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Comparative Assessment of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis, by Dynamic Enhanced Magnetic Resonance Imaging

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Objective. **Ethical constraints on the conduct of placebo-controlled trials evaluating new therapies for serious chronic diseases, such as rheumatoid arthritis (RA), indicate the need for discerning methods to assess treatment effect in active-controlled clinical trials. Dynamic gadolinium-enhanced magnetic resonance imaging (DEMRI) is a sensitive technique for the detection of synovial inflammation in RA. Therefore, this investigation was undertaken to evaluate DEMRI as an efficacy assessment tool for differentiating treatment effect in a randomized, active-controlled trial comparing leflunomide and methotrexate.**

Methods. **Patients with active RA (n = 39) were randomized in a 2-center, prospective, double-blind clinical trial to receive either leflunomide (n = 18) or methotrexate (n = 21) therapy for 4 months. DEMRI scans were obtained at baseline and at 4 months, and the initial rate of enhancement (IRE) and the maximal signal intensity (SI) enhancement (ME) were calculated from the SI curves. Clinical improvement was assessed by conventional outcome measures.**

Results. **Thirty-four patients (17 treated with leflunomide and 17 with methotrexate) had usable baseline and end point DEMRI scans. Leflunomide treatment was associated with a significantly greater improvement in IRE compared with methotrexate treatment ($P < 0.05$). Average values of ME indicated reduction of inflammation with both leflunomide and methotrexate. The improvement in clinical signs and symptoms, as measured by traditional assessments, was comparable for both active treatments.**

Conclusion. **Results of this study validate the sensitivity of DEMRI in detecting inflammatory changes in active RA in response to treatment. Improvement in synovial inflammation as measured by IRE was significantly better with leflunomide than with methotrexate over 4 months of therapy.**

Rheumatoid arthritis (RA) is a chronic debilitating disease associated, in the active state, with early and permanent joint damage (1). Poor disease control, therefore, may result in long-term irreversible disability (2), raising questions about the ethical value of future placebo-controlled trials of new agents for the treatment of RA (2,3). The alternative is active-controlled trials that compare new therapies with current standards of care, possibly requiring new techniques of evaluating treatment efficacy, with greater sensitivity or resolution of treatment effect.

Magnetic resonance imaging (MRI) techniques have shown remarkable sensitivity for detecting changes in synovial inflammation (4). Synovitis is a characteristic feature of RA associated with the continued synovial inflammation that leads to structural damage, including the erosions and joint space narrowing detectable by plain film radiography (5). While a direct link between synovitis and bone damage is still controversial, recent data suggest that early bone changes, such as bone edema, rarely occur in the absence of synovitis (6).

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Radiographic assessment of disease progression is considered the "gold standard" for outcome measurement in RA clinical trials (5), is insensitive to early changes, and has a high "noise" ratio, making comparison between two active therapies problematic.

MRI offers distinct advantages over conventional radiography in its ability to image the soft tissues, including the synovial membrane and synovial fluid, as well as bone (4). In addition, contrast enhancement with gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) administered intravenously (IV) allows MRI to effectively measure inflammation (4). The technique of dynamic gadolinium-enhanced MRI (DEMRI) provides a quantitative assessment of inflammation based on analysis of changes in the signal intensity (SI) resulting from Gd-DTPA enhancement that are proportional to the Gd-DTPA concentration (7–10). DEMRI, combined with computer-assisted quantitative analysis, provides a measure of blood perfusion, capillary permeability, and extracellular volume, all of which reflect the inflammatory process of synovitis (11,12). The implementation of active treatment strategies for patients newly diagnosed as having RA may delay the progression of radiographically evident bone damage. Also, acknowledging that placebo-controlled trials of new therapeutic agents are not ethically feasible, an accurate assessment of synovial inflammation in response to treatment may prove to be a more valid measure of treatment efficacy, especially in early RA.

