# Effects of Double Filtration Plasmapheresis, Leflunomide, and Methotrexate on Inflammatory Changes Found Through Magnetic Resonance Imaging in Early Rheumatoid Arthritis

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*ABSTRACT.* ***Objective.*** To evaluate the effects of double filtration plasmapheresis (DFPP) in combination with leflunomide and methotrexate (MTX) on magnetic resonance imaging (MRI)-detected inflammatory changes (synovitis and bone edema) in patients with early rheumatoid arthritis (RA) with high disease activity.

***Methods.*** Sixty RA patients with highly active disease of 6 months' to 3 years' duration were randomized to receive DFPP in combination with leflunomide and MTX (DFPP group), and leflunomide plus MTX (no-DFPP group). The primary endpoint was the improvement in MRI-detected synovitis from baseline over 6 months. Secondary endpoint variables included DAS28 remission and American College of Rheumatology (ACR) criteria responses for 6 consecutive months.

***Results.*** The study achieved significant improvement in synovitis and bone edema, with significantly lower synovitis and bone edema scores in the DFPP group compared with the no-DFPP group ($p < 0.001$). Synovitis scores in 48.39% of patients (15/31) in the DFPP group were 0 at Month 6. Bone edema scores in 32.26% of patients (10/31) in the DFPP group were 0 at Month 6. We observed significantly greater ACR20, ACR50, ACR70, and ACR90 responses and DAS28 remission rates in the DFPP group than in the no-DFPP group ($p < 0.001$). Sustained DAS28 remission and ACR90 response for at least 6 months were achieved in 100% of patients receiving DFPP therapy.

***Conclusion.*** The combination of DFPP and disease-modifying antirheumatic drugs (DMARD) was superior to DMARD alone for reducing MRI-detected signs of synovitis and bone edema in patients with early highly active RA. DFPP therapy enabled rapid and more complete suppression of inflammation in patients with highly active RA. Nearly half the patients (48.39%) who had received DFPP therapy achieved both clinical remission and imaging remission, a state characterized as true remission. (First Release April 15 2012; J Rheumatol 2012;39:1171–8; doi:10.3899/jrheum.110978)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS
MAGNETIC RESONANCE IMAGING
DOUBLE FILTRATION PLASMAPHERESIS
SYNOVITIS

Rheumatoid arthritis (RA) is a chronic disease with a poor prognosis in which synovitis induces progressive destruction of bones and joints, which leads to marked impairment of the activities of daily living. More timely and effective therapy for RA has contributed to increasing rates of clinical remission. However, progression of structural damage may still occur in patients who have satisfied remission criteria[1,2,3]. Most patients with RA who satisfied the remission criteria with normal findings on clinical and laboratory studies had synovitis detected on imaging, which may explain the observed discrepancy between disease activity and outcome in RA[4,5]. The remission state should represent an absence of inflammation, synonymous with no clinical symptoms or signs, and should result in optimal structural, functional, and quality of life outcomes.

We previously studied a cohort of patients with active RA who were treated with double filtration plasmapheresis (DFPP) plus disease-modifying antirheumatic drugs (DMARD), and who had sustained American College of Rheumatology 20% (ACR20), ACR50, and ACR70 responses of 100%, 92.9%, and 81.0%, respectively, and

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Health Assessment Questionnaire (HAQ) improvement for 22 months[6]. These results suggested a consistently good outcome.

In a cohort of patients with highly active RA we performed an evaluation by magnetic resonance imaging (MRI) of treatment with DFPP in combination with DMARD. Our aim was to investigate the response to DFPP therapy of imaging-detected synovitis in highly active RA.

## MATERIALS AND METHODS

*Patients and study protocol*. Patients who were enrolled in the study were inpatients between March 20, 2008, and May 10, 2010. Patients eligible for our study were at least 18 years old but not older than 65 years and met the 1987 revised criteria of the ACR (formerly, the American Rheumatism Association) for the classification of RA[7], with a disease duration of 6 months to 3 years. Patients had to have active disease with ≥ 8 swollen joints, ≥ 10 tender joints, and erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) concentration ≥ 20 mg/l. Patients had to achieve a 28-joint Disease Activity Score (DAS28) > 5.1. Patients who were receiving treatment with corticosteroid hormones or biological agents were excluded.

