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

IPC, psoriasis preceptor ship
Verona, 13 June 2013
Psoriasis
the need of new therapies

- Only a portion of patients in need receive a treatment
- Many patients have contraindications to current therapy
- A portion of patients is not responding to current therapy
- Patients may lose response in the long term (10-15% every year)
- Need of more specific drugs
- Drugs with improved safety profile
- Easier to administer
- Cheaper drugs

Evolution of psoriasis treatments
- therapeutic target evolution -

- Inflammatory cells
- keratinocytes
- cytokines
- mediators
- Signal transduction pathways
- small molecule drugs
  - e.g. MTX, CsA
- large biotech molecule drugs
  - e.g. anti-TNF
- small molecule drugs
  - e.g. tofacitinb, apremilast
  - Signal transduction pathways

Novel systemic drugs under investigations for the treatment of psoriasis


Copyright
Psoriasis pathogenesis
selectivity of biological therapy

Innate immunity  Adaptive immunity

- myeloid DC
- plasmocytoid DC
- neutrophils
- natural killer cells
- TNF-α
- IL-12
- Th1, Th17, Th22
- IFN-γ
- IL-17

Environment

- TLRs

TNF-α
IL-12
IL-23
IL-22
IL-17

IL-17-producing cells are present in several chronic inflammatory diseases

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Psoriasis</th>
<th>Selectivity of biological therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Pathologies | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 | IL-12 | IL-23 | IL-17 |
|-------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Inflammation | 30%  | 25%  | 10%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   |
| Selectivity | 30%  | 25%  | 10%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   | 5%    | 15%   | 85%   |

IL-17 family members

<table>
<thead>
<tr>
<th>Member</th>
<th>Alternate names</th>
<th>Target receptor</th>
<th>Main functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A</td>
<td>CTCL-F</td>
<td>IL-17RA and IL-17A</td>
<td>Neutrophil recruitment, host defense against extracellular pathogens, immunopathology</td>
</tr>
<tr>
<td>IL-17B</td>
<td>C3, NERF</td>
<td>IL-17B</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17C</td>
<td>C3, NERF</td>
<td>IL-17C</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17D</td>
<td>IL-28, IL-27, IL-27</td>
<td>Unknown</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17E</td>
<td>IL-25</td>
<td>IL-17B and IL-17F</td>
<td>Stimulates Th2 responses; suppresses Th17 responses</td>
</tr>
<tr>
<td>IL-17F</td>
<td>ML-1</td>
<td>IL-17A and IL-17C</td>
<td>Neutrophil recruitment[?], host defense against extracellular pathogens[?], immunopathology?</td>
</tr>
</tbody>
</table>

IL-17 family cytokines and receptors

IL-17 protects skin and mucosal immunity from bacterial and fungal infections

- IL-17RA deficiency is associated with recurrent or persistent mucocutaneous infections caused by Candida albicans and, to a lesser extent, Staphylococcus aureus
- Mutation in the IL-17F gene can cause chronic mucocutaneous candidiasis, but with incomplete clinical penetrance
- Neutralizing autoantibodies against IL-17 and IL-22 present in patients with thymoma or autoimmune polyendocrinopathy-candidiasis-ectodermal syndrome type I
- A variety of genetic defects leading to impaired Th17/22 immunity are associated with increased susceptibility to mucosal and cutaneous fungal (candidal and dermatophyte): DECTIN1, caspase recruitment domain-containing protein 9 (CARD9), STAT3, STAT1, DKK1

IL-17A producing cells

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ Th17 cells</td>
<td>+++</td>
</tr>
<tr>
<td>CD8+ Tc17 cells</td>
<td>++</td>
</tr>
<tr>
<td>γδ T cells (Vγ9Vδ2)</td>
<td>+++ (?)</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>++</td>
</tr>
<tr>
<td>Mast cells</td>
<td>+</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>+</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>+</td>
</tr>
</tbody>
</table>
IL-17+ Cells in Psoriasis

A. Cavani
IDI, Rome

T Cells in Inflammatory Skin Diseases

Potential role of IL-17 in the pathogenesis of psoriasis
TNF-α and IL-17 synergize in modulating chemokine synthesis in cultured keratinocytes

Th17 cell products and downstream mediators are rapidly down-modulated with etanercept treatment compared with Th1 and Th2 cell products

Targeting IL-17 in the therapy of psoriasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Composition</th>
<th>Target</th>
<th>Dose and administration*</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>human IgG1κ mAb</td>
<td>IL-17A</td>
<td>SC, 150-300 mg</td>
<td>Novartis</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>humanized IgG4 mAb</td>
<td>IL-17A</td>
<td>SC, 25-75 mg</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>human IgG2aκ mAb</td>
<td>IL-17RA</td>
<td>SC, 7b-210 mg</td>
<td>Amgen</td>
</tr>
</tbody>
</table>

