Combing etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial

Conclusions
Individualized treatment strategy in patients with psoriasis

- Patients with moderate and severe psoriasis should be offered a systemic therapy
- Choice of systemic therapy is not difficult in most cases based on the indication and contraindication of each drug.
- Drugs can be used safely and a balanced therapy can be offered to all patients
- Flexible therapy is very important to accommodate life events, for patients with long-lasting remission and for cost reduction

Topical therapy for psoriasis
Giampiero Girolomoni
Topical therapies for psoriasis

- Indications
- 80% of patients with psoriasis have mild to moderate disease which can be treated with topicals only, ideally:
  - BSA ≤ 5% (up to 10)
  - Early in the course of treatment / non recalcitrant disease
- Patients with more extensive disease, concurrently treated with UV light or systemic agents, can adjunctively apply topicals on limited resistant lesions

- Choice of treatment
- Compounds
- Vehicles
- Scheme
- Body sites
- Patient’s needs
- Large amount of experience, few evidence-based recommendations on optimal use, treatment strategies and selection of first line agent.

Menter A et al. JAMA 2008;30:843-59
De Mozzi et al. BJD 2011;166:252-60
Paul C et al. JEADV 2012;26 (S3):1-10
Choice of topical therapies for psoriasis

Compounds
- Topical steroids
- Vitamin D analogues
- Combination of vitamin D analogues + steroids
- Others: tazarotene, salicylic acid, dithranol and tar.

Corticosteroids

Efficacy of topical steroids in mild-to-severe body plaque psoriasis: parallel-group studies

Number of daily applications:
- Fluocinonide once-a-day vs. a 4-times-a-day application schedule for 6 weeks = no significant difference in terms of efficacy.

Oclusive dressings:
- once daily for 30 days with either BMV 0.1% tape (30 µg/cm²) > BMV 0.12% cream (standard dose of 100 µg/cm²): higher reductions from baseline in PASI (mean reduction 61.7% vs 39.5%). Moreover, skin hydration was significantly increased with BMV tape but not with BMV cream when evaluated with a corneometer.

Formulation:
- the efficacy is similar for the lotion and the cream.

Corticosteroids

Optimal dosing (grade D, experts agreement 7.93/10)
- Monotherapy in psoriasis BSA ≤ 10%; on larger surface areas should be limited to exceptional circumstances.
- Initial treatment:
  - potent or superpotent topical steroid once a day, for 4 weeks, with a maximum weekly dose of 30 g. The aim is to achieve an improvement of 75% in severity at the end of the 4-week induction phase.
  - Occlusion is recommended for thick plaques and for palmar and plantar psoriasis.
  - Low and medium potency topical steroids are indicated only for psoriasis of the face and skin folds.
- Maintenance treatment: twice weekly.
- A dermatological review should be carried out after 6–12 weeks.

Safety (Experts agreement (mean): 9.98/10)
- The risk of skin infection during treatment with topical steroids is very low (grade D).
- When used according to recommendations, there is no risk of skin atrophy. The risk of significant systemic absorption and HPA axis suppression is very low (grade A).

Vitamine D analogues

- Calcipotriol
- Calcitriol
- Tacalcitol

Efficacy of topical vitamin D analogues as monotherapy over 4-12 weeks:
- Treatment success rate 4%-40.7%.
- Satisfactory response rate 22.3-96%.
- Experts agreement (mean): 8.76/10
Vitamine D analogues

Safety (Experts agreement (mean): 8.76/10)
- The correct use of vitamin D analogues does not expose the patient to hypercalcaemia following application to a skin surface area of ≤ 30% (grade A).
- It was not possible to answer to the question on maximum dose of topical vitamin D analogue not to be exceeded with the systematic literature review. So, the dosage recommendation was based on the body area to be treated.

Optimal dosing (Experts agreement (mean): 8.76/10):
- Vitamin D analogues as monotherapy are not indicated as induction treatment except for the face and skin folds (grade D).


Combined steroids + Vitamin D analogues

Efficacy (Experts agreement (mean): 8.76/10):
- The treatment success rate defined by ‘clear or almost clear’ or PASI 90 varied from 27.2 to 55.3% at 4–6 weeks.
- The meta analysis showed that the probability of success is twice higher with the combination with a topical steroid as compared with the vitamin D analogue monotherapy (OR= 2.09 95% CI 1.47–2.96).
- The efficacy of the combination between a vitamin D analogue and a topical steroid is higher than a vitamin D analogue alone, with a 50% success rate (grade A).

Devaux S et al. JEADV 2012;26:S3:52-60.

