Efficacy of conventional immunosuppressants in relapsing or refractory eosinophilic granulomatosis with polyangiitis: evidence from a Canadian single-centre cohort

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Received on October 20, 2019; accepted in revised form on March 9, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 124): S171-S175.

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Key words: eosinophilic granulomatosis with polyangiitis, conventional immunosuppressants, mepolizumab, rituximab, remission

Funding: this work was supported by the Canadian Rheumatology Association (CRA) who funded N. Pulenzas for a Summer Studentship.

Competing interests: C. Pagnoux reports receiving fees for serving on advisory boards from Chemocentryx, GlaxoSmith-Kline, Sanofi and Hoffman-La Roche; he also reports lecture fees and research grant support from Hoffman-La Roche and GSK. N. Pulenzas received salary support from the "Canadian Rheumatology Association Summer Studentship 2017" program. The other co-authors have declared no competing interests.

ABSTRACT

Objective. *To describe the efficacy of conventional immunosuppressants in disease control of relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) compared to recently published mepolizumab and rituximab studies.*

Methods. *A retrospective analysis from the Toronto Vasculitis Clinic was conducted. Patients with relapsing or refractory EGPA with similar entry criteria as the main mepolizumab (MIRRA) or rituximab (case-series) studies, who were started on conventional immunosuppressants, were assessed for remission at 24- and 52-weeks. Remission was defined as a Birmingham Vasculitis Activity Score of 0 and a prednisone dose of ≤4mg/day, ≤7.5mg/day, corresponding to the mepolizumab trial, or any prednisone dose per day, as in the rituximab study.*

Results. *Among 110 cohort patients, 24 with relapsing or refractory EGPA met eligibility criteria. Conventional immunosuppressants used were methotrexate (n=15), azathioprine (n=8) or leflunomide (n=1). Remission rates at 24-weeks were 8.3% with prednisone ≤4mg/day (vs. 28.0% in the mepolizumab trial); 41.6% with prednisone ≤7.5mg/day (vs. 45% in the mepolizumab trial) and 62.5% with any prednisone dose (vs. 34% in the rituximab study). Remission at 52-weeks was 50.0% with any prednisone dose (vs. 49% in the rituximab study), whereas sustained remission at week 52 (as of week 24) was 4.2% with prednisone ≤4mg/day (vs. 19% in the mepolizumab trial), and 33.3% with prednisone ≤7.5mg/day (vs. 24% in the mepolizumab trial).*

Conclusion. *Though our study was small and retrospective, rates of remission observed with conventional immunosuppressants were substantial. This should be kept in mind when interpreting results of placebo-controlled or retrospective studies on biologics in EGPA.*

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, systemic necrotising small-sized vessel vasculitis, with only a few published series from North America (1, 2). The mainstay of treatment in patients with non-severe EGPA is glucocorticoid (GC) therapy (3, 4); however, 79-85% of patients are GC dependent, and 25-42% have a limited response and/or relapse requiring additional immunosuppressant(s) (5-8). If severe, life-threatening and/or major organ involvement occurs, a combination of GC and an immunosuppressant, mainly cyclophosphamide (CYC), is recommended for induction (3, 4). Despite the initial severity, up to 41% of patients experience a vasculitis relapse at 2 years, and 80% of the patients remain steroid-dependent, mainly because of persistent asthma (8). Over the last few years, novel insights have been made regarding EGPA classification and therapies to address unmet needs (9).

Recent placebo-controlled trials and retrospective studies suggested that mepolizumab (10) or rituximab (11) have some efficacy in disease control for these latter patients with relapsing or refractory disease. Surprisingly, comparable data on conventional non-biologic immunosuppressants, which have been prescribed for much longer, remain limited. The purpose of this study was to describe a new cohort of adults with EGPA followed in the Vasculitis Clinic in Toronto, Canada, and determine the efficacy of conventional immunosuppressants in those patients

