A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis – The HUMOR trial

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ABSTRACT

Objective: To assess the efficacy of adalimumab in patients with erosive hand osteoarthritis (OA).

Method: Patients >50 years old, meeting the ACR criteria for hand OA, with pain >50 on 100mm VAS, morning stiffness >30 minutes and ≥1 erosive joint on x-ray with synovitis present on MRI were included in a randomised double-blind placebo-controlled crossover trial. Patients were randomised to adalimumab (40 mg subcutaneous injections every other week) or identical placebo injections for 12 weeks followed by an 8-week washout and then crossed over treatment groups for another 12 weeks. The primary outcome was change in VAS hand pain over 12 weeks. Secondary outcomes included change in AUSCAN pain, function and stiffness subscales from baseline to 4, 8 and 12 weeks, change in MRI-detected synovitis and bone marrow lesions (BMLs) from baseline to 12 weeks and change in VAS from baseline to 4 and 8 weeks.

Results: We recruited 51 patients and 43 were randomised to either Group 1 (N=18, active then placebo) or Group 2 (N=25, placebo then active). At 12 weeks there was no difference between the groups on the primary outcome measure (mean decrease in VAS pain of 3.2mm (SD 16.7) for adalimumab versus 0.8mm (SD 29.6) for placebo). The adjusted treatment effect was -0.7mm (95% CI -9.3 to 8.0), P=0.87. No statistically significant differences were found for any secondary outcomes.

Conclusion: Adalimumab did not show any effect on pain, synovitis or BMLs in patients with erosive hand OA with MRI-detected synovitis as compared to placebo after 12 weeks.

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5 keywords: hand osteoarthritis, synovitis, magnetic resonance imaging, anti-TNF

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INTRODUCTION

Erosive hand osteoarthritis (OA) is considered a more inflammatory hand OA phenotype[1]. Patients are often difficult to treat with a high level of pain and disability. It is characterised by articular cartilage damage, erosions and remodelling of the subchondral bone[2].

Tumour necrosis factor (TNF) α is a pro-inflammatory cytokine produced by the synovial cells and chondrocytes and has been implicated in the development and progression of OA[3, 4]. This makes TNF α a target for therapy to reduce pain and slow disease progression; however, there is limited data on the effect of anti-TNF α therapy in patients with hand OA[5-8] and studies to date show mixed findings with regard to clinical and structural progression. In a randomised, double-blind, placebo-controlled trial over 6 months, Chevalier et al reported that adalimumab treatment was not superior to placebo to alleviate pain in patients with hand OA not responding to analgesics and non-steroidal anti-inflammatory drugs (NSAIDS)[6]. Another randomised controlled trial (RCT) showed that 1-year of adalimumab treatment did not reduce symptoms or erosive progression assessed by x-ray[5]. However, post-hoc findings from this trial suggested that adalimumab therapy halted erosive progression in a subset of hand OA patients with clinically swollen joints at baseline[5]. Therefore, the aim of our study was to assess the efficacy of adalimumab (Humira, AbbVie Pty Ltd), 40 mg subcutaneous injections every other week, for 12 weeks in a randomised double-blind placebo-controlled crossover trial for patients with erosive hand OA and evidence of magnetic resonance imaging (MRI)-defined synovitis.

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METHODS

Trial design

This study was a randomised double-blind placebo-controlled crossover trial of adalimumab versus placebo. In a randomised crossover trial participants are assigned randomly to a sequence of treatments and each participant serves as his/her own control in estimating treatment effects[9]. As a result, fewer patients are required for a crossover trial because it can achieve the same precision as a parallel group trial with less than half the sample size[9].

Settings and locations

Participants were recruited from July 2013 to June 2015 through advertising in local print media in Hobart, Tasmania, Australia, from the private practice of a study investigator (GJ), and referrals from other rheumatologists in Hobart. Participants attended clinics at the Menzies Institute for Medical Research, Hobart, Tasmania.

Participants and Screening Procedure

Participants were first screened over the telephone to determine their interest and initial eligibility to participate in the trial, after which they were invited to attend the study centre for a face-to-face screening visit. Screening and clinical examinations were performed by a rheumatologist (GJ) and two study nurses (MG and KB). Participants had a clinical examination, supplied a blood sample (for a range of laboratory tests, see Supplementary Table 1), had a chest x-ray (to exclude tuberculosis), a standard AP hand radiograph and a hand MRI scan. This research was conducted in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All participants gave informed written consent.

