Effect of Low-dose Oral Prednisolone on Symptoms and Systemic Inflammation in Older Adults with Moderate to Severe Knee Osteoarthritis: A Randomized Placebo-controlled Trial

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Effect of Low-dose Oral Prednisolone on Symptoms and Systemic Inflammation in Older Adults with Moderate to Severe Knee Osteoarthritis: A Randomized Placebo-controlled Trial

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ABSTRACT. Objective. To investigate the efficacy of 6 weeks of daily low-dose oral prednisolone in improving pain, mobility, and systemic low-grade inflammation in the short term and whether the effect would be sustained at 12 weeks in older adults with moderate to severe knee osteoarthritis (OA).

Methods. A total of 125 patients with primary knee OA were randomized 1:1; 63 received 7.5 mg/day of prednisolone and 62 received placebo for 6 weeks. Outcome measures included pain reduction and improvement in function scores and systemic inflammation markers. Pain was assessed using the visual analog pain scale (0–100 mm). Secondary outcome measures included the Western Ontario and McMaster Universities Osteoarthritis Index scores, patient global assessment (PGA) of the severity of knee OA, and 6-min walk distance (6MWD). Serum levels of interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF)-α, and high-sensitivity C-reactive protein (hsCRP) were measured.

Results. There was a clinically relevant reduction in the intervention group compared to the placebo group for knee pain, physical function, PGA, and 6MWD at 6 weeks. The mean difference between treatment arms (95% CI) was 10.9 (4.8–18.0), p < 0.001; 9.5 (3.7–15.4), p < 0.05; 15.7 (5.3–26.1), p < 0.001; and 86.9 (29.8–144.1), p < 0.05, respectively. Further, there was a clinically relevant reduction in the serum levels of IL-1, IL-6, TNF-α, and hsCRP at 6 weeks in the intervention group when compared to the placebo group. These differences remained significant at 12 weeks. The Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International responder rate was 65% in the intervention group and 34% in the placebo group (p < 0.05).

Conclusion. Low-dose oral prednisolone had both a short-term and a longer sustained effect resulting in less knee pain, better physical function, and attenuation of systemic inflammation in older patients with knee OA (Clinical Trials.gov identifier NCT01619163). (First Release Dec 1 2013; J Rheumatol 2014;41:53–9; doi:10.3899/jrheum.130199)

Key Indexing Terms: KNEE OSTEOARTHRITIS  LOW-DOSE CORTICOSTEROIDS  PAIN  FUNCTION

Osteoarthritis (OA) is a progressive disease representing the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intraarticular stress. OA is considered a complex, multifactorial disease with patients classified as heterogeneous patient populations exhibiting varying degrees of inflammation, in some cases comparable with rheumatoid arthritis (RA).1,2,3 Inflammation has been implicated in the pathogenesis of OA. Inflammation may either be a primary event in OA or secondary to other aspects of the disease such as biochemical changes within the cartilage. Thus, while the etiology of OA remains elusive, it appears that OA is initiated as a consequence of altered mechanical loading due to excessive stress. In this context the chondrocytes become activated and increase the levels of interleukin 1β (IL-1β) and tumor necrosis factor (TNF)-α expression in the affected joint. The upregulation of IL-1β and TNF-α acts in both an autocrine and paracrine fashion, orchestrating the formation of superficial fractures and fissures in the articular cartilage.4,5 As the disease progresses, synovial hyperplasia and hypertrophy develop, and joint architecture becomes compromised. Synovial inflammation and proliferation has emerged as a key component of OA and as a potential predictor of worsening disease. Synovitis is common in early and advanced OA and is associated with knee pain and progression of cartilage degeneration.6,7 Knee pain, the
leading symptom of knee OA, is common in older adults and is often chronic in nature, leading to significant morbidity and disability.

Thus, in terms of clinical management, pain reduction and functional improvement are of paramount importance in the treatment of knee OA. Current treatment options have had limited symptomatic effect and are associated with significant side effects. Given the limitations in terms of both efficacy and safety of the available nonspecific symptom-relieving drugs such as analgesics, guidelines acknowledge the need for medications that not only offer acceptable short-term symptom control, but also have a role in the medium-term and long-term management of OA.

