Therapeutic pulsed ultrasound with or without intra-articular methotrexate in the management of rheumatoid arthritis

Alaa A. Labeeb[a,b], Roberto Casale[a], Samar G. Soliman[b], Waleed A. Mosa[c]

[a]Department of Clinical Neurophysiology & Pain Rehabiliation Unit, Foundation 'Salvatore Maugeri' IRCCS, Montescano, Italy, [b]Department of Rheumatology, Physical Medicine and Rehabilitation and [c]Department of Radiology, Menoufia University, Menoufia, Egypt

Correspondence to Alaa A. Labeeb, PhD, Department of Clinical Neurophysiology & Pain Rehabiliation Unit, 17 eisha street, Almay - Shibin Alkom El-Menoufia Governorate, Menoufia, Egypt Tel/fax: +2 048 2333827; e-mail: alaalabeeb@gmail.com

Received 5 April 2013
Accepted 15 July 2013

Egyptian Rheumatology & Rehabilitation
2013, 40:198-202

Objectives
The aim of the study was to evaluate the role of combined therapeutic pulsed ultrasound with intra-articular methotrexate as against pulsed ultrasound treatment program alone in the management of chronic synovitis in rheumatoid arthritis patients.

Patients and methods
A total of 38 patients were enrolled in the study. All patients were above 18 years of age with inadequate clinical response in the form of persistent monoarthritis. Of them, 24 completed the study. Patients were divided into two equal treatment groups: The first group (12 patients) received three consecutive intra-articular methotrexate injections and daily therapeutic pulsed ultrasound sessions, whereas the second group (12 patients) received daily therapeutic low-intensity pulsed ultrasound sessions. All patients were subjected to clinical, laboratory, and ultrasound evaluation before and after treatment.

Results
Patients were subjected to an ultrasound evaluation before and after treatment to detect synovial thickness, hot spots, erosions and effusion, with highly statistically significant difference observed in the number of swollen joints, tender joint count, visual analogue scale scores and synovial thickness at the wrist (P<0.01) in the group of patients who received ultrasound and methotrexate. In addition, there was a statistically significant difference with respect to hot spots, number of erosions and joint space narrowing (P<0.05).

Conclusion
The combination of pulsed ultrasound therapy with repeated intra-articular methotrexate can give us better results in the form of decreased effusion, tenderness, inflammation and synovial membrane thickness, all of which translate into significant recovery of function and reduction in pain in rheumatoid patients with resistant monoarthritis or oligoarthritis, with the least number of side effects and without the need of adding another disease-modifying agent and/or resorting to surgical synovectomy.

Keywords:
intra-articular, methotrexate, pulsed ultrasound

Egypt Rheumatol Rehabil 40:198-202

1110-161X

Introduction

Remission should be the treatment goal in the management of patients with rheumatoid arthritis (RA) because joint damage may progress in RA patients with low disease activity but it is presumed that it does not progress in patients in clinical remission [1]. However, our definition of remission status nowadays allows for considerable residual disease activity [1].

Frequent pain due to chronic synovitis severely interferes with the quality of life of these patients. For these reasons, a large number of very different interventions to control pain and disability have been used so far [2].

Of the mini-invasive treatments generally used in clinics, intra-articular injections with different substances and formulations have been tried with variable results. These include intra-articular anesthetics, steroids, chemical synovectomy and arthroscopic lavage [3]. Some of these substances are used only to temporarily reduce pain, others to subside inflammation, such as triamcinolone hexacetonide, [4,5] and some substances are used to decrease the size of synovial thickening, such as radioactive yttrium and osmoic [6]. In addition, methotrexate (MTX), an immunosuppressive agent, was tried in some short-term studies because of its anti-inflammatory actions and its ability to prolong the intra-articular effect of steroids [6–9].

The combined use of ultrasound (US) with intra-articular MTX as a therapeutic tool in an animal model was found to promote the uptake of MTX into synovial cells, which resulted in enhancement of the anti-inflammatory effect of MTX [10]. Furthermore, low-intensity pulsed US is suggested to shorten the healing period of fractures because of promotion of endochondral ossification and neovascularization and

thus is also suggested as a potential therapeutic strategy in itself [11–13].

Thus, the combination of intra-articular MTX and US could be used in the treatment of chronic synovitis as it has a high safety profile and is a much less invasive procedure and can replace ineffective oral treatment as well as more-invasive surgical procedures such as synovectomy [10].

We aimed to evaluate the role of combined therapeutic pulsed US with intra-articular MTX as against pulsed US treatment program alone in the management of chronic synovitis in rheumatoid arthritis patients.