Table I. Main clinical characteristics at diagnosis of 110 patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Characteristics	All (n=110)	ANCA-positive (n=50)	ANCA-negative (n=56)	*p*-value[a]
Sex, n, M/F	56/54	30/20	25/31	0.11
Age at diagnosis, years, mean ± SD	47.7 ± 16	46.1 ± 16	50.8 ± 16	0.94
Diagnosis in 2010 or before, n (%)	56 (50.9%)	24 (48.0%)	24 (44.4%)	0.72
Asthma, n (%)	105 (95.4%)	48 (96.0%)	53 (94.6%)	1.00
Duration of asthma to EGPA diagnosis, months, mean ± SD	106.3 ± 151	118.9 ± 160	100.3 ± 147	0.73
Duration of other EGPA symptoms (not asthma) to EGPA diagnosis, months, mean ± SD	36.0 ± 61	34.5 ± 46	38.5 ± 73	0.37
Maximum eosinophils, count/mm^3, mean ± SD	9.15 ± 8.7[b]	7.76 ± 6.1	10.0 ± 10.3	0.11
Biopsy confirming vasculitis, n (%)	17 (29.3%)[c]	10 (37.0%)[e]	7 (22.5%)[f]	0.23
Birmingham Vasculitis Activity Score at diagnosis, mean ± SD	17.2 ± 6.7	17.1 ± 7.7	17.2 ± 6.0	0.49
Clinical manifestations[d], n (%)				
Fever ≥38.5^{0}C	20 (18.2%)	9 (18.0%)	6 (10.7%)	0.20
Musculoskeletal	44 (40.0%)	31 (62.0%)	12 (21.4%)	<0.0001
Arthralgia	32 (29.0%)	21 (42.0%)	10 (17.9%)	0.006
Myalgia	19 (17.2%)	14 (28.0%)	4 (7.1%)	0.008
Cutaneous	32 (29.1%)	18 (36.0%)	12 (21.4%)	0.01
Purpura	31 (28.2%)	18 (36.0%)	11 (19.6%)	0.08
Eye	5 (4.6%)	2 (4.0%)	2 (3.6%)	1.00
Ear, Nose and Throat	81 (73.6%)	36 (72.0%)	42 (75.0%)	0.73
Lung (not including asthma)	71 (64.5%)	28 (56.0%)	42 (75.0%)	0.04
Cardiac	32 (29.1%)	9 (18.0%)	20 (35.7%)	0.04
Cardiomyopathy	20 (18.2%)	3 (6.0%)	16 (28.6%)	0.003
Congestive heart failure	17 (15.4%)	3 (6.0%)	13 (23.2%)	0.02
Gastrointestinal	15 (13.6%)	6 (12.0%)	8 (14.3%)	0.78
Renal	25 (22.7%)	16 (32.0%)	9 (16.1%)	0.05
Proteinuria	13 (11.8%)	9 (18.0%)	4 (7.1%)	0.09
Neurologic	59 (53.6%)	29 (58.0%)	28 (50.0%)	0.41

[a]For comparison of ANCA-positive by immunofluorescence (IF) or MPO/PR-3 by ELISA *versus* ANCA-negative patients; [b]Over 85 patients with available data; [c]In 58 patients who had a biopsy; [d]Detailed clinical manifestations in each of these categories are listed only if *p*-value <0.10 when comparing patients with or without ANCA; [e]In 27 patients who had a biopsy; [f]In 31 patients who had a biopsy.

with relapsing or refractory EGPA, using the same definitions of remission as in the recently published mepolizumab (10) and rituximab (11) studies.

Patients and methods

Patient population

The current study was a retrospective analysis of 110 patients diagnosed with EGPA from 1967-2017, followed in the Vasculitis Clinic in Toronto. Data was extracted from patient charts and entered into the Canadian network for research in vasculitides (CanVasc) database. Patients enrolled in the study were at least 18 years of age at diagnosis and met the American College of Rheumatology 1990 criteria (12) and/or the revised 2012 Chapel Hill definition (13) for EGPA. The study protocol was approved by the Mount Sinai Hospital Research Ethics Board (14-0052 D) and research was performed in accordance with the Declaration of Helsinki.

