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ORIGINAL ARTICLE

Intra-articular methotrexate versus corticosteroid injections in medium-sized joints of rheumatoid arthritis patients—an intervention study

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Abstract The effects of intra-articular methotrexate (I/A MTX) in knee synovitis in rheumatoid arthritis have been previously evaluated. I/A MTX has not been studied in other joints. Ultrasonography (US) has been little studied in monitoring the effect of I/A MTX. The aim of the study is to test the efficacy of I/A MTX in suppression of persistent synovitis in medium-sized joints (ankle, wrist, and elbow) in rheumatoid arthritis patients. Patients were divided into two groups: group 1 (methotrexate group): 56 patients in which 84 joints (32 ankles, 28 wrists, and 24 elbows) were injected intra-articularly by 10 mg of methotrexate in the targeted joint on a weekly basis for 8 weeks and group 2 (steroid group): 44 patients in which 70 joints (26 ankles, 24 wrists, and 20 elbows) were injected once by *Triamcinolone acetonide* 40 mg. Clinical, ultrasonographic, and power Doppler US (PDUS) evaluation was done before the first injection (W0), after 2 months (W8), and after 5 months (W20). Synovial thickness and the intra-articular power Doppler signal were graded on a semiquantitative scale from 0 to 3 during the US examination. Clinical parameters improved significantly in both groups between baselines and 2 months. In both groups, gray-scale US and power Doppler US showed that synovial thickness and intra-articular power signals were reduced significantly between W0 and W8. The improvement of clinical parameters continued in the methotrexate group up to W20, but in the corticosteroid group, clinical parameters at W20 were similar to clinical parameters at W0. In the methotrexate group, there was an insignificant increase in synovial thickness between W8 and W20 while there was a significant increase in power Doppler signals between W8 and W20, $p < 0.05$. In the corticosteroid group, there was a significant increase in both synovial thickening and power Doppler signals between W8 and W20, $p < 0.001$. In the MTX group, all patients at week 0 showed that the Doppler signal in grades 2 and 3 is 100%; at 8 weeks, most of the patients showed that the power Doppler in grade 0 is 76%; and at week 20, most of the patients showed that the power Doppler signal in grade 0 is 28% and in grade 1 is 47%, while in grades 2 and 3 is 23.6%, so there is an improvement compared to the baseline of treatment. Repeated I/A MTX resulted in a decrease in the degree of synovitis of medium-sized joints in RA patients both clinically and by power Doppler US.

Keywords Corticosteroid injections · Intra-articular methotrexate · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease in which inflammation of the cells lining the synovium produces pain, swelling, and progressive erosion of the synovial joints [1].

Table 1 Demographic and clinical characteristics of both groups

Variables	Group 1 (no = 56)	Group 2 (no = 44)	Test of sign	*p* value	Sig
Age (years) $\bar{X} \pm$ SD	35.2 ± 5.02	36.3 ± 4.7	$t = 1.1$	0.2	NS
Sex					
Females	38 (67.8%)	34 (77%)	$\chi^2 = 0.001$	0.9	NS
Males	18(32.2%)	10(23%)			
Mean duration of disease (years) $\bar{X} \pm$ SD	4.23 ± 3.06	3.7 ± 2.9	$t = 0.9$	0.3	NS
Duration of MS (min) $\bar{X} \pm$ SD	46.9 ± 9.5	49.2 ± 8.6	$t = 1.5$	0.1	NS
Seropositive RF	36 (64.2%)	28 (63.3%)	$\chi^2 = 0.01$	0.9	NS

MS: morning stiffness, *RF*: rheumatoid factor

Methotrexate (MTX) is the current cornerstone of pharmacological management for most patients with rheumatoid arthritis (RA). The 2015 ACR recommendations for the use of disease-modifying anti-rheumatic drugs (DMARDs) in RA support the use of MTX as the first-line therapy for most patients [2]. Similarly, according to recent EULAR recommendations for management of RA based on broad systematic literature review, MTX should be part of the first treatment strategy for patients with active RA [3].

Methotrexate has been tried intra-articularly and has been shown to be effective as reported in various trials [4]. Repeated intra-articular injections of MTX result in a decrease of local as well as systemic inflammatory signs in RA [5]. Intra-articular MTX therapy results in a strong decrease of SF-granulocyte counts. This effect may be due to the impairment of IL-8-mediated chemotaxis by decreased IL-8 synthesis in synovial fluid mononuclear cells [6].