Corticosteroids are used for symptom modification in OA, with publications confirming the efficacy of intraarticular corticosteroids in knee OA. Glucocorticoids (GC) have a pivotal role in managing inflammatory arthritis, because of their antinflammatory and immunosuppressive roles. Additionally, systemic administration of cortico-

MATERIALS AND METHODS

Study design. Our study was a single-center double-blind randomized placebo-controlled clinical trial conducted at the Main University Hospital of our institution. The overall design of the study consisted of a 6-week treatment period followed by a 6-week posttreatment followup. The study protocol was approved by the Ethics Committee of our institution and was conducted in accordance with the principles of the Declaration of Helsinki and its amendments (2008).

Patient selection and eligibility criteria. One hundred twenty-five community-dwelling adults aged 60 years and above were enrolled. They were attending the outpatient clinic of our institution, and had primary knee pain in the target knee defined as the most prolonged, most disabling, and most painful knee joint of OA.

Participants were invited for a screening visit. At the screening visit, patients had at least 2 of the following 4 clinical signs of inflammation: warmth over the joint area; joint margin tenderness; synovial effusion; soft tissue swelling around the knee) as well as primary and secondary measures of disease assessment. An experienced rheumatologist, blinded to treatment assignment, performed the clinical assessments. All assessments were performed at screening, baseline, 6 weeks, and 12 weeks. There was a 24-h washout of analgesics drugs before each visit for symptom assessment and clinical evaluation.

Outcome measures. The primary outcome criterion defined as a priori was pain reduction using a VAS 0-100 mm. Secondary outcome measures included the reduction in systemic inflammation and improvements in physical function scores. Improvements in physical functioning were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscores for pain, stiffness, and function; the patient global assessment (PGA) of the severity of knee OA measured on a 0-100 mm VAS; and the 6-minute walk distance (6MWD).

Systemic inflammation was assessed by measuring the serum levels of IL-1β, IL-6, TNF-α, and high-sensitivity CRP (hsCRP). Serum levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α were measured by a high-sensitivity ELISA system (R & D Systems). To measure hsCRP, an

Exclusion criteria. Participants were excluded if they had secondary arthritides related to systemic inflammatory arthritis including RA, ankylosing spondylitis, psoriatic arthritis, traumatic arthritis, postinfectious arthritis, crystal arthropathies including chondrocalcinosis by serological evaluation [erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor, and synovial fluid analysis]. Patients with previous treatment with corticosteroid tablets, intraarticular steroid, or hyaluronom injections into the knees within 6 months of screening were excluded. Other exclusion criteria were administration of oral corticosteroid treatment, intraarticular steroid, or hyaluronom injections into the knees within 6 months of screening. Patients with severe comorbidity (specifically severe renal, heart, lung, or neurological disease) and patients with insulin-requiring diabetes, diabetes mellitus requiring more than 1 oral hypoglycemic agent, coronary artery disease, recent stroke, and congestive heart disease were excluded.

Randomization and treatment allocation. At baseline, all patients meeting the eligibility criteria were randomized using a computerized random number list in a 1:1 ratio — 63 received 7.5 mg/day of oral prednisolone tablets and 62 received placebo tablets that were identical in aspect, odor, and flavor for 6 weeks. The study medication was given orally as a single early morning dose for a total of 6 weeks. Both the investigators and partici-

patients received a chart to record the analgesics taken daily, and the use of rescue drug at each visit to assess compliance and use of rescue drug change.

Clinical assessment. Clinical assessment consisted of an initial interview (including questioning about number of flares, pain, comitant conditions, and analgesics) and physical examination for signs of inflammation (all patients had at least 2 of the following 4 clinical signs of inflammation: warmth over the joint area; joint margin tenderness; synovial effusion; soft tissue swelling around the knee) as well as primary and secondary measures of disease assessment. An experienced rheumatologist, blinded to treatment assignment, performed the clinical assessments. All assessments were performed at screening, baseline, 6 weeks, and 12 weeks. There was a 24-h washout of analgesics drugs before each visit for symptom assessment and clinical evaluation.

Outcome measures. The primary outcome criterion defined as a priori was pain reduction using a VAS 0-100 mm. Secondary outcome measures included the reduction in systemic inflammation and improvements in physical function scores. Improvements in physical functioning were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscores for pain, stiffness, and function; the patient global assessment (PGA) of the severity of knee OA measured on a 0-100 mm VAS; and the 6-minute walk distance (6MWD).
ELISA kit (Hemagen Diagnostics Inc.) was used with a lower limit of detection of 0.5 mg/l. Data were collected at baseline, 6 weeks, and 12 weeks to determine any change in results from those obtained at baseline.

