

Efficacy of leflunomide in the treatment of vasculitis

N. Mustapha¹, L. Barra², S. Carette¹, D. Cuthbertson³, N.A. Khalidi⁴, C.L. Koenig⁵, C.A. Langford⁶, C.A. McAlear⁷, N. Milman⁸, L.W. Moreland⁹, P.A. Monach¹⁰, P. Seo¹¹, U. Specks¹², A.G. Sreih⁷, S.Y. Ytterberg¹³, P.A. Merkel¹⁴, C. Pagnoux¹, on behalf of the Canadian Vasculitis Research Network (CanVasc) and Vasculitis Clinical Research Consortium (VCRC)

Affiliations: page S117.

Noura Mustapha, MD, FRCPC
Lillian Barra, MD, MPH
Simon Carette, MD, FRCPC, MPhil
David Cuthbertson, MS
Nader A. Khalidi, MD, FRCPC
Curry L. Koenig, MD
Carol A. Langford, MD, MHS
Carol A. McAlear, MA
Nataliya Milman, MD, MSc, FRCPC
Larry W. Moreland, MD
Paul A. Monach, MD, PhD
Philip Seo, MD, MHS
Ulrich Specks, MD
Antoine G. Sreih, MD
Steven Y. Ytterberg, MD
Peter A. Merkel, MD, MPH, Prof.
Christian Pagnoux, MD, MSc, MPH

Please address correspondence to:
Christian Pagnoux,
Vasculitis Clinic, Mount Sinai Hospital,
60 Murray Street, Ste 2-220,
Toronto, Ontario, M5T 3L9, Canada.
E-mail:

christian.pagnoux@sinaihealthsystem.ca

Received on March 31, 2020; accepted in revised form June 29, 2020.

Clin Exp Rheumatol 2021; 39 (Suppl. 129): S114-S118.

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Key words: leflunomide, vasculitis, ANCA, efficacy, safety

Funding: N. Mustapha was funded by a vasculitis fellowship granted by the Vasculitis Program (University of Toronto) and the Royal College of Physicians of Canada. The Vasculitis Clinical Research Consortium (VCRC) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Science (NCATS). The VCRC is funded through collaboration between NCATS and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), U54 AR057319 and has received funding from the National Center for Research Resources (U54 RR019497).

Competing interests: page S117.

ABSTRACT

Objective. Only a few small case series, case reports, and one small clinical trial suggested some benefit of leflunomide (LEF) in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and other vasculitides. We analysed the clinical efficacy and tolerability of LEF in a large cohort of patients with various vasculitides.

Methods. This was a retrospective analysis of patients who received LEF for treatment of their vasculitis enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Study and in 3 additional centres from the Canadian vasculitis research network (CanVasc).

Results. Data for 93 patients were analysed: 45 had granulomatosis with polyangiitis (GPA), 8 microscopic polyangiitis (MPA), 12 eosinophilic granulomatosis with polyangiitis (EGPA), 14 giant-cell arteritis (GCA), 9 Takayasu's arteritis (TAK), and 5 polyarteritis nodosa (PAN). The main reason for initiation of LEF was active disease (89%). LEF was efficacious for remission induction or maintenance at 6 months for 62 (67%) patients (64% with GCA, 89% with TAK, 80% with PAN, 69% with GPA, 75% with MPA, 33% with EGPA); 20% discontinued LEF before achieving remission because of persistent disease activity. Overall, 22 adverse events (gastrointestinal symptoms being the most common) led to drug discontinuation in 18 (19%) patients, of which 12 stopped LEF before month 6, before showing any benefit in 8/12 of these patients.

Conclusion. Leflunomide can be an effective therapeutic option for various vasculitides, especially for non-severe refractory or relapsing ANCA-associated vasculitis or large-vessel vasculitis. No new safety signals for LEF were identified in this population.

Introduction

Primary vasculitides are a group of diseases of unknown origin associated with a high risk of morbidity and/or mortality. Successful treatment of vasculitis usually requires induction with high-dose glucocorticoids for initial induction of remission, often associated with another agent in severe or refractory disease, followed by use of a non-glucocorticoid immunosuppressive agent for maintenance of remission.

