



Methotrexate in patients with hand osteoarthritis refractory to analgesics: a randomized, double-blind, placebo-controlled trial

Stéphanie Ferrero

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FACULTE DE MEDECINE

Année 2019

THESE

Pour le

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Par

FERRERO Stéphanie

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**Methotrexate in patients with hand osteoarthritis
refractory to analgesics: A randomized, double-blind,
placebo-controlled trial**

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LISTE DES ABREVIATIONS

BML: bone marrow lesion

EHOA: Erosive hand osteoarthritis

GUSS: Ghent University score system

HOA: Hand osteoarthritis

MRI: magnetic resonance imaging

MTX: Methotrexate

NSAID: non-steroidal anti-inflammatory drug

OMERACT: Outcome measures in rheumatology

SYSADOA: Slow-acting drug in osteoarthritis

VAS: Visual analogue scale

N: Normal

S: Stable

J: Loss of joint space

E=erosive

E/R=erosive in remodeling phase

R=remodeling

F=fusion

ARTICLE POUR PUBLICATION

Soumission

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Revue ciblée

Annals of rheumatic deseases « ARD »

Abstract : 250 words

Article : <3000 words

Article

(Ci-après)

Methotrexate in patients with hand osteoarthritis refractory to analgesics: A randomized, double-blind, placebo-controlled trial

Correspondence to:

FERRERO Stephanie: Department of Rheumatology, Pasteur Hospital, Nice University Hospital, Nice Sophia Antipolis University, F-06000. Nice, France
E-mail: ferrero.s@chu-nice.fr

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ABSTRACT

Objectives: No studies have assessed the effect of methotrexate (MTX) in osteoarthritis of the hand (HOA). The purpose of our study was to examine the effect of MTX on pain and structural evolution in symptomatic erosive HOA (EHOA).

Methods: This 1-year prospective, monocentric, randomized, double-blind, placebo-controlled study (NCT1968405) followed patients with symptomatic EHOA. Patients were randomized into two groups: 10 mg MTX per week or placebo. The primary endpoint was pain assessment at 3 months, and the secondary endpoints were clinical features (visual analogue scale "VAS" pain), radiographic features (anatomical radiographic score and Gent University Score System), and magnetic resonance imaging (MRI) at 12 months.

Results: Sixty-four patients with HOA were randomized to either the placebo or MTX group. At 3 months, there was no significant difference in the mean decrease in VAS pain score (MTX: 17.5 (28.4) vs placebo: 8.4 (25.2); p=0.2). Erosive joints progressed significantly more to a remodeling phase in MTX group than in placebo group (27% vs 15%) (p=0.03). Joints with joint space loss appeared to be less eroding in MTX group than in placebo group (8% vs 29%; p=0.2). The level of IL6 ($p<0.0001$) and presence of synovitis on MRI ($p=0.02$) at baseline were found to be predictive factors for erosive structural evolution of non-erosive joints.

Conclusion: MTX did not effectively relieve pain after 3 months in EHOA. However, MTX significantly stopped the progression of joint damage compared to placebo. The presence of systemic and local inflammation at baseline was a predictor of erosive progression.

Keywords: Erosive Hand osteoarthritis, Methotrexate, treatment, MRI, radiography

INTRODUCTION

Hand osteoarthritis (HOA) is the most common form of osteoarthritis in women >60 years (1). Erosive HOA (EHOA) is a subgroup associated with pain, reduced function, and disability (2–4), with a lack of effective therapies. EHOA is characterized by a succession of erosive phases and remodeling (5–8), suggesting the involvement of pro-inflammatory cytokine cascades known to cause cartilage degradation and bone resorption (9–12). In recent years, imaging data has confirmed the presence of inflammation in EHOA joints (13–18). The clinical presentation and imaging data brings this entity closer to inflammatory rheumatism such as rheumatoid arthritis (RA) and psoriatic arthritis. Such similarities have justified the use of treatments used in inflammatory rheumatism to treat EHOA (1,19–21). However, no study has assessed the effect of methotrexate (MTX) on EHOA.

Therefore, we aimed to assess the efficacy of MTX in a prospective, randomized, double-blind, placebo-controlled study in EHOA patients resistant to usual treatment. The primary endpoint was the assessment of pain at 3 months, and the secondary endpoint was the structural effect of MTX at 12 months.

METHODS

Patient inclusion/exclusion

Seventy-one patients with EHOA were recruited at the Rheumatology Department of the Nice Hospital Center. Inclusions were conducted from May 2010 to April 2013. Patients were eligible if they were 45-85 years old, they had HOA according to the American College of Rheumatology criteria, if at least one joint had erosion (stage "E" according to the Verbruggen-Veys classification) on radiography, and if at least one joint had a pain level >40 mm for >3 months (global pain in the last 48 h). For outpatients, slow-acting drug in osteoarthritis must have been stopped for >3 months, and treatment with non-steroidal anti-inflammatory drug or level 1 antalgics must have been stable for >4 weeks. The exclusion criteria were patients treated with hyaluronic acid or injectable corticosteroids at the thumb base or interphalangeal joints in the last 3 months, psoriasis, inflammatory rheumatism, microcrystalline arthropathy, joint prosthesis in one of the hand joints, pregnancy, a possible contraindication to magnetic resonance imaging (MRI), or previous dose of MTX or anti-TNF alpha.