Inclusion and exclusion criteria

We recruited participants aged >50 years, who met the American College of Rheumatology (ACR) criteria for hand OA[10], and had pain >50 on 100mm visual analogue scale (VAS),

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morning stiffness >30 minutes, and ≥1 erosive joint on x-ray with synovitis present on MRI. The exclusion criteria are outlined in Supplementary Table 1.

Selection of the index joint

Following a clinical examination, hand x-ray and hand MRI scan, one joint was nominated as the index joint and this joint was studied throughout the trial. Firstly, clinical examinations and screening of joint erosion on x-ray was performed by the principal investigator (GJ), who is a rheumatologist with over 10 years of experience reading X-rays. Patients who had joint erosion in their clinically eligible joint were then sent for a 1.5T non contrast MRI scan of their erosive joint to determine whether their erosive hand OA was inflammatory, defined by the presence of synovitis on MRI. If >1 erosive joints were identified during initital screening the most painful joint was used. Screening for the presence of synovitis was undertaken by an experienced MRI reader (PB), a member of the Outcome Measures in Rheumatology (OMERACT) MRI Inflammatory arthritis group, and co-author of the OMERACT hand OA MRI score (HOAMRIS)[11].

Interventions

Patients were randomised to adalimumab (40 mg subcutaneous injections every other week) or placebo for 12 weeks (treatment period 1) followed by an 8-week washout and then the converse treatment for 12 weeks (treatment period 2) (Figure 1).

Outcomes

The primary outcome was change in VAS hand pain over 12 weeks. Secondary outcomes included change in the AUSCAN pain, function and stiffness subscale from baseline to 4, 8 and 12 weeks, improvement in MRI-detected synovitis and BMLs from baseline to 12 weeks and change in the VAS pain subscale from baseline to 4 and 8 weeks.

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Outcome measures

Pain, function and stiffness

Hand pain was measured using a 100mm VAS by asking "on this line, where would you rate your pain, using the last 7 days as a timeframe?" Hand pain, function and stiffness were measured using the Australian/Canadian Hand OA Index (AUSCAN)[12] on eight occasions (baseline, 4, 8 and 12 weeks of each treatment period), using the last 48h as a timeframe. AUSCAN contains five items referring to hand pain, nine items relating to difficulty with hand functions and one question on severity of morning stiffness. The questions were scaled on a 100 mm VAS. Total pain, function and stiffness subscale scores were calculated by adding each of the items together. The possible range of scores was 0–500 for pain, 0–900 for function and 0–100 for stiffness.

MRI measures

Images of the index joint were acquired at baseline and 12 weeks of each treatment period with a 1.5T whole-body magnetic resonance unit (Siemens, Espree) using five sequences (Supplementary Table 2). One reader (IKH) read the baseline and 12 week MRIs with known time sequence for each treatment period (blinded to treatment allocation). Synovitis and BMLs were scored according to the OMERACT HOAMRIS[11] or the OMERACT thumb base OA MRI scoring system (TOMS)[13]. The reliability of these scoring systems, as previously published, shows good to very good ICC values[11, 13]. Synovitis was assessed without the use of gadolinium contrast. Thickened synovium were scored: 0=Normal, 1=Mild, 2=Moderate, 3=Severe. The 1-3 scores are defined by thirds of the presumed maximum volume of the synovial compartment. BMLs were defined as a signal characteristic consistent with increased water content and with ill-defined margins within the trabecular bone and were scored as follows: 0=Normal, 1=Mild: 1-33% of bone volume, 2=Moderate: 34-66% of bone volume, 3=Severe: 67-100% of bone volume; where "bone volume" refers to the proximal

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and distal part of the joint combined. Changes in synovitis and BMLs over 12 weeks were documented in 0.5 increments in case changes in these features were present, but were not enough to be scored within the next category. This is standard practice for performing longitudinal measurements using these scoring systems[11, 13]. Improvement in synovitis or BMLs in the index joint was defined as a decrease by 0.5 or more over the treatment period. What level reflects clinical significance is uncertain and has not yet been studied.

Concomitant medication/analgesic use

To maintain the pragmatic nature of the trial, there were no restrictions with regard to concomitant analgesic medications (including corticosteroids). All participants were allowed to continue taking the medications that they were taking at their screening visit for the duration of the trial. Participants were asked to keep medications as stable as possible but if a participant experienced an increase in pain requiring an increase in the dose of analgesics the reason for the dose increase and the dose used was documented. Medication usage was recorded at baseline, 4, 8 and 12 weeks of each treatment period.

