Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

Mepolizumab

Nonsponsored Review

Therapeutic area: Eosinophilic granulomatosis with polyangiitis (EGPA)

Clinical and Pharmacoeconomic Report

Table of Contents

List of Tables

List of Figures

Abbreviations

ACQ-6	6-item Asthma Control Questionnaire
AE	adverse event
ANCA	antineutrophil cytoplasmic antibody
BVAS	Birmingham Vasculitis Activity Score
CI	confidence interval
EGPA	eosinophilic granulomatosis with polyangiitis
ENT	ear-nose-throat
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HRQoL	health-related quality of life
IL	interleukin
ITC	indirect treatment comparison
ITT	intention-to-treat
LS	least squares
MPO	myeloperoxidase
NR	not reported
OCS	oral corticosteroid
OR	odds ratio
RR	rate ratio
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SNOT-22	22-item Sino-Nasal Outcome Test
SoC	standard of care
VDI	Vasculitis Damage Index

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Mepolizumab 100 mg/mL solution for subcutaneous injection
Health Canada indication	As an add-on to corticosteroids for the treatment of adult patients with EGPA
Indication under consideration for reimbursement	For the treatment of EGPA, with or without oral corticosteroids and/or immunosuppressive therapy
Health Canada approval status	NOC
NOC date	July 17, 2018
Requester	FWG

EGPA = eosinophilic granulomatosis with polyangiitis; FWG = Formulary Working Group; NOC = Notice of Compliance.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by tissue and blood eosinophilia, small to medium-size vessel vasculitis, extravascular granulomas, asthma, and sinonasal symptoms.[1,2] There are 2 forms of EGPA: antineutrophil cytoplasmic antibody (ANCA)-positive EGPA, and ANCA-negative EGPA.[3] It is a rare disease, with approximately 12 to 59 cases per 1,000,000 people.[4-6] Patients with EGPA experience acute relapses with periods of remission, and relapses increase the likelihood of developing organ damage including cardiomyopathy, chronic kidney disease, and peripheral neuropathy, along with signs of active vasculitis including pulmonary infiltrates, gastrointestinal involvement, and palpable purpura.[7,8] The goals of treatment for patients with EGPA include induction of remission, prevention of relapses, prevention of organ damage, maintenance of remission, long-term treatment of asthma and ear-nose-throat (ENT) manifestations, and minimizing the harms associated with treatments used in patients with EGPA.[9]

Currently in Canada, corticosteroids with or without cyclophosphamide (depending on EGPA severity) are recommended to induce remission in patients with active EGPA, and oral corticosteroids (OCSs) and immunosuppressive therapies, including methotrexate and azathioprine, are used for maintaining remission of EGPA.[10] However, long-term use of OCSs is associated with considerable toxicities as well as weight gain, reductions in bone mineral density and osteoporosis, hyperglycemia and development of type 2 diabetes, electrolyte abnormalities, infections, and neuropsychiatric adverse events.[11]

Mepolizumab is an anti-interleukin (IL)-5 monoclonal antibody that reduces blood eosinophil counts by preventing IL-5 from recruiting, activating, and binding to eosinophils.[12] Mepolizumab currently has a Health Canada indication as an add-on to corticosteroids for the treatment of adult patients with EGPA.[12] The Formulary Working Group requested a review of mepolizumab for the treatment of EGPA and a reimbursement recommendation. The clinical and pharmacoeconomic evidence for the review were identified through the CADTH Non-Sponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with

mepolizumab and comparators deemed to be appropriate based on feedback from clinical experts and public drug programs for patients with EGPA.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups, clinician groups, drug programs, and industry representatives who responded to CADTH's call for input, and from clinical expert(s) consulted by CADTH for the purpose of this review. The input received was prepared by CADTH staff and summarized in this report. The full input is available on the CADTH website.

Patient Input

One patient group, Vasculitis Foundation Canada, submitted input for this review that was collected from 6 patients. Patients' experience with currently available treatments included several lengthy hospitalizations, multiple courses of high-dose IV steroids, and a number of immune-suppressing treatments to induce disease remission. All patients remained on some form of therapy to maintain remission, often a combination of azathioprine and oral prednisone as well as a variety of asthma inhalers, and most patients required lifelong maintenance treatment. Mepolizumab had not been used by any of the patients interviewed. Steroid treatments for EGPA remain the mainstay of treatment, but they have many short- and long-term side effects. Therefore, steroid-sparing drugs such as mepolizumab are needed to treat patients with EGPA and other vasculitis conditions.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of EGPA provided input. The clinical experts noted that most patients with EGPA have a poor quality of life due to ongoing severe fatigue and most have glucocorticoid-induced toxicity. The clinical experts stated that an important treatment goal for patients with EGPA is to reduce tissue and organ damage, especially cardiac and neurologic damage. As more than 60% of patients with EGPA are steroid-dependent because of their asthma and/or ENT disease and conventional immunosuppressants do not work well for these aspects of the EGPA disease, more effective and safer treatments are needed to manage the long-term symptoms of EGPA.

Given limited access to the drug at present, the clinical experts stated that mepolizumab is mostly used to treat steroid-dependent asthma or chronic rhinosinusitis with nasal polyps in their patients with EGPA. However, the dosing of mepolizumab for asthma (100 mg subcutaneous [SC] once monthly) is lower than the recommended dose for EGPA (300 mg SC once monthly). While some patients with EGPA treated with 100 mg experienced benefit, some have only partial responses, and it is not possible to know if outcomes would have been different or improved had these patients been treated with a 300 mg dose (the dose evaluated in EGPA and as approved by Health Canada).

The clinical experts indicated that all patients with EGPA could be considered for mepolizumab treatment, but they noted that those with steroid-dependent asthma or chronic rhinosinusitis with nasal polyps and those with frequent relapses should clearly be eligible. The question remains as to whether it should be directly prescribed for every patient or only for those (more than 60% of patients) who appear to be steroid-

dependent based on the requirement of more than 7.5 mg a day of oral prednisone. In addition, patients with severe neurologic or cardiac disease could benefit from the early addition of an anti-IL-5 antibody, as it may further control the inflammation within the affected tissues. Mepolizumab should also be considered early in patients who are more susceptible to side effects from prednisone to try and expedite the tapering of prednisone in these patients. Mepolizumab has a good safety profile to date. That is, in the experts' opinion, it is clearly better than conventional immunosuppressants such as azathioprine or methotrexate and should be available for patients of all ages, including the rare cases of children with EGPA (1 to 4 new pediatric cases per year in Canada). Children are at high risk of growth retardation on prednisone, and any option to reduce prednisone use should be considered.

One of the clinical experts indicated that, of a group of 175 patients, the 40 to 50 patients they treated with mepolizumab experienced positive results. That is, around 70% of the patients treated with mepolizumab felt better, and steroid treatment could be tapered in 90% of patients or even stopped in around 25% of patients, as their asthma and/or ENT disease became well controlled. The clinical experts noted that they had some patients doing well on 100 mg doses, but they wanted to increase the dose to 300 mg for some patients to determine if the higher dose led to better outcomes (although this was only possible for a handful of patients who had private insurance and in whom the dosage increase worked in around 75% of the cases). The clinical expert further noted that in patients with EGPA and a high eosinophil count, underdosing with 100 mg may be harmful (rebound due to partial blockade only).

Input From Clinician Groups

Clinician input was submitted by 1 clinician group: vasculitis specialists at McMaster University and St. Joseph's Healthcare, which is an affiliated group of clinicians from rheumatology, nephrology, radiology, and respiratory medicine who provide care for patients with all forms of vasculitis and other rare, multisystemic autoimmune conditions.

The clinician group noted that there is currently a lack of approved treatments for EGPA in Canada and that current treatments are often insufficient, particularly for a large number of patients with refractory eosinophilic symptoms. To control their symptoms, these patients need high-dose glucocorticoids, which are associated with both short- and long-term complications such as infection, osteoporosis, diabetes, cardiovascular risk, weight gain, and neuropsychiatric effects. These patients often continue to experience sinopulmonary symptoms that have a negative impact on health-related quality of life (HRQoL). Current doses of mepolizumab used to treat eosinophilic asthma (100 mg SC per month) are often insufficient for EGPA.

Patients who are best suited for treatment with mepolizumab are those with active EGPA despite treatment with glucocorticoids and immunosuppressants or those requiring high-dose glucocorticoids (over 7.5 mg daily prednisone equivalent) for symptom control. It is likely that patients whose disease is associated with hypereosinophilia (as evidenced on blood tests, bronchoalveolar lavage, fraction of excreted nitrous oxide, tissue findings, or other indices) would benefit most from treatment with mepolizumab. However, mepolizumab may benefit individuals with any manifestation of EGPA, even those which have been previously attributed to vasculitis (a pathophysiologic process that may have a looser association with

inappropriate eosinophil activity). These patients are best identified by clinicians who care for them and who have specialist knowledge of these tests and their appropriate interpretation.

The clinician group indicated that a response to mepolizumab is best observed through improved control of symptoms of EGPA (reduced flares of sinopulmonary disease, reduced chronic sinopulmonary symptoms, and improved HRQoL) and a reduction in the need for OCSs to control symptoms. A clinically meaningful response is often determined through patient-reported improvement or progressive de-escalation of OCSs for symptom management, which is well documented in the MIRRA trial.[13] As assessments of asthma and chronic rhinosinusitis have become standardized, demonstrating this benefit across patient populations and contexts is now a simple task. This response is often seen within the first 4 to 12 weeks of treatment and is assessed through both clinical encounters as well as improvements in blood test results, pulmonary function testing, and imaging.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are available on the CADTH website.

Industry Input

Industry input was provided on the research protocol by GlaxoSmithKline Inc., the manufacturer of mepolizumab (brand name Nucala). The manufacturer noted that the goals of treatment of EGPA are to induce remission, prevent relapses, limit disease-related damage, minimize treatment-related morbidity, and improve survival. Treatment is tailored based on the severity of symptoms; patients with more severe disease usually receive more intense immunosuppressive agents. OCSs and systemic glucocorticoids are the foundation in the standard of care (SoC) for EGPA. While glucocorticoids alone are usually sufficient to induce remission in patients with nonsevere EGPA, for patients with severe disease, high-dose glucocorticoids are used to achieve remission with the addition of cyclophosphamide or rituximab. These patients are then switched to either azathioprine or methotrexate maintenance. Despite adequate control of the vasculitis manifestations with glucocorticoids, a large proportion of patients become glucocorticoid-dependent due to ongoing symptoms mostly related to asthma exacerbations or ENT symptoms. Thus, limiting the use of glucocorticoids during treatment is a challenge.

