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

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

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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.


**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).

**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

| Table 1 Age and sex distribution of the studied groups |
|------------------------------------------------------|
| **US only \((N=12)\)** | **US + MTX \((N=12)\)** | **Test of significance** | **P-value** |
| Age \((mean \pm SD)\) \((years)\) | 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 \((mean \pm SD)\)** | 5.5 ± 4.2 | 5.2 ± 3.6 | *t* = 0.56 | 0.58 |
| **Number of tender joints \((mean \pm SD)\)** | 7.2 ± 7.7 | 6.4 ± 6.7 | *t* = 1.84 | 0.07 |
| **VAS \((mean \pm SD)\)** | 6.6 ± 1.7 | 5.7 ± 1.3 | *t* = 2.59 | 0.03 |
| **Synovial thickness at wrist joint \((mean \pm SD)\)** | 4.2 ± 1.3 | 4.4 ± 1.7 | *t* = 0.48 | 0.65 |

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

### 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 (72)  | 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*               | 0.002   |
| **Number of tender joints (mean±SD)** | 6.9±3.8 | 4.4±2.4 | t=2.88*               | 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   |

*Wilkoxon test.
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.

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Conflicts of interest
None declared.

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