Adverse Events with Disease Modifying Antirheumatic Drugs (DMARD): A Cohort Study of Leflunomide Compared with Other DMARD

GRANT W. CANNON, WILLIAM L. HOLDEN, JUHAERI JUHAERI, WANJU DAI, LINDA SCARAZZINI, and PAUL STANG

ABSTRACT. ***Objective.*** To determine and compare the incidence of serious adverse events (AE) during treatment of rheumatoid arthritis (RA) with disease modifying antirheumatic drugs (DMARD), focusing on leflunomide (LEF).

Methods. A retrospective cohort study of a large US insurance claims database was performed. Study groups were patients with RA classified by DMARD exposure as either no-DMARD therapy, single-agent DMARD (monotherapy), or combination-DMARD therapy. Specific DMARD examined were leflunomide (LEF) and methotrexate (MTX), compared to other DMARD (penicillamine, hydroxychloroquine, sulfasalazine, gold, etanercept, infliximab) and no DMARD (nonsteroidal antiinflammatory drugs, COX-2 inhibitors). All AE reported were considered endpoints; primary endpoints included hepatic, dermatologic, hematologic, infectious, respiratory, hypertension, and pancreatitis AE.

Results. The 40,594 RA patients of the study period (September 1998 to December 2000) accumulated 83,143 person-years (PY) of followup. Followup for each of the groups was: DMARD-monotherapy, 46,054 PY (55% of total); combination-DMARD, 25,830 PY (14%); and no-DMARD, 11,259 PY (14%). The incidence rate of all AE combined was significantly lower for LEF monotherapy (94 events/1000 PY) than MTX (145 events/1000 PY), other DMARD (143 events/1000 PY), or no DMARD (383 events/1000 PY) ($p < 0.001$ for all comparisons). The "all-AE" rates during combination therapy with LEF + MTX (43/1000 PY) and LEF + other DMARD (59/1000 PY) were lower than the "all-AE" rate for DMARD + MTX (70/1000 PY; $p = 0.002$). LEF monotherapy had the lowest rate of hepatic events in the DMARD monotherapy groups.

Conclusion. The rates of AE in the LEF group, alone and combined with MTX, were generally lower than or comparable to the AE rates seen with MTX and other agents. (J Rheumatol 2004;31:1906–11)

Key Indexing Terms:
ADVERSE EFFECTS ANTIRHEUMATIC AGENTS METHOTREXATE COHORT STUDIES

Hepatic and other adverse events (AE) during treatment of patients with rheumatoid arthritis (RA) with leflunomide (LEF) have been reported in clinical trials prior to approval by regulatory authorities. The frequency of these reported events as well as other rare AE may not be well described during clinical trials because of small sample sizes. The use of large databases in postmarketing surveillance allows identification of uncommon AE and a comparison of the incidence rates of AE during different RA treatments. These postmarketing data are also important to evaluate AE during clinical practice other than clinical trials[1-4].

This retrospective cohort study of 40,594 patients with RA compared AE during treatment with disease modifying antirheumatic drugs (DMARD). The investigation encompassed more than 83,000 person-years (PY) of followup. The principal aim of the study was to determine and compare the incidence rates of serious hepatic (e.g., liver necrosis, hepatitis, acute liver failure), cutaneous (Stevens-Johnson syndrome, toxic epidermal necrolysis), hematologic (aplastic anemia, pancytopenia), hypertensive, respiratory (bronchitis, influenza), and pneumonitis AE during treatment with LEF, methotrexate (MTX), and other DMARD as monotherapy and combination therapy. In addition, the rates of AE were also compared to rates in patients with RA not receiving DMARD therapy.

MATERIALS AND METHODS

This retrospective cohort study utilized data from the Aetna-US Healthcare claims database. This database contains health information on 6,470,000 covered persons, with linkage to medical, pharmacy, and laboratory data.

From the Veterans Affairs Salt Lake City Health Care System and Division of Rheumatology, University of Utah, Salt Lake City, Utah; Aventis Pharmaceuticals, Bridgewater, New Jersey; and Galt Associates, Inc., Sterling, Virginia, USA.