Patients and methods

This study was performed at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Menoufia University Hospital (Egypt) and was approved by its ethical committee.

After giving their informed consent, 38 patients were enrolled in the study. All patients were over 18 years of age and diagnosed as having rheumatoid arthritis according to ACR revised criteria [14], with inadequate clinical response in the form of persistent monoarthritis of the wrist joint. Only 24 patients completed the study (Fig. 1).

Patients were divided into two treatment groups as follows:

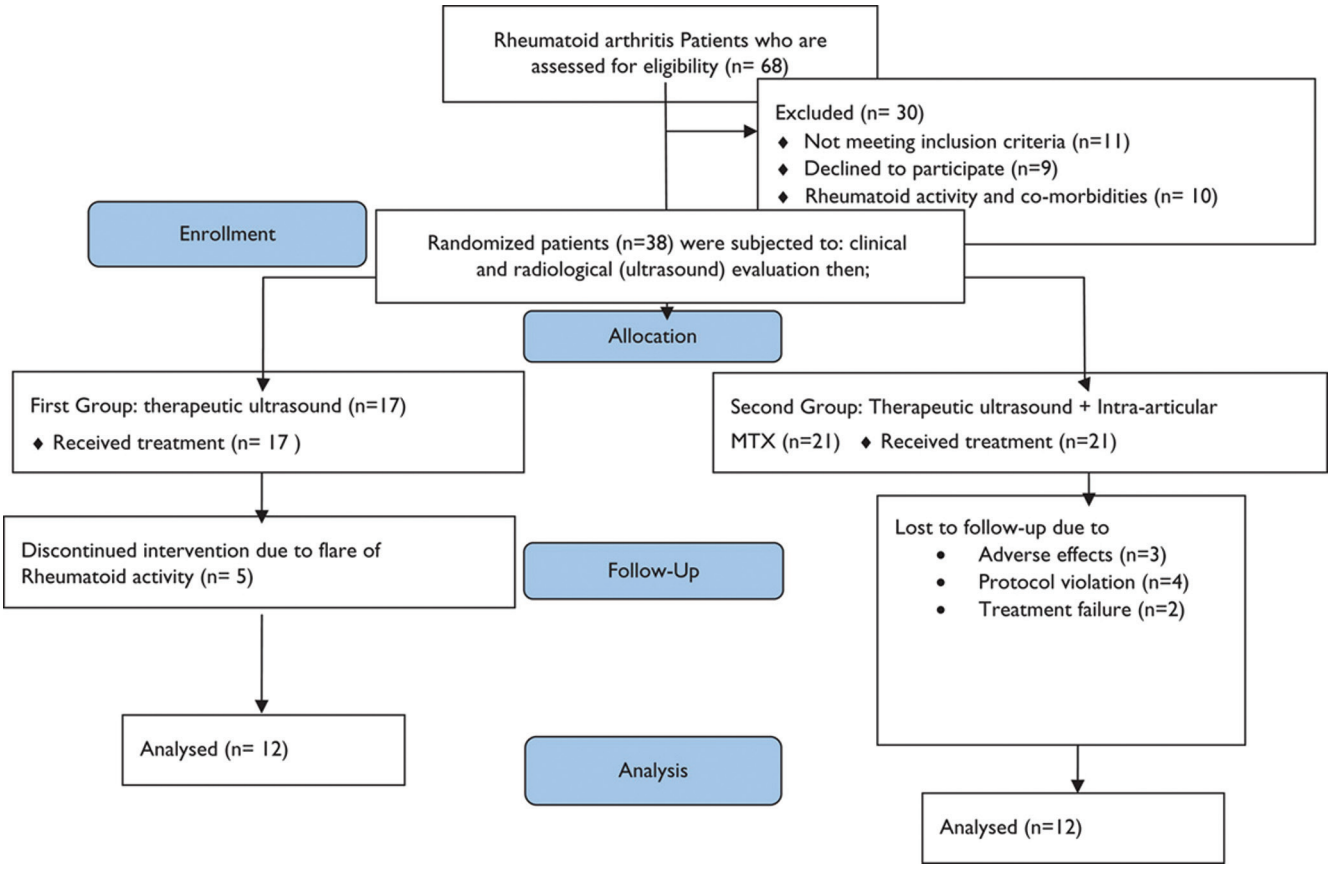
The first group received three consecutive intra-articular MTX injections of 10 mg MTX over 3 consecutive weeks and daily therapeutic low-intensity pulsed US sessions (20 min duration/session). The injections were administrated following aspiration to dryness using a sterile nontouch technique [15].

