The SMILE Study — Safety of Methotrexate in Combination with Leflunomide in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To assess the safety of treating patients with rheumatoid arthritis with a combination of methotrexate (MTX) and leflunomide (LEF) in comparison to MTX monotherapy, in clinical practice.

Methods. The Safety of Methotrexate in Combination with Leflunomide in Rheumatoid Arthritis (SMILE) study was a multicenter, observational, cross-sectional, retrospective safety study. The study was conducted by the Optimising Patient Outcomes in Australian Rheumatology-Quality Use of Medicines Initiative (OPAL QUMI). Data were deidentified for patient, clinic, and clinician prior to collection from 13 participating rheumatology practices (25 rheumatologists). Comparative analysis of safety for the different treatments, primarily with regard to neutropenia and liver abnormalities, was performed.

Results. In total, 2975 patients were included in the study: 74% female, 26% male, mean age 62 years (SD 13.6). Distribution of therapy: MTX monotherapy 52.2%, LEF monotherapy 7.3%, MTX plus LEF 13.9%, and neither MTX nor LEF 26.6%. Comorbid liver disease was reported in 8.1% of patients. Liver function abnormalities were reported in 12% of the MTX monotherapy group, 16% of the LEF monotherapy group, 19% of the MTX-LEF combination group, and 14% of the group not taking either drug. Neutropenia was reported in 2.3% of the MTX monotherapy group, 5.5% of the LEF monotherapy group, 3.9% of the MTX-LEF combination group, and 4.2% of the group not taking either drug.

Conclusion. The combination of MTX and LEF was well tolerated, with adverse events comparable to those of monotherapy and the other nonbiologic disease-modifying antirheumatic drug treatment group. (First Release Jan 15 2013; J Rheumatol 2013;40:228–35; doi:10.3899/jrheum.120922)

Key Indexing Terms:
RHEUMATOID ARTHRITIS METHOTREXATE LEFLUNOMIDE

The combination of the disease-modifying antirheumatic drugs (DMARD), methotrexate (MTX), and leflunomide (LEF) is efficacious in treating rheumatoid arthritis (RA)[1,2,3,4,5]. In addition, LEF is a potential alternative to MTX if intolerance or lack of efficacy is apparent.

In Australia the combination of MTX and LEF was used frequently until 2010. This was due in part to federal legislation mandating treatment with MTX and 2 other agents for 3 months, with subsequent LEF therapy if this combination failed. This regimen was a prerequisite to government-funded biologic therapy.

Hepatotoxicity and neutropenia are 2 of the most common adverse effects associated with this combination in published studies[6]. Until recently, due to lack of comprehensive clinical data, it had not been possible to accurately determine the safety profile of the drug combi-

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nation in clinical practice across the RA population in Australia.

The primary objective of our study was to assess the safety of treating patients with RA with a combination of MTX and LEF in comparison to MTX monotherapy.

MATERIALS AND METHODS

Study design. The Safety of Methotrexate in Combination with Leflunomide in Rheumatoid Arthritis (SMILE) study was a multicenter, observational, cross-sectional, retrospective study of the safety of DMARD use in patients with RA. The study was conducted by the Optimising Patient Outcomes in Australian Rheumatology-Quality Use of Medicines Initiative (OPAL QUMI) consortium. Data were obtained from 13 participating rheumatology community practices comprising 24 rheumatologists who were using the client-server-based clinical software program Audit4 [Software 4 Specialists (S4S), Australia] as their comprehensive electronic medical record. The S4S Audit4 program utilizes point-of-care data entry by the clinician for prescribing and recording drug therapies, adverse events, drug cessations, reasons for cessation, as well as clinical measures including joint counts, measures of function and disease activity. An homunculus has been developed to assist determination of joint scores (Figure 1). Pathology results obtained from independent external private pathology providers are automatically downloaded over the Internet and incorporated into patient records; the Disease Activity Score (DAS) is calculated automatically. The software allows real-time entry of data during the clinical consultation, so the data collected are a true reflection of current daily practice.

The rheumatologists, representing 4 of the 7 states/territories of Australia and predominantly city-based, community practices, had been using Audit4 from 2 to 4 years regarding the cutoff timepoint for the study, which was in October 2010.