A number of traditional disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine (13,14), methotrexate (15), and ciclosporin A (16), all of which suppress the acute-phase response, have also been shown to delay the progression of cartilage and bone damage. Leflunomide, a new DMARD, has demonstrated efficacy in the treatment of RA, both clinically and in slowing radiographic progression (14,17,18). Leflunomide is a prodrug rapidly converted into the active metabolite A77 1726, which acts predominantly by inhibiting dihydroorotate dehydrogenase, an enzyme critical for the de novo biosynthesis of pyrimidine, thus prohibiting the clonal expansion of activated T cells (19).

In the present study, leflunomide and methotrexate were compared in patients with active RA, according to traditional clinical assessments and by their effect on synovial inflammation as assessed by DEMRI. The knee was chosen since it is the largest synovial joint in the body and therefore reflects most accurately the state of synovitis in a patient. An evaluation of synovial biopsy samples using immunohistochemical techniques that address changes in cytokine production was conducted concurrently and has previously been reported (20).

PATIENTS AND METHODS

Thirty-nine men and women ages ≥18 years, with active RA as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria (21), were prospectively randomized in a double-blind, parallel-design, clinical trial at two centers, comparing leflunomide treatment with methotrexate treatment. Active disease was defined as ≥6 swollen or tender joints, as well as by physician and patient global assessment of disease activity as moderate or worse. In addition, the inclusion criteria required at least 1 knee joint with active disease, defined by clinically detectable synovitis at that site. Low-dose prednisolone (<10 mg/day) and concomitant stable doses of nonsteroidal antiinflammatory drugs were allowed during the study period. No patient enrolled in the study had prior treatment with either leflunomide or methotrexate, and those receiving other DMARD therapy were required to stop treatment, followed by a washout period of 28 days, before starting study medication. Intraarticular corticosteroid injections were not allowed during the trial period.

Patients were randomly assigned to receive either leflunomide or methotrexate treatment in a 1:1 ratio. Patients randomized to receive leflunomide were given study medication with an initial loading dose of 100 mg/day for 3 days, followed by a maintenance dosage of 20 mg/day for the duration of the study. Patients assigned to the methotrexate group received an initial dose of 7.5 mg/week that was increased in a stepwise manner to 15 mg/week over 12 weeks.

Clinical assessment at baseline and after 4 months of treatment included tender and swollen joint counts (28-joint assessment), duration of morning stiffness in minutes, physician and patient global assessment of disease activity and patient pain assessment (each on a 0–100-mm visual analog scale [VAS]), Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, quantitative determination of rheumatoid factor (RF), and patient functional ability assessed by the modified Stanford Health Assessment Questionnaire (M-HAQ; 0–24 scale) (22). Overall response to treatment was determined by ACR criteria for clinical response (23).

Dynamic MRI scans. MRI examination of affected knees was performed on identical 1.5T Gyroscan ACS-NT MRI Scanners (Philips Medical Systems, Best, The Netherlands) equipped with a quadrature knee coil, using the same protocol at the two participating centers. The image matrix was 205 × 256 and the signal average was 1. Patients were positioned supine with the signal knee placed within the knee coil. Following an initial localizing scan, multiple coronal and axial T1-weighted images were obtained to provide anatomic landmarks in the suprapatellar pouch and tibiofemoral joint, which were used to define a reproducible patient position for the sequential DEMRI acquisition in the sagittal plane. This was perpendicular to the two planes, joining both the most posterior margins, localized axially, and the most inferior margins, localized coronally, of the femoral condyles.

The voxels selected for analysis included those with

maximal SI enhancement (ME) of at least 30% over baseline. A pilot group of 5 randomly selected data sets was used to select this threshold. For this particular sequence and the amount of injected Gd-DTPA, a 30% cutoff eliminates most of the muscle enhancement. This pilot set was also used to determine cutoff values for background noise and signal from large blood vessels. Conservative cutoff values were chosen in order to include all synovial voxels while accepting a certain degree of contamination from the background and blood vessels. These selection criteria were subsequently applied to all DEMRI data sets.

