Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 49, No. 6, December 15, 2003, pp 745–751
DOI 10.1002/art.11452

ORIGINAL ARTICLE

Leflunomide Use During the First 33 Months After Food and Drug Administration Approval: Experience With a National Cohort of 3,325 Patients

CHOKKALINGAM SIVA,[1] SETH A. EISEN,[1] REBECCA SHEPHERD,[1] FRANCESCA CUNNINGHAM,[2] MEIKA A. FANG,[3] WILLIAM FINCH,[4] DON SALISBURY,[5] JASVINDER A. SINGH,[6] RICHARD STERN,[7] AND S. ALIREZA ZARABADI[8]

Objective. **To describe leflunomide (LEF) use in a national cohort of 3,325 veterans.**
Methods. **Prescriptions for LEF and 9 disease-modifying antirheumatic drugs written between October 1998 and June 2001 at all Veterans Affairs (VA) medical centers were obtained from VA national databases.**
Results. **LEF was initiated with a loading dose of 100 mg daily for 3 days in 61% of patients, and 42% of patients discontinued LEF. LEF was more likely to be discontinued if a 3-day 100-mg loading dose was prescribed, patients were younger than 44 years or older than 75 years, or reported an annual family income <$60,000. Review of medical records of 291 discontinuers revealed that the most common reasons for discontinuation were inefficacy (30%), gastrointestinal symptoms (29%), medication noncompliance or lost to followup (14%), and elevated liver enzymes (5%).**
Conclusion. **LEF is relatively safe in clinical practice. The VA's national databases provide an excellent, inexpensive resource for postmarketing evaluation of rheumatologic medications.**

KEY WORDS. Immunosuppressive agents; Rheumatoid arthritis; Hepatitis, drug induced; Treatment failure; Drug therapy, combination; Leflunomide.

INTRODUCTION

The results of randomized controlled trials (RCTs) conducted in carefully controlled clinical research environments often do not reflect the actual practice settings in which the medications are subsequently prescribed (1). For example, the narrow eligibility criteria employed to enroll patients in RCTs tend to exclude elderly patients with multiple concurrent illnesses, who are at higher risk for experiencing adverse events. RCTs may exaggerate treatment benefits by including more skillful physicians and participants with a greater likelihood for improving. Important but infrequent adverse events may not be recognized for years after the medication has been extensively used in the community (2). Postmarketing studies on newly approved drugs thus have a vital role in detecting toxicities not identified in RCTs and evaluating drug efficacy in nonresearch populations and environments.

The Food and Drug Administration (FDA) approved leflunomide (LEF), a disease-modifying antirheumatic drug (DMARD), for the treatment of rheumatoid arthritis (RA) in October 1998. LEF inhibits lymphocyte proliferation and hence the clonal expansion of T cells in RA by blocking dihydro-orotate dehydrogenase, an enzyme critical for de novo pyrimidine synthesis (3). Several multinational RCTs have demonstrated that LEF is a safe and effective DMARD equivalent to methotrexate and sulfasalazine for treating the signs and symptoms of RA and retarding disease progression as measured by radiography (4–10). Although longer-term tolerability and effectiveness have been reported in some postmarketing studies (11,12), high discon-

Supported by the Arthritis Foundation, Eastern Missouri Chapter.
[1]Chokkalingam Siva, MD, MS, Seth A. Eisen, MD, MSc, Rebecca Shepherd, MD: St. Louis VAMC and Washington University School of Medicine, St. Louis, Missouri; [2]Francesca Cunningham, PharmD: Department of Veterans Affairs, Hines, Illinois; [3]Meika A. Fang, MD: Veterans Affairs Greater Los Angeles Healthcare System and University of California Los Angeles School of Medicine; [4]William Finch, MD: Phoenix VAMC, Phoenix, Arizona; [5]Don Salisbury, DO: Albuquerque VAMC, Albuquerque, New Mexico; [6]Jasvinder A. Singh, MD: Minneapolis VAMC, Minneapolis, Minnesota; [7]Richard Stern, MD: Dallas VAMC, Dallas, Texas; [8]S. Alireza Zarabadi, DO: Tampa VAMC, Tampa, Florida.
Address correspondence to Seth A. Eisen, MD, MSc, St. Louis VAMC (151JC), 915 North Grand, St. Louis, MO 63106. E-mail: seisen@im.wustl.edu.
Submitted for publication December 17, 2002; accepted in revised form June 29, 2003.

tinuation rates in daily practice have also been noted (13–15).