G.W. Cannon, MD, Professor of Medicine, Veterans Affairs Salt Lake City Health Care System and University of Utah; W.L. Holden, PhD; J. Juhaeri, PhD; W. Dai, MD, DrPH; L. Scarazzini, MD, Aventis Pharmaceuticals; P. Stang, PhD, Galt Associates, Inc.

Address reprint requests to Dr. G.W. Cannon, Division of Rheumatology 4B200, University of Utah Medical Center, 30 North 1900 East, Salt Lake City, UT 84132-2404. E-mail: grant.cannon@med.va.gov

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Aetna is one of the leading administrators of health care benefits in the United States, serving about 13,000,000 members with 11,300,000 participants in dental programs and 11,700,000 members in medical programs as of June 30, 2003. There are over 579,000 healthcare services providers, including over 249,000 primary care and specialist physicians associated with 3589 participating hospitals. The age distribution of the source members mimics the age distribution of the US population. These data may be abstracted for evaluation of specific populations and case validation in medical records. This claims database has been used in similar programs to evaluate colorectal cancer screening[1] and asthma[2].

Patient selection

Inclusion criteria. Patients were required to have a diagnosis of RA by ICD-9 code (714.0) and/or a prescription for LEF while enrolled in the claims database at any time during the period September 1998 to December 2000. A prescription of LEF was considered a surrogate marker for the diagnosis of RA as LEF is approved only for the treatment of RA. Patients were 18 years of age or older at the time of enrollment into the cohort. All patients were required to have at least a 90-day observation period prior to entry into the cohort.

Exclusion criteria. Patients receiving DMARD other than LEF were excluded if they experienced any of the hepatic events of interest (Table 1) in the 90-day period prior to entry into the cohort. However, all LEF users were included in the study, whether they had a history of hepatic disease or not. Patients were excluded if data were not available to determine the patient's sex or date of birth.

Exposure group assignment

The cohort groups were defined on the basis of DMARD exposure. The DMARD evaluated were LEF, MTX, gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept. Groups were defined as no-DMARD therapy, single-agent DMARD (monotherapy), or combination-DMARD therapy. Specific DMARD examined were LEF and MTX, in comparison to "other DMARD" and no DMARD. Other DMARD were evaluated as a group and included patients treated with gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept. All these patients could be receiving nonsteroidal antiinflammatory drugs (NSAID) and/or cyclooxygenase-2 (COX-2) inhibitors as well. The no-DMARD group consisted of RA patients without LEF, MTX, or other-DMARD treatment as defined above. These no-DMARD patients could be receiving NSAID including COX-2 inhibitors. LEF monotherapy and LEF + MTX patients were used as reference groups. Comparison groups for LEF monotherapy included MTX, other-DMARD, and no-DMARD patients; LEF + MTX combination therapy patients were compared to LEF + other-DMARD combination therapy and DMARD + MTX combination therapy patients. Only 2-drug combinations were evaluated in this analysis.

This was a dynamic retrospective cohort study, a design that has the ability to identify a large number of exposure groups — defined by diagnosis and medication exposure — and follow patients through their course of therapy to determine the strength of the association between exposure and AE over a period of time.

The dynamic design means that patients could contribute exposure and followup time to several exposure groups. Each exposure group member's person-time began with the first dispensing of the drugs of interest (LEF, MTX, other DMARD, or no DMARD) and continued through the end of the last prescription dispensed plus an associated washout period. The washout period was defined as 5 drug half-lives. For example, LEF has a relatively long half-life (about 12 days), and the washout period was set at 5 times the half-life, or 60 days. Thus, the person-time for a single LEF prescription included each day from the date of the first prescription dispensed through the last day for that prescription plus 60 days, or the first day of the next prescription dispensed, whichever came first. If a patient had overlapping prescriptions for different RA medications, the person-time was apportioned to the appropriate combination exposure category for that period of overlap time. These calculations were readily accomplished with the database, which records the drug-specific information as number of days' supply, units dispensed, strength, and date of dispensing.

