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Weekly leflunomide as monotherapy for recent-onset rheumatoid arthritis

To the Editor:

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that may cause permanent disability related to a poor response to treatment. The therapeutic armamentarium for RA includes nonsteroidal antiinflammatory drugs (NSAIDs), which reduce pain and joint swelling but do not halt the disease course; disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) or leflunomide; and biologic therapy, such as interleukin 1 and tumor necrosis factor α antagonists, which have shown to diminish the acute phase response and to limit or avoid joint damage.

Leflunomide has demonstrated efficacy for the treatment of RA, but adverse effects are often seen (1,2). The conventional therapeutic leflunomide dosing scheme for RA is a loading dose of 100 mg/day for 3 days followed by 20 mg/day thereafter (1). However, in a previous study, we reported that leflunomide administered in a weekly dose of 100 mg had similar therapeutic effects to that observed with the commonly used dosage in patients with refractory RA (3). The aim of this open-label trial was to compare the therapeutic effect of weekly administration of leflunomide to that observed with conventional administration of either leflunomide or MTX in patients with recent-onset RA.

Thirty patients diagnosed as having RA according to the American College of Rheumatology (ACR; formerly American Rheumatism Association) criteria (4) were selected from the outpatient clinic. Time since disease onset had been <1 year for all patients. No patient had been treated previously with any DMARD. Patients were consecutively allocated to 1 of 3 treatment groups: 1) leflunomide at 100 mg/week after a loading dose of 100 mg/day for 3 days; 2) leflunomide at 20 mg/day after a loading dose of 100 mg/day for 3 days; and 3) MTX at 7.5 mg/week adjusted up to 15 mg/week as needed. Current treatment with prednisone (<7.5 mg/day; 3 patients in each group) or NSAIDs was not modified throughout the study in those patients who received them. All patients had active disease evidenced by at least 8 painful joints and at least 8 swollen joints based on the 28-joint count assessment (5), morning stiffness >45 min, and an erythrocyte sedimentation rate (ESR) of at least 28 mm/hour. Exclusion criteria were pregnancy or lactation; positive test result for hepatitis B, C, or HIV; infections; hypertension; abnormal liver function test results; gastrointestinal disturbances; or other inflammatory or chronic diseases. Women were advised to use a contraceptive method. All patients were informed about the objectives of the protocol and gave their written consent. The study was approved by the Institutional Review Board of our hospital. All patients were evaluated every other month for 6 months and at months 9 and 12. The ACR improvement criteria (6) were applied at each visit. Furthermore, complete blood cell count, urinalysis, creatinine, urea, and liver function tests were also performed monthly during the study.

Baseline characteristics were compared using one-way analysis of variance. The proportion of patients who reached ACR 20%, 50%, and 70% improvement in each group at each evaluation were compared using Fisher's exact test. Two patients dropped out of the study (at months 5 and 10, respectively); they were included in the analysis up to these months and were excluded after this time for all calculations. P values < 0.05, two-tailed, were considered significant.

The 3 groups were comparable in their demographic and clinical characteristics at the beginning of the study. There were no statistically meaningful differences between treatment groups in patient age, sex, visual analog scale for pain, visual analog scale for global assessment, number of tender or swollen joints, physician global assessment, morning stiffness, or ESR.

Patients in any given group improved by month 2, however, the response at month 2 in the daily leflunomide group was more evident ($P = 0.0001$) than that in the MTX ($P = 0.03$) or the weekly leflunomide ($P = 0.001$) groups. Thus, at the second month, all patients treated with the daily leflunomide scheme reached the ACR 20% improvement rate. Moreover, 4 of 10 and 1 of 10 patients accomplished the ACR 50% and ACR 70%, respectively. On the other hand, in the weekly leflunomide group or the MTX group, 8 of 10 and 7 of 10 patients, respectively, reached the ACR 20% improvement criteria. In addition, 2 of 10 patients in the MTX group reached the ACR 50%, but none in the weekly leflunomide group did. Nevertheless, when ACR improvement criteria were compared between groups, only those taking leflunomide were found to be different ($P = 0.025$, daily versus weekly). The clear-cut improvement observed in the daily leflunomide group prevailed at month 4 over the other 2 groups ($P = 0.047$ and $P = 0.021$, MTX and weekly leflunomide, respectively). Notwithstanding, 5 of 10 patients in both the weekly leflunomide and MTX groups reached the ACR 50% criteria by this time, and 1 in the latter group reached the ACR 70% criteria (Figure 1).

