This is an author produced version of Evidence of response to IL-6 inhibition in some cases of refractory spondyloarthritis-associated peripheral synovitis.

White Rose Research Online URL for this paper: http://eprints.whiterose.ac.uk/103003/

Article:
Merashil, M, De Marco, G, Podgorski, M et al. (2 more authors) (2016) Evidence of response to IL-6 inhibition in some cases of refractory spondyloarthritis-associated peripheral synovitis. Annals of the Rheumatic Diseases, 75 (7). pp. 1418-1420. ISSN 0003-4967

https://doi.org/10.1136/annrheumdis-2016-209275

(c) 2016, The Authors. This is an author produced version of a paper published in Annals of the Rheumatic Diseases. Uploaded in accordance with the publisher's self-archiving policy.
Letter to the Editor:

Title:

Evidence for a Role of Interleukin-6 in Refractory Spondyloarthritis associated Peripheral Synovitis

Authors and affiliations:

Mira Merashi¹, Gabriele De Marco¹, Mark Podgorski², Dennis McGonagle¹, Helena Marzo-Ortega¹

  ¹ NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

  ² Hornsby Kuringai Hospital, Sydney, Australia

Corresponding Author: Dr. Helena Marzo-Ortega

Address of correspondence:

Leeds Institute of Rheumatic and Musculoskeletal Medicine
Second floor, Chapel Allerton Hospital
Chapeltown Road, Leeds LS7 4SA
Phone: +44 (0) 113 392 4848
Fax: +44 (0) 113 392 4991
Email Address: H.Marzo-Ortega@leeds.ac.uk

Key Words: ankylosing spondylitis, interleukin-6, psoriatic arthritis, Tocilizumab, peripheral arthritis
Sir,

The Spondyloarthopathies (SpA) are complex polygenic disorders with mixed clinical phenotypes. Pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin (IL)-17 and -23 play key pathogenetic roles in SpA, with their blockade being effective in many, but not all cases. Inhibition of IL-6 effectively suppresses synovitis in rheumatoid arthritis (RA)\textsuperscript{1} but has failed to show efficacy in ankylosing spondylitis (AS), the prototype SpA, in two controlled clinical trials.\textsuperscript{2,3} This is surprising since genetic and experimental studies indicate a potential role for IL-6 in some SpA subsets.\textsuperscript{4,6} Here, we report our experience in 4 male patients with AS and severe, recurrent peripheral synovitis. Detailed clinical and laboratory characteristics are summarized in Table 1 but briefly they all fulfilled the modified New York criteria for AS with two cases (2 and 4) also meeting CASPAR criteria for PsA. Advanced spinal fusion and deforming asymmetrical erosive polyarthritis in peripheral joints had led to extensive replacement and reparative surgery to improve function in all cases.

All four subjects had negative CCP and RF antibodies and they had previously experienced primary or secondary non-response to multiple TNF inhibitors (TNFi). Based on limited therapeutic options at the time and the proven efficacy of IL-6 inhibition in RA associated polyarthritis, tocilizumab (TCZ) was given with dramatic effect on laboratory and clinical parameters of disease (Table 1). All cases showed objective responses in both the peripheral synovitis and axial symptoms. Tocilizumab treatment was well tolerated in all cases and is currently ongoing with a mean of 2 years exposure.

We believe that our findings suggest a role for IL-6 inhibition in a subset of cases with a clinical phenotype of aggressive, destructive peripheral arthritis resembling RA suggesting that the role of IL-6 in the pathogenesis of SpA, particularly in certain subsets merits further consideration. Indeed, genetic studies have shown evidence for IL-6R SNPs being associated with AS. Intriguingly, SNPs in the TNFAIP3 gene which codes for the A20 negative regulatory of NF kappa B have been associated with RA, psoriasis, PsA and AS.\textsuperscript{7} An animal model with myeloid conditional knockout of A20 was originally reported to represent a model of RA which was TNF independent but IL-6 dependent.\textsuperscript{7} However, it has been recently shown that this model starts in fact at the entheses and synovio-enthesal complex.\textsuperscript{4} Furthermore, a study evaluating the blocking effect of IL-6 in synovial fibroblasts of eight patients with non-radiographic axial SpA showed that IL-6 expression was reduced by TCZ following fibroblast priming with TLR 2 and 4 after the in vitro administration,\textsuperscript{5} possibly suggesting an effect for synovitis. Anti-IL-6 therapy is associated with CRP reductions and in our cases it was also beneficial in subjective outcomes of disease activity, function and pain.