Topical vitamin D analogues + steroids: a systematic review. 19 studies
Treatment success rate 27.2-55.3%.

Devaux S et al. JEADV 2012;26:S3:52-60.
Combined steroids + Vitamin D analogues

Topical vitamin D analogues + steroids (VDS) versus vitamin D analogues alone (VD)

Metaanalysis: 9 studies
VDS have a probability of success twice higher than VD

Devaux S et al. JEADV 2012;26 (S3):52-60.

Combined steroids + Vitamin D analogues

Safety (Experts agreement (mean): 8.76/10):

- The correct use of vitamin D analogues does not expose the patient to hypercalcemia following application to a skin surface area of ≤ 30% (grade A).
- Hypercalcemia is very seldom reported (0.01%-1.2%); mostly transient hypercalcemia without any clinical implication, vitamin D analogue were stopped in exceptional cases.
- Skin atrophy was reported in two studies
- Only few studies investigated long-term treatment therefore no conclusion could be drawn.

Paul C et al. JEADV 2012;26 (S3):1-10.
Devaux S et al. JEADV 2012;26 (S3):52-60.

Combined steroids + Vitamin D analogues

Optimal dosing (Experts agreement (mean): 8.76/10):

- Monotherapy in psoriasis BSA ≤ 10%; must be used sparingly over more extensive areas.
- Induction treatment: once a day for 4 weeks (grade A).
  The recommended maximal dose for an affected body surface area of 10% is ≤ 2 x 60 g tubes per month (grade D).
- Maintenance treatment: twice weekly on the lesions site (grade A).

Paul C et al. JEADV 2012;26 (S3):1-10.
Topical retinoids and classical topicals

Tazarotene (Experts agreement (mean): 8.36/10):
- About 50% of patients treated with tazarotene experienced a 50% or higher improvement in severity score with no differences between formulations.
- Tazarotene can be used sparingly and over a limited surface area in association with topical steroids for resistant plaques (grade A).
- Classical therapies, such as coal tar and dithranol, some decades ago first-line in the treatment, now have a restricted use. However, in case first-line treatments are not effective or contraindicated, or patients are unsuitable for systemic therapies, classical topicals in a combination schedule at specialized units can provide an important solution as ultimum refugium.
- Experts agreement (mean): 8.36/10
- Use of tar has progressively been abandoned.
- Dithranol and tars are no longer used in current practice (grade D).

Penetration enhancers

Salicilic acid (Experts agreement: 8.36/10):
- Treatment with corticosteroids + penetration enhancers is more efficacious than monotherapy with either component (grade B).
- Salicylic acid + (superpotent) topical steroids → 44% and 60.8% improvement in efficacy as compared with both monotherapies after 7 and 21 day respectively.
- Combination therapy is well tolerated with only mild to minor side effects.
- Salicylic acid can be proposed at a concentration ≥ 5% as adjunct treatment for thick, limited psoriatic lesions (grade D).
- Clobetasol propionate + salicylic acid → PASI reduction of 83.4% after 15 weeks.

Choice of topical therapies for psoriasis

- Induction schemes
  - Based on efficacy data, adherence and cost, the recommended first-line induction treatment for plaque psoriasis is a combination of a vitamin D analogue and a topical steroid (grade D).
  - The association betamethasone dipropionate plus calcipotriol was 1.2–1.8 times more cost-effective than a vitamin D analogue monotherapy.

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<tr>
<th>Table 1: Cost per success of psoariosis in the context of 3-week topical treatment of 25% body surface area</th>
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<tr>
<td>Topical treatment</td>
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<td>Clobetasol + calcipotriol dipropionate</td>
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<td>Clobetasol + calcipotriol</td>
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<td>Salicylic acid + betamethasone dipropionate</td>
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<td>Salicylic acid + salicylic acid</td>
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<td>Salicylic acid</td>
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Paul C et al. JEADV 2012;26 (S3):1-10.
Choice of topical therapies for psoriasis

- **Maintenance schemes**
  - VD on week day + TS on week-end > TS on week-end alone at 6 months (p=0.045)
  - VD on week day + TS on week-end > VD on week day + vehicle on week-end at 6 months (85% vs 62% maintained or continued improvement)
  - VDS once daily > VD once daily at 48 weeks (p=0.025)

Kragballe K et al. Dermatology (Basel) 2006;213:319–326.