The manufacturer noted that the results of the phase III MIRRA trial support the use of mepolizumab for the treatment of patients with EGPA, noting that this evidence formed the basis of Health Canada regulatory approval of mepolizumab as an add-on to corticosteroids for the treatment of adult patients with EGPA.

Clinical Evidence

Protocol Selected Studies

Description of the Trials

The main evidence base for this review includes the MIRRA and the MANDARA trials.[13,14] The MIRRA trial was a randomized, double-blind, placebo-controlled, phase III trial of mepolizumab 300 mg administered SC once every 4 weeks plus SoC (n = 68) versus identical-appearing placebo plus SoC (n = 68) for 52 weeks in patients 18 years of age and older with relapsing or refractory EGPA.[13] SoC was defined as receipt of an OCS, with or without a stable dose of immunosuppressive therapy. There were 2 primary end points: the accrued weeks of remission over 52 weeks, and the proportion of patients in remission at both weeks 36 and 48.[13] Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0, plus a daily dose of oral prednisone or prednisolone of 4.0 mg or less. The mean age of the trial population was 49 years, 38% of patients who were randomized to mepolizumab and 44% of patients randomized to placebo were male, and the average duration of EGPA was 5 years.[13]

The MANDARA trial was a randomized, double-blind, double-dummy, phase III noninferiority trial that compared benralizumab 30 mg SC once every 4 weeks plus SoC (n = 70) to mepolizumab 300 mg SC once every 4 weeks plus SoC (n = 70) for 52 weeks in patients 18 years of age and older with relapsing or refractory EGPA.[14] Mepolizumab was the control arm in this trial, as mepolizumab had already been approved for EGPA when the trial began. Similarly to the MIRRA trial, SoC was defined as receipt of an OCS, with or without a stable dose of immunosuppressive therapy. The primary end point was the proportion of patients in remission at both weeks 36 and 48, and the prespecified noninferiority margin was −25%.[14] Remission was defined as a BVAS of 0, plus a daily dose of oral prednisone or prednisolone of 4.0 mg or less. The mean age of the MANDARA trial population was 52 years, 60% of patients were female, and the mean time since diagnosis of EGPA was 5 years.[14]

Critical Appraisal

The process for randomization in both trials was appropriate. Procedures were in place to maintain blinding throughout the trials, including using an identical-appearing placebo in both trials, administering a double-dummy placebo in the MANDARA trial, and ensuring trial investigators did not have access to blood eosinophil results. Most prognostic factors were balanced between the treatment and control groups.

The MANDARA trial used a noninferiority design to compare benralizumab to mepolizumab. The noninferiority margin for the primary end point of achievement of remission at weeks 36 and 48 was prespecified as a difference of −25%.[14] However, it is unclear as to whether −25% would be considered the largest clinically acceptable difference between benralizumab and mepolizumab.

In general, the outcomes assessed in the MIRRA and MANDARA trials were clinically relevant and important to patients and clinicians. Intention-to-treat (ITT) populations were used for the efficacy analyses in both trials and were defined as patients who were randomized and received at least 1 dose of trial medication.[13,14] All patients in each trial received at least 1 dose of trial medication and were therefore included in the

efficacy analyses.[13,14] However, it was unclear how missing data for a number of end points was handled in the ITT analyses.

The statistical analysis in the MIRRA and MANDARA trials was generally acceptable. Statistical comparisons for the primary and secondary end points were controlled for type I error in the MIRRA trial; however, the other end points were not controlled for type I error.[13] In addition, it is important to note that the secondary and other end points in the MANDARA trial were not controlled for type I error.[14] The confidence intervals (CIs) around the point estimates for a number of the comparisons in the MIRRA and MANDARA trials were very wide; as a result, there is uncertainty with the effect estimates due to imprecision.[14]

The trial eligibility criteria were generally clinically relevant; however, patients with severe active EGPA (defined as having ongoing or recent organ-threatening or life-threatening EGPA within 3 months before screening) were excluded from the trial. Patients also needed to have EGPA for at least 6 months before inclusion in the trial; therefore, newly diagnosed patients were excluded. In addition, patients under the age of 18 years were not included in the trial, so no conclusions can be drawn in pediatric patients with EGPA, although EGPA in pediatric patients is noted to be rare.[15] Lastly, patients were required to have asthma for inclusion in both trials, thereby excluding the up to 10% of patients with EGPA who do not have asthma.[7,9] It is unclear whether the response to mepolizumab in patients with EGPA without asthma would be similar to those with asthma.

Efficacy Results

The key results from the MIRRA and MANDARA trials are available in Table 2. In the MIRRA trial, 19 patients (28%) in the mepolizumab group and 2 (3%) in the placebo group had remission for at least 24 weeks (odds ratio [OR] = 5.91; 95% CI, 2.68 to 13.03; P < 0.001). In addition, a greater proportion of patients randomized to mepolizumab had remission at weeks 36 and 48 (32% versus 3%; OR = 16.74; 95% CI, 3.61 to 77.56) compared to patients randomized to placebo.[13] In the MANDARA trial, benralizumab was noninferior but not superior to mepolizumab for the adjusted percentage of patients with remission at weeks 36 and 48 (59% in the benralizumab group and 56% in the mepolizumab group; risk difference [RD] = 3%; 95% CI, −13 to 18; P < 0.05 for noninferiority; P = 0.73 for superiority).[14] The relative odds for accrued weeks of remission over 52 weeks in patients randomized to benralizumab compared to mepolizumab was 1.36 (95% CI, 0.75 to 2.48).

The average daily OCS dose during weeks 48 to 52 in the MIRRA trial was lower in patients in the mepolizumab group compared to patients in the placebo group (9.2 mg versus 13.5 mg; OR = 0.20; 95% CI, 0.09 to 0.41); in the MANDARA trial, the average daily OCS dose during weeks 48 to 52 was 2.98 mg in the benralizumab group and 3.43 mg in the mepolizumab group (OR = 1.42; 95% CI, 0.77 to 2.62).[13,14] Cardiovascular end points and survival, both identified as important efficacy end points, were not evaluated as efficacy end points in either trial.[13,14] Lastly, the change in patient-reported outcome measures was only presented graphically in both trials, and no information was identified reporting the psychometric properties of these instruments in patients with EGPA.[13,14]

Harms Results

A summary of the harms is provided in Table 2. In the MIRRA trial, 66 patients (97%) in the mepolizumab arm and 64 patients (94%) in the placebo arm experienced at least 1 adverse event (AE).[13] The most common AEs were headache (32% in the mepolizumab arm vs 18% in the placebo arm), sinusitis (21% vs 16%) nasopharyngitis (18% vs 24%), arthralgia (22% vs 18%), and upper respiratory tract infection (21% vs 16%).[13] Twelve patients (18%) in the mepolizumab arm and 18 patients (26%) in the placebo arm experienced a serious adverse event (SAE). Worsening or exacerbation of asthma was the most frequent SAE (3% in the mepolizumab arm vs 6% of in the placebo arm). AEs leading to discontinuation occurred in 2 patients (3%) in the mepolizumab arm and 1 patient (1%) in the placebo arm. One death was reported in the mepolizumab arm.[13]

Table 2: Summary of Key Results From the MIRRA and MANDARA Trials

Outcome	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (N = 68)	Placebo (N = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Efficacy				
Remission				
Total accrued weeks of remission, n (%)				
0 weeks	32 (47)	55 (81)	9 (13)	15 (21)
More than 0 weeks to less than 12 weeks	8 (12)	8 (12)	12 (17)	10 (14)
12 weeks to less than 24 weeks	9 (13)	3 (4)	8 (11)	8 (11)
24 weeks to less than 36 weeks	10 (15)	0 (0)	21 (30)	19 (27)
36 weeks or more	9 (13)	2 (3)	20 (29)	18 (26)
OR (95% CI)	5.91 (2.68 to 13.03) P < 0.001		1.36 (0.75 to 2.48)[a] P = NR	
Remission at weeks 36 and 48, n (%)	22 (32)	2 (3)	41 (59)[b]	40 (56)[b]
Comparison (95% CI)	OR = 16.74 (3.61 to 77.56) P < 0.001		RD = 3% (−13 to 18) P < 0.05 for noninferiority P = 0.73 for superiority	
OCS end points				
Average OCS dose during weeks 48 to 52, n (%)				
0 mg/day	12 (18)	2 (3)	29 (41)	19 (27)
More than 0 mg/day to 4.0 mg/day	18 (26)	3 (4)	20 (29)	30 (43)
More than 4.0 mg/day to 7.5 mg/day	10 (15)	18 (26)	14 (20)	13 (19)
More than 7.5 mg/day	28 (41)	45 (66)	7 (10)	8 (11)
OR (95% CI)	0.20 (0.09 to 0.41) P < 0.001		1.42 (0.77 to 2.62)[a] P = NR	

Outcome	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (N = 68)	Placebo (N = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Percentage reduction from baseline in average OCS dose at weeks 48 to 52, n (%)				
No reduction or withdrawal from treatment	14 (21)	33 (49)	3 (4)	7 (10)
Less than 25% reduction	8 (12)	9 (13)	0	2 (3)
25% to less than 50% reduction	8 (12)	11 (16)	7 (10)	9 (13)
50% to less than 75% reduction	16 (24)	11 (16)	20 (29)	17 (24)
75% to less than 100% reduction	10 (15)	3 (4)	11 (16)	17 (24)
100% reduction	12 (18)	1 (1)	29 (41)	18 (26)
OR (95% CI)	4.32 (2.28 to 8.19)[a] P < 0.001		1.80 (0.98 to 3.28)[a] P = NR	
Harms				
AEs, n (%)	66 (97)	64 (94)	63 (90)	67 (96)
SAEs, n (%)	12 (18)	18 (26)	4 (6)	9 (13)
Discontinuation or trial withdrawal due to AEs, n (%)	2 (3)	1 (1)	0	2 (3)
Injection-site reaction, n (%)	10 (15)	9 (13)	NR	NR
Deaths, n (%)	1 (1)	0	0	0

AE = adverse event; CI = confidence interval; NR = not reported; OCS = oral corticosteroid; OR = odds ratio; RD = risk difference; SAE = serious adverse event.

