Efficacy of etanercept for treatment of Crohn’s related spondyloarthritis but not colitis

H Marzo-Ortega, D McGonagle, P O’Connor, P Emery

The seronegative spondyloarthopathies (SpAs) are associated both with clinical and subclinical colitis. Recently biological blockade with the tumour necrosis factor alpha (TNFα) antagonists infliximab and etanercept has been shown to be effective in the treatment of SpA. However, only infliximab is efficacious in the treatment of colitis in patients with Crohn’s SpA. We report on two patients with SpA and associated Crohn’s disease treated with etanercept whose arthritis showed an excellent response with complete resolution of spinal pathology, whereas their Crohn’s disease persisted or flared. These findings suggest that the effect of TNFα blockade in SpA differs between the joint and the bowel.

Patient 1

Patient 1, a 27 year old HLA-B27 positive man, had a 10 year history of large bowel Crohn’s disease (fig 1) which had been controlled over the years with mesalazine, azathioprine, and oral corticosteroids. Ankylosing spondylitis had been diagnosed five years before his presentation to our clinic, although symptoms had started around the same time as the colitis. He had no associated extra-articular features and no family history of note. His musculoskeletal symptoms were largely confined to the axial skeleton and the peripheral joints were not affected. At the time of assessment in our clinic, symptoms were affecting the cervical spine, lumbar spine, and sacroiliac joints. He was at that stage receiving no drugs as he had recently finished a course of steroids for his Crohn’s disease. He had a past history of iritis and family history of skin psoriasis. Drugs for his arthritis and colitis at the time of presentation included a combination of sulfasalazine and methotrexate as well as ibuprofen. Despite this, bowel symptoms were active with up to five movements a day associated with mucus. Initial investigations showed inflammatory markers to be raised (PV 1.84 mPa.s, C reactive protein (CRP) 40 mg/l). Magnetic resonance imaging (MRI) of his lumbar spine and sacroiliac joints showed acute lesions consistent with active spinal and sacroiliac joint disease. Bowel symptoms were controlled with one daily solid movement and no abdominal pain. Etanercept at a dose of 25 mg subcutaneously twice weekly was started, with prompt resolution of his musculoskeletal symptoms only a week after starting treatment (table 1). Ten weeks after starting etanercept, bowel symptoms returned with crampy lower abdominal pain and increased frequency of bowel motions. This was accompanied by a steady rise in the CRP despite the fact that the arthritis remained asymptomatic (table 1). A repeat MRI scan after six months of etanercept treatment showed that the spinal lesions had completely resolved (fig 2B), at a time when the bowel was most symptomatic.

Patient 2

Patient 2, a 26 year old man, had a diagnosis of juvenile HLA-B27 positive ankylosing spondylitis and a subsequent diagnosis of colonic Crohn’s disease. He had a past history of iritis and family history of skin psoriasis. Drugs for his arthritis and colitis at the time of presentation included a combination of sulfasalazine and methotrexate as well as ibuprofen. Despite this, bowel symptoms were active with up to five movements a day associated with mucus. Initial investigations showed inflammatory markers to be raised (PV 1.88 mPa.s, CRP 39 mg/l) (table 2). The lumbar and cervical spine and hips were the most symptomatic areas. Sulfasalazine was stopped and...
Treatment was started with etanercept 25 mg subcutaneously twice weekly in combination with methotrexate. A rapid and sustained response was seen in his spine and joints (table 2), whereas the bowel symptoms remained unchanged for the duration of the treatment with persistent abdominal pain, diarrhoea, and mucus.