The second group received therapeutic low-intensity pulsed US sessions (daily sessions with 20 min duration/session). The treatment period for both groups was 4 weeks.

All patients were subjected to evaluation as follows.

Clinical and laboratory evaluation: Pretreatment and post-treatment evaluations were carried out by assessing the disease activity score-28 [16], tender joint count, swollen joint count, goniometry, pain [0–10 visual analogue scale (VAS)], erythrocyte sedimentation rate, and C-reactive protein.

Figure 1



Study diagram. MTX, methotrexate.

US evaluation: Pretreatment and post-treatment US evaluations were carried out to determine effusion, synovial thickness, hot spots, and number of erosions.

Results

Table 1 shows that there was no statistically significant difference between the two groups with respect to demographic data ($P > 0.05$).

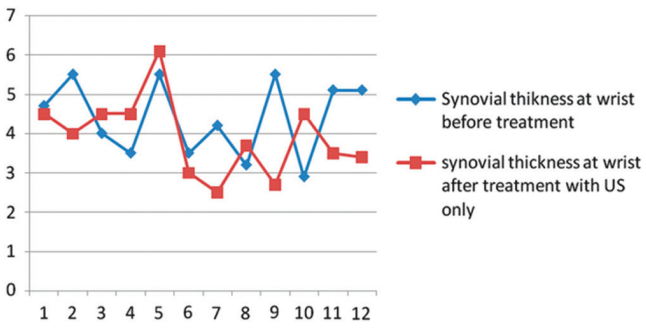
Table 2 shows that there was no significant difference between the diagnostic US finding before therapy and after therapy in patients who received therapeutic US ($P > 0.05$), except in the effusion level and VAS, which were statistically significant ($P < 0.05$) (Graph 1).

Table 3 shows that there was a highly statistically significant difference in the number of swollen joints, number of tender joints, VAS and synovial thickness at the wrist joint ($P < 0.01$) in the group of patients who received US+MTX; in addition, there was a statistically significant difference with respect to hot spots, number of erosions, and joint space narrowing ($P < 0.05$) (Graph 2).

Discussion

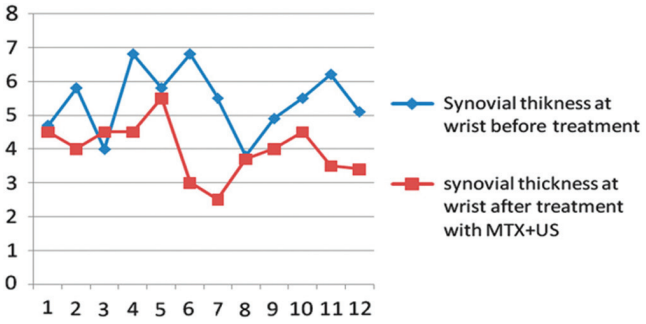
The use of US with intra-articular MTX as a therapeutic tool in an animal model was found to promote the uptake of MTX into synovial cells, which resulted

Graph 1



This graph shows no statistically significant difference in synovial thickness after treatment with ultrasound alone.

Graph 2



This graph shows a statistically significant decrease in synovial thickness after treatment with ultrasound and intra-articular methotrexate.

Table 1 Age and sex distribution of the studied groups

	US only ($N=12$)	US + MTX ($N=12$)	Test of significance	P-value
Age (mean ± SD) (years)	45.10 ± 10.01	42.08 ± 7.19	t-test = 0.82	0.42
Sex [N (%)]				
Male	3 (25)	4 (33)	Fisher exact test = 0.49	0.65
Female	9 (75)	8 (67)		

MTX, methotrexate; US, ultrasound .

Table 2 Comparison of the clinical and diagnostic ultrasound findings before and after therapy in patients who received ultrasound therapy alone

	Before	After	Test of significance	P-value
Effusion [N (%)]				
No effusion	4 (40)	5 (50)	Fisher's exact test = 6.67	0.048
Mild effusion	6 (60)	5 (50)		
Hot spots [N (%)]				
No	5 (50)	4 (40)	Fisher's exact test = 3.64	0.571
Few	4 (40)	3 (30)		
Multiple	1 (10)	3 (30)		
Erosions [N (%)]				
Absent	3 (30)	6 (60)	Fisher's exact test = 2.86	0.200
Present	7 (70)	4 (40)		
Joint space narrow [N (%)]				
Absent	9 (90)	10 (100)	Fisher's exact test = 0.00	1.00
Present	1 (10)	0 (0)		
Number of swollen joints (mean ± SD)	5.5 ± 4.2	5.2 ± 3.6	$t = 0.55^a$	0.58
Number of tender joints (mean ± SD)	7.2 ± 7.7	6.4 ± 6.7	$t = 1.84^a$	0.07
VAS (mean ± SD)	6.6 ± 1.7	5.7 ± 1.3	$t = 2.59$	0.03
Synovial thickness at wrist joint (mean ± SD)	4.2 ± 1.3	4.4 ± 1.7	$t = 0.48$	0.65

