Intra-articular corticosteroid injections in osteoarthritis: do they work and if so, how?

Intra-articular (IA) corticosteroids are recommended in several guidelines for the treatment of patients with knee osteoarthritis (OA). They are also widely used: a recent survey of rheumatologists in the United States suggested that over 95% use them at least ‘sometimes’ and 53% ‘frequently’. Before considering mechanisms of action of IA corticosteroids we should first consider the evidence that they are effective in OA.

A recent systematic review summarised evidence from five controlled studies of IA corticosteroid in patients with OA knee. Using a quality rating system (originally designed to assess methodology and reporting of NSAID studies), critical analysis showed that none of the studies achieved a score of more than 3 out of a possible 8 for design. It would not be unreasonable, therefore, to conclude that our knowledge of the efficacy of corticosteroid in OA is based on inadequate data. Table 1 summarises the five studies, and two more recent studies. Generally, they show a positive effect but one that is short lived and confounded by a powerful response to placebo (in all cases an equal volume of saline). In one study, for example, both placebo and corticosteroid groups showed significant decreases in pain at one week, lasting for the duration of the study (eight weeks). A more recent double blind, placebo controlled, crossover study found a significantly greater decrease in pain with corticosteroid than placebo at three weeks. The inability to detect an effect of corticosteroids beyond three weeks may reflect insensitivity of pain as an outcome measure, rather than a lack of corticosteroid effect.

Table 1 Controlled trials of intra-articular corticosteroids in OA (modified with permission from ref 4). All drugs given by intra-articular injection unless otherwise stated.

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Number (randomised)</th>
<th>Number (completing)</th>
<th>Design</th>
<th>Duration (weeks)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cederlof 1966</td>
<td>prednisolone 25 mg v placebo</td>
<td>44</td>
<td>44</td>
<td>parallel</td>
<td>8</td>
<td>Equal</td>
</tr>
<tr>
<td>Pfeils 1980</td>
<td>TH 20 mg v placebo</td>
<td>34</td>
<td>31</td>
<td>parallel</td>
<td>8</td>
<td>TH &gt; placebo at 1 week only</td>
</tr>
<tr>
<td>Deppen 1980</td>
<td>TH 20 mg v placebo</td>
<td>12 + 16</td>
<td>12 + 16</td>
<td>parallel/cross over</td>
<td>6 and 2</td>
<td>TH &gt; placebo at 2 weeks only</td>
</tr>
<tr>
<td>Valtonen 1981</td>
<td>TH 20 mg v beta-methasone 6 mg</td>
<td>42</td>
<td>42</td>
<td>parallel</td>
<td>24</td>
<td>TH &gt; betamethasone</td>
</tr>
<tr>
<td>Sambrook 1989</td>
<td>MP 80 mg v 80 mg peripaticular</td>
<td>38</td>
<td>32</td>
<td>parallel</td>
<td>12</td>
<td>Equal</td>
</tr>
<tr>
<td>Gaffney 1995</td>
<td>TH 20 mg v placebo</td>
<td>84</td>
<td>84</td>
<td>parallel</td>
<td>6</td>
<td>TH &gt; placebo at week 1 only</td>
</tr>
<tr>
<td>Jones 1996</td>
<td>MP 40 mg v placebo</td>
<td>59</td>
<td>47</td>
<td>cross over</td>
<td>8</td>
<td>MP &gt; placebo at 3 weeks only</td>
</tr>
</tbody>
</table>

TH=triamcinolone hexacetonide; MP=methylprednisolone.
(prostaglandins, leukotrienes, and interleukins 1 and 6) may sensitize primary afferent nociceptors to mechanical or other stimuli. Corticosteroids, by inhibiting phospholipase A2, reduce the production of these mediators and hence reduce inflammatory pain.

Despite a reasonable theoretical basis, demonstrating an in vivo anti-inflammatory effect of IA corticosteroid in OA has, to date, been difficult. A reduction in synovial permeability, as measured by clearance of 99m-Tc labelled albumin, has been reported; the clinical response being proportional to the degree of reduction. The thermographic index, a measure of warmth and hence inflammation, is reduced one week after corticosteroid injection. One problem may be definition of subgroups. The ‘osteoarthritic disorders’ are a heterogeneous group of conditions and it is probable that the role of inflammation (and hence, presumably, response to corticosteroids) varies between groups and at different time points. Moreover, OA may be a phasic condition: damage occurring in short bursts rather than in a linear progression. Bone scan appearances, for example, appear to switch on and off over time with evidence of bone activity preceding radiographic change. Radiographic findings indicate that many joints in patients with established OA remain stable and some may even improve, suggesting that the process responsible for damage to the joint is no longer active. Equally, symptoms of OA do not necessarily remain constant over a two year period: 23% patients in one study reported an improvement in pain. Inflammation may play a more important part at times of accelerated joint damage: perhaps corticosteroid given at these times would be particularly beneficial.

