Evaluation of changes in magnetic resonance images following 24 and 52 weeks of treatment of rheumatoid arthritis with infliximab, tocilizumab, or abatacept

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Abstract

Objectives. To compare MRI findings in rheumatoid arthritis (RA) patients treated with biologic disease-modifying anti-rheumatic drugs (DMARDs).

Methods. The study subjects were 43 RA patients treated with biologic DMARDs (13 with infliximab, 15 with tocilizumab, and 15 with abatacept). They were evaluated using Simplified Disease Activity Index (SDAI) and low-field extremity MRI at baseline, and at 24 weeks and 52 weeks of treatment.

Results. Synovitis scores were significantly lower by 24 weeks in all groups, compared with baseline ($P<0.05$). Significant improvement in bone marrow edema (BME) scores were noted from baseline to 24 weeks in infliximab and abatacept groups ($P<0.05$), but from 24 weeks to 52 weeks in tocilizumab group ($P<0.01$). No significant change was found in erosion score. The synovitis score at baseline correlated significantly with SDAI at 24 weeks ($P<0.05$), and the score at 24 weeks correlated significantly with SDAI at 52 weeks ($P<0.05$).

Conclusions. The results suggest that the inflammatory improvement by infliximab and abatacept may express earlier than those by tocilizumab, despite similar improvement in SDAI. MRI-detected synovitis could be a useful predictor of SDAI at 24 weeks of treatment. The MRI remains the best tool to detect and assess the effects of biologic DMARDs in RA.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic and progressive autoimmune disease [1]. Patients with RA develop significant deformity, dysfunction, and destruction of the affected joints and, if left untreated, are at increased risk of morbidity and mortality [2]. Persistent inflammation or synovitis leads to pannus formation and, ultimately, to bone destruction [3].

The management of RA rests primarily on the use of disease-modifying anti-rheumatic drugs (DMARDs). Since the end of the last decade of the 20th century, biologic DMARDs therapy raised the standards of medical treatment by preventing the progression of joint destruction [4,5] and by providing symptom relief and improving employment opportunities [6,7]. Infliximab (IFX) is a chimeric antibody that binds with high affinity to human tumor necrosis factor alpha (TNFα) [8]. The ASPIRE clinical trial reported little radiographic progression in patients treated with IFX and methotrexate combination therapy compared with those treated with methotrexate alone [9]. Tocilizumab (TCZ) is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor [10]. Treatment with TCZ blocks IL-6 signaling within inflammatory and immune cells, and improves the clinical symptoms of autoimmune diseases such as RA, juvenile idiopathic arthritis, and Castleman disease [11,12]. Abatacept (ABT) is a recombinant fusion protein comprising the extracellular domain of human CTLA-4 [13]. ABT binds to CD80 and CD86 on T cells, thereby inhibiting the binding of these molecules to CD28 and preventing T-cell activation [14].

Durez et al. [15] reported that treatment with the combination of IFX and methotrexate was superior to methotrexate alone for reducing magnetic resonance imaging (MRI)-detected synovitis and bone marrow edema (BME) in RA patients by 18 weeks. The ACT-RAY clinical trial of RA patients compared the efficacy and safety of TCZ monotherapy with the TCZ—methotrexate dual therapy [16]. In the ACT-RAY MRI substudy, Conaghan et al. [17] reported significant improvement in MRI-detected synovitis after 2 weeks of treatment. The ASSET clinical trial evaluated the effects of ABT on various MRI findings, such as synovitis, BME, and bone erosion [18]. The present retrospective study compared the MRI findings in RA patients treated with the biologic DMARDs; IFX, TCZ, and ABT during 52 weeks.

Patients and methods

Patients

All patients were treated at the University of Tsukuba Hospital. In this retrospective study, the RA activity was determined using...
Simplified Disease Activity Index (SDAI). Therapeutic response was measured in accordance with the European League against Rheumatism (EULAR) response criteria, and clinical remission was defined as SDAI score < 3.3. All patients of this study were diagnosed with RA based on the American College of Rheumatology (ACR) criteria [19], had received monotherapy with IFX, TCZ, or ABT.