In this article, we describe the use of LEF in clinical practice, including initial dosage, coadministration with other DMARDs, duration of administration, and reasons for discontinuation, in a large national cohort of American veterans during the 33 months immediately following the drug's introduction. The Department of Veterans Affairs (VA) administers the largest integrated health care system in the United States (16). Its unique national databases permit a large number of patients for whom LEF has been prescribed to be easily identified and their medication use characterized.

METHODS

Appropriate approvals were obtained from the human studies subcommittees (HSS) at the St. Louis Veterans Affairs Medical Center (VAMC) and at the 6 collaborating VAMCs where individual patient clinical records were reviewed.

VA computer databases. VA facilities use standardized computer systems that link patients across databases with the social security number (SSN). Three national VA databases, created from outpatient encounters captured by individual VA health care facilities, were utilized in the present study: the Outpatient Care (OPC) file, the Patient Treatment File (PTF), and the Pharmacy Benefits Management (PBM) file.

Data in the OPC includes patient sociodemographic characteristics, outpatient International Classification of Diseases, Ninth Revision diagnostic codes, clinic visits, and procedures. The PTF contains hospitalization dates and discharge diagnoses and deaths. Since October 1998, the VA has maintained a centralized pharmacy database, the PBM, that contains data on all prescriptions issued at VA facilities, the names of the medications, the identity of the facility at which the prescription originated, number of tablets dispensed, and dosing instructions. Data on all LEF prescriptions in the first 33 months after FDA approval (October 1, 1998 to June 30, 2001) were obtained. A total of 3,325 patients received 26,146 LEF prescriptions, including refills. Prescription data for the following 9 other DMARDs issued to the 3,325 LEF recipients during the same period were also retrieved: oral and parenteral methotrexate, oral and parenteral gold, sulfasalazine, hydroxychloroquine, etanercept, infliximab, minocycline, azathioprine, and cyclosporine.

Definitions. The 33 months of prescription data were divided into 11 consecutive calendar quarters. Because the maximum and most common "days supply" that can be dispensed at the VA is 90 for drugs such as LEF, any patient who did not receive a prescription within 90 days of the last prescription was defined as having discontinued LEF. All prescriptions occurring in the last quarter (between April 1, 2001 and June 30, 2001) were defined as being censored because their discontinuation status could not be determined. Prescriptions for any other DMARD occurring within 90 days of the reference LEF prescription were defined as concurrent use.

Data collection from individual VAMCs. Ten medical centers with the largest number of deemed discontinuers were identified: Albuquerque (60 discontinuers), Phoenix (58), Los Angeles (45), Durham (38), Tampa (38), Dallas (37), Richmond (30), Minneapolis (28), Milwaukee (27), and St. Louis (25). Individual medical records of discontinuers were reviewed at 7 of these centers. The St. Louis VAMC (the coordinating research center) distributed the SSNs of discontinuers to the Albuquerque, Dallas, Los Angeles, Minneapolis, Phoenix, and Tampa VAMCs. Participating physicians used a standardized data collection form to review the clinical records of 291 discontinuers (8.75% of the total 3,325 patients and 20.9% of the 1,391 patients who discontinued LEF) to identify the reasons for discontinuation. The following data were abstracted from clinic notes using a standardized form: disease for which LEF was prescribed, LEF-associated adverse events, preexisting liver disease, and liver function abnormalities associated with LEF therapy.

Data analyses. Descriptive statistics were performed on sociodemographic data, loading patterns, and number of LEF prescriptions per quarter. Kaplan-Meir life-table analysis was used to estimate the duration of treatment. Logistic regression and Cox proportional hazards modeling were used to determine the variables predictive of discontinuation. The Cox proportional hazards method accounted for the duration of LEF treatment in each individual while developing a model to identify variables predictive of discontinuation. PC-SAS software (SAS Institute, Cary, NC) was used for all statistical analyses.

RESULTS

This cohort was predominantly male (92%), older (47% were over 65 years of age), and white (63% were white, 7% African American, and race was undocumented in 26%) (Table 1). The mean annual income was $23,000 (SD $48,000, median $14,000).