Musculoskeletal ultrasonography (US) on B-mode has demonstrated greater sensitivity than clinical assessment for detecting synovitis and tenosynovitis in RA target joints [7, 8].

US on Doppler mode detects pathological synovial blood flow, which reflects joint inflammatory activity. An important capability aspect is that US-detected subclinical synovitis, mainly synovial Doppler signal, has shown predictive value in relation to radiographic damage progression and disease flare or relapse [9, 10].

Patients

One hundred RA patients attending the outpatient clinic of Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig University, were selected for the study from May 2013 to January 2014. All patients included in the study were fulfilling the following inclusion criteria: (1)fulfilling 2010 American college of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis [11], (2) DAS28 ESR < 2.6, (3) arthritis in one or two medium-sized joints (wrists, elbows, and ankles) resistant to systemic DMARDs including methotrexate.

Patients known to have diabetes mellitus, hepatitis C, or B infection were excluded from the study. Patients with joint sepsis or bleeding disorders are also excluded. All patients were on their conventional systemic DMARDs including methotrexate without any modification of doses. None of the patients included in the study received biologic therapy. Patients were randomized using a simple randomization method into two groups: group 1 (methotrexate group): 56 patients

Table 2 Clinical parameters of both groups before, after 8 weeks, and 20 weeks of follow-up

Swelling	Group 1 (joint = 84) N0 (%)	Group 2 (joint = 70) N0 (%)	χ^2	*p*	Sig
Before treatment					
0	5 (6)	8 (11.5)	1.4	0.2	NS
1	79 (94)	62 (88.5)			
After 8 weeks					
0	65 (77)	52 (74)	0.2	0.6	NS
1	19 (23)	18 (26)			
After 20 weeks					
0	53 (63)	32 (46)	4.6	0.03	S
1	31 (37)	38 (54)			
Cochran *Q*	$p < 0.0001$ (HS)	$p < 0.0001$ (HS)			

Table 3 Clinical parameters of both groups before, after 8 weeks, and 20 weeks of follow-up

Tenderness	Group 1 (joint = 84) N0 (%)	Group 2 (joint = 70) N0 (%)	χ^2	p	Sig
Before treatment					
1	5 (6)	3 (4.5)	0.24	0.88	NS
2	64 (76)	55 (78.5)			
3	15 (18)	12 (17)			
After 8 weeks					
0	66 (78.6)	56 (80)	0.2	0.6	NS
1	9 (10.7)	9 (13)			
2	9 (10.7)	5 (7)			
After 20 weeks					
0	21 (25)	11 (15.7)	9.6	0.02	S
1	33 (40)	18 (25.7)			
2	26 (30)	39 (55.7)			
3	4 (5)	2 (2.9)			
Frideman test	$p < 0.0001$ (HS)	$p < 0.0001$ (HS)			

(38 females and 18 males) in which 84 joints (32 ankles, 28 wrists and 24 elbows) were injected intra-articularly under complete aseptic technique by 10 mg of methotrexate without dilution in the targeted joint on a weekly basis for 8 weeks. The total received dose for the single joint was 80 mg MTX per 8 weeks and the maximum total received dose for a patient was 160 mg MTX per 8 weeks. Group 2 (steroid group) included 44 patients (34 females and 10 males) in which 70 joints (26 ankles, 24 wrists, and 20 elbows) were injected under complete aseptic technique once by *Triamcinolone acetonide* (kenacort) 40 mg. All injections were done guided by ultrasonography.

This study was approved by ethics committee of our university and all patients give written consent for injections after explaining the side effects.

Clinical and laboratory evaluation

All patients were subjected to full history taking including the duration of disease and duration of morning stiffness (MS) and drug therapy, general musculoskeletal examination. Visual analogue scale (VAS) for pain in the targeted joints was measured using a 10-cm horizontal scale with ten possible scores. Tenderness and swelling in the targeted joints were graded on a semiquantitative scale from 0 to 3. A clinical evaluator was blinded to the type of local injections. All patients were investigated as regards ESR, CRP, rheumatoid factor, CBC, liver functions, hepatitis markers, and kidney functions at weeks 0, 8, and 20.

