Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study

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Abstract

Objective. To examine the relationship between ultrasound (US)-detected synovial pathology in hand OA and the clinical response to parenteral corticosteroids.

Methods. People with symptomatic OA of the hand completed questionnaires [visual analogue scale (VAS) pain, Australian Canadian Osteoarthritis Hand Index and VAS global] and underwent an US examination of both hands prior to receiving an i.m. dose of methylprednisolone. Four- and twelve-week assessments were performed to assess therapeutic response.

Results. Thirty-six subjects with established OA were enrolled. Twenty-four (67\%) subjects met the primary end-point of a 20\% reduction in VAS pain, 25 (69.4\%) met the Osteoarthritis Research Society International response criteria at 4 weeks. Overall in the group, there was a reduction in levels of pain in the most painful joint, pain in all joints and in global disease activity at 4 weeks ($P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively). Reduction in symptoms was not associated with a statistically significant reduction in US-detected synovial hypertrophy or power Doppler signal.

Conclusions. In this observational study, parenteral corticosteroids were associated with a statistically significant reduction in symptoms, but no statistically significant reduction in US-detected synovial inflammation. The latter finding may, however, reflect the relatively low levels of synovial inflammation detected ultrasonographically in hand joints.

Key words: Ultrasonography, Hand, Osteoarthritis, Synovitis, Corticosteroid.

Introduction

Current therapy for OA is aimed at reduction of symptoms, as there are no well-established structure-modifying agents [1–3]. Corticosteroids are commonly used for symptom modification in OA, with recent publications confirming the efficacy of IA corticosteroids in knee OA [4, 5]. Additionally, systemic delivery of corticosteroids may have analgesic efficacy [6]: a recent publication found an oral corticosteroid compound had significantly better analgesic effects than placebo in hand OA [7]. While not currently recommended as management of OA by the European League Against Rheumatism (EULAR) [3], anecdotally i.m. corticosteroids are used for symptom control in OA of the small joints of the hand, as IA injections may not be feasible for multiple joints.

The mechanism of action of corticosteroids in OA is not well understood [8]. The accepted hypothesis is that their mechanism of analgesic efficacy is mediated through direct anti-inflammatory effects on the synovium [8]. However, despite years of experience with these drugs, the anti-inflammatory effects of corticosteroids on OA synovium have been difficult to examine in vivo [9]. As a result, the effects of corticosteroids on synovium in OA...
and the correlation with symptoms have not been well examined. The advent of modern imaging techniques has allowed non-invasive objective measurement of synovial pathology including inflammation, thereby facilitating studies into the effects of therapy on OA synovium and symptoms.

Modern imaging techniques have documented that synovial inflammation is common in OA, supporting the hypothesis that inflammation may be important in both peripheral nociception and response to anti-inflammatory medications [10–11]. Arthroscopic and imaging studies have also provided some evidence that inflammation may be important in mediating symptoms in OA [10, 12–13]. This study aimed to observe the effects of parenteral corticosteroids on US-detected synovial pathology and to correlate this with changes in symptoms.

Methods

Clinical assessment

This observational study was approved by the institutional ethics committee (Harrogate Research Ethics Committee), and all participants gave written informed consent. The study was an observational study. Subjects were recruited from musculoskeletal clinics of the Leeds Teaching Hospital NHS Trust. All subjects were considered likely to benefit symptomatically from a therapeutic trial of i.m. steroids, which is the routine therapy in this unit. As the study was observational, we observed the response to clinically indicated therapy.

As there are no available data on imaging-detected synovitis or symptomatic response to i.m. corticosteroid in hand OA, a pragmatic decision was made to recruit 36 subjects. Subjects with clinically symptomatic hand OA diagnosed by consultant rheumatologist, either meeting ACR criteria or with structural changes as assessed clinically or radiographically, were recruited and gave written informed consent. In keeping with other recent studies, we included subjects who did not meet ACR criteria [14], as our criteria allowed subjects with generalized disease and those with predominant base of thumb disease to be studied. People with a history of inflammatory arthritis were excluded, as were subjects with a raised CRP or a positive test for RFs.