This was a prospective, randomized, controlled study. Sixty patients were randomly assigned by computer, 31 to the DFPP group and 29 to the no-DFPP group. All patients received leflunomide 10 mg, 2 times daily, plus methotrexate (MTX) 15 mg orally once weekly. DFPP was performed in the DFPP group once every 1–2 weeks for 3 sessions. Patients in the no-DFPP group did not receive sham DFPP. For longterm treatment, patients continued to take the same doses of medications.

Our study was approved by the Ethics Committee of Traditional Chinese Medicine-Western Medicine Hospital of Cangzhou, Hebei. Written informed consent was obtained from all subjects.

*Double filtration plasmapheresis*. DFPP was conducted by application of a double-filtration technique with a membrane plasmapheresis apparatus (Plasauto iQ, Asahi Medical Co., Tokyo, Japan). EC-30W and OP-08W were used as a plasma fractionator and separator. The volume of filtered plasma was 4% of the patient's weight (kg). About 10% of the filtered plasma was discarded, with concomitant isovolumetric hydroxyethyl-starch supplementation. Fraxiparine was used as anticoagulant. Vascular access was with a double-lumen catheter in a central vein, or with arterial and venous punctures. Blood extraction rate was 100 ml/min.

*Study endpoints*. The primary endpoint was the improvement in MRI-detected synovitis from baseline over 6 months. Secondary endpoint variables included clinical remission in DAS28 and ACR20, ACR50, ACR70, and ACR90 responses for 6 consecutive months.

*Study assessments*. Joint examinations were performed by an independent assessor who had no knowledge of the patient's treatment assignment. Other assessments included patient's self-evaluation of pain on a visual analog scale (VAS; range 0–10 cm), patient's and evaluator's global disease assessment, and patient's self-evaluation of functional status using the Disability Index of the HAQ (HAQ-DI). We used 28 joints for joint assessments. Blood samples were obtained for measuring ESR, serum CRP, rheumatoid factor (RF), and anticitrullinated protein antibody (ACPA) levels, including anticyclic citrullinated peptide antibody, antiperinuclear factor, and antikeratin antibody, as well as for determining the presence of antinuclear antibodies and anti-dsDNA antibodies. MRI of the right wrist was obtained at baseline, 1 month, and 6 months. Evaluations were done once a month in followup for 12 months.

*MRI assessment*. MR imaging of the right wrist was performed with a 1.5-T whole-body system (Magnetom Avanto, Siemens, Germany) using a small circular flexible coil. Patients were positioned in the "superman" position (prone with the arm extended above the head). A hand coil was used to minimize movement and standardize position. The imaging protocol consisted of T1-weighted and gadolinium-enhanced (15 ml gadopentetate dimeglumine) T1-weighted spin-echo axial and coronal images (SE-T1WI), fat-suppressed T2-weighted and fat-suppressed gadolinium-enhanced T1-weighted spin-echo axial and coronal images (TSE-T2WI+FS and SE-T1WI), and a fat-suppressed proton density weighted coronal sequence (PD+FS). The slice thickness of all MR images was 3 mm, and the slice distance was 0.6 mm in the axial plane and 0.3 mm in the coronal plane.

The scoring of synovitis and bone edema of the right wrist joint was done according to the Outcome Measures in Rheumatology Clinical Trials group RA-MRI Scoring system[8] by a single experienced reader who was blinded to all other clinical findings. Synovitis was scored on a 0–3 scale at 3 different locations: radioulnar joint, radiocarpal joint, and intercarpal-carpometacarpal joints (total maximum score = 9). A score of 0 is normal, with no enhancement or enhancement up to the thickness of normal synovium, while scores from 1 to 3 (mild, moderate, severe, respectively) refer to increments of one-third of the presumed maximum volume of enhancing tissue in the synovial compartment. The carpal bones, distal radius, distal ulna, and metacarpal base (15 locations) were scored separately for bone edema (scored 0–3 based on the volume of edema, where 1: 1%–33%; 2: 34%–66%; and 3: 67%–100%). The maximum score for bone edema was 45. The metacarpophalangeal (MCP) joints were not evaluated, as they were not completely covered in the image sets.