Leflunomide (LEF) has been a well-recognised treatment for rheumatoid arthritis since 1998 and has also been prescribed for a variety of auto-immune or rheumatological conditions such as Sjögren's syndrome (SS) (1), psoriatic arthritis (2) and bullous pemphigoid (3). Leflunomide's most common potential side effects include gastrointestinal (GI) symptoms, rash, alopecia, and elevated levels of hepatic transaminases (4), which are usually reversible and mild.

Only a few reports have focused on the efficacy of LEF for treating vasculitis. One small randomised controlled trial has been completed and suggested superior efficacy of LEF over methotrexate in granulomatosis with polyangiitis (GPA) (5). Otherwise, only a few small case series or case reports suggested some efficacy of LEF in ANCA-associated vasculitides (6), cutaneous polyarteritis nodosa (cPAN), leukocytoclastic vasculitis (7), giant cell arteritis (GCA) (8), Takayasu's arteritis (TAK) (9), and Cogan's syndrome (10).

In this study, we report the use of LEF in a cohort of patients with various well-defined vasculitides from different North American centres.

Material and methods

Study population

Patients were included if they had anti-neutrophil cytoplasm antibody

(ANCA)-associated vasculitides (GPA, microscopic polyangiitis [MPA], or eosinophilic granulomatosis with polyangiitis [EGPA]), GCA, TAK, or PAN, as defined by the Chapel Hill Nomenclature (11), and received LEF for treatment of their vasculitis during the course of their disease. Patients with other concomitant systemic diseases, such as rheumatoid arthritis (RA) or SS, were excluded.

Patients were identified from two sources: the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies and the Canadian Vasculitis research network (CanVasc). The VCRC was initiated in 2003; the Longitudinal Studies are conducted at 6 centres in the United States and 2 centres in Canada. The CanVasc network involves clinics in 18 Canadian cities, including the 2 VCRC centres.

Studied parameters

Data were collected in both the VCRC and CanVasc using standardised protocols and data collection forms. Data from patients enrolled in both the VCRC and CanVasc were only included once for these analyses. The treating investigator-physicians for all patients included in this study were contacted and asked to provide additional and specific information about the use of LEF, including the main indication (induction, maintenance, or other), the start and, if applicable, end dates of the treatment, concomitant treatments with glucocorticoid and other immunosuppressive agents, efficacy and LEF-related adverse events.

Efficacy was defined as a response to LEF at 6 months after its initiation as per the treating physician's clinical judgment (based on clinical and laboratory features and imaging such as computerised tomography, magnetic resonance imaging and positron emission tomography scans), with the ability to taper glucocorticoids, if applicable, the relief of symptoms for which LEF was started, or the maintenance of remission without the need to add (or switch to) another agent. Efficacy was further analysed at 12 and 24 months. The validation of efficacy also required the absence of active disease, corresponding to a Birmingham

Table I. Characteristics of patients who received leflunomide for treatment of vasculitis (n=93).

Characteristics	Values
<i>Demographic features</i>	
Age at diagnosis, mean \pm SD [range], years	48 \pm 19.3 [4-80]
Number of females	66 (71%)
Race	
Caucasian	73 (79%)
Asian	6 (7%)
Black or African American	4 (4%)
<i>Vasculitis diagnosis</i>	
Granulomatosis with polyangiitis ANCA-positive	45 (48%)
Microscopic polyangiitis ANCA-positive	31 (33%)
Eosinophilic granulomatosis with polyangiitis	8 (9%)
Takayasu's arteritis	8 (9%)
Giant cell arteritis	12 (13%)
Polyarteritis nodosa	9 (10%)
14 (15%)	
5 (5%)	
<i>Previous treatments</i>	
Glucocorticoids	87 (94%)
Oral or intravenous cyclophosphamide	65 (70%)
Methotrexate	64 (69%)
Azathioprine	51 (55%)
Rituximab	15 (16%)
Mycophenolate mofetil	12 (13%)
Infliximab	6 (7%)
Others*	21 (23%)

Data are n (%) of patients, unless otherwise indicated.