Person-time at risk was aggregated into the different time windows according to LEF, MTX, other-DMARD, and no-DMARD use, and continued until one of the following occurred: earliest confirmed event of interest, end of washout for a given medication, date of last enrollment, death, or end of the study period.

Table 1. Codes for hepatic events.

Diagnosis	ICD-9CM
Acute or subacute liver necrosis*	570
Hepatitis, noninfectious toxic*	573.3
Jaundice	782.4
Cirrhosis of liver, no alcohol	571.5
Biliary cirrhosis	571.6
Hepatitis, noninfectious	573.3
Other specified liver disorder	573.8
Unspecified liver disorder	573.9
Hepatic coma	572.2
Elevated transaminase/lactic acid dehydrogenase	790.4

* Cases of particular interest.

Primary endpoints

Any inpatient or outpatient experience coded in the database for the predefined ICD-9 codes was an endpoint. Primary endpoints included codes for hepatic events (acute and subacute necrosis, biliary cirrhosis, hepatic coma, noninfectious hepatitis, cirrhosis, unspecified chronic liver disease, other unspecified liver disease, jaundice, elevated enzymes; Table 1); hematologic events (acquired pancytopenia, aplastic anemia); cutaneous events (Stevens-Johnson syndrome, toxic epidermal necrolysis); hypertension; pneumonitis; acute pancreatitis; and respiratory tract infections (influenza and bronchitis). Whereas a representative sample of serious hepatic events was validated by chart review, other adverse events were not independently validated.

Case validation

The validation process was an independent chart review of the claims data, abstracted from the source medical records according to an established procedure of the US Food and Drug Administration, using forms developed by that agency. The validation effort was directed to a random sample of the hepatic events, but included 100% of the liver necrosis events. Of the hepatic AE reported, a random sample of the following conditions was validated — 100% of liver necrosis, 20% of biliary cirrhosis, 25% of hepatic coma, 25% of noninfectious toxic hepatitis, 10% of nonalcoholic liver cirrhosis, 12% of unspecified chronic liver disease, 10% of unspecified liver disorder, 12% of jaundice, and 10% of elevated liver enzyme cases. This analysis resulted in validation of 100 of 651 cases. The validation process involved a review of outpatient and inpatient medical records, liver biopsy reports, radiographic reports, and hepatic chemistries. These data were abstracted by a trained nurse-abstractor.

Data analysis. Simple demographic characteristics of the cohort were generated, in addition to total subjects, person-time, mean length of exposure time, and number of events. Incident rates were calculated to compare events between LEF monotherapy patients and a series of comparator patients (e.g., MTX monotherapy and other DMARD), along with 95% confidence intervals (CI).

Adjustment for potential confounders was performed using combined age, sex, and comorbidity data in a Poisson regression model. The Poisson model was chosen because it presumes that the number of outcomes of interest is small compared to the total cohort size, and that the outcomes are statistically independent events — even if the same individuals contribute

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person-time to more than one exposure group. Poisson regression theory also presumes that the rarity of outcome events in any one timeframe has little effect on the probability of a specified number of events in the next timeframe[5–8]. The Charlson Index[9], a weighted scoring scheme, was employed to calculate the comorbidity score used in the model.

RESULTS

A total of 40,594 patients with RA were entered into the cohort study. These patients contributed roughly 83,143 person-years (PY) of total followup. DMARD-monotherapy exposure accounted for 46,054 PY of followup, combination-DMARD therapy for 25,830 PY of followup, and no-DMARD therapy for an additional 11,259 PY of followup. Patient demographic data are presented in Table 2. The cumulative PY exposure, mean exposure time, and the number of patients in the database on the therapies of interest are displayed in Table 3. DMARD exposure was the longest in the monotherapy groups, with the mean exposure time of MTX and LEF users being similar; DMARD + MTX had the longest average exposure time among the 2-drug therapies.

Comorbidities in the different exposure groups were evaluated to determine the groups' comparability. This analysis was limited to the monotherapy groups, as determining comorbidities on 2-drug therapy was difficult given the lack of ability to pinpoint when a comorbidity occurred relative to the start of a given therapy. Seventy-two different conditions were examined prior to the index date, defined as the date on which a person was entered in the cohort. The number of comorbidities at the index date in the LEF (mean = 1.6) and MTX (mean = 1.8) monotherapy groups was slightly lower than the other DMARD monotherapy group (mean = 2.7), although no statistically significant differences were found. The comorbidities are potential confounders and as such were included in the Poisson regression model.