Use of LEF was widely adopted in the VA system shortly after FDA approval, as indicated by the observation that prescriptions were being written by providers at 110 VAMCs within 9 months following the drug's introduction. The number of patients newly started on LEF rapidly increased following FDA approval from 75 patients in the 4th quarter of 1998 to 325 patients in the 4th quarter of 1999. As noted in Table 2, the number of patients receiving new prescriptions remained relatively constant, in the range of 230 to 425. In the second quarter of 2001, nearly 2,000 patients received at least 1 LEF prescription.

Because of LEF's prolonged half-life and the desirability of rapidly attaining a steady state blood level, the FDA approved an oral loading dose of 100 mg daily for 3 days, followed by 10–20 mg daily. In clinical practice, significant variations in the loading patterns were observed because only 61% received the recommended loading sequence, 4% received 100-mg tablets daily for 2 days, 3%

Table 1. Sociodemographic characteristics of 3,325 leflunomide recipients

Characteristic	Leflunomide recipients, % (n)
Sex	
Female	8.0 (267)
Male	91.3 (3,038)
Missing	0.6 (20)
Age, years	
<34	1.6 (53)
35–44	6.0 (192)
45–54	20.7 (689)
55–64	24.5 (813)
65–74	31.6 (1,051)
>74	15.3 (507)
Race	
White	62.5 (2,080)
African American	6.9 (230)
Other	4.7 (140)
Missing	26.6 (875)
Annual income in 1998–2001	
<$20,000	61.4 (2,043)
$20,000–$40,000	28.2 (938)
$40,001–$60,000	4.2 (140)
>$60,000	5.2 (174)
Missing	0.9 (30)

received some other loading pattern, and 31% did not receive any loading dose (Table 3).

LEF was prescribed without any other DMARD in 33% of patients, with methotrexate in 24%, hydroxychloroquine in 11%, hydroxychloroquine + methotrexate in 10%, or with other combinations in 22% (Table 4). LEF was discontinued in 42% (1,391 of 3,325) of patients. The median time to LEF discontinuation, estimated by survival analysis, was 17.6 months (95% confidence interval [95% CI] 15.7–18.7; Figure 1). Of the patients who discontinued LEF, 570 (41%) did so within 3 months and 876 (63%) within 6 months (Table 5). Logistic regression results indicated increased odds for LEF discontinuation with 3-day loading (odds ratio [OR] = 2.0, 95% CI 1.76–2.4), age <44 years (OR = 1.6, 95% CI 1.2–2.1), age >75 years (OR = 1.8, 95% CI 1.4–2.2), and annual income <$60,000 (OR = 1.8, 95% CI 1.3–2.5). Reduced odds for discontinuation were associated with loading patterns other than 100 mg for 3 days (OR ranging from 0.2 to 0.6) and annual incomes >$60,000 (OR = 0.6, 95% CI 0.4–0.8). Results were identical when the analysis was repeated with Cox proportional hazard modeling. At the time of discontinuation, LEF was being administered alone in 34%, in combination with methotrexate in 17%, with etanercept in 10%, with hydroxychloroquine in 9%, or with other combinations in 30% (Table 6).

Table 3. Leflunomide loading patterns

Loading pattern	% (n)
100 mg for 3 days	61.2 (2,037)
100 mg for 2 days	4.4 (147)
100 mg once weekly for 3 weeks	0.5 (18)
No load; begin 10 mg/day	5.4 (180)
No load; begin 20 mg/day	25.8 (859)
Other loading pattern	2.5 (84)

The medical records of 291 patients who discontinued LEF at 7 VAMCs were reviewed. Of these discontinuers, most (80%) were being treated for RA, the only approved indication; 8% received LEF for psoriatic arthritis, and 12% for other indications, e.g., discoid lupus, lupus, polymyositis, polymyalgia rheumatica, and giant cell arteritis. The most commonly cited reasons for discontinuation were lack of efficacy (30%), gastrointestinal symptoms including diarrhea (29%), and noncompliance and lost to followup (14%) (Table 7). Of the discontinuers, 19 (6.5%) were eventually restarted on LEF, often at a lower dosage.