* Phase 2 studies
IxEkizumab in the therapy of psoriasis

![Graph showing percentage of improvement with IxEkizumab and placebo.](Leonardi et al. NEJM 2012;366:1190-9)

IL-17 neutralization (IxEkizumab) results in decreased keratinocyte proliferation and differentiation, leukocyte infiltration, and keratinocyte release of inflammatory cytokines

![Histological images showing changes with and without IxEkizumab.](Krueger JS et al. JACI 2012;130:145-54)

Brodalumab in the therapy of psoriasis

![Graph showing percentage improvement with Brodalumab and placebo.](Papp et al. NEJM 2012;366:1181-9)
Secukinumab in the therapy of psoriasis

Huober et al. SciTransl Med 2010;2:52ra72

IL-17A-blocking mAb secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects


Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study

The main objective of the study was to evaluate the efficacy and safety of secukinumab, an IL-17A-blocking mAb, in the treatment of moderate-to-severe plaque psoriasis.

Weeks 12 and 24: secukinumab demonstrated significant improvements in PASI and PGA compared to placebo. In addition, secukinumab showed a favorable safety profile, with no unexpected adverse events reported.

Secukinumab at doses of 12 and 15 mg showed a significant improvement in PASI and PGA compared to placebo. The 30 mg dose also demonstrated significant improvements, but the results were not statistically different from the 12 and 15 mg doses.

In conclusion, secukinumab at doses of 12, 15, and 30 mg showed significant improvements in PASI and PGA compared to placebo, with a favorable safety profile. These results support the potential use of secukinumab in the treatment of moderate-to-severe plaque psoriasis.
Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase III regime-finding study


Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study

Ongoing studies

- Secukinumab and ixekizumab are in phase III clinical development for plaque psoriasis (NCT01365455 ERASURE, NCT01406938 SCULPTURE, NCT01365478 FIXTURE, NCT01412944 STATUERE for secukinumab and NCT01507245 UNCOVER-2 for ixekizumab).

- Secukinumab (150 mg and 300 mg) will be compared with etanercept (50 mg) and with placebo in the FIXTURE study. Similarly, the UNCOVER-2 study will compare ixekizumab (80 mg) and etanercept (50 mg) or placebo.

- The secukinumab SCULPTURE study will investigate secukinumab (150 mg) in a retreatment at start of relapse regimen.

- Other diseases where anti-IL-17 blockers are under investigation include psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, uveitis, asthma, multiple sclerosis.
Secukinumab very effective for inducing clearance of skin psoriasis

A randomized, double-blind, multicenter study of subcutaneous secukinumab, assessing PASI response and maintenance of response subjects with moderate to severe chronic plaque-type psoriasis on either a fixed dose regimen or on a retreatment at start of relapse regimen.

No adverse events reported
Effect of Secukinumab, a Fully Human Anti-IL-17A Monoclonal Antibody on C-Reactive Protein (CRP) Levels in Patients With Moderate-to-Severe Plaque Psoriasis: Result of a Dose-Ranging Study

R. G. Langley, G. Girolomoni, A. Guettner, C. Papavassilis, H. B. Richards
Dalhousie University, Halifax, Canada; University of Verona, Verona, Italy; Novartis Pharma AG, Basel, Switzerland

Study Design: Induction Period

The secukinumab 3x150 mg and 3x75 mg groups at Week 12 met the primary endpoint of achieving significantly higher rates of PASI 75 response than placebo (81.5% and 57.1% vs. 9.1%; p<0.001 and p=0.002; respectively)

CONCLUSIONS

• The primary endpoint of this study was met with the secukinumab 3x75 mg and 3x150 mg cohorts achieving significantly greater PASI 75 responses than placebo at Week 12
• The results of this post-hoc analysis suggest that secukinumab at clinically efficacious doses results in reductions in hs-CRP levels indicating that secukinumab may decrease cardiovascular risk in patients with moderate-to-severe plaque psoriasis
• More specific target
• Phase 2/3 trials indicate a very fast and effective therapeutic effect in skin psoriasis in the short term and sustained response in the long term
• IL-17 inhibition is expected to impact less on the immune system and host defense against microorganisms and cancer as compared to TNF-α or IL-12/IL-23 inhibition
• Targeting IL-17A/F rather than IL-17RA may have a more favorable safety profile
<table>
<thead>
<tr>
<th>Therapy of psoriasis with IL-17 blockers - Important questions to be addressed -</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efficacy on PsA (including synovitis, enthesitis, axial disease, and radiologic damage)</td>
</tr>
<tr>
<td>• Flexibility (possibility of stopping and restart treatment maintaining efficacy)</td>
</tr>
<tr>
<td>• Safety (or even positive effects) on cardio-metabolic co-morbidities</td>
</tr>
<tr>
<td>• Development of anti-drug antibodies</td>
</tr>
<tr>
<td>• Long term safety (infection and cancer risk)</td>
</tr>
<tr>
<td>• Efficacy on pustular psoriasis</td>
</tr>
</tbody>
</table>