The quantitative measurements were derived from a dynamic T1-weighted gradient-echo imaging sequence (repetition time 30 msec, echo time 5.3 msec, flip angle 60°), which allowed the acquisition of 5 mm–thick images and 5-mm interspace temporal resolution of 8 seconds acquired over a period of 321 seconds. Administration of Gd-DTPA by IV bolus (0.1 ml/kg body weight), administered via a 21-gauge butterfly needle inserted into the antecubital fossa vein, was carried out 1 second after the first image acquisition of the series was commenced. The injection was performed over 15 seconds by the same radiographer to enable reproducible results.

A total of 40 dynamic images was acquired, each with an 8-second temporal resolution. Image analysis was performed using software developed in house (Medical Physics Department, University of Leeds) and Analyse Vw software (Mayo Clinics, New York, NY). Two measurements of synovial inflammation were obtained based on the DEMRI change in the sigmoidal SI curves following Gd-DTPA injection: the initial rate of enhancement (IRE) and the ME. As gadolinium traverses the synovium, it enhances the individual voxels that define the knee joint and constitute the MR image. The color-gated spectrum from minimum enhancement to maximal enhancement (red to yellow) determined at each point in the scanning sequence allows the determination of the rate of gadolinium enhancement. A typical SI change over time derived from individual voxels is presented in Figure 1.

The IRE corresponds to the steepest gradient on the normalized SI curve, expressed as a relative change of the SI rise compared with precontrast enhancement (Figure 1). This gradient is measured over the 40-second window (at 5 successive time points) and is expressed in seconds^{-1}, or s^{-1} (IRE gives percent SI change per second). The ME corresponds to the plateau phase of the SI curve following the rapid sigmoidal rise. The plateau persists as the gadolinium establishes pharmacokinetic equilibrium toward the end of the scanning sequence. ME is expressed as a relative change or elevation of the plateau portion of the sigmoidal SI curve compared with pre–gadolinium enhancement (ME-1 gives percent SI change over baseline). Pooled histograms were obtained for the entire series of dynamic images and normalized with respect to the baseline, precontrast SI. The image analysis is fully automated and as such is 100% reproducible.

Statistical analysis. Statistical analysis of the clinical outcome assessments (continuous variables) was based on mean changes from baseline to end point in the intent-to-treat population, and comparison among treatments was by analysis of covariance. Statistical comparison of those meeting the ACR 20% improvement criteria (23) (ACR 20% responders) was by Fisher's exact test.

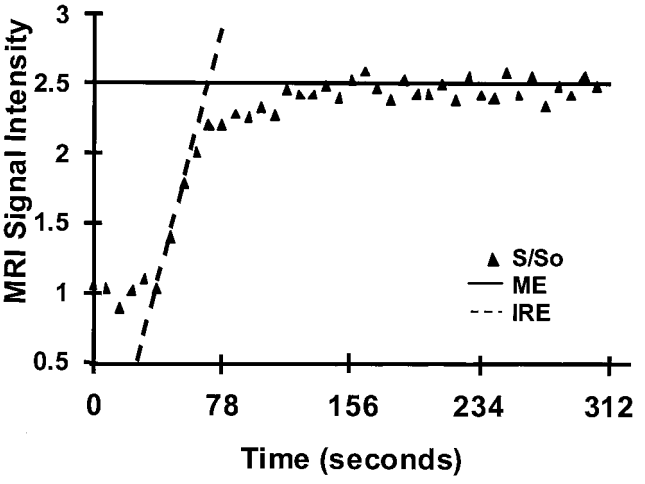

Figure 1. Characteristic signal intensity curve showing the temporal increase in tissue enhancement following infusion of gadolinium. The dashed line corresponds to the slope or initial rate of enhancement (IRE). The maximal signal intensity enhancement (ME) corresponds to the plateau region of the plot after equilibrium of contrast enhancement is established. S represents the signal intensity in a voxel at any given time. S_0 represents the baseline normalized signal intensity. S/S_0 denotes the normalized signal intensity. MRI = magnetic resonance imaging. See Patients and Methods for explanation of calculation of IRE and ME.