This study was reported on www.ClinicalTrial.gov (NCT1968405) and was conducted in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the ethics committee of the Nice University Hospital Center. All patients benefited from written information and signed a consent.

Sample size calculation

The primary analysis compared the visual analogue scale (VAS) between the control group (placebo) and experimental group (MTX) at 3 months. Estimates of the VAS baseline and the standard deviation (SD) of the control group, 60 mm (\pm 16), were obtained from personal data from the same population and the results of the Pavelka study (Abstract, EULAR congress 2006). We expected a diminution of 30% in the experimental group and 10% in the control group to account for a potential placebo effect. We obtained a VAS at 3 months of 42 mm and 54 mm for the experimental and control groups, respectively. Assuming a pooled SD of 16, with a power of 80% and an α error rate at 0.05 (two-sided test), the number of patients required for inclusion was 29 in each group or 58 in total (Nquery[©] Advisor v 7.0). To account for a 25% rate of lost to follow-up, the global sample size was 72 patients.

Randomization and treatment

Patients were allocated to either placebo or MTX groups at a ratio of 1:1 based on computer generated random numbers. The active treatment and placebo product were visually identical. Participants and staff involved in patient care remained blinded to treatment allocation throughout the trial. Patients were randomized to either the 10 mg MTX group (four MTX tablets on Mondays and one Speciafoldine tablet on Wednesday) or the placebo group (four placebo tablets on Mondays and one Speciafoldine tablet on Wednesdays) for a duration of 12 months. One month of treatment was dispensed per visit to the center. The boxes were retrieved at each visit to check the compliance of the subjects.

Outcomes

The primary endpoint was VAS pain at 3 months. The secondary clinical outcomes were VAS pain and functional evaluation (Dreiser and Cochin index) at 12 months. Secondary imaging endpoints were the structural evolution assessed by anatomical score (22) and GUSS scores (7), and the MRI change at 12 months.

Clinical evaluation

After inclusion, all patients received a monthly clinical examination at the center for 12 months. The pain VAS was assessed on the pain assessment of the last 48 hours by the patient prior to the consultation (23). The swelling or pain of the proximal and distal interphalangeal joints, function, and tolerance of the treatment were evaluated by an independent investigator.

Radiological evaluation

All patients underwent a postero-anterior x-ray of both hands at baseline and 12 months. All interphalangeal joints (proximal and distal) were studied, except the thumb because of reduced visibility (metacarpophalangeal and trapeziometacarpal were also excluded). In total, 16 joints per patient were analyzed, totaling 1024 interphalangeal joints. Two validated rating systems were used to evaluate the erosive progression of interphalangeal lesions (7,22). The first was the Verbruggen-Veys anatomical score (22) to characterize osteoarthritis progression. It has been shown that non-erosive osteoarthritic joints ("S" stable or stationary) entered a phase "J" called osteoarthritis with joint space loss, which then become "E" phase if erosive structural changes appear. Then, the affected interphalangeal joint shows signs of repair following an "R" phase of remodeling, up to an "F" phase fusion of the joints. The second joint reading system was the Ghent University Score System (GUSS) score (7). It includes three sub-scores assessing

the subchondral bone, subchondral plate, and joint space loss. Each sub score is rated from 0 to 100, which are combined to obtain the total GUSS score ranging from 0 (severe joint destruction) to 300 (no damage). This score was applied for each interphalangeal joint. On average, the "E" phase joints have lower GUSS scores than the "J" or "R" joints. The smallest detectable change was a 30-point change in the GUSS score.

Blind evaluation of the radiographs was performed by two independent expert readers (SF and RW). A comparison of the two readings was performed on erosive joints. The reproducibility of the GUSS score was analyzed using interclass correlation (0.73).