Table 3 Comparison of the clinical and diagnostic ultrasound findings before and after therapy in patients who received ultrasound+methotrexate

	Before	After	Test of significance	*P*-value
Effusion [*N* (%)]				
No effusion	2 (16.7)	6 (50)	Fisher's exact test = 3.49	0.182
Mild	9 (75)	6 (50)		
Moderate	1 (8.3)	0 (0)		
Hot spots [*N* (%)]				
No	6 (50)	7 (58.3)	Fisher's exact test = 8.91	0.013
Few	2 (16.7)	2 (16.7)		
Multiple	4 (33.3)	3 (25)		
Erosions [*N* (%)]				
Absent	8 (66.7)	6 (50)	Fisher's exact test = 6.00	0.061
Present	4 (33.3)	6 (50)		
Joint space narrow [*N* (%)]				
Absent	10 (83)	10 (83)	Fisher's exact test = 12.00	0.015
Present	2 (17)	2 (17)		
Number of swollen joints (mean ± SD)	4.3 ± 1.3	3.1 ± 1.2	$t = 3.07$[a]	0.002
Number of tender joints (mean ± SD)	6.9 ± 3.8	4.4 ± 2.4	$t = 2.68$[a]	0.007
VAS (mean ± SD)	5.6 ± 1.7	5.7 ± 1.3	$t = 4.75$	0.001
Synovial thickness at wrist joint (mean ± SD)	5.7 ± 0.79	4.1 ± 0.84	$t = 12.20$	0.000

[a]Wilcoxon test.

in enhancement of the anti-inflammatory effect of MTX [10]. In addition, it was found that US exposure increased transfection efficiency of gene construction because of increased cell membrane porosity and acoustic cavitations [11,12].

Low-intensity pulsed US was suggested to shorten the healing period of fractures because of promotion of endochondral ossification. Immunohistochemical analysis showed marked expression of vascular endothelial growth factor and neovascularization in the fibrous tissue comprising the periosteum that surrounded the whole callus [13].

US exerted an influence downstream of syndecan-4 and protein kinase C to specifically activate Rac1 (a critical regulator of tissue repair) and to a lesser extent RhoA (a regulator of tissue repair). The ability of US to bypass syndecan-4 signaling, which is known to facilitate efficient tissue repair, explains the reduction in healing time observed in US-treated patients. By substituting for one of the key axes of adhesion-dependent signaling, US therapy has considerable potential as a clinical technique [17].

Our study results showed that the combination of intra-articular MTX with pulsed US leads to decrease in effusion, inflammation (hot spots), number of swollen joints, tender joint count, and synovial thickness when compared with pulsed US therapy alone, which only reduces pain and effusion (Table 2). Our results are similar to the results of the study by Nakaya *et al.* [10] (an in-vivo study) who combined US therapy with intra-articular MTX and found that US enhances the uptake of MTX inside the cells, which leads to an increase in its anti-inflammatory effect. In addition, they concluded that the technique of MTX US combination may reduce synovitis and increase rehabilitation efficacy, replacing or delaying surgical synovectomy as much as possible.

Other studies either used MTX alone or combined it with corticosteroids or rifampicin [18,19], and their results were in agreement with our study with respect to reduction in pain and cessation of the progression of erosion [19]. However, none of them evaluated the synovial thickness or effusion objectively; besides they used a single intra-articular injection without repetition. In addition, according to our knowledge, no studies included synovial thickness as a measure after repeated MTX injection or combined MTX–pulsed US in humans. In a study on MTX+corticosteroid by Hasso *et al.* [20] , the authors recommended repeated injections for better results.

With respect to the role of MTX alone, our results were similar to those of a study conducted by William *et al.* [21], who concluded that a single intra-articular MTX injection exerted a rapid anti-inflammatory effect in a rabbit model, with significant reduction in knee swelling noted 1 day after injection and almost completely resolved swelling after 3 weeks.