Ultrasonographic examination

Ultrasonographic examination of the targeted joints was performed with a 5–12-MHz linear probe (medison R3) on the same days of clinical assessments. The method of US examination was according to the guidelines published by Backhaus et al. [12]. Synovitis was defined according to the published OMERACT definitions [13]. Synovitis on gray-scale US was evaluated using a semiquantitative 4-grade scale of 0–3, where 0 = absence of synovial thickening, 1 = mild synovial thickening, 2 = moderate

Table 4 Clinical parameters of both groups before, after 8 weeks, and 20 weeks of follow -up

VAS	Group 1 (no = 56) $\bar{X} \pm SD$	Group 2 (no = 44) $\bar{X} \pm SD$	t	p
Before treatment	8.3 ± 1.2	8.2 ± 1.7	0.6	0.5 (NS)
After 8 weeks	3.4 ± 2.2	5.8 ± 1.9	5	0.0001 (HS)
After 20 weeks	6.7 ± 1.6	7.6 ± 1.2	3.	0.002 (S)
F time measured test	$p < 0.0001$ (HS)*	$p < 0.0001$ (HS)*		

VAS: visual analogue scale

Table 5 Grades of synovial thickness detected by gray ultrasonography before and after injection

Synovial thickness	Group 1 (joint = 84) N0 (%)	Group 2 (joint = 70) N0 (%)	χ^2	p	Sig
Before treatment					
2	56 (66.7)	46 (66)	0.015	0.9	NS
3	28 (33.3)	24 (34)			
After 8 weeks					
0	64 (76)	44 (63)	3.2	0.07	NS
1	20 (24)	26 (37)			
After 20 weeks					
0	44 (52)	26 (37)	15.5	0.04	S
1	35 (42)	24 (34)			
2	5 (6)	15 (22)			
3	0	5 (7)			
	$p < 0.0001$ (HS)	$p < 0.0001$ (HS)			

synovial thickening, and 3 = marked synovial thickening. An ultrasonographer was blinded to the clinical parameters and the type of local injection.

Power Doppler ultrasonography

Synovial blood flow was evaluated in the same joints. Active synovitis was defined with power Doppler signals. Intra-articular power Doppler signal was graded semiquantitatively using a 4-grade scale of 0–3, where 0 = absence of signal, no intra-articular flow, 1 = mild, 1 or 2 vessels (including 1 confluent vessel) for small joints and 2–3 signals for large joints (including 2 confluent vessels), 2 = moderate confluent vessels in < 50% of the synovium, and 3 = marked vessel signals in > 50% of the synovium [14].

Clinical, ultrasonographic, and power Doppler US evaluation was done before the first injection (W0), after 2 months (W8), and after 5 months (W20).

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as the mean ± SD and qualitative data were expressed as absolute frequencies (number) and relative frequencies (percentage). Independent sample Student's t test was used to compare between the two groups of normally distributed variables while one-way repeated measures ANOVA was used to compare between more than two matched groups of continuous data. Friedman's test was used to compare between more than two matched groups of ordinal data. Cochran Q test was used to compare between more than two matched groups of dichotomies data. Percent of categorical variables were compared using the chi-square test (χ^2). All tests were two sided. p value < 0.05 was considered statistically

Table 6 Power Doppler grades before and after injection

Power Doppler US	Group 1 (joint = 84) N0 (%)	Group 2 (joint = 70) N0 (%)	χ^2	p	Sig
Before treatment					
2	48 (57)	42 (60)	0.12	0.7	NS
3	36 (43)	28 (40)			
After 8 weeks					
0	64 (76)	54 (77)	1.3	0.5	NS
1	16 (19)	10 (14)			
2	4 (5)	6 (9)			
After 20 weeks					
0	24 (28.6)	8 (11.5)	8.1	0.04	S
1	40 (47.6)	36 (51.5)			
2	14 (16.8)	16 (23)			
3	6 (7)	10 (14)			
Frideman test	$p < 0.0001$ (HS)	$p < 0.0001$ (HS)			