Safety

Adverse events were defined as any untoward event occurring during the trial regardless of whether it was considered medication-related. Serious adverse events were defined as unplanned hospital admissions, new cancer diagnoses or death during the study.

Sample size

The power calculations were conducted considering the cross-over trial design, where each participant experiences both treatments assigned in random order. Enrolling a total of 40 patients gave us 97% power, and 5% probability of type 1 error (alpha=0.05) to detect a 15mm difference between adalimumab and placebo on the VAS scale (SD of pain change

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23.8mm, based on in-house data[14]). We assumed a correlation of 0.5 between readings made on the same person.

Randomisation and sequence generation

Participants were allocated to either placebo or adalimumab at a ratio of 1:1 based on computer-generated random numbers. The random allocation sequence was automatically generated, and a security protected central automated allocation procedure was used to allocate participants to treatment arms. This was then used by one author (LL) who had no contact with participants to dispense the syringes of allocated medication. Research nurses enrolled participants in the trial, and then gave the allocated medication to each individual patient. The active treatment and placebo product were visually identical. Participants and staff involved in patient care remained blinded to treatment allocation throughout the trial.

Statistical methods

We used Stata 12.0 (StataCorp LP) for statistical analyses. Statistical significance was set as a P value <0.05. Analysis was by intention to treat (ITT) as randomised in those receiving at least one dose of the intervention in both treatment periods of the study. Change in each outcome was assessed using the difference between the factor at baseline and each study visit (4, 8 and 12 weeks). Baseline values were considered week 0 of treatment period 1 or 2 (see Figure 1), as recommended for crossover trials[9, 15]. The primary outcome was change over 12 weeks as assessed by the VAS pain scale.

For continuous outcomes, including change in VAS, AUSCAN pain, function and stiffness subscales, treatment effects were calculated using a repeated measures modelling approach adjusting for the difference in each participants baseline value during treatment period 1 and period 2 (i.e. adjusting for within-subject baseline difference, method IV as recommended in Mehrotra[16]). Data was checked for normality and for homogeneity of variance. For

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categorical outcomes, including improvement in synovitis and BMLs, χ^2 tests were used to examine differences in the proportion of participants improving during each treatment period. We then used log-binomial generalised estimating equations (GEE) analysis to explore the risk of having an improvement in synovitis or BML score in the active versus placebo groups. In all methods we clustered on participant ID, and adjusted for the order in which the participant received their treatment (e.g. Active then placebo, or Placebo then active). χ^2 tests were used to compare numbers of adverse events.

There was a discordance between the investigator who screened the study patients for synovitis at enrollment and the scoring of synovitis at the completion of the study. This resulted in four study patients in the trial who did not have synovitis according to HOAMRIS[11] and/or TOMS[13] scoring system. Analyses were repeated with these four study participants excluded.

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RESULTS

Study participants

In total 51 participants attended screening for the study, of whom 8 were excluded (Figure 1). The remaining 43 participants were randomised to receive either adalimumab (n=18) or placebo (n=25) over treatment period 1. There were 5 study participants that either withdrew during the study, or had missing primary outcome data at 12 weeks.

Table 1 shows the baseline characteristics of study participants by treatment received during treatment period 1. At baseline, participants (n=43) had a mean age of 61 years (SD 8.4), mean BMI of 28.9 (SD 4.2), mean VAS pain level of 63.6 (SD 17.7) out of 100 (indicating highly symptomatic disease), and 77% were women. There were five study participants that were enrolled based on the presence of erosive OA in the first carpometacarpal (CMC1) joint. The remaining participants had erosive OA in an interphalangeal joint.

Outcomes

Data on the main outcomes are shown in Figure 2 and Tables 2-5.

Primary outcome

At 12 weeks there was no difference in change of VAS pain between the groups (Table 3). Mean decrease in VAS pain was 3.2mm (SD 16.7) following adalimumab treatment versus 0.8mm (SD 29.6) following placebo treatment. The adjusted treatment effect was -0.7mm (95% CI -9.3 to 8.0), P=0.87). During treatment period 1, the adalimumab treated group had a decrease in pain of 1.9mm (Table 2 and Figure 2). This group had an increase in pain of 5.1mm when they received placebo during treatment period 2. During treatment period 1, the placebo treated group had a decrease in pain of 5.0mm. This group also had a decrease in pain of 4.2mm when they received adalimumab during treatment period 2. These changes are small and are not considered clinically important.

