. ↑side effects at higher doses (&gt;50 mg/d)</td>
</tr>
<tr>
<td></td>
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<td>label phase with 50 mg/d x 16 weeks</td>
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<tr>
<td>Gollnick et al</td>
<td>175</td>
<td>10,25 or 50 mg /d of acitretin – 8 weeks</td>
<td>Average ↓ in PASI 46% (10 mg/d), 43% (25 mg/d), &amp; 49% (50 mg/d)</td>
</tr>
<tr>
<td></td>
<td>(multicentric)</td>
<td></td>
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</tbody>
</table>
“Acitretin 35 mg/day was observed to be more efficacious compared to 25 mg/day and 50 mg/day dosing, whereas its safety profile is better than 50 mg/day dosing in the management of severe plaque type psoriasis in adult patients.”
Contraindications

- Pregnancy-category X drug
- Severely impaired renal/ liver function
- Significant chr. abnormality of lipid metabolism
- Hypersensitivity to retinoids
- Nursing mothers & children less than 12yr
Lab. evaluations

Baseline:
► CBC
► LFT
► Lipid profile
► Pregnancy test

To be repeated monthly x 2mths & if normal, less often thereafter
ADR

- Teratogenicity
- Mucocutaneous toxicity
- Myalgia, arthralgia
- Hyperlipidemia
- Hepatotoxicity
- Skeletal
- Pseudotumour cerebri
- Drug interactions
- Ophthalmologic
- Psychiatric effects
Limitations

- Slow & unsatisfactory effect as monotherapy in commonest types of PSO
- Risk of teratogenicity
- Restrictions for use in children
- Restrictions for use in men wanting to father a child
- Long duration of precautions
- Repeated investigations
Expert opinion

• Combination therapy with acitretin will become increasingly important in management of recalcitrant psoriasis

• Only FDA approved systemic therapy that is not immunosuppressant

• With/without phototherapy, it is a very important treatment option for pts with chronic infections
Yes, he is repeating the same ideas. But it's our job to look at them in fresh light.
# Combination therapy

<table>
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<tr>
<th>Accelerator</th>
<th>Maintainer</th>
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<tbody>
<tr>
<td>Cyclosporine</td>
<td>Acitretin</td>
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<tr>
<td>Acitretin</td>
<td>PUVA</td>
</tr>
<tr>
<td>UVB</td>
<td>Acitretin</td>
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</tbody>
</table>
Sequential therapy

• Involves use of agents in a deliberate sequence to maximize rate of initial improvement & minimize long term toxicity to improve overall outcome
Second tier systemic agents
Azathioprine

- Purine analogue
- Slow onset of action (6-8wks for significant results)
- Level of evidence for efficacy weaker
- May be considered in cases of Pso + autoimmune bullous diseases
- TPMT levels should be done to know risk of myelosuppression
Fumaric acid esters

- Used commonly in northern Europe
- Combination of dimethyl fumarate & monoethyl fumarate salts
- MOA: Inhibit T cells & shift from Th1 to Th2
- PASI improvement between 50 & 80% after 12-16 wks
- ADR: GI symptoms, flushing, lymphopenia
Hydroxyurea

- Synthesized by Dressler & Stein (1869)
- May work by itself or through conversion to metabolites like acetohydroxamic acid
- Impairs DNA synthesis though inhibition of ribonucleotide diphosphate reductase
- Dose: 1-1.5 g / day
- Acts slowly & is preferred for use in combination or as maintenance therapy
- ADR: Myelosuppression, cutaneous effects
Pharmacology and therapeutics

Rediscovering hydroxyurea: its role in recalcitrant psoriasis

Bhushan Kumar, MD, MNAMS, Abir Saraswat, MD, and Inderjeet Kaur, MD, MNAMS

Abstract
Background There is an acute paucity of second-line systemic agents for the treatment of extensive chronic plaque psoriasis (CPP). Recent studies using hydroxyurea in patients with HIV infection and sickle cell anemia have rekindled interest in this old drug and have provided more data regarding safety and dosage.

Objective We wanted to test the efficacy and tolerability of hydroxyurea in patients with extensive CPP who had to discontinue first-line oral agents for any reason.

Methods The study was a prospective nonrandomized series. Thirty-one patients, including 26 with prior history of systemic antipsoriatic therapy were given hydroxyurea 1–1.5 g per day for a median duration of 36 weeks. They were followed up for a mean period of 36.1 ± 13.8 weeks.

Results Almost 75% of the patients showed an adequate response (35% reduction in Psoriasis Area and Severity Index at or before 8 weeks) with over half showing more than 70% reduction in PASI score. All adverse effects were mild and reversible and none of the patients required cessation of therapy.

Conclusion Hydroxyurea is an effective, very safe but relatively slower acting alternative for patients with extensive CPP over the short-to-medium term.

Hydroxyurea 1-1.5 gm/day

- 75% patients - about 35% ↓ PASI score 8 weeks
- 50% had > 70% ↓ PASI score
- All adverse effects were mild and reversible
- Effective, cheap, safe but relatively slower acting

Combination – Acitretin
Mycophenolate mofetil

- Prodrug of mycophenolic acid
- Works by inhibiting proliferation of both B & T cells
- Specially useful in cases with Psoriasis + immunobullous diseases & in organ transplant recipients
- Common side effects include GI effects, leucopenia, GU effects
Leflunomide

- DMARD agent that inhibits pyrimidine synthesis
- Approved for use in RA
- May be used in Pso + PSA
- More effective on arthritis signs & symptoms
- ADR: GI, increase liver enzymes, cutaneous, bone marrow, teratogenicity
Thank you