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Concise report

Methotrexate for pain relief in knee osteoarthritis: an open-label study

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Abstract

Objective. Synovitis is very common in knee OA and associated with pain. This open-label study evaluated an anti-synovitis therapy, MTX, for pain relief in knee OA.

Methods. Inclusion criteria included pain visual analogue scale (VAS) >40/100 mm, ACR clinical criteria for knee OA and intolerance/inefficacy of NSAID and opioids. US at baseline and 24 weeks assessed effusion and synovial thickness. Patients received MTX up to 20 mg/week for 24 weeks.

Results. Thirty participants were recruited; mean age 64.5 years, median pain VAS 68 mm. At 24 weeks, 13/30 (43%) achieved ⩾30% reduction in pain VAS, 7 (23%) achieved ⩾50% reduction and 4 (13%) had worsened. Thirteen achieved Osteoarthritis Research Society International (OARSI) responder criteria. All had effusion/synovitis at baseline. There was no correlation between change in imaging and change in pain scores at 24 weeks.

Conclusion. This open-label trial suggests analgesic efficacy for MTX in OA knee and suggests that a randomized controlled trial is warranted.

Trial Registration. Current controlled trials, http://www.controlled-trials.com/, ISRCTN66676866.

Key words: knee, osteoarthritis, methotrexate, pain.

CLINICAL SCIENCE

Introduction

OA is the most common arthritis worldwide and causes significant pain and disability [1]. While current treatment guidelines recommend both pharmacological and non-pharmacological management [2], recent expert and evidence-based reviews of therapies suggest that the effect size of many of these therapies is small and current analgesic therapies have significant side effects [3]. With the exception of joint replacement surgery, there are no current safe, long-term effective treatments for OA pain.

MRI studies have demonstrated that synovitis is highly prevalent in knee OA and associated with pain [4–7]. Studies have also noted an association with change in synovitis and change in pain [6, 8]. MTX is an effective and now commonly used anti-synovial treatment for inflammatory arthritis with good long-term safety data [9]. There are two small, published studies using low-dose MTX in OA. The first, a randomized trial of 58 people, used 7.5 mg MTX weekly *vs* placebo for painful knee OA and did not find a reduction in pain at 4 months [10]. A 2-month open-label study for erosive hand OA used 10 mg MTX and demonstrated a significant improvement in pain [11].

We hypothesized that treatment with modern-dose MTX would improve OA symptoms and may offer a novel and safe, long-term treatment option. This open-label study examined whether analgesic response would justify a randomized controlled trial (RCT).

Methods

This study was conducted with the approval of the Leeds (West) Research Ethics Committee of the NHS National Research Ethics Service and informed consent was gained from all participants. The International Standard Randomised Controlled Trial Number is 66676866.

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People with ACR clinical criteria and tibio-femoral radiographic knee OA [Kellgren–Lawrence (KL) $\geqslant 1$], with insufficient pain relief from, or inability to tolerate, traditional analgesics including NSAIDs and opioids, were recruited from secondary care clinics. Self-reported knee pain was at least 40/100 mm on a visual analogue scale (VAS), with symptoms present on most days for at least 3 months. Exclusion criteria included inflammatory arthritis, IA hyaluronans within 6 months, any CS within 2 months and knee injury/surgery or diagnostic arthroscopy within 3 months.

Study design

This was a single-centre, open-label study for 24 weeks. Participants entering the study commenced MTX 7.5 mg, increasing to 20 mg (if tolerated) at 6 weeks, with follow-up visits at 4, 8 (telephone visit), 12 and 24 weeks. Participants were asked to remain on the same dose of concomitant analgesic medications throughout.

Full clinical examination was performed at baseline, 12 and 24 weeks. Outcome measures included a VAS recording average knee pain in the signal knee (the most painful knee) during the previous 48 h. Patient- and physician-reported 48 h disease activity VAS, WOMAC (3.0 Likert scale), Hospital Anxiety and Depression Scale and Osteoarthritis Quality of Life questionnaire were completed at baseline, weeks 12 and 24. A VAS recording average knee pain during the previous 48 h in the non-signal knee was also completed at baseline, 12 and 24 weeks. Participants did not have access to scores from previous visits when completing questionnaires.