Treatment with biologic DMARDs
IFX was prescribed at a dose of 3 mg/kg body weight (KBW) in 12 patients and 5 mg/KBW in 1 patient. It was administered at 0, 2, and 6 weeks, and every 8 weeks thereafter till week 52. TCZ was administered at a dose of 8 mg/KBW, every 4 weeks in all patients. ABT was dosed in 13 patients at 5 mg/KBW in 11 patients and 7.5 mg/KBW in 2 patients. ABT was administered by intravenous infusion at 0, 2, and 6 weeks, and every 8 weeks thereafter till week 52.

Low-field extremity MRI
MR images of the bilateral wrists, MCP, and PIP joints were obtained for all patients at baseline and at 24 weeks using low-field extremity MRI (CompacTscan; Cross Tech Corporation, Tokyo, Japan). For this MRI, the patient sat in front of the magnet and inserted one hand into the RF coil for imaging. The MR sequences were set as follows: coronal 3-dimensional (3D) gradient-recalled echo T1-weighted images (repetition time [TR]/echo time [TE] = 50/9 ms; matrix size = 512 × 160 × 48 pixels; field of view [FOV] = 204.8 × 128 × 76.8 mm; scan time = 7 min and 10 s) and coronal 3D fast short-tau inversion-recovery (STIR) images (TR/TE/inversion time [TI] = 1000/60/100 ms; matrix size = 256 × 160 × 32 pixels; FOV = 204.8 × 128 × 51.2 mm; scan time = 9 min and 36 s). MRI of both hands was taken at baseline, 24 weeks, and 52 weeks.

Image analysis
Synovitis, BME, and bone erosion were evaluated using the compact MRI score (cMRIS) [20]. cMRIS was developed because the OMERACT-RAMRIS scoring system [21] is not available for PIP joints, which can be detected by CompacTscan imaging. Moreover, cMRIS is an easier system to use than RAMRIS for evaluating bone erosion. Images were scored by two independent readers.

Statistical analysis
Data related to patient characteristics were expressed as mean ± standard deviation or percentage values. The Wilcoxon signed-rank test was used to compare the difference in RA activity and MRI scores from baseline to 24 weeks, and to 52 weeks. Dunnett's multiple comparison test was used for comparison of ⊿SDAI (change from baseline to 24 weeks, and to 52 weeks) and ⊿MRI finding scores among the three treatment groups. The Spearman's rank correlation coefficient was performed to estimate the correlation between SDAI and MRI finding scores. Probability values less than 0.05 were considered significant. All analyses were conducted using IBM SPSS Statistics software, version 22.0 (IBM SPSS, Chicago, IL, USA).

Results
Patient characteristics
In this study, 13 patients were treated with IFX, 15 with TCZ, and another 15 patients with ABT. The baseline demographic and clinical data of these patients were similar (Table 1). There were no statistically significant differences of SDAI score and CRP at baseline among the three groups. None of the patients treated with IFX had been previously treated with another anti-TNF biologic. Six patients of TCZ group had been previously treated with anti-TNF biologics. Four patients of ABT group had been previously treated with anti-TNF or anti-IL-6R biologics.

Clinical assessment
The SDAI scores were significantly decreased at 24 weeks of treatment in all groups (IFX: 20.81 ± 8.45 to 7.68 ± 6.40, 47.11 ± 15.23 to 17.39 ± 11.98, and 60 ± 12 to 17.39 ± 11.98 for IFX, TCZ, and ABT, respectively).