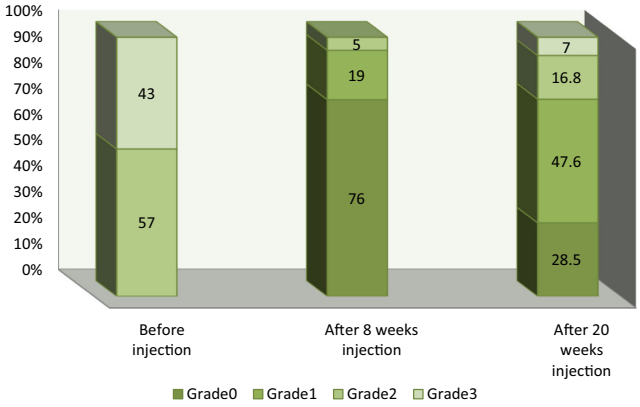

Fig. 1 Grades of Doppler ultrasound activity of methotrexate intra-articular injection group

significant (S), p value < 0.001 was considered highly statistically significant (HS), and p value ≥ 0.05 was considered statistically insignificant (NS).

Results

One hundred patients with RA was divided into two groups (Table 1): group (1): 56 patients (38 females and 18 males), their mean age was 35.2 ± 5.02 years and the disease duration was 4.23 ± 3.06 years and 36 patients (64.2%) had positive rheumatoid factor; and group (2): a total of 44 patients (34 females and 10 males), their mean age was 37.3 ± 3.7 years and the mean duration of disease was 3.7 ± 2.9 years and 28 patients (63.6%) had rheumatoid factor positive.

Clinical parameters (VAS for pain, tenderness, and swelling) improved significantly in both groups between baselines (W0) and 2 months later (W8) (Tables 2, 3, and 4). While the improvement of clinical parameters continued in the methotrexate group up to 3 months later W20, in the corticosteroid group, there was no significant differences between clinical parameters at W0 and clinical parameters at W20.

In both groups gray US and power Doppler US showed that synovial thickness and intra-articular power signals was reduced significantly between (W0 and W8) (Tables 5 and 6). In the methotrexate group, there was an insignificant increase in synovial thickness between W8 and W20, while there was a significant increase in power Doppler signals between W8 and W20, $p < 0.05$ (Tables 3 and 4). In the corticosteroid group, there was a significant increase in both synovial thickening and power Doppler signals between W8 and W20.

As regards side effects, two participants in the MTX group reported multiple oral ulcerations during the study, one participant in the same group reported post-injection nausea, and three participants in the corticosteroid group reported post-injection flare of arthritis. In both groups, there were no significant differences in renal and liver functions after injections in both groups.

Figures 1 and 2 show the grades of Doppler ultrasound activity of the two groups and show that at 20 weeks, there were more activity in Doppler in group 2.

Figures 3 and 4 show the grades of synovial thickness detected by gray ultrasound of the two groups, showing different grades of synovial thickness between the two groups at 20 weeks.

Supplementary Figures 5, 6, and 7 show the power Doppler images.

Discussion

The results reported suggest that intra-articular methotrexate has a more prolonged anti-inflammatory effect than intra-articular corticosteroids. This anti-inflammatory effect appeared clinically as improvement in VAS for pain and as decreases in the grades of tenderness and swelling and confirmed laboratory (by the decrease in ESR and CRP) and ultrasonographically (by the decrease in grades of synovial thickness as detected by gray-scale US and the decrease in power Doppler activities as detected by power Doppler US (PDUS)). While in the MTX group, this anti-inflammatory was persistence up to 32 weeks and in the corticosteroid group, the anti-inflammatory effects continued only for 8 weeks.

The improvement of clinical parameters and gray-scale parameters is in agreement with a study done by Iagnocco and colleagues [4]; their patients were treated with IA knee injections of MTX 10 mg every 7 days for 8 weeks. An increase of

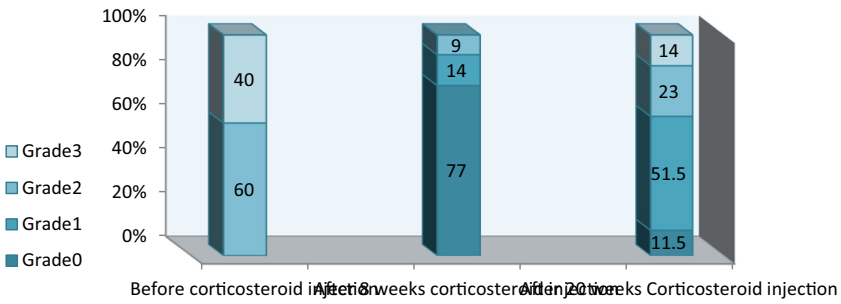

Fig. 2 Grades of Doppler ultrasound activity of corticosteroid intra-articular injection group. Figures 1 and 2 showed that at 20 weeks, there were more activities in Doppler in group 2

