Emerging a New Era in Osteoarthritis Therapies

METHODS - A RANDOMIZED CONTROLLED TRIAL OF METHOTREXATE TO TREAT HAND OSTEOARTHRITIS WITH SYNOVITIS

Keywords: Disease-modifying drugs (DMARDs), Randomized control trial, Osteoarthritis

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Background: Hand osteoarthritis (OA) with synovitis is a common clinically identifiable phenotype which is associated with pain and disease progression. Methotrexate is a low-cost, well-established and effective treatment for inflammatory arthritis with a well-described safety profile. A previous randomized controlled trial showed no superiority of 10 mg of methotrexate over placebo in pain relief at 3 or 12 months in patients with erosive hand OA[1]. No study has examined methotrexate in hand OA with inflammatory synovitis.

Objectives: To examine whether methotrexate reduced pain and improved function over 6 months in patients with hand OA and synovitis.

Methods: In a multicentre, randomized, double-blind, placebo-controlled trial, patients with symptomatic hand OA and MRI-detected synovitis were recruited and randomly assigned in a 1:1 ratio to receive methotrexate 20 mg (n=50) or identical placebo (n=47) once weekly for 6 months. The primary outcome was pain reduction (assessed by 100 mm visual analogue scale, VAS) at 6 months. Secondary outcomes included changes in physical function and quality of life assessed using Australian Canadian Osteoarthritis Hand Index (AUSCAN), Functional Index for Hand Osteoarthritis (FIHOA), Health Assessment Questionnaire (HAQ), and Michigan Hand Outcomes Questionnaire (MHQ). Adverse events were recorded. The primary analysis was by intention to treat, including all participants in their randomized groups. Mixed linear regression models were fit to continuous outcomes, adjusting for baseline values of outcome, sex and site, and the clustering of measurements within participants.

Results: Of 97 patients [mean age 61.4 (SD 6.7) years, 68 (70.1%) female], 82 (84.5%) provided the 6-month primary outcome. At 6 months, the methotrexate group had greater reduction in VAS pain (-15.2 vs. -7.7, difference -9.9, 95% CI [-19.3 to 0.6]) (Figure 1), AUSCAN pain [-55.3 vs. -13.5, diff -41.7, 95% CI [-91.5 to -2.5] and stiffness [-14.5 vs -2.9, diff -11.4, 95% CI [-20.8 to -2.0]) than the placebo group (Table 1). The between-group differences were not clinically meaningful for change in AUSCAN function [-52.7 (+1273 to 21.9)], FIHOA [-0.9 (-3.4 to 1.7)], HAQ [-0.0 (-0.2 to 0.2)], or MHQ [5.5 (-0.3 to 11.3)]. Incidence of adverse events was 62.0% in methotrexate and 59.6% in placebo group.

Conclusion: This study provides high-quality evidence for the effect of methotrexate (20 mg once weekly) on reducing pain and stiffness over 6 months in patients with hand OA and synovitis. The results have the potential to inform clinical practice guidelines for the management of hand OA with the inflammatory phenotype.

REFERENCE:

Figure 1. Pain at each time point over the study period (mean with standard error)

Table 1. Primary and secondary outcomes at 6 months, using a multiply imputed dataset

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>Change between baseline and 6 months Mean (SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate Placebo</td>
<td>(N=50)</td>
<td>(N=47)</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint VAS</td>
<td>61.5 (15.7)</td>
<td>65.2 (18.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUSCAN pain</td>
<td>233.6 (84.1)</td>
<td>242.7 (107.4)</td>
<td>0.038</td>
</tr>
<tr>
<td>AUSCAN</td>
<td>47.4 (23.1)</td>
<td>46.8 (25.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>SF36</td>
<td>51.8 (17.1)</td>
<td>51.5 (16.7)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Adjusted for baseline measure of outcome, sex, and study site

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METHODS - A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND PHASE 2 STUDY AND OPEN LABEL EXTENSION PHASE

REFERENCES:
LOW-DOSE COLCHICINE IS ASSOCIATED WITH LOWER INCIDENCE OF KNEE AND HIP REPLACEMENTS: A POST-HOC ANALYSIS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Keywords: Osteoarthritis, Cartilage

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Methods: We performed a post-hoc analysis of data collected in the LoDoCo2 trial to determine the time to first knee or hip replacement. A Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for colchicine 0.5 mg daily as compared to placebo. Sensitivity analyses were performed by excluding patients known with gout at baseline (to avoid possible carry-over effects as colchicine is used to prevent gout attacks) or by excluding the patients who had joint surgery within the first 3 months after randomization (to avoid any bias related to planned joint surgery prior to randomization). All analyses were performed on an intention-to-treat basis.

Results: Among the 5522 randomized LoDoCo2 trial participants, 2762 received colchicine and 2760 placebo during a median duration of follow-up of 28.6 months (interquartile range, 20.5 to 44.4). The mean (SD) age was 66 (8.6) years and 846 (15.3%) were female. During the trial, TKR/THR was performed in 68 patients (2.5%) in the colchicine group and in 97 patients (3.5%) in the placebo group (HR, 0.69; 95% CI, 0.51-0.95; p = 0.02) (Table 1 and Figure 1). In a sensitivity analysis that excluded patients with gout similar results were obtained, while omitting joint replacements that took place in the first three months of follow-up yielded in an even larger rate reduction of TKR/THR (Table 1).

Table 1. Incidence rates and hazard ratios for hip and knee replacements according to treatment.

<table>
<thead>
<tr>
<th>Trial cohort/subgroup</th>
<th>Placebo (n=2760)</th>
<th>Colchicine (n=2762)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients/total no. (%)</td>
<td>No. of events/100 person-yrs</td>
<td>No. of patients/total no. (%)</td>
<td>No. of events/100 person-yrs</td>
</tr>
<tr>
<td>Full trial population TKR/THR events</td>
<td>97/2760 (3.5)</td>
<td>1.30</td>
<td>68/2762 (2.5)</td>
</tr>
<tr>
<td>Participants with gout at baseline excluded TKR/THR events</td>
<td>89/2734 (3.2)</td>
<td>1.30</td>
<td>61/2542 (2.4)</td>
</tr>
<tr>
<td>TKR/THR in the first three months excluded TKR/THR events</td>
<td>96/2760 (3.5)</td>
<td>1.29</td>
<td>59/2762 (2.1)</td>
</tr>
</tbody>
</table>

Conclusion: In this post-hoc analysis of the LoDoCo2 trial, use of colchicine 0.5 mg daily was associated with a reduced risk of TKR/THR. Further investigation of long-term therapy with colchicine to slow disease progression in osteoarthritis is warranted.

REFERENCES:

Acknowledgements: NIL.

Disclosure of Interests: None Declared.

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