Table 1. Baseline characteristics of the study patients.*

|              | IFX          | TCZ          | ABT          |
|--------------|--------------|--------------|--------------|
| No.          | 13           | 15           | 15           |
| Age, y       | 56.77 ± 7.64 | 53.07 ± 14.47 | 53.94 ± 17.68 | NS           |
| Female (%)   | 9 (69)       | 14 (93)      | 13 (87)      | NS           |
| Duration, y  | 6.23 ± 3.85  | 6.80 ± 4.72  | 6.80 ± 8.77  | NS           |
| Joint swelling| 6.00 ± 4.18  | 8.53 ± 4.07  | 6.07 ± 4.35  | NS           |
| Joint tenderness | 5.69 ± 4.46  | 2.60 ± 1.45  | 3.87 ± 5.17  | NS           |
| Patient VAS, mm | 39.69 ± 18.11 | 43.53 ± 26.30 | 38.87 ± 21.55 | NS           |
| CRP, mg/dL   | 1.59 ± 1.32  | 2.42 ± 2.14  | 1.35 ± 1.29  | NS           |
| RF, IU/mL    | 100 ± 143    | 83 ± 78      | 146 ± 160    | NS           |
| MMP-3, ng/mL | 239 ± 204    | 393 ± 312    | 193 ± 180    | NS           |
| ACPA positive (%) | 100          | 93           | 82          | NS           |
| SDAI          | 20.81 ± 8.45 | 22.80 ± 7.43 | 17.39 ± 11.98 | NS           |
| MTX (%)       | 1001112      | 4711         | 6012         | 12P < 0.01   |
| (mg/wk)      | 8.00 ± 1.15  | 7.43 ± 1.51  | 8.67 ± 1.73  | NS           |
| PSL (%)      | 92           | 73           | 67           | NS           |
| (mg/d)       | 5.09 ± 2.46  | 5.91 ± 2.06  | 5.80 ± 3.12  | NS           |

VAS, visual analog scale, CRP C-reactive protein, RF rheumatoid factor, MMP-3 matrix metalloproteinase-3, ACPA anticyclic citrullinated peptide antibody, SDAI Simplified Disease Activity Index, MTX methotrexate, PSL prednisolone.

*Values are the mean ± SD.
Table 2. Retention rate in RA patients treated with biologic DMARDs in our hospital (2010–2013).

| Group   | IFX | TCZ | ABT |
|---------|-----|-----|-----|
| Continued over 52 weeks, No. | 117 | 80  | 42  |
| Discontinued until 52 weeks, No. | 20  | 12  | 10  |
| Retention rate (%) | 85.4 | 87.0 | 80.8 |

P < 0.01; TCZ: 22.80 ± 7.43 to 9.26 ± 6.48, P < 0.01; ABT: 17.98 ± 11.98 to 5.23 ± 4.05, P < 0.01; Figure 1A). The ΔSDAI scores were similar among the three groups. (IFX: −11.50 ± 9.50; TCZ: −16.18 ± 9.84; ABT: −12.29 ± 9.69; Figure 1B). Clinical remission was achieved in 20% of the IFX group, 26% of the TCZ group, and 33% of the ABT group (Figure 1C). No significant differences in the remission rate were noted among the groups.

MRI assessment

Figure 2 shows changes in synovitis, BME, and bone erosion scores. There was no significant difference in baseline MRI-finding scores among the three groups. In all groups, the synovitis score was significantly decreased at 24 weeks of treatment (IFX: 7.07 ± 3.95 to 4.92 ± 2.87, P = 0.01; TCZ: 8.73 ± 6.28 to 5.20 ± 4.14, P = 0.01; ABT: 11.21 ± 8.62 to 5.71 ± 4.14, P < 0.01; Figure 2A). No significant differences in the Δsynovitis score were noted among the three groups (IFX: −3.15 ± 3.29; TCZ: −3.46 ± 4.90; ABT: −5.64 ± 8.85; Figure 3A).