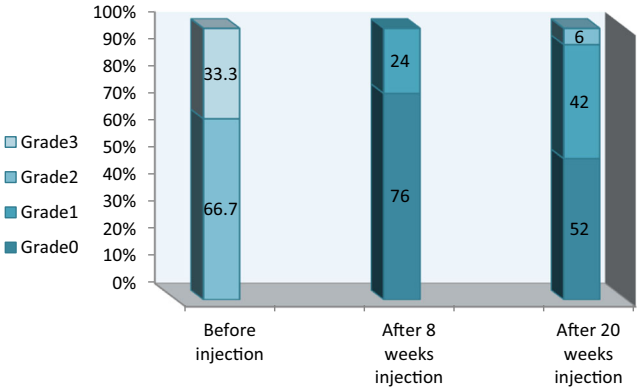

Fig. 3 Grades of synovial thickness detected by gray ultrasound of methotrexate intra-articular injection group

the mean value of maximal knee flexion angle and a reduction of the mean values of ESR and VAS between W9 and W17 were demonstrated. US evaluation showed significant reduction of synovial thickness and joint effusion. They concluded that repeated intra-articular injections of MTX resulted in a decrease of local as well as systemic inflammatory signs.

The superior clinical effects of repeated intra-articular MTX in comparison with intra-articular corticosteroids presented in these results also agree with a study done by Gao and colleagues [6]on patients with RA and knee effusions in the two groups; the first group were treated with up to six intra-articular injections of 10 mg MTX every 3 to 7 days and the control group received a single IA injection of 40 mg corticosteroids. They found also that the intra-articular granulocyte counts and IL-8 levels decreased in all MTX-treated patients on days 10–13 and stayed low in those patients after 13 weeks.

This agreed with the results of Blyth and colleagues [15] who found that the addition of 600 mg rifampicin or 50 mg methotrexate gave more pain relief after injection of the rheumatoid knee with 20 mg triamcinolone hexacetonide (TH). The improvement was detected clinically and themographically.

Our results agreed also with that of Tqweem and colleagues [16] who reported improvement in pain, swelling, flexion, and ESR after injecting with MTX 12.5 mg twice but he did not study how long this improvement lasted.

Many studies confirmed the role of power Doppler US in monitoring the response to therapy in RA [17]. In 2006, Filippucci and colleagues monitored treatment with adalimumab for 2 weeks with power Doppler US and demonstrated a rapid decrease in synovial pathological flow after treatment. In [18] 2008, Naredo and colleagues found sensitivity of change in PDUS in 28 joints of RA patients on anti-TNF therapy, showing a correlation with the improvement in DAS-28 and a predictive value for radiological progression.

Peter P and Bhasin S [19] found that PDUS correlates significantly with clinical findings and inflammatory markers. It has the ability to detect subclinical synovitis not detected by clinical assessment. So it can be used to predict that the efficacy of intra-articular MTX injection will end shortly which has to be confirmed in a more longitudinal studies.

The presented results are in contrary with many early studies like those with Hall and colleagues [20], which did not detect any clinical effects to intra-articular methotrexate. However, these early studies used a single MTX injection, which may be not enough to give clinical effects.

The present study confirm the safety of intra-articular MTX injection that presented in earlier studies [4, 5], with only two patients reported oral ulcers and one patient reported nausea which may be related to a minor systemic absorption. It may be of interest that while three patients in the corticosteroid group reported a post-injection flare, none of our patients in the methotrexate group reported such side effects.

To our knowledge, this the first study to confirm the effect of intra-articular MTX in synovial joints other than the knee joint which may encourage physicians to consider repeated intra-articular MTX injection as an option in treatment of resistant synovitis that does not respond to systemic therapy including systemic MTX.

While it seems that intra-articular MTX is cost-effective, this was not one of the targets of our study and we did not calculate the costs of injections for the different participants with different insurance systems. This should be discussed in further studies.