From month 6 up to the end of the study, there were no significant differences between groups at any given time in all evaluations performed. The development of side effects deserves particular attention because they were made clear in both the daily leflunomide and MTX groups. Thus, 8 patients in the daily leflunomide group developed 11 adverse events that included diarrhea, alopecia, transient transaminasemia (<2 upper limit of normal [ULN]), gastritis, weight loss, and abdominal colic pain. Two of these patients withdrew from the study at months 5 and 10 due to untreatable diarrhea. Six patients in the MTX group

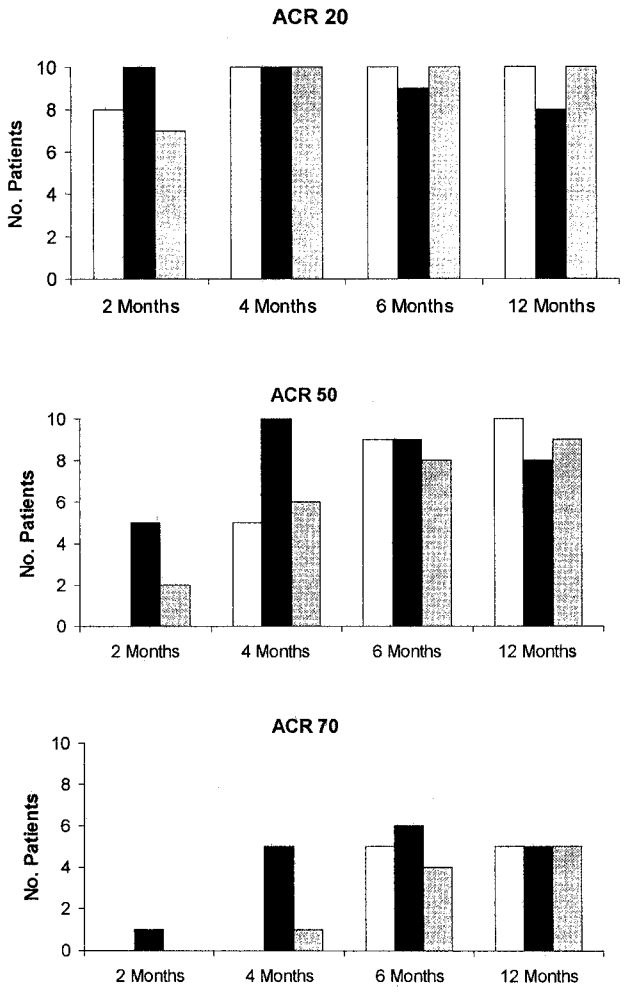

Figure 1. American College of Rheumatology (ACR) improvement rate throughout the study. The cumulative number of patients achieving the ACR 20%, ACR 50%, and ACR 70% improvement according to their treatment is shown in the graphics. At month 6, the daily leflunomide group had 9 participants and at month 12, it had 8 participants. Open bar = weekly leflunomide group; solid bar = daily leflunomide group; shaded bar = methotrexate group.

developed side effects that included nausea, mild and transitory increased transaminases (<2 ULN), alopecia, gastritis, and stomatitis. These effects disappeared spontaneously or after symptomatic treatment. In the group receiving weekly leflunomide, only 4 patients presented transitory diarrhea, nausea, alopecia, or mild transaminasemia, which resolved without treatment.

Because RA is a progressive and disabling disease, patients must receive treatment throughout their lives, even patients with a benign disease course. As a high incidence of therapeutic failures persists, a quest for an ideal DMARD prevails. After several years of treating RA with leflunomide, a daily dose of 20 mg after a loading dose of 100 mg for 3 days has been established as the conventional scheme. However, considering the prolonged half life of the A77-1726 metabolite, it has been previously shown that leflunomide administered in a weekly dose of 100 mg had the same efficacy and was less toxic than the conventional dosage in patients with refractory RA (3).

In the present study, weekly leflunomide was efficacious in the control of recent-onset RA. Such improvement was similar between the 3 groups after 1 year of treatment. Given the small number of patients, however, we cannot affirm that such a treatment schedule is as effective as daily leflunomide or weekly MTX.