*Clinical remission by DAS28 score*. Clinical remission was assessed by DAS28, a validated composite index with measures of tender joint count and swollen joint count; the patient's general health, measured on 100 mm VAS; and serum levels of acute-phase reactants (ESR and CRP). Clinical remission was defined as DAS28 < 2.6[9]. Scoring of DAS28 was done with use of the DAS Calculator[10].

*ACR response*. The ACR20 was defined in a manner analogous to the ACR definition of improvement[11,12,13]. Patients were considered to have achieved an ACR20 response if the following 3 criteria were met: (1) ≥ 20% improvement from baseline in tender joint count; (2) ≥ 20% improvement from baseline in swollen joint count; and (3) ≥ 20% improvement from baseline in at least 3 of the following 5 measures: patient assessment of pain on VAS (range 0–10 cm), patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of physical function (HAQ), and acute-phase reactant values (CRP, ESR). ACR50, ACR70, and ACR90 responses according to ACR criteria were assessed in a similar manner.

*Physical function assessment*. Arthritis-related functional disability and health-related quality of life were measured using the HAQ, a validated self-administered form that assesses functional ability and quality of life in a variety of areas; most rheumatologists in China use a HAQ of 9 questions, including abilities to dress, arise, eat, walk, maintain personal hygiene, reach, grip, shop, and perform sexual behavior[14], on a scale ranging from 0 (no difficulty) to 3 (unable to perform the activity).

*Adverse events*. Patients were monitored for occurrence of adverse events throughout and after the DFPP sessions.

*Statistical analysis*. Analysis was done in the per-protocol sample. This analysis set was characterized as patients having no missing values for the primary efficacy variables and minor protocol deviations only. T test or Mann-Whitney U test was used for continuous variables and chi-squared test or Fisher's exact test for binary variables. The Statistical Package for the Social Sciences version 14.0 (SPSS, Chicago, IL, USA) was used for all analyses. P values < 0.05 were considered statistically significant.

## RESULTS

*Patient characteristics*. Sixty patients were randomized to receive study therapy. Characteristics of the study patients with RA were similar between the 2 groups, with mean disease duration of 15.65 ± SD 11.10 months for the DFPP group and 15.35 ± 10.87 months for the no-DFPP group. The measures of joint counts, ESR, CRP, HAQ, and DAS28

indicated that study patients had a high level of disease activity. All patients were taking 1–2 nonsteroidal antiinflammatory drugs and 16.67% (10/60) of patients were taking 1–2 DMARD at baseline. Seventy-five percent (45/60) of patients had previously received corticosteroid hormones 1 to 6 months prior to baseline as permitted in the protocol design. Similar percentages of patients in each group were receiving treatment with DMARD (Table 1).

*Efficacy. MRI findings*. Our study achieved a significant reduction in synovitis compared with baseline (Figure 1), with a reduction of 7 in the median synovitis score from baseline to Month 6 in the DFPP group, and 0 in the median synovitis score from baseline to Month 6 for the no-DFPP group ($p < 0.001$). Bone edema was significantly improved (Figure 1), with a reduction of 6 in the median bone edema score from baseline to Month 6 in the DFPP group compared with an increase of 1 in the median bone edema score from baseline to Month 6 for the no-DFPP group ($p < 0.001$; Table 2, Figure 2). Synovitis scores in 48.39% (15/31) of patients in the DFPP group were 0 at Month 6 (Figure 1). Bone edema scores in 32.26% (10/31) of patients in the DFPP group were 0 at Month 6. Both synovitis scores and bone edema scores in 25.81% (8/31) of patients in the DFPP group were 0 at Month 6.