Imaging

A radiograph of the signal knee was undertaken at the screening visit using a weight-bearing semi-flexed anteroposterior view. To explore mechanism of action, an US of the signal knee was performed at baseline and final study visit by the same experienced musculoskeletal radiologist, using a Siemens Acuson Antares machine with a 13-5 linear array probe. Synovitis (defined as hypoechoic tissue that is non-displaceable and poorly compressible) [12] and effusion (defined as hypoechoic or anechoic IA material that was displaceable and compressible, but did not exhibit Doppler signal) [12] were assessed in the suprapatellar pouch and medial and lateral recesses with the knee in full extension and in 45° flexion. The maximum value in millimetres (mm) for synovitis and effusion at each site was recorded. The intra-class correlation coefficient of this reader for measuring effusion was 0.94 and for synovitis was 0.93.

Statistical analysis

Data was analysed using SPSS version 19 IBM SPSS Statistics (Armonk, NY, USA). Wilcoxon signed rank test compared the changes in VAS measurements and questionnaires at 12 and 24 weeks from baseline. The OMERACT-OARSI responder criteria were also tested: in summary, a person is classed as a responder if there is a 50% reduction in pain (48-h pain VAS) or function (WOMAC functional subscale) or a 20% reduction with an absolute reduction of $\geqslant 10$ in two out of three of 48-h pain VAS, WOMAC functional subscale or patient activity VAS [13].

Results

Clinical results

Sixty people were invited to join the study, of whom 18 declined to participate and 12 did not fulfil inclusion criteria. Thirty people, as the suggested number required for a pilot study [14], were recruited within 14 months (baseline characteristics presented in Table 1). Five participants withdrew within the first 12 weeks from side effects and were excluded from assessment of change. Two participants withdrew from inefficacy, at 12 weeks ($n = 1$) and 17 weeks ($n = 1$), and were included in assessment of change at 12 weeks. All participants who withdrew were included in the analysis as non-responders at 24 weeks. Twenty of the 23 participants who completed the trial received $\geqslant 15$ mg MTX per week. Three received between 7.5 and 12.5 mg (dose limited by side effects). VAS scores for eight participants were not available at the 12-week visit. Three participants, all of whom completed the 24-week study, requested an IA CS injection during the first 12 weeks (as per protocol) to reduce pain. The data from these participants have been excluded from assessment of change and they have been classed as non-responders at 24 weeks.

At 12 weeks, there was a median [interquartile range (IQR)] reduction in signal knee 48-h pain VAS of 9 mm (−1 to 36) and a median (IQR) reduction in patient-reported disease activity VAS of 20 mm (−1 to 48). At 24 weeks, there was a median (IQR) reduction in 48-h pain VAS of 27 mm (4–38) and a median (IQR) reduction in patient-reported disease activity VAS of 39 mm (16–52) (Table 2).

At baseline, 12 participants had non-signal knee pain of >40 mm and fulfilled ACR clinical criteria for OA of the knee. Twenty-four-week data were available for 11 of these participants demonstrating a median (IQR) reduction in pain VAS of 21 (3–29) mm (Table 2).

At 24 weeks, 13/30 participants (43%) had achieved $\geqslant 30\%$ reduction in pain VAS, of whom 7 (23%) had achieved $\geqslant 50\%$ reduction. Four participants (13%) had experienced a flare (Table 2). Thirteen of 30 (43%) participants achieved OARSI responder criteria. All participants who withdrew ($n = 7$) or received IA CS ($n = 3$) were classified as non-responders.

While there was a significant reduction in anxiety score at 24 weeks, there was no change in depression or quality of life scores (Table 2). Eleven of the 23 participants who completed the study chose to remain on MTX.

Concomitant medication

At baseline, 16 people were using NSAIDs and 20 were using opioids (codeine or tramadol). By 12 weeks, two people had stopped NSAIDs, but no other changes in