Similarly, statistical analysis of the DEMRI parameters IRE and ME was based on mean changes from baseline to end point in the intent-to-treat population. Comparison between treatment groups was by the Mann-Whitney test. *P* values less than 0.05 were considered significant.

RESULTS

Patient baseline characteristics. Thirty-nine RA patients were included in the study (18 treated with leflunomide and 21 treated with methotrexate). Of these, a total of 34 patients had paired DEMRI scans (17 each in the leflunomide- and methotrexate-treated groups). One patient receiving methotrexate died of acute myocardial infarction (unrelated to study medication) before the 4-month data could be collected. The remaining methotrexate- and leflunomide-treated patients underwent both scan acquisitions, but due to technical difficulties, the baseline data for 4 patients were lost.

The leflunomide-treated patients included 9 men and 9 women with a mean age of 60 years (range 36–77 years), a mean disease duration of 3.25 years (range 2 months–12 years), and a mean of 1.1 previous DMARD treatment regimens (range 0–3). The methotrexate-treated patients included 9 men and 12 women with a

Table 1. Summary of changes from baseline in clinical outcome assessments after 4 months of treatment*

Parameter	Treatment		
	Leflunomide (n = 18)	Methotrexate (n = 21)	*P*
Tender joint count†	−9.9 ± 9.0	−5.9 ± 6.4	0.1738
Swollen joint count†	−4.6 ± 7.1	−4.6 ± 7.0	0.9628
Patient global assessment‡	−0.9 ± 0.9	−1.0 ± 1.1	0.9604
Physician global assessment‡	−0.9 ± 0.8	−0.8 ± 1.0	0.5293
Morning stiffness, minutes	−120 ± 318	−76.2 ± 165	0.9218
Pain intensity‡	−16.2 ± 25.8	−10.1 ± 17.7	0.4072
M-HAQ score, 0–24	−6.44 ± 8.89	−4.1 ± 7.82	0.3042
ESR, mm/hour	−3.3 ± 18.3	−11.6 ± 22.1	0.2445
CRP level, mg/dl	−17.1 ± 33.8	−14.1 ± 27.0	0.6464
RF, units/ml	−65.7 ± 104.6	−40.3 ± 105.1	0.8477
ACR 20% responders, %	50	47.6	1.000

* Except where otherwise indicated, values are the mean ± SD. M-HAQ = modified Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACR = American College of Rheumatology.
† Twenty-eight–joint assessment.
‡ 0–100-mm visual analog scale (VAS).

mean age of 61 years (range 27–77 years), a mean disease duration of 6 years (range 3 months–26 years), and a mean of 2.1 previous DMARD treatment regimens (range 0–4). One patient in the leflunomide group and 1 patient in the methotrexate group took prednisolone (5 mg/day).

Clinical efficacy. Comparable changes from baseline in outcome measures of efficacy (Table 1) were observed in the leflunomide- and methotrexate-treated patients after 4 months of therapy. Nine of 18 patients (50%) in the leflunomide group and 10 of 21 patients (48%) in the methotrexate group met the ACR 20% response criteria. Overall, there was no statistically significant difference between treatment groups, although leflunomide-treated patients exhibited greater improvement in tender joint count, duration of morning stiffness, pain intensity (on a VAS), M-HAQ score, CRP level, and RF titer (Table 1). Methotrexate-treated patients showed greater improvement in ESR compared with baseline (Table 1).

Dynamic MRI. A representative selection of 5 DEMRI sagittal T1-weighted sequence scans acquired post–Gd-DPTA injection is shown in Figure 2. SI curves were obtained over 321 seconds for sagittal slices through the knee and normalized with respect to baseline (precontrast). Figure 3 shows pooled histograms of the IRE for 17 scans pre- and posttreatment with either leflunomide or methotrexate. In the leflunomide-treated patients, the average IRE represented by the pooled histogram shows that the curve shifted left, reflecting an overall improvement in these patients. Conversely, the methotrexate IRE curve exhibits a slight right shift in the tail portion of the posttreatment curve, indicating a slight deterioration in IRE for the group.

