Combination Nonbiologic Therapy in Psoriasis

Sushil Tahiliani, MBBS, MD
Agenda

• Rationale
• Preferred and less preferred combination
• Morphology-specific preferred combinations
• Doses used in combinations
• Potential long term adverse effects
• How to monitor?
• Combination in patients with CLD/CKD/CHF/CAD/Metabolic syndrome
• Possible drug interactions
Psoriasis

- **Psoriasis** is a chronic inflammatory skin disease with an estimated global prevalence ranging from **0.5% to 4.6%**.

- **10–20%** of psoriasis patients have moderate-to-severe disease and require phototherapy or systemic treatment.

- Sometimes *systemic monotherapy does not result in adequate disease clearance*—combination of systemic modalities for variable time periods are required.

- Majority of patients can’t afford ‘out of pocket’ cost of biologics/biosimilars.
Rationale of combination therapy

- Less cumulative or acute toxicity
- Additive or synergistic effect
- Increased possibility of tailoring therapy to patient’s needs

Improved therapeutic outcome

Improved patient adherence
• Combination therapy

• Sequential therapy
Combination Therapy With Methotrexate
Methotrexate and NBUVB

• **Synergistic action of MTX and NBUVB**
  - Significant anti-inflammatory properties and anti-mitotic and anti-proliferative action on infiltrating T lymphocytes
  - Reduction in the scaling and infiltration of the lesions by MTX - enabling deeper penetration of NBUVB

• **The risk of increased incidence of non-melanoma skin cancer** remains largely theoretical esp. in the Indian context
<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Protocol</th>
<th>Results</th>
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<tbody>
<tr>
<td>Asawanonda et al</td>
<td>J Am Acad Dermatol. 2006;54:1013-18</td>
<td>MTX -15 mg/wk NBUVB -3 times/week Till achievement of PASI 90 or 24 weeks</td>
<td>90.9% of patients on MTX + NBUVB achieved clearance after a median time of 4 weeks compared with only 38.4% in the placebo/NBUVB group</td>
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</table>
| Soliman et al          | J Dermatolog Treat, 2015; 26(6): 528-534      | MTX - 7.5 mg-30 mg/week NBUVB-twice weekly                                | MTX/NBUVB as compared to MTX monotherapy had  
• Higher clearance rate (100% versus 83%)  
• Earlier onset of improvement                                                                                           |
| PGI study (Mahajan et al.) | JEADV. 2010;24:595-600                  | MTX 0.5 mg/kg/weekly upto 30 mg/week NBUVB – Started on the next day oral medication – 3 times/weekly on non-consecutive days. Starting dose - 280 mJ/cm² | Combination group had:  
• Higher clearance rate (100% versus 77.7%)  
• Lesser mean time to achieve clearance  
• Lesser cumulative dose of NBUVB  
• No significant difference with regards to side effects and relapse                                                   |
• **Long term follow up for cutaneous malignancy** – theoretical risk of NMSC.

• **Extremely rarely, methotrexate** can induce an acute or delayed phototoxic reaction following phototherapy.

• **In order to minimize this risk**, there should be maximum amount of time (at least 1 day gap) between methotrexate and the next phototherapy session.

MTX induced phototoxic reaction
Methotrexate and PUVA

- **Combination of MTX and PUVA** can reduce the disease clearance time in plaque type psoriasis compared to either as monotherapy.

- **Main disadvantage** - additive carcinogenesis, especially increased risk of squamous cell carcinoma.

- **May have limited long term utility** in patients previously unresponsive to PUVA treatment.

- **After treatment, many of the formerly PUVA resistant patients** experienced flare-ups or needed relatively high maintenance doses of UVA.

Methotrexate and Retinoids

- MTX was combined with either acitretin or etretinate in seven studies (25 patients)
- Available retrospective data (no RCT available) and case reports all show that MTX combined with retinoids led to disease clearance.
- Concomitant use of systemic retinoids and MTX has been discouraged due to risk of hepatotoxicity (FDA warning, based mainly on etretinate)
- Based on retrospective data of 18 patients, Lowenthal et al concluded that combination therapy with acitretin and methotrexate was well tolerated and often effective.