[a]Adjusted percentage: adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

Comparisons between mepolizumab and placebo in the MIRRA trial were adjusted for baseline dose of prednisolone or prednisone, baseline BVAS, and geographic region (North America, Europe, or Japan).[13]

Comparisons between benralizumab and mepolizumab in the MANDARA trial were adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

[b]Analyses were not controlled for type I error.[13,14]

Sources: Wechsler et al., 2017;[13] Wechsler et al., 2024.[14]

In the MANDARA trial, 63 patients (90%) in the benralizumab arm and 67 (96%) in the mepolizumab arm experienced at least 1 AE, and the most common AEs were COVID-19 infection (21% and 27%, respectively), headache (17% and 16%), arthralgia (17% and 11%), and nasopharyngitis (9% and 14%).[14] Four patients (6%) in the benralizumab group and 9 patients (13%) in the mepolizumab group experienced an SAE; no patients in the benralizumab group discontinued treatment due to AEs, whereas 2 patients (3%) in the mepolizumab group discontinued treatment.[14] There were no deaths during the MANDARA trial.[14]

Cost Information

- The economic review included a comparison of the treatment costs of mepolizumab with or without OCSs and/or immunosuppressive therapies and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.
- The annual patient cost of mepolizumab monotherapy is $86,338. When used in combination with OCSs, the annual patient cost of mepolizumab is $86,363. When used in combination with

immunosuppressive therapies, the annual patient cost of mepolizumab ranges between $86,456 (mepolizumab + methotrexate) and $87,422 (mepolizumab + mycophenolate mofetil). Whether used as a standalone treatment or as part of a combination therapy, mepolizumab is more costly than OCSs (annual cost: $8 to $96), immunosuppressive therapies (annual cost: $118 to $38,716), and benralizumab (annual cost: $32,367). CADTH notes that benralizumab is not publicly funded for the treatment of patients with EGPA by any jurisdiction. Clinical experts consulted by CADTH indicated that some patients with EGPA access benralizumab off-label through private insurance or trial participation.

As such, mepolizumab monotherapy results in incremental costs compared with OCSs ($86,314), immunosuppressive therapies ($47,662 to $86,221), and benralizumab ($53,972). When used alongside OCSs or in combination with immunosuppressive therapies, the incremental cost of mepolizumab compared with OCSs or immunosuppressive therapies alone amounts to $86,338. This cost comparison is based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

Evidence from the MIRRA trial demonstrated that patients randomized to mepolizumab 300 mg SC once every 4 weeks had a greater total accrued weeks of remission and proportion in remission at weeks 36 and 48 when compared to placebo; however, the amount of benefit associated with mepolizumab was uncertain given the imprecise CIs.[13] The mean daily OCS dose was reduced and the percentage reduction in daily OCS dose was greater in patients randomized to mepolizumab compared to patients randomized to placebo.[13] In the MANDARA trial, benralizumab 30 mg SC once every 4 weeks was noninferior and not superior to mepolizumab 300 mg SC once every 4 weeks for proportion in remission at weeks 36 and 48.[14] In addition, there were no statistical differences between benralizumab and mepolizumab for total weeks accrued remission, mean daily OCS dose between weeks 48 and 52, and percentage reduction in OCS dose at weeks 48 and 52.[14] More patients who were randomized to mepolizumab in the MANDARA trial experienced an increased likelihood of EGPA remission at weeks 36 and 48, an increased duration of accrued remission, a greater reduction in OCS dose from baseline, and a reduction in relapse compared to the patients randomized to mepolizumab in the MIRRA trial. This could be due to differences in trial design (e.g., an active-controlled versus placebo-controlled trial) or the more aggressive OCS tapering plan in the MANDARA trial, changes in clinical practice over time, and the impact of isolation and social distancing during the COVID-19 pandemic.[13,14]

AEs were common in both trials: in the MIRRA trial, 97% of patients in the mepolizumab group and 94% of patients in the placebo group experienced an AE, and in the MANDARA trial, 90% of patients in the benralizumab group and 96% in the mepolizumab group experienced an AE.[13,14] In the MIRRA trial, 18% of patients in the mepolizumab group and 26% of patients in the placebo group experienced a SAE, and in the MANDARA trial, 6% of patients in the benralizumab arm and 13% in the mepolizumab arm experienced a SAE.[13,14] Discontinuation due to AEs was rare in both trials.

The results of the cost comparison of drug acquisition costs demonstrate that, when compared to OCSs, immunosuppressive therapies, or benralizumab, the reimbursement of mepolizumab with or without OCSs

and/or immunosuppressive therapies is expected to increase treatment costs. This increase translates to incremental costs ranging from $47,662 to $86,314 per patient per year.

Based on the clinical review conclusions, mepolizumab in combination with SoC likely results in improved duration of accrued remission, improved reduction in relapse rate, and improved reduction in OCS use compared with SoC alone. Given that mepolizumab in combination with SoC is associated with incremental costs and incremental benefit compared with SoC alone, a cost-effectiveness analysis would be required to determine the cost-effectiveness of mepolizumab relative to SoC alone. As this was not available, the cost-effectiveness of mepolizumab in combination with SoC relative to SoC alone for the treatment of patients with EGPA could not be determined.

The clinical review further concluded that benralizumab was noninferior and not superior to mepolizumab with regard to duration of accrued remission, reduction of relapse rate, and reduction in OCS use. Benralizumab is less costly than mepolizumab. Neither is publicly funded for this indication.

Introduction

Disease Background

EGPA (formerly referred to as Churg-Strauss syndrome) is a rare disease characterized by tissue and blood eosinophilia, small to medium-size vessel vasculitis, extravascular granulomas, asthma, and sinonasal symptoms.[1,2] The prevalence of EGPA ranges from 12 to 59 cases per 1,000,000 people, with 1 to 4 new cases diagnosed per 1,000,000 person-years.[4-6] The average age at diagnosis is 50 years, and prevalence is similar between women and men.[6] Development of EGPA in childhood is very rare but may be associated with a poorer prognosis than EGPA that develops in adulthood.[15] Lastly, EGPA is associated with considerable health care resource utilization due to the morbidity associated with EGPA, which results in hospitalization (17% to 42% of patients over 1 to 2.5 years) and emergency department visits (25% to 42% of patients over 1 to 1.5 years).[5,6,16]

The clinical presentation of EGPA is heterogeneous; however, more than 90% of patients are affected by asthma, and 60% to 80% of patients have ENT disease. Other manifestations of EGPA include glomerulonephritis, peripheral neuropathy, cardiomyopathy, pulmonary infiltrates, gastrointestinal involvement, and palpable purpura. EGPA is characterized 2 different forms: ANCA-associated EGPA based on myeloperoxidase (MPO) or proteinase 3 (ANCA-positive EGPA), and eosinophilic EGPA (ANCA-negative EGPA), and the type of EGPA influences presentation.[9] Patients with ANCA-positive EGPA are more likely to have necrotizing vasculitis with glomerulonephritis, neuropathy, purpura, and alveolar hemorrhage, whereas patients with eosinophilic EGPA are more likely to have eosinophilic and granulomatous inflammation with lung infiltrates, cardiomyopathy, and gastrointestinal disease. Approximately 30% to 35% of patients have ANCA-positive EGPA.[3]

The course of EGPA is characterized by periods of remission with acute relapses, defined as “the new appearance, recurrence, or worsening of clinical EGPA manifestations (excluding asthma and ENT

symptoms) that require a change of therapy, or a dose increase."[16,17] Relapses increase the likelihood of developing organ damage, and as a result, the prevention of relapses in patients with EGPA is an important treatment goal. Other important treatment goals for patients with EGPA are to induce remission, prevent organ damage, maintain remission, maintain or improve HRQoL, and minimize the harms associated with treatments used in patients with EGPA.[9]

Standards of Therapy

Based on the Canadian Vasculitis Research Network consensus recommendations for the management of antineutrophil cytoplasm antibody–associated vasculitis,[10] as well as international guidelines,[9,17-19] corticosteroids are the mainstay of treatment for both induction and maintenance of remission in patients with EGPA. For patients newly diagnosed with EGPA, induction therapy with cyclophosphamide and a glucocorticoid (1 mg/kg/day to a maximum of 80 mg per day) is recommended; and for patients with nonsevere EGPA without poor prognostic factors or major organ involvement, glucocorticoid monotherapy is recommended for induction.[10] Rituximab may also be used to induce remission in patients with severe active EGPA.[9,18]

Drugs used for maintenance of remission include OCSs, adjusted to the lowest possible dose to minimize harms.[9,10,18] However, relapses can occur after titration of OCSs.[9,18] As such, immunosuppressive therapy such as azathioprine, methotrexate, leflunomide, and mycophenolate mofetil, is sometimes used in combination with OCSs for maintenance of remission; however, the quality of the evidence for use of immunosuppressive therapy in EGPA is poor and their efficacy for asthma and ENT manifestations is minimal.[9,10,17-19] Lastly, it is recommended that mepolizumab 300 mg, administered SC once every 4 weeks, be considered for patients with relapsing or refractory EGPA who are dependent on OCSs.[9,10,18,19]

Drug

IL-5 is the main cytokine involved with the proliferation, maturation, and prolonged survival of eosinophils.[20] Mepolizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, preventing IL-5 from binding to the surface of eosinophils, thereby preventing the growth, recruitment, activation, and survival. As a result, blood eosinophil counts are reduced.[12] Mepolizumab currently has a Health Canada indication as an add-on to corticosteroids for the treatment of adult patients with EGPA.[12] Mepolizumab is available as a 100 mg/mL lyophilized powder or solution for SC injection. The recommended dose for EGPA is 300 mg SC once every 4 weeks.[12]

In December 2023, CADTH received a request from the Formulary Working Group to conduct a review of mepolizumab for the treatment of EGPA. The current CADTH nonsponsored reimbursement request for mepolizumab is for all patients (children and adults) with EGPA, with or without OCSs and/or immunosuppressive therapy.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is available on the CADTH website.

One patient group, Vasculitis Foundation Canada, submitted patient input for this review. Information was gathered for the input from interviews with 6 patients with EGPA from 5 provinces in February 2024.

The patients indicated that the most important aspects of EGPA are to ensure an early diagnosis and treatment initiation, to prevent organ involvement and tissue damage, and to have new treatments available that are effective for the treatment of EGPA. Access to treatments that reduce the impact of high doses of steroids, which are often repeated, and avoid the need for immune suppression like cyclophosphamide, that are associated with harms, were also emphasized by the patients.