A quantitative comparison of averages of the DEMRI parameters of IRE and ME for the leflunomide- and methotrexate-treated groups is summarized in Table 2. Change in ME with respect to baseline following treatment was observed in leflunomide-treated patients (2.38%) and methotrexate-treated patients (0.38%). Statistical comparison of the mean change in ME for the leflunomide- and methotrexate-treated patients showed no significant difference between therapies, although the improvement in ME for leflunomide-treated patients was 6-fold greater. Comparison of the changes in IRE

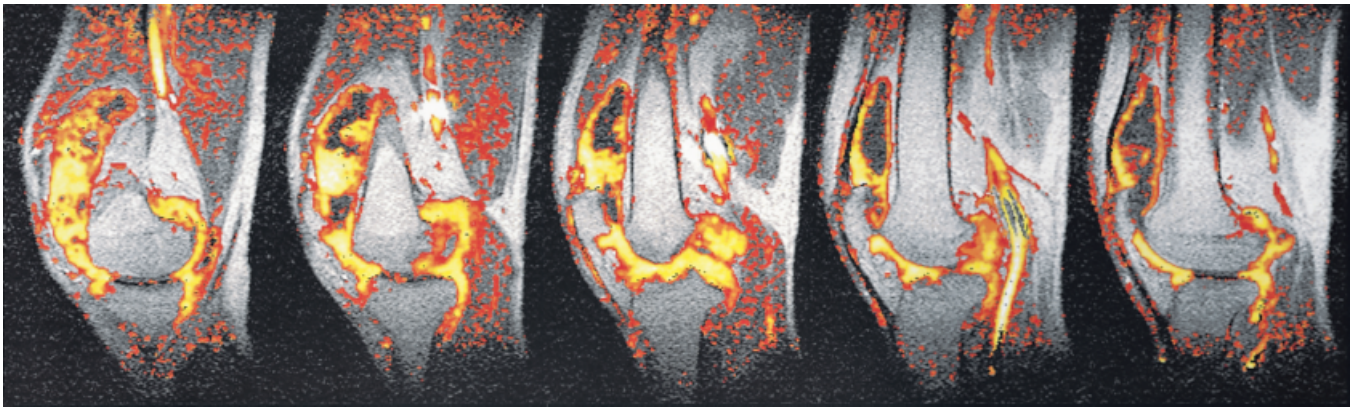

Figure 2. Five characteristic dynamic gadolinium-enhanced magnetic resonance imaging sagittal scans across synovial space following gadolinium enhancement.