Interestingly, the BME scores at 24 weeks were significantly lower than those at baseline in the IFX and ABT groups (IFX: 4.52 ± 4.60 to 2.02 ± 3.33, P = 0.04; TCZ: 8.33 ± 8.78 to 4.42 ± 4.72, P = 0.12; ABT: 4.73 ± 6.49 to 1.52 ± 2.26, P = 0.04; Figure 2B). In addition, the BME score at 52 weeks was significantly lower than that at 24 weeks in the TCZ group (IFX: 2.02 ± 3.33 to 1.73 ± 2.31, P = 0.73; TCZ: 4.42 ± 4.72 to 2.33 ± 4.12, P < 0.01; ABT: 1.52 ± 2.26 to 0.71 ± 2.00, P = 0.16; Figure 2B). The ΔBME scores for baseline to 24 weeks were significant in the IFX and ABT groups (IFX: −2.50 ± 3.64, P = 0.03; ABT: −3.21 ± 7.15, P = 0.04; Figure 3B). The ΔBME score for 24–52 weeks was significant in the TCZ group (TCZ: −2.08 ± 3.46, P < 0.01; Figure 3B). However, no significant change in the bone erosion scores
In the 2013 EULAR recommendations for the management of RA, biologic DMARDs, including IFX, TCZ, and ABT, were equally recommended as first-line therapy for those patients with poor response to methotrexate and/or other conventional synthetic DMARD strategies [22]. Furthermore, Durez et al. [15] reported that the combination of IFX and methotrexate was superior to methotrexate alone in reducing MRI-detected synovitis and BME by 18 weeks [15]. The ACT-RAY MRI substudy reported early improvement of synovitis of RA patients after initiation of treatment with TCZ [17]. The ASSET trial evaluated the clinical efficacy and safety of ABT as well as the effect of treatment on MRI findings [18]. To our knowledge, the present study is the first to compare MRI findings in RA patients treated with these three biologics.

In the present study, it was interesting that both BME score and synovitis score improved significantly at the early phase (0–24 weeks) of treatment with IFX and ABT; on the other hand, only synovitis score improved significantly at the early phase (0–24 weeks) of treatment with TCZ. No significant changes were found in the erosion scores. *BME bone marrow edema.

**Discussion**

In the 2013 EULAR recommendations for the management of RA, biologic DMARDs, including IFX, TCZ, and ABT, were equally recommended as first-line therapy for those patients with poor response to methotrexate and/or other conventional synthetic DMARD strategies [22]. Furthermore, Durez et al. [15] reported that the combination of IFX and methotrexate was superior to methotrexate alone in reducing MRI-detected synovitis and BME by 18 weeks [15]. The ACT-RAY MRI substudy reported early improvement of synovitis of RA patients after initiation of treatment with TCZ [17]. The ASSET trial evaluated the clinical efficacy and safety of ABT as well as the effect of treatment on MRI findings [18]. To our knowledge, the present study is the first to compare MRI findings in RA patients treated with these three biologics.

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In addition, the BME scores improved significantly at the early phase (0–24 weeks) of treatment with IFX and ABT, but at the late phase (24–52 week) with TCZ. A similar pattern was observed in ⊿BME scores. Although the reason for the difference in the improvement phase among the above three biologics is unknown, we speculate the following two possibilities. One is the difference in administration schedule of each biological DMARD. In IFX and ABT, the first interval of loading administration was shortened. In contrast, TCZ was administered every 1 month without shortening the initial interval. Although not reflected in SDAI, this shortening could result in faster improvement of MRI findings, especially BME, in RA patients treated with IFX and ABT. Another reason could be related to differences in inhibition of the inflammatory cytokine cascade by the different biologic DMARDs. In other words, IFX and ABT inhibit the upstream of the cascade of inflammatory cytokine compared with TCZ [24]. IFX inhibits TNF-α, which is located upstream of the cascade, compared with IL-6 [24]. ABT inhibits activation of naive T cells, which activate macrophages and synovial fibroblasts to produce TNF-α [13]. Further analysis of the relationship between changes in serum cytokines and MRI changes is necessary.

In RA patients treated with biologic DMARDs, there were no significant correlations between ⊿SDAI and ⊿total cMRI score. Similarly, no significant correlation was found between ⊿SDAI and each component of ⊿total cMRI score (i.e., ⊿synovitis, ⊿BME, and ⊿erosion score). On the other hand, synovitis score at baseline correlated significantly with SDAI at 24 weeks. A similar correlation was found between synovitis score at 24 weeks and SDAI at 52 weeks. These results suggest that MRI-detected synovitis may predict SDAI after 24 weeks.