Patients' experiences with currently available treatments included several lengthy hospitalizations, multiple courses of high-dose IV steroids, and a number of immune-suppressing treatments to induce disease remission. All patients remain on some form of therapy to maintain remission, often a combination of oral azathioprine and low dose oral prednisone as well as a variety of asthma inhalers, and most patients require lifelong maintenance treatment. Most patients have asthma and some form of motor nerve damage, commonly foot or hand drop, and require ongoing physiotherapy. All but 1 patient indicated that they tolerate current medications. Mepolizumab had not been used by any of the patients interviewed. Steroid treatments for EGPA remain the mainstay of treatment, but they have many short- and long-term side effects. Therefore, steroid-sparing drugs such as mepolizumab are needed to treat patients with EGPA and other vasculitis conditions.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of EGPA.

Unmet Needs

Most patients have a poor quality of life due to ongoing severe fatigue, and most experience (often severe) glucocorticoid-induced harms. Many patients have ongoing ENT disease despite current treatment (including anti-IL-5 treatment). Some patients also have ongoing heart involvement, which may result in early but also sometimes delayed mortality from cardiovascular events. The clinical experts indicated that an important treatment goal for patients with EGPA is to reduce tissue and organ damage, especially cardiac

and neurologic damage, by using more rapidly acting drugs with a different mechanism of action to those currently available. As more than 60% of patients with EGPA are steroid-dependent because of their asthma and/or ENT issues, and conventional immunosuppressants do not work well for these aspects of the EGPA disease, more effective and safer treatments are needed to manage the long-term symptoms of EGPA.

Mepolizumab is almost never reimbursed for the EGPA dose of 300 mg. In addition, the duration of maintenance therapy is unclear. For maintenance with conventional immunosuppressants, it is for at least 2 to 4 years. When using mepolizumab or similar biologics, a treatment duration of at least 4 to 6 years or even longer may be needed, as asthma or chronic rhinosinusitis with nasal polyps tend to recur within months after stopping these agents. Mepolizumab reimbursement is often stopped after 1 year.

Place in Therapy

The clinical experts indicated that at present, given limited access to the drug, mepolizumab is mostly used to treat steroid-dependent asthma or chronic rhinosinusitis with nasal polyps in their patients with EGPA. It is the first-line treatment for active (nonsevere) disease when manifestations persist or worsen after 4 weeks of remission induction therapy. Mepolizumab is also first-line treatment for patients with EGPA with frequent relapses.

The experts noted that even access to the asthma dosing of 100 mg every 4 weeks is difficult and there are no other treatment options to offer patients, other than remaining on prednisone doses of more than 10 mg per day, which is not compatible with a normal life (risks of such a dose of long-term prednisone are well known). The clinical experts believed that using mepolizumab earlier could achieve better steroid-sparing effects and fewer side effects, and avoid disease relapse when tapering down prednisone, which could result in a full EGPA relapse with more neurologic or cardiac involvement and damage.

Patient Population

The clinical experts indicated that every EGPA patient could be considered for mepolizumab treatment but those with steroid-dependent asthma or chronic rhinosinusitis with nasal polyps, and those with frequent relapses, should clearly be eligible. The question remains as to whether it should be directly prescribed to every patient or only to those (more than 60% of patients) who appear to be steroid-dependent based on needing more than 7.5 mg a day of prednisone. In addition, patients with severe neurologic or cardiac disease could benefit from the early addition of anti-IL-5, as it may further control the inflammation within the affected tissues. Mepolizumab should also be considered early on in patients who are more susceptible to severe harms due to steroids (e.g., patients with avascular bone necrosis or patients with diabetes), to try and expedite the tapering of prednisone in these patients. Mepolizumab has a good safety profile to date and should be available for patients of all ages, including the rare cases of children with EGPA (1 to 4 new pediatric cases per year in Canada). Children are at high risk of growth retardation on prednisone, and any option to reduce prednisone use should be considered. There is not a lot of data on the use of mepolizumab during pregnancy, thus use in patients in periconception should likely be avoided.

The dose of mepolizumab for EGPA should follow the dose used in EGPA studies and that has been approved for EGPA — that is, 300 mg per month. One could consider decreasing to 100 mg after a few years,

but that remains to be studied. Some patients with EGPA have been treated with 100 mg with benefits, although it is not possible to know if outcomes would have been different or improved had these patients been treated with a 300 mg dose. There seems to be clear dose relationship between dosing and a decrease in eosinophil count. Thus, patients with active EGPA and a high eosinophil count should receive the full dosing, while others with a lower count may do well with the 100 mg dosing later in the course of treatment. Patients with eosinophilic asthma have lower eosinophil counts (around 0.3 to 0.5 × 10^9/L compared to EGPA around 7 × 10^9/L at diagnosis on average).

Assessing Response to Treatment

Considering the different phases in EGPA, response to treatment may be assessed differently at each stage. The clinical experts noted that after diagnosis, the first goal of treatment is to stop the progression of this potentially lethal condition, hence survival is the most pertinent outcome. The next goal is achieving a sustained control of the vasculitic manifestations, usually referred to as remission of vasculitis. At such time patients may be feeling well; have no active skin, cardiac, kidney, or neurologic disease (patients can still have some organ damage); have normal c-reactive protein and eosinophil counts; and have controlled or partially controlled asthma on some dose of prednisone.

The clinical experts listed important outcomes, which are also used in clinical trials. These include (in addition to survival), remission using BVAS, assessment of organ damage using the Vasculitis Damage Index (VDI), improvement in HRQoL and symptoms (e.g., SF-36, fatigue), prevention of relapses, prevention of asthma exacerbation, prevention of ongoing ENT disease, and prevention of cardiovascular events.

Discontinuing Treatment

The clinical experts indicated that there is a lack of evidence to inform when mepolizumab should be discontinued. One clinical expert noted that they only had to stop mepolizumab in 1 patient who had an ongoing ENT disease. Some evidence in the asthma setting may be used to inform decisions regarding discontinuation of treatment. The other clinical expert noted that there is evidence from studies of patients with asthma and some studies in EGPA in which mepolizumab was stopped at month 12, and all the benefit of treatment was lost by 3 months after discontinuation. Hence, the duration of mepolizumab treatment is likely to be at least 3 to 5 years at present. While some preliminary data in asthma raise optimism that treatment may be stopped after 3 to 5 years without risk of rebound, there is no firm evidence on the optimal duration of treatment and discontinuation for patients with EGPA. It was noted that clinicians may also consider tapering mepolizumab from 300 mg to 100 mg monthly at some point (e.g., after 3 years) in patients with EGPA who have been off prednisone and doing well (BVAS = 0 and controlled asthma and/or ENT).

The clinical experts noted that AEs with mepolizumab are rare, but they do not yet have any patients that have been treated with mepolizumab for more than 10 years. Therefore, late-emerging adverse events may still occur. If a patient with EGPA relapses on mepolizumab (approximately 10% for vasculitis at 5 years, and around 50% for asthma control), a transient increase of prednisone is needed, and consideration of stopping and switching to another drug (e.g., benralizumab, tezepelumab, or dupilumab for asthma and/or ENT issues, and cyclophosphamide or rituximab for more serious vasculitis concerns) must be discussed.

Prescribing Conditions

Based on the experience of the clinical experts with the patient support program for asthma, no special setting is needed. However, specialists with experience in treating asthma or EGPA and in management of biologics in general would be best suited to initiate and monitor the effect of treatment with mepolizumab. The clinical experts noted that mepolizumab should be accessible for any general internist, rheumatologist, respirologist, or even an ENT specialist who requires it for EGPA. However, other specialties can be involved (neurology, nephrology, dermatology), but this is rare and would be the exception. Mepolizumab is a SC injection, and the patient support program is effective (based on their experience with the asthma patient support program) for providing training for patients, sometimes at a clinic first, with patients self-administering the treatment independently after.

One of the clinical experts noted that given that EGPA is a rare disease (prevalence around 40 per 1,000,000, with 1,000 patients in Canada at various stages of their disease), patients are often referred to local physicians with experience in EGPA. The Canadian Vasculitis Research Network has helped identify those doctors across Canada who could help and guide the management of these patients (without necessarily having to take ownership of the cases).

Adverse Events to Monitor

The clinical experts noted that long-term safety (more than 10 years) of mepolizumab remains unknown, but the clinical experts have not encountered any major adverse events in their practice when using mepolizumab to treat patients with EGPA. Some patients have injection-site reaction, and others have allergic reactions to their first injections. Allergic reactions, injection-site reactions, antimepolizumab antibody monitoring (clinical relevance unknown), and helminth infections should be monitored.

Additional Considerations

One of the clinical experts indicated that they have had a positive experience treating 40 to 50 patients with mepolizumab among a group of 175 patients. In their experience, around 70% of treated patients feel better, and steroid treatment could be tapered in 90% of patients or even stopped in around 25% of patients, as their asthma and/or ENT had become well controlled. The clinical experts noted that they had some patients doing well on 100 mg dosing and others for whom they wanted to increase the dosing to 300 mg to determine if the higher dose led to better outcomes (although this was only possible for a handful of patients with private insurance, in whom the dosage increase worked in around 75% of the cases). The clinical expert further noted that in patients with EGPA and a high eosinophil count (as seen in EGPA), underdosing with 100 mg may be harmful (rebound due to partial blockade only).

Other points for consideration are that the harms of mepolizumab in children under 6 years of age and during pregnancy and lactation have not been studied. In addition, the role of new antiasthma treatment in EGPA (i.e., monoclonal antibodies such as anti-IL-13, anti-IL-21, or antithymic stroma lymphopoietin) remains uncertain.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups. The full clinician group input is available on the CADTH website.

Clinician input was submitted by 1 clinician group: vasculitis specialists at McMaster University and St. Joseph's Healthcare, which is an affiliated group of clinicians from rheumatology, nephrology, radiology, and respiratory medicine who provide care for patients with all forms of vasculitis and other rare, multisystemic autoimmune conditions.

Unmet Needs

The clinician group noted that there is currently a lack of approved treatments for EGPA in Canada and that current treatments are often insufficient, particularly for a large number of patients with refractory eosinophilic symptoms. To control their symptoms, these patients need high-dose glucocorticoids, which are associated with both short- and long-term complications such as infection, osteoporosis, diabetes, cardiovascular risk, weight gain, and neuropsychiatric effects. These patients often continue to experience sinopulmonary symptoms that have a negative impact on HRQoL. Current doses of mepolizumab used to treat eosinophilic asthma (100 mg per month) are often insufficient for EGPA.