Evidence from experimental models of OA suggest that corticosteroids, both intra-articular and systemic, may also have a disease modifying role via an effect on cartilage. In a rabbit partial meniscectomy model, for example, intra-articular triamcinolone hexacetonide given before onset of OA resulted in reduced osteophyte formation, cartilage fibrillation, and chondrocyte cloning. Similar findings have been reported in a guinea pig model and in the Pond-Nuki dog model, in which even dogs with established OA showed a beneficial effect. A dose dependent reduction in the cartilage proteolytic enzyme stromelysin was demonstrated, accompanied by a reduction in interleukin 1β and the oncogenes c-fos and c-myc, both of which may be important for synthesis of metalloproteinases. This is presumably the mechanism by which triamcinolone hexacetonide results in the observed reduction in osteophyte size and severity of cartilage lesions. Reduced metalloproteinase synthesis after corticosteroids in human OA cartilage explants has also been reported. It should be noted that not all animal studies have shown IA corticosteroids to be protective against development of OA and some actually suggest an increase in loss of cartilage proteoglycan. These effects seem to be less relevant for primates: cartilage and reports of a Charcot-like accelerated joint destruction after corticosteroid injection in human hip OA may reflect the disease itself rather than the treatment.

How could mechanisms of action be investigated further? Selection of subjects with features of inflammation can be attempted by clinical examination using soft tissue tenderness and joint swelling as surrogate measures of synovitis. However, presence of these features does not predict greater response to NSAIDs over paracetamol and the reliability of such clinical measures is uncertain. Recently, magnetic resonance imaging has been shown to be an extremely sensitive method of detecting synovial inflammation. In rheumatoid arthritis, IA corticosteroids can be shown to reduce synovial effusion volume and synovial inflammation as measured by rate of enhancement after intravenous contrast (Gd-DTPA), an effect being detectable within one day of injection and lasting for several weeks. Magnetic resonance imaging is also capable of detecting synovial inflammation in OA and thus represents a potentially useful tool. Again, using RA as a model, synovial biopsy specimens have shown that corticosteroids decrease expression of genes that play a part in the arthritic destruction such as TIMP, collagenase, and HLA-DR: this could also be studied in OA. Finally, biochemical markers may be useful though, to date, results have been generally disappointing. A decrease in serum keratan sulphate after a single IA corticosteroid injection in OA has been reported suggesting a possible reduction in catabolism of aggrecan but as corticosteroids may also reduce formation of matrix components interpretation of these results is complex.

In summary, the mechanism of action of IA corticosteroids in OA is difficult to evaluate, especially when evidence for efficacy is relatively weak. Rheumatologists are likely to continue to use them either when all else fails or when we perceive there to be a moderate inflammatory component to the patient’s symptoms: in the future we may be able to refine patient selection using techniques such as magnetic resonance imaging or use of serum or synovial markers of inflammation. We should be cautious about extrapolating a protective effect of IA corticosteroids in animal models to human OA. However, if we were able to predict ‘at risk’ groups using prospective studies of subjects with early disease we would at least be able to test the hypothesis that selective anti-inflammatory intervention may reduce progression in OA.

The author wishes to thank Paul Dieppe and Marc Hochberg for comments during manuscript preparation.

Division of Rheumatology and Clinical Immunology,
Department of Medicine, University of Maryland,
10 S Pine Street, Baltimore, Maryland 21201-1192, USA

P CREAMER

11 Roivainen A, Soderstrom KO, Pirila L, Aro H, Kortekangas P, Merilahti Y. The activity is relatively weak. Rheumatologists are likely to continue to use them either when all else fails or when we perceive there to be a moderate inflammatory component to the patient’s symptoms: in the future we may be able to refine patient selection using techniques such as magnetic resonance imaging or use of serum or synovial markers of inflammation. We should be cautious about extrapolating a protective effect of IA corticosteroids in animal models to human OA. However, if we were able to predict ‘at risk’ groups using prospective studies of subjects with early disease we would at least be able to test the hypothesis that selective anti-inflammatory intervention may reduce progression in OA.