In the 2013 EULAR recommendations for the use of imaging in the clinical management of RA, it was suggested that MRI or ultrasound are superior to clinical examination in the detection of joint inflammation [25]. Actually, some patients still showed residual synovitis or BME despite achieving clinical remission in this study. The CIMESTRA study explained that baseline BME score was an independent predictor of radiographic progression [26]. Therefore, MRI can be useful in identifying the true activity of RA.

Several limitations must also be considered in the interpretation of these data presented in this study. In the present study, we included only RA patients who could continue treatment with the same biologic DMARDs for 52 weeks. In fact, some patients treated at our facility did not show adequate response to other drugs or discontinued before 52 weeks, and these patients were not included in the present study. However, for the patients treated with these biologic DMARDs at our hospital between 2010 and 2013, the retention rate up to 52 weeks was not significantly different (IFX: 85.4%, TCZ: 87.0, and ABT: 80.8%) (Table 2).

In conclusion, MRI-detected BME in RA patients treated with IFX and ABT improved significantly at the early phase of treatment (0–24 weeks), whereas BME in those treated with TCZ only decreased at the late phase (24–52 weeks). These results suggest that the therapeutic effects of IFX and ABT may appear more rapidly compared with those of TCZ despite similar improvement in SDAI. In addition, the synovitis scores at baseline and 24 weeks could be potentially useful to predict the clinical response to treatment at 24 weeks and 52 weeks. The MRI remains the best tool to detect and assess the effects of biologic DMARDs in RA.

Figure 3. Comparison of (A) ⊿synovitis score, (B) ⊿BME score, and (C) ⊿erosion score from baseline to 24 weeks and to 52 weeks. ⊿Synovitis scores decreased significantly form baseline to 24 weeks in all groups. Significant difference in the ⊿BME scores was noted in the infliximab and abatacept groups from baseline to 24 weeks, and in the tocilizumab group from 24 weeks to 52 weeks. No significant change in the bone erosion scores was noted. For all MRI findings at 24 weeks and 52 weeks, there were no significant differences among the three groups. Data are mean ± SD. †1 All groups did or did not show significant changes. †2 No significant difference was noted among the three groups. †3 Significant changes were noted in the infliximab and abatacept groups but not the tocilizumab group. †4 Significant changes were noted in the tocilizumab group but not the other two groups. *BME: bone marrow edema.

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Figure 4. (A) Correlation between SDAI and \(\Delta\) total cMRI scores from baseline to 52 weeks. No significant correlation was found. (B) Correlation between synovitis scores at baseline and SDAI at 24 weeks. The SDAI at 24 weeks correlated significantly with synovitis scores at baseline. (C) Correlation between synovitis scores at 24 weeks and SDAI at 52 weeks. The SDAI at 52 weeks correlated significantly with synovitis scores at 24 weeks.
Conflict of interest
H.T. received lecture fee and/or honoraria from Bristol-Myers Squibb (BMS). I.M. received research grants, lecture fee, and/or honoraria from BMS. T.S. received research grants, lecture fee and/or honoraria from BMS, Mitsubishi Tanabe Pharma Corporation, and Chugai Pharmaceutical Corporation.