Participants were asked to identify their most painful joint, and complete a 10-cm visual analogue pain scale (VAS) for that joint (most painful joint VAS). Additional parameters included a VAS pain for all the joints in both hands (all joints pain VAS), a VAS for global disease activity (global VAS), early morning stiffness in minutes and Australian and Canadian Osteoarthritis Hand Index (AUSCAN, a self-administered validated OA hand questionnaire addressing pain, stiffness and disability) [15]. Drug history, including NSAID use, was documented. Outcome measures were chosen in accordance with contemporary Osteoarthritis Research Society International guidelines (OARSI, an international scientific organization focused on the prevention and treatment of OA) [16]. Subjects were asked not to alter their analgesic or NSAID use for the duration of the study.

Ultrasound assessment

Ultrasound (US) examinations were performed by a rheumatologist experienced in ultrasonography, using a HDI Philips 5000 scanner (Philips, Eindhoven, The Netherlands) with a multi-linear 15–7 MHz hockey stick probe. Power Doppler was assessed with a pulse repetition frequency of 750 Hz and medium wall filter. Gain was adjusted until background signal was removed.

At baseline, subjects were assessed with an US of the small joints of the hand, including bilateral first CMC joints, MCP joints 1–5, PIP joints 1–5 and DIP joints 2–5. Joints were assessed globally in both transverse and longitudinal planes on both the dorsum and palmer surfaces of the hands. Acquiring, scoring and storing US images of all the joints of both hands took ~1 h per visit. For this reason, both hands were examined at baseline (30 joints per person); however, at Weeks 4 and 12, only the hand with the most painful joint underwent US examination (15 joints per person) so that US changes in the hand with the most painful joint could be compared with baseline findings. Joints were assessed for the presence of grey-scale synovitis, as defined by the Disease Characteristics in Hand OA (DICHOA) group, and scored according to a semi-quantitative scale of 0–3, where 0 is no pathology and 3 is severe pathology [17]. Power Doppler signal was also assessed at each joint according to DICHOA definitions [18], and graded from 0 to 3, where 0 was no signal and 3 was strong signal.

Trial design and statistical analysis

All subjects received 120 mg of i.m. methylprednisolone at baseline, and were followed up at 4 and 12 weeks with repeat examination, questionnaires and US examination. A parenteral route was chosen for the corticosteroid, as it was not thought ethically acceptable to inject multiple small joints, and we wished to limit the duration of corticosteroid therapy. Additionally, this was the method of choice used in our clinical practice. The primary end-point was determined a priori as a 20% reduction in the most painful joint VAS. Meeting a 20% reduction in the most painful joint VAS acted as a dichotomous variable to allow testing for an association between clinical response and synovial inflammation using \( \chi^2 \)-analysis. A secondary analysis was undertaken using the OARSI responder criteria [28], whereby a patient is deemed to have responded if there is a 50% reduction in pain (using most painful joint VAS) or function (AUSCAN functional subscale) or a 20% reduction in two of the most painful joint VAS, AUSCAN functional subscale or global VAS.

It was determined a priori that all hypotheses would be tested at the 5% level of significance, with family-wise corrections for multiple comparisons made according to the Holm modification of the Bonferroni correction. Ultrasonographer intra-reader reliability was assessed by re-reading stored images of 10 subjects for a minimum of 12 weeks post-acquisition, and determining weighted
κ-values, percentage exact agreement (PEA) and percentage close agreement (PCA). All analyses were undertaken using a SPSS 15.0 software package.

Results

Thirty-six subjects with symptomatic OA of the small joints of the hand were examined in this observational study, 31 (86%) met ACR criteria for hand OA. One thousand and seventy-seven joints were scanned at baseline, and 537 joints of the 36 subjects were examined at each time point, as only the 15 joints of the most symptomatic hand were examined at follow-up visits (one subject had previous traumatic amputation of three joints).

Demographics are presented in Table 1. All subjects attended the follow-up visit at Week 4, although one subject withdrew at this time point due to lack of efficacy, and hence only 35 subjects attended follow-up at Week 12.