Studied parameters

Collected parameters included main demographics, clinical manifestations at diagnosis, biology (maximum blood eosinophil count, anti-neutrophil cytoplasm antibody [ANCA] reactivity) and induction and maintenance treatments. ANCA-positive or ANCA-negative status was defined as any positive or negative reactivity on immunofluorescence and/or ELISA, respectively. The Birmingham Vasculitis Activity Score (BVAS) version 3 was used (14), with retrospective calculations for patients diagnosed prior to the score publication.

Patient selection

Patients were selected based on unifying definition from the main mepolizumab (10) and rituximab (11) studies for relapsing or refractory EGPA. Relapsing disease was defined as an increase in BVAS requiring an increase in GC requirement and/or initiation or reinstitution of any immunosuppressive therapy. Refractory disease was defined as failure to attain remission following standard induction therapy for 3 months or recurrence of symptoms of EGPA while tapering GC therapy to a dose of ≥7.5mg/day within the previous 6 months. Patients with major organ, severe or life-threatening EGPA within the last 6 months were excluded, as was the case in the mepolizumab trial (10). Patients had to be started on an additional conventional immunosuppressant that was not CYC (restricted to patients with severe or life-threatening disease), rituximab or mepolizumab.

Response to treatment was assessed at 24- and 52-weeks after conventional treatment initiation. For patients who had no 24- or 52-week visit, but had a 36- or 64-week visit, the results of the latter were used in the 24- or 52-week visit data, respectively. Remission was defined as a BVAS of 0 and a prednisone dose of ≤4mg/day or ≤7.5mg/day, corresponding to the mepolizumab trial definitions (10), or any prednisone dose per day, as in the main rituximab study (11). The mepolizumab trial defined remission with a prednisone dose of ≤4mg/day in their primary end-point (which was remission based on accrued

weeks) (10). Another definition of remission was a BVAS of 0 on a prednisone dose ≤7.5mg/day, which was used as a secondary endpoint in the mepolizumab trial (10) and corresponds to the EULAR (European League Against Rheumatism) definition of remission (15). Sustained remission at week 52 was defined as remission, as defined above, at both consecutive 24- and 52-week visits.

Statistical analyses

Descriptive statistics were computed calculating the mean±SD or median (IQRs) for continuous variables and count (%) for categorical variables. Quantitative variables were compared using Student's t-test or one-way ANOVA, and categorical variables were compared using Pearson chi-square or Fisher's exact test. Statistical significance was defined as p-values <0.05. Analyses were performed using Stata Software, v. 12 (StataCorp).

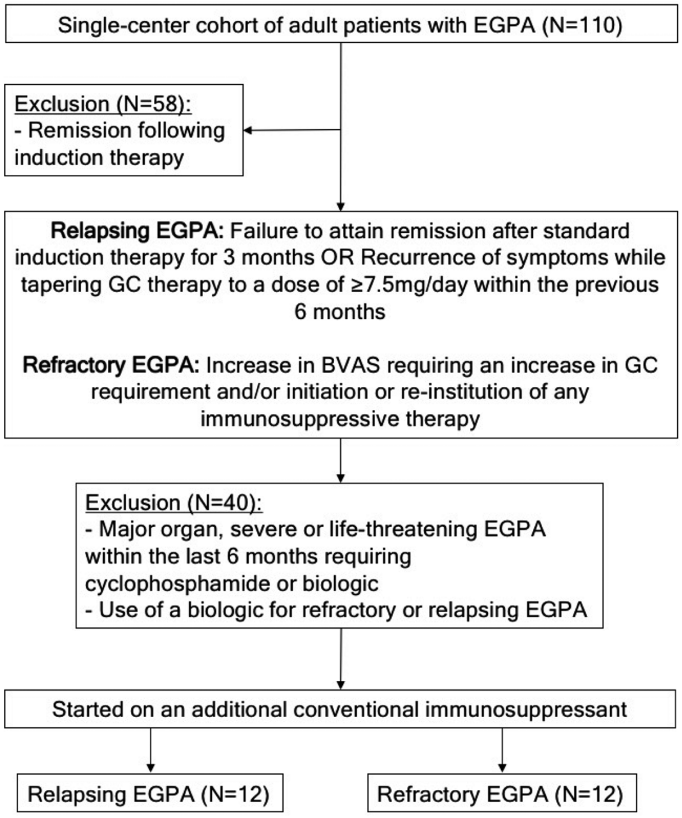

Fig. 1. Inclusion and exclusion criteria for subset cohort of patients with relapsing or refractory EGPA.
EGPA: eosinophilic granulomatosis with polyangiitis;
GC: glucocorticoids.