Safety evaluation. Safety and tolerability to treatment were assessed at each visit. Safety was assessed by identifying adverse events (a treatment-related adverse event was any reported event first occurring or worsening in severity during treatment, compared to baseline period) using open-ended questions and a checklist including common oral corticosteroid side effects, physical examination including assessment of body weight, and laboratory assessment, which included fasting and 2-h postprandial blood sugar level measurement. Adverse events were collected at each visit and up to 6 weeks after the end of treatment and were analyzed with regard to their seriousness, intensity, and causal relationship with treatment and outcome.

Statistical analyses. Analyses were conducted using SAS version 9.1 (SAS Institute Inc.). To detect a clinically important difference of 20 mm for severity of pain on a 100 mm VAS pain scale between patients treated with low-dose prednisolone and placebo, with 90% power, significant at the 5% level and allowing for a 10% dropout/loss to followup, it was calculated that a sample size of 62 patients was required in each treatment group. Statistical analyses were performed as intention-to-treat analysis. Multiple imputations based on regression techniques were used to replace missing values. This method controls for a possible bias caused by noncompleters and was applied to all outcome measures. Patients with missing data at Week 6 were considered nonresponders using nonresponder imputation.

RESULTS

Patient population. A total of 211 individuals were screened during a 4-month recruitment period for eligibility (Figure 1). Of these, 86 (41%) were screening failures. That left 125 patients who were eligible and enrolled in the study. Ninety-four percent (117) completed the study. The demographic and clinical variables were similar between the 2 groups of the study population at baseline (Table 1). Overall, most of the patients (91%) were women and the

![Flow diagram of the study progress](image-url)
mean age was 68 years, with a mean body mass index of 27.5 and a mean disease duration of 6.6 years; 91% used NSAID and 96% used paracetamol.

**Efficacy.** After 6 weeks, patients with symptomatic knee OA who received low-dose prednisolone had significantly greater improvement in both primary and secondary efficacy measures compared to patients who received placebo.

**Primary endpoint.** Knee OA pain scores on the VAS decreased to a significantly greater degree in the low-dose prednisolone group from 65.3 (17.5) to 44.8 (18.8) mm at 6 weeks compared to the placebo group [65.2 (17.8) to 54.6 (19.6)]; that is, the change from baseline was −20.5 vs −10.6 and the mean difference between treatment arms was 9.9 (95% CI, 4.8 to 15.0, p < 0.001; Table 2). These differences remained clinically relevant for physical function at 12 weeks (−13.6 vs −4.4) and the mean difference between treatment arms was 9.2 (95% CI, 0.4 to 18.0, p < 0.01). The proportion of patients who had a reduction in VAS of > 20 mm at both timepoints was significantly higher in the low-dose prednisolone group compared to the placebo group.

**Secondary endpoints.** Table 2 shows the results of the secondary endpoints in the intervention and placebo groups. Scores on all WOMAC subscales improved significantly in the low-dose prednisolone group compared to the placebo group. There was a clinically relevant reduction in the intervention group compared to the placebo group for WOMAC score for pain (−3.0 vs −1.4, p < 0.05), physical function (−13.5 vs −4.0, p < 0.001), and WOMAC stiffness score (−1.9 vs −0.5, p < 0.05) at 6 weeks; the mean difference between treatment arms was 1.6 (95% CI, 0.7 to 2.5), 9.5 (3.7 to 15.3), and 1.4 (0.5 to 2.3), respectively (Table 2). These differences remained clinically relevant for physical function at 12 weeks: the mean difference between treatment arms was −9.6 (95% CI, 2.2 to 17.0); p < 0.01.

Regarding the PGA of the severity of knee OA, there was a clinically relevant reduction in the intervention group compared to the placebo group (−22.1 vs −6.4; p < 0.001) at 6 weeks. The mean difference between treatment arms was 15.7 (95% CI, 5.3 to 26.1; Table 2). At followup the clinical benefit persisted at 12 weeks: the mean difference between treatment arms was 10.5 (95% CI, 6.2 to 14.8, p < 0.05).

There was a clinically relevant improvement in the intervention group compared to the placebo group for 6MWD (105.8 vs 18.9, p < 0.05); the mean difference between treatment arms was 86.9 (95% CI, 39.8 to 134.0) at 6 weeks (Table 2). This clinical benefit persisted at 12 weeks: the mean difference between treatment arms was 73.2 (95% CI, 21.8 to 124.6, p < 0.01).

**Systemic inflammation.** Following therapy with low-dose prednisolone, all the markers of systemic inflammation

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**Table 1.** Baseline demographic and clinical characteristics of the study population. None of the characteristics showed a statistically significant intergroup comparison.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low-dose Prednisolone, n = 63</th>
<th>Placebo, n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>67.9 (6.2)</td>
<td>68.0 (5.8)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>58/5</td>
<td>56/6</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>27.6 (4.9)</td>
<td>27.5 (5.1)</td>
</tr>
<tr>
<td>Disease duration, yrs, mean (SD)</td>
<td>6.7 (4.9)</td>
<td>6.6 (4.7)</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13 (21)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>III</td>
<td>36 (57)</td>
<td>37 (60)</td>
</tr>
<tr>
<td>IV</td>
<td>14 (22)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Morning stiffness, &lt; 30 min, n (%)</td>
<td>58 (92)</td>
<td>57 (92)</td>
</tr>
<tr>
<td>Clinical synovitis, n (%)</td>
<td>63 (100)</td>
<td>62 (100)</td>
</tr>
<tr>
<td>Analgesic use, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>61 (97)</td>
<td>59 (95)</td>
</tr>
<tr>
<td>NSAID</td>
<td>58 (92)</td>
<td>56 (90)</td>
</tr>
</tbody>
</table>

BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs.

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<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Baseline Prednisolone</th>
<th>Mean (SD) Change Prednisolone</th>
<th>Mean (SD) Baseline Placebo</th>
<th>Mean (SD) Change Placebo</th>
<th>Mean Difference in Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (0–100 mm)</td>
<td>65.3 (17.5)</td>
<td>−20.5 (−14.7 to −26.3)</td>
<td>65.2 (17.8)</td>
<td>−10.6 (−4.2 to −17.0)</td>
<td>9.9 (4.8 to 15.0)*</td>
</tr>
<tr>
<td>WOMAC Pain Score (0–20)</td>
<td>9.9 (6.6)</td>
<td>−3.0 (−0.9 to −5.1)</td>
<td>9.9 (6.9)</td>
<td>−1.4 (−0.7 to −2.1)</td>
<td>1.0 (0.7 to 2.5)*</td>
</tr>
<tr>
<td>WOMAC Function Score (0–68)</td>
<td>43.1 (11.5)</td>
<td>−13.5 (−10.0 to −17.0)</td>
<td>43.5 (11.7)</td>
<td>−4.0 (−0.7 to −7.3)</td>
<td>9.5 (3.7 to 15.3)*</td>
</tr>
<tr>
<td>WOMAC Stiffness Score (0–8)</td>
<td>6.4 (2.6)</td>
<td>−1.9 (−0.5 to −3.3)</td>
<td>6.5 (2.5)</td>
<td>−0.5 (−0.1 to −1.0)</td>
<td>1.4 (0.5 to 2.3)*</td>
</tr>
<tr>
<td>PGA (0–100 mm VAS)</td>
<td>66.7 (20.3)</td>
<td>−22.1 (−11.2 to −33.0)</td>
<td>66.5 (19.9)</td>
<td>−6.4 (−2.1 to −10.7)</td>
<td>15.7 (5.3 to 26.1)*</td>
</tr>
<tr>
<td>Six-min walk distance (m)</td>
<td>358.1 (19.5)</td>
<td>105.8 (75.9 to 135.7)</td>
<td>358.5 (19.1)</td>
<td>18.9 (9.0 to 28.8)</td>
<td>86.9 (39.8 to 134.0)‡</td>
</tr>
<tr>
<td>IL-1 (pg/ml)</td>
<td>20.5 (8.9)</td>
<td>−6.4 (−2.1 to −10.7)</td>
<td>20.3 (9.4)</td>
<td>−2.1 (−1.0 to −3.2)</td>
<td>4.3 (1.3 to 7.5)‡</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5.8 (6.5)</td>
<td>−1.8 (−0.5 to −3.1)</td>
<td>5.7 (6.2)</td>
<td>−0.6 (−0.2 to −1.0)</td>
<td>1.2 (0.4 to 2.0)*</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>15.8 (9.8)</td>
<td>−4.7 (−2.1 to −7.3)</td>
<td>15.9 (9.4)</td>
<td>−1.4 (−0.6 to −2.2)</td>
<td>3.3 (0.9 to 5.7)*</td>
</tr>
<tr>
<td>hsCRM (mg/l)</td>
<td>3.8 (1.8)</td>
<td>−1.2 (−0.2 to −2.2)</td>
<td>3.7 (1.9)</td>
<td>−0.5 (−0.04 to −1.1)</td>
<td>0.7 (0.1 to 1.3)‡</td>
</tr>
</tbody>
</table>

* p value < 0.001; † p value < 0.05. VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PGA: patient global assessment of the severity of knee pain; IL: interleukin; TNF-α: tumor necrosis factor-α; hsCRM: high-sensitivity C-reactive protein.
assessed showed a clinically relevant reduction compared to baseline values associated with improvement in signs of clinical synovitis. There was a clinically relevant reduction in the intervention group compared to the placebo group for warmth, swelling, and joint margin tenderness (37% vs 59%, p < 0.01; 42% vs 64%, p < 0.01; and 48% vs 69%, p < 0.05; respectively, at 6 weeks). In the mean (SD) levels of the inflammatory markers, IL-1 decreased from 20.5 (8.9) to 15.7 (9.9) at 6 weeks compared to the placebo group from 20.3 (9.4) to 19.2 (9.2), that is, the change from baseline was –6.4 vs –2.1 and the mean difference between treatment arms was 4.3 (95% CI, 1.3 to 7.3, p < 0.05; Table 2). The mean levels of IL-6 decreased from 5.8 (6.5) to 4.1 (7.5) at 6 weeks compared to the placebo group 5.7 (6.2) to 5.2 (6.6); the change from baseline was –1.8 vs –0.6 and the mean difference between treatment arms was 1.2 (95% CI, 0.4 to 2.0, p < 0.001). The mean levels of TNF-α decreased from 15.8 (9.8) to 11.5 (11.1) at 6 weeks compared to the placebo group 15.9 (9.4) to 14.5 (9.8); the change from baseline was –4.7 vs –1.4 and the mean difference between treatment arms was 3.3 (95% CI, 0.9 to 5.7, p < 0.05). The mean levels of hsCRP decreased from 3.8 (1.8) to 2.1 (2.2) at 6 weeks compared to the placebo group [(3.7 (1.9) to 3.4 (1.8)]; the change from baseline was –1.2 vs –0.5 and the mean difference between treatment arms was 0.7 (95% CI, 0.1 to 1.3, p < 0.05). These differences remained clinically relevant at 12 weeks.

The OMERACT-OARSI responder rate was 65% in the low-dose prednisolone group compared to 34% in the placebo group (p < 0.05).

There was a clinically significant reduction in the percentage of analgesic (NSAID and paracetamol) users in the low-dose prednisolone group compared to the placebo group at both 6 weeks (73% vs 92%, p < 0.01) and 12 weeks (78% vs 93%, p < 0.01).

Safety. The assessment of safety and tolerability showed that there were no substantial differences in the incidence of adverse events between the 2 groups. There were no deaths or severe life-threatening events during the study. There was a higher incidence of gastritis and peripheral edema in the intervention group compared to the placebo group at 6 weeks. No serious gastrointestinal adverse events occurred and none of the participants developed hyperglycemia. Weight gain was observed in 3% of the intervention group compared to 2% of the placebo group (Table 3). Routine laboratory investigations did not reveal any significant abnormalities in metabolic functions or system organs in either of the 2 groups (data not shown).

DISCUSSION

In the absence of any disease specific therapy for OA, current pain treatment is based on a multidisciplinary approach combining different sets of measures depending on the individual patient’s complaints and disease status. Oral prednisolone dramatically ameliorates the symptoms of inflammatory diseases, and GC are established components of the treatment regimens for many inflammatory arthritides.

There is a growing interest in defining the role inflammation plays in OA, which is often associated with low-grade synovitis. Synovitis has been associated with symptoms and progression of cartilage degeneration17.

In our study, we sought to primarily determine the efficacy of low-dose prednisolone to reduce pain and to improve function and mobility in older adults with moderate to severe knee OA. We have demonstrated that in patients with moderate to severe OA with clinical evidence of synovitis, a 6-week course of oral low-dose prednisolone is superior to placebo in reducing pain and that there was still a trend for this benefit to be maintained at 12 weeks in the majority of patients, evidenced by a reduction in the primary and secondary outcome measures. A significant reduction in pain on the VAS in the drug-treated group compared to the placebo-treated group was evident at both timepoints. There was also a significant improvement in pain as measured by the WOMAC pain subscale and the PGA in the low-dose prednisolone group compared to the placebo group in the short term with a trend for this improvement to be maintained at 12 weeks. These findings are in accordance with a limited number of studies that have shown that corticosteroids given intraarticularly or orally are effective in controlling the cardinal symptoms of OA (pain, decreased function, and decreased mobility)19,18.

The analgesic effect of low-dose prednisolone observed in the intervention group may be mediated by means of their antiinflammatory mechanism of action, particularly in ameliorating the synovitis. This assumption was further verified by the observation in this study that following therapy with low-dose prednisolone, all the markers of systemic inflammation (hsCRP, IL-1, IL-6, and TNF-α) assessed showed significant reduction compared to baseline values. Similar results have been reported by several studies that have shown increasing cytokine production in patients with OA20,21. Our findings suggest that the low-grade...
inflammation induced by OA has a systemic effect. The levels of hsCRP decreased significantly in the low-dose prednisolone group compared to the placebo group at both timepoints. Similar results were reported in a study by Stannus and colleagues who showed that systemic inflammation is an independent predictor of worsening knee pain over 5 years. Increased hsCRP levels in sera have been associated with disease progression as well as with severity of pain in OA.

Inflammation may thus be contributing to the symptoms and progression of OA. In patients with OA, it is recognized that low-grade synovial inflammation is often present and correlates with pain severity. Indeed, inflammation may be the crucial link between local noxious stimuli and recruitment of centrally mediated pathways. When inflammatory mediators such as cytokines and chemokines are released intraarticularly from damaged tissue, they can modulate both central and peripheral nociceptors. In addition, we now have a better understanding of the morphologic and molecular evidence of destruction not only of the articular cartilage but of the bone and synovium as well, and suspect that OA involves crosstalk between tissues on the cellular and cytokine levels, at least in some subgroups or phenotypes.

In our study, all patients were selected because they had clinical synovitis. The association between synovitis and pain indicate that inflammation may have a pivotal role in causing knee pain. Inflammatory mediators play a pivotal role in the 3 most recognized phenotypes, including the aging phenotype. OA now is recognized as a disease with an inflammatory component, if not a disease driven by pro-inflammatory cytokines. Further, inflammation is suggested to drive OA, evidenced by the existence of flares in OA that often resemble other inflammatory arthritis, characterized by nocturnal pain, stiffness, and swelling.

Improvement in the 6MWD and WOMAC scores that reflect function were particularly noteworthy in patients taking low-dose prednisolone compared to those receiving placebo. WOMAC scores measure physical function, and an improvement in WOMAC scores indicate better functioning ability as a result of less pain and stiffness and fewer functional limitations. When interpreting physical function scores, one needs to keep in mind the progressive nature of OA. Thus, an improvement in WOMAC scores or even a stable physical function score represents a treatment success. This may in itself justify the use of low-dose corticosteroids in patients with OA.

Data from the present study showed that NSAID and paracetamol usage had decreased significantly at 6 weeks and at 12 weeks in the low-dose prednisolone-treated group compared to the placebo group. Safety analysis confirmed that low-dose prednisolone was mostly well tolerated, with lack of severe or life-threatening events.

This is, to our knowledge, the first randomized placebo-controlled trial conducted to determine the efficacy of low-dose corticosteroid in knee OA; however, the results should be interpreted in light of several limitations. The levels of inflammatory biomarkers were measured in serum, as opposed to synovial fluid. Synovitis was detected clinically rather than by imaging studies, which might have provided more detailed information. This was also an acute treatment trial based on a 6-week study, which may explain why there was less pain response than that reported in most OA trials in the placebo group. The trial format could also explain the low incidence of all adverse effects, and the fact that the results may not generalize to a longer duration of treatment. Hence longer-term trials are required to fully assess the safety and efficacy of prednisolone in a longer time course.

Our findings demonstrate a reduction in all measured symptom outcomes after low-dose prednisolone, which suggests that prednisolone can have the dual beneficial effect of reducing pain symptoms and improving function (particularly mobility). Both these effects improve quality of life in older adults with knee OA.

Despite the limitations of our study, our findings showing the efficacy of low-dose prednisolone in reducing pain may well be applicable to the subset of patients with OA displaying persistent inflammation and pain despite conventional pain-reducing medications. Further larger-scale longitudinal studies are needed to replicate these effects.

REFERENCES