MRI evaluation

MRI (0.3 Tesla, C-Scan Esaote Biomedica, Genoa, Italy) was performed at baseline and 12 months. Only the proximal and distal interphalangeal joints from the 2nd to the 5th radius of the dominant hand were analyzed. The analysis focused on bone edema, erosions, and the presence of synovitis (24). For each sequence, axial and coronal plans were performed, Spin Echo 3DTI (repetition time (TR): 35 ms, echo time (TE): 16 ms, field of view (FOV): 160x160 mm, matrix: 192x192 mm), STIR (TR: 1460 ms, TE: 26 ms, FOV 190x190 mm, matrix: 192x168 mm, thickness: 3 mm sections). High GE 16 T1 before and after Gadolinium injection (TR: 500 ms, TE: 16 ms, FOV 160x160 mm, matrix 192x192 mm, thickness: 2 mm cuts) were chosen according to the OMERACT protocols. A reading under the OMERACT (25) HOA MRI Scoring System model was performed by a senior reader (DL) blinded to the clinical data. Because of the low spatial resolution ($0.99 \times 1.1 \text{ mm}^2$) with a slice thickness of 3 mm, we decided to score MRI features according to the following manner: osteophytes (grade 0-3, distal/proximal) and erosions (grade 0-3, distal/proximal). Synovitis, Bone marrow lesion (BMLs), and joint destruction were scored according to a binary analysis (absent/present). For MRI scoring, a blind evaluation of inter-reader and intra-reader reproducibility with Cohen's kappa (erosion: 0.75, osteophytes: 0.77, destruction: 0.93, synovitis: 0.91, BMLs: 0.94) was performed on a representative sample of 20 patients (160 joints) with a delay of 6 weeks between the two scores (EA).

Safety

Safety was evaluated at each visit. Adverse events were defined as any unexpected event occurring during patient follow-up. The investigator judged a possible relationship with the

study treatment and its intensity. Any unscheduled hospitalization was considered a serious adverse event.

Statistical analysis

Continuous variables were presented as means (\pm SD) or medians (interquartile range), and categorical variables as numbers and percentages. Pain VAS at 3 months evolution (baseline-3 months) between MTX and placebo were compared using an unpaired and paired t-test, respectively. The main analysis was performed intent-to-treat by imputing missing values with the LOCF method. Pain VAS evolution analysis was repeated at 12 months without imputation data.

Function evolution, defined by the Cochin and Dreiser index between 0-12 months, was analyzed by a t-test and Mixed effect Model Repeat Measurement. Structural evolution, defined by the Verbruggen-Veys score and GUSS score difference from 0-12 months, was compared using the χ^2 and Student t-tests, respectively.

The decline in the Verbruggen-Veys and GUSS scores was also analyzed using a univariate and multivariate generalized estimating equation model with a logit link function. The multivariate model was adjusted for the score at 0 months. Degradation was defined by a decrease of at least 30 points at 12 months for the GUSS score and joint modification of the erosive joint for the Verbruggen-Veys score.

We also examined, using the univariate and multivariate generalized estimating equation (GEE) model, predictive factors of a decline in the Verbruggen-Veys and GUSS score, only in the dominant hand.

Finally, MRI scores were compared using the Wilcoxon rank sum test and reproducibility was performed using a Kappa coefficient. Analyses were performed with SAS Enterprise Guide software, version 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Sixty-four patients were included and randomized into each group (n=32) (Figure 1). Baseline characteristics were well balanced between the two groups; 97% and 91% of subjects in the MTX and placebo groups were women, respectively. The mean age was 67.5 (7.9) years in the placebo group and 64.9 (7.3) years in the MTX group. The number of painful joints in the placebo and MTX groups (50% vs 52%), swollen joints (22% vs 23%), and erosive joints (24% vs 25%) were substantially equivalent (Table 1).

Table 1. Baseline demographic, clinical, and radiology data (n=64)

		Placebo (n=32)	MTX (n=32)
Demographics			
Female	n (%)	29 (91%)	31 (97%)
BMI	Mean ± SD	24.6 ± 4	24.2 ± 4
Age	Mean ± SD	67.5± 8	64.9± 7
Treatments			
Paracetamol	n (%)	15 (58)	17 (68)
Topical NSAIDs	n (%)	8 (31)	13 (52)
SYSADOA	n (%)	17 (65)	21 (84)
Clinical data			
Cochin score	Mean ± SD (n)	29.9 ± 18 (29)	26.6 ± 23 (28)
Dreiser score	Mean ± SD	12.6 ± 5 (30)	12.2 ± 7 (30)
Painful joint	% (n/N tot)	49.8% (255/512)	51.9% (266/512)
Nodosity *	% (n/N tot)	50.2% (257/512)	56.8% (291/512)
Swelling*	% (n/N tot)	22.1% (113/512)	23.4% (120/512)
Radiological data ***+			
N	% (n/Nt)	8.01% (41/512)	21.09% (108/512)
S	% (n/Nt)	44.1% (226/512)	27.5% (141/512)
J	% (n/Nt)	4.7% (24/512)	4.3% (22/512)
E	% (n/Nt)	24.2% (124/512)	25.2% (129/512)
E/R	% (n/Nt)	1.2% (6/512)	1.6% (8/512)
R	% (n/Nt)	9% (46/512)	14.06% (72/512)
F	% (n/Nt)	0.6% (3/512)	0.4% (2/512)
Missing	% (n/Nt)	8.01% (41/512)	5.7% (29/512)
IRM++			
Erosion	% (n/N tot)	56.2% (113/288)	51.6% (98/288)
Synovitis	% (n/N tot)	9% (18/288)	6.3% (12/288)
Osteophyte	% (n/N tot)	74.1% (149/288)	68.9% (131/288)
Bone edema	% (n/N tot)	12.4% (25/288)	14.2% (27/288)
Biological assays			
Adiponectine (µg/mL)	Mean ± SD	25.9 ± 29	13.3 ± 6
DKK-1 (pmol/L)	Mean ± SD	83.8 ± 48	79.2 ± 42
Leptine (µg/L)	Mean ± SD	15.8 ± 12	18.6 ± 12
IL-6 (picog/ml)	Mean ± SD	2.05 ± 1	4.06 ± 11