Clinical response to i.m. methylprednisolone

The symptoms at each time point are presented in Table 2. Twenty-four (66.7%) subjects achieved a 20% reduction in most painful joint VAS at 4 weeks. Twenty-five (69.4%) subjects achieved an OARSI response. At 12 weeks, 16 (44.4%) subjects achieved a 20% reduction in most painful joint VAS and 13 (36.1%) achieved an OARSI response. The clinical outcomes for the group are also presented in Table 2, demonstrating statistically significant improvements in all clinical parameters with time. Despite being asked to maintain stable doses of analgesics, 12 subjects reported decreased NSAID use at 4 weeks, and 6 reported increased NSAID use, although neither action occurred more commonly in responders than non-responders (χ², P = 0.318).

Ultrasonography response to i.m. methylprednisolone

The intra-reader reliability for semi-quantitative grey scale synovitis score was substantial with a \( \kappa_w \) of 0.62 (PEA 54.0%, PCA 90.0%) and for semi-quantitative power Doppler signal score was excellent with a \( \kappa_w \) of 0.87 (PEA 92.0%, PCA 98.0%).

There was no statistically significant change in the amount of grey-scale synovitis or power Doppler signal in the most painful joint, or in the number of joints with grey-scale synovitis or power Doppler signal in an

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (n = 36)</th>
<th>Responders (n = 24)</th>
<th>Non-responders (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>58 (53.25–66.5)</td>
<td>57 (52.0–66.5)</td>
<td>59 (57.0–66.5)</td>
<td>0.400*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>31.0 (86.1)</td>
<td>20 (83.3)</td>
<td>11 (91.7)</td>
<td>0.496**</td>
</tr>
<tr>
<td>Symptom duration, median (IQR), months</td>
<td>51.0 (24.0–102.0)</td>
<td>61 (24.2–114.0)</td>
<td>46.0 (21.0–70.0)</td>
<td>0.466**</td>
</tr>
<tr>
<td>Post-menopausal, n (%)</td>
<td>21.0 (72.4)</td>
<td>13.0 (68.4)</td>
<td>8.0 (80.0)</td>
<td>0.507**</td>
</tr>
<tr>
<td>BMI, mean (95% CI)</td>
<td>27.3 (25.9, 28.7)</td>
<td>26.0 (24.6, 27.4)</td>
<td>30.0 (27.2, 32.8)</td>
<td>0.005***</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>5.0 (13.8)</td>
<td>4 (17.4)</td>
<td>1 (10.0)</td>
<td>0.426**</td>
</tr>
<tr>
<td>Most painful VAS, median (IQR)</td>
<td>76.5 (46.2–91.5)</td>
<td>79.0 (50.8–92.2)</td>
<td>60.0 (41.2–90.5)</td>
<td>0.261*</td>
</tr>
<tr>
<td>Pain VAS, median (IQR)</td>
<td>65.0 (41.0–83.0)</td>
<td>67.5 (46.25–83.5)</td>
<td>53.0 (11.0–76.0)</td>
<td>0.176*</td>
</tr>
<tr>
<td>Global VAS, median (IQR)</td>
<td>65.5 (45.0–84.2)</td>
<td>61.0 (44.0–84.7)</td>
<td>68.5 (42.5–81.2)</td>
<td>0.955**</td>
</tr>
<tr>
<td>AUSCAN pain, median (IQR)</td>
<td>299.0 (199.0–354.2)</td>
<td>293.0 (189.0–373.8)</td>
<td>305.0 (228.2–330.8)</td>
<td>0.524*</td>
</tr>
<tr>
<td>AUSCAN stiffness, median (IQR)</td>
<td>61.0 (32.0–80.8)</td>
<td>64.0 (31.8–85.2)</td>
<td>59.0 (32.0–74.8)</td>
<td>0.513*</td>
</tr>
<tr>
<td>AUSCAN function, median (IQR)</td>
<td>523.0 (433.2–713.8)</td>
<td>568.0 (345.8–756.5)</td>
<td>506.0 (462.5–607.5)</td>
<td>0.603*</td>
</tr>
<tr>
<td>Early morning stiffness, mean (95% CI), min</td>
<td>36.3 (23.3, 49.3)</td>
<td>45.4 (27.5, 63.4)</td>
<td>18.8 (4.8, 32.6)</td>
<td>0.046***</td>
</tr>
<tr>
<td>NSAID use, n (%)</td>
<td>22.0 (61.1)</td>
<td>16 (66.7)</td>
<td>6 (50.0)</td>
<td>0.334**</td>
</tr>
<tr>
<td>Grey-scale synovitis in the most painful join, median (IQR)</td>
<td>1 (1–2.8)</td>
<td>1 (0.2–3)</td>
<td>1.5 (1–2)</td>
<td>0.503**</td>
</tr>
<tr>
<td>Power Doppler synovitis in the most painful joint, median (IQR)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0.5 (0–2.8)</td>
<td>0.635**</td>
</tr>
</tbody>
</table>