Place in Therapy

The clinician group indicated that mepolizumab is considered a first-in-mechanism treatment that can directly control a central pathogenic pathway in EGPA. As such, it would be ideal as front-line therapy for patients with EGPA who do not have organ- or life-threatening manifestations of disease. The clinician group believes that the approval and funding of mepolizumab would provide a standard access pathway to mepolizumab for patients with EGPA who have been refractory to less intensive treatment. This may slightly shift the treatment paradigm. However, as a significant fraction of patients with EGPA have symptoms that are only now treated by anti-IL-5 agents and where availability is driven by private insurance, this approval would improve equity in treatment access for patients.

Considering the multiple available treatments for EGPA, the cost of mepolizumab, and the improvement in patient outcomes it offers, it should be expected that patients with EGPA, especially those with sinopulmonary disease, are treated with other therapies (inhaled corticosteroids, OCSs, rituximab, cyclophosphamide, azathioprine, or other agents as appropriate) before commencing mepolizumab. However, since the diagnosis of EGPA is often made after a patient has been refractory to conventional treatments, in many cases mepolizumab may be the appropriate first-line therapy after a diagnosis of EGPA.

Patient Population

Patients who are best suited to treatment with mepolizumab are those with active EGPA despite treatment with glucocorticoids and immunosuppressants or those requiring high-dose glucocorticoids (over 7.5 mg daily prednisone equivalent) for symptom control. It is likely that patients whose disease is associated with hypereosinophilia (as evidenced on blood tests, bronchoalveolar lavage, fraction of excreted nitrous oxide, tissue findings, or other indices) would benefit most from treatment with mepolizumab. However, mepolizumab may benefit individuals with any manifestation of EGPA, even those that have been previously

attributed to vasculitis (a pathophysiologic process that may have a looser association with inappropriate eosinophil activity). These patients are best identified by clinicians who care for them and who have specialist knowledge of these tests and their appropriate interpretation.

Assessing Response to Treatment

The clinician group indicated that a response to mepolizumab is best observed through improved control of symptoms of EGPA (reduced flares of sinopulmonary disease, reduced chronic sinopulmonary symptoms, and improved HRQoL) and a reduction in the need for oral glucocorticoids to control symptoms. A clinically meaningful response is often determined through patient-reported improvement or progressive de-escalation of oral glucocorticoids for symptom management, which is well documented in the MIRRA trial.[13] As assessments of asthma and chronic rhinosinusitis have become standardized, demonstrating this benefit across patient populations and contexts is now a simple task. This response is often seen within the first 4 to 12 weeks of treatment and is assessed through both clinical encounters as well as improvements in blood test results, pulmonary function testing, and imaging.

Discontinuing Treatment

The clinician group noted 2 contexts in which drug discontinuation of mepolizumab needs to be addressed: refractory disease and disease in persistent remission.

For patients with refractory disease with ongoing symptoms or damage despite multimodal therapy, mepolizumab is often used with escalating doses of oral and/or inhaled glucocorticoids. If insufficient, other anti-IL-5 agents such as benralizumab and reslizumab, which are currently only available with insurance approval or trial participation, may be used. In this context, mepolizumab is typically stopped for new agents rather than continued, however, there are cases where combination therapy with mepolizumab and non-IL-5 agents (e.g., dupilumab) may manage refractory symptoms.

For patients who have had a remission with adequate symptom control, there is a paucity of data on how long patients should be treated or if treatment may be deintensified. Treatment with mepolizumab is typically continued as long as medications are available; it is possible that a trial of de-intensification to lower doses of mepolizumab or other agents may be able to take place; however, this is done on a case-by-case basis without data to guide such practices at this time. Important factors for these decisions include duration of disease control, other therapies needed to control disease, patient values and preferences, adverse effects of treatment, damage from disease, and the risk of organ- or life-threatening events on relapse.

Prescribing Conditions

Mepolizumab is best prescribed by clinicians with experience in treating patients with EGPA, namely respirologists and rheumatologists. The treatment may be started in an inpatient or outpatient setting safely and does not need inpatient monitoring for its first dose. Patients should be monitored by specialists clinically, as well as with blood tests, relevant imaging, and assessment of pulmonary and physical function for the entire duration of their treatment.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's nonsponsored reimbursement review processes by identifying issues that may impact their ability to implement a recommendation.

The implementation questions and corresponding responses from the clinical experts consulted by CADTH are available on the CADTH website.

Industry Input

This section was prepared by CADTH based on the input provided by industry.

Industry input was provided on the research protocol by GlaxoSmithKline Inc., the manufacturer of mepolizumab (brand name Nucala).

The manufacturer noted that the goals of treatment of EGPA are to induce remission, prevent relapses, limit disease-related damage, minimize treatment-related morbidity, and improve survival. Treatment is tailored based on the severity of symptoms; patients with more severe disease usually receive more intense immunosuppressive agents. OCSs and systemic glucocorticoids are the foundation in the SoC for EGPA. While glucocorticoids alone are usually sufficient to induce remission in patients with nonsevere EGPA, for patients with severe disease, high-dose glucocorticoids are used to achieve remission with the addition of cyclophosphamide or rituximab. These patients are then switched to either azathioprine or methotrexate maintenance. Despite adequate control of the vasculitis manifestations with glucocorticoids, a large proportion of patients become glucocorticoid-dependent due to ongoing symptoms mostly related to asthma exacerbations or ENT symptoms. Thus, limiting the use of glucocorticoids during treatment is a challenge.

The manufacturer noted that current immunosuppressive therapies available for EGPA (e.g., cyclophosphamide, rituximab, azathioprine, methotrexate) are associated with a range of side effects (such as infection, cancer, and infertility) and require dose monitoring and/or adjustments. Although patients with severe or nonsevere EGPA are initially treated with systemic glucocorticoids, many patients will either relapse and/or progress when tapering off these treatments. They also noted that cumulative exposure to glucocorticoids may lead to long-term complications including diabetes, myopathy, osteoporosis, hypercortisolism, and vertebral fractures. As such, patients with EGPA have an unmet treatment need for effective and licensed treatment options for relapsing and remitting EGPA that have an acceptable safety profile.

The manufacturer described the results of the phase III MIRRA trial[13] in support of mepolizumab for the treatment of patients with EGPA, noting that this evidence formed the basis of regulatory Health Canada approval of mepolizumab as an add-on to corticosteroids for the treatment of adult patients with EGPA.

The full Industry Input is available on the CADTH website.

Clinical Evidence

The clinical evidence included in the review of mepolizumab is presented in 4 sections. The first section, the systematic review, includes studies that were selected according to an a priori protocol. The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no relevant indirect evidence was identified. The third section would include long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review, however, no relevant evidence was identified. The fourth section includes an appraisal of the outcome measures used in the included trials.

Systematic Review (Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of mepolizumab for the treatment of EGPA, with or without OCSs and/or immunosuppressants.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 3. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 3: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Patients with EGPA Subgroups: • Age (less than 6 years, 6 to 17 years, 18 years and older) • MPO-ANCA negative, MPO-ANCA positive • Severe, nonsevere
Intervention	Mepolizumab 300 mg once every 4 weeks, administered subcutaneously, with or without OCSs and/or immunosuppressants
Comparators	Placebo, OCSs, methotrexate, azathioprine, cyclophosphamide, rituximab, mycophenolate mofetil, benralizumab, omalizumab
Outcomes	**Efficacy outcomes:** • Achievement of remission (vasculitis or asthma) • Relapse (vasculitis or asthma) • Change in OCS dose • Organ damage (e.g., VDI) • Asthma control (e.g., ACQ-6 score) • HRQoL (e.g., SNOT-22) • Cardiovascular events • Survival **Harms outcomes:**

Criteria	Description
	• AEs, SAEs, WDAEs, deaths • Notable harms – allergic reactions, injection-site reactions, severe infections, helminth infections, shingles, ENT adverse events (rhinitis, pharyngitis)
Study design	Published phase III and IV RCTs

ACQ-6 = 6-item Asthma Control Questionnaire; AE = adverse event; ANCA = antineutrophil cytoplasmic antibody; EGPA = eosinophilic granulomatosis with polyangiitis; ENT = ear-nose-throat; HRQoL = health-related quality of life; MPO = myeloperoxidase; OCS = oral corticosteroid; RCT = randomized controlled trial; SAE = serious adverse event; SNOT-22 = 22-item Sino-Nasal Outcome Test; VDI = Vasculitis Damage Index; WDAE = withdrawal due to adverse event.

An information specialist performed the literature search for clinical studies using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings, and keywords. Search concepts were developed based on the elements of the patient population, intervention, comparators, outcome, and study design (PICOS) framework and research questions. The main search concepts were mepolizumab and eosinophilic granulomatosis with polyangiitis. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on January 10, 2024. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee on July 4, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

A focused literature search for indirect treatment comparisons (ITCs) evaluating mepolizumab and eosinophilic granulomatosis with polyangiitis was run in MEDLINE on January 9, 2024. No limits were applied. In addition, a focused literature was conducted for publications evaluating the psychometric properties of the instruments evaluated in this review. This search was conducted on April 4, 2024.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Of 320 records identified by the searches, 5 were screened by full text, and 3 reports of 2 trials (MIRRA[13,22] and MANDARA[14]) were included. The flow diagram for study selection is available in Appendix 2.

Two studies were excluded after full-text review.[23,24] One was post hoc subgroup analysis of the MIRRA trial that evaluated subgroups not relevant to this report,[23] and the second was a systematic review of antieosinophilic therapies for EGPA, of which the MIRRA trial was included.[24]

Characteristics of Included Trials

The MIRRA and MANDARA trials are summarized in Table 4.