* Sixteen joints were evaluated (proximal interphalangeal 2-5 and distal interphalangeal 2-5 of both hands; interphalangeal P1 is excluded)

+ 1024 joints were evaluated in 64 patients

** Verbruggen-Veys Score: N= Normal, S=Stationary non-erosive osteoarthritis, J=Loss of joint space, E=erosive, E/R=erosive in remodeling phase, R=remodeling, F=fusion

NSAIDs = non-steroidal anti-inflammatory drug

SYSADOA = Slow-acting drug in osteoarthritis

++ MRI performed on a dominant hand

Nt = total number of joints in the placebo or methotrexate group

Pain evaluation

At 3 months, there was no difference in the change of the VAS pain between the two groups ($p=0.2$) (primary outcome, LOCF method). The mean decrease in VAS pain was 17.5 (28.4) in the MTX group and 8.4 (25.2) in the placebo group. The decrease in VAS pain in the MTX group was significant at 3 months ($p=0.002$) and 12 months ($p=0.001$); however, no significant difference was observed in the placebo group at 3 months but it was significant at 12 months (3 months, $p=0.07$; 12 months, $p=0.005$) (Table 2). At 12 months, there was no difference in the change of VAS pain between the two groups ($p=0.6$).

Table 2. Evolution of pain comparison between two groups

	Baseline Mean (SD)	M3 Mean (SD)	Δ baseline- M3 Mean (SD)	P*	P**	M12 Mean (SD)	Δ baseline- M12 Mean (SD)	P ⁺	P ⁺⁺
Placebo n=32	63.9 (16)	55.5 (22)	8.4 (25)	0.07		48.2 (22)	17.8 (29)	0.005	
MTX n=32	65.7 (16)	48.2 (24)	17.5 (28)	0.002		47.5 (25)	14.3 (19)	0.001	
					0.2				0.6

* Intragroup comparison between baseline and M3

** Comparison between different group evolution (Δ baseline-M3)

⁺ Intragroup comparison between baseline and M3

⁺⁺ Comparison between different group evolution (Δ baseline-M12)

MTX: Methotrexate

Function evaluation

No statistically significant differences were observed between the MTX and placebo groups when comparing the functional evolution (Table 3).

Table 3. Effect of MTX on function: between group evolution comparison

Evaluation of secondary criteria: functionalities					
	Placebo		MTX		P value*
	N	Mean (SD)	N	Mean (SD)	
Cochin score					
M0	29	29.9 (18)	28	26.6 (23)	0.3
M12	24	27.9 (20)	26	27.7 (20)	0.9
Mean (SD) change baseline to M12**	21	2,3 (14)	23	2,8 (17)	0,3
Dreiser score					
M0	30	12.6 (5)	30	12.20 (7)	0.8
M12	25	11.8 (7)	26	11.77 (7)	0.9
Mean (SD) change baseline to M12**	23	0,2 (5)	24	0,33 (5)	0,9

* comparison between MTX group and placebo using Wilcoxon rank sum test

** student t test

Structural evolution -Verburggen-Veys score

In total, 1024 joints were analyzed. Initially, 46 joints were "J" phase, 267 joints were "E" phase, (placebo: 130 (25.4%); MTX: 137 (25.8%)), 118 were "R" phase, and five joints were fused. At 12 months, 15% of "E" joints in the placebo group had become "R", compared to 27% in the MTX group ($p=0.03$). Furthermore, 29% of "J" joints were degraded in the placebo group, compared to 8% in the treatment group ($p=0.2$). Of the 680 non-erosive joints at baseline (placebo: 337; MTX: 343), twelve became erosive in the placebo group and six in the MTX group ($p=0.2$) (Table 4).