Topical therapies for specific body sites

**Flexural psoriasis**
- 2 studies 4-6 weeks
- M-PASI reduction at 4 weeks: 86.3% betamethasone, 62.4% calcipotriol, 38% pimecrolimus, 21.1% vehicle: all three active agents are superior to vehicle, but without significant differences among them.
- 0.1% tacrolimus ointment (60% clear/almost clear at week 6) > calcitriol ointment (33% clear/almost clear at week 6)


**Scalp Psoriasis Management**
1. Difficult to treat localization
2. Choice of therapy to be tailored to patient needs
3. Therapy may vary at different times for same patient
4. Patient’s education is imperative
5. Patient’s compliance and adherence to therapy is difficult
Topical therapies for specific body sites

Scalp psoriasis

- 9 studies 4-52 weeks
- Treatment success: VDS (68.4-83%) > VD (28.4-60%)
- VDS > VD or S alone
- VD lotion < clobetasol shampoo at 4 weeks
- VD (calcipotriol) solution > betametasone valerate solution at 4 weeks
- VD (calcipotriol) solution > placebo


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Summary of relative risk of response for all interventions based on patient’s assessment of response

Trunk and limb psoriasis
Scalp psoriasis

Adherence rates 50-100% in prospective studies up to 8 weeks (too short to be reliable)
Short-term treatment compliance is inadequate with approximately 50% of the recommended applications effectively performed (grade C).
Adherence to treatment did not vary between the topical preparations

Factors associated with better adherence:
- Higher age
- Female sex
- Level of education
- Age at onset
- Severity
- Men married
- Employed
- Medications free of charge
- Message of reassurance by doctor
- Timeframe and extent of beneficial effects expected
- Written instructions on medication use

Causes of non-adherence (reported by patients):
- Low efficacy of topical preparations
- Inconvenience factors
- Fear of side effects

Paul C et al. JEADV 2012;26 (S3):1-10

Patients’ adherence in psoriasis

Factors associated with better adherence:
- No
- Partial
- Yes
- May vary

Causes of non-adherence (reported by patients):
- Low efficacy of topical preparations
- Inconvenience factors
- Fear of side effects

Paul C et al. JEADV 2012;26 (S3):1-10

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Adherence to medical therapy

**Patient-related factors**
1. Younger age
2. Ethnicity
3. Literacy (including health literacy)
4. Health beliefs
5. Socioeconomic conditions
6. Others factors (substance abuse and psychiatric illness such as depression)

**Medication-related factors**
1. Side-effects
2. Pill burden
3. Dosing frequency
4. Regimen complexity
5. Polypharmacy
6. Cost


Patients’ adherence

- Patients want to take treatment, but is prevented to doing so by barriers behind his control:
  - Poor recall
  - Poor comprehension of instructions
  - Difficulties in administering the treatment
  - Forgetting
  - Difficulties in affording the treatment

- Patients decide not to take treatment (up to 44%):
  - Cognitive and emotional factors influence the inclination to start or continue the treatment

There is a degree of overlap. Motivation may overcome resource barriers and resource barriers may reduce motivation. Each individual is a unique mix of both interventions should be tailored.


Patients’ adherence in psoriasis

**Causes of non-adherence:**
- Lack of belief in the efficacy of medication
- Perceptions made inappropriate use of treatment (20%) (e.g., “I do not need to use this medication”)
- Difficulties in administering the treatment
- Forgetting
- Difficulties in affording the treatment
- The use of terms “sparingly” and “liberally” is confusing for patients
- Inadequate instructions

**Consequences of non-adherence:**
- 10% decrease in adherence is associated with an increase in disease severity (tacrolimus ointment)
- Better adherence (obtained by specifying the amount of medication to be used) resulted in 70% of previous non-responders achieving a 60% decrease in PASI score (calcipotriene)


Horne R. The art of adherence: optimizing patient outcomes in rheumatological arthritis and psoriasis.
Patients’ adherence in psoriasis

Recommendations for better adherence (grade D: Experts agreement (mean): 8.62/10):
- Limit the number of products and the complexity of the prescription.
- Limit the use of topical agents to a surface area of 10% or less.
- Take into account the type and location of the lesions.
- Inform the patient and involve him/her in the choice of treatment (molecule, galenic).
- Take into account the patient’s objectives and lifestyle, and gather motivation.
- Introduce a regular follow-up program.
- Explain to the patient the different phases of topical treatments: induction phase and maintenance phase.

Secure the maximum of compliance

- Establish a relationship with patients.
- Encourage patients to participate in planning treatment
  - Including choice of vehicle.
- Don’t scare patients with side effects
  - Don’t use the word “steroid”.
- Choose fast-acting agents so patients see a change.
- See patients for a return visit.

Anti-IL-17 biological agents

Giampiero Girolomoni