Because of the natural history of RA, the optimal therapy must be the one found to be safe and effective over prolonged time and that halts disease progression with the minimal drug requirement. This report proposes a novel therapeutic modality for disease control for recent onset RA that deserves to be explored further.

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Quality of myositis case reports open to improvement

To the Editor:

Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies with a presumed autoimmune pathogenesis (1,2). The generally accepted first-choice therapy is high-dose prednisone (2). When this treatment fails because of insufficient improvement, frequent relapses during tapering of the dosage, or unacceptable side effects, a second-line therapy is started. Many different treatments are being used for second-line treatment in PM and DM, and there is no consensus on which is the best choice (2).

Efficacy of therapies can only be assessed appropriately with randomized controlled trials (RCTs). When RCTs are not available, other types of controlled studies can be useful, although they provide a lower level of evidence because of their potential for bias. If there are not a sufficient number of controlled studies on which to base a treatment decision, as is often the case in rare diseases, the clinician's decision must be based on reports of uncontrolled observations and the opinion of experts (3).

Criteria for good-quality RCTs have been well established (4) and are applied widely. Criteria for a clear and adequate description of single cases and case series have also been formulated (5), but the methodologic quality of this type of evidence in published reports has never been evaluated (6). This hampers the appreciation of their validity and practical value. Controlled studies in PM and DM are extremely rare, but in contrast, there is a large body of reported single cases and uncontrolled case series. We undertook a study to assess the quality of reported descriptions of uncontrolled observations on the second-line treatment of PM and DM.

Single case reports and case series reports of second-line therapy in adult DM, PM, or myositis associated with a connective tissue disease or malignancy were found by searching Medline and Embase for articles published in English, French, or, German between 1966 and the end of 2001 using the following search terms: "dermatomyositis," "polymyositis," "inflammatory myopathy," "treatment," and "therapy." We hand-searched all reference lists of identified publications and of relevant review articles for additional publications. Excluded were controlled studies, abstracts, and publications on inclusion body myositis, juvenile DM, and aspects of myositis other than weakness (e.g., pulmonary involvement).

Two investigators systematically and independently examined all eligible reports. A third investigator helped resolve differences through discussion. All articles were reviewed for a clear and adequate case description, which would allow a clinician to recognize his or her own patient in the patient described in the study, copy the described treatment, and get a fair impression of the treatment effects (5). On the basis of these requirements, we arbitrarily predesigned the following 10 criteria with which we would assess the reports: 1) sex and age; 2) credible diagnosis; 3) clear description of disease duration; 4) clear description of previous therapies; 5) clear description of severity of the disease at initiation of second-line treatment; 6) reason for failure of previous treatments; 7) dosage, mode of administration, and duration of the second-line therapy; 8) clear description of effect of the therapy on muscle strength or function; 9) description of side effects; and 10) followup at least 6 months (because of the chronicity of these diseases).

For a credible diagnosis of DM, reference to the criteria of Bohan and Peters sufficed (1), but a mere reference to these diagnostic criteria was accepted for PM only if it was clear from the text that the symptoms had evolved over weeks to months. This criterion was chosen as a feasible attempt to rule out inclusion body myositis and muscular dystrophies in the studied publications (obviously, nowadays specific investigations of muscle biopsy material are considered to be required for an accurate diagnosis of PM). By applying this criterion, we may have judged the diagnosis as not credible in some patients with slowly evolving PM.

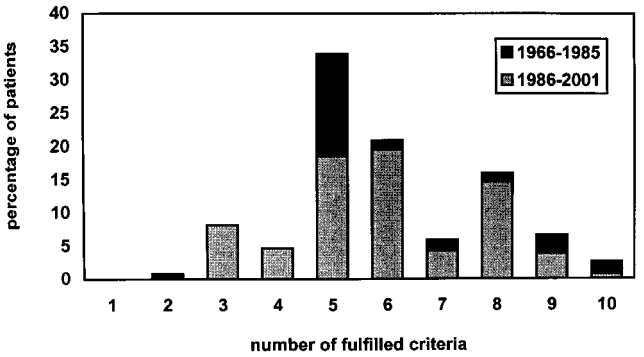

Figure 1. Number of criteria fulfilled.