Table 4. Evolution of the Verbruggen-Veys score from baseline to 12 months

	Placebo				MTX				P value*
	degraded IP	%	stable IP	%	degraded IP	%	stable IP	%	
N	6/31	19,4	25/31	80,7	19/80	23,8	61/80	76,3	0,6
S	11/177	6,2	166/177	93,8	6/119	5,04	113/119	94,9	0,7
J	5/17	29,4	12/17	70,6	1/13	7,7	12/13	92,8	0,2
E and E/R	14/92	15,2	78/92	84,8	31/110	27,2	79/110	71,8	0,03

Sixteen joints were evaluated (proximal interphalangeal 2-5 and distal interphalangeal 2-5 of both hands; interphalangeal P1 is excluded)

N= Normal, S=Stationary non-erosive arthrosis, J=Loss of joint space, E=erosive,

E/R=erosive in remodeling phase, R=remodeling, F=fusion

IP = interphalangeal

P value = Evolution of the Verbruggen-Veys score from baseline to month 12 in degraded joints (χ^2 test)

We repeated this analysis using a logistic model with a GEE estimate to account for intra-individual correlation due to the fact that each patient had a different number of treated joints. In the multivariate analysis, no difference between the two treatment groups was found (GEE odds ratio (OR): 1.7, 95% confidence interval (CI): 0.5-5.9).

Structural evolution - GUSS score

The univariate and multivariate analysis show no significant difference in GUSS score differences between the two groups (placebo: +22.6 (45) vs. MTX: +21.3 (54); p=0.8). “J” joints increased their GUSS score by 46.5 (36) points in the placebo group compared to an average of 18.5 (62) points in the treatment group (p=0.09) (data not shown).

Predictors for erosive evolution

From the baseline characteristics, two variables were associated with a higher risk of erosive evolution in non-erosive joints using the GUSS score at 12 months: Level of IL-6 (OR: 1.04, 95% CI: 1.03-1.06; p<0.0001) and the presence of synovitis at inclusion (OR: 4.7, 95% CI: 1.25-17.90; p<0.02). Male sex was a protective factor (p<0.0001) (Table 5).

Table 5: Exploration of potential risk factors for more erosive disease (degradation GUSS)

Parameters	OR [95% CI]	P value
Treatment group	1.2 [0.38-3.54]	0.8
Age (years)	1.00 [0.93-1.07]	0.9
Sex (male)	0.1 [0.08-0.25]	<0.0001
BMI (kg/cm ²)	1.0 [0.90-1.07]	0.7
Painful joint at inclusion	1.6 [0.51-5.10]	0.4
Inflated joint at inclusion	2.0 [0.63-6.20]	0.2
Joint with osteophyte at inclusion	4.06 [0.49-33.59]	0.2
Joint with synovitis at inclusion	4.7 [1.25-17.90]	0.02
DKK-1 rate at inclusion	1.01 [0.99-1.02]	0.3
Adiponectin rate at inclusion	1.00 [0.97-1.01]	0.4
Leptin rate at inclusion	1.00 [0.96-1.05]	0.9
Level of IL6 at inclusion	1.04 [1.03-1.06]	<0.0001

OR and 95% CI obtained by GEE modelling (multivariate analysis).

MRI - Evolution of the GUSS score in patients with synovitis

Twenty-nine out of 1024 joints had baseline synovitis. In the MTX group, 12 joints had synovitis including two distal interphalangeal joints (1 DIP2 and 2 DIP4) and nine proximal interphalangeal joints (2 PIP2, 3 PIP3, 2 PIP4, and 2 PIP5). In the placebo group, 17 joints had synovitis at baseline, including 1 DIP4, and 5 PIP2, 7 PIP3, and 4 PIP5.

There was no significant difference in evolution between the two groups from baseline to 12 months between total GUSS and synovitis at MRI ($p=0.9$).

Adverse events

The overall rate of adverse events was 30.5%, which was similar in both groups. Among them, 31% of subjects had serious adverse reactions (nausea, malaise, pericarditis, weight loss, and cough), 54% refused to continue, and 15% for other reasons (history of nasal cavity cancer).

DISCUSSION

Our study is the first randomized placebo-controlled study to assess the effect of MTX in EHOA. We report no significant difference in pain progression at 3 and 12 months between MTX and placebo-treated groups. However, our results show that the presence of MRI synovitis at baseline and a reduced level of IL6 are predictive factors for structural evolution. Furthermore, MTX could prevent this structural evolution by increasing bone remodeling.

Our results regarding pain are similar to previous reports (1,21), which found no significant difference in progression between subjects treated with Adalimumab and placebo but a more pronounced effect on pain was observed in the biological group. Our results show no difference in progression between the two groups at 3 and 12 months, but a significant improvement in pain in the MTX group at 3 and 12 months. It is possible that the lack of difference between the two groups in our study was related to a too low dose of MTX. The placebo effect (26,27), which is known to be very important in osteoarthritis, may explain this difficulty in obtaining a significant result in the comparison. In addition, the stress on the joints caused by already well-established lesions such as joint space loss and bone reconstruction can easily explain the persistence of pain felt by patients once the inflammatory part has been removed.