*n=4: hydroxychloroquine; n=4: intravenous immunoglobulin; n=3: plasma exchange; n=3: etanercept; n=2: tocilizumab; n=3: sulfasalazine; n=1: cyclosporine; and n=1: eculizumab (in a paediatric patient with severe refractory GPA).

Vasculitis Activity Score of 0. Finally, efficacy needed to be validated by the two main authors (NM and CP).

Ethics

All patients provided signed consent for enrolment in the VCRC Longitudinal Studies and/or CanVasc protocol. The study was approved by the Mount Sinai Hospital Research Ethical Board (14-0236 C) and the VCRC Steering Committee.

Statistical analysis

Categorical data are expressed as numbers (percentage) and continuous data as medians (range) or mean \pm SD.

Results

A total of 93 adult patients (45 GPA, 8 MPA, 12 EGPA, 9 TAK, 14 GCA,

and 5 PAN) were included (Table I): 54 were from the VCRC and 39 from three CanVasc centres. Mean disease duration was 10.7 \pm 7.4 years.

The main reasons for starting LEF was inefficacy of previous agents in 83 (89%) patients and issues regarding poor tolerability of previous agents in 10 (11%). The mean number of flares before treatment with LEF was 1.8 \pm 2.4 per patient (range, 0-10). LEF was used for maintenance of remission after severe relapse in 9 patients, all with ANCA-associated vasculitis (for destructive sino-bronchial disease or after cyclophosphamide, for alveolar haemorrhage or glomerulonephritis).

The mean duration of treatment with LEF was 2.3 \pm 2.3 years. The daily dose of LEF was 20 mg in 35/49 (71%) patients with that information available, 10 mg in 7 (14%) patients, and 30 mg in the 7 (14%) remaining patients, without any receiving loading doses. LEF was used with glucocorticoids (with often varying and decreasing doses, but mostly low-dose prednisone during longer periods of time), at least initially, for 73 patients (79%); as monotherapy without glucocorticoids for 17 (18%) patients, as a single agent for 68 (73%) patients, and in addition to another glucocorticoid-sparing agent for 25 (27%) patients.

Treatment with LEF was considered effective at 6 months in 62 (67%) patients (Table II). Efficacy was noted even earlier, within 3 months of the initiation of LEF in 71 (76%) patients. Remission was maintained at 24 months in 46 (50%) patients. For the 31 patients with treatment failure, 15 had persistent disease activity, 3 had minor relapses, 1 had a major relapse (glomerulonephritis), and 12 experienced adverse effects leading to discontinuation of LEF before month 6 (mostly within 3 months, and essentially due to GI symptoms).

Overall, 37 (70%) patients with GPA or MPA had a positive response to LEF at 6 months. Among the 16 patients with GPA or MPA without response to treatment at 6 months, 7 (all with GPA) showed persistent active disease, mostly due to persistent sinus symptoms or progressing bronchial inflammation. The remaining 9 patients experienced

Table II. Response to treatment with leflunomide among patients with vasculitis.

	All patients	Type of vasculitis					
		GPA	MPA	EGPA	GCA	TAK	PAN
Number of patients (%)	93	45	8	12	14	9	5
Efficacy at 6 months	62 (67%)	31 (69%)	6 (75%)	4 (33%)	9 (64%)	8 (89%)	4 (80%)
Reason for treatment inefficacy							
Active disease	19 (20%)	7 (16%)	-	6 (50%)	4 (29%)	1 (1%)	1 (20%)
Adverse events	12 (13%)	7 (16%)	2 (25%)	2 (17%)	1 (7%)	0	0
Sustained remission at 12 months	54 (58%)	27 (63%)	6 (75%)	4 (33%)	7 (54%)	8 (89%)	3 (60%)
Sustained remission at 24 months	46 (50%)	23 (58%)	5 (71%)	4 (33%)	7 (54%)	7 (88%)	2 (40%)

Given percentages are for the proportion of patients in each type of vasculitis with available data, which was incomplete at 12 and/or 24 months for 7 individuals (2 lost to follow-up after 12 months [MPA and TAK]; 4 had not yet reached 12 and/or 24 months with LEF [3 GPA and 1 GCA]; one with GPA died of natural causes before 24 months of LEF).