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Secondary outcomes

No statistically significant differences between adalimumab treatment versus placebo treatment was seen for any secondary symptomatic outcomes (Table 3). There were small changes in synovitis and BML scores in both groups and no significant difference between the groups was observed (12% had an improvement in synovitis score with adalimumab vs 10% with placebo (P=0.63); 5% had an improvement in BML score with adaliumumab vs 7% with placebo (P=0.67) (Tables 4-5)).

The results for the primary and secondary outcomes were unchanged when the four patients without synovitis according to the HOAMRIS[11] and/or TOMS[13] scoring system were excluded. The results were also unchanged when the five patients with erosive OA in their CMC1 joint were excluded. Analgesic use throughout both treatment periods was similar between groups (data not shown).

Adverse events

Adverse events were common, with 55% (n=23) of the placebo group and 36% (n=15) of the active group experiencing at least one adverse event (Table 6). Differences in the total number of adverse events and prevalence of events were not statistically significant. One participant had a serious adverse event with a non-elective hospitalization for treatment of cellulitis after cutting his/her finger whilst in the adalimumab arm. Cellulitis was possibly causally related to the study drug.

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DISCUSSION

This RCT demonstrated that 12 weeks of treatment with adalimumab (40 mg subcutaneous injections every other week) was no different to placebo to alleviate pain, synovitis or BMLs in patients with erosive hand OA presenting with synovitis on MRI. The main clinical outcome (change over 12 weeks as assessed by VAS pain) was not different between the adalimumab and placebo groups. Furthermore, no clinically or statistically significant differences were found for any of the secondary outcomes including patient-reported outcomes and MRI-assessed structural abnormalities (synovitis and BMLs). The results suggest that pain and inflammation are not responsive to TNF α inhibition in this patient population.

Anti-TNF α therapies have been very successful for treating pain and structural disease progression in inflammatory arthritis such as RA[17]. There is limited data on the effect of anti-TNF α therapy in patients with hand OA[5-8] and studies to date show mixed findings with regard to clinical and structural progression. Evidence from trial data has consistently shown that anti-TNF α therapy does not improve symptoms in hand OA patients[5-7] and the findings from our study support this. In a randomised, double-blind, placebo-controlled trial over 6 months, Chevalier et al reported that adalimumab was not superior to placebo to alleviate pain in patients with hand OA not responding to analgesics and NSAIDS[6]. Similarly Verbruggen et al showed that 1-year of adalimumab treatment did not reduce symptoms including pain, stiffness, function and number of tender joints[5].

Despite these previous negative trial findings, we hypothesised that adalimumab may be effective in erosive hand OA when inflammation was present (assessed in our study as MRI-

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detected synovitis), given TNF α's pro-inflammatory role in the synovial membrane[18]. In support of this, a previous study by Verbruggen et al suggested that adalimumab could halt erosive progression on x-ray in a subset of patients with clinically swollen joints at baseline[5]. However, despite selecting a sub-group of erosive hand OA patients with synovitis, our trial failed to show an effect for pain or structure (assessed as synovitis and BMLs on MRI as secondary outcomes). The failure of adalimumab in painful hand OA may indicate that TNF α may not be the right treatment target, even in those with definite synovitis. Unlike RA, inflammation in OA may be present as a result of joint damage as opposed to primary immune activation. It may not be driving the disease but rather represent a consequence of the disease process. However, in contrast to this theory, several studies have shown that synovitis on both MRI[19] and ultrasound[20] as well as clinical signs of inflammation[21] predict future structural progression. Whether other features that are co-occurring with synovitis are of larger importance than the synovitis itself, should be further explored.