*ACR response*. ACR20, ACR50, ACR70, and ACR90 responses for 6 consecutive months were achieved in 100%, 100%, 100%, and 100%, respectively, of patients in the DFPP group, compared with 37.93%, 20.69%, 10.34%, and 0% of patients in the no-DFPP group ($p < 0.001$). Similar statistically significant patterns were observed for ACR20, ACR50, ACR70, and ACR90 responses at Month 1, Month 3, and Month 6. Following 1 month of treatment, ACR70 and ACR90 responses had been achieved in 100% and 41.94% of patients in the DFPP group. At Month 3 and Month 6, ACR70 and ACR90 responses had been achieved in 100% and 100% of patients in the DFPP group (Table 3). Patients achieving ACR70 and ACR90 responses had no swollen joints and tender joints at Month 3 and Month 6 in the DFPP group. Patients achieving ACR70 and ACR90 responses for 6 consecutive months had no swollen and tender joints, and no increase in CRP and ESR in the DFPP group.

*Table 1*. Baseline patient characteristics.

| Characteristic | DFPP Group, n = 31 | No-DFPP Group, n = 29 |
|---|---|---|
| Age, mean ± SD, yrs | 50.55 ± 9.16 | 51.31 ± 7.79 |
| Women, n (%) | 25 (80.65) | 24 (82.76) |
| Duration of disease, mean ± SD, mo | 15.65 ± 11.10 | 15.35 ± 10.87 |
| Previously took corticosteroids, n (%) | 23 (74.19) | 22 (75.86) |
| Taking DMARD, n (%) | 5 (16.13) | 5 (17.24) |
| Taking NSAID, n (%) | 31 (100) | 29 (100) |
| Tender joint count, mean ± SD | 19.06 ± 5.81 | 18.96 ± 5.57 |
| Swollen joint count, mean ± SD | 15.52 ± 6.41 | 15.19 ± 5.59 |
| HAQ score, mean ± SD | 2.10 ± 0.46 | 2.09 ± 0.51 |
| DAS28 score, mean ± SD | 7.77 ± 0.89 | 7.74 ± 0.86 |
| ESR, mean ± SD, mm/h | 92.55 ± 24.60 | 92.50 ± 24.70 |
| CRP level, mean ± SD, mg/l | 78.93 ± 43.11 | 78.35 ± 38.91 |
| RF level, mean ± SD, IU/ml | 1235.16 ± 2767.29 | 1246.35 ± 1748.54 |
| MRI synovitis score, mean ± SD | 8.52 ± 0.72 | 8.45 ± 0.69 |
| Bone edema score, mean ± SD | 12.52 ± 9.26 | 11.93 ± 5.87 |

DFPP: double filtration plasmapheresis; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MRI: magnetic resonance imaging; RF: rheumatoid factor.

*Clinical remission in DAS28 scores*. Clinical remission (defined as DAS28 < 2.6[9]) for 6 consecutive months was achieved in 100% of patients in the DFPP group, compared with 6.90% of patients in the no-DFPP group ($p < 0.001$). Similar statistically significant patterns were observed for clinical remission at Month 1, Month 3, and Month 6. Clinical remissions were achieved in 54.84%, 100%, and 100%, respectively, of patients in the DFPP group at Month 1, Month 3 and Month 6 (Table 3). Patients in clinical remission had no swollen joints and tender joints at Month 3 and Month 6 in the DFPP group. Patients in clinical remission for 6 consecutive months had no swollen joints and tender joints, and no increase in CRP and ESR in the DFPP group.

*Improvement in physical function (HAQ)*. Patients in the DFPP group had significantly greater improvement in HAQ score at Month 1, Month 3, and Month 6 (0, 0, and 0, respectively), compared with patients in the no-DFPP group (2.07 ± 0.53, 2.04 ± 0.57, and 1.79 ± 0.87, respectively) at Month 1, Month 3, and Month 6 ($p < 0.001$).

*Characteristics of autoantibodies*. Levels of RF were significantly lower in patients who received DFPP therapy at Month 1 and Month 6 (132.48 ± 231.16 and 116.14 ± 240.75 IU/ml, respectively) compared with baseline (1235.16 ± 2767.29 IU/ml; $p < 0.001$), and compared with those patients who received DMARD therapy at Month 1 and Month 6 (1245.29 ± 1697.19 and 1237.59 ± 1682.96 IU/ml; $p < 0.001$). The rates of ACPA-positivity were significantly lower in the patients who received DFPP therapy at Month 1 and Month 6 (29% and 26%, respectively) compared with baseline (87%; $p < 0.001$), and compared with those patients who received DMARD therapy at Month 1 and Month 6 (86% and 86%; $p < 0.001$).

