Efficacia di un nuovo inibitore pegilato del TNF alfa sulla psoriasi artropatica

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PSORIASI ARTROPATICA (PsA):

- E’ una spondiloartrite sieronegativa

- **Prevalenza:** 0,02-0,25% nella popolazione generale e interessa il 6-48% dei pazienti psoriasici

- **Patogenesi:** sono implicati fattori di tipo ereditario ed anche fattori esacerbanti quali infettivi, traumatici, stress etc.

PsA

- **Esordio**: tra 35 e i 55 anni, con percentuali sovrapponibili nei due sessi

- **Decorso**: variabile e imprevedibile (cronico-recidivante)

- Infiammazione dei tessuti articolari che si traduce in lesioni di tipo osteolitico ed erosivo delle articolazioni interessate

- **Clinicamente**: dolore, tumefazione e conseguenti deformità, fino alle forme più gravi francamente mutilanti

In base alle caratteristiche cliniche, si distinguono, secondo la Classificazione di Moll e Wright (1973), cinque forme di psoriasi artropatica:

- **Oligoartrite asimmetrica** (dattilite)
- **Poliartrite simmetrica** (o simil-reumatoide)
- **Classica** (a prevalente interessamento delle articolazioni interfalangee distali)
- **Assiale** (o Spondilitica)
- **Mutilante**
Established inflammatory articular disease (joint, spine, or enthesesal) with three or more of the following

**Psoriasis**
(a) Skin or scalp disease present today as judged by a qualified health professional
(b) History of psoriasis obtained from patient, or qualified health professional
(c) Family history of psoriasis in a first or second degree relative

**Nail changes**
Typical nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination

**RF negative** (except latex method)

**Dactylitis**
(a) Current Swelling of an entire digit
(b) History of dactylitis recorded by a qualified health professional

**Radiological evidence of iuxta articular new bone formation**
defined ossification near joint margins (excluding juxta-articular new osteophyte formation) on plain x-rays of hand or foot

APPROCCIO TERAPEUTICO:

• I DMARDs sono il primo step terapeutico:
  - Azatioprina
  - Sali d’oro
  - Methotrexato
  - Ciclosporina
  - Leuflonide
  - Sulfasalazina
  - Idrossiclorochina

• Non esistono tuttavia evidenze cliniche che questi siano in grado di arrestare la progressione del danno articolare

• Gli anti TNFα costituiscono l’unica alternativa terapeutica laddove i DMARDs siano risultati inefficaci

• Sono gli unici farmaci per i quali è stata dimostrata la capacità di inibire la progressione del danno articolare

Effetti destrucenti del TNF-α

Riassorbimento osseo
Erosione ossea

Infiammazione articolare
Dolore Tumefazione

Degradazione della cartilagine
Riduzione rima articolare

M-CSF
RANKL
RANK
RANKL
RANK
RANK
RANKL

Precursori degli osteoclasti
articolazione
Sangue, BM

TNF-α
IL-1

osteoclasti
sinoviociti
condrociti

↓ osteoprotegerin

Kastelan D. et al. Med Hypotheses. 2006; Jul 14
## Treatments

<table>
<thead>
<tr>
<th></th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Golimunab</th>
<th>Ustekinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Human fusion protein of IgG1 and p75 receptor</td>
<td>Chimeric MAb</td>
<td>Human MAb</td>
<td>Human Mab</td>
<td>Human Mab</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>50 mg ow JRA 0.4 mg/kg SC biweekly</td>
<td>3 –10 mg/kg Q 4-8 weeks intravenous</td>
<td>40 mg q 1 to 2 wks</td>
<td>50 mg sc 1/month</td>
<td>45 mg sc 1-3 months</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2.9 days</td>
<td>9.5 days</td>
<td>12-14 days</td>
<td>14 days</td>
<td>21 days</td>
</tr>
<tr>
<td><strong>Fixes complements</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lyses TNF-expressing cells</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Binds LTX</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>MTX therapy</strong></td>
<td>Optional</td>
<td>Required</td>
<td>Recommended</td>
<td>Recommended</td>
<td>Optional</td>
</tr>
</tbody>
</table>
Therapy