S4S assisted each participating center to execute a study-specific extract of their routine clinical data, which were deidentified and encrypted and sent by Internet to a central repository for aggregation.

For each participating center, all relevant data were extracted on each patient from the time when Audit4 was first used until the date the patient was last seen. Although longitudinal data were acquired, this was essentially a cross-sectional study focusing on observations in relation to the status of each patient as of the date last seen; where repetitive observations were recorded, e.g., multiple pathology results over time, only the observations closest to the date last seen were used for the analysis. Similarly, only current drug therapies as of date last seen were used in the analysis of drug treatments so that no single patient contributed to more than 1 drug treatment group. However, all drug cessations up to 2 years prior to date last seen were analyzed (2 years being selected as the minimum time all participants had been using Audit4).

The study was approved by the University of New South Wales Human Research Ethics Committee.

Patient population. All patients with a diagnosis of probable or definite RA as determined by the treating physician at an OPAL QUMI participating clinic, and over the age of 18 years at the time of data collection, were eligible for inclusion into the study. Patients treated with MTX and LEF in combination, MTX monotherapy, LEF monotherapy, and patients treated with neither MTX nor LEF and who had a recorded visit within the 12-month period prior to and a recorded liver function test (LFT) at the time of data collection were included. Exclusion criteria included prior treatment with a biologic DMARD therapy including abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab, or other experimental biological agents.

Clinical observations. Measures collected for each participating patient included patient demographics (sex and age); diagnoses (date first and last seen for RA, onset date of all other conditions and autoantibody status, rheumatoid factor and/or anticitrullinated protein antibody positivity); medications [RA medications with initiation dates including steroids, nonsteroidal antiinflammatory drugs (NSAID), and paracetamol; MTX and LEF details of maximum and cumulative doses and reasons for treatment cessation; and other medications that might affect transaminases] and disease measures [DAS28, tender joint count (TJC), swollen joint count (SJC), general health by visual analog scale (VAS), inflammatory markers, transaminases, specifically hepatocellular measures of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), neutrophil count and renal function].

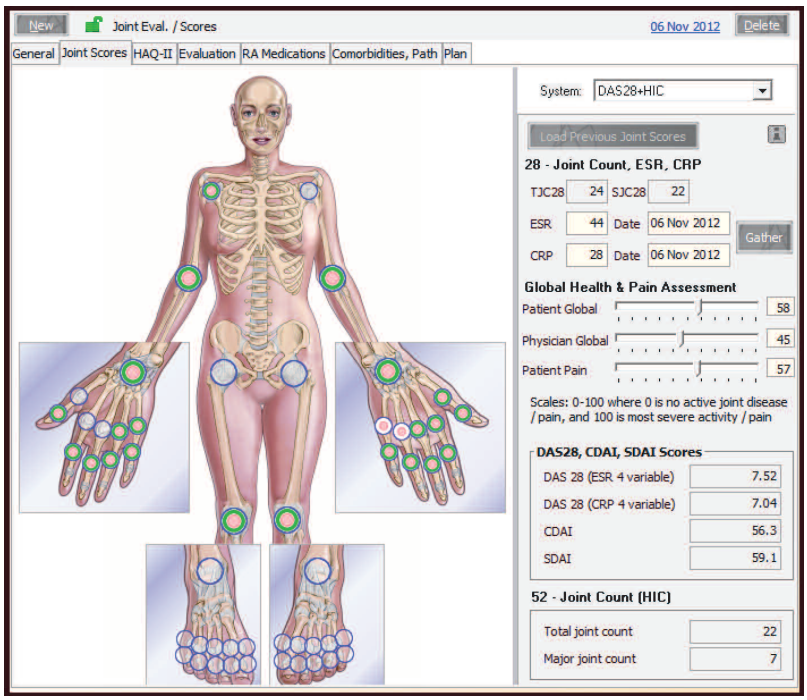

Figure 1. An homunculus was developed to assist determination of joint scores.

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Pulmonary complications associated with monotherapy or combination therapy were recorded. For patients in whom a serious pulmonary complication was identified, further data were sought from clinicians to determine the nature of the abnormality as per ethics approval.