*Adverse events*. Three of 31 patients felt mild weakness after DFPP, which resolved within 20 hours. There was no evidence of bleeding, allergic reaction, dizziness, hypotension, or arrhythmias with DFPP.

## DISCUSSION

This randomized, controlled exploratory study evaluated a remission-induction approach using double filtration plasmapheresis in combination with leflunomide plus MTX

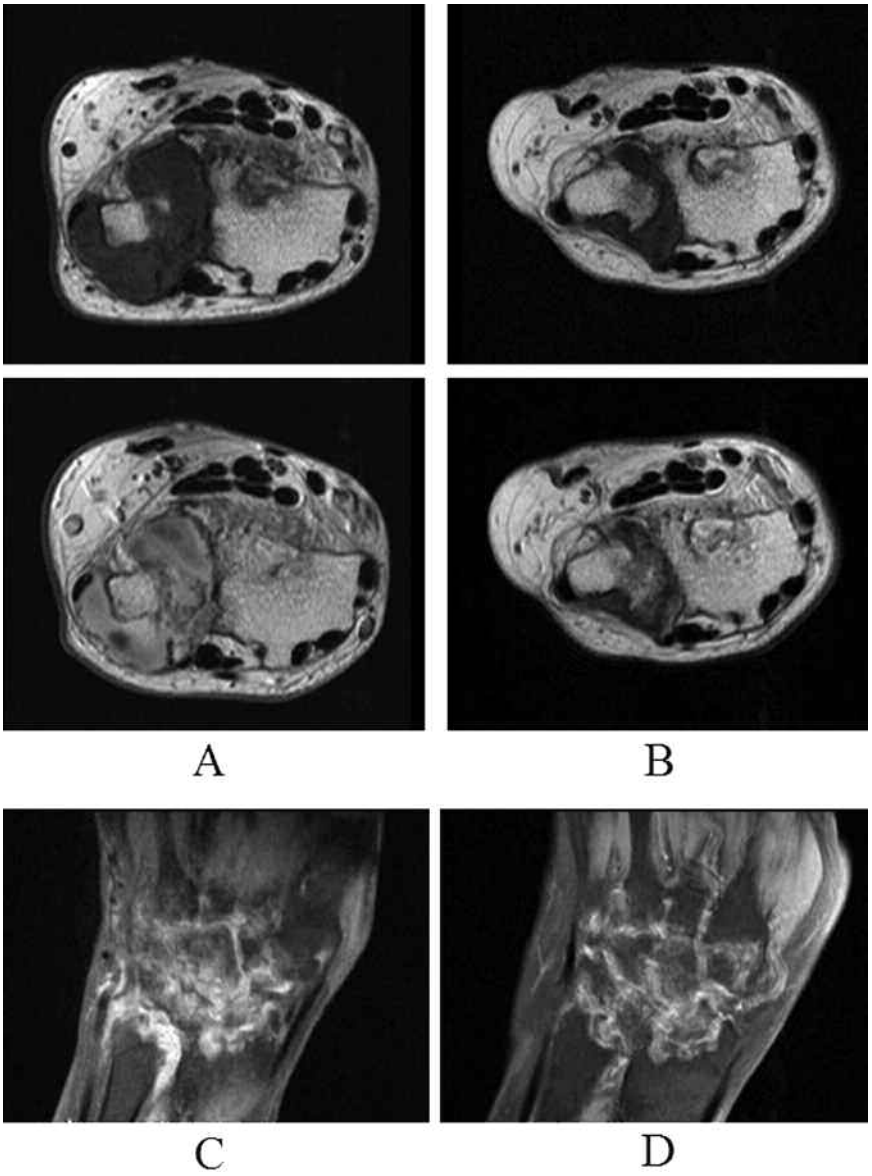


*Figure 1*. A. Baseline axial T1-weighted images pre- and post-intravenous contrast, showing grade 3 synovitis in the distal radioulnar joint. B. Corresponding 6-month images, showing grade 0 synovitis. C. Baseline coronal fat-suppressed proton density-weighted MR images, showing severe bone edema in the carpal bones. D. Corresponding images at 6 months, showing significant improvement of bone edema changes in the carpal bones.