Table 1 Baseline characteristics

Baseline characteristics	
Age, mean (range), years	64.5 (53–85)
BMI, mean (S.D.), kg/m^2	31.4 (5.9)
Disease duration, mean (range), months	49 (6–122)
NSAID usage, *n* (%)	16 (53)
Opioid usage, *n* (%)	20 (67)
Clinically detectable effusion, *n* (%)	21 (70)
K/L score, *n* (%)	
K/L 1	6 (20)
K/L 2	20 (67)
K/L 3	3 (10)
K/L 4	1 (3)
Signal knee pain VAS, median (IQR), 48 h, mm	68 (42–86)
Other knee pain VAS[a], median (IQR), 48 h, mm	70 (58–73)
Patient activity VAS, median (IQR), mm	75 (66–85)
Physician activity VAS, median (IQR), mm	60 (46–65)
WOMAC pain, median (IQR)	10 (8–13)
WOMAC stiffness, median (IQR)	4 (3–5)
WOMAC function, median (IQR)	36 (28–43)
HADS anxiety, median (IQR)	7 (3–10)
HADS depression, median (IQR)	4 (2–8)
OAQoL, median (IQR)	11 (5–18)
Imaging at baseline	
Total effusion, median (IQR), mm	9.1 (7.1–16.5)
Maximum effusion, median (IQR), mm	5.4 (3.4–7.2)
Total synovitis, median (IQR), mm	8.6 (5.0–13.7)
Maximum synovitis, median (IQR), mm	3.8 (2.3–6.7)

Total effusion/synovitis: sum of effusion/synovitis for all three compartments imaged. Maximum effusion/synovitis: highest individual compartment measurement. [a]For those participants with other knee pain VAS >40/100 mm. HADS: Hospital Anxiety and Depression Scale; OAQoL: Osteoarthritis Quality of Life score.

NSAID dose was made throughout the study. Opioid dose was reduced in one person and increased in another at the 12-week visit, and by 24 weeks, two people had increased opioid dose due to increased knee and hip pain.

Imaging results

All patients had synovitis (effusion or synovial hypertrophy ⩾2 mm) at baseline and 25/30 demonstrated both pathologies. US at the final study visit (including three participants who withdrew after 12 weeks) demonstrated synovitis in 22 people. There was a median (IQR) reduction in total synovial thickness of 1.3 mm (−0.7 to 3.8) ($n = 26$) and a median (IQR) reduction in total effusion measurement of 0.6 mm (−1.3 to 3.6) ($n = 26$) (Table 2) ($P > 0.05$). Baseline synovitis or effusion (whether total values summated across the three knee compartments or maximum individual compartment scores) were not substantively correlated with baseline pain or change in 48-h pain VAS at 24 weeks ($\rho < 0.2$). Changes in synovitis and effusion at 24 weeks were similarly not substantively correlated with changes in pain (all $\rho < 0.2$).

Adverse events

Twelve participants noted nausea, headache or lethargy. Transient mild elevation in ALT was frequent; three participants required dose reduction for raised ALT and/or mild neutropenia.

Discussion

This first open-label study of oral MTX for painful knee OA using modern dosing demonstrated a high proportion of participants with important reduction in pain, comparable to that achieved with commonly used NSAIDs [15] and also comparable to the mean pain reduction achieved with opioids [16]. The participants in this study had inadequate analgesia or side effects from either NSAIDs or opioids; therefore, MTX has demonstrated analgesic effect for people with at least moderate OA knee pain who are refractory to traditional analgesics. Side effects resulting in discontinuation of MTX were similar to those reported in RA (15–17%) [17] but are much lower than those reported for opioid use [16], with fewer than half of people taking opioids still using them 7 months after starting therapy.

The previous negative study of MTX in knee OA used fixed dose 7.5 mg/week, while 20 of 23 participants who completed our study received ⩾15 mg; however, the previous study was placebo controlled [10]. The entry criteria in the previous study included a pain VAS of >50/100 mm (compared with 40/100 mm in this study) and participants had more structural damage, with over 90% having a KL score of 3, with the majority in our study scoring KL score 2. It is likely, however, that the vast majority of participants from both studies had synovitis given recent studies using sensitive imaging [5, 7].

US was used in this study to explore possible mechanisms of MTX action. There was no correlation with the degree of baseline synovitis/effusion and pain scores, nor were changes in synovitis or effusion associated with change in pain, possibly because of the small number of participants, all of whom had moderate–high pain scores. Two recent, large MRI studies of knee OA [5, 6] again demonstrated the prevalence of synovitis and noted an association between synovitis and pain with the odds ratio for knee pain increasing as the synovitis score increased [5]. A previous non-contrast MRI study noted a weak but statistically significant association between change in synovitis and change in pain ($r = 0.21$, $P < 0.05$) [4]. A recent large MRI study of over 600 people with knee OA reported that reduction in synovitis score was not associated with a reduction in pain [6]. However, neither of these studies used optimal contrast-enhanced MRI to detect synovitis, and assessed synovitis at few sites, limiting their ability to detect change in synovitis. There are several possible reasons for the lack of association between change in imaging-detected synovitis and change in clinical symptoms in this study. First, the number of people in this study is small. Secondly, the synovial thickness was measured at only three sites in the knee. Also, little is known as to the