Data extracted in April 2002 from the central VA data-

Table 2. Initiation and discontinuation of leflunomide as a function of calendar quarter

Calendar quarter	Leflunomide prescriptions written, n (%)	Patients on whom leflunomide treatment was		Patients who received leflunomide during quarter, n
		Initiated* n (%)	Discontinued† n (%)	
4th 1998	161 (0.6)	75 (2.3)	2 (0.14)	75
1st 1999	791 (3.0)	231 (7.0)	56 (4.0)	304
2nd 1999	1,108 (4.2)	275 (8.3)	69 (5.0)	490
3rd 1999	1,917 (7.3)	325 (9.8)	116 (8.3)	752
4th 1999	2,352 (9.0)	322 (9.7)	122 (8.8)	937
1st 2000	2,826 (10.8)	379 (11.4)	167 (12.0)	1,175
2nd 2000	2,257 (8.6)	243 (7.3)	158 (11.4)	1,168
3rd 2000	3,385 (13.0)	424 (12.8)	243 (17.5)	1,476
4th 2000	2,827 (10.8)	324 (9.7)	173 (12.4)	1,476
1st 2001	4,099 (15.7)	381 (11.4)	285 (20.5)	1,792
2nd 2001	4,423 (16.9)	346 (10.4)	NA	1,934
Totals	26,146	3,325	1,391	

* Initiation of leflunomide is defined as patients who received their first prescription for leflunomide in the indicated quarter.
† Discontinuation of leflunomide is defined as patients who received a leflunomide prescription in the indicated quarter but in no successive quarter. NA = not available.

Table 4. DMARD combinations at initiation of LEF among 3,325 patients*

DMARD combination	% (n)
LEF only	32.6 (1,086)
LEF + MTX	23.4 (780)
LEF + MTX + SSZ	1.6 (55)
LEF + MTX + HCQ	10.3 (345)
LEF + MTX + HCQ + SSZ	1.4 (49)
LEF + HCQ	10.8 (361)
LEF + HCQ + SSZ	1.5 (51)
LEF + SSZ	3.0 (101)
LEF + etan.	2.7 (90)
LEF + AZA	2.4 (83)

* DMARD = disease-modifying antirheumatic drug; LEF = leflunomide; MTX = methotrexate; SSZ = sulfasalazine; HCQ = hydroxychloroquine; etan. = etanercept; AZA = azathioprine.

base (PTF) indicated that 103 of the 3,325 LEF recipients had died, including 78 patients who were in the group of 1,391 discontinuers. The median interval between the last LEF prescription and the date of death was 3.6 months (mean 8 months, SD 8.6 months); for 31 patients (44%) the date of death occurred at least 6 months after their last LEF prescription. Seven of the 78 discontinuers who died were patients at 1 of the 7 medical centers that collaborated in the present study, and their medical records were reviewed. An additional 17 deaths, not reported in the central VA database, were noted on chart review at participating medical centers. Among all patients (291) whose charts were reviewed, 24 were dead but no deaths were attributed to LEF, although it was being taken at the time of death in 11 patients.

DISCUSSION

We report the use of LEF in a national cohort of predominantly elderly, low-income, male veterans. Only 61% received the recommended loading dose of 100 mg daily for 3 days. LEF was initially prescribed without any other DMARD in one-third of patients, with methotrexate alone or with methotrexate and other DMARDs in 37% of patients, and with DMARDs other than methotrexate in the remainder. Forty-two percent of patients discontinued

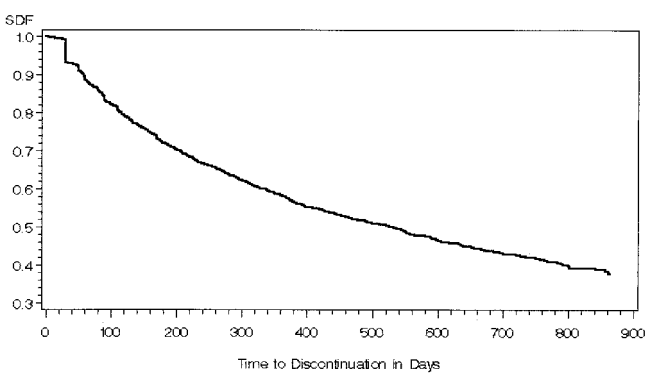

Figure 1. Discontinuation of leflunomide: Kaplan-Meir survival analysis. SDF = survivor density function (proportion with no event at a given time).