*Table 2*. Differences in MRI synovitis and bone edema scores between DFPP group and no-DFPP group.

| | Score Change from Baseline | | | |
|---|---|---|---|---|
| | Synovitis | | Edema | |
| | Month 1 | Month 6 | Month 1 | Month 6 |
| DFPP group, n = 31, median (minimum, maximum) | 0 (–1, 0) | –7 (–9, –3) | 0 (–2, 1) | –6 (–24, –1) |
| No-DFPP group, n = 29, median (minimum, maximum) | 0 (0, 0) | 0 (–1, 2) | 0 (0, 0) | 1 (–2, 11) |
| p | 0.013 | 0.000 | 0.179 | 0.000 |

MRI: magnetic resonance imaging; DFPP: double filtration plasmapheresis.

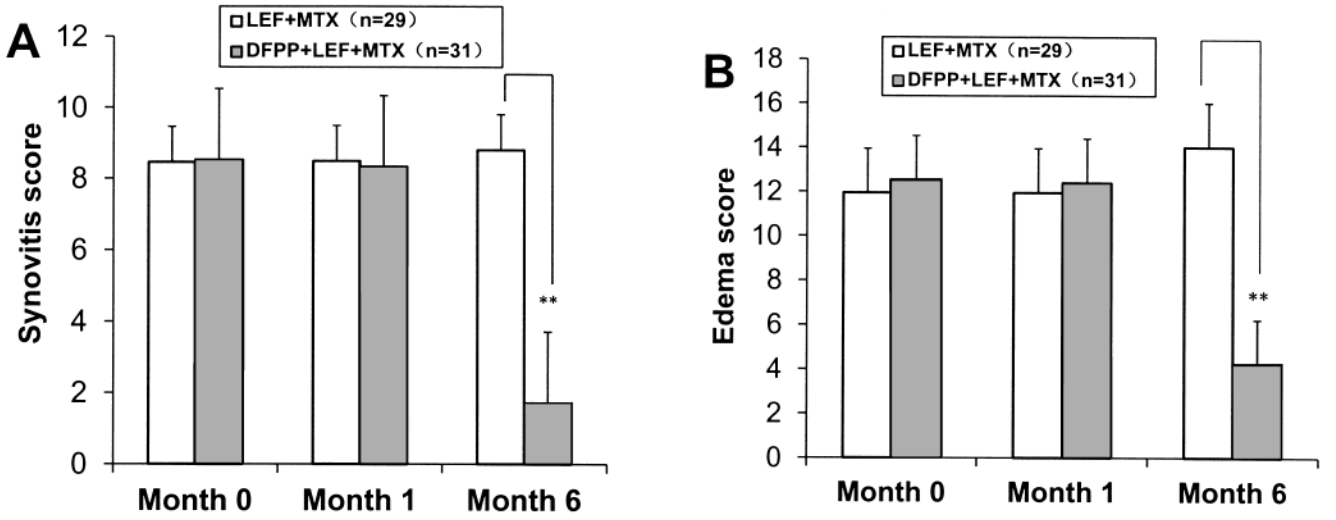


*Figure 2*. Progression over time of MRI-derived scores for synovitis (A) and edema (B) in patients treated with double filtration plasmapheresis (DFPP) in combination with leflunomide (LEF) and methotrexate (MTX), or LEF plus MTX. ** Significantly lower synovitis score or edema score in patients treated with DFPP in combination with LEF and MTX than patients treated with LEF and MTX only; $p < 0.001$.