Table 2 Clinical and imaging outcomes at final study visits

Variable	Reduction at 12 weeks	*n*, *Z*, *P*	Reduction at 24 weeks	*n*, *Z*, *P*
Signal knee pain VAS, median (IQR), 48 h, mm	9 (−1 to 36)	19, −2.5, 0.01	27 (4 to 38)	20, −2.7, 0.008
Patient activity VAS (mm), median (IQR)	20 (−1 to 48)	17, −2.9, 0.003	39 (16 to 52)	19, −3.6, <0.001
Physician activity VAS, median (IQR), mm	28 (−1 to 35)	17, −2.9, 0.003	19 (−2.4 to 44)	19, −2.4, 0.015
VAS non-signal knee, median (IQR), 48 h, mm	16 (−10 to 40)	11, −1.4, 0.16	21 (3 to 29)	11, −2.4, 0.02
WOMAC pain, median (IQR)	1 (−1 to 3)	24, −0.9, 0.35	1.5 (0 to 3.8)	20, −2.3, 0.02
WOMAC stiffness, median (IQR)	1 (−1 to 2)	24, −1.7, 0.09	1.0 (0 to 2)	20, −1.8, 0.07
WOMAC function, median (IQR)	4 (−3 to 13)	24, −2.0, 0.04	2.5 (−1.8 to 11.3)	20, −0.9, 0.36
HADS anxiety, median (IQR)	1 (−1 to 3)	23, −2.0, 0.03	1.5 (0 to 3.8)	20, −2.1 0.03
HADS depression, median (IQR)	0 (−1 to 3)	23, −0.8, 0.41	−1.0 (−1.8 to 1.8)	20, −0.48, 0.63
OAQoL, median (IQR)	1 (−1 to 4)	23, −1.5, 0.15	−1.5 (−4.8 to 1.5)	20, −1.0, 0.31
Imaging			Reduction at final study visit [12 weeks (*n* = 2), 17 weeks (*n* = 1), 24 weeks (*n* = 23)]	
Total effusion, median (IQR), mm	NA	NA	0.6 (−1.3 to 3.6)	26, −1.28, 0.20
Maximum effusion, median (IQR), mm	NA	NA	0.0 (−0.9 to 2.8)	26, −1.13, 0.26
Total synovitis, median (IQR), mm	NA	NA	1.3 (−0.7 to 3.8)	26, −1.92, 0.06
Maximum synovitis, median (IQR), mm	NA	NA	1.1 (−0.4 to 1.8)	26, −1.75, 0.08

Total effusion/synovitis: sum of effusion/synovitis for all three compartments imaged. Maximum effusion/synovitis: highest individual compartment measurement. NA: not applicable; HADS: Hospital Anxiety and Depression Scale; OAQoL: Osteoarthritis Quality of Life score.

natural history of change in synovial thickening and effusion over time. However, work from our group has demonstrated that there is no change in US-detected synovitis or effusion over a 2-week time period in an untreated cohort of people with OA knee (H. I. Keen, personal communication). Furthermore, the effect of MTX on the synovium may be qualitative rather than quantitative in OA, so that the overall volume or thickness imaging measurements may be unchanged, but there may be a change on a cellular or cytokine level. Importantly, this study could not assess other features that have been associated with pain in the OA knee, such as bone marrow lesions [18] or bone attrition [19].

This study does have limitations. The number of participants, although 30 is the suggested minimum number suitable for a pilot study [14], is small, particularly when only 23 people completed the full 24 weeks in the study. This study was not placebo-controlled; therefore, participants may have had an expectation of pain relief which could have affected their responses to the questionnaires. The placebo response in OA is well described [20]. In summary, this small open-label study of MTX for treating painful knee OA suggests that MTX may have analgesic efficacy in knee OA, suggesting that a placebo-controlled RCT is warranted.

Rheumatology key message

- Treating inflammation in OA with anti-synovitis therapies may provide desperately needed new therapeutic options.

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