*Mann–Whitney U-test, **χ², ***Student’s t-test. IQR: interquartile range.
individual, or in the individual's summative scores (summed across all joints in the signal hand) for grey-scale synovitis or power Doppler signal compared with baseline with time, as demonstrated in Table 2.

In 64% of joints, there was no change in the semi-quantitative score for grey-scale synovitis between baseline and Week 4, with another 30% of joints changing by only 1 score. Similarly, 89% of joints demonstrated no change in their power Doppler signal score, with a further 5% demonstrating a change of only 1. Hence, the vast majority of joints demonstrated no change in their US-detected synovitis score after i.m. methylprednisolone. Figure 1 shows an example of a joint that demonstrated a change over time.

Relationship between clinical improvement and US improvement

Responders (as assessed by a 20% reduction in most painful joint VAS at Week 4) did not have significantly higher levels of grey-scale synovitis or power Doppler signal in the most painful joint at baseline ($\chi^2 = 0.449$, df 1, $P = 0.503$ and $\chi^2 = 0.226$, df 1, $P = 0.635$, respectively) (Table 1). Similarly, responders did not have statistically lower levels of grey-scale synovitis or power Doppler signal in the most painful joint at Week 4 ($\chi^2 = 0.708$, df 1, $P = 0.400$ and $\chi^2 = 1.36$, df 1, $P = 0.243$, respectively). If response was assessed by OARSI criteria (which requires improvement in several parameters, rather than just pain in the most painful joint), then responders meeting OARSI response criteria had more, albeit not statistically significant, grey-scale synovitis and power Doppler signal at baseline (Table 3).

**Table 2** Clinical and US parameters of the entire cohort at each time point

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most painful joint VAS, median (IQR)</td>
<td>76.5 (46.25–91.5)</td>
<td>40.5 (22.2–60)</td>
<td>56.0 (29–74.0)</td>
</tr>
<tr>
<td>Pain VAS, median (IQR)</td>
<td>65.0 (41.0–82.0)</td>
<td>29.0 (10.5–47.5)</td>
<td>44.0 (23.0–65.0)</td>
</tr>
<tr>
<td>Global VAS, median (IQR)</td>
<td>65.5 (45.0–84.2)</td>
<td>26.5 (17.2–49.8)</td>
<td>37.0 (26.0–62.0)</td>
</tr>
<tr>
<td>AUSCANN pain, median (IQR)</td>
<td>298.0 (199.0–354.2)</td>
<td>181.5 (115.0–247.2)</td>
<td>232.0 (169.0–346.0)</td>
</tr>
<tr>
<td>AUSCANN stiffness, median (IQR)</td>
<td>61.0 (32.0–80.8)</td>
<td>35.0 (13.25–53.0)</td>
<td>54.0 (33.0–69.0)</td>
</tr>
<tr>
<td>AUSCANN function, median (IQR)</td>
<td>523.0 (433.2–713.8)</td>
<td>363.5 (208.5–573.2)</td>
<td>573.0 (326.0–632.0)</td>
</tr>
<tr>
<td>EMS, mean (95% CI)</td>
<td>36.3 (23.3, 49.3)</td>
<td>13.3 (7.2, 19.4)</td>
<td>31.2 (12.2, 50.1)</td>
</tr>
<tr>
<td>Grey-scale synovitis in the most painful joint, median (IQR)</td>
<td>1.0 (1.0–2.8)</td>
<td>1.0 (0.2–2.0)</td>
<td>1.0 (0.0–3.0)</td>
</tr>
<tr>
<td>Power Doppler synovitis in the most painful joint, median (IQR)</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–2.0)</td>
</tr>
<tr>
<td>Summative grey-scale synovitis score (max 45), mean (95% CI)</td>
<td>9.4 (7.4, 11.4)</td>
<td>9.0 (7.3, 10.7)</td>
<td>10.8 (8.4, 13.2)</td>
</tr>
<tr>
<td>Summative PD score (max 45), mean (95% CI)</td>
<td>1.9 (1.0, 2.8)</td>
<td>1.5 (0.5, 2.4)</td>
<td>1.7 (0.9, 2.4)</td>
</tr>
<tr>
<td>Number of joints with grey-scale synovitis (max 15), mean (95% CI)</td>
<td>6.5 (5.5, 7.6)</td>
<td>6.1 (5.2, 7.0)</td>
<td>6.5 (5.3, 7.7)</td>
</tr>
<tr>
<td>Number of joints with PD signal (max 15), mean (95% CI)</td>
<td>1.1 (0.7, 1.5)</td>
<td>0.9 (0.4, 1.5)</td>
<td>1.1 (0.7, 1.4)</td>
</tr>
</tbody>
</table>