Table 4: Details of the MIRRA and MANDARA Trials

	MIRRA trial[13]	MANDARA trial[14]
Design and population		
Trial design	Phase III, randomized, double-blind, placebo-controlled trial	Phase III, randomized, double-blind, double-dummy noninferiority trial
Locations	31 centres in 9 countries (2 centres in Canada)	50 centres in 9 countries (4 centres in Canada)
Trial time frame	February 2014 until September 2016	October 2019 until August 2023 (benralizumab open-label extension phase is ongoing)
Randomized (N)	136 patients: • Mepolizumab n = 68 • Placebo n = 68	140 patients: • Benralizumab n = 70 • Mepolizumab n = 70
Stratification factors	• Participation in a mechanistic–biomarker substudy in the US (yes/no) • Region (Japan, rest of world)	Region (North America, Japan, Western Europe)
Inclusion criteria	• Age 18 years or older • Relapsing or refractory EGPA for at least 6 months • Taking prednisone or prednisolone 7.5 mg to 50 mg per day for at least 4 weeks before baseline (visit 2) • If taking immunosuppressive therapy, dosage must be stable for at least 4 weeks before baseline (visit 2) • QTc less than 450 msec or for patients with bundle branch block, less than 480 msec	• Age 18 years or older • Relapsing or refractory EGPA for at least 6 months • Taking prednisone or prednisolone 7.5 mg to 50 mg per day for at least 4 weeks before baseline (visit 2) • If taking immunosuppressive therapy, dosage must be stable for at least 4 weeks before baseline (visit 2)

	MIRRA trial[13]	MANDARA trial[14]

Exclusion criteria	• Microscopic polyangiitis
	• Granulomatosis with polyangiitis
	• Organ-threatening or life-threatening EGPA within 3 months before screening (visit 1)
	• Active malignancy or remission within 12 months
	• Unstable liver disease, cirrhosis, and known biliary abnormalities
	• Severe cardiovascular disease not controlled with standard treatments
	• Chronic hepatitis B
	• HIV
	• Patients receiving any of the following before screening visit 1:
	  ◦ Omalizumab within 130 days before visit 1
	  ◦ Rituximab within 12 months
	  ◦ IV or SC immunoglobulin within 6 months
	  ◦ Interferon-alpha within 6 months
	  ◦ Anti–tumour necrosis factor within 12 weeks
	  ◦ Anti-CD52 (alemtuzumab) within 6 months
	  ◦ Mepolizumab with 1 year
	• Patients receiving any of the following before baseline visit 2:
	  ◦ OCS dose of more than 50 mg per day, or any IV or SC corticosteroids within 4 weeks
	  ◦ Oral cyclophosphamide within 2 weeks and IV cyclophosphamide within 3 weeks
		• Microscopic polyangiitis
		• Granulomatosis with polyangiitis
		• Organ-threatening or life-threatening EGPA within 3 months before screening (visit 1)
		• Current or history of malignancy or liver disease
		• Uncontrolled cardiovascular disease
		• Infectious disease or parasitic infection
		• Chronic stable hepatitis B or C
		• Known immunodeficiency disorder including HIV
		• Patients receiving any of the following before screening visit 1:
		  ◦ Omalizumab within 130 days before visit 1
		  ◦ Rituximab within 6 months
		  ◦ IV or SC immunoglobulin within 30 days
		  ◦ Interferon-alpha within 6 months
		  ◦ Anti–tumour necrosis factor within 12 weeks
		  ◦ Anti-CD52 (alemtuzumab) within 6 months
		• Patients receiving any of the following before baseline visit 2:
		  ◦ OCS dose of more than 50 mg per day, or any IV, IM, or SC corticosteroids within 4 weeks
		  ◦ Oral cyclophosphamide within 2 weeks and IV cyclophosphamide within 3 weeks
		• Any prior or current treatment with mepolizumab, reslizumab, dupilumab, or benralizumab

Drugs		
Intervention	Mepolizumab 300 mg q.4.w., administered in 3 SC injections	Benralizumab 30 mg q.4.w., administered in 1 SC injection, plus placebo (0.9% sodium chloride) matching mepolizumab administered in 3 SC injections
Comparator(s)	Matching placebo (0.9% sodium chloride) q.4.w., administered in 3 SC injections	Mepolizumab 300 mg q.4.w., administered in 3 SC injections, plus placebo (0.9% sodium chloride) matching benralizumab administered in 1 SC injection

	MIRRA trial[13]	MANDARA trial[14]
Duration		
Trial duration	1 to 4 weeks of screening, 52 weeks of double-blind treatment, and 8 weeks of follow-up	1 to 4 weeks of screening, 52 weeks of double-blind treatment, and at least 1 year of open-label extension of benralizumab
End points		

Primary end points	• Total accrued remission (proportion of patients in each of the following categories):
	  ◦ 0 weeks
	  ◦ More than 0 weeks to less than 12 weeks
	  ◦ 12 weeks to less than 24 weeks
	  ◦ 24 weeks to less than 36 weeks
	  ◦ 36 weeks or more
	• Proportion of patients in remission at both weeks 36 and 48 of the trial treatment period
		Proportion of patients in remission at both weeks 36 and 48 of the trial treatment period

Secondary end points[a]	• Proportion of patients who achieve remission within the first 24 weeks of the study and then remained in remission until week 52
	• Time to first EGPA relapse
	• Proportion of patients with an average daily prednisolone or prednisone dose during the last 4 weeks of the trial treatment period (48 through 52) in each of the following categories:
	  ◦ 0 mg
	  ◦ More than 0 mg to 4.0 mg
	  ◦ More than 4.0 mg to 7.5 mg
	  ◦ More than 7.5 mg
		• Total accrued remission (proportion of patients in each of the following categories):
		  ◦ 0 weeks
		  ◦ More than 0 weeks to less than 12 weeks
		  ◦ 12 weeks to less than 24 weeks
		  ◦ 24 weeks to less than 36 weeks
		  ◦ 36 weeks or more
		• Time from randomization to first EGPA relapse
		• Proportion of patients in each category of average daily prednisolone or prednisone dose during weeks 48 to 52 in the following categories:
		  ◦ 0 mg
		  ◦ More than 0 to 4.0 mg
		  ◦ More than 4.0 mg to 7.5 mg
		  ◦ More than 7.5 mg
		• The proportion of subjects with a percentage reduction in the average prednisolone or prednisone dose during weeks 48 through 52 compared with baseline in each of the following categories:
		  ◦ No reduction or withdrawal from treatment
		  ◦ Less than 25%
		  ◦ 25% to less than 50%
		  ◦ 50% to less than 75%

	MIRRA trial[13]	MANDARA trial[14]
		◦ 75% to less than 100% • Annualized relapse rate • Proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period • Change from baseline over the 52-week trial period: BVAS, VDI, pulmonary function testing, asthma symptoms (ACQ-6), sinonasal symptoms (including SNOT-22 and SSQ), HRQoL (SF-36v2)
Other end points	• Total duration of sustained remission: longest uninterrupted period of weeks where BVAS of 0 plus prednisolone or prednisone 4.0 mg/day or less over the 52-week study treatment period, reported as proportion of subjects achieving sustained remission in the following categories: ◦ 0 weeks ◦ More than 0 weeks to less than 12 weeks ◦ 12 weeks to less than 24 weeks ◦ 24 weeks to less than 36 weeks ◦ 36 weeks or more • Frequency of EGPA relapses • Frequency of major EGPA relapses • Time to first major EGPA relapse • Change from baseline in daily prednisolone or prednisone dose over the 52-week trial treatment period • The proportion of subjects with a percentage reduction in the average prednisolone or prednisone dose during weeks 48 through 52 compared with baseline in each of the following categories: ◦ No reduction or withdrawal from treatment ◦ Less than 25% ◦ 25% to less than 50% ◦ 50% to less than 75% ◦ 75% to less than 100% ◦ 100% • Change from baseline in BVAS • Change from baseline in VDI • Change from baseline in ACQ-6 • Change from baseline in lung function tests (FEV_1 and FVC)	Cumulative OCS dose

	MIRRA trial[13]	MANDARA trial[14]
	• Change from baseline in SF-36 scores (domains, Physical Component Summary, Mental Component Summary) • Change from baseline in SNOT-22 score	
Harms end points	• Frequency of AEs • Frequency of SAEs • Systemic or local injection-site reactions • Cardiovascular AEs	• Frequency of AEs • Frequency of SAEs • Death • Discontinuation due to AEs
Outcome definitions	• Remission for the primary and secondary end points defined as BVAS of 0 plus a daily prednisone or prednisolone dose of 4.0 mg/day or less over the 52-week trial • Remission for the other end points defined as a BVAS of 0 plus a daily prednisone or prednisolone dose of 7.5 mg/day or less over the 52-week trial • Relapse was defined as an increase of prednisone or prednisolone to more than 4.0 mg/day, or initiation of or increase in immunosuppressive therapy, or hospitalization due to: ◦ Active vasculitis (BVAS of more than 0), or ◦ Active asthma signs or symptoms with a corresponding worsening in the score of the ACQ-6, or ◦ Active nasal or sinus disease with corresponding worsening in at least 1 of the SNOT-22 items • Major relapse was defined as a life-threatening or organ-threatening event, or a BVAS of 6 or more, or an asthma or sinonasal relapse requiring hospitalization	• Remission was defined as a BVAS of 0 plus a daily prednisone or prednisolone dose of 4.0 mg/day or less • For supportive analyses, remission was defined as a BVAS of 0 and a daily prednisone or prednisolone dose of 7.5 mg/day or less • Relapse was defined as an increase of prednisone or prednisolone to more than 4.0 mg/day, or initiation of or increase in immunosuppressive therapy, or hospitalization due to: ◦ Active vasculitis (BVAS of more than 0), or ◦ Active asthma signs or symptoms with a corresponding worsening in the score of the ACQ-6, or ◦ Active nasal or sinus disease with corresponding worsening in at least 1 of the SNOT-22 items
Notes		
Publications included	Wechsler et al. (2017)[13] Terrier et al. (2023)[22]	Wechsler et al. (2024)[14]
Sources of support	GlaxoSmithKline; NIAID, National Institutes of Health; and the Division of Intramural Research, NIAID, National Institutes of Health	AstraZeneca

ACQ-6 = 6-item Asthma Control Questionnaire; AE = adverse event; BVAS = Birmingham Vasculitis Activity Score; EGPA = eosinophilic granulomatosis with polyangiitis; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRQoL = health-related quality of life; IM = intramuscular; NIAID = National Institute of Allergy and Infectious Diseases; OCS = oral corticosteroid; q.4.w. = every 4 weeks; QTc = corrected QT interval; SAE = serious adverse event; SC = subcutaneous; SF-36 = 36-item Short Form Survey; SNOT-22 = 22-item Sino-Nasal Outcome Test; SSQ = Sinus Symptom Questionnaire; VDI = Vasculitis Damage Index.

