SHORT-TERM EFFECTIVENESS OF LEFLUNOMIDE IN THE TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS

Amjad Taqweem, Ibrar Ahmed, Nowsherwan, Zafar Ali, Amjad Mehboob

Department of Medicine
Lady Reading Hospital Peshawar - Pakistan

ABSTRACT

Objective: *To measure the effectiveness of 6-month treatment with Leflunomide in patients with active rheumatoid arthritis.*

Material and Methods: *This descriptive study was conducted in Medical B Unit, Lady Reading Hospital Peshawar from August 2008 to August 2009 and included 103 active Rheumatoid Arthritis patients who received Leflunomide 20mg daily for 6 months. The primary effectiveness endpoint was a ≥20% response according to the American College of Rheumatology criteria 20 and disease activity score 28 response after 6 months.*

Results: *All the 103 selected patients were treated with Leflunomide. The mean age was 56.12% ± 4.796 years. According to the disease activity score 28, 46.6% of patients had a good response, 41.7% had a moderate response and 11.7% were non-responders. Improvements in tender joint count were –8.63 ± 3.418 (from baseline of 15.74 ± 2.9), in swollen joint count were –4.26 ±3.058 (from baseline of 9.34 ± 2.383), Erythrocyte Sedimentation Rate improves to 14.74± 11.527 from baseline of 60.58 ± 9.608 and physical global assessment improves to 17.38± 15.35 from baseline of 70.24 ± 7.933. The American College of Rheumatology criteria 20 response criteria show improvement in 87.4% patients. Treatment related adverse events were reported in 23.3% of patients. 17% of total patients discontinue the due to non compliance and side effects.*

Conclusion: *This 6-month study carried out under daily routine practice conditions showed a favorable treatment response for Leflunomide in a dose of 20 mg daily in a typical sample of Rheumatoid Arthritis patients.*

Keywords: *Rheumatoid Arthritis (RA), Leflunomide, American College of Rheumatology 20 criteria (ACR 20), Disease Activity Score 28 (DAS 28), Disease Modifying Antirheumatic Drugs (DMARDs)*

INTRODUCTION

Rheumatoid arthritis (RA) is a major disabling disease. It is slowly progressive disease. There should be an effective treatment to halt the progress of disease. The main features in the treatment of RA are use of Non steroidal anti inflammatory drugs (NSAIDs) disease modifying anti rheumatic drugs (DMARDs) [1]. NSAIDs are used for controlling pain[2] while DMARDs slows the destructive biological process[3]. Leflunomide is an immunosuppressant and anti inflammatory DMARD that has been approved in USA, Central and South America, Australia and Europe[4]. The use of Leflunomide is not common in our section of population. The studies regarding their efficacy are not published in our local setup.

Leflunomide in an isoxazole derivative approved for treatment of RA. Leflunomide is an oral drug and is rapidly absorbed from the gastrointestinal tract. It is converted to active form a malononitrilamide known as teriflunomide[5]. The major action is the inhibition of a pyrimidine known as ribonucleotide uridine monophosphate pyrimidine (rUMP). It decreases the synthesis of rUMP through inhibition of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) which leads to inability of activated cells to move from G1 to the S Phase. Leflunomide has many effects on the immune and inflammatory responses like inhibition of leukocyte adhesion[6-8], interference with dendritic **c**ell function, decrease level of synovial infiltration of lymphocytes and Type1

synoviocytes[9], inhibition of tyrosine kinases[10], increase synthesis of transforming growth factor-beta[11] etc. Some of them explain the mode of action of Leflunomide.

The phase II and III clinical trial programme involving more than 1300 patients with active RA demonstrated therapeutic efficacy and safety of Leflunomide not only compared with placebo[12], but also in direct comparisons with methotrexate[13, 14] and sulfasalazine[15, 16].

This descriptive study was conducted to assess whether effectiveness of leflunomide in adult RA at the standard dosage of 20 mg/day for 6 months can be extra-polated to everyday practice. The study was conducted, keeping in view of our local factors as no such study has been conducted to date. The purpose was to build the confidence of our physician in this new drug. This study will help in doing further studies regarding long term assessment and efficacy of the drug. The American College of Rheumatology 20 (ACR 20) response rate ($\geq$ 20%) and the disease activity score 28 (DAS28) were defined as the primary effectiveness endpoints[17].

The assessment of disease activity in RA is defined by several principles. If active RA remains for prolonged period of time, it leads to severe joint destruction, functional disability and impaired health status[18-25]. The disease activity is monitored at regular and short term interval. The appropriate modification of DMARDS therapy improve radiological and functional outcome in patient with RA[26-28].

Common indicators of disease activity in RA included the following[29]; Swollen and tender joint count, pain, patient and evaluator assessment of disease activity, ESR and C-reaction protein level, duration of morning stiffness, fatigue, measure of functions (the health assessment questionnaire) and Health status (e.g. the short form 3).

Thus composite indices containing several core set of variable are developed. Formulas are complex and sometime difficult to calculate[23, 30-34]. These are disease activity Score 28, simplified disease activity index (SADI) and clinical disease activity index (CDAI). The DAS 28 is more practical to implement. It eliminated grading of joints and reduced the number of joints to 28 [30-33].

The calculator for DAS 28 is also available. A range of DAS 28 corresponds to high, moderate and low disease activity and remission. High disease activity is labeled when score is > 5.1, moderate disease activity is > 3.2-<5.1, low disease activity is regarded when the score is in the range of 3.2-2.6 and in remission when it is <2.6.

MATERIALS AND METHODS

This descriptive study was conducted in Medical B unit, Lady Reading Hospital Peshawar from August 2008 to August 2009. A total 103 patients were included in the study, 60.2% patients were male while 39.8% were female. All the patients were diagnosed as a case of RA on the basis of ACR criteria 1987. A written consent was obtained from the patients or attendants after informing about the study.

Those patients who had intraarticular or parenteral corticosteroid treatment in the last four weeks prior inclusion in the study, oral corticosteroids in a dose higher than 10 mg of prednisone equivalent and treatment with DMARDs in past two weeks were excluded from the study. As well as those having contraindi-cations to leflunomide like hypersensitivity, serious immunodeficiency, anemia (Haemoglobin of 10gm/dl), leucopenia (White Blood Count <3000/mm) thrombocytopenia (<1000000/mm), serious infections, hepatic insufficiency, severe hyponatremia, pregnant or breastfeeding patients were also excluded from the study.

The clinical trial included five visits: screening, baseline (1–4 weeks after the screening visit), and follow-up visits after 1, 3 and 6 months (end of study), respectively, or before in the case of a premature withdrawal. Laboratory tests (red and white cell count, platelet count, blood pregnancy test, Alanine tranaminase [ALT], Aspartate transaminase [AST], serum creatinine, albumin and renal function) were performed at the baseline visit and at visits 3, 4 and 5.

If after oral administration of 20mg of Leflunomide an increase in ALT levels twice the upper limit of normal occurred and persisted, the dosage was reduced. In any case, if ALT levels persisted between two and three times the upper limit of normal (ULN) for more than 2 weeks, Leflunomide treatment was stopped.

Stable doses of NSAIDs and oral corticosteroids as concomitant medication were allowed during the study period. Other DMARDs, any other investigational drug and live vaccines were not allowed.

At each study visit the ACR 20 response rate (the primary effectiveness criteria) was assessed with the following, tender joint count (TJC; 28 joints evaluated) [35], swollen joint count (SJC), investigator's and patient's global evaluation of health (on a visual analogue scale [VAS]), patient evaluation of pain (on a VAS), functional

index (Health Assessment Questionnaire [HAQ]) [36], and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

The DAS28 was calculated based on the SJC, TJC, ESR and general health scale (GH) [37]. The disease activity was labeled to be low if the DAS28 score was $\leq$3.2, as moderate if the score was >3.2 and $\leq$5.1, and as high in the case of a DAS28 score >5.1. The duration of morning stiffness was assessed by asking the patient to estimate the time required after waking up to be able to perform usual everyday activities, and recorded in minutes. For the assessment of pain by the patient, a VAS using a 100mm horizontal scale (0 = no pain; 100mm = maximum, non-bearable pain) was used to record overall pain, pain at rest and pain on movement. Safety and tolerability were assessed on the basis of adverse events, physical examination, weight and blood pressure, laboratory tests (red and white cell counts and platelet count, serum ALT, serum pregnancy tests).

The adverse events evaluated during the study were observed by all the authors or reported by the patient that developed or worsened during the period of treatment. Severity (mild, moderate or severe) was rated according to the assessment. An adverse event was classified as serious if it met any of the following criteria: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was otherwise an important medical event.

Compliance of study patients was assessed by tablet counts and patients were questioned about medication intake. It was rated as good if the intake was $\geq$80%.

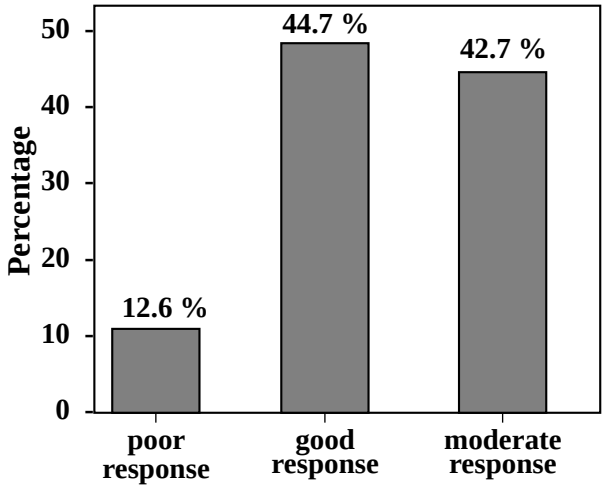
RESULTS

A total of 103 patients meeting the inclusion criteria were included in the study after taking informed consent. All the 103 patients were treated with Leflunomide in a dose of 20mg daily. During the study period, 57 patients received concomitant corticosteroid therapy. Twenty patients had a dosage decrease during the study.

At baseline, the RA had been present for more than 2 years in 80.4% of patients. Patients had mean disease duration of 7.2 years, and 29% had already been treated with a DMARD. The most frequently reported previous DMARD treatments were Methotrexate (14%), Sulphasalazine (8%) and Hydroxychloroquine (7%).

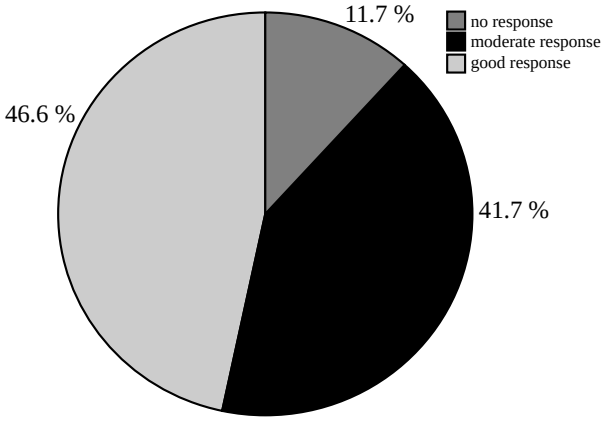
Effectiveness: Of 103 patients, 87.4 % responded (good and moderate of 44.7% and 42.7% respectively) to Leflunomide treatment according to the ACR 20 criteria. 12.6% patients were non-responders as shown in the figure 1.

Figure 1: American College of Rheumatology Score of the sample.



Disease activity according to the DAS28 was assessed from the data of 103 patients. 88.3% patients were responders in which 46.6% had a good response while 41.7% had moderate response. 11.7%patients were non-responders as shown in the figure 2.

Figure 2: Disease Activity Score of the Sample



Improvements in tender joint count were –8.63 ± 3.418 (from baseline of 15.74 ± 2.9) and in swollen joint count were –4.26 ±3.058 (from baseline of 9.34 ± 2.383). ESR improved to 14.74± 11.527 from baseline of 60.58 ± 9.608 and physical global assessment improves to 17.38± 15.35 from baseline of 70.24 ± 7.933 (Table 1).

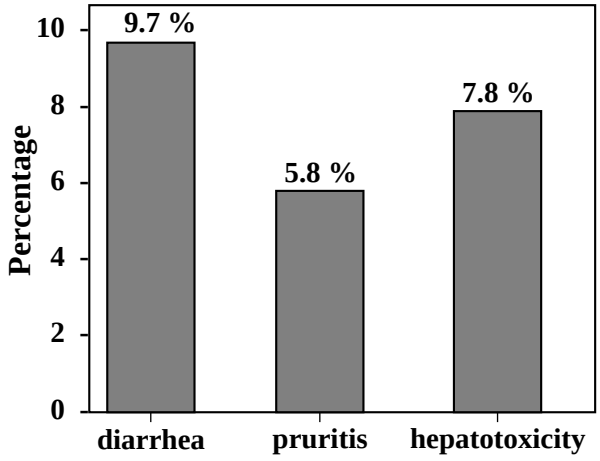
Table 1: Leflunomide Response

Tender Joint Count	
Baseline	15.74 ± 2.9
△(6 Months)	8.63 ± 3.418
Swollen Joint Count	
Baseline	9.34 ± 2.383
△(6 Months)	4.26 ± 3.058
ESR	
Baseline	60.58 ± 9.608
△ (6 Months)	14.26 ± 11.522
Physical Global Assessment	
Baseline	70.24±7.933
△ (6 Months)	17.38±15.353

The analyses of the RA disease activity criteria revealed an improvement in all criteria between baseline and at end of the study. Biological signs (CRP and ESR) were reduced with leflunomide treatment. The TJC Safety and SJC decreased according to both patients' and investigators' judgment.

Adverse Events: Adverse events were reported in 23.3%. The most frequently reported adverse event was diarrhea in 9.7% patients while pruritis and hepatotoxicity was observed in 5.8% and 7.8% patients respectively (Figure 3).

Figure 3: Reported/Observed Adverse Events



DISCUSSION

Rheumatoid arthritis is one of the most common diseases of our community. If the patient is not treated effectively, they gradually become bedbound. The treatment with DMARDs should be started as soon as the disease is diagnosed. Leflunomide is an important DMARD used in the treatment of RA. The use of this agent has a beneficial effect on survival like healing of erosive disease. The experience regarding use of Leflunomide is not well established in our local setup.

This study was conducted for the first time in a typical office based physician setup in our out-patient department. The efficacy and safety of Leflunomide monotherapy was established in large phase 2 trials[38] and in some large randomized double blind comparative multicentre study[39-42].

In some clinical studies Leflunomide was used in a loading dose of 100mg/ day for three days followed by 20mg/day but due to high likelihood of side effects, particularly diarrhea and other gastrointestinal disturbances the current approach is to start without a loading dose[3, 43]. So the recommended dose form start is 20mg/day as also used in our study.

The effectiveness of Leflunomide observed in the study is 87.4% according to ACR 20 criteria. This rate was higher as compared with the results in previous phase II and III trials which reported ACR 20 response rate of 60 %[38] and 55%[40, 41]. When these results were compared with placebo controlled studies[38, 40, 41] the responses in the present trail are slightly higher. The shorter duration of disease and different patient's characteristics might explain the higher response rate. The disease activity in the present study was lower which contribute the higher response rate. The mean disease duration was 6.4 years which was shorter than 7 years in that study performed by Smolen et al. So, shorter disease duration might be better and had quicker response after the initiation of Leflunomide treatment. The DAS 28 score is independent of disease duration[44], which shows improvement during the study and thus shows the beneficial effects of Leflunomide. According to DAS 28 activity score the response rate with Leflunomide is 88.3%.

The major side effects are hypertension[45], diarrhea and nausea occurring in 10-15 percent of cases taking Leflunomide[46]. Serum aminotrasaminases levels increases up to three times upper limit of normal leading to discontinuation of drug[46, 47].

Peripheral neuropathies develop in patients on Leflunomide. In a study of 50 patients about 5 patients develop peripheral neuropathy, which improved after discontinuation of drug[48]. Other side effects are rash and alopecia in 15 percent of cases, leucopenia etc.

The present study confirms the beneficial safety profile of Leflunomide. The overall frequency of side effect is 23.3%, which higher as compared to the study performed by Smolen et al

(14%) [40] Emery et al (19%) [42] and Strand et al (22%) [39].

This study confirms that diarrhea, increase in ALT and pruritis are known and expected side effects. The intensity of most events was slight or moderate. Diarrhea was the most common of all side effects (10%), however it improved after 1 month, may be because of anti proliferative effects of Leflunomide on intestinal tissue. The increase in ALT was observed in 7.8% of Patients which is more than observed by Strand et al (4.4%) [39] and Emery at al 2.4% [42].

Lack of effectiveness was mentioned as a reason for withdrawal of Leflunomide after six months about 10.7% which is lower as compared to phase 3 trials[39, 41]. Many patients have to discontinue the medicine because of waning effectiveness or because of adverse events[49, 50]. These patients may then be candidate of combination therapy of Leflunomide and methotrexate[51]. Leflunomide can be given as monotherapy or in combination with other DMARDS like methotrexate or cyclosporine[42, 52-54].

Leflunomide is contraindicated in pregnant and nursing mothers. If a patient became pregnant while taking Leflunomide, the elimination of drug is accelerated by giving cholestyramine (8 gm three times daily for 11 days) [14].

CONCLUSION

In a typical active RA patient sample, 6-month treatment with Leflunomide in a dose of 20mg was effective and well tolerated. Patients with disease at its early stage had a better response to Leflunomide. This study will promote the need of a randomized controlled trial on leflunomide for assessment of its long term efficacy and side effects in our setup.

REFERENCES

1. Moreland LW, Russell AS, Paulus HE. Management of rheumatoid arthritis: the historical context. J Rheumatol 2001;28:1431-52.
2. Choy EH, Scott DL. Drug treatment of rheumatic diseases in the 1990s: achievements and future developments. Drugs 1997;53:337-48.
3. Alldred A, Emery P. Leflunomide: a novel DMARD for the treatment of rheumatoid arthritis. Expert Opin Pharmacother 2001;2:125-37.
4. Prakash A, Jarvis B. Leflunomide: a review of its use in active rheumatoid arthritis. Drugs 1999;58:1137-64.
5. Panek JJ, Jezierska A, Mierzwicki K, Latajka Z, Koll A. Molecular modeling study of leflunomide and its active metabolite analogues. J Chem Inf Model 2005;45:39-48.
6. Xu X, Blinder L, Shen J, Gong H, , , et al. In vivo mechanism by which leflunomide controls lymphoproliferative and autoimmune disease in MRL/MpJ-lpr/lpr mice. J Immunol 1997;159:167-74.
7. Dimitrijevic M, Bartlett RR. Leflunomide, a novel immunomodulating drug, inhibits homotypic adhesion of mononuclear cells in rheumatoid arthritis. Transplant Proc 1996;28:3086-7.
8. Grisar J, Aringer M, Koller MD, Stummvoll GH, Eselböck D, Zwölfer B, et al. Leflunomide inhibits transendothelial migration of peripheral blood mononuclear cells. Ann Rheum Dis 2004;63:1632-7.
9. Kraan MC, Reece RJ, Barg EC, Smeets TJ, Farnell J, Rosenburg R, et al. Modulation of inflammation and metalloproteinase expression in synovial tissue by leflunomide and methotrexate in patients with active rheumatoid arthritis. Findings in a prospective, randomized, double-blind, parallel-design clinical trial in thirty-nine patients at two centers. Arthritis Rheum 2000;43:1820-30.
10. Siemasko K, Chong AS, Jack HM, Gong H, Williams JW, Finnegan A. Inhibition of JAK3 and STAT6 tyrosine phosphorylation by the immunosuppressive drug leflunomide leads to a block in IgG1 production. J Immunol 1998;160:1581-8.
11. Cao WW, Kao PN, Aoki Y, Xu JC, Shorthouse RA, Morris RE. A novel mechanism of action of the immunomodulatory drug, leflunomide: augmentation of the immunosuppressive cytokine, TGF-beta 1, and suppression of the immunostimulatory cytokine, IL-2. Transplant Proc 1996;28:3079-80.
12. Mladenovic V, Domljan Z, Rozman B, Jajic I, Mihajlovic D, Dordevic J, et al. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis: results of a randomized, placebo-controlled, phase II study. Arthritis Rheum 1995;38:1595-603.
13. Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1322-8.
14. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate: leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med 1999;159:2542-50.
15. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and

sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259-66.

16. Scott DL, Smolen JS, Kalden JR, van de Putte LB, Larsen A, Kvien TK, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60:913-23.
17. Felson D, Anderson J, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
18. Van Leeuwen MA, Van der Heijde DM, van Rijswijk MH, Houtman PM, van Riel PL, van de Putte LB, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts and acute phase reactants. J Rheumatol 1994;21:425-9.
19. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, van Riel PL, Kuper IH, van de Putte LB, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. J Rheumatol 1997;24:20-7.
20. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-17.
21. Aletaha D, Machold KP, Nell VP, Smolen JS. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology (Oxford) 2006;45:1133-9.
22. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 1999;42:1854-60.
23. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:796-806.
24. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005;52:2625-36.
25. Smolen JS, van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E, 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;54:702-10.
26. Goekoop-Ruiterman YP, de Vrie-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.
27. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263-9.
28. Smolen JS, Sokka T, Pincus T, Breedveld FC. A proposed treatment algorithm for rheumatoid arthritis: aggressive therapy, methotrexate, and quantitative measures. Clin Exp Rheumatol 2003;21:209.
29. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheum Dis Clin North Am 2006;32:9.
30. Prevoo MLL, van't Hof MA, Kuper HH, 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 rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
31. van der Heijde DM, van't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579-81.
32. Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al. Clinical studies with an articular index for the assesment of joint tenderness in patients with rheumatoid arthritis. Q J Med 1968;37:393-406.
33. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244-57.
34. Siegel JN, Zhen BG. Use of the American College of Rheumatology N (ACR-N) index of improvement in rheumatoid arthritis: argument in favor. Arthritis Rheum 2005;52:1637-41.
35. 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 rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.

36. Guillemin F, Braincon S, Pourel J. Measurement of the functional capacity in rheumatoid polyarthritis: a French adaptation of the Health Assessment Questionnaire (HAQ) [in French]. Rev Rhum Mal Osteoartic 1991;58:459-65.
37. Vrijhoef H, Diederiks J, Spreeuwenberg C. Applying low disease activity criteria using the DAS28 to assess stability in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:419-22.
38. Mladenovic V, Domljan Z. Safety and effectiveness of leflunomide in the treatment of patients with active rheumatoid arthritis: results of a randomized, placebo-controlled, phase II study. Arthritis Rheum 1995;38:1595-603.
39. Strand V, Cohen S, Schiff M. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate: leflunomide rheumatoid arthritis investigators group. Arch Intern Med 1999;159:2542-50.
40. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353:259-66.
41. Scott DL, Smolen JS, Kalden JR, van de Putte LB, Larsen A, Kvien TK, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. Ann Rheum Dis 2001;60:913-23.
42. Emery P, Breedveld FC, Lemmel EM, Kaltwasser JP, Dawes PT, Gomor B, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2000;39:655-65.
43. Smolen JS, Graninger WB, Emery P. Leflunomide, a new disease-modifying anti-rheumatic drug and the never ending rheumatoid arthritis story. Rheumatology (Oxford) 2000;39:689-92.

Address for Correspondence:
Dr. Amjad Taqweem
Associate Professor,
Department of Medicine,
Lady Reading Hospital Peshawar - Pakistan

44. Prevoo ML, van't Hof MA, Kuper HH. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
45. Nurmohamed MT, van Halm VP, Dijkmans BA. Cardiovascular risk profile of antirheumatic agents in patients with osteoarthritis and rheumatoid arthritis. Drugs 2002; 62:1599-609.
46. Cohen SB, Iqbal I. Leflunomide. Int J Clin Pract 2003;57:115-20.
47. Strand V, Fox R, Cohen S, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med 1999;159:2542-50.
48. Bharadwaj A, Haroon N. Peripheral neuropathy in patients on leflunomide. Rheumatology (Oxford) 2004;43:934.
49. Ward MM, Fries JF. Trends in antirheumatic medication use among patients with rheumatoid arthritis, 1981-1996. J Rheumatol 1998;25:408-16.
50. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992;19:1885-94.
51. Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. Clin Exp Rheumatol 1999;17:66-8.
52. Dayer JM, Cutolo M. Is there a rationale to using leflunomide in early rheumatoid arthritis? Clin Exp Rheumatol 2005;23:404-12.
53. Reece RJ, Kraan MC, Radjenovic A, Veale DJ, O'Connor PJ, Ridgway JP, et al. Comparative assessment of leflunomide and methotrexate for the treatment of rheumatoid arthritis, by dynamic enhanced magnetic resonance imaging. Arthritis Rheum 2002;46:366-7.
54. Schnarr S, Hulsemann JL, Zeidler HK. Unproven hypothesis that leflunomide is better than methotrexate as measured by magnetic resonance imaging: comment on the article by Reece et al. Arthritis Rheum 2003;48:270-1.