Table 5. Duration of leflunomide therapy among 1,391 discontinuers

Months to discontinuation	% (n)
1	17.8 (247)
2	13.2 (184)
3	10.5 (146)
4–6	21.6 (301)
7–9	12.6 (175)
10–12	9.4 (31)
13–18	9.7 (134)
>18	5.3 (73)

LEF, 41% within 3 months and 63% within 6 months. Patients were more likely to discontinue LEF if they had initially received a 3-day 100-mg loading dose, were younger than 44 years or older than 75 years, and reported an annual family income of less than $60,000. Abnormal liver function test results were cited as a reason for discontinuation in only 5% of these patients. No deaths were attributed to LEF. Our data therefore support the conclusion that LEF is a relatively safe drug in clinical practice, and that a loading dose of less than 100 mg daily for 3 days is better tolerated.

The in vivo activity of LEF is attributed to its active metabolite A-771726 (M1), which has a minimum half-life of 15 days. In the absence of a loading dose, it has been estimated that attainment of steady-state plasma concentrations would require nearly 2 months. The 25 mg/day regimen was found to be most effective, but subsequently a dose of 20 mg/day was determined to maximize the probability of clinical success based on a population pharmacokinetic model analysis (17). In the pivotal multinational clinical trials (4–7), a 100-mg loading dose for 3 days followed by 20 mg/day was used to ensure rapid attainment of steady-state levels. Only in the open label (18) and randomized (19) studies to evaluate the combination of LEF and methotrexate, was 100 mg loading for 2 days and an optional daily dose of 10 mg used.

Anecdotal evidence suggests that rheumatologists omit loading doses or prescribe alternate loading patterns to avoid gastrointestinal toxicity. In our cohort, besides some

Table 6. DMARD combinations at discontinuation among 1,391 patients who discontinued LEF*

DMARD combination	% (n)
LEF only	34.3 (477)
LEF + MTX	17.4 (242)
LEF + MTX + etan.	5.5 (77)
LEF + MTX + HCQ	5.1 (71)
LEF + MTX + HCQ + etan.	1.9 (27)
LEF + HCQ	9.4 (130)
LEF + HCQ + etan.	2.7 (38)
LEF + SSZ	1.8 (25)
LEF + etan.	10.0 (139)
LEF + AZA	1.6 (22)

* DMARD = disease-modifying antirheumatic drug; LEF = leflunomide; MTX = methotrexate; etan. = etanercept; HCQ = hydroxychloroquine; SSZ = sulfasalazine; AZA = azathioprine.

Table 7. Reasons for discontinuation of leflunomide among 291 patients*

Reason for discontinuation	% (n)
Lack of efficacy	30 (87)
All gastrointestinal	29 (83)
Diarrhea	15 (45)
Unknown	15 (22)
Noncompliance or lost for followup	14 (41)
Other reasons	10 (28)
Liver function test result elevation	5 (15)
Rash	4 (12)
Death†	4 (11)
Weight loss	2 (6)
Leukopenia	2 (5)
Asthenia	1 (3)
Alopecia	1 (3)
Headache	1 (2)

* Reasons do not add up to unity because more than 1 reason was cited for discontinuation in 15% of patients.
† No death was attributed to leflunomide.

common regimens (Table 3), 3% of patients received unconventional loading regimens, such as 60 mg for 3 days and 40 mg daily for a week. Patients were less likely to discontinue if they received loading patterns other than 100 mg for 3 days. Although it is possible that the alternative loading regimens may compromise clinical efficacy, such regimens seem to be tolerated better and help ensure continuation of therapy. Our study did not examine whether the higher discontinuation rate with the 3-day loading dose was caused by a higher frequency of side effects, but such an association between 3-day loading and occurrence of early adverse events has been reported (20).

Combination DMARD therapy is frequently used by rheumatologists (21). Although there have been no RCTs to evaluate combination of LEF with DMARDs other than methotrexate, such combinations are used in practice. In our cohort, 34% of patients were started on LEF without another DMARD, and 49% were prescribed LEF with some combination of methotrexate and/or hydroxychloroquine. Among the 1,391 patients who discontinued LEF, 34% were taking only LEF at the time of discontinuation, and 52% were taking some combination of methotrexate and/or hydroxychloroquine.