Nail Psoriasis: A Review of Treatment Options

Marcel C. Pasch

Topical

- Corticosteroids
- Corticosteroids + Vitamin D3 analogs
- Tazarotene
- Calcineurin Inhibitors
- Anthralin
- 5-Fluorouracil
- Allopurinol
- Intrallesional Corticosteroids/Methotrexate
- Colloidal Silicic Acid
- Indigo Naturalis Extract

Systemic

- Methotrexate
- Cyclosporine
- Retinoids
- Apalimast
- Fumaric Acid Esters
- Sulfasalazine
- Leflunomide

Systemic

- Anti TNF-alpha
  - Infliximab
  - Adalimumab
  - Etanercept
  - Golimumab
  - Certolizumab
  - Ixekizumab
  - Anti IL-12/23
  - Ustekinumab
  - Apalimast
  - Tofacitinib
  - Anti IL-17
  - Secukinumab

Non-pharmacological

- Laser Therapy
- Phototheraphy
- Photodynamic therapy
- Radiotherapy
Anti-TNF treatment in PsA

**Recommendation**

European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies

TNF inhibitors have demonstrated efficacy in PsA, both for skin and joint involvement, as well as in preventing radiographic damage.
Properties of PEG and PEGylated Molecules

• Potential Effects of PEGylation:

- May improve the pharmacokinetics of therapeutic agents
- May improve bioavailability
- May enhance penetration and retention of macromolecules into various diseased tissues
- May reduce immunogenicity of some proteins (at this time this has not been shown for CZP)
• CZP is the only **PEGylated** anti-TNF-α

• Site-specific PEGylation resulted in:
  - Designed half life of ~14 days
  - Enhanced **penetration of CZP into inflamed tissue** (in animal models)*

• **No Fc region**

  May avoid potential Fc-mediated effects such as CDC or ADCC*

  No recycling by FcRn which may lead to longer residency in inflamed tissue

  Non-clinical studies suggest **low or negligible level of placental transfer** of a homologue Fab-fragment of certolizumab pegol

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CDC=complement-dependent cytotoxicity
ADCC=antibody-dependent cell-mediated cytotoxicity
To demonstrate efficacy of CZP on the **signs and symptoms of active PsA** and on the **inhibition of progression of structural damage** in adults with active PsA

To assess the effects on **safety and tolerability** and to demonstrate the effects of CZP on: Health outcomes, Psoriatic skin disease in the subgroup of affected patients (>3% BSA) at baseline, Dactylitis, Enthesitis
At week 12, 58.0% and 51.9% in the CZP 200 mg Q2W and CZP 400 mg Q4W groups vs 24.3% in the placebo group achieved an ACR20 response.

A clinically significant difference in ACR20 response between both CZP treatment groups and placebo was observed as early as week 1.

PASI90 Response at Weeks 24

Nominal p value <0.001; J Mease et al, Ann Rheum Dis. Epub. 2013; SCT-IMNL-CGR-039_04/2015
Efficacy of Licensed Biologic Treatments in PsA

Not a H2H comparison; direct comparisons cannot be made.

**ACR20 Responders (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>ACR20 Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast&lt;sup&gt;2&lt;/sup&gt; (30 mg BID)</td>
<td>36.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.3</td>
</tr>
<tr>
<td>Ustekinumab&lt;sup&gt;2&lt;/sup&gt; (45 mg Q2W)</td>
<td>42.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>22.8</td>
</tr>
<tr>
<td>Etanercept&lt;sup&gt;3&lt;/sup&gt; (25 mg BiW)</td>
<td>50.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.0</td>
</tr>
<tr>
<td>Secukinumab&lt;sup&gt;4&lt;/sup&gt; (150 mg Q4W)</td>
<td>50.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>17.3</td>
</tr>
<tr>
<td>Golimumab&lt;sup&gt;5&lt;/sup&gt; (50 mg Q4W)</td>
<td>52.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.0</td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;6&lt;/sup&gt; (5 mg/kg)</td>
<td>54.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>16.0</td>
</tr>
<tr>
<td>Secukinumab&lt;sup&gt;7&lt;/sup&gt; (300 mg Q2W)</td>
<td>54.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>15.3</td>
</tr>
<tr>
<td>Adalimumab&lt;sup&gt;8&lt;/sup&gt; (40 mg Q2W)</td>
<td>57.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>15.0</td>
</tr>
<tr>
<td>Certolizumab Pegol&lt;sup&gt;9&lt;/sup&gt; (200 mg Q2W)</td>
<td>63.8</td>
</tr>
</tbody>
</table>

**ACR20 Response at Week 24**

**Notes:**
- BID: Twice Daily
- BiW: Twice Weekly
- Q2W: Every 2 Weeks
- Q4W: Every 4 Weeks
- Q12W: Every 12 Weeks
Efficacy of Licensed Biologic Treatments in PsA

Not a H2H comparison; direct comparisons cannot be made

PASI75 Responders (%)

PASI75 Response at Week 24: In Patients with Psoriasis ≥3% BSA at Baseline

BID: Twice Daily, BiW: Twice Weekly, Q2W: Every 2 Weeks, Q4W: Every 4 Weeks; Q12W: Every 12 Weeks
Anti-TNFα do not seem to carry any significant risk of adverse pregnancy outcome.

As the half-life of monoclonal anti-TNF-α antibodies is prolonged to several months in newborns, an increased risk of infection in the child exists during late pregnancy exposure.

CZP differs from other anti-TNF-α in that it has no Fc region and is not actively transported through the placenta.

Confirmed Diagnosis of Pregnancy → interruption of treatment is advised but not compulsory.

Assessment of Benefits/Risks Ratio on a case-by-case basis (concurrent therapies risk– disease relapse – irreversible joint damage due to PsA ).
Study Populations:

- **Inclusion criteria**: patients unresponsive or intolerant to conventional therapies or unresponsive to other biologics drugs.

- **Exclusion criteria**: active or past serious medical conditions that contraindicate therapy with biologics.

- **Initial assessment**:
  - PASI (severity of psoriasis index)
  - DAS44 (joint involvement index)
  - VAS (visual analogue scale of severity disease)

- **BASELINE**: medical history and EO, haematological routine, hepatitis markers, TB Gold and chest X-ray, ECG, Echocardiogram.
## OUR STUDY POPULATION

<table>
<thead>
<tr>
<th>Mean AGE</th>
<th>Sex</th>
<th>Naïve to Biologics</th>
<th>PSA</th>
<th>PSA/PSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.8±8</td>
<td>16 M; 25 F</td>
<td>14</td>
<td>5</td>
<td>36</td>
</tr>
</tbody>
</table>

- **41 patients**
- **32 patients (group A)** completed three months of treatment
- **12 patients** completed six months of treatment (**group B**)

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Active rheumatic disease was considered if $\text{DAS44} > 3.7$

Adequate clinical response was indicated by $\text{DAS44-ESR} \leq 2.4$

Remission was considered if $\text{DAS44} < 1.6$

- **Dropped out:** 1 alopecia, 1 failure, 1 bariatric surgery complication
The clinical efficacy was consistent on both cutaneous and rheumatic components as demonstrated by the reduction of:

- **mean PASI** score from 4.4±4.7 at BL to 2.3±3.7 at W12 (group A) and from 5.1±5.7 at BL to 0.8±1.2 at W24 (group B)
- and decreasing of **DAS44-ESR** from 4.4±0.6 at BL to a mean of 2.2±0.9 at W12 (group A) and from 4.1±0.6 at BL to a mean of 1.9±0.5 at W24 (group B)
GROUP A

**PASI T0 vs PASI W12**
- 95% CI: 0.001

**DAS-44 T0 vs DAS-44 W12**
- 95% CI: 0.001

**VAS T0 vs VAS W12**
- 95% CI: 0.001
GROUP B

- **DAS-44**
  - T0: 4.2 ± 0.5
  - W12: 2.8 ± 0.3
  - W24: 2.5 ± 0.4

  *p* = 0.0001

- **PASI**
  - T0: 7.5 ± 2.0
  - W12: 5.0 ± 1.5
  - W24: 3.0 ± 0.5

  *p* = 0.0301

- **VAS**
  - T0: 120 ± 10
  - W12: 70 ± 5
  - W24: 50 ± 5

  *p* = 0.0031
Our experience result: case 1 (naive)

**BASELINE**

**W 12**
Our experience result: case 1
12 months
16 months
US after 6 months