Editorial

Rheumatological Creativity and Leflunomide

Rheumatologists have always been willing to try something new, even trying old drugs in new ways. Methotrexate (MTX) was first used for arthritis in the 1970s, when it was borrowed from dermatology and oncology. Cyclophosphamide, chlorambucil, and nitrogen mustard were first used in oncology and then in patients with severe rheumatoid arthritis (RA). Gold was originally used to treat tuberculosis. Physicians treating arthritis had a need to be innovative. Few treatments previously available offered any degree of sustained relief. However, many disease modifying antirheumatic drugs (DMARD) now prescribed offer a significantly greater measure of effectiveness than typically achieved in the past. Yet there still exists a need to be creative — perhaps not for precisely the same reasons.

In the past, the desire for new drug regimens was driven by the need to control rampant disease. We have not yet cured the RA beast, but with the use of new agents, we are achieving greater degrees of effectiveness than were possible before. Ironically, clinicians are beginning to recognize that most of the RA patients they now treat have a measure of disease control, as reflected in total joint counts, that would render them ineligible for entry into any of the investigations that were originally designed to test the same new agents[1,2]. Of course, this is not necessarily a bad thing unless you are in the business of developing new products for rheumatology and finding appropriate subjects to study.

One of the pressing practical issues now is gaining access to the expensive drugs that can provide these improved outcomes. Newer biological agents and leflunomide are even less readily available in Latin America and developing nations, where resources are insufficient to treat all patients needing treatment. Unfortunately, this is also the case for many uninsured individuals within the United States.

It was such uninsured patients who first received the sample doses of 100 mg of leflunomide. Anecdotal stories were common describing creative regimens of 100 mg tablets given once or twice weekly, often with positive results. The 100 mg dose of leflunomide, provided as free starter samples in the past in order to accelerate the process of getting patients to steady-state on a drug with a long half-life, is somewhat without precedent in the context of the use of other DMARD. There is no equivalent alternative dosing regimen of any of the other DMARD that is sampled to rheumatologists for use within their offices.

Thus, 2 critical elements for experimental innovation are present: first, a need to treat patients unable to afford new treatments; second, the availability of the actual drug, in an alternative dosing form, in the sample closets. Given the history of our discipline and the often hard realities of drug access, it is not surprising that treatment with the 100 mg tablet of leflunomide, designed as a loading dose for a drug with a 15 day half-life, would be creatively employed at times for chronic treatment as well.

The purpose of this editorial is not to focus upon the fact that physicians within the United States and in the rest of the world should have to channel their therapeutic creativity to devise new ways to access expensive drugs in order to outsmart the payer system. It would nevertheless be inappropriate not to acknowledge this inequity.

In this issue of *The Journal*, Jaimes-Hernandez and colleagues report an open study of 50 patients with RA treated with a loading dose of leflunomide 100 mg for 3 consecutive days, followed by the same dose given once weekly[3]. At the end of the 24 week treatment period, American College of Rheumatology 20%, 50%, and 70% responses were equivalent to those measured in several other studies of new agents given in combination with MTX. These responses were also seen as early as 12 weeks, perhaps facilitated by the loading dose employed. The authors report no serious adverse events during the investigation.

Abnormalities in liver enzymes, measured at baseline and then every 2 months, were seen in only 5 subjects

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(10%). The highest levels of aspartate aminotransferase and alanine aminotransferase noted during the trial were 66 IU/l and 76 IU/l, respectively. Headache was noted in 8 subjects (16%) and myalgias and urticaria were seen in 5 (10%) and 4 (8%), respectively, along with alopecia in 5 subjects (10%).

As the authors of the investigation suggest, the results of an open study of only 6 months' duration in a cohort of patients in which only 20 (40%) had received prior DMARD treatment and 38 (76%) had a disease duration of less than 5 years can only be generalized to other populations with extreme caution. The mean age of patients in the cohort (45.6 years) is also somewhat lower than the typical mean age of about 55 years reported in most recent trials of new interventions, and may have also favorably influenced the relatively low rate of adverse events. It is also possible that independent cultural attitudes or genetic factors in the population of Mexican patients reported in this investigation could have affected patient reporting and perception of both efficacy and toxicity.

The rationale for studying weekly dosing is not described by the authors, other than the attractiveness of the long half-life of leflunomide. Other motivations should not necessarily be ascribed, so my comments on the difficulty of access to traditional dosing schedules of newer DMARD apply only to the situation within the United States, with which I am familiar. Nevertheless, even with all the potential confounders noted, it is still intriguing that these results were achieved utilizing a dosing regimen not previously studied.

As noted, in North America a weekly dosing regimen has been employed only as a pragmatic maneuver to provide drug to patients who might not be able to afford it through traditional routes. It should be recognized that many of the dosing regimens we employ are somewhat arbitrary, including the weekly dosing of MTX, also found to be efficacious in many patients when administered every 2 weeks[4]. MTX and leflunomide are both antimetabolites whose intracellular effects extend to a variety of complex metabolic pathways. It is likely that sufficient genetic variation and complexity exists within these pathways to allow for alternative dosing regimens in many individuals treated. It is possible then that alternative dosing regimens of leflunomide may exist that could be better tolerated or more efficacious in certain individuals. As noted by Jaimes-Hernandez and colleagues, it is possible that a weekly cumulative dose of 100 mg is safer than one of 140 mg (i.e., 20 mg daily for 7 days). We simply do not know.

As with most of the clinical situations we encounter on a daily basis, a well established, evidence-based rationale for continuing to do things in one particular way, and one way only, is unusual. Alternative treatment doses and administration schedules of leflunomide should be studied in a prospective blinded manner so that the interesting observations presented by Jaimes-Hernandez and colleagues can be either confirmed or refuted. In the meantime, clinicians will be creative.

JOEL M. KREMER, MD,
Clinical Professor of Medicine,
Albany Medical College,
Director of Research,
The Center for Rheumatology,
1367 Washington Avenue,
Albany, New York 12206, USA
E-mail: jkremer@joint-docs.com

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