Transition strategies for systemic therapies

**Initial methotrexate-add acitretin**
- Begin tapering methotrexate over a 2 to 3 month period
- Introduce acitretin when the patient has been on 7.5 mg for 2 months
- Monitor liver function carefully

**Initial acitretin-add methotrexate**
- Both can be given at full doses concurrently
- Acitretin can be tapered or stopped abruptly
- Monitor liver function carefully
Monitoring

• Cautious monitoring of liver function test in view of cumulative hepatotoxicity

• Cautious monitoring of platelet count- risk of thrombocytopenia both by MTX and Acitretin

• Complete blood count

• Lipid profile

• P3NP/ Fibroscan
Methotrexate and cyclosporine

• **Statistically significant difference in favour of combination therapy** compared to methotrexate alone in PASI and psoriatic arthritis\(^1\)

• **Initially, use of methotrexate in combination with cyclosporine** was discouraged due to fear of cumulative toxicity\(^2\)

• **However, subsequent studies found methotrexate–cyclosporine combination** to have good results, with minor, transient, and manageable short-term adverse effects\(^3,4\)

Transition strategies for MTX-CsA

**Initial methotrexate-add cyclosporine**
- Add low or full-dose cyclosporine to methotrexate regimen. If previous methotrexate dose is high reduce dosage immediately (e.g. 30 mg/d to 20 mg/d).
- Continue cyclosporine until patient responds
- Taper or discontinue cyclosporine following clearing
- Monitor renal function, CBC carefully.

**Initial cyclosporine-add methotrexate**
- Add low-dose methotrexate to cyclosporine regimen
- Continue methotrexate until patient responds
- Taper or discontinue cyclosporine or methotrexate following clearing
- Monitor renal function, CBC carefully
Monitoring

• **LFT**- although not very frequent with cyclosporine, hepatotoxicity can be seen- cumulative hepatotoxicity risk with MTX

• **RFT**- Increase in kidney ADRs (e.g., hypertension or increase in serum creatinine) in RA patients treated with cyclosporine plus MTX in comparison to patients receiving cyclosporine alone.

Combination therapies with retinoids
Acitretin and phototherapy

- **Combination also exerts a retinoid dose-sparing effect**, 10 to 25 mg/d dose of acitretin sufficient for both reUVB and rePUVA, compared to the doses often necessary for clearing in monotherapy, which can reach 50 mg/d or more.

- **In reUVB, low-dose acitretin (10-25 mg daily) is started** about 2 weeks before the addition of UVB.

- **Acitretin can cause thinning of the stratum corneum**. To avoid phototoxicity, UVB doses should therefore be reduced 50% in the early stages of this combination therapy.
Transition strategies for systemic therapies

• **Initial phototherapy-add acitretin**
  - Decrease phototherapy dose by 50%, 1 wk after starting acitretin
  - Dose may be increased if no phototoxicity occurs
  - Add acitretin at 10-25 mg/day
  - Gradually increase acitretin until the patient has an effective response; 25 mg qd is usually optimal
  - Maintain acitretin at doses of 10/25mg/day

• **Initial acitretin-add phototherapy**
  - Add phototherapy at 50% usual dose to acitretin regimen
  - Acitretin can be tapered or discontinued once clearing occurs
Other combination therapies including retinoids

• Ezquerra et al. demonstrated a significantly greater PASI reduction in the combination group of acitretin and oral calcitriol compared to acitretin monotherapy\(^1\)

• Mittal et al. demonstrated a significant difference in PASI reduction in favour of combination therapy of acitretin and pioglitazone as compared to acitretin alone\(^2\)

• Combination of etretinate and eicosapentaenoic acid (omega-3 fatty acid) was found superior to acitretin and placebo in efficacy\(^3\)

Combination therapies with cyclosporine
Cyclosporine and Retinoids

- **Combination of cyclosporine and retinoids** has been found to be effective in few studies

- **CsA is “accelerator” of clinical response, acitretin is “maintainer”**

- **Advantage of combination** - possible limitation by the acitretin of development of tumoral and pretumoral skin lesions

- **Lipid profile must be closely monitored** because both retinoids and CsA may increase serum cholesterol and triglyceride levels.
Regimens for combination

- **Initial cyclosporine-add acitretin**
  - Add low-dose acitretin (10-25 mg/d or 25 mg/every other d) to full-dose cyclosporine
  - Taper cyclosporine over 3 months
  - Gradually increase acitretin according to response
  - Monitor lipids / LFT/ RFT carefully
  - Maintain on acitretin

- **Initial acitretin-add cyclosporine**
  - Acitretin can be tapered or stopped abruptly
  - Monitor lipids / LFT/ RFT carefully
  - Both can be given at full doses concurrently
Combination regimens for cyclosporine

Rescue therapy

• A short course of cyclosporine can be used in severe flares of disease as “rescue” or “bridging” therapy because of its rapid onset of action until an alternative maintenance treatment is instituted.