As only the most symptomatic hand underwent US at follow-up, this analysis includes only the US of the most symptomatic hand at baseline and at follow-up. *Friedman test, **paired samples t-test (comparison between baseline and Week 4 only). IQR: interquartile range; PD: power Doppler.

**Discussion**

This study of subjects with symptomatic OA of the hands demonstrated a reduction in all measured symptom outcomes after parenteral corticosteroids. Two-thirds of the subjects met the predefined clinical response. This was an open-labelled study, and the clinical response may be attributable to a placebo effect [19]. However, the findings in relation to symptom control are in keeping with the knowledge that low-dose IA corticosteroid is efficacious in knee OA, and the limited evidence that oral corticosteroid compounds are efficacious in hand OA [4, 5, 7]. Although the assumption is that the analgesic response to corticosteroids seen in OA is mediated through the anti-inflammatory action of corticosteroids on synovium, little evidence exists to support this hypothesis. In particular, clinical and biochemical signs of inflammation are not consistently demonstrated to predict response to corticosteroids in knee OA [4, 20–24].

In this cohort, US-detected grey-scale synovitis was common but generally low grade, whereas US-detected power Doppler signal was less common. No statistically significant reduction in grey-scale synovitis or power Doppler signal was detected at 4 or 12 weeks after parenteral corticosteroid. Those who responded beneficially to corticosteroid therapy did not have greater levels of power Doppler signal in the dominant hand at baseline.

It is interesting to consider these results in light of the limited data on corticosteroid effects on synovial inflammation *in vivo*. Corticosteroids have been demonstrated to show analgesic efficacy in OA. While it is not known for certain, the mechanism of action has been thought to be
Images of a PIP joint demonstrating US-detected improvement and associated improvement in pain.

Grey-scale images in the dorsal longitudinal plane over PIP joints, (A) at baseline, (B) 4 weeks post i.m. corticosteroid (CS) and (C) 12 weeks post i.m. CS (Ai, Bi, Ci, correspond to power Doppler images). The joint was scored as 3 for Doppler signal at baseline, 0 at Week 4 and 3 at Week 12. These images show improvement in US-detected Doppler signal at Week 4, not maintained to Week 12. This subject reported a 50% reduction in pain in this joint at 4 weeks and 50% decrease in global VAS at Week 4.

**TABLE 3** US findings (in the hand with the most painful joint) of the cohort at baseline, presented for the entire cohort and then separated by OARSI response at 4 weeks

<table>
<thead>
<tr>
<th>Summative grey-scale synovitis (max. 45), mean (95% CI)</th>
<th>Total (n=36)</th>
<th>Responders (n=26)</th>
<th>Non-responders (n=10)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summative power Doppler signal (max. 45), mean (95% CI)</td>
<td>1.9 (1.0, 2.8)</td>
<td>2.1 (0.9, 3.4)</td>
<td>1.4 (0.6, 2.3)</td>
<td>0.489</td>
</tr>
<tr>
<td>Number of joints with grey-scale synovitis (max. 15), mean (95% CI)</td>
<td>6.5 (5.5, 7.6)</td>
<td>6.9 (5.7, 8.1)</td>
<td>5.6 (3.4, 7.9)</td>
<td>0.254</td>
</tr>
<tr>
<td>Number of joints with power Doppler signal (max. 15), mean (95% CI)</td>
<td>1.1 (0.7, 1.5)</td>
<td>1.2 (0.6, 1.7)</td>
<td>1.0 (0.4, 1.6)</td>
<td>0.710</td>
</tr>
</tbody>
</table>

*Student’s t-test.
via their anti-inflammatory effects on the synovium, although clinical markers of inflammation have not been found to reliably predict response to corticosteroids in OA [8]. In inflammatory arthritis, corticosteroids have been demonstrated to reduce synovial inflammation as determined histologically and by synovial hypertrophy/volume in imaging studies [25–29], but there is very little evidence that this occurs in OA. The current study did not demonstrate a relationship between reduction in symptoms and reduction in synovial volume. There are several possible explanations for this.

Synovial inflammation in OA reportedly differs from that in RA quantitatively rather than qualitatively [30–31], and the present cohort reflects this with frequent but low levels of inflammation; it may therefore be difficult to demonstrate change in such a cohort using US.

While subjects were asked to maintain stable doses of analgesics, the majority of subjects altered NSAID intake. There is some preliminary evidence that NSAIDs can result in a reduction of US-detected synovitis in knee OA [32]. Alterations in NSAID use in this cohort may have confounded any anti-synovial effects of corticosteroid on US-detected synovitis in the hands. Insisting on compliance with potentially toxic NSAIDs in participants who have benefited symptomatically from therapy would be ethically inappropriate.

The US technology used in this study may not have been sensitive enough to detect synovial changes in hand OA. The semi-quantitative scoring system used in this study is analogous to scoring systems used by other groups [25, 33–35] who have demonstrated sensitivity to change in inflammatory arthritis [25, 26, 34–38], but not in OA of the small joints of the hand.

Additionally, in established OA, the synovium may be poorly responsive to corticosteroids. The synovium in early OA has been demonstrated to be more inflammatory than in established OA (defined as >12 months of symptoms), demonstrating greater synovial thickness, inflammatory cell infiltrate and vascularity [39]. Given this, it is possible that the synovial changes in late OA may not be very responsive to corticosteroids. The cohort examined in this study had a median symptom duration of 51 months and radiographic structural changes, and may have been unable to demonstrate synovial changes in response to corticosteroids. Of course, such changes may have been evident at the microscopic level.

The current study did not find statistically higher baseline levels and power Doppler signal in those who responded clinically (Table 3). This observation is in contrast to a recent study from our group in which the efficacy of i.m. methylprednisolone in a heterogeneous cohort of 91 subjects, with inflammatory hand pain, was associated with the presence of US-detected grey-scale synovitis at baseline [40]. The main reason for this difference is probably due to over a quarter of the previous cohort having positive RF or elevated CRP and consequently a sizeable proportion of inflammatory arthritis patients. The current work included OA only and the numbers recruited in this pilot observational study may not have been large enough to demonstrate a statistical difference.

In this small, observational, open-labelled, longitudinal study, i.m. corticosteroid in OA of the hand was associated with a reduction in pain, but this was not associated with a reduction in grey-scale synovitis or power Doppler signal. Further investigation into the utility of ultrasoundography in hand OA is required, to determine whether larger controlled studies using US may allow better understanding of the relationship between peripheral sources of pain and therapies in this common disease.

Rheumatology key messages

- In this observational pilot study, parenteral corticosteroids were associated with a statistically significant reduction in symptoms.
- There was no statistically significant reduction in US-detected synovial inflammation in response to parenteral corticosteroids.
- Larger placebo-controlled studies are required to better understand peripheral sources of pain and response to therapy.

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