Severity of disease before and after second-line treatment was preferably described in terms of MRC scores, dynamometry, or accepted scales of disability or handicap, but we also accepted any ad hoc scales and mere descriptions of functional abilities as long as they gave a fair impression of muscle strength or function. A clear description of the reason for failure of previous treatments was considered mandatory because the therapeutic prospects are probably quite different for a patient who had improved on prednisone, but did not tolerate it, than for a patient who did not benefit from previous therapies.

We analyzed articles published before and after 1985 (when evidence-based medicine became into general use) separately. We made a distinction between single case reports (in which the patient or patients are described individually) and case series reports (in which patients are described as a group).

We identified 148 publications, of which 92 were eligible for the study (references available from the authors). These 92 publications described a total of 915 patients (median 2 per publication; 75th percentile = 7). Ninety-two patients were described more than once in different articles. There were 74 single case reports and 18 case series reports. Most (77%) of the studies were retrospective, 14% were prospective, and the design was equivocal in 9%.

The number of fulfilled criteria by percentage of patients studied is shown in Figure 1. All 10 criteria were fulfilled in 9 publications (10%), describing 2.6% of all patients. All 9 articles were single-case reports (references available from the authors). The number of publications fulfilling each criterion is shown in Table 1. Four criteria (previous treatment, reason for initiating second-line treatment, and disease severity before and after treatment) were met in $<50\%$ of described patients. For example, treatment results were often indicated using such phrases as "remarkable improvement of strength," "better than ever," "doing well," and "muscle condition satisfactory." Of the 10 criteria, 9 were fulfilled in single case reports more often than in case series reports. Reports published after 1985 were

not of better quality than those published earlier (Figure 1).

In conclusion, we found the methodology of patient descriptions (the evidence) unsatisfactory in single case reports and case series reports of second-line treatments in PM and DM. Therefore, the added value of these reports for making treatment decisions in clinical practice, or for identifying new treatments of interest, is dubious. Also, any attempts at doing a systematic review of treatment results reported in these articles are unrealistic (6). It is noted that readers have a better chance of finding relevant and complete information in single case reports than in reports of large series of patients (Table 1). Our results further show that introduction of the principles of evidence-based medicine in recent years has not lead to more adequate data presentation in these types of studies. We conclude that reports of uncontrolled observations can improve considerably if criteria for good quality are taken into account.

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Table 1. Number of publications and patients fulfilling criteria for good quality*

Criteria	Single case reports† n = 74	Case series reports† n = 18	Patients n = 915
1. Sex and age	73 (99)	15 (83)	692 (76)
2. Credible diagnosis	58 (78)	13 (72)	473 (52)
3. Duration of disease prior to 2nd-line treatment	68 (92)	10 (56)	598 (65)
4. Previous treatment	36 (49)	4 (22)	311 (34)
5. Disease severity prior to 2nd-line treatment	43 (58)	3 (17)	265 (29)
6. Reason for starting 2nd-line treatment	66 (89)	7 (39)	357 (39)
7. Dose and scheme 2nd-line treatment	74 (100)	15 (83)	716 (78)
8. Disease severity after 2nd treatment	51 (69)	6 (33)	434 (47)
9. Side effects	51 (69)	15 (83)	738 (81)
10. Follow up at least 6 months	56 (76)	10 (56)	593 (65)

* Values are number (%).
† Articles were considered fulfilling a specific criterion if at least one patient described in this article fulfilled that criterion.

Applications Invited for Editor of *Arthritis & Rheumatism*, 2005–2010 and Editor of *Arthritis Care & Research*, 2005–2009

During the summer and fall of 2004, the American College of Rheumatology Committee on Journal Publications will review applications for the position of Editor, *Arthritis & Rheumatism*, 2005–2010 term and the position of Editor, *Arthritis Care & Research*, 2005–2009 term. The official term of the next *Arthritis & Rheumatism* editorship is July 1, 2005–June 30, 2010; however, some of the duties of the new Editor will begin during a transition period starting April 1, 2005. The official term of the next *Arthritis Care & Research* editorship is July 1, 2005–June 30, 2009; however, some of the duties of the new Editor will begin during a transition period starting April 1, 2005. Applications will be available beginning February 4, 2004. The deadline for completed applications is June 1, 2004, and the final selection will be announced by November 2004. It is requested, but not required, that those who plan to apply for either position submit a nonbinding letter of intent by April 15, 2004. For additional information or to request an application or submit a letter of intent, contact Jane Diamond, Managing Editor, at the ACR office.