EGPA: eosinophilic granulomatosis with polyangiitis; GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa; TAK: Takayasu's arteritis.

adverse events leading to discontinuation of LEF. Two patients with GPA showed loss of efficacy after an initial response at 6 months, with progression of kidney disease and sino-nasal symptoms. Two patients stopped LEF, which was effective at 6 months, because of an adverse event, and 1 patient with GPA died from cardiac arrest, which was not considered LEF-related. The remaining patients were still on LEF at the end of the study period. In the nine cases in which LEF was started for severe relapse, all responses were sustained at 6 months except in one, where it was stopped early due to an adverse event. Patients with EGPA had the lowest rate of response at 6 months (4/12; 33%), poor control of asthma or sinus symptoms being the reason for failure in half the cases. However, in all 4 patients who responded at 6 months, the efficacy of LEF was sustained at 24 months. Nine patients with GCA (64%) and 8 with TAK (89%) showed response to LEF at 6 months. In the 5 patients with GCA without response, LEF was not tolerated in one and was associated with persistent disease activity in 4 (no symptomatic relief in 3; aortic dissection after 4 months of use in 1). LEF was effective in 4/5 (80%) patients with PAN at 6 months. One patient had a relapse of skin nodules within the first 6 months on LEF, but another had a skin rash after 12 months of treatment.

Five of 93 (5%) patients experienced nausea, vomiting, or diarrhoea. Neuropathy was reported in 4, which re-

solved after LEF cessation in 1. The three other patients had symptoms of minor sensory neuropathy at 1, 3, and 9 months, and stopped LEF, but the association of this problem with LEF remained unclear. Infections were reported in 4 patients and mild transient elevation of transaminase levels in 3. One patient with GCA, also receiving glucocorticoids, died from sepsis within 6 months of starting LEF. Leucopenia was reported in 2 patients, but none had infection. New-onset hypertension was reported in a 63-year-old patient after 12 months of use of LEF. Twenty-two adverse events led to drug discontinuation in 18 (19%) patients, of which 12 stopped the drug before 6 months of use, and before showing any benefit in 8/12 of these patients. Overall, 31 (33%) patients were still on LEF at the time of data collection, 27 for more than 24 months.

Discussion

This retrospective study found a favourable response to treatment with LEF in two-thirds of patients with various types of vasculitis. LEF appeared to be similarly effective in patients with GPA, MPA, or large-vessel vasculitis, but less so in PAN and EGPA, mainly because of poor asthma control in EGPA.

Results of only one randomised controlled trial of LEF for vasculitis, comparing LEF to methotrexate in GPA, have been published (5). In this study of 54 patients with GPA in remission after induction with cyclophosphamide and prednisone, relapse-free survival at

2 years was 77% with LEF (100 mg/day for 3 days then 30 mg/day) versus 50% with methotrexate (starting at 7.5mg/week and reaching 20mg/week). The remaining evidence for LEF in vasculitis is based on case reports or series (Supplementary Table S1), with the current being the largest series to date. In a previous series of 20 patients with GPA, LEF at 20 to 40 mg/day was effective with sustained complete or partial remission in 55% of patients after 2.5 years of LEF, with a rate of adverse events similar to that for patients with rheumatoid arthritis (6).

The current report shows that LEF achieves comparable results to other agents used to maintain remission of vasculitis, such as azathioprine or methotrexate, a finding also suggested by a network meta-analysis (12)(13). However, in a few patients, LEF failed to control tracheal, bronchial, or sinus disease, all manifestations of GPA known to be difficult to treat.

In 14 patients with GCA, LEF was effective in preventing relapse in more than 50% at 12 months. A previous series from Norway showed complete or partial remission in all 9 patients treated with LEF for GCA (14). A recent update with an extension to 27 patients showed that LEF was associated with achieving remission with a prednisolone dose of ≤ 5 mg/day in 26% of patients (vs. 21% of 24 patients receiving methotrexate), with a shorter duration of treatment before achieving remission in patients with higher disease activity (49 weeks vs. 105 weeks with

methotrexate) (15). Finally, in recent open-label study from another European centre, relapse rate at 48 weeks was only 13% among 30 patients receiving glucocorticoids and LEF (10 mg/day) versus 39% for 46 patients receiving glucocorticoids alone (16). However, 23% of the patients stopped LEF because of adverse events, mostly hair loss or diarrhoea.