• Particularly useful in the treatment of erythrodermic, suberythrodermic, or generalized pustular psoriasis.

• In this instance, a reducing dose approach is used subsequent to commencing at a dose of 5 mg/kg/day.
• **Overlapping cyclosporine with alternative treatments**, such as methotrexate and biologic therapies, can avoid further deterioration of disease at the early stages of treatment while the new drug is taking effect.

• **In an open-label multicenter study of 33 patients** with erythrodermic psoriasis treated initially with cyclosporine 4.2 mg/kg/day, then gradually decreased after remission by 0.5 mg/kg/day every 2 months, 67% achieved complete remission and **27% achieved significant improvement at 2 to 4 months.**
Monitoring

• **Lipid profile** - deranged lipid profile - common side effect of both drugs

• **Myopathy** - reported as common side effect of both drugs, although seen rarely

• **LFT** - can be deranged by cyclosporine as well rarely

• **Cumulative risk of neurotoxicity** - although rare.
## Other combination modalities with CsA Cyclosporine

<table>
<thead>
<tr>
<th>Modality</th>
<th>Status</th>
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<tbody>
<tr>
<td>Cyclosporine and phototherapy</td>
<td>Not much evidence in support. Considered contraindicated due to the increased risk of SCC</td>
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| Cyclosporine with either mycophenolate mofetil or hydroxyurea | Two prospective studies combined and showed an overall good effect on PASI  
| Rapamycin and cyclosporine                   | No difference in PASI reduction as compared to cyclosporine monotherapy after 8 weeks  
| Cyclosporine and hydroxyurea                 | Low-dose cyclosporine has been used successfully with hydroxyurea in short-course therapy.  
Care must be taken in patients who have been on long-term cyclosporine therapy with possible resultant renal damage. Because hydroxyurea is renally secreted, the combination could increase the possibility of bone-marrow toxicity  
Br J Dermatol 1999; 140: 186-7                                                              |
Other newer combinations
<table>
<thead>
<tr>
<th>Modality</th>
<th>Status</th>
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| Apremilast in combination with other therapy (NBUVB, MTX, acitretin, etc.) | 81% of patients achieved PASI-75 who continued on drug past 12 weeks in a retrospective chart review.  
| Gliptins and phototherapy **Trials.** 2016 Jan 15;17:29                  | Ongoing randomised clinical trial in Ireland assessing dipeptidyl peptidase-4 inhibition (sitagliptin) therapy in psoriasis in combination with NB-UVB.                                    |
| Combination with fumaric acid esters **Dermatology.** 2015;230(2):119-27 | In a retrospective chart review of 17 patients, fumarates were combined with MTX, acitretin, cyclosporine, and biologics to treat recalcitrant psoriasis or psoriatic arthritis and the combination were found safe and effective. |
| Acitretin and hydroxyurea                                              | Have been used by us in patients resistant to monotherapy with acitretin or having affordability issue with Cyclosporin.  
Hydroxyurea 500 bd with acitretin 10mg od which can be increased to 25 mg. Data has not been analysed but it has proven to be an effective and safe combination. |
| Methotrexate/ acitretin and Metformin                                   | Useful in obese patients or metabolic syndrome                                                                                                                                   |
Possible combinations of therapies

<table>
<thead>
<tr>
<th>Primary treatment</th>
<th>Therapies with which primary treatment can be combined</th>
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<tbody>
<tr>
<td>UVB</td>
<td>PUVA, retinoids, MTX, CsA,* hydroxyurea,* MM,* 6TG*</td>
</tr>
<tr>
<td>PUVA</td>
<td>UVB, retinoids, MTX,† CsA,† hydroxyurea,* MM,* 6TG*</td>
</tr>
<tr>
<td>Retinoids</td>
<td>UVB, PUVA, MTX,† CsA, hydroxyurea,* MM,* 6TG*</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>UVB, PUVA,† retinoids,† CsA, hydroxyurea, sulfasalazine</td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>UVB,* PUVA,† retinoids, MTX, hydroxyurea, MM, 6TG*</td>
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</table>