**DISCUSSION**

The role of TNF-α in the pathogenesis of Crohn’s disease is well established, and previous studies with the chimeric monoclonal antibody infliximab have shown that TNF-α blockade is highly efficacious in inducing remission in patients with moderate to severely active Crohn’s disease and for closure of enterocutaneous fistulas. Likewise, infliximab has been shown to be efficacious in the treatment of different subtypes of SpA, both with and without associated colitis. It is thought that the abnormal mucosal permeability associated with colitis in SpA leads to access of triggering microbes to the circulation, thus leading to activation of the innate immune response at certain predisposed sites. Therefore, possibly, one of the mechanisms of action of TNF-α blockade in SpA is by the amelioration of colitis, preventing access of microbes to the circulation. However, our experience with etanercept does show that although the drug can control the musculoskeletal features associated with the arthritis, and in particular the enthesal pathology that characterises these clinical entities, it is not effective in controlling the bowel symptoms. These findings are in agreement with those of a randomised controlled clinical trial in patients with Crohn’s disease, which show that etanercept is not efficacious in this setting.

**Figure 2** (A) Sagittal T2 weighted fat suppressed image of the lumbar spine of a patient with Crohn’s disease associated spondylitis, showing end plate oedema of the T10 inferior, T11 superior, L4 inferior, and L5 superior vertebral bodies (black asterisks). (B) The follow up scan after treatment with etanercept, showing complete resolution of the bone oedema at all sites.

### Table 1 Clinical characteristics of patient 1

<table>
<thead>
<tr>
<th>Characteristic (normal range)</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI (0–100 mm)</td>
<td>8</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VAS pain night (0–100 mm)</td>
<td>83</td>
<td>50</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VAS pain day (0–100 mm)</td>
<td>80</td>
<td>50</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CRP (&lt;10 mg/l)</td>
<td>40</td>
<td>10</td>
<td>16</td>
<td>37</td>
<td>68</td>
</tr>
<tr>
<td>PV (&lt;1.70 mPa s)</td>
<td>1.84</td>
<td>1.61</td>
<td>1.74</td>
<td>1.74</td>
<td>1.88</td>
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<tr>
<td>Bowel symptoms</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; VAS, visual analogue score; CRP, C reactive protein; PV, plasma viscosity.

### Table 2 Clinical characteristics of patient 2

<table>
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<tr>
<th>Characteristic (normal range)</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
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<td>BASDAI (0–10 mm)</td>
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<td>VAS pain night (0–10 mm)</td>
<td>80</td>
<td>64</td>
<td>20</td>
<td>12</td>
<td>0</td>
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<tr>
<td>VAS pain day (0–10 mm)</td>
<td>70</td>
<td>66</td>
<td>43</td>
<td>5</td>
<td>0</td>
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<tr>
<td>CRP (&lt;10 mg/l)</td>
<td>39</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>PV (&lt;1.70 mPa s)</td>
<td>1.88</td>
<td>1.69</td>
<td>1.51</td>
<td>1.52</td>
<td>NA</td>
</tr>
<tr>
<td>Bowel symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; VAS, visual analogue score; CRP, C reactive protein; PV, plasma viscosity.
Some differences between infliximab and etanercept may account for their different effects on Crohn's disease. Infliximab is a monoclonal antibody to TNFα made up of a chimeric protein that directly inhibits the action of TNFα and can bind to cells expressing TNFα in membrane bound form. Etanercept, by contrast, is a fully human, genetically engineered fusion protein consisting of two identical chains of the recombinant human soluble receptor TNFR p75 monomer fused with the Fc domain of human IgG1, which binds and inactivates TNFα and lymphotoxin. Although both drugs can bind to free and membrane bound TNFα, it has been proposed that the differential effects of infliximab and etanercept in Crohn's disease are due to the ability of the former to induce macrophage apoptosis by direct binding to the cell surface. This suggests that the efficacy of both etanercept and infliximab in the treatment of the arthritis in SpA may be due only to removal of excess joint TNFα.

Although our patients' Crohn's disease did not improve, there was a dramatic symptomatic change in their arthropathy, which was paralleled by resolution of the osteitis seen on MRI (fig 2B). These findings suggest that the effect of etanercept on arthritis may occur when persistent bowel inflammation is present. By implication, this suggests that biological blockade with anti-TNFα in SpA is directly efficacious at the site of arthropathy, but for treatment of Crohn's disease an additional mechanism such as cell lysis or cell regulation seems to be necessary.

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REFERENCES
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