In TAK, methotrexate has shown limited benefit (17). Among the 9 patients with TAK in the current series, 8 (89%) showed response to LEF. In a previous series of 15 patients with TAK from Brazil treated with LEF, 12 (80%) were in remission at 9 months, but only 5 on LEF were still in remission after 43 months of follow-up (18). In a recent series of 56 Chinese patients with TAK, clinical remission was achieved in 68% at 6 months, and 55% after 12 months (19).

The safety profile of use of LEF in vasculitis appears acceptable with GI symptoms being the main observed adverse events. The safety and tolerability profile of LEF has been well described in many rheumatologic diseases. In rheumatoid arthritis, serious adverse events were even less frequent with LEF than methotrexate (20). LEF was also well tolerated in trials of patients with SS (1, 21), but in patients with psoriatic arthritis the reported rate of treatment discontinuation due to toxicity (diarrhoea, alopecia, renal) was as high as 35% (22).

The main limitations of this study include its retrospective nature and small sample size, especially for individual vasculitides, and fairly short follow-up. Several parameters or outcomes could not be studied, such as changes in doses of concomitant glucocorticoids (although the inability to taper glucocorticoids was used as a criterion for non-efficacy). The design of this study and data collection process did not allow direct comparison with other agents used for treating vasculitis. Finally, the assessment of efficacy was based on a BVAS of zero. Whereas the BVAS is a validated tool in vasculitis, it may be more suitable for ANCA-associated vasculitis than other types of vasculitides. For the latter reason, assess-

ment of response was also based on the judgment of treating investigator-physicians (based on clinical, biochemical, and imaging features), all being vasculitis specialists, and required validation by the main authors.

Conclusion

This study provides evidence that LEF may be an effective and safe therapeutic option for several vasculitides, especially after failure of previous treatments for GPA and MPA, for refractory or relapsing large-vessel vasculitis, or in cases of intolerance or contraindications to other more commonly used immunosuppressant medications. LEF is an inexpensive and widely available drug and is a reasonable treatment option for patients with vasculitis. It would be appropriate to conduct additional randomised trials to test the efficacy of LEF in various forms of vasculitis.

Affiliations

¹Vasculitis Clinic, Division of Rheumatology, Mount Sinai Hospital, University of Toronto, ON, Canada; ²Division of Rheumatology, St. Joseph's Health Care London Hospital, London, ON, Canada; ³Department of Biostatistics, University of South Florida, Tampa, FL, USA; ⁴Division of Rheumatology, McMaster University, Hamilton, ON, Canada; ⁵Division of Rheumatology, University of Utah, Salt Lake City, UT, USA; ⁶Division of Rheumatology, Cleveland Clinic, Cleveland, OH, USA; ⁷Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, USA; ⁸Division of Rheumatology, University of Ottawa, ON, Canada; ⁹Division of Rheumatology, University of Pittsburgh, PA, USA; ¹⁰Division of Rheumatology, Brigham and Women's Hospital, Boston, MA, USA; ¹¹Division of Rheumatology, Johns Hopkins University, Baltimore, MD, USA; ¹²Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA; ¹³Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, MN, USA; ¹⁴Division of Rheumatology and Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, PA USA.

Competing interests

N. Khalidi reports personal fees and non-financial support from Roche, non-financial support from Bristol Myers Squibb outside the present work.

A.G. Sreih is an employee of Bristol Myers Squibb.

P.A. Merkel reports receiving funds for the following activities in the past 2 years: Consulting: AbbVie, AstraZeneca, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, CSL Behring, Forbuis, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Insmad, Janssen, Kiniksa, Kyverna, Magenta, Novartis, Pfizer, Sparrow, Takeda, Talaris; Research Support: AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, Forbuis, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx; Royalties: UpToDate.

C. Pagnoux reports receiving fees for serving on advisory boards from Chemocentryx, Glaxo-SmithKline, Sanofi, and Hoffman-LaRoche; he also reports lecture fees and research grant support from Hoffman-La Roche.

The other co-authors have declared no competing interests.

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