In addition, our results were in agreement with the study by Nakaya *et al.* [10] in which US therapy decreased effusion. They attributed this to the bioeffects of US in the form of inertial cavitations and violent oscillations and the collapse of bubbles in the surrounding fluid that leads to rapid elimination of the fluid by distribution or phagocytosis, besides the role of US in increasing membrane porosity.

Thus, we can conclude that the combination of pulsed US therapy with repeated intra-articular MTX can give us better results in the form of decreased effusion, tenderness, inflammation, and synovial membrane

thickness, all of which translate into significant recovery of function and reduction in pain in rheumatoid patients with resistant monoarthritis or oligoarthritis, with the least number of side effects and without the need of adding another disease-modifying agent and/or resorting to surgical synovectomy.

Acknowledgements

Conflicts of interest

None declared.

References

1 Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? Clin Exp Rheumatol 2006; **24 (Suppl 43)**: S7–S13.

2 Jorge LL, Gerard C, Revel M. Evidences of memory dysfunction and maladaptive coping in chronic low back pain and rheumatoid arthritis patients: challenges for rehabilitation. Eur J Phys Rehabil Med 2009; **45**:469–477.

3 Creamer P, Keen M, Zananiri F, Waterton JC, Maciewicz RA, Oliver C, *et al*. Quantitative magnetic resonance imaging of the knee: a method of measuring response to intra-articular treatments. Ann Rheum Dis 1997; **56**:378–381.

4 Dixon ASJ, Cosh JA, Kersley GD. Local corticosteroid therapy for painful rheumatic states. A comparison of triamcinolone hexacetonide (Lederspan) and prednisolone acetate (Precortisyl). Clin Trials J 1972; **9**:14–18.

5 Bain LS, Balch HW, Wetherly JM, Yeadon A. Intraarticular triamcinolone hexacetonide: double-blind comparison with methylprednisolone. Br J Clin Pract 1972; **26**:559–561.

6 Oka M, Menkes C, Ruotsi A. Nonsurgical synovectomy. Scand J Rheumatol Suppl 1975; **12**:132–133.

7 Hall GH, Head AC. Intra articular methotrexate. Lancet 1975; 2:409.

8 Tiliakos NA, Lawrence T, Wilson C. Intra-articular methotrexate in RA. Arthritis Rheum 1982; **25**:554.

9 Durk H, Kotter I, Saal JG. Intra-articular methotrexate in corticosteroid resistant monoarthritis. Arthritis Rheum 1994; **37 (Suppl):** 554.

10 Nakaya H, Shimizu T, Isobe KI, Tensho K, Okabe T, Nakamura Y, *et al*. Microbubble-enhanced ultrasound exposure promotes uptake of methotrexate into synovial cells and enhanced antiinflammatory effects in the knees of rabbits with antigen-induced arthritis. Arthritis Rheum 2005; **52**:2559–2566.

11 Tachibana K, Uchida T, Ogawa K, Yamashita N, Tamura K. Induction of cell-membrane porosity by ultrasound. Lancet 1999; **353**:1409.

12 Kim HJ, Greenleaf JF, Kinnick RR, Bronk JT, Bolander ME. Ultrasound-mediated transfection of mammalian cells. Hum Gene Ther 1996; **7**:1339–1346.

13 Katano M, Naruse K, Uchida K, Mikuni Takagaki Y, Takaso M, Itoman M, *et al*. Low intensity pulsed ultrasound accelerates delayed healing process by reducing the time required for the completion of endochondral ossification in the aged mouse femur fracture model. Exp Anim 2011; **60**:385–395.

14 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; **31**:315–324.

15 Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2005; **2**:CD005328.

16 Prevoo ML, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LB, Van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; **38**:44–48.

17 Mahoney CM, Morgan MR. Therapeutic approaches to the treatment of tissue: therapeutic ultrasound bypasses canonical syndecan-4 signaling to activate Rac1. J Biol Chem 2009; **284**:8898–8909.

18 Hetland ML, Stengaard Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, *et al*. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum 2006; **54**:1401–1409.

19 Blyth T, Stirling A, Coote J, Land D, Hunter JA. Injection of the rheumatoid knee: does intra-articular methotrexate or rifampicin add to the benefits of triamcinolone hexacetonide?Br J Rheumatol 1998; **37**:770–772.

20 Hasso N, Maddison PJ, Breslin A. Intra-articular methotrexate in knee synovitis. Rheumatology 2004; **43**:779–782.

21 Williams AS, Camilleri JP, Goodfellow RM, Williams BD. A single intra-articular injection of liposomally conjugated methotrexate suppresses joint inflammation in rat antigen-induced arthritis. Br J Rheumatol 1996; **35**:719–724.