Statistical and analytical assessments. The distributions of continuous variables including ALT, AST, and blood white cell count (WCC) were expressed as percentages for each treatment group.

RESULTS

Patients. A total of 2975 patients diagnosed with RA with a recorded visit and liver function testing within the prior 12-month period were included in the analysis. Patient demographic data were comparable between the therapy groups (Table 1), showing a female predominance of 74% and a mean age of 62 years (SD 13.6).

Treatment. Patients received the following therapies: MTX monotherapy 52.2% (n = 1552), LEF monotherapy 7.3% (n = 217), MTX plus LEF 13.9% (n = 415), and neither MTX nor LEF 26.6% (n = 791). The mean MTX dose was 14.6 mg/week (SD 9.1) in the monotherapy group and 15.4 mg (SD 5.9) in the MTX-LEF combination group. The mean LEF dose was 17.4 mg/day (SD 4.6) in the monotherapy group and 15.7 (SD 5.2) in the MTX-LEF combination group. The percentages of patients receiving prednisone and NSAID in each of the therapy groups are presented in Table 1.

Neutropenia. Across all treatment groups, 88% of patients (n = 2610) had a neutrophil count in the range > 2.0×10^9/l, 3% (n = 101) had a count < 2.0×10^9/l, and 9% (n = 264) did not specify the count. Neutropenia, defined by a neutrophil count < 2.0×10^9/l, was reported in 2.3% (n = 35) of the MTX monotherapy group, 5.5% (n = 12) of the LEF monotherapy group, 3.9% (n = 16) of the MTX-LEF combination group, and 4.2% of the group taking neither drug (Figure 2).

Transaminase abnormalities. Preexisting liver disease (including viral hepatitis, steatohepatitis, and other liver disease) was recorded in 8.0% (n = 240) of patients with RA. Liver function abnormalities were reported in 12% (n = 186) of patients in the MTX monotherapy group, 16% (n = 35) in the LEF monotherapy group, 19% (n = 79) in the MTX-LEF combination group, and 14% (n = 109) in the group taking neither medication (Figure 2).

Treatment cessation. Adverse reactions leading to cessation were analyzed retrospectively. Patients who had previously received MTX or LEF and who had stopped the treatment more than 28 days prior to data recording were included in the analysis. Data for cessation due to adverse events in all treatment groups are presented in Table 2 and Figure 3.

Pulmonary abnormalities. Eight patients were identified with pulmonary complications listed as the reason for treatment cessation by the treating physician (Table 3). Given the potential importance of this finding, specific ethics approval was obtained and a request for further information (Appendix 1) was sent to the treating physician. Patient deidentification was maintained using code encryption so that only the treating physician was able to identify the selected patients.

The subanalysis identified patients with documented lung disease attributed by the treating physician to MTX or LEF or the combination. Physicians were asked to grade the severity of the pulmonary disease, and make a decision

Table 1. Characteristics of the RA cohort.

Characteristic	MTX Monotherapy	LEF Monotherapy	MTX + LEF	Neither*
N (%)	1552 (52.2)	217 (7.3)	415 (13.9)	791 (26.6)
Sex, %				
Female	72.7	75.9	72.7	76.7
Male	27.3	24.1	27.3	23.3
Mean age, yrs (SD)	63.0 (13.8)	63.0 (12.8)	60.0 (12.8)	62.0 (13.7)
DAS28 available, n (%)	892 (57)	100 (46)	228 (54)	235 (29)
DAS28, mean (SD)	2.9 (1.2)	3.2 (1.2)	3.3 (1.4)	2.8 (1.3)
Other medications				
Prednisone, %	34.0	37.3	39.3	22.9
Prednisone daily dose, mean (SD)	6.8 (6.2)	5.4 (2.6)	6.5 (4.0)	7.4 (5.9)
NSAID	19.4	14.7	19.5	15.5
Comorbidities, %				
Viral hepatitis	0.1	0.5	0.0	0.3
Other liver disease	0.5	3.7	0.5	1.1
Diabetes	4.6	4.6	4.1	4.4
Steatohepatitis	0.2	0.9	0.0	0.3
Blood disorders	2.3	1.8	2.9	4.3
Infectious diseases	0.8	0.0	1.9	1.0

* Nonbiologic disease-modifying antirheumatic drug other than MTX and LEF. MTX: methotrexate; LEF: leflunomide; DAS: Disease Activity Score; NSAID: nonsteroidal antiinflammatory drug.