MTX may also have an effect on local inflammation in patients with EHOA, facilitating bone reconstruction and shortening the erosive phase. Indeed, we found that MTX patients with EHOA remodeled significantly faster than patients on placebo. Interestingly, Kloppenburg et al (20) found a similar effect with Etanercept, suggesting that an effect on inflammation inherent in this type of osteoarthritis could have a structural effect. In that study, remodeling was even more important as there was slight joint swelling initially, and especially if there was a synovitis on the MRI or ultrasound (US).

Several studies (20,28) have suggested the possibility of having a lower structural evolution in EHOA by analyzing the GUSS score with biological treatments. In our subgroup analysis, joints classified as "J" in the MTX group showed a smaller change in the GUSS score. However, there was less "J"-joints in the MTX group than in the placebo group. Also, we did not analyze whether the GUSS score was more severe in the MTX group than in the placebo group.

Our study focused on factors predicting structural evolution at 1 year. A previous study showed that swelling at baseline was predictive of pejorative structural evolution (28), which could

reflect the effect of inflammation. We also confirm the important role of inflammation in structural evolution since we show that synovitis at baseline is predictive of structural evolution at 1 year, as well as the IL6 level.

While the IL6 level has an impact on structural evolution assessed by the Verbruggen-Veys and GUSS score, synovitis only influenced the GUSS, which could be explained by the fact that the GUSS score is more accurate in its short-term assessment. The absence of a relationship between joint swelling and structural evolution in our study is probably related to the study including subjects with severe EHOA; therefore, most subjects already had a large number of joint swellings at baseline. The relationship between synovitis and structural changes indicates that early implementation of treatment will have a strong impact on inflammation and should target subjects with significant local inflammation in analogy with RA (29). It is likely that the relative failure of biological treatments in EHOA to date is related to delayed treatment or poor selection of target subjects.

Our study has several limitations, including the MTX dosage used. We chose 10 mg/week based the literature and because subjects with digital osteoarthritis are generally an older population and more prone to side effects. However, we show no difference between the two groups in terms of occurrence of side effects or stopping the study. Another limitation is the sample size, which was calculated based on very fragmented data at the time and is most likely insufficient to overcome the placebo effect. The use of dedicated MRI to assess structural evolution and joint inflammation could be discussed for low field MRI, but has been shown in RA to have the same sensitivity as high field MRI to detect synovitis (30).(30)

In conclusion, MTX did not demonstrate superior efficacy over placebo on pain and function in subjects with EHOA; however, our results show a structural effect of MTX, which facilitated bone remodeling. These results should encourage new studies and discussions into the treatment of early stage HOA.

REFERENCES BIBLIOGRAPHIQUES

1. 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. *Annals of the Rheumatic Diseases.* sept 2015;74(9):1697-705.
2. Zhang Y. Prevalence of Symptomatic Hand Osteoarthritis and Its Impact on Functional Status among the Elderly: The Framingham Study. *American Journal of Epidemiology.* 1 déc 2002;156(11):1021-7.
3. Dahaghin S. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Annals of the Rheumatic Diseases.* 1 mai 2005;64(5):682-7.
4. Kwok WY, Kloppenburg M, Rosendaal FR, van Meurs JB, Hofman A, Bierma-Zeinstra SMA. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. *Annals of the Rheumatic Diseases.* 1 juill 2011;70(7):1238-42.
5. Wittoek R, Carron P, Verbruggen G. Structural and inflammatory sonographic findings in erosive and non-erosive osteoarthritis of the interphalangeal finger joints. *Annals of the Rheumatic Diseases.* 1 déc 2010;69(12):2173-6.
6. Gazeley DJ, Yeturi S, Patel PJ, Rosenthal AK. Erosive osteoarthritis: A systematic analysis of definitions used in the literature. *Seminars in Arthritis and Rheumatism.* févr 2017;46(4):395-403.
7. Verbruggen G, Wittoek R, Cruyssen BV, Elewaut D. Morbid anatomy of « erosive osteoarthritis » of the interphalangeal finger joints: an optimised scoring system to monitor disease progression in affected joints. *Annals of the Rheumatic Diseases.* 1 mai 2010;69(5):862-7.
8. Verbruggen G. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint OA. :2.
9. Kobayashi K, Takahashi N, Jimi E, Udagawa N, Takami M, Kotake S, et al. Tumor Necrosis Factor α Stimulates Osteoclast Differentiation by a Mechanism Independent of the OD F/ RANKL–RANK Interaction. :11.
10. Güler-Yüksel M, Allaart CF, Watt I, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, van Schaardenburg D, et al. Treatment with TNF- α inhibitor infliximab might reduce