A treatment for erosive hand OA would need to improve symptoms in order for it to be successful. Our study duration of 12 weeks to assess the effect on pain is sufficient, as symptom modification should ideally be achieved by this time, otherwise patients would not be motivated to continue treatment. Anti-TNF α therapy in inflammatory arthritis such as PsA, RA and ankylosing spondylitis is associated with a rapid pain response (starting as early as 2-4 weeks and reaching maximum efficiency by 8-12 weeks)[17]. It is possible that anti-TNF α therapy may exert differential effects on pain and structure. Our 12 week study may not have been long enough to see structure modification. Furthermore, our crossover study design was not the ideal design to examine changes in structure. The structural/imaging outcomes in our study were synovitis and BMLs which likely reflect inflammation. Over 12 weeks we

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297 found only small changes in synovitis and BML scores and no difference between the
298 treatment versus placebo groups. A successful therapy for erosive hand OA would ideally
299 slow or prevent the destructive subchondral remodeling that occurs in this disease. Erosions
300 and inflammation may represent different pathological processes[22].
301
302 Hand OA trials have shown to have high placebo effects[23], and this was also the case in the
303 previous studies that trialled adalimumab for hand OA[6, 7]. In our trial we did not see large
304 effects from placebo, in fact, pain improvement in the VAS and AUSCAN pain scales was
305 well below the level of clinical relevance in both the adalimumab and placebo groups. This
306 could be due to the crossover study design, as crossover trials are less prone to placebo
307 effects[24].
308
309 Advantages of a crossover study design include smaller sample sizes over parallel designs,
310 the elimination of between subject variability as each participant serves as his/her own
311 control and enhanced recruitment as potential participants are aware they will receive the
312 active treatment at some point. However, there are some considerations to this study design
313 that need to be discussed. Firstly, as outlined above, crossover study designs are not ideal to
314 examine structural modification. Secondly, crossover studies can be limited because
315 treatment from the first period may have a carryover effect[9]. To mitigate against this, we had
316 an 8-week washout, in which the treatment could 'wear off' before the participant started the
317 next treatment period. The average half-life of adalimumab is 2 weeks, ranging between 10 to
318 20 days[17]. While the optimal length of a washout period is unclear, for a drug trial it is
319 suggested to be between 3-5 times the half-life of a drug. This would suggest that our
320 washout period was reasonable. Furthermore, our data do not show any carryover effects as

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there was very little improvement in pain, regardless of the order they received the treatments. As recommended[9, 15], our analysis accommodated the paired nature of the design and we reported our data in a manner that facilitates understanding of any carryover effects and missing data. Furthermore, the continuous outcomes were adjusted for the difference in each participants baseline value during treatment period 1 and period 2 (i.e. adjusted for within-subject baseline difference, method IV as recommended in Mehrotra[16]).

There are potential limitations to this study. First, synovitis was assessed without the use of gadolinium contrast, which may be less sensitive to detect changes in synovitis. Also, synovitis was moderate at baseline and the level of inflammation may have been too low to detect meaningful changes. Second, following a clinical examination, x-ray and MRI scan, one joint was nominated as the index joint and this joint was studied throughout the trial. We did not collect information about the number of other hand joints involved (including the presence of tender or swollen joints) and improvements may have occurred in these joints. Similarly the MRI scans were only taken of the index joint therefore we could not assess MRI changes in the other hand joints. Furthermore, we included patients with both interphalangeal and thumb base OA. It has been proposed that thumb base OA may be a unique phenotype. We did perform a sensitivity analysis, excluding the five patients that were included based on erosive CMC1 OA in their index joint, and our results were unchanged. However, as we did not collect information about other hand joints, we are unable to say how many of our patients in total had CMC1 involvement. Third, hand x-rays were performed for screening purposes only, and were not scored to define disease severity in these patients. Therefore the level of disease severity and phase of erosion damage[25] was not quantified and could not be

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examined in exploratory analysis. Screening of erosions was performed by the principal investigator (GJ), who is a rheumatologist with over 10 years of experience reading X-rays.

CONCLUSIONS

Adalimumab did not show any effect on pain, synovitis or BMLs in patients with erosive hand OA with MRI-detected synovitis, as compared to placebo after 12 weeks treatment. This suggests that pain and inflammation are not responsive to TNF α inhibition in this patient population.

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Figure legends and Tables

Figure 1: Study flow chart

Figure 2: Mean VAS pain score ± standard error over each 12 week treatment period.