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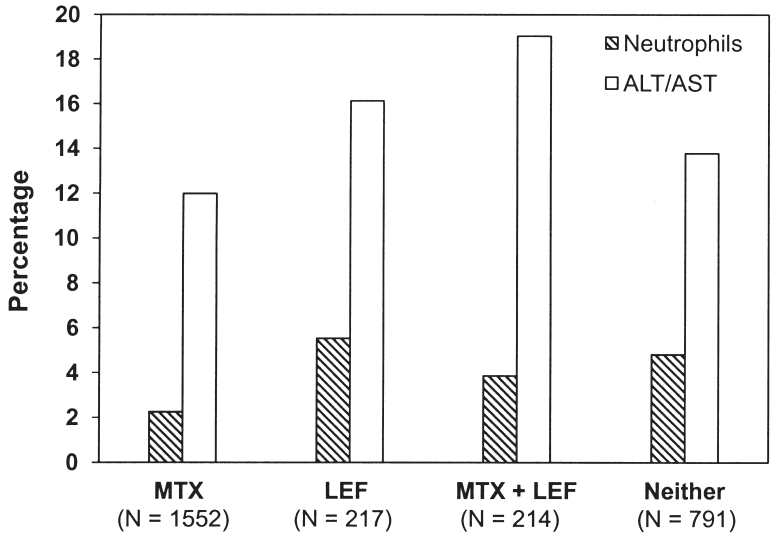

Figure 2. Neutropenia (neutrophils < 2.0×10^9/l) and abnormal transaminases (ALT/AST > 1.0 times upper limit of normal) across the treatment groups. MTX: methotrexate; LEF: leflunomide; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 2. Therapy cessation because of adverse reactions.

	MTX	MTX in MTX + LEF	LEF	LEF in MTX + LEF	MTX + LEF
Total cessations, n	71	49	31	71	6
Because of adverse reaction, n (%)	25 (35)	37 (76)	17 (55)	28 (39)	4 (67)
Hepatic	2 (8)	4 (11)	1 (6)	2 (7)	0
Hematologic	3 (12)	1 (3)	0	1 (4)	2 (50)
Solid malignancy	2 (8)	0	0	0	0
Other*	18 (72)	32 (65)	16 (52)	25 (35)	2 (50)
Because of other, n (%)	46 (65)	12 (24)	14 (45)	43 (61)	2 (33)

* Cessation was reported without record of adverse reaction. MTX: methotrexate; LEF: leflunomide.

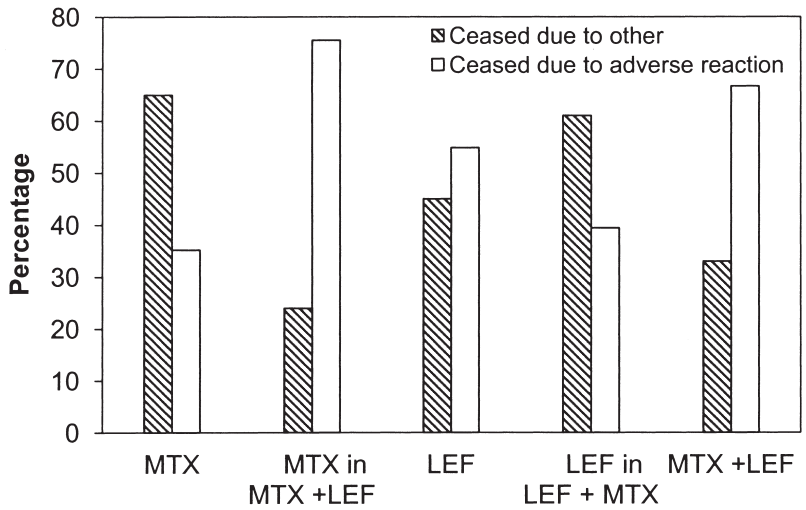

Figure 3. Cessation because of adverse reactions; other: cessation was reported with no record of adverse reaction. MTX: methotrexate; LEF: leflunomide.

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Table 3. Patients with reported pulmonary abnormalities.

Patient	Adverse Event Recorded	Supporting Investigations	Severity Grade*	Causality** MTX or LEF
1	Pleural effusion	CT, PFT	4	Unrelated
2	Interstitial lung disease	CT, PFT	2	LEF unrelated, MTX possible
3	Fibrosing alveolitis	CT, PFT	2	Unrelated
4	Pulmonary infiltrate	CT, PFT, bronchoscopy, biopsy	3	MTX probable, LEF unrelated
5	Interstitial lung disease	CT	3	LEF unrelated, MTX possible
6	Fibrosing alveolitis	None	3	LEF unrelated, MTX unlikely
7	Pneumonia	CT	2	MTX possible, LEF unrelated
8	Interstitial lung disease	CT	2	Unrelated

* According to the Common Terminology Criteria for Adverse Events[7]. ** Relationship to study drug. CT: computed tomography; PFT: pulmonary function tests; MTX: methotrexate; LEF: leflunomide.

based on available evidence on the relationship to MTX and/or LEF. Grading of the pulmonary adverse event was undertaken using the Common Terminology for Adverse Events (CTCAE) Version 4.03[7]. The treating physicians graded the majority of patients as having mild disease; 2 were graded as severe.

MTX was implicated as causal in 4 of the cases, with no case deemed related to LEF. In 3 cases, the adverse event resolved upon cessation of drug treatment, with the remainder unchanged after drug cessation.

DISCUSSION

LEF is indicated for the treatment of RA either as monotherapy or in combination with MTX. The European League Against Rheumatism guidelines list LEF as one of the initial alternative agents when MTX is contraindicated[8]. LEF and MTX are therefore commonly prescribed synthetic disease-modifying drugs, either as monotherapy or in combination, for treatment of active RA.

Federal regulations regarding therapeutic regimes in RA before biologic therapy provided a unique situation in Australia. Following treatment with MTX and 2 other agents for 3 months, physicians were required to prescribe LEF for 3 months. If there was no response after this regimen, access to biologic agents was granted and funded by the federal government. Therefore, the prescription rate of MTX and LEF remained constant in the years before June 2010, when the regulations were altered.

The most common serious adverse effects associated with LEF monotherapy and MTX-LEF combination therapies have been reported as hepatotoxicity, blood dyscrasias, and pulmonary toxicity[6,9,10,11,12]. These adverse events were specifically sought for in our study, as follows.

Hepatotoxicity. The rate of transaminase elevation in the early studies of MTX and LEF in combination showed transaminase elevations higher in the combination group (MTX and LEF) compared with MTX monotherapy (MTX and placebo)[2]. In the study by Kremer, *et al*, ALT elevation was recorded in 31.5% of patients in the combination group compared with 6.8% in the MTX monotherapy group. The majority of the elevations (21.5%) were less than 2 times the upper limit of normal (ULN). AST elevation was noted in 16.9% of patients compared with 4.6% in the placebo group. The majority (16%) were less than 2 times the ULN[2].

The CORRONA registry data were used to establish OR for the development of LFT abnormalities with MTX monotherapy or with the MTX-LEF combination[10]. Interestingly, the OR was dependent on the MTX dose, and not on the DMARD combination. At a dose of LEF 20 mg in combination with MTX 7.5 mg, the OR for developing liver abnormalities was 2.15, increasing to an OR of 3.98 if MTX 20 mg weekly was used[10].

In our study, transaminase elevations were recorded based upon variations of ULN, as per previous studies. Our data were stratified into > 1.0 ULN, < 1.5 ULN, > 1.5 ULN. Our study shows results comparable to those previously reported. The combination of MTX and LEF resulted in LFT abnormalities in 19% of patients. These results are reassuring, and even allowing for underreporting, they suggest a rate of LFT abnormalities commensurate with published reports.

Neutropenia. Neutropenia in patients taking MTX for treatment of RA is well reported. At-risk patients include the elderly[13], those with concomitant use of dihydrofolate reductase inhibitors[14], and patients with renal impairment.

Neutropenia has been reported in postmarketing surveillance of LEF. In a large study of patients with psoriatic arthritis receiving DMARD therapy, treatment-emergent reductions in neutrophil levels to ≤ 1500 cells/mm^3 were reported in 4 LEF-treated patients[15]. Cessation of LEF

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therapy was not required in any of the patients, and blood abnormalities were not accompanied by infection. The results of our study mirror these data, showing low rates of neutropenia with treatment cessation, occurring in 1 patient in the combination therapy group.

Pulmonary abnormalities. Lung disease associated with MTX and LEF therapy, either alone or in combination, is a well recognized but rare complication (0.08% of treated patients)[16]. Factors contributing to the risk of LEF- or LEF-MTX-induced lung injury are preexisting interstitial lung diseases, cigarette smoking, low body weight, and the use of a LEF loading dose[17].

In our study, pulmonary abnormalities were recorded in 8 patients in the treatment-cessation group. Further investigation of these patients was undertaken as discussed. There were no adverse pulmonary events attributed to LEF, but 2 pulmonary adverse events were deemed secondary to MTX. It is difficult to make firm conclusions without the benefit of more detailed data, but the low number of pulmonary events across the population was reassuring and commensurate with published data.

Study limitations. The OPAL study group uses a software program designed for point-of-care data entry. This provides the advantage of recording real data from clinicians at the time of patient consultation. A potential disadvantage is that coding errors may occur. The software program allows review of previously entered data for corrections at each consultation, and pathology data are sourced directly from downloaded results, minimizing data entry error. Although data entry issues for laboratory results (data entry error or missing data) are rare, coding errors can occur when physicians assign causation if an adverse reaction occurs. In addition, omission of causes for cessation of medication can influence the final data.

The second issue is the duration of therapy. Data for this study did not contain drug duration information. This could influence the rate of laboratory abnormalities and adverse events.

Our findings nevertheless provide a real-world insight into daily clinical rheumatology practice, unique in its point-of-care approach.

These cross-sectional, real-world data provide reassuring safety information regarding MTX and LEF, used alone or in combination, in patients with RA. Liver function abnormalities and neutropenia in the MTX-LEF combination group were mild and were equivalent to those seen in MTX monotherapy and in LEF monotherapy.

Levels of liver function abnormalities in the combination therapy group were lower than those reported in previous trials. MTX and/or LEF cessations due to adverse reaction were recorded in only a minority of patients. Pulmonary abnormalities were minimal, with 2 serious pulmonary complications identified. These were possibly related to MTX, but none of the pulmonary abnormalities was deemed related to LEF.

The results of our study are reassuring, demonstrating MTX and LEF are well tolerated alone or in combination, and result in only a small number of hematologic, hepatic, or pulmonary abnormalities. Our results are unique, to our knowledge, because they represent a large cohort of real-world patients, providing reassuring data for clinicians using MTX and LEF in clinical practice for the treatment of RA.

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APPENDIX 1. Adverse event questionnaire.

OPAL SMILE Study - Adverse Event Questionnaire

Site: **Rheumatologist:**

Patient ID: **Adverse Event:**

1. Which of the following diagnostic tests were performed to confirm the diagnosis?

CT	**Yes** ☐	**No** ☐
Results		
Pulmonary Function	**Yes** ☐	**No** ☐
Results		
Bronchoscopy	**Yes** ☐	**No** ☐
Results		
Biopsy	**Yes** ☐	**No** ☐
Results		

2. What grade was the AE?

1☐ 2☐ 3☐ 4☐ 5☐

Please refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (over page)
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

3. Was the AE related to the following medications? * see definitions over page

	Unrelated	Unlikely	Possible	Probable	Definite
MTX	☐	☐	☐	☐	☐
LEF	☐	☐	☐	☐	☐

4. Did the AE resolve upon cessation of the treatment?	**Yes** ☐	**No** ☐
5. Was the patient rechallenged?	**Yes** ☐	**No** ☐
6. Was a respiratory physician consulted?	**Yes** ☐	**No** ☐

7. What was the final diagnosis? _____

Comments _____

Assessment of Causality

Unrelated	The Adverse Event is **clearly not** related to the medication
Unlikely	The Adverse Event is **doubtfully** related to the medication
Possible	The Adverse Event **may be** related to the medication
Probable	The Adverse Event is **likely** related to the medication
Definite	The Adverse Event is **clearly** related to the medication

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