Review: Antitumor necrosis factor-α–directed therapies are recommended for NSAID-refractory spondyloarthritis


**Question**
In patients with spondyloarthritis, what is the optimal use of biologic response modifiers (antitumor necrosis factor-α [anti-TNF-α] agents)?

**Data Sources**
Studies were identified by searching MEDLINE using the terms ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, psoriatic arthritis, infliximab, etanercept, and tumor necrosis factor. Abstracts from the 1999 to 2002 proceedings for 2 rheumatology annual meetings were also reviewed.

**Study Selection and Assessment**
Studies were selected if they were randomized, placebo-controlled trials (RCTs) or nonrandomized clinical trials evaluating anti-TNF-α agents in patients with spondyloarthritis. A consensus group graded the evidence according to the guidelines of the Agency for Healthcare Research and Quality, and recommendations were made: Level A: evidence from ≥ 1 RCT; level B: evidence from clinical studies without randomization; and level C: evidence from opinions of expert committees, postmarketing surveillance, or recommendations from regulatory agencies.

**Outcomes**
Relief of signs and symptoms (pain, stiffness, and swelling), improvement in physical function, quality of life, delay in progression of structural damage, and prevention of disability.

**Main Results**
Level A evidence was available for 2 studies of infliximab and 4 studies of etanercept. Infliximab was given intravenously, 5 mg/kg over 2 hours at 0, 2, and 6 weeks. Etanercept was given subcutaneously, 25 mg by twice-weekly injections. Clinical response was achieved by more patients receiving anti-TNF-α agents than placebo (Table). Improvements were also seen in disease activity, physical function, quality of life, spinal mobility, and acute-phase reactants, and disability was decreased.

**Conclusion**
In patients with spondyloarthritis who have not responded to therapy with nonsteroidal antiinflammatory drugs or methotrexate, antitumor necrosis factor-α agents (infliximab and etanercept) provide effective symptom control and improve physical function and quality of life.

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**Antitumor necrosis factor-α agents vs placebo for spondyloarthritis**

<table>
<thead>
<tr>
<th>RCT duration</th>
<th>Number of patients</th>
<th>Outcomes</th>
<th>Infliximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 wk</td>
<td>70</td>
<td>ASAS 20% response</td>
<td>70%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASAS 50% response</td>
<td>53%</td>
<td>9%</td>
</tr>
<tr>
<td>12 wk</td>
<td>60</td>
<td>PARC</td>
<td>87%</td>
<td>23%</td>
</tr>
<tr>
<td>12 wk</td>
<td>205</td>
<td>ACR 20% response</td>
<td>73%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACR 50% response</td>
<td>50%</td>
<td>3%</td>
</tr>
<tr>
<td>16 wk</td>
<td>40</td>
<td>Clinical response</td>
<td>80%</td>
<td>30%</td>
</tr>
<tr>
<td>6 wk</td>
<td>30</td>
<td>50% regression in disease activity</td>
<td>57%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*RCT = randomized controlled trial; ASAS = Assessments in Ankylosing Spondylitis; PARC = Psoriatic Arthritis Response Criteria; ACR = American College of Rheumatology.

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**Commentary**

TNF-α plays a role in the pathogenesis of many chronic inflammatory diseases. TNF-blocking therapy has been shown to be efficacious in ankylosing spondylitis and psoriatic arthritis. Consensus exists on treating active and refractory ankylosing spondylitis with both the anti-TNF-α agent infliximab (1) and the TNF-receptor fusion protein etanercept (2). Etanercept has also shown efficacy in psoriatic arthritis (3).

The review by Maksymowych and colleagues addresses several important questions in the management of spondyloarthritis. The conclusions reached by the authors are presented as a position statement on the use of anti-TNF-α–directed therapies in this group of vexing conditions. However, during scrutiny of the authors’ assertions, 2 particular issues need to be recognized. First, only case-report evidence is available on the role of anti-TNF-α therapy in reactive arthritis, undifferentiated spondyloarthropathy, or arthropathy in inflammatory bowel disease. Second, switching between different anti-TNF-α agents (as has perhaps been inferred in the review) has not been approved by drug regulatory agencies.

While at least 1 open-label study (4) has shown good tolerability at 1 year, longer-term safety data on anti-TNF-α therapy in spondyloarthritis do not exist. Furthermore, while there is a tendency to regard the literature on anti-TNF-α blocking therapy in rheumatoid arthritis as a guide to what sort of longer-term side-effect profile might apply in spondyloarthritis, such comparisons may not be generalizable. Reasons for such lack of generalizability may include that patients with rheumatoid arthritis have a higher rate of spontaneous infection and a greater load of previous immunosuppressive therapies.

Anti-TNF-α therapies expand the treatment spectrum for patients with spondyloarthritis. The short-term efficacy on disease activity has been dramatic, but more work is needed to inform us of their longer-term efficacy and safety.

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**References**