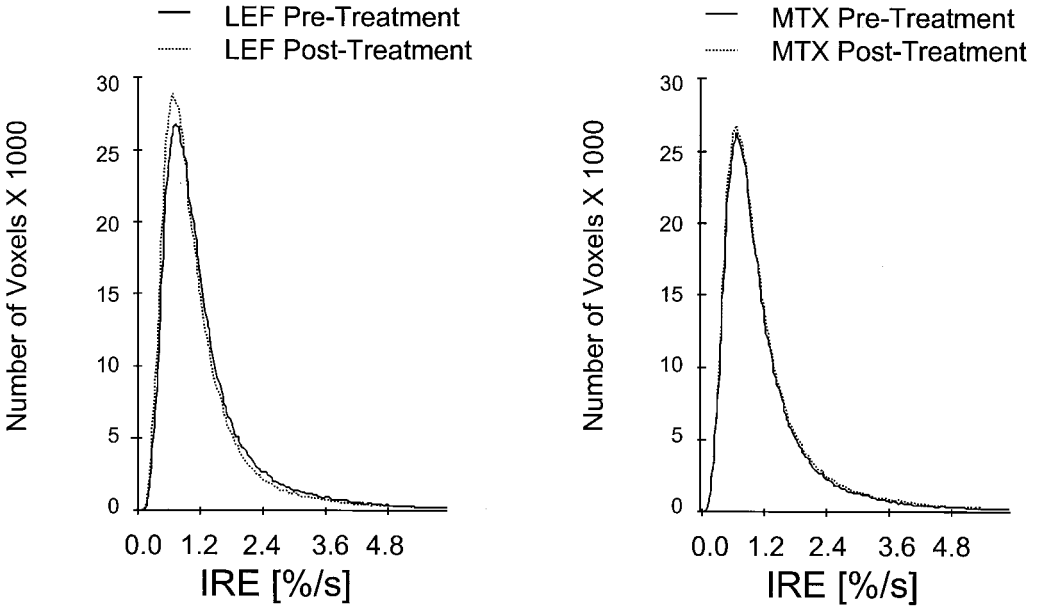

Figure 3. Pooled initial rate of enhancement (IRE) histograms for patients in the leflunomide (LEF)– and methotrexate (MTX)–treated groups (n = 17 in each group), at baseline and after 4 months of therapy. The curve approximating leflunomide treatment for 4 months is shifted to the left, showing an improvement in the IRE and in synovial inflammation. The histogram of IRE values for methotrexate-treated patients shows virtually no change other than a slight shift to the right of the tail portion of the curve. s = seconds; %/s = percent signal intensity change per second. See Patients and Methods for explanation of calculation of IRE.

between treatment groups (Table 2 and Figure 4) indicated a significantly greater improvement in IRE for leflunomide-treated patients compared with methotrexate-treated patients (10.48% versus −2.61%; $P < 0.05$). For leflunomide, the difference between baseline and posttreatment absolute values for IRE was also significant ($P < 0.05$).

DISCUSSION

The objective of this study was to evaluate the sensitivity of DEMRI in detecting treatment differences in a randomized, active-controlled trial comparing leflunomide and methotrexate therapies for active RA. During the 4-month treatment interval with 39 patients enrolled, both DMARDs showed generally comparable treatment effects in terms of the ACR 20% response criteria, representing a composite efficacy assessment.

Although leflunomide treatment resulted in greater improvement in tender joint counts and patient self-assessed health-related quality of life (M-HAQ score), as well as in decreased pain, these improvements were not statistically significant compared with those resulting from methotrexate treatment. DEMRI mea-

Table 2. Quantitative summary of ME and IRE*

	ME		IRE	
	Leflunomide	Methotrexate	Leflunomide	Methotrexate
Baseline	1.57 ± 0.121	1.55 ± 0.101	0.0124 ± 0.0022	0.0115 ± 0.0022
Four months posttreatment	1.53 ± 0.095	1.54 ± 0.094	0.0111 ± 0.0023†	0.0117 ± 0.0023
Change from baseline	0.0373 ± 0.0582	0.0059 ± 0.0515	0.0013 ± 0.0017‡	−0.0003 ± 0.0021

* Values are the mean ± SD. See Patients and Methods for explanation of calculation of maximal signal intensity enhancement (ME) and initial rate of enhancement (IRE).
† $P < 0.05$ versus baseline leflunomide IRE value.
‡ $P < 0.05$ versus change from baseline in methotrexate IRE value.

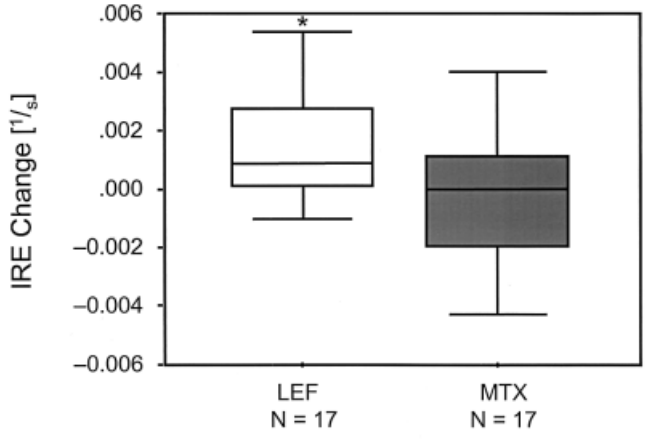

Figure 4. Plot of the average change in IRE in response to 4 months of therapy with leflunomide or methotrexate. Leflunomide treatment resulted in a significantly greater improvement in IRE (* = $P < 0.05$ versus methotrexate treatment). See Patients and Methods for explanation of calculation of IRE. See Figure 3 for definitions.