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Table 1: Baseline characteristics of study participants, by treatment received during treatment period 1

Baseline characteristics	N	Adalimumab Mean (SD)	N	Placebo Mean (SD)
Age, years	18	63.1 (8.4)	25	61.2 (8.4)
Women, n (%)	18	15 (83)	25	18 (72)
Weight, kg	18	77.3 (12.9)	25	79.3 (15.0)
Height, cm	18	162.7 (8.7)	25	166.0 (8.3)
Body Mass Index, kg/m^2	18	29.2 (3.8)	25	28.7 (4.5)
VAS pain score (0-100 mm)	18	63.9 (17.1)	25	63.4 (18.5)
AUSCAN pain subscale score (0-500)	18	332 (98.5)	25	308.4 (96.4)
AUSCAN function subscale score (0-900)	18	622.5 (181.9)	25	559.8 (165.6)
AUSCAN stiffness subscale score (0-100)	18	73.7 (21.3)	25	66.9 (17.0)
Medication use				
Paracetamol, n (%)	18	7 (39)	25	13 (52)
Average paracetamol dose, mg	7	1588 (1168)	13	1387 (954)
COX-2 inhibitors, n (%)	18	1 (6)	25	4 (16)
NSAIDS, n (%)	18	7 (39)	25	11 (44)
Number of pain medicines, n (%)				
0		5 (28)		6 (24)
1		6 (33)		6 (24)
2		6 (33)		9 (36)
3		1 (6)		3 (12)
4		0		1 (4)
Synovitis (0-3)	18	1.3 (0.6)	24	1.2 (0.8)
Bone marrow lesions (BMLs) (0-3)	18	1.0 (0.8)	25	1.3 (0.7)

AUSCAN - Australian/Canadian Hand OA Index, VAS - Visual Analogue Scale, COX-2 - Cyclooxygenase-2, NSAIDS - Non-steroidal anti-inflammatory drugs.

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Table 2: Change in primary outcome (VAS pain score from baseline to 12 weeks) over the two treatment periods, based on the order in which they received the treatment

	Treatment period		Within-individual difference: Active-placebo
Treatment sequence	**1**	**2**	
Active then placebo			
Mean (SE)	-1.9 (3.4)	5.1 (8.5)	-7.1 (8.6)
N	18	16	16
Placebo then active			
Mean (SE)	-5.0 (5.5)	-4.2 (3.9)	1.2 (6.1)
N	23	23	22

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Table 3: Change in secondary outcomes by treatment group, and the adjusted treatment effect							
	N	**Placebo Mean change (SD)**	**N**	**Active Mean change (SD)**	**N**	**Adjusted treatment effect* Mean difference (95% CI)**	**P-value**
Primary outcome							
Change in VAS pain							
Baseline to 12 weeks	39	-0.8 (29.6)	41	-3.2 (16.7)	41	-0.7 (-9.3 to 8.0)	0.87
Secondary outcomes							
Change in VAS pain							
Baseline to 4 weeks	41	-4.1 (23.0)	40	-6.1 (22.7)	41	-0.2 (-8.1 to 7.6)	0.95
Baseline to 8 weeks	39	-5.2 (27.4)	41	-7.7 (21.5)	41	-0.4 (-10.2 to 9.4)	0.94
Change in AUSCAN pain							
Baseline to 4 weeks	42	-12.9 (132.2)	41	-31.0 (102.4)	41	-1.9 (-40.7 to 36.9)	0.92
Baseline to 8 weeks	41	-18.7 (140.9)	41	-41.5 (97.2)	41	-4.3 (-52.7 to 44.1)	0.86
Baseline to 12 weeks	40	-4.9 (142.6)	41	-20.9 (83.7)	41	8.7 (-34.0 to 51.4)	0.68
Change in AUSCAN function							
Baseline to 4 weeks	41	-23.0 (169.5)	40	-21.9 (166.7)	41	23.2 (-34.1 to 80.5)	0.42
Baseline to 8 weeks	41	-8.0 (198.7)	41	-61.4 (189.0)	41	-19.4 (-103.1 to 64.4)	0.64
Baseline to 12 weeks	40	-6.7 (215.8)	41	-23.0 (136.9)	41	18.5 (-46.4 to 83.5)	0.57
Change in AUSCAN stiffness							
Baseline to 4 weeks	42	-4.9 (25.7)	41	-4.1 (23.2)	41	1.0 (-8.7 to 10.7)	0.84
Baseline to 8 weeks	40	-7.5 (25.9)	41	-4.3 (21.4)	41	4.9 (-6.6 to 16.3)	0.39
Baseline to 12 weeks	40	-5.3 (28.8)	41	-2.9 (22.4)	41	3.3 (-5.5 to 12.1)	0.45