The most frequently reported adverse events related to LEF include diarrhea, nausea, rash, and alopecia. Liver toxicity, most commonly mild transaminitis, was also reported in early trials (4,5,22). The combination of methotrexate and LEF has been associated with particularly high levels of liver toxicity, with up to 63% of patients in other studies developing transaminitis or more severe liver damage (18,23). The European Agency for the Evaluation of Medicinal Products reported 296 cases of hepatic adverse events during 104,000 person years of LEF therapy, of whom 232 patients developed liver enzyme abnormalities, 2 patients developed cirrhosis, 15 patients developed liver failure, and 15 patients died (10 deaths possibly related to LEF) (24). In our cohort, presumed LEF-induced liver enzyme elevation was the reason for drug discontinuation in only 15 patients (15 of 291 or 5% of reviewed medical records of discontinuers), and no deaths were attributed to LEF. The explanation for the relatively low prevalence of liver damage we observed is speculative, but may include differences in patient clinical characteristics and the retrospective design of this study.

The number of withdrawals and the reasons for discontinuation in the 3 major clinical trials on LEF are summarized in Table 8. The overall discontinuation rates were about 20–30% in these trials. In a large postmarketing study on 4,250 RA patients receiving LEF between 1998 and 2000, Wolfe et al (11) reported that 25% of the patients had discontinued the medication at 1.1 years. This cohort was predominantly white (90%) and female (80%) with a median annual income of $35,000. The best predictor of discontinuing therapy was the occurrence of side effects, although prior DMARD use and concomitant use of prednisone or methotrexate also increased discontinuation. In contrast, in a community-based practice in the US (14),

Table 8. Withdrawal rates reported in the pivotal leflunomide randomized clinical trials

Characteristic	Clinical trial			
Name of the trial	US301	MN301	MN302	MN302
Reference number	4	5	7	7
Total number of patients randomized to leflunomide	182	133	501	292
Duration, years	1	0.5	1	2
Discontinuation rate, %	47	28	30	20
Reasons for discontinuation, %*				
Adverse events	22	14	19	8
Lack of efficacy	17	7	7	6
Protocol violation	0	NA†	NA†	NA†
Noncompliance	0.5	NA†	2	2
Lost to followup	0.5	NA†	NA†	NA†
Voluntary	6	NA†	NA†	NA†
Death	NA†	NA†	1	<1
Other	0.01	6	1	4

* Percentage of patients randomized to leflunomide.
† Not reported or not available.

52% of patients discontinued LEF within a year, 35% because of inefficacy, and 17% because of adverse events. Similarly, in a cohort of 99 RA patients from a community practice in the Netherlands, LEF was discontinued in 61 patients (62%) after a median of 12 weeks (range 1–64 weeks) with 55% of them discontinuing due to side effects (13). In a Swedish postmarketing surveillance study, only 22% of patients were still receiving LEF at 20 months, and most withdrawals were due to side effects that occurred in the few weeks following initiation (15). Our study is more in agreement with these studies than the RCTs or the postmarketing study of Wolfe et al (11).

The primary strengths of this study are that virtually every individual who received LEF from the VA was identified and included in the data analyses. In addition, to our knowledge, this is the first study of LEF use that includes a large number of older males from predominantly lower income groups.

The major limitations of this study are that it is retrospective, and (because of logistical difficulties associated with obtaining HSS approval from a large number of VAMCs) medical record review was performed only on patients who discontinued LEF at 7 academically affiliated facilities. In addition, race was undocumented in 26% of patients, which diminishes the validity of this variable in the model developed to predict discontinuation; the cohort was diagnostically heterogeneous; it was not possible to examine the association between disease duration or severity and outcome; the definition of inefficacy was based on individual physician interpretation rather than standardized definitions; drug toxicity was not defined in a consistent manner across medical centers; it was not possible to assess the relationship between comorbid medical illnesses or non-DMARD medication use and risk for drug toxicity; the discontinuation rate likely represents the highest estimate because review of medical records revealed that 6.5% of the patients who met criteria for discontinuers subsequently resumed the drug; and the definitions applied to identify overlapping DMARD use at the initiation and discontinuation of LEF probably do not precisely establish intended combination treatment regimens in all patients.

In this large, predominantly male, low-income national cohort with significant numbers of elderly patients, LEF was used with relative safety. The VA's national pharmacy and clinical databases provide an excellent resource for postmarketing evaluation of medication use and toxicity, particularly for an older male population that typically does not participate in clinical trials.

REFERENCES

1. McKee M, Britton A, Black N, McPherson K, Sanderson C, Bain C. Interpreting the evidence: choosing between randomized and non-randomized studies. BMJ 1999;319:312–5.
2. Venning GR. Identification of adverse reactions to new drugs, II: how were 18 important adverse reactions discovered and with what delays? BMJ 1983;286:289–92.
3. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis 2000;59: 841–9.
4. 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. Arch Intern Med 1999;159:2542–50.
5. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al, the European Leflunomide Study Group. Efficacy and safety of leflunomide compared with sulfasalazine in active rheumatoid arthritis: a double-blind, randomized, multicenter trial. Lancet 1999;353:259–66.
6. Strand V, Tugwell P, Bombardier C, Maetzel A, Crawford B, Dorrier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Arthritis Rheum 1999;42:1870–8.
7. 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 2000;39:655–65.
8. Tugwell P, Wells G, Strand V, Maetzel A, Bombardier C, Crawford B, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide compared with methotrexate in patients with rheumatoid arthritis: sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. Arthritis Rheum 2000;43:506–14.
9. Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olsen N, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Arthritis Rheum 2001;44:1984–92.
10. 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.
11. Wolfe F, Stephenson B, Doyle J. RA patients remain on leflunomide as long as methotrexate in clinical practice: accumulating evidence of long-term tolerability and effectiveness of leflunomide in RA [abstract]. Arthritis Rheum 2001;44 Suppl 9:S144.
12. Kalden J, Schattenkirchner M, Sorensen H, Emery P, Deighton C, Rozman B, et al. Five year follow-up: efficacy and safety of leflunomide in patients with active rheumatoid arthritis [abstract]. Arthritis Rheum 2001;44 Suppl 9:S173.
13. Van Pelt PA, van Schaardenburg D, Bultink IEM, Dijkmans BAC. High discontinuation rate of treatment with leflunomide in daily practice [abstract]. Arthritis Rheum 2001;44 Suppl 9:S143.
14. Miller ML, Morton GL, Anderson LG, Keroack BJ, Radis CD. One-year community based experience with leflunomide in the treatment of rheumatoid arthritis [abstract]. Arthritis Rheum 2000;43 Suppl 9:S343.
15. Geborek G, Crnkic M, Peterson IM, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up program in southern Sweden. Ann Rheum Dis 2002;61:793–8.
16. Boyko EJ, Koespell TD, Gaziano JM, Horner RD, Feussner JR. US Department of Veterans Affairs Medical Care System as a resource to epidemiologists. Am J Epidemiol 2000;151:307–14.
17. Schiff MH, Strand V, Oed C, Loew-Friedrich I. Leflunomide: efficacy and safety in clinical trials for the treatment of rheumatoid arthritis. Drugs Today (Barc) 2000;36:383–94.
18. Weinblatt ME, Kremer J, 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.
19. Kremer JM, Caldwell JR, Cannon GW, Genoves M, Cush JJ, Bathon J, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on methotrexate alone: a double-blind placebo controlled study [abstract]. Arthritis Rheum 2000;43 Suppl 9:S224.
20. Erra A, Moreno E, Tomas C, Sans X, Arnal C, Barcelo P, et al.

Efficacy and safety of leflunomide in rheumatoid arthritis patients: relationship between adverse events and loading dose. Ann Rheum Dis 2002;61 Suppl I:379.
21. Mikuls TR, O'Dell J. The changing face of rheumatoid arthritis therapy: results of serial surveys. Arthritis Rheum 2000;43: 464–5.
22. 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.
23. Weinblatt ME, Dixon JA, Falchuk KP. Serious liver toxicity in a patient receiving methotrexate and leflunomide. Arthritis Rheum 2000;43:2609–11.
24. The European Agency for the Evaluation of Medicinal Products. EMEA public statement on leflunomide (Arava): severe and serious hepatic reactions. Accessed August 8, 2002. URL: www.emea.eu.int/pdfs/human/press/pus/561101en.pdf.