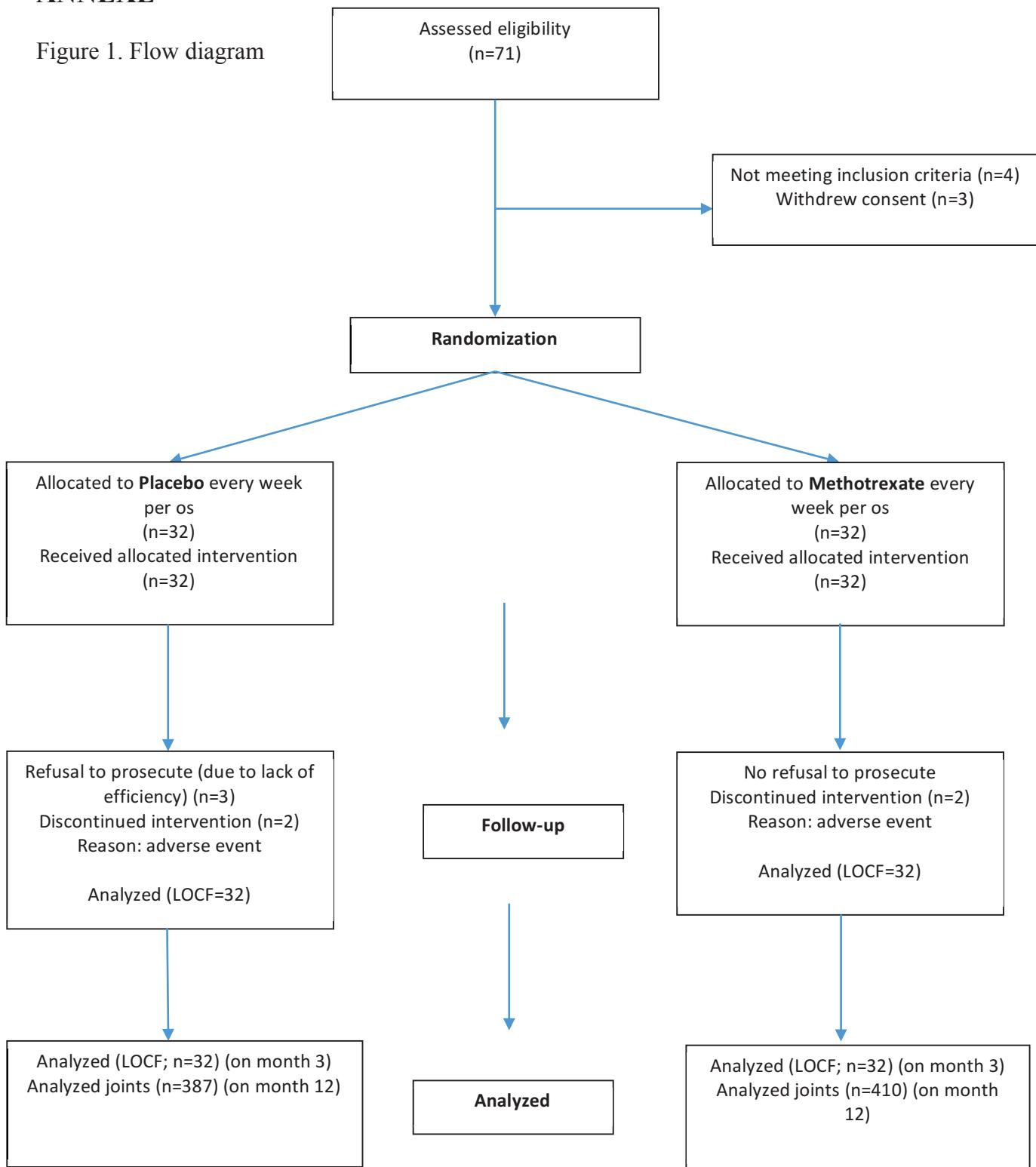
hand osteoarthritis in patients with rheumatoid arthritis. *Osteoarthritis and Cartilage.* oct 2010;18(10):1256-62.

11. Goldring MB. Anticytokine therapy for osteoarthritis. *Expert Opin Biol Ther.* 2001;13.
12. Benito MJ. Synovial tissue inflammation in early and late osteoarthritis. *Annals of the Rheumatic Diseases.* 1 sept 2005;64(9):1263-7.
13. Kortekaas MC, Kwok W-Y, 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. *Annals of the Rheumatic Diseases.* sept 2015;74(9):1720-4.
14. Kortekaas MC, Kwok W-Y, Reijnierse M, Huizinga TWJ, Kloppenburg M. In erosive hand osteoarthritis more inflammatory signs on ultrasound are found than in the rest of hand osteoarthritis. *Annals of the Rheumatic Diseases.* juin 2013;72(6):930-4.
15. Damman W, Liu R, Bloem J, Rosendaal F, Reijnierse M, Kloppenburg M. Bone marrow lesions and synovitis on MRI associate with radiographic progression after 2 years in hand osteoarthritis. *Annals of the Rheumatic Diseases.* janv 2017;76(1):214-7.
16. Haugen IK, Slatkowsky Christensen B, Bøyesen P, Sesseng S, van der Heijde D, Kvien TK. Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis. *Annals of the Rheumatic Diseases.* avr 2016;75(4):702-8.
17. Haugen IK, Mathiessen A, Slatkowsky-Christensen B, Magnusson K, Bøyesen 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 and Cartilage.* avr 2016;24(4):647-54.
18. Roux CH, Foltz V, Maheu E, Baron G, Gandjbakhch F, Lukas C, et al. MRI and serum biomarkers correlate with radiographic features in painful hand osteoarthritis. :9.
19. Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N, et al. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoArthritis – the HUMOR trial. *Osteoarthritis and Cartilage.* juill 2018;26(7):880-7.
20. Kloppenburg M, Ramonda R, Bobacz K, Kwok W-Y, Elewaut D, Huizinga TWJ, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Annals of the Rheumatic Diseases.* déc 2018;77(12):1757-64.
21. Lee W, Ruijgrok L, Boxma-de Klerk B, Kok MR, Kloppenburg M, Gerards A, et al.