Comparisons between mepolizumab and placebo in the MIRRA trial were adjusted for baseline dose of prednisolone or prednisone, baseline BVAS, and geographic region (North America, Europe, or Japan).[13] Comparisons between benralizumab and mepolizumab in the MANDARA trial were adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

[a]Secondary end points in the MANDARA trial were not controlled for type I error.[14]

Trial Design

The MIRRA trial was a multicentre, double-blind, placebo-controlled phase III trial that assessed the efficacy and safety of mepolizumab in patients with relapsing or refractory EGPA.[13] The trial was conducted in 31 centres across 9 countries, including 2 sites in Canada (n = 6 patients). Patients (n = 136) were randomly assigned in a 1:1 fashion to receive either mepolizumab 300 mg SC once every 4 weeks with SoC or placebo SC once every 4 weeks with SoC for 52 weeks.[13] SoC was defined as receipt of a stable dose of either prednisone or prednisolone, with or without an immunosuppressant. Randomization was completed using a centralized computer-generated permuted block schedule. To maintain blinding, placebo was identical-appearing to mepolizumab, and clinicians managing patients in the trial were unaware of the patient's white blood cell and differential counts during the trial.[13] Patient enrolment was from February 2014 until June 2015, and follow-up continued until September 2016. The trial was sponsored by GlaxoSmithKline; the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health; and the Division of Intramural Research, NIAID, National Institutes of Health.[13]

The MANDARA trial was a multicentre, double-blind, double-dummy, phase III noninferiority trial comparing benralizumab to mepolizumab in patients with relapsing or refractory EGPA.[14] The trial was conducted from October 2019 until August 2023 in 50 centres across 9 countries, including 4 sites in Canada (n = 19 patients). Patients (n = 140) were randomized in a 1:1 ratio to benralizumab 30 mg SC once every 4 weeks with SoC or mepolizumab 300 mg SC once every 4 weeks with SoC for 52 weeks. SoC was defined as receipt of a stable dose of prednisone or prednisolone, with or without a stable dose of immunosuppressive therapy.[14] Randomization was conducted via a central computerized system using an interactive voice response system or interactive web response system. To maintain blinding, a double-dummy process was used, where patients randomized to benralizumab also received placebo that was identical-appearing to mepolizumab, and patients randomized to mepolizumab received placebo that was identical-appearing to benralizumab. In addition, hematology assessments were conducted by a central laboratory, and eosinophil, basophil, and monocyte results were redacted when sent to the study sites. Also, for local laboratory test results, an individual not involved in patient management at each study site was assigned to blind basophil, eosinophil, and monocyte results before sending to local study investigators. The trial was funded by AstraZeneca.[14]

The trial flow process for both the MIRRA and MANDARA trials included a screening period that was a minimum of 1 week and up to 4 weeks in duration, and the 52-week blinded trial treatment period. For both trials, screening began at visit 1 with confirmation of eligibility criteria.[13,14] Visit 2 was the baseline visit where patients were randomized after reconfirmation of eligibility criteria and confirmation that their OCS and immunosuppressive therapy doses had been stable for at least 4 weeks before the visit. The last dose of trial therapy (mepolizumab or placebo in the MIRRA trial and benralizumab or mepolizumab in the MANDARA trial) was administered at week 48, for a total of 13 doses of trial medication. Following the 52-week trial period, the MIRRA trial had an 8-week follow-up period, whereas the MANDARA trial has an ongoing open-label extension period evaluating benralizumab that is of least 1 year in duration (not described herein).[13,14]

Inclusion and Exclusion Criteria

For both trials, eligible patients were 18 years or older and had a diagnosis of relapsing or refractory EGPA at least 6 months before screening visit 1; the definitions of EGPA, relapsing EGPA, and refractory EGPA were the same in the MIRRA and MANDARA trials and are listed in Table 5.[13,14] Patients needed to be taking prednisone or prednisolone at a stable dose of 7.5 mg to 50 mg per day for at least 4 weeks before baseline visit 2. Also, patients could be taking immunosuppressive therapy (except cyclophosphamide), but it needed to be at a stable dose for the 4 weeks before baseline visit 2. In patients who received cyclophosphamide for induction therapy, patients could be included after a minimum of 2 weeks from the last dose of oral cyclophosphamide or a minimum of 3 weeks after the last pulsed IV dose before the baseline visit 2, if their total white blood cells were 4 X 10^9/L or higher before randomization. Patients were excluded if they had granulomatosis with polyangiitis, microscopic polyangiitis, or if they had organ-threatening or life-threatening EGPA within 3 months before screening.[13,14] The definitions for organ-threatening and life-threatening EGPA are also listed in Table 5. In addition, patients were excluded from the trial if they received parenteral corticosteroids 4 weeks before baseline visit 2, omalizumab within 130 days before screening visit 1, rituximab within 6 months (MIRRA trial) or 12 months (MANDARA trial) of screening visit 1, or alemtuzumab within 6 months before screening visit 1. Lastly, patients were excluded from the MIRRA trial if they received mepolizumab within a year before screening, whereas patients were excluded from the MANDARA trial if they had any prior or current treatment with mepolizumab, reslizumab, dupilumab, or benralizumab.[13,14]

For the MANDARA trial population, the proportion of patients included in the trial with ANCA positivity at trial screening was restricted to 10%, and the proportion with an eosinophil count of less than 0.15 × 10^9/L at screening was restricted to 40%.[14] No such restrictions were applied in the MIRRA trial.

Table 5: Definitions of EGPA, Relapsing EGPA, and Refractory EGPA for Inclusion in the MIRRA and MANDARA Trials

EGPA type	Definitions used in the MIRRA and MANDARA trials[13,14]

EGPA	• Diagnosis of asthma, and
	• Blood eosinophil level of more than 10% or an absolute eosinophil cell count of more than 1 × 10^9/L, and
	• At least 2 criteria typical to EGPA:
	  ○ Histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophilic-rich granulomatous inflammation
	  ○ Mono- or polyneuropathy (motor deficit or nerve conduction abnormality)
	  ○ Pulmonary infiltrates (nonfixed)
	  ○ Sinonasal abnormality
	  ○ Cardiomyopathy (established by echocardiography or MRI)
	  ○ Glomerulonephritis (hematuria, red cell casts, proteinuria)
	  ○ Alveolar hemorrhage (by bronchoalveolar lavage)
	  ○ Palpable purpura
	  ○ ANCA positivity (MPO or PR3)

EGPA type	Definitions used in the MIRRA and MANDARA trials[13,14]
Relapsing EGPA	History of at least 1 confirmed EGPA relapse within the past 2 years that occurred at least 12 weeks before screening (visit 1), requiring an increase in OCS dose, initiation or increased dose of an immunosuppressive therapy, or hospitalization, in patients taking at least 7.5 mg per day of prednisolone or equivalent. For patients in Japan only, initiation or increase in dose of IV immunoglobulin was included in the definition of EGPA relapse.
Refractory EGPA	Within 6 months before screening (visit 1), either: • Failure to attain remission (BVAS score = 0 and OCS dose of 7.5 mg/day or less of prednisolone or equivalent) following induction treatment with a standard regimen, administered for at least 3 months; or • Recurrence of EGPA symptoms while tapering OCS, occurring at any dose level of 7.5 mg/day or more prednisolone or equivalent.
Organ-threatening EGPA	Based on EULAR criteria,[25] within 3 months before screening (visit 1): • Organ failure due to active vasculitis • Serum creatinine more than 513 µmol/L
Life-threatening EGPA	Any of the following within 3 months before screening (visit 1): • Intensive care required • Severe alveolar hemorrhage or hemoptysis requiring transfusion or ventilation or hemoglobin less than 80 g/L or a drop in hemoglobin of more than 20 g/L over a 48-hour period due to alveolar hemorrhage • Rapidly progressive glomerulonephritis with a creatinine of more than 221 µmol/L or a rise in creatinine of more than 177 µmol/L over a 48-hour period • Severe gastrointestinal involvement; for example, gangrene or bleeding requiring surgery • Severe central nervous system involvement • Severe cardiac involvement, for example, life-threatening arrhythmia, cardiac failure: ejection fraction less than 20%, New York Heart Association Class III/IV, acute myocardial infarction

ANCA = antineutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; EGPA = eosinophilic granulomatosis with polyangiitis; EULAR = European Alliance of Associations for Rheumatology; OCS = oral corticosteroid; MPO = myeloperoxidase; PR3 = proteinase 3.

Sources: Wechsler et al., 2017;[13] Wechsler et al., 2024.[14]

Interventions

For the MIRRA trial, patients were randomized to mepolizumab 300 mg SC every 4 weeks for 52 weeks (13 total doses), or an identical-appearing placebo (0.9% sodium chloride) SC every 4 weeks for 52 weeks (13 total doses). Each dose consisted of 3 injections of mepolizumab 100 mg or placebo, administered by a blinded staff member.[13]

For the MANDARA trial, patients were randomized to benralizumab 30 mg SC every 4 weeks for 52 weeks (13 total doses), administered as 1 SC injection, plus 3 SC injections of placebo (0.9% sodium chloride) that was identical-appearing to mepolizumab, or to mepolizumab 300 mg SC every 4 weeks for 52 weeks (13 total doses) as 3 SC injections of 100 mg, plus 1 SC injection of placebo (0.9% sodium chloride) that was identical-appearing to benralizumab. All injections were administered by blinded health care professionals from the trial.[14]

Concomitant Medications

Patients in both trials received SoC, defined as an OCS (prednisone or prednisolone), with or without immunosuppressive therapy.[13,14] For patients who were on immunosuppressive therapy at the time of trial enrolment, the dose was required to remain stable throughout the trial, but could be reduced for safety reasons.

Given that reduction in OCS dose was an end point in both trials, investigators were provided with instructions for tapering OCSs based on a standardized recommended tapering schedule. For the MIRRA trial, the dose of OCS needed to remain stable between baseline and week 4 of the trial, after which the investigator could taper the OCS dose at their discretion.[13] For the MANDARA trial, increases in the dose of OCS were permitted between baseline and week 4. From week 4 onward, if the patient had a BVAS of 0, the OCS was tapered based on standard practice. For patients with a BVAS of more than 0, the investigator could taper the OCS at their discretion.[14]

Outcomes

The outcomes identified in the CADTH systematic review protocol that were assessed in the MIRRA and MANDARA trials are included and defined in Table 4 and are summarized below.