*Table 3*. ACR20, ACR50, ACR70, and ACR90 response and DAS28 remission rates (%) at different timepoints in 2 study groups.

| | DFPP + LEF + MTX, n = 31 | | | | LEF + MTX, n = 29 | | | |
|---|---|---|---|---|---|---|---|---|
| | Month 1 | Month 3 | Month 6 | 6 Consecutive Months | Month 1 | Month 3 | Month 6 | 6 Consecutive Months |
| ACR20 | 100 | 100 | 100 | 100 | 3.45 | 20.69 | 41.38 | 37.93 |
| ACR50 | 100 | 100 | 100 | 100 | 0 | 10.34 | 24.14 | 20.69 |
| ACR70 | 100 | 100 | 100 | 100 | 0 | 0 | 13.79 | 10.34 |
| ACR90 | 41.94 | 100 | 100 | 100 | 0 | 0 | 6.90 | 0 |
| DAS28 | 54.84 | 100 | 100 | 100 | 0 | 0 | 10.34 | 6.90 |

ACR20: American College of Rheumatology 20% response; DAS28: Disease Activity Score in 28 joints; DFPP: double filtration plasmapheresis; LEF: leflunomide; MTX: methotrexate. $p < 0.001$, DFPP + LEF + MTX versus LEF + MTX.

compared with only leflunomide plus MTX in patients with early highly active RA. Our study used MRI to assess inflammatory outcomes, with clinical observations of DAS28 remission, ACR responses, and HAQ scores. Our findings demonstrate that combination therapy with DFPP plus DMARD was superior to DMARD therapy alone in the treatment of patients with early highly active RA. The superiority with respect to improvement in the synovitis and bone marrow edema detected on MRI, DAS28 remission, ACR responses, and improvement in HAQ scores was seen after 6 months of therapy. These indicated that the DFPP therapy enabled more rapid and more complete suppression of inflammation in patients with early highly active RA.

We found that 96% of patients with RA who satisfied the remission criteria had ongoing active synovitis observable on MRI. The term "true remission" should be reserved for patients who are not only in a state of clinical remission, but also show an absence of synovitis on imaging studies[4]. In our study, patients who received DFPP in combination with DMARD showed significantly greater improvement in the MRI synovitis score compared with patients who received DMARD alone. We found that 48.39% of the patients receiving DFPP therapy had complete resolution in MRI-detected synovitis, and imaging remission was achieved.

DAS28 remission and ACR70 and ACR90 response was achieved in 54.84%, 100%, and 41.94%, respectively, of patients at 1 month, and in 100% at 3 months of patients who received DFPP therapy. Sustained DAS28 remission and ACR90 response for at least 6 months were also reached in 100% of patients who received DFPP therapy. The rapid disease control was paralleled by a rapid, sustained, and significant improvement in function and quality of life (by HAQ).

A rapid and complete suppression of inflammatory joint disease (joint counts and MRI synovitis), with normalization of the systemic acute-phase response (CRP and ESR), indicates that nearly half of the patients (48.39%) who had received DFPP therapy achieved both clinical remission and imaging remission, i.e., a true remission.

Our study has shown significantly greater ACR20,

ACR50, ACR70, and ACR90 responses, clinical remission rates, and sustained clinical remission in the DFPP group than in the no-DFPP group ($p < 0.001$), than in other studies[15,16,17,18,19,20,21,22]. Patients in DAS28 remission may have relatively large numbers of residual joint counts, especially swollen joints[20,21,22]. Patients achieving an ACR70 response were at a higher level of disease activity, as assessed by 3 objective measures of disease activity — swollen and tender joint counts and ESR — than patients achieving a DAS28 remission[20]. Looking at patients in sustained remission, residual swollen joints were seen in 13% of patients in DAS28 remission[21]. In our study, patients with DAS28 remission and ACR70 responses had no swollen joints and tender joints. Patients in DAS28 remission and achieving an ACR70 response for 6 consecutive months had no swollen joints and tender joints and no increase in CRP and ESR in the DFPP group. These findings indicate the complete absence of any measurable disease activity markers on clinical and laboratory assessments. Notable in this study was the complete absence of MRI-detected inflammatory changes achieved in 25.81% of the patients with DFPP therapy; bone marrow edema showed complete resolution in 10 (32.26%) of the 31 patients in the DFPP group, and in 8 of these 10 patients, synovitis also resolved.