Results

Descriptive analysis

A total of 110 patients with EGPA were included in this cohort. Patient characteristics are summarised in Table I. All but 4 patients had known ANCA status; 50 had at least one ANCA-positive result (47.2%): 41 were p-ANCA-positive (82.0%), 7 were c-ANCA-positive (14.0%), 2 were atypical-ANCA-positive (4.0%); whereas 56 were ANCA-negative (50.9%). Mean follow-up after diagnosis was of 99.1±103 months (median, 64.2 months).

Initial induction and maintenance therapies

Of the 110 patients with EGPA, 48 (43.6%) underwent induction therapy, 9 requiring two agents at any point in time for induction. For induction therapy, aside from GC, CYC was used in 18 patients (16.4%), azathioprine (AZA) in 24 (21.8%), methotrexate (MTX) in 14 (12.7%) or mycophenolate in 1 (0.9%). Of those who underwent induction therapy, 27 patients experienced a relapse during their follow-up. Cyclophosphamide was used in 26 (23.6%) of our patients at any time during their disease course; AZA or MTX in 54 each (49.1%); LEF and biologic therapy in 7 each (6.4%); and mycophenolate in 4 (3.6%).

Remission with conventional immunosuppressants in relapsing or refractory disease

Vasculitis relapse or refractory EGPA occurred in 52 patients (47.3%), among whom 24 (21.8%) met our study eligibility criteria for further analysis of the efficacy of conventional immunosuppressants (Fig. 1); 12 (50%) had relapsing EGPA and 12 (50%) had refractory EGPA; 16 were ANCA-positive. The mean duration of disease at time of institution of conventional immunosuppressants for relapsing or refractory disease was 6.0±6.5 years. Seventeen (70.8%) of these patients received or were receiving immunosuppressive therapy (MTX in 7 [29.6%], AZA in 9 [37.5%], CYC in 2 [8.3%]) and 7 (29.2%) had received prednisone alone. Conventional immunosuppressant started as a new line of therapy were MTX (n=15), AZA (n=8), and LEF (n=1). The median BVAS at initiation (baseline) of this new immunosuppressant was 3 (IQR 2-4.5), and decreased to 0 (0-2; available for 21) at 24-weeks and 0 (0-2; available for 19) at 52-weeks (mean BVAS were 3.8±2.8, 1.7±3.8, and 1.4±2.6, respectively; p=0.03).

Remission rates at 24- and 52-weeks and sustained remission at week 52 (as of week 24) for comparison to the mepolizumab study(10) are illustrated in Table II; along with remission at 52-weeks in ANCA-positive and -negative patients. Remission rates in all three remission-defined groups at 24- and 52-weeks were not significantly different when comparing ANCA status (p=0.51 and p=0.36, respectively) or AZA *vs*. MTX (p=0.25 and p=0.31, respectively).

The median prednisone dose at baseline was 20mg/day (IQR 10-30mg; n=24), 7mg/day (5-10mg; n=23) at 24-weeks, and 6mg/day (2.5-8.6mg; n=20) at 52-weeks. Only 3 patients were off prednisone at 24-weeks and were still off at 52-weeks. At 52 weeks, 10 patients continued to have active EGPA requiring another change in immunosuppressant therapy; 1 had a new diagnosis of colorectal cancer and 1 developed transient AZA-induced transaminitis resolving after AZA cessation.

Table II. Remission rates in patients with refractory or relapsing EGPA at 24- and 52- weeks with varying doses of prednisone and according to ANCA status who were started with a conventional immunosuppressant compared to results from the mepolizumab(10) and rituximab(11) trials.