Table 2. Demographic characteristics of patients.

Age group, yrs	Men	Women	Total (%)
18–30	408	1554	1962 (5)
31–50	3341	9951	13,292 (33)
51–64	3499	9485	12,984 (32)
65+	3598	8758	12,356 (30)
Total (%)	10,846 (27)	29,748 (73)	40,594

Table 3. Descriptive statistics of person-time exposures across selected drug groups.

Exposure Group	Person-year Exposure	Mean Exposure Time, days	Patients on Therapy
DMARD monotherapy			
LEF	4214	585	2633
MTX	10,682	410	9514
DMARD	31,158	766	14,861
No-DMARD	11,259	377	10,896
DMARD combination			
LEF + MTX	1415	215	2408
LEF + DMARD	5551	753	2692
DMARD + MTX	18,864	790	8725

Case validation. The data validation showed that 98% of the cases selected for validation had a defined liver disease diagnosis. The overall agreement between original and validation diagnoses was 81.3%. The concurrence for specific diagnoses was 100% for nonalcoholic cirrhosis, biliary cirrhosis, other specified liver disorder, unspecified nonalcoholic chronic liver disease, elevated liver enzymes; 79% for unspecified liver disorder, 75% for noninfectious hepatitis, and 50% for jaundice. The concurrence rates were similar for cases associated with LEF, MTX, and other DMARD.

Adverse event rates for all endpoints. LEF had the lowest crude and adjusted incidence rate for the "all-AE" endpoint compared to the other monotherapies (Table 4). This rate was significantly lower than rates for all the comparators: 94.1 events/1000 PY (adjusted for age, sex, and comorbidities) compared to 143.7 events/1000 PY in DMARD users and 145.0/1000 PY among MTX users ($p < 0.0001$ for both comparisons).

LEF + MTX had an "all-event" rate of 42.8/1000 PY, significantly lower than the non-LEF combination DMARD + MTX (69.5 events/1000 PY; $p = 0.0005$). The LEF + MTX rate was also lower than the LEF + DMARD group (58.7/1000 PY; $p = 0.03$).

Hepatic events. A total of 651 hepatic events were observed in this cohort study. LEF had a hepatic event rate of 4.1/1000 PY, significantly lower than those among no-DMARD users (13.02/1000 PY; $p < 0.001$), but not significantly different from those of other DMARD monotherapy (4.2/1000 PY) and MTX (6.2/1000 PY). Among 2-drug therapy groups, hepatic event rates were not significantly different across the groups.

Of the 651 hepatic events observed in this study, 61% were noninfectious toxic hepatitis, 4% were biliary cirrhosis, 4% were acute necrosis of the liver, 2% were

Table 4. Incidence rates (per 1000 person-years) of any adverse event.

Exposure Group (n)*	Crude Rate (95% CI)	Adjusted Rate (95% CI)
LEF mono (465)	110.4 (100.8, 120.8)	94.1 (84.4, 104.8)
MTX mono (1789)	167.5 (159.9, 175.4)	145.0 (136.3, 154.3)
DMARD mono (5475)	175.7 (171.1, 180.4)	143.7 (137.4, 150.3)
LEF + MTX (72)	50.9 (40.4, 64.1)	42.8 (32.8, 55.9)
LEF + DMARD (370)	66.7 (60.2, 73.8)	58.7 (52.0, 66.2)
DMARD + MTX (1512)	80.2 (76.2, 84.3)	69.5 (65.0, 74.3)
No DMARD (4934)	438.3 (426.2, 450.7)	382.3 (365.8, 399.6)

* Number of events.

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hepatic coma, and 28% were "orphan events," i.e., AE not assigned to any drug exposure because they did not occur within the defined exposure windows. There were 4 cases of adverse hepatic events among LEF + MTX users: noninfectious hepatitis (n = 3) and elevated liver enzymes (n = 1). The incidence rates of hepatic outcomes of interest, in total and separately, are presented in Tables 5 and 6.

Hematologic events. There were 105 aplastic anemia and pancytopenia events in the cohort, 19 of which were orphan events. Among the monotherapy exposure group, LEF had a rate of 0.7/1000 PY (95% CI 0–1.5), MTX 0.8 (95% CI 0.2–1.3), and DMARD 1.4 (0.9–1.8). The rarity of the events overall, and in any combination group, precluded calculation of adjusted rates. No hematologic events were seen in the LEF + MTX combination group.

Severe skin reactions. There were 32 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in this study, 5 of which were orphan events. No events were seen in either the LEF monotherapy group or the LEF + MTX combination group. Of note were 14 events observed in the other DMARD group, yielding an unadjusted rate of 0.5/1000 PY, similar to the rate in MTX users (0.6 events/1000 PY).

Table 5. Incidence rates (per 1000 person-years) of hepatic events (hepatic failure, hepatic necrosis, biliary cirrhosis, liver cirrhosis, hepatitis, other specified liver disorder, unspecified liver disorder, and elevation of enzymes).

Exposure Group (n)*	Crude Rate (95% CI)	Adjusted Rate (95% CI)
LEF mono (22)	5.2 (3.0, 7.4)	4.1 (2.4, 7.0)
MTX mono (87)	8.1 (6.4, 9.9)	6.9 (5.1, 9.3)
DMARD mono (246)	7.9 (6.9, 8.9)	4.2 (3.3, 5.3)
LEF + MTX (7)	4.9 (1.3, 8.6)	4.6 (1.9, 11.1)
LEF + DMARD (19)	3.4 (1.9, 5.0)	2.6 (1.5, 4.7)
DMARD + MTX (64)	3.4 (2.6, 4.2)	2.9 (2.1, 4.1)
No DMARD (199)	17.3 (14.9, 19.8)	13.0 (10.4, 16.3)

* Number of events.

Hypertension. Given its considerable prevalence in the general population, hypertension was relatively common. LEF users had an adjusted rate of 33.2 cases/1000 PY, significantly lower than both MTX (51.2 cases/1000 PY; $p < 0.0001$) and other DMARD (47.6 cases/1000 PY; $p < 0.0001$). LEF + MTX also had a relatively low rate, 13.1 cases/1000 PY, which was lower than the DMARD + MTX combination (22.8/1000 PY; $p = 0.008$) and the DMARD + LEF group (19.6/1000 PY; $p = 0.07$).

Pulmonary events. Respiratory events included acute laryngopharyngitis, acute bronchitis, influenza, bronchitis, and respiratory infection not otherwise specified. The lowest rate was found in the LEF group (20 cases/1000 PY), which was significantly lower than the other monotherapy rates (other DMARD group, 36.9/1000 PY; MTX group, 38.9/1000 PY; $p < 0.0001$ for both comparisons). Of the 868 cases observed in the 2-drug combination exposure groups, 17 were seen in LEF + MTX users; the rate (11.8 cases/1000 PY) was not statistically different from comparators [LEF + DMARD, 11.6 (95% CI 8.9–15.1), DMARD + MTX, 19.0 (95% CI 16.7–21.5)]. An effort was also made to identify episodes of drug-induced pneumonitis; however, using available codes for pneumonitis (other specified allergic alveolitis and pneumonitis 495.8, unspecific allergic alveolitis and pneumonitis 495.9, chemical 506.0, other unspecific alveolar and parietoalveolar pneumonopathies 516.8, pulmonary eosinophilia 518.3, and postinflammatory pulmonary fibrosis 515) there were 1038 events reported. No coding was considered to be sensitive, specifically for the identification of drug-induced pneumonitis. The rates of pneumonitis were all similar in the monotherapy groups. The rate in the LEF + MTX group was similar to that seen in the other 2-drug combinations, although generally any 2-drug combination with MTX had higher rates.

Pancreatitis. A rare event overall, pancreatitis occurred in 213 patients in this study, including 8 LEF monotherapy patients, for a rate of 1.2/1000 PY, similar to comparator groups. Only one of the 32 events in the 2-drug exposure

Table 6. Rates of individual liver events. Rates (with number of events) presented per 10,000 person-years, by event (ICD-9 code).

	Necrosis (570)	Hepatic Coma (572.2)	Biliary Cirrhosis (571.6)	Cirrhosis (571.5)	Jaundice (782.4)	Noninfectious Hepatitis (573.3)	Chronic Liver (571.9)	Unspecified (573.9)	Elevated Enzymes (790.4)	Other Unspecified 573.8)
LEF	2.37 (1)	—*	—	—	2.37 (1)	21.36 (9)	—	7.11 (3)	14.24 (6)	4.75 (2)
MTX	0.64 (2)	—	—	0.96 (3)	1.28 (4)	9.95 (31)	—	8.34 (26)	3.53 (11)	3.21 (10)
DMARD	6.55 (7)	4.68 (5)	8.43 (9)	23.40 (25)	6.55 (7)	71.15 (76)	2.81 (3)	30.89 (33)	48.68 (52)	27.15 (29)
LEF + MTX	—	—	—	—	—	35.35 (5)	—	—	14.14 (2)	—
LEF + DMARD	—	1.80 (1)	—	—	1.80 (1)	10.81 (6)	—	10.81 (6)	5.40 (3)	3.60 (2)
DMARD + MTX	—	—	0.53 (1)	3.18 (6)	1.59 (3)	6.89 (13)	0.53 (1)	10.07 (19)	7.95 (15)	3.18 (6)
No DMARD	1.78 (2)	1.78 (2)	3.55 (4)	7.11 (8)	7.11 (8)	52.40 (59)	3.55 (4)	37.31 (42)	39.08 (44)	23.09 (26)

* No event.

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groups occurred in the LEF + MTX group; the resulting rate was also similar to comparators.

DISCUSSION

A detailed analysis of reported hepatic events was undertaken to clarify the relationship between these events and leflunomide. Overall, only a small number of hepatic events were identified in this analysis. No cases of biliary cirrhosis, hepatic coma, cirrhosis, unspecified chronic liver disease, or jaundice were observed in the leflunomide monotherapy cohort. The leflunomide monotherapy group did have a rate of acute and subacute necrosis of 2.4 cases/10,000 (based on one case), which was higher than the rate calculated for MTX (0.6 cases/10,000 PY, 2 cases) and lower than the rate for other DMARD (6.6 cases/10,000 PY, 7 cases), but these rates were not statistically significantly different. When all hepatic events were combined, the LEF exposure group had a rate of hepatic AE not statistically different from the other DMARD exposure group ($p = 0.92$) or MTX exposure group ($p = 0.08$). The LEF users did have significantly lower hepatic rates compared to non-DMARD users ($p < 0.001$). In addition, severe hepatic events were grouped together (including hepatic necrosis, hepatic coma, cirrhosis, jaundice, and noninfectious hepatitis). When the 3 monotherapies were compared, no differences were found between the rates: LEF, 2.61/1000 PY (95% CI 1.07–4.15), MTX, 3.74/1000 PY (95% CI 2.58–4.91), and DMARD, 3.85/1000 PY (95% CI 3.16–4.54).

In the LEF + MTX group, the rate of hepatic events was similar to rates in comparator 2-drug combinations. Indeed, rates of hepatic events were not significantly different across 2-drug therapy groups (Tables 5 and 6).

One interesting finding was that the AE rates associated with monotherapy use were generally higher than the AE rates with 2-drug combination therapy. The lower AE rates in the 2-drug exposure groups may be the result of a "depletion of susceptibles" effect, whereby patients who continue taking the drugs are those who can tolerate them, while those who are "susceptible" to AE select themselves (or are selected) out of the population at risk. Thus, if a proportion of monotherapy patients experienced a hepatic event (the susceptibles) and discontinued the drug, they would not be available for 2-drug therapy; only those who "survived" or who continued the monotherapy would be. Those continuing the monotherapy may be healthier, in the sense that they had not experienced an AE requiring discontinuation of therapy, and might be appropriate candidates for additional therapy. However, the differences in rates were not generally large.

In this study, the other-DMARD cohort had the highest rates of individual hepatic disease. Although MTX is known to be associated with hepatic damage[10–15], there is little direct evidence that other DMARD are associated with low risks of AE. Most studies of DMARD toxicity are short-term and monitor relatively small numbers of patients under clinical trial protocols. The results of such studies may be contradicted by longterm results from clinical practice, which depend on unselected populations of patients. This observation may have been the result of "channeling" bias. A channeling bias may occur if a practitioner specifically assigns treatment on the basis of susceptibility to an AE. For example, because MTX and LEF are known to have potential hepatic side effects, RA patients with known (or potential to develop) hepatic disease may not be prescribed MTX or LEF but rather other DMARD. These susceptible patients would then be more likely to experience hepatic AE that would then result in an apparently higher rate of hepatic AE in the other DMARD exposure group. This process of "channeling" assigns patients with a higher potential to AE to or away from a specific therapy in a nonrandom manner.

In the largest observational study of the adverse effects of DMARD in the United Kingdom, investigators utilizing computerized records of DMARD use and AE in an RA clinic found that the rate of abnormal liver function (not defined in the study) was 0.63/100 PY for sulfasalazine, 2.50/100 PY for MTX, and 2.67/100 PY for azathioprine[16]. In 2 other large studies of longterm results of DMARD therapy, the incidence rates of hepatic abnormalities were 1/100 PY (including elevated liver function tests, but otherwise not defined)[17] and 4.7/100 PY[18] among MTX users.

Liver abnormalities have been reported in RA patients without a clear correlation with therapeutic interventions. Studies of the natural history of RA are for the most part not available independent of treatment[19,20]. However, it has been reported that RA patients develop biochemical evidence of hepatocellular dysfunction and histologic liver abnormalities[21,22]. A recent autopsy study found hepatic fibrosis in 11% of cases reviewed; diffuse fibrosis with no identifiable cause was found in 8.2%[23]. Studies in Scotland revealed that approximately 13% of RA patients had definable liver disease[24,25].

The data collected and analyzed in this study came from a claims database. Insurance claims databases are commonly used in pharmacoepidemiology research, as these evaluations often reflect clinical practice. These databases offer to the investigator large numbers of subjects as well as data on medical services, pharmacy services, and clinical outcomes. However, these databases are not specifically designed for research purposes and the therapies provided to patients are not determined by clinical protocol, but by individual patient circumstances and provider preferences. Limitations of claims databases include lack of data on over-the-counter medications, alcohol use, potential omission of services provided, potential diagnostic and procedural coding errors, lack of indicators of disease severity, limited clinical detail, no data on compliance, potential exposure misclassification, varying and differential lag times for pharmacy and medical claims, and lack of

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lifetime history of the disease under study along with its treatment[26–29]. Furthermore, the quality of the data in the claims database is dependent on the willingness of the physician to fill out (electronically or otherwise) claims forms with the level of detail needed in epidemiologic research. For example, the presence of elevated hepatic enzymes may not be universally and consistently reported by the clinicians in the claims database, resulting in under-reporting of these AE. Inconsistencies in reporting could produce reporting bias, particularly if the severity of the hepatic enzyme abnormalities and/or concurrent therapy such as MTX or LEF treatment influenced the likelihood of reporting a claims event. In addition, information on the severity of RA was not available, nor were data on RA treatments prior to the observation period known.

In conclusion, the incidence rate of the "all-AE" endpoint was significantly lower for patients with RA treated with LEF monotherapy compared to subjects receiving MTX monotherapy, other DMARD monotherapy, and no DMARD. The incidence of the "all-AE" endpoint in the LEF + MTX group was also lower compared to other 2-drug therapy combinations, including DMARD + MTX, although this was not statistically significant. For hepatic events, the calculated incidence rates were comparable for leflunomide and the other monotherapy comparators. Overall, the risk of the evaluated adverse events observed with leflunomide, alone and in combination with MTX, was comparable to the risk with other disease modifying antirheumatic agents used in the treatment of RA.

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