Current methods used to evaluate remission in RA largely rely on composite scores based on clinical and laboratory assessments, and include the ACR preliminary criteria for clinical remission in RA[23] and the DAS[9,24,25,26]. Such measures have the disadvantage of not measuring inflammation directly at the primary site of pathology[27,28]. Our study demonstrates that current methods of assessing remission do not necessarily correlate with an absence of disease, and so they may be inaccurate measures of true RA remission. MRI studies are considered to play an important role in directly and accurately evaluating the pathology, i.e., the inflammatory changes (synovitis and bone marrow edema) and destructive changes (bone erosion), of RA, and MRI is therefore thought to be a superior imaging method, as well as being useful in objectively verifying the efficacy of drug therapy and to predict the prognosis.

In recent years, reports on clinical studies using MRI for assessment of RA have been published[29,30,31,32]. To our knowledge, ours is the first study to evaluate the response of RA to DFPP therapy by MRI. MRI scoring of bilateral wrists and MCP joints does not have much additional value compared with scoring of unilateral wrist[33]. Most MRI studies of patients with RA have focused on 1 joint region — the wrist or the second through fifth MCP joints[30,31,32,34,35,36,37,38].

RA is a systemic inflammatory disease and a disease of an aberrant immune response in a genetically predisposed host that leads to chronic progressive synovial inflammation and destruction of the joint architecture. It is characterized by the production of autoantibodies, cytokines, acute-phase reactant proteins, and immunoglobulin[39]. The availability of biologic agents has provided additional improvements in efficacy in patients with RA[15,16,17,19]. However, RA is an autoimmune disease that involves multiple molecules and pathways. Autoantibodies and cytokines represent classes of immune cell-secreted proteins postulated to have a variety of roles in RA, from regulating the initiation and perpetuation of chronic inflammatory responses to joint destruction[40,41,42]. A biologic agent could target only a single inflammatory mediator and limited pathogenic pathways, it could not suppress all the inflammatory pathways and may show unsatisfactory results[43,44]. The major mode of action of DFPP is rapid depletion of specific disease-associated plasma factors[45]. Yeh, *et al*[46,47] showed that DFPP was able to remove immunoglobulin. DFPP can also reduce cytokines, as evidenced by lower levels of transcripts for interleukin 8, tumor necrosis factor-α, and interleukin 2 at the end of each individual course of DFPP[48]. In agreement with this, the levels of RF and CRP were significantly decreased after DFPP, with significant improvement of the signs and symptoms of active RA and in physical function (HAQ) that were maintained during 6–12 months' followup in our previous studies[6,49,50]. These were confirmed in studies by Liu, *et al*[51] and Matsuda, *et al*[52]; our results agree well with these findings. The rapid disease control that was accompanied by rapid, sustained, and significant improvement in function and quality of life indicates that a rapid and complete suppression of autoimmune inflammation was achieved, with lowering of disease-associated plasma factors, after DFPP treatment. The safety of DFPP treatment has been confirmed by our findings and other studies[6,47].

We acknowledge the limitations of our study and the preliminary nature of our results. This was an open non-blinded study and the control subjects did not receive sham DFPP. We could therefore not evaluate potential placebo effects.

The study used MRI to assess short-term inflammatory outcomes in a randomized design for 6 months, with further clinical observations for DAS28 remission and ACR responses for 6 consecutive months in patients with early RA with high baseline disease activity. Our study demonstrates the magnitude of response that can be achieved in patients with highly active RA in their early stages with DFPP plus DMARD therapy, and establishes the superiority of DFPP combination therapy to DMARD therapy. The results showed significant responses in MRI-detected synovitis and bone marrow edema. The results also show that a significant proportion of patients with early highly active RA can achieve ACR20, ACR50, ACR70, and ACR90 responses and DAS28 remission. Further, a significant proportion of patients with early highly active RA receiving DFPP therapy had achieved both clinical remission and imaging remission, i.e., a true remission. This confirms the effectiveness of DFPP therapy not only in adequate disease suppression over time, but also in rapid disease suppression

for optimal improvement in the outcomes of physical function and quality of life. By the end of the sixth month, there was a marked improvement in MRI-detected synovitis and bone edema in the patients who received DFPP therapy. We give the results of the 6 months of followup with MRI. Longterm MRI followup studies are under way. After the encouraging results of this trial, a multicenter randomized clinical trial study and long period of followup seem to be important.

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