Magnetic Resonance Imaging Quantification of Hand Synovitis in Patients with Rheumatoid Arthritis Treated with Adalimumab

ANASTASIA K. ZIKOU, MARIA I. ARGYROPOULOU, PARASKEVI V. VOULGARI, VASSILIOS G. XYDIS, SPYROS N. NIKAS, STAVROS C. EFREMIDIS, and ALEXANDROS A. DROSOS

ABSTRACT. ***Objective.*** To investigate the clinical response and to evaluate by magnetic resonance imaging (MRI) the inflammatory tissue changes in patients with refractory rheumatoid arthritis (RA) treated with adalimumab.

Methods. Thirteen patients with refractory RA who were treated with adalimumab (40 mg every 2 weeks subcutaneously) were examined with MRI of the dominant affected wrist and hand before treatment and one year after therapy. The volume of the enhanced inflammatory tissue (VEIT) was evaluated in fat-suppressed contrast-enhanced T1-weighted MRI images using the Analyse 4.0 software. Disease activity was evaluated using the Disease Activity Score 28-joint (DAS-28). Clinical improvement was evaluated according to the American College of Rheumatology 20% response criteria (ACR20%).

Results. We studied 12 women and one man, with mean age 52.0 ± 10.9 years and mean disease duration 13.0 ± 8.5 years. Eight patients had positive IgM rheumatoid factor. One year after treatment, 11 (84.6%) patients showed a decrease of the VEIT. Moreover the values of C-reactive protein (CRP; 4.3 ± 6.6 mg/l), the erythrocyte sedimentation rate (ESR; 26.3 ± 19.5 mm/h), the DAS-28 (3.5 ± 1.1), and the VEIT (21.6 ± 10.7 cm^3) after treatment were significantly lower compared to the corresponding values before treatment (CRP 41.6 ± 39.2), (ESR 54.3 ± 28.6) (DAS-28 5.8 ± 0.8), and (VEIT 36.9 ± 16.8) ($p < 0.01$). All but 3 (76.9%) patients with RA achieved the ACR20% response, while 7 (53.8%) and 5 (38.5%) patients achieved ACR50% and ACR70% response, respectively. A positive correlation between VEIT, swollen joint count, and ESR was found before treatment ($r = 0.59$, $r = 0.64$, respectively; $p < 0.05$).

Conclusion. In patients with refractory RA, treatment with adalimumab resulted in improvement of clinical, laboratory, and MRI findings. MRI assessment of the VEIT may represent an additional tool for investigation of joint disease activity and responsiveness to treatment. (J Rheumatol 2006;33:219-23)

Key Indexing Terms:
RHEUMATOID ARTHRITIS | SYNOVITIS | ADALIMUMAB
MAGNETIC RESONANCE IMAGING | GADOLINIUM

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial membrane inflammation leading to joint damage. Proliferative synovitis results in the formation of pannus in close contact with the interface of articular cartilage and the bare areas of the bone. This formation leads to the production of marginal erosions, which are an essential radiologic feature of RA[1]. Articular involvement of the hand and the wrist is the presenting site in about 70% of the patients with RA, and frequently reflects the patient's overall disease condition[1,2]. Although conventional radiography remains the standard of reference for assessing joint destruction, it lacks sensitivity in depicting early erosive changes and does not enable direct visualization of the inflamed synovial membrane[3-5].

Grey-scale and power Doppler ultrasonography has gained acceptance for studying joint, tendon, and bursal involvement in patients with RA. In a few comparative studies evaluating the role of ultrasound and magnetic resonance imaging (MRI) in detecting synovitis, ultrasound was found to be either comparable to or more sensitive than MRI[4,6,7]. However, in these studies experienced investigators performed the ultrasound and it is well known that results depend on the skill of the examiner. MRI scoring systems and computerized measurements of synovial volumes have

From the Department of Radiology and the Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece.

A.K. Zikou, MD, Attending Radiologist; M.I. Argyropoulou, MD, Associate Professor of Radiology; V.G. Xydis, MD, Attending Radiologist; S.C. Efremidis, MD, Professor of Radiology, Department of Radiology; P.V. Voulgari, MD, Lecturer in Rheumatology; S.N. Nikas, MD, Fellow in Rheumatology; A.A. Drosos, MD, FACR, Professor of Medicine/Rheumatology, Rheumatology Clinic, University of Ioannina Medical School.

Address reprint requests to Dr. A.A. Drosos, Department of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece. E-mail: adrosos@cc.uoi.gr

Accepted for publication September 19, 2005.

been found to be useful for the evaluation of disease activity and response to treatment[8-12].

Tumor necrosis factor (TNF) is a proinflammatory cytokine that is involved with normal inflammatory and immune responses and with the pathogenesis of chronic inflammatory medical conditions, such as RA. The newest therapies for these inflammatory conditions include the TNF biologic response inhibitors. Adalimumab is a human recombinant immunoglobulin G1 anti-TNF-α monoclonal antibody. Response to treatment with adalimumab has been evaluated by clinical and laboratory assessment, as well as by serial radiographs[13,14]. There are no studies that have used MRI for the evaluation of response to adalimumab therapy in patients with RA.

We investigated the response to adalimumab therapy in patients with refractory RA by assessing with MRI changes in the volume of the enhanced inflammatory tissue (VEIT) in the dominant hand and wrist.

MATERIALS AND METHODS

Patients. Thirteen patients with RA according to the American College of Rheumatology (ACR) criteria[15] were enrolled in the study. All patients had active disease, defined as follows: tender joint count or swollen joint count ≥ 6 and erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) ≥ 10 mg/l. There were 12 women and one man, aged 35–70 years (mean 52.0 ± 10.9 yrs). The average disease duration was 13.0 ± 8.5 years (range 2–28 yrs) at the beginning of the study. Of the 13 patients, 8 were positive for IgM rheumatoid factor (RF). The patients were refractory or did not tolerate at least 2 disease modifying antirheumatic drugs (DMARD). Refractory RA was defined as increasing DMARD dosage above standard dosage regimen, using combination therapy, and adding or increasing the dosage of corticosteroids[16]. The current treatment included 10 patients receiving methotrexate (MTX) and 3 leflonumide. In addition, all patients received small doses of prednisone (≤ 7.5 mg/day). The patients taking MTX had refractory disease or did not tolerate injections of gold salts, plus hydroxychloroquine, plus prednisone, while the patients taking leflunomide were refractory or did not tolerate MTX, plus hydroxychloroquine and prednisone.

The patients were treated with 40 mg adalimumab subcutaneously every 2 weeks for a total period of 12 months. Patients were excluded from the study if they had: (1) history or presence of malignant disease; (2) liver or kidney abnormalities or history of viral hepatitis B or C; (3) major complicating diseases such as amyloidosis or heart or lung disease; or (4) positive tuberculin skin test using PPD-RT23 (2 IU/0.1 ml) or abnormal chest radiograph suggesting chronic infectious disease or granulomatous disease or other pathologic findings.

Clinical and laboratory evaluation. Each patient underwent a complete physical examination before treatment and at each patient visit until the end of the study. Clinical disease variables included: (1) duration of morning stiffness (min); (2) grip strength (mm Hg); (3) total joint count with tenderness or swelling; (4) number of swollen joints; (5) number of tender joints; and (6) pain score [on visual analog scale (VAS)] (cm). Laboratory disease variables included CRP (mg/l) and ESR (mm/h), performed at each patient's visit, which corresponded to adalimumab monitoring every 2 months for a total period of 12 months. For assessing disease activity, the Disease Activity Score for 28 joints (DAS-28) was calculated for each patient[17]. Clinical improvement was evaluated according to the ACR20% response criteria[18].

Imaging evaluation. All MRI examinations were performed in the same MR unit with a 1.5 Tesla Gyroscan ACS NT (Philips Medical Systems, Best, The Netherlands) using a surface coil 20 cm with 22 cm field of view. The patient lay prone with the arm to be studied extended overhead toward the midline. To obtain the best alignment between the metacarpals and the phalanges, the hand and wrist were immobilized, palm downward, with tight restraining bands. The imaging protocol consisted of (1) axial and coronal turbo spin-echo T2-weighted images with 4000/120 (repetition time, ms/echo time, ms), 3 mm slice thickness, 0.3 intersection gap, 4 excitations, 256 × 256 imaging matrix; and (2) coronal spin-echo fat-suppressed, T1-weighted images with 590/15 (repetition time, ms/echo time, ms), 3 mm slice thickness, 0.3 intersection gap, 4 excitations, and 256 × 256 imaging matrix, before and immediately after intravenous administration of 0.1 mmol/kg Gd-DTPA (Magnevist, Schering, Germany). Intravenous contrast injection was performed through a vein in the contralateral arm. T1-weighted images before and after contrast administration were displayed with the same window and grey-scale level. Contrast enhanced images were evaluated for enhanced inflammatory tissue consisting of inflammatory synovium and active hypervascularized pannus within bone erosions. Due to grey-scaling phenomena, normal cartilage and muscle exhibited higher signal on fat-suppressed T1-weighted images than on T1 images without fat suppression[19]. However, the enhanced inflammatory tissue was brighter than the normal cartilage and was always identified in each contrast enhanced image by comparison with the corresponding plain image (Figure 1). Diffusion of contrast material into joint effusions and fibrotic pannus enhancement was avoided since the duration of post-contrast imaging was 2.5 min[9].

Evaluation of all MRI examinations was performed randomly. Two radiologists (MIA and VGX) blinded to patients' identity, clinical status, and treatment regimen evaluated the VEIT together. Analyse 4.0 software (Biomedical Imaging Resources, Mayo Clinic, Rochester, MN, USA) was used for VEIT measurements.

The areas of the enhanced inflammatory tissue were outlined using the "auto trace" function: the operator picks a seed point inside the area and interactively specifies an intensity threshold range. All pixels with values

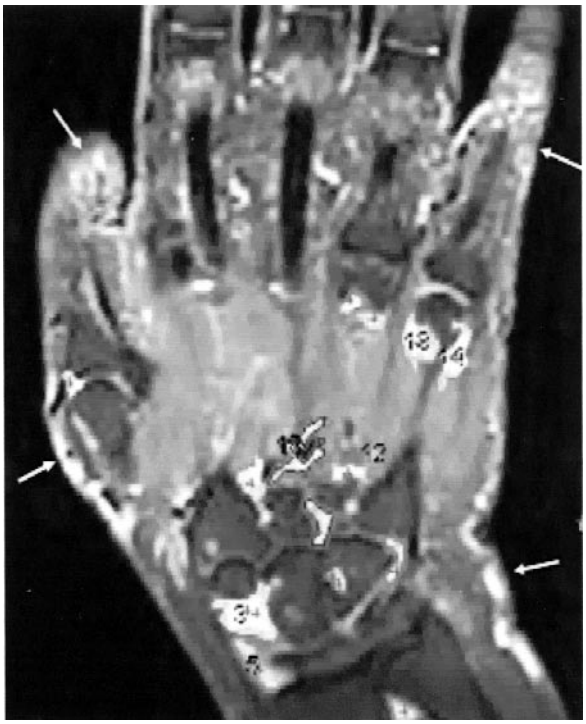

Figure 1. Coronal fat-suppressed T1-weighted contrast-enhanced scan of the dominant hand showing area tracings of the active inflammatory tissue from which the volume of enhanced inflammatory tissue was calculated. The serpentine bright structures represent vessels (arrows).

within the range are connected to the seed point and a trace is automatically drawn around the connected region. The operator can manually add limits to the area trace when the border of the region is "broken." The area of the enhanced inflammatory tissue was measured in all series of scans where it was visible (Figure 1). The measured areas were multiplied by the sum of the slice thickness with the interslice gap to determine the volume of the outlined structures. This process was repeated for all slices and the VEIT was computed by summing the corresponding volumes of all slices.

Statistical analysis. Statistical analysis was performed with SPSS base 11.5 for Windows. The normality of distribution of parameters was assessed using the Kolmogorov-Smirnov test. Unpaired 2-tailed Student t test was used to study differences in clinical parameters, laboratory parameters, and VEIT before and after treatment with adalimumab. The Pearson product-moment linear correlation coefficient was used to evaluate the relationship between the VEIT and clinical and laboratory parameters.

RESULTS

After one year of treatment, significant reductions of ESR, CRP, DAS-28, and VEIT were noted (Table 1). Eleven (84.6%) patients showed decrease of VEIT (Figure 2A, 2B). Moreover, all patients but 3 (76.9%) achieved the ACR20% response, 7 (53.8%) the ACR50%, and 5 (38.5%) the ACR70%. In addition, European League Against Rheumatism response criteria based on DAS-28 were as follows: 11 (84.6%) patients had moderate response, while 6 (46.1%) had good response. After treatment, one patient did not achieve the ACR20% response, but on followup the MRI showed increase of VEIT.

Only before treatment did the VEIT show a positive correlation with swollen joint count and ESR ($r = 0.59$, $r = 0.64$, respectively; Figure 3A, 3B).

DISCUSSION

TNF-α is a cytokine that is involved with inflammatory and immune responses in many autoimmune rheumatic diseases. Patients with active RA have elevated concentrations of TNF-α in their synovial tissue, which induces the pathologic inflammation leading to joint damage and bone destruction. Adalimumab is a fully human IgG1 anti-TNF-α monoclonal antibody. As monotherapy or in combination with MTX or other traditional DMARD, adalimumab can produce improvement of the signs and symptoms associated with RA and can slow progression of joint destruction[13,14,20]. Recently, in a 52 week, double-blind, placebo controlled study, 619 patients with active RA who had an inadequate response to MTX were randomized to receive adalimumab 40 mg subcutaneously every other week, adalimumab 20 mg subcutaneously every week, or placebo plus concomitant MTX. The primary endpoints were radiograph-

Table 1. Clinical, laboratory, and imaging changes in patients with RA treated with adalimumab. Variables are expressed as mean values ± standard deviation.

Variables	Before Treatment	After Treatment	p
Disease Activity Score for 28 joints	5.8 ± 0.8	3.5 ± 1.1	< 0.01
Erythrocyte sedimentation rate, mm/h	54.3 ± 28.6	26.3 ± 19.5	< 0.01
C-reactive protein, mg/l	41.6 ± 39.2	4.3 ± 6.6	< 0.01
Volume of enhanced inflammatory tissue, cm^3	36.9 ± 16.8	21.6 ± 10.7	< 0.01

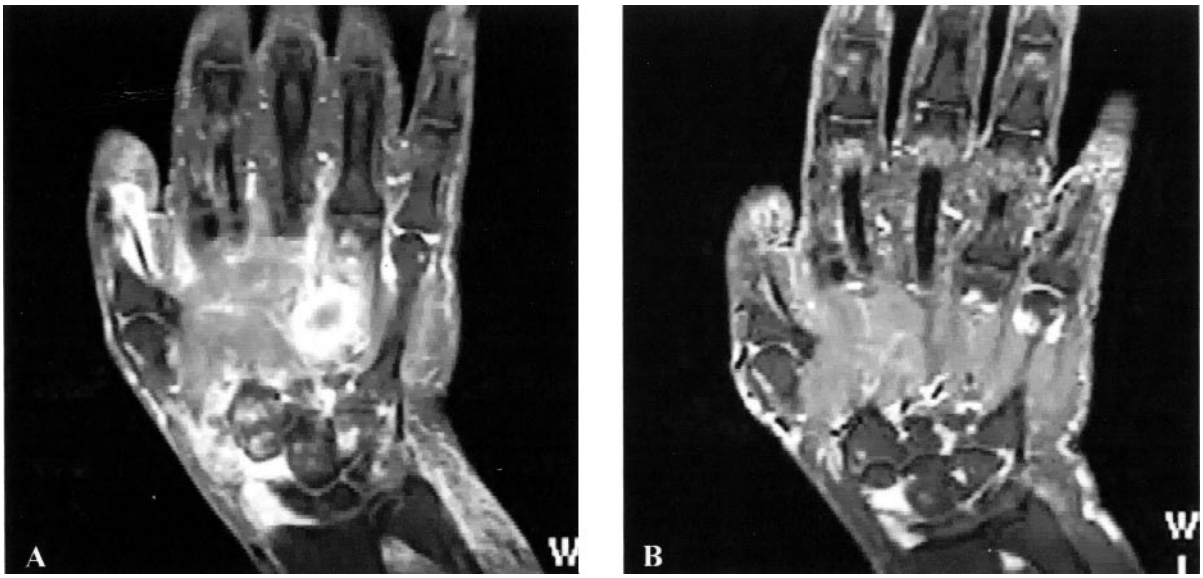

Figure 2. Coronal fat-suppressed T1-weighted contrast-enhanced scan of the dominant hand showing enhanced inflammatory tissue before (A) and after (B) treatment with adalimumab. A significant decrease of enhanced inflammatory tissue was observed after therapy.

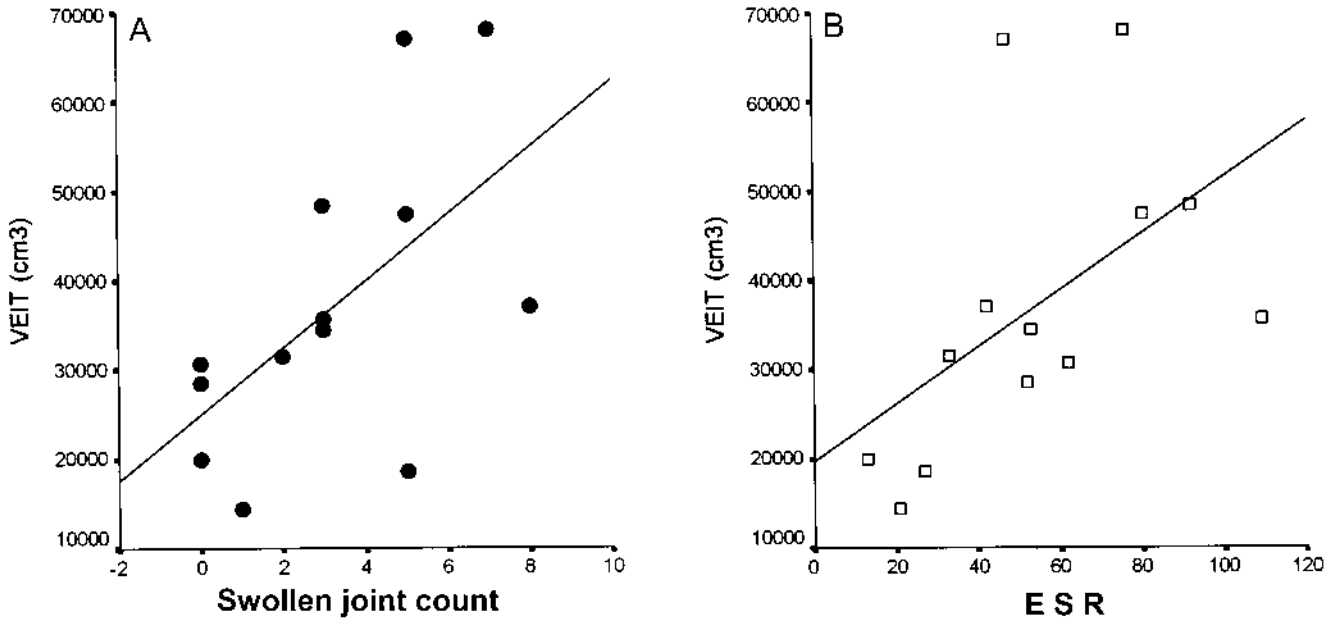

Figure 3. A. Volume of enhanced inflammatory tissue (VEIT) compared to swollen joint count ($r = 0.59$; $p < 0.01$). B. VEIT compared to ESR ($r = 0.64$; $p < 0.01$).

ic progression at Week 52, clinical response at Week 24, and physical function at Week 52. It was shown that adalimumab was more effective than placebo at inhibiting progression of structural joint damage, reducing signs and symptoms, and improving physical function[21]. In previous studies conventional radiography of the hand and wrist has been used for evaluation of disease progression and response to treatment with DMARD or TNF biologic response modifiers[20,22]. However, radiographs can visualize only the late destructive consequences of preceding synovitis, while neither the inflamed synovial membrane nor early erosive disease can be detected.

MRI allows assessment of the soft tissue structures and cartilage and bone lesions (edema, cysts, erosions), depicts early inflammatory changes in the joint, especially synovitis and tenosynovitis, and distinguishes between active inflammatory and chronic fibrotic synovial tissue[8]. Quantitative MRI assessment of synovitis may prove valuable to determine joint disease activity and to predict progressive joint destruction in RA[12]. Volume measurements, although time-consuming, are more precise compared with scoring systems[5]. Contrast enhanced MRI depicts acute synovitis and active inflammatory pannus within bone erosions, and therefore is a useful method to assess response to treatment targeting the swollen inflammatory synovium and active pannus within bone erosions[9,23,24].

In this study MRI quantification of active inflammatory pannus in the hand and wrist was used to evaluate the response to treatment with adalimumab in patients with RA. Used appropriately, contrast enhanced MRI can differentiate active inflammatory tissue from fibrotic tissue[24,25]. MR images obtained a few minutes after intravenous contrast injection show enhancement of the acute inflammatory tissue clearly demarcated from the intraarticular fluid[25,26]. In our study images of hand and wrist were obtained 2.5 minutes after contrast injection, and enhanced tissues revealed acute inflammatory synovitis. A decrease of the VEIT was observed one year after adalimumab therapy, and this was associated with clinical response (improvement of DAS-28). Moreover, these MRI changes were associated with a decrease of the acute phase reactants. These findings are in agreement with reports that treatment with adalimumab results in clinical improvement and reduction of acute phase reactants[21,27,28].

A positive correlation between the VEIT and ESR was found only before treatment. This is probably because MR images, by directly depicting the acute inflammatory tissue, are more sensitive than clinical evaluation to objectively define the extent of synovial involvement. One study has shown that patients with RA in clinical remission still had considerable synovitis revealed by MRI[29]. We found no correlation between VEIT, CRP, and ESR after treatment. This could be related to the fact that CRP and ESR as acute phase reactants indicate a systemic inflammation, while evaluation of VEIT shows the inflammatory status in a specific area studied. Even though our patients did not attain a complete clinical remission after treatment, the findings of this previous study support our results.

This study has some possible limitations: (1) the slices of the sequence used for VEIT evaluation were not continuous, and an interslice gap of 10% of the slice thickness was included for volume measurements; (2) patients were not evaluated for bone edema and cartilage destruction. Indeed, for some authors synovial inflammation and joint destruction are 2 independent processes in RA[30,31]. For others, synovitis is the primary abnormality and bone damage does not occur in its absence[32]. In our study active hypervascularized

pannus within bone erosions was part of the enhanced inflammatory tissue that was quantified.

We conclude that in patients with refractory RA treatment with adalimumab showed a substantial clinical and laboratory response, which was associated with improvement of the MRI findings. MRI assessment of the volume of enhanced inflammatory tissue in RA may be useful for the investigation of joint disease activity and responsiveness to treatment.

REFERENCES

1. Harris ED Jr. Mechanisms of disease: rheumatoid arthritis pathophysiology and implications for therapy. N Engl J Med 1990;322:1277-89.
2. Odeh M. New insights into the pathogenesis and treatment of rheumatoid arthritis. Clin Immunol Immunopathol 1997;83:103-16.
3. Ribbens C, Andre B, Marcelis S, et al. Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor–α treatment: pilot study. Radiology 2003;229:562-9.
4. Backhaus M, Kamradt T, Sandrock D, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum 1999;42:1232-45.
5. Ostergaard M, Hansen M, Stoltenberg M, et al. Magnetic resonance imaging-determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. Arthritis Rheum 1999;42:918-29.
6. Weidekamm C, Koller M, Weber M, Kainberger F. Diagnostic value of high-resolution B-mode and Doppler sonography for imaging of hand and finger joints in rheumatoid arthritis. Arthitis Rheum 2003;48:325-33.
7. Terslev L, Torp-Pedersen S, Savnik A, et al. Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. Arthritis Rheum 2003;48:2434-41.
8. Cimmino MA, Bountis C, Silvestri E, Garlaschi G, Accardo S. An appraisal of magnetic resonance imaging of the wrist in rheumatoid arthritis. Semin Arthritis Rheum 2000;30:180-95.
9. Sugimoto H, Takeda A, Kano S. Assessment of disease activity in rheumatoid arthritis using magnetic resonance imaging: quantification of pannus volune in hands. Br J Rheumatol 1998;37:854-61.
10. Bird P, Lassere M, Shnier R, Edmonds J. Computerized measurement of magnetic resonance imaging erosion volumes in patients with rheumatoid arthritis: a comparison with existing magnetic resonance imaging scoring systems and standard clinical outcome measures. Arthritis Rheum 2003;48:614-24.
11. Ostergaard M, Duer A, Moller U, Ejbjerg B. Magnetic resonance imaging of peripheral joints in rheumatic diseases. Best Pract Res Clin Rheumatol 2004;18:861-79.
12. Argyropoulou MI, Glantzouni A, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine Epub 30 March 2005.
13. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med 2004;350:2167-79.
14. Baker DE. Adalimumab: human recombinant immunoglobulin g1 anti-tumor necrosis factor monoclonal antibody. Rev Gastroenterol Disord 2004;4:196-210.
15. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. van de Putte LB, Krool EJ, van Riel PL. Management of refractory rheumatoid arthritis. Rheumatology Oxford 1999;38:32-4.
17. 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 rhewmatoid arthritis. Arthritis Rheum 1995;38:44-8.
18. Felson DT, Anderson JJ, Boers A, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727/35.
19. Nakahara N, Uetani M, Hayashi K, Kawahara Y, Matsumoto T, Oda J. Gadolinium-enhanced MR imaging of the wrist in rheumatoid arthritis: value of fat suppression pulse sequences. Skeletal Radiol 1996;25:639-47.
20. den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiologic course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis 2002;61:311-8.
21. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400-11.
22. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
23. Ostergaard M, Stoltenberg M, Gideon P, et al. Effect of intraarticular osmic acid on synovial membrane volume and inflammation, determined by magnetic resonance imaging. Scand J Rheumatol 1995;24:5-12.
24. Kalden-Nemeth D, Grebmeier J, Antoni C, Manger B, Wolf F, Kalden JR. NMR monitoring of rheumatoid arthritis patients receiving anti-TNF-alpha monoclonal antibody therapy. Rheumatol Int 1997;16:249-55.
25. Konig H, Sieper J, Wolf KJ. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. Radiology 1990;176:473-7.
26. Yamato M, Tamai K, Yamaguchi T, Ohno W. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. J Comput Assist Tomogr 1993;17:781-5.
27. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA Trial. Arthritis Rheum 2003;48:35-45.
28. Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis threated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology Oxford 2004;43:712-8.
29. Lee J, Lee SK, Suh JS, Yoon M, Song JH, Lee CH. Magnetic resonance imaging of the wrist in defining remission of rheumatoid arthritis. J Rheumatol 1997;24:1303-8.
30. Geiler T, Kriegsmann J, Keyszer GM, Gay RE, Gay S. A new model for rheumatoid arthritis generated by engraftment of rheumatoid synovial tissue and normal human cartilage into SCID mice. Arthritis Rheum 1994;37:1664-71.
31. Zvaifler NJ, Firestein GS. Pannus and pannocytes. Alternative models of joint destruction in rheumatoid arthritis. Arthritis Rheum 1994;37:783-9.
32. Conaghan PG, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum 2003;48:64-71.