surement showed no difference in ME, although there was a 6-fold greater improvement in the leflunomide-treated group. However, in this small, randomized, active-controlled trial, DEMRI determination of synovial inflammation measured by IRE showed clear statistical differences between active treatments. Leflunomide treatment resulted in a significantly greater improvement in IRE ($P < 0.05$) compared with methotrexate treatment, probably as a consequence of the loading dose. This highlights the sensitivity achieved from resolving differences in effect between two effective therapies for RA.

There are two dominant MRI methods of evaluating synovial inflammation. The first is based on measurement of synovial membrane volume, while the second is based on the rate of synovial enhancement following the injection of Gd-DTPA. The measurement of synovial volume has been correlated with clinical signs of inflammation and with an overall histologic score incorporating an assessment of infiltrating leukocytes and other signs of inflammation (8). Another study showed a correlation between treatment-related changes in metabolic activity (as measured by fludeoxyglucose–positron emission tomography) and synovial volume (as measured by MRI) (24).

The second method is based on the experimental observation that the rate of synovial enhancement following Gd-DPTA injection is proportional to the degree of synovial inflammation (4,11,12,25). The "E-ratio," defined as the rate of increased synovial enhancement after Gd-DPTA injection divided by the baseline SI of the synovium, was first proposed as a measure of synovitis by Tamai et al (11). This investigation showed that the E-ratio correlated with histologic signs of inflammation. Gaffney et al (12) later revised this analysis, proposing that the initial rate of synovial enhancement was a more absolute measure of synovitis than the steady-state E-ratio. The methods employed in this investigation parallel the technique developed by Gaffney et al (12).

Recently, Kraan et al (20) reported the results of a study using paired synovial biopsy samples obtained from the same patient population and during the same treatment period as those of the current study. These samples were compared at baseline and after 4 months of therapy, via immunohistochemical techniques. They were analyzed for the presence of inflammatory cells and the expression of adhesion molecules, and for the expression of inflammatory as well as antiinflammatory cytokines. Kraan et al's investigation showed that leflunomide effectively reduced macrophage migration and numbers of adhesion molecules and also suppressed inflammatory cytokines more than antiinflammatory cytokines. The early reduction of synovial inflammation, as shown by the reduced IRE and numbers of immunologic markers (20), may offer a physiologic explanation for the early improvement in RA signs and symptoms with leflunomide treatment observed in clinical trials (26).

An alternative joint to image, rather than the knee, could be the wrist, where the synovial compartments are less distensible and consequently allow less fluid to accumulate. Thus, the wrist could have an advantage for the analysis of synovial volume, and would allow a more precise matching of individual slices for analysis of perfusion changes in DEMRI. In the current study, a 21-gauge butterfly needle was used for the manual injection of gadolinium; using a larger catheter with a power injector, a tighter bolus profile could have been achieved. However, because of the shortened time of delivering contrast to the synovium, and the consequent rapid enhancement, a shorter interval between same-slice images would be required.

The inevitable formation of permanent structural damage in poorly controlled active RA clearly raises a question about the ethical conduct of placebo-controlled trials; therefore, active-controlled trials offer the most viable methodology for assessing the efficacy of new therapeutic agents in RA. The comparison of active treatments will in turn require more sensitive outcome assessments in order to discern smaller differences between such therapies. The IRE has been shown by this

investigation to be a sensitive tool for assessing the treatment response of synovial inflammation in RA. Over the 4-month study period, leflunomide, in comparison with methotrexate, significantly reduced synovial inflammation as measured by IRE. The early treatment effect observed in patients receiving leflunomide therapy may be accounted for by the loading-dose regimen. It is important to stress that this finding does not allow for conclusions to be drawn about the relative clinical efficacy of the two drugs.

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