In conclusion, the present report shows that repeated intra-articular MTX injection resulted in a decrease in degree of synovitis of medium-sized joints in RA patients both clinically and by power Doppler US, while the clinical effects and decrease in synovial thickness by gray US continue after 6 months. The power Doppler signals tend to increase after 6 months. On the other hand, both synovial thickness and power Doppler signals tend to increase in steroid-injected joints after 3 months.

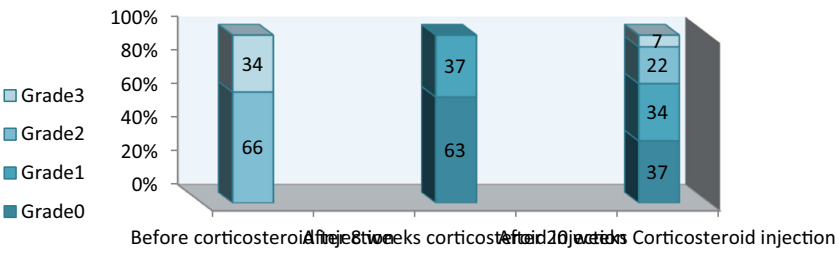

Fig. 4 Grades of synovial thickness detected by gray ultrasound of corticosteroid intra-articular injection group. Figures 3and 4 showing different grades of synovial thickness between two groups at 20 weeks

Compliance with ethical standards This study was approved by ethics committee of our university and all patients give written consent for injections after explaining the side effects.

Disclosures None.

References

1. McInnes I, O'Dell J (2010) State-of-the-art: rheumatoid arthritis. Ann Rheum Dis 69:1898–1906
2. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC et al (2016) American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 68(1):1–26
3. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M et al (2014) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 73(3):492–509
4. Iagnocco A, Cerioni A, Coari G, Ossandon A, Masciangelo R, Valesini G (2006) Intra-articular methotrexate in the treatment of rheumatoid arthritis and psoriatic arthritis: a clinical and sonographic study. Clin Rheumatol 25(2):159–163
5. Hasso N, Maddison PJ, Breslin A (2004) I/A methotrexate in knee synovitis. Rheumatology 43:779–782
6. Gao IK, Leins C, Bohlen H, Heilig B (1998) LemmelEM: Inhibition of interleukin-8 synthesis by intraarticular methotrexate therapy in patients with rheumatoid arthritis. Z Rheumatol 57(2):95–100
7. Backhaus M, Burmester GR, Sandrock D, Loreck D, Hess D, Scholz A, Blind S, Hamm B, Bollow M (2002) Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Ann RheumDis 61(10):895–904
8. Filippucci E, Gabba A, Di Geso L, Girolimetti R, Salaffi F, Grassi W (2012) Hand tendon involvement in rheumatoid arthritis: an ultrasound study. Semin Arthritis Rheum 41(6):752–760
9. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P (2008) An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 58(10):2958–2967
10. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, Bourgeois P, Fautrel B (2012) Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum 64(1):67–76
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd et al (2010) Rheumatoid arthritis classification criteria. Arthritis Rheum 62(9):2569–2581
12. Backhaus M, Burmester G, Gerber T, Grassi W, Machold K et al (2001) Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 60:641–649
13. Wakefield R, Balint P, Szkudlarek M et al (2005) Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol 32(12):2485–2487
14. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen H (2003) OstergaardM: Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum 48:955–962
15. Blyth T, Stirling A, Coote J, Land D, Hunter JA (1998) Injection of the rheumatoid knee: does intra-articular methotrexate or rifampicin add to the benefits of triamcinolone hexacetonide? Br J Rheumatol 37(7):770–772
16. Taqweem M, Kan H, Takreem A, Alam I (2008) Intra-articular (I/A) methotrexate in rheumatoid arthritis. Int J Rheumatol 6(1)
17. Filippucci E, Iagnocco A, Salaffi F et al (2006) Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. Ann Rheum Dis 65:1433–1437
18. Naredo E, Moller I, Cruz A et al (2008) Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum 58:2248–2256
19. Peter P, Bhasin S (2015) The role of power doppler ultrasonography as disease activity marker in rheumatoid arthritis. Dis Markers 2015:325909 9 pages
20. Hall GH, Jones BJM, Head AC (1978) Intra-articular methotrexate. Clinical and laboratory study in rheumatoid and psoriatic arthritis. Ann Rheum Dis 37:351–356