Achievement of Remission

The 2 primary end points of the MIRRA trial were total accrued remission in weeks, and the proportion of patients who were in remission at both weeks 36 and 48 of the trial.[13] The primary end point for the MANDARA trial was proportion of patients in remission at both weeks 36 and 48 of the trial.[14] Remission for the primary end points in both trials was defined as a BVAS (version 3) of 0 plus a daily prednisone or prednisolone dose of 4.0 mg or less over the 52-week trial. Assessment of total weeks accrued remission in the MIRRA trial was assessed categorically; categories were defined as proportions of patients who had remission for 0 weeks, for more than 0 weeks but less than 12 weeks, for at least 12 weeks but less than 24 weeks, for at least 24 weeks but less than 36 weeks, and for 36 weeks or more.[13] Total weeks of accrued remission was a secondary end point in the MANDARA trial and was assessed categorically using the same categories as the MIRRA trial.[14]

The proportion of patients who had remission within the first 24 weeks and continued to have remission until week 52 was a secondary end point in both the MIRRA and MANDARA trials.[13,14]

Relapse

The definitions of relapse and major relapse used in the MIRRA and MANDARA trials is included in Table 4. Time to first EGPA relapse was a secondary end point in the MIRRA and MANDARA trials.[13,14] In addition, the annualized relapse rate was a secondary end point in the MANDARA trial and another end point in the MIRRA trial. Time to first major relapse was also another end point in the MIRRA trial.[13]

Change in OCS Dose

The proportions of patients with an average prednisolone or prednisone dose of 0 mg per day, of more than 0 mg to 4.0 mg per day, of more than 4.0 mg to 7.5 mg per day, and of more than 7.5 mg per day during weeks

48 through 52 was a secondary end point in both the MIRRA and MANDARA trials.[13,14] Other end points in the MIRRA trial included the average dose of prednisone or prednisolone from weeks 48 to 52.[13] The other end point in the MANDARA trial was the cumulative OCS dose over the 52-week treatment period.[14]

Organ Damage

The BVAS was evaluated at baseline and every 4 weeks until week 52 in both the MIRRA and MANDARA trials.[13,14] The BVAS is a clinician-reported instrument that was developed to capture acute damage due to active systemic vasculitis.[26] The most recent version of the BVAS, version 3, captures abnormalities associated with the following organ systems: general (e.g., fever, myalgias); cutaneous; mucous membranes, including the eyes; ENT; chest; cardiovascular; abdominal; renal; nervous system; and "other."[27] Scores on the BVAS range from 0 to 63, with higher scores reflecting higher vasculitis disease activity.[27]

The BVAS version 3 was evaluated in terms of convergent validity and interobserver reliability in a cohort of 238 patients, 23 (9%) of which had EGPA.[28] The BVAS version 3 demonstrated convergent validity with the vasculitis activity index (spearman's correlation coefficient = 0.82; 95% CI, 0.77 to 0.85) and physician's global assessment (Spearman correlation coefficient = 0.85; 95% CI, 0.81 to 0.88), but had no correlation with the VDI (Spearman correlation coefficient = −0.10; 95% CI, −0.22 to 0.03).[28] Inter-rater reliability was strong (intraclass correlation coefficient = 0.996; 95% CI, 0.990 to 0.998).[28]

The VDI was evaluated at baseline, week 24, and week 52 in both the MIRRA and MANDARA trials.[13,14] The VDI is a clinician-reported instrument that was developed to assess chronic damage due to systemic vasculitis.[29] It is not intended to capture acute damage; rather, the VDI captures any damage that has occurred and persisted for at least 3 months since the start of vasculitis. There are 11 organ systems that are evaluated: musculoskeletal, skin and/or mucous membranes, ocular, ENT, pulmonary, cardiovascular, peripheral vascular disease, gastrointestinal, renal, neuropsychiatric, and "other."[29] VDI scoring ranges from 0 to 63, with higher scores reflecting more damage. It is also important to note that scoring is cumulative, so it does not decline over time, even with clinical improvement in vasculitis.[29] Lastly, no evidence was identified evaluating the psychometric properties of the VDI in patients with EGPA.

Asthma Control

Asthma control was evaluated in both the MIRRA and MANDARA trials using the 6-item Asthma Control Questionnaire (ACQ-6) and forced expiratory volume in 1 second (FEV_1).[13,14] Forced vital capacity was also evaluated in the MIRRA trial.[13] Change in ACQ-6 score, and least squares (LS) mean change in FEV_1 and FVC were evaluated from baseline until 52 weeks.

The ACQ-6 is a patient-reported outcome measure that was developed to evaluate control of asthma over the past week, and includes questions relating to shortness of breath, wheezing, limitations in activities, being woken by asthma symptoms during the night, asthma symptoms upon waking in the morning, and the frequency of use of a short-acting bronchodilator.[30] Scores range from 0 to 6, with higher scores reflecting worse asthma control (0 = well-controlled, 6 = extremely poorly controlled).[30] No evidence was identified evaluating the psychometric properties of the ACQ-6 in patients with EGPA.

Health-Related Quality of Life

The change from baseline to 52 weeks in the 22-item Sino-Nasal Outcome Test (SNOT-22) was evaluated in both the MIRRA and MANDARA trials.[13,14] The SNOT-22 is disease-specific HRQoL measure that was developed to capture HRQoL associated with sinonasal conditions.[31] The SNOT-22 includes 22 items related to sinonasal symptoms, sleep, fatigue, concentration, and emotional impact.[31] Scoring on the SNOT-22 ranges from 0 to 110, with higher scores reflecting worse HRQoL.[31] No evidence was identified evaluating the psychometric properties of the SNOT-22 in patients with EGPA.

The Medical Outcomes Study 36-item Short Form Survey version 2 (SF-36v2) was evaluated in the MANDARA trial.[32,33] The SF-36v2 is a patient-completed generic health profile measure that consists of 36 items representing 8 domains: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items).[32,33] In addition, there are 2 summary scores derived from the 8 domains: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[32,33] Change in PCS, MCS, and domain scores from baseline to 52 weeks were evaluated in the MANDARA trial.[14] No evidence was identified evaluating the psychometric properties of the SF-36v2 in patients with EGPA.

Although the MIRRA trial reported evaluating the SF-36v2 in the trial protocol, results of this were not reported.[13]

Sensitivity Analyses

In addition to the more stringent definition of remission (a BVAS of 0 and a prednisone or prednisolone dose of 4.0 mg/day or less), supportive analyses were conducted using a more permissive remission definition of a BVAS of 0 and a prednisone or prednisolone dose of 7.5 mg/day or less. The more permissive remission definition was evaluated for the end points of total accrued weeks of remission over the 52-week period, the proportion of patients who had remission at both week 36 and week 48, and the proportion of patients who had remission within the first 24 weeks and continued to have remission until week 52 in the MIRRA trial.[13] For the MANDARA trial, supportive analyses were conducted using the more permissive remission definition on the following end points: proportion of patients achieving remission at both weeks 36 and 48, total accrued duration of remission, and proportion of patients who achieved remission within the first 24 weeks and remained in remission until the end of the 52-week trial.[14]

Harms

In terms of harms end points, AEs and SAEs were similarly defined in the MIRRA and MANDARA trials. AEs were defined as "the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment," and a SAE was defined as "an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria: results in death; is immediately life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect; is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above."[14]

Statistical Analysis: MIRRA Trial

Investigators used the primary end point of the total accrued weeks of remission over the 52-week trial period to calculate the trial sample size. They estimated that a total sample of 130 patients (65 patients in each arm) would provide at least 90% power to detect a between-group difference (at a 2-sided P value of 0.05) of 29% in the proportion of patients who had remission for at least 24 weeks, assuming that 25% of patients in the placebo group and 54% of patients in the mepolizumab group had an accrued remission of 24 weeks or more.[13]

The type I error rate was controlled using a closed testing procedure with the primary end points (both primary end points were required to be statistically significant to proceed to the secondary end points), and a hierarchical procedure within the secondary end points.[13] The order in which the secondary end points were analyzed was time to first EGPA relapse; average daily prednisone or prednisolone dose from weeks 48 to 52; the proportion of patients who achieved remission (BVAS = 0 and a prednisone or prednisolone dose of 4.0 mg or less per day) within the first 24 weeks and remained in remission to the end of week 52; total accrued duration of remission over the 52 week trial (BVAS = 0 and a prednisone or prednisolone dose of 7.5 mg or less per day); the proportion of patients in remission (BVAS = 0 and a prednisone or prednisolone dose of 7.5 mg or less per day) at weeks 36 and 48; and the proportion of patients who achieved remission (BVAS = 0 and a prednisone or prednisolone dose of 7.5 mg or less per day) within the first 24 weeks and remained in remission to the end of week 52.[13] The other end points were not adjusted for type I error.

The primary end point of total accrued duration of remission was analyzed using a proportional odds regression model for ordered categorical data to calculate an OR and 95% CI. The proportional odds assumption was checked before completing this analysis. The primary end point of remission at both weeks 36 and 48 was conducted using a logistic regression model to calculate an OR and 95% CI. Covariates included in both models were baseline prednisone or prednisolone dose, baseline BVAS, and region (North America, European Union, Japan).[13]

Other end points with ordered categorical data were analyzed using a proportional odds regression model, and binary end points were analyzed using a logistic regression model. Time to first relapse and first major relapse were analyzed using a Cox proportional hazards model, and frequency of relapse and major relapse were analyzed using a negative binomial generalized linear model with a log-link function. Baseline prednisone or prednisolone dose, baseline BVAS, and region (North America, European Union, Japan) were included as covariates in the models.[13] Safety end points were reported descriptively.

For time to event analyses, patients were censored if they withdrew from the trial on the date of withdrawal or at the completion of the trial.[13]

The last observation carried forward approach was used for missing data (BVAS, OCS dose) in the primary end points. Patients with missing remission data due to withdrawal from the trial were assumed to not be in remission from the data of withdrawal until the end of the trial treatment period. For patients with missing data for OCS end points, it was assumed that their final average daily OCS dose was the average during the

4 weeks immediately following the last dose of trial medication. It was unclear how other analyses handled missing data.

The preplanned subgroup analyses in the MIRRA trial did not include the relevant subgroups identified in the systematic review protocol. However, Terrier et al. conducted a post hoc subgroup analysis based on ANCA-positivity status, and this is discussed in the Results section.[22]

The efficacