Leflunomide improves active rheumatoid arthritis equivalently to methotrexate

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Aim

Leflunomide, an isoxasole immunomodulatory agent and a reversible inhibitor of *de novo* pirimidine synthesis, was shown to be effective in a previous clinical trial in active rheumatoid arthritis (RA). A multicenter, randomized, double blind, placebo, and active controlled 12-month study compared the efficacy and safety of leflunomide therapy with placebo and methotexate (MTX) in active RA patients (pts).

Methods

485 RA pts, diagnosed according to ACR criteria, were enrolled in the study. Active RA was defined by 3 of the following criteria: 9 or more tender joints, 6 or more swollen joints, morning stiffness ≥ 45 minutes, erythrocyte sedimentation rate (ESR) 28 mm/hr or greater. Pts could not have previously taken MTX, and all other disease modifying antirheumatic drugs must have been discontinued for at least 30 days. Prednisone (≤ 10 mg/dy) or the equivalent and nonsteroidal anti-inflammatory (NSAIDs) were permitted if dosages had been stable for at least 30 days before enrollment and remained stable during the treatment. Baseline clinical assessment included tender and swollen joint counts (28 joints), patient's and physician's global assessment of disease activity [on a visual analog scale (VAS) 0-100 cm], patient assessment of pain (VAS 0-100 cm), the modified Health Assessment Questionnaire (MHAQ) score, and ESR and C reactive protein (CRP) levels. Rheumatologic assessments were performed biweekly during weeks 4 through 12 and monthly thereafter. The Health Assessment Questionnaire (HAQ), problem elicitation technique (PET) questionnaire (a disease-specific instrument designed to identify and rank activities most affected by RA) and the medical outcomes study 36-item short form health survey (SF-36) were performed at baseline and 24 and 52 weeks of treatment or at the time of the study exit. Radiographs of hand and feet were obtained at baseline and at 52 weeks or at the time of early study exit. The ACR response criteria were used, which require an improvement of 20% or greater in 3 to 5 measures: patient's self-assessed function disability (MHAQ), patient's global assessment, physician's global assessment, patient's assesment of pain, and PCR/ESR values. The ACR response rates for improvement of 50% and greater and 70% and greater were calculated, as well.

Pts were randomly assigned to 1 of 3 treatment groups: leflunomide (20 mg/day), placebo, or MTX (7.5 mg/week). All pts received 1 mg folate once or twice daily. If a patient failed to meet the ACR remission criteria after 16 weeks of treatment, the initial study drug could be discontinued and the patient could elect to receive alternate therapy. Pts who were initially assigned to MTX or placebo and chose to elect an alternate therapy, were placed on leflunomide. Those who were originally assigned to leflunomide received MTX.

The principal aim of the study was to compare leflunomide therapy with placebo. Comparisons of leflunomide with MTX and MTX with placebo were secondary aims. The primary outcome measure was fulfillment of the ACR response criteria and the completion of 52 weeks of therapy (ACR success criteria). Other outcome measures were the ACR response rates for improvement of ≥ 50% and ≥ 70% at 12 months, mean changes in each of the components of the ACR response criteria, disease progression as assessed by radiographs, and improvement in function and health-related quality of life using the "intent to treat" population.

Results

482 out of the 485 enrolled pts received at least 1 dose of a study drug or placebo and were evaluated for drug safety; 480 had at least 1 follow-up visit to evaluate efficacy (182 pts received leflunomide, 118 received placebo and 180 received MTX). The 482 pts studied were predominantly women (mean age 54 years and mean disease duration 6.7 years) for whom a mean of 0.8 DMARDs had failed. Two hundred forty-eight pts completed 52 weeks of the initially prescribed treatment (leflunomide, 53%, placebo, 31% and MTX 58%); 108 of 132 eligible pts received the alternative therapy (leflunomide, 13%; placebo, 44%; MTX, 18%). In all, 346 pts completed the protocol treatment (leflunomide, 66%; placebo, 75%; MTX, 77%)

Early discontinuation occurred more frequently with placebo (69%) than with leflunomide (47%) or MTX (42%): These discontinuations were caused by a lack of efficacy in 53% of the pts taking placebo, with respect to 17% of the pts receiving leflunomide and 24% receiving MTX.

The ACR response and success rates for pts receiving leflunomide (52% and 41%, respectively) and MTX (46% and 35%, respectively) were significantly higher compared to pts taking placebo (26% and 19%, respectively) ($P < 0.001$), and they were statistically equivalent. The mean time to initial response to therapy was 8.4 weeks for pts taking leflunomide versus 9.5 weeks for pts receiving MTX. X-rays showed less disease progression with leflunomide ($P \leq 0.001$) and MTX ($P < 0.02$) than with placebo. Leflunomide and MTX improved the measures of physical function and health-related quality of life parameters significantly more than placebo ($P < 0.001$ and $P < 0.05$, respectively).

Commons side effects with leflunomide included gastrointestinal symptoms, skin rash and reversible alopecia. Asymp-

tomatic raised transaminase levels resulted in treatment discontinuation for 7.1 % pts taking leflunomide, 1.7% pts taking placebo, and 3.3% pts taking MTX.

Conclusion

Leflunomide appears to be safe, statistically more efficacious than placebo and as efficacious as MTX in improving the signs and symptoms of active RA and in delaying disease progression, as demonstrated by x-rays, and in improving joint function and health-related quality of life. Therefore, leflunomide could represent an important alternative choice in the disease modifying strategy in RA.

Comment

During the past few years we have seen more drugs added to the therapeutic armamentarium for the treatment of Rheumatoid Arthritis than any other single time period in the past. Even more striking has been the use of uniform response measures to assess outcome of therapy with novel agents. Several global outcome measures have been described but the measure that is used most often is the ACR response rate. Using this measure a patient achieves a response when there is improvement greater than a set point of 20%, 50% or 70% of both tender and swollen joints and similar improvement of 3 of the following five measures: patient self-assessed functional/disability (MHAQ), patient global assessment, physician global assessment, patient assessment of pain and acute-phase reactant value (ESR or CRP).

In this study patients were randomly assigned, in a double-blind fashion, to receive methotrexate (7.5 mg/week), leflunomide (20 mg/day) or placebo. Patients could have their therapy changed after 16 weeks to either leflunomide or methotrexate for lack of efficacy or toxicity. The ACR recommendations for monitoring methotrexate therapy were followed for all patients and the drug was adjusted accordingly. The investigators observed that both methotrexate and leflunomide were significantly better than placebo for the treatment of RA and that there was relatively little difference between leflunomide and low dose methotrexate with regard to efficacy. Both methotrexate and leflunomide caused adverse reactions although more patients discontinued leflunomide for this than methotrexate (22% vs 10.4%, respectively). Moreover, both active drugs appeared to halt radiographic progression. The only significant differences between the two drugs were in the patient self-assessed functional disability index (MHAQ) in which leflunomide was superior to methotrexate.

Perhaps the only criticism that can be made of this study is that the dose of methotrexate used is lower than that which is currently used by most rheumatologists to treat RA. The low dose of methotrexate employed may account for the advantage of leflunomide over methotrexate with respect to the MHAQ. It is interesting to note that we will never see a study like this again; with the advent of effective therapy for RA there is no excuse for conducting a placebo-controlled trial of a second-line drug. This marks the beginning of an era when we can offer a choice of safe and effective therapies for Rheumatoid Arthritis.

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