*Combinations that have not been studied extensively but have been used by the authors.
†Combinations that have been used safely, but are not recommended for routine use.
Combination therapies with Apremilast

- A total of 81 patients were treated with apremilast in combination with at least 1 other therapy (NB-UVB, methotrexate, acitretin, cyclosporine etc) in a retrospective chart review.

- 81% of patients achieved PASI-75 who continued on drug past 12 weeks.

- Apremilast can be safely and effectively combined with phototherapy, systemic, and/or biological agents in patients not responding adequately to these agents alone.

- Gastrointestinal side effects were manageable in the majority of patients.

Combinations in special situations

• Erythrodermic/pustular psoriasis
  • Combinations of cyclosporine with other drugs (MTX, Acitretin) can be used for rapid clearance with cyclosporine and maintenance with MTX, Acitretin

• Pregnancy
  • Although category C, cyclosporine can be combined with NBUVB in severe or treatment refractory cases.

• Renal impairment-
  • NBUVB in combination with MTX/acitretin in low dose as both the drugs have renal excretion
• **Hepatic impairment**
  • Acitretin although hepatotoxic is relatively safer than MTX and can be combined with cyclosporine or hydroxyurea.
  • Cyclosporine can be combined with hydroxyurea

• **Metabolic syndrome**
  • Combination using gliptins and metformin can be used with systemic modalities.
  • Although MTX, acitretin and cyclosporine, all are relatively contraindicated – combination of these can be used under close monitoring

• **Congestive heart failure/ Coronary artery disease**
  • NBUVB combination with MTX/Acitretin (Lipid profile monitoring in case of Acitretin
<table>
<thead>
<tr>
<th>Modalities</th>
<th>Reason for contraindication</th>
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<tbody>
<tr>
<td>Hydroxyurea and methotrexate or azathioprine</td>
<td>Bone marrow suppression</td>
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<tr>
<td>Cyclosporine and PUVA/NBUVB</td>
<td>Petzelbauer et al found that the cumulative UVA dose required for clearance and the incidence of severe and early relapses were significantly higher in a group of patients on a regimen of cyclosporine and PUVA, compared with those receiving rePUVA.</td>
</tr>
<tr>
<td></td>
<td>Br J Dermatol 1997;136:275-8</td>
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# Drug interactions in co-morbid conditions

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<tr>
<th>Drug</th>
<th>Co-morbid condition</th>
<th>Caution</th>
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| Statins and other hypolipidemic drugs     | Coronary artery disease, Hyperlipidemia, metabolic syndrome | 1) Concurrent use of methotrexate or retinoids may increase the risk of hepatotoxicity  
2) Serious risk of rhabdomyolysis with cyclosporine and statins  
3) Retinoid use may lead to further dyslipidemia leading to dose adjustment of hypolipidemic drugs |
| Aspirin                                   | Coronary artery disease                     | Nephrotoxicity with cyclosporine  
May increase the levels of Methotrexate  
Phototoxic reaction with phototherapy |
| Sulfonylureas                              | Diabetes                                   | Photosensitivity with phototherapy                                       |
| Spironolactone                            | Heart failure                              | Hyperkalemia with cyclosporine                                           |
| Furosemide, thiazide                      | Heart failure                              | Nephrotoxicity with cyclosporine  
Photosensitivity with phototherapy                                      |
Conclusion

- **Very few good quality studies** on the role of combination of systemic therapies in psoriasis.

- **Combination of retinoids and phototherapy** - generally considered safe and effective - one of the most widely used and thoroughly investigated modality

- **MTX and CsA can be combined optimally** resulting in lower dosing and better outcomes

- **CsA and retinoid combination therapy** is also effective and safe with proper monitoring

- **Combining MTX with a retinoid** is not considered absolutely contraindicated, caution due to potential risk of life-threatening hepatotoxicity.

- Newer combinations are being investigated, with small molecules like apremilast and tofacitinib poised to enter India