References
1. Choi EK, Gatensby PA, McGill NW, Bateman JF, Cole WG, York JR. Autoantibodies to type II collagen: occurrence in rheumatoid arthritis, other arthritides, autoimmune connective tissue diseases, and chronic inflammatory syndromes. Ann Rheum Dis. 1988;47(4):313–22.
2. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long term outcome of treating rheumatoid arthritis: results after 20 years. Lancet. 1987;1(8542):108–11.
3. Shiozawa K, Shiozawa S, Shimizu S, Fujita T. Fibronectin on the surface of articular cartilage in rheumatoid arthritis. Arthritis Rheum. 1984;27(6):615–22.
4. van der Heijde D, Klarskog L, Landewe R, Bruyn GAW, Cantagrel A, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56(12):3928–39.
5. Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. Clin Rheumatol. 2009;28(4):413–9.
6. Hyrich KL, Deighton C, Watson KD, Symmons DPM, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford). 2009;48(10):1323–7.
7. Augustsson J, Nceuvis M, Cullinan-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis. 2010;69(1):126–31.
8. Yamanaka H, Tanaka Y, Sekiguchi N, Inoue E, Saito K, Takeuchi T, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM). Mod Rheumatol. 2007;17(1):28–32.
9. Smolen JS, van der Heijde MFM, Clair EW, Paul Emery P, Bala M, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab; Results from the ASPIRE Trial. Arthritis Rheum. 2006;54(3):702–10.
10. Nishimoto N, Miyazaki N, Yamamoto K, Kawai S, Takeuchi T, Azuma I, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12–19.
11. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Kishimoto T, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371(9617):998–1006.
12. Matsuyama M, Suzuki T, Tsuboi H, Ito S, Mamura M, Sumida T, et al. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman’s disease. Intern Med. 2007;46(11):771–4.
13. Kremer JM, Westhovens R, Leon M, Giorgio ED, Alten R, Moreland LW, et al. Treatment of rheumatoid arthritis by selective inhibition of t-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003;349(20):1907–15.
14. Takeuchi T, Matsubara T, Nitobe T, Suematsu E, Ohta S, Miyasaki N, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol. 2013;23(2):226–35.
15. Durez P, Malghem J, Toukap AN, Depresseux G, Lauwerys BR, Verschueren P, et al. Treatment of early rheumatoid arthritis; a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum. 2007;56(12):3919–27.
16. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Huizinga TWJ, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013;72(1):43–50.
17. Conaghan PG, Peterfy C, Olech E, Kaine J, Ridley D, Troum O, et al. The effects of tocilizumab on osteitis, synovitis and erosion progression in rheumatoid arthritis: results from the ACT-RAY MRI substudy. Ann Rheum Dis. 2014;73(5):810–6.
18. Conaghan PG, Durez P, Rieke E, Alten RE, Burmester GR, Tak PP, et al. Impact of intravenous abatacept on synovitis, ostitis and structural damage in patients with rheumatoid arthritis and an inadequate response to methotrexate: the ASSET randomised controlled trial. Ann Rheum Dis. 2013;72(8):1287–94.
19. 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(3):315–24.
20. Suzuki T, Ito S, Handa S, Kose K, Okamoto Y, Sumida T, et al. A new low-field extremity magnetic resonance imaging and proposed compact MRI score: evaluation of anti-tumor necrosis factor biologics on rheumatoid arthritis. Mod Rheumatol. 2009;19(4):358–65.
21. McQueen F, Lassere M, Edmonds J, Conaghan P, Peterfy C, Østergaard M, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies, Summary of OMERACT 6 MR imaging module. J Rheumatol. 2003;30(6):1387–92.
22. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492–509.
23. Freeston JE, Brown AK, Hensor EM, Emery P, Conaghan PG. Extremity magnetic resonance imaging assessment of synovitis (without contrast) in rheumatoid arthritis may be less accurate than power Doppler ultrasound. Ann Rheum Dis. 2008;67(9):1351.
24. Smolen JS, Aletaha D, Koeberl M, Weisman MH, Emery P, New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370(9602):1861–74.
25. Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint TWJ, et al. Adding tocilizumab or switching to tocilizumab monotherapy for rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab; Results from the ASPIRE Trial. Arthritis Rheum. 2006;54(3):702–10.
26. Nishimoto N, Miyazaki N, Yamamoto K, Kawai S, Takeuchi T, Azuma I, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12–19.
27. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Kishimoto T, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371(9617):998–1006.
28. Matsuyama M, Suzuki T, Tsuboi H, Ito S, Mamura M, Sumida T, et al. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman’s disease. Intern Med. 2007;46(11):771–4.

Evaluation of changes in magnetic resonance images

Supplementary material available online
Supplementary Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069471