In conclusion, these observations point towards a possible role for IL-6 in TNF resistant axial SpA with associated peripheral synovitis. Remarkably, this phenotype has already been noted in experimental models. Further clinical studies are needed to determine whether some of the clinical heterogeneity in SpA may be related to the IL-6 cytokine pathway.
Table 1. Clinical characteristics and previous biologic exposure of cases reported.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease duration (years)</strong></td>
<td>12</td>
<td>30</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>-ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>Skin Psoriasis</td>
<td>N</td>
<td>Plaque</td>
<td>N</td>
<td>Plaque</td>
</tr>
<tr>
<td>IBD</td>
<td>Crohn’s</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Uveitis</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Radiographic findings</strong></td>
<td>Sacroilitis</td>
<td>Fusion of SIJs and spine</td>
<td>Fusion of SIJs and cervical spine</td>
<td>Fusion of SIJs, vertebral bodies C4-C6</td>
</tr>
<tr>
<td></td>
<td>Erosive, deforming involvement of hands and feet</td>
<td>Erosive, deforming involvement of hands and feet</td>
<td>Erosive involvement of odontoid peg with synovitis on MRI</td>
<td></td>
</tr>
<tr>
<td>Previous biologics and reason for discontinuation</td>
<td>ADA, Gol, INF. All stopped due to either primary or secondary non-response.</td>
<td>ETA (Articular chondritis and GI intolerance) INF (Shortness of breath). ADA (Shortness of breath and GI intolerance)</td>
<td>ETA (Cutaneous Pseudoporphyria)</td>
<td>INF, ADA, ETA, Anakinra, INF, Abatacept, Secukinumab. All stopped due to either primary or secondary non-response.</td>
</tr>
<tr>
<td>Duration of TCZ exposure (months)</td>
<td>62</td>
<td>9</td>
<td>38</td>
<td>48</td>
</tr>
</tbody>
</table>

Clinical parameters and patient reported outcomes pre TCZ and after mean 6.2 month exposure:

<table>
<thead>
<tr>
<th></th>
<th>Pre-TCZ 6 mo</th>
<th>Pre-TCZ 6 mo</th>
<th>Pre-TCZ 6 mo</th>
<th>Pre-TCZ 6 mo</th>
<th>Pre-TCZ 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>171</td>
<td>1</td>
<td>103</td>
<td>&lt;5</td>
<td>26</td>
</tr>
<tr>
<td>TJC (68)</td>
<td>10</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>SJC (66)</td>
<td>10</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>20</td>
</tr>
</tbody>
</table>
- **BASDAI**
  - 9
  - NA
  - 5.8
  - 3.9
  - 9.8
  - 2.6
  - 5.9
  - 4

- **BASFI**
  - NA
  - NA
  - 9.3
  - 9.7
  - 10
  - 0
  - 5
  - 4.8

- **VAS spine pain (10 cm)**
  - NA
  - NA
  - 5
  - 2
  - 7
  - 0
  - 5
  - 5

NA: not available; ADA: Adalimumab; CZA: Cimzia; ETA: Etanercept; INF: Infliximab; TCZ: Tocilizumab

**Acknowledgements:** To the patients presented here and clinical colleagues involved in their clinical care in particular Paul Emery, Anna Moverley and Sudipto Das.

**Competing Interests and funding:** Nothing to declare for all authors.

**References:**


5. S.Y. L. IL-6 maybe a crucial role in peripheral arthritis of ankylosing spondylitis by toll-like receptor 2 and 4 Annals of the Rheumatic Diseases 2014;73(0003-4967 ).