Remission	Prednisone dose	This study N=24	Sustained remission	Mepolizumab trial (10), N=136	Rituximab study (11), N=41
24 weeks	≤ 4 mg/day	8.3%		28%	
	≤ 7.5 mg/day	41.6%		45%	
	Any dose	62.5%			34%
52 weeks	≤ 4 mg/day	16.7%	*4.2%	*19%	
	ANCA (+), n=16	18.8%			
	ANCA (-), n=8	12.5%			
	≤ 7.5 mg/day	45.8%	*33.3%	*24%	
	ANCA (+), n=16	56.3%			
	ANCA (-), n=8	25%			
	Any dose	50%			49%
	ANCA (+), n=16	56.2%			
	ANCA (-), n=8	37.5%			

*Remission at week 52 (as of week 24).
EGPA: eosinophilic granulomatosis with polyangiitis; ANCA: anti-neutrophil cytoplasm antibody.

Discussion

In this descriptive analysis of a new EGPA cohort, whose main characteristics were comparable to other reported cohorts (2, 12), we found that the use of conventional immunosuppressants in the subset of patients with relapsing or refractory disease showed very comparable rates of remission at 24- and 52-weeks to the ones recently reported with mepolizumab (10) or rituximab (11).

Patients treated with conventional immunosuppressants in our study achieved high response rates with 42-63% of them being in remission at 24- and 52-weeks while on ≤7.5mg/day or any dose of prednisone. Few patients however achieved remission with ≤4mg/day of prednisone (8% *vs*. 17% at 24- and 52-weeks, respectively). Although there was a significant reduction in GC dose with the addition of a conventional immunosuppressant, only 17% of our cohort was off prednisone completely. However, this is a similar proportion to what was seen in the mepolizumab trial (10) and the rituximab study (11). A greater but not statistically significant (possibly due to lack of statistical power) proportion of the ANCA-positive patients were able to achieve remission with conventional immunosuppressants when compared to ANCA-negative patients; a finding also found with rituximab (11).

The main, randomised, double-blind, placebo-controlled mepolizumab trial included 136 patients with relapsing and refractory disease and demonstrated that patients randomised to mepolizumab achieved more accrued time in remission as compared to patients randomised to placebo (10). They also had a lower frequency of relapse allowing for a reduction of GCs (10). Notably, only a proportion (54-71%) of the study population at baseline had a BVAS>0 (10). The main rituximab study was, like ours, a small retrospective case series of 41 patients, with a small proportion of new-onset disease (12%), that found high rates of improvement in disease activity and reduced requirements of GC (11). Importantly, these study populations represent only a small and specific subset of EGPA patients, with only 22% of our cohort eventually meeting study eligibility criteria of relapsing or refractory EGPA.

The patients in this new and large cohort were followed in a single centre and were likely to have been more homogenously managed and assessed. Yet, their main characteristics closely resemble those previously described (2, 12) and the rates of relapse observed were also comparable to another large EGPA cohort (8). Hence, the results of our study raise some important and likely valid points but, given its retrospective nature and relative small sample size, should still be interpreted with caution. Our patients may have had different levels of disease activity than those included in the mepolizumab or rituximab studies, given their lower BVAS at baseline when compared to the rituximab study (11) (median BVAS of 11 [IQR 6–17.5] (11) vs. 3 [2-4.5] in our patients), but only 54-71% of the patients had a baseline BVAS>0 in the mepolizumab trial (10) compared to 100% our patients. We used definitions of remission, like in the mepolizumab and rituximab studies, but were unable to study the accrued duration of remission, as was done in the mepolizumab study (10). We did not study a wider variety of conventional immunosuppressants, (in particular CYC, as we excluded severe EGPA, like in the mepolizumab trial (10)). Finally, we did not use any specific tool to evaluate asthma control with conventional immunosuppressants (*e.g*. asthma control questionnaire), as some agents may be more effective on asthma.

Conclusions

In conclusion, our study shows that remission can be achieved with conventional immunosuppressants in a substantial proportion of patients with relapsing or refractory EGPA, to an extent not much lower than with recently developed biologic therapies. However, a substantial proportion of patients continue to remain steroid-dependent. Large, randomised controlled trials comparing head-to-head biologics and conventional immunosuppressant therapies should be favoured over placebo controlled trials.

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