*The treatment effect was adjusted for within-subject baseline difference and the order in which the participant received their treatment (e.g. Active then placebo, or Placebo then active). VAS - Visual Analogue Scale, range: 0 – 100; AUSCAN - Australian/Canadian Hand OA Index pain range: 0 – 500; AUSCAN - Australian/Canadian Hand OA Index function range: 0 – 900; AUSCAN - Australian/Canadian Hand OA Index stiffness range: 0 – 100; CI – confidence interval

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Table 4: Proportion of participants with an improvement in synovitis score from baseline to 12 weeks, the estimated treatment effect, and the proportion of participants with an improvement based on the order in which they received the treatment

	Treatment effect		
Active, Improved n (%)	5 (12%)		
N	42		
Placebo, Improved n (%)	4 (10%)		
N	41		
Treatment effect*			
Relative risk	1.2		
95% CI	0.3 to 4.6		
P-Value	P=0.74		
	Treatment period		**χ^2 P-Value for difference**
Treatment sequence	**1**	**2**	
Active then placebo			
Improved, n (%)	2 (11%)	0 (0%)	N/A
N	18	17	
Placebo then active			
Improved, n (%)	4 (17%)	3 (13%)	P=0.41
N	24	24	

*The treatment effect was adjusted for the order in which the participant received their treatment (e.g. Active then placebo, or Placebo then active).

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Table 5: Proportion of participants with an improvement in bone marrow lesion (BML) score from baseline to 12 weeks, the estimated treatment effect, and the proportion of participants with an improvement based on the order in which they received the treatment

	Treatment effect		
Active, Improved n (%)	2 (5%)		
N	42		
Placebo, Improved n (%)	3 (7%)		
N	41		
Treatment effect*			
Relative risk	0.7		
95% CI	0.1 to 4.0		
P-Value	0.65		
	Treatment period		**χ^2 P-Value for difference**
Treatment sequence	**1**	**2**	
Active then placebo			
Improved, n (%)	0 (0%)	0 (0%)	N/A
N	18	17	
Placebo then active			
Improved, n (%)	3 (13%)	2 (8%)	0.58
N	24	24	

*The treatment effect was adjusted for the order in which the participant received their treatment (e.g. Active then placebo, or Placebo then active).

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Table 6: Prevalence and number of adverse events, by treatment received

	Placebo N=42	Active N=42
Adverse events		
Prevalence of at least one adverse event (n, %)	23 (54.8)	15 (35.7)
Total number of adverse events	32	27
Prevalence of (n, %):		
Fall	0	2 (4.8)
Headache	5 (11.9)	3 (7.1)
Other joint pain	6 (14.3)	2 (4.8)
Insomnia	1 (2.4)	0
Upper respiratory tract infection	5 (11.9)	1 (2.4)
Sinusitis	2 (4.8)	1 (2.4)
Vertigo	0	2 (4.8)
Eczema	1 (2.4)	0
Increased hand pain/swelling	1 (2.4)	2 (4.8)
Sore eyes	2 (4.8)	0
Mouth ulcers	2 (4.8)	0
Nausea/vomiting	1 (2.4)	2 (4.8)
Fatigue	1 (2.4)	0
Hashimoto's disease	0	1 (2.4)
Hypertension	0	1 (2.4)
Rhinitis	0	1 (2.4)
Urinary tract infection	1 (2.4)	1 (2.4)
Reaction at site	0	3 (7.1)
Rash or itching	2 (4.8)	2 (4.8)
Shortness of breath	1 (2.4)	0
Shingles	0	1 (2.4)
Cataract Removal	1 (2.4)	0
Gastroscopy	0	1 (2.4)
Cellulitis	0	1 (2.4)
Serious adverse events		
Number of non-elective hospital admissions	0	1
Death	0	0
Cancer	0	0

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Southern Tasmanian Health and Medical Human Research Ethics Committee

The trial was registered on the Australian New Zealand Clinical Trials Registry: ACTRN12612000791831

PATIENT CONSENT
Obtained.

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AUTHORS ROLES/CONTRIBUTORS

DA was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft, and completed manuscript revisions.

LL was responsible for randomisation, dispensing the medication, participated in analysis and interpretation of the data, and critically revised the manuscript.

FP participated in analysis and interpretation of the data, and critically revised the manuscript.

IKH was responsible for data collection, participated in analysis and interpretation of the data, and critically revised the manuscript.

PO advised the data analysis, participated in analysis and interpretation of the data, and critically revised the manuscript.

NB helped to design the study, participated in analysis and interpretation of the data, and critically revised the manuscript.

PB designed and carried out the study planning, participated in analysis and interpretation of the data, and critically revised the manuscript.

GJ designed and carried out the study planning, participated in analysis and interpretation of the data, assisted with the initial manuscript draft,

and critically revised the manuscript.

All authors have approved the final manuscript. DA and GJ are the guarantors.

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REFERENCE LIST

1. Haugen IK, Mathiessen A, Slatkowsky-Christensen B, Magnusson K, Boyesen P, Sesseng S, et al. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? Osteoarthritis Cartilage 2016;24:647-54.

2. Greenspan A. Erosive osteoarthritis. Semin Musculoskelet Radiol 2003;7:155-9.

3. Stannus OP, Jones G, Blizzard L, Cicuttini FM, Ding C. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Ann Rheum Dis 2013;72:535-40.

4. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, et al. Circulating levels of IL-6 and TNF-alpha are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage 2010;18:1441-7.

5. Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. Ann Rheum Dis 2012;71:891-8.

6. Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis 2015;74:1697-705.

7. Magnano MD, Chakravarty EF, Broudy C, Chung L, Kelman A, Hillygus J, et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. J Rheumatol 2007;34:1323-7.

8. Guler-Yuksel M, Allaart CF, Watt I, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Schaardenburg D, et al. Treatment with TNF-alpha inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. Osteoarthritis Cartilage 2010;18:1256-62.

9. Li T, Yu T, Hawkins BS, Dickersin K. Design, Analysis, and Reporting of Crossover Trials for Inclusion in a Meta-Analysis. PLoS One 2015;10:e0133023.

10. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3:3-70.

11. Haugen IK, Eshed I, Gandjbakhch F, Foltz V, Ostergaard M, Boyesen P, et al. The Longitudinal Reliability and Responsiveness of the OMERACT Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (HOAMRIS). J Rheumatol 2015;42:2486-91.

12. Jones G, Cooley HM, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. Osteoarthritis Cartilage 2001;9:606-11.

https://doi.org/10.1016/j.joca.2018.02.899

13. Kroon FP, Conaghan PG, Foltz V, Gandjbakhch F, Peterfy C, Eshed I, et al. Development and Reliability of the OMERACT Thumb Base Osteoarthritis Magnetic Resonance Imaging Scoring System. J Rheumatol 2017;44:1694-8.

14. Laslett LL, Quinn SJ, Darian-Smith E, Kwok M, Fedorova T, Korner H, et al. Treatment with 4Jointz reduces knee pain over 12 weeks of treatment in patients with clinical knee osteoarthritis: a randomised controlled trial. Osteoarthritis Cartilage 2012;20:1209-16.

15. Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. Design, analysis, and presentation of crossover trials. Trials 2009;10:27.

16. Mehrotra DV. A recommended analysis for 2 x 2 crossover trials with baseline measurements. Pharm Stat 2014;13:376-87.

17. Poddubnyy D, Rudwaleit M. Efficacy and safety of adalimumab treatment in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Expert Opin Drug Saf 2011;10:655-73.

18. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237-47.

19. Haugen IK, Slatkowsky-Christensen B, Boyesen P, Sesseng S, van der Heijde D, Kvien TK. MRI findings predict radiographic progression and development of erosions in hand osteoarthritis. Ann Rheum Dis 2016;75:117-23.

20. Kortekaas MC, Kwok WY, Reijnierse M, Kloppenburg M. Inflammatory ultrasound features show independent associations with progression of structural damage after over 2 years of follow-up in patients with hand osteoarthritis. Ann Rheum Dis 2015;74:1720-4.

21. Meersseman P, Van de Vyver C, Verbruggen G, Elewaut D, Wittoek R. Clinical and radiological factors associated with erosive radiographic progression in hand osteoarthritis. Osteoarthritis Cartilage 2015;23:2129-33.

22. Kirwan J, Byron M, Watt I. The relationship between soft tissue swelling, joint space narrowing and erosive damage in hand X-rays of patients with rheumatoid arthritis. Rheumatology (Oxford) 2001;40:297-301.

23. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008;67:1716-23.

24. Enck P, Klosterhalfen S, Zipfel S. Novel study designs to investigate the placebo response. BMC Med Res Methodol 2011;11:90.

25. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum 1996;39:308-20.

https://doi.org/10.1016/j.joca.2018.02.899