- Efficacy of Hydroxychloroquine in Hand Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Care & Research*. sept 2018;70(9):1320-5.
22. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. *Arthritis & Rheumatism*. févr 1996;39(2):308-20.
23. Kloppenburg M, Maheu E, Kraus VB, Cicuttini F, Doherty M, Dreiser R-L, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis and Cartilage*. mai 2015;23(5):772-86.
24. Tan AL, Grainger AJ, Tanner SF, Shelley DM, Pease C, Emery P, et al. High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis. *Arthritis & Rheumatism*. août 2005;52(8):2355-65.
25. Haugen IK, Eshet I, Gandjbakhch F, Foltz V, Østergaard M, Bøyesen P, et al. The Longitudinal Reliability and Responsiveness of the OMERACT Hand Osteoarthritis Magnetic Resonance Imaging Scoring System (HOAMRIS). *The Journal of Rheumatology*. déc 2015;42(12):2486-91.
26. Campos GC de. Placebo effect in osteoarthritis: Why not use it to our advantage? *World Journal of Orthopedics*. 2015;6(5):416.
27. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*. 1 déc 2008;67(12):1716-23.
28. Verbruggen G, Wittoek R, Cruyssen BV, 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. *Annals of the Rheumatic Diseases*. juin 2012;71(6):891-8.
29. Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino M-A, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Annals of the Rheumatic Diseases*. juin 2013;72(6):804-14.
30. Ejbjerg BJ. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography. *Annals of the Rheumatic Diseases*. 1 sept 2005;64(9):1280-7.

ANNEXE

Figure 1. Flow diagram



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette École, de mes chers condisciples et devant l'effigie d'Hippocrate,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'Exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous l'emprise de la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses !

Que je soit couvert d'opprobre et méprisé de mes confrères si j'y manque.

RESUME EN FRANCAIS

Objectif

Aucune étude n'a évalué l'effet du méthotrexate (MTX) sur l'arthrose de la main. Le but de notre étude était d'examiner l'effet du MTX sur la douleur et sur l'évolution structurelle de l'arthrose digitale érosive symptomatique.

Méthodes

Cette étude prospective d'un an, monocentrique, randomisée, en double aveugle, contrôlée contre placebo (NCT1968405), a suivi des patients présentant une arthrose digitale érosive symptomatique. Les patients ont été répartis au hasard en deux groupes : 10 mg de MTX par semaine ou placebo. Le critère d'évaluation principal était l'évaluation de la douleur à 3 mois, et les critères d'évaluation secondaires étaient les caractéristiques cliniques (douleur sur l'échelle visuelle analogique "EVA"), les caractéristiques radiographiques (score radiographique anatomique et système de score de l'Université de Gand) et l'imagerie par résonance magnétique (IRM) à 12 mois.

Résultats

Soixante-quatre patients atteints d'arthrose digitale ont été randomisés dans le groupe placebo ou le groupe MTX. A 3 mois, il n'y avait pas de différence significative dans la diminution moyenne de l'EVA douleur (MTX : 17,5 (28,4) vs placebo : 8,4 (25,2) ; p=0,2). Les articulations érosives ont progressé significativement plus vers une phase de remodelage dans le groupe MTX que dans le groupe placebo (27% vs 15%) (p=0,03). Les articulations avec perte d'espace articulaire semblent s'éroder moins dans le groupe MTX que dans le groupe placebo (8 % vs 29 % ; p=0,2). Le taux d'IL6 ($p<0,0001$) et la présence d'une synovite à l'IRM ($p=0,02$) à l'inclusion, se sont avérés être des facteurs prédictifs de l'évolution structurelle érosive des articulations non érosives.

Conclusion

Le MTX n'a pas soulagé efficacement la douleur à 3 mois dans l'arthrose digitale érosive. Cependant, le MTX a considérablement stoppé la progression des lésions articulaires par rapport au placebo. La présence d'une inflammation systémique et locale au départ était prédicteur de la progression érosive.

Mots-clés : Arthrose digitale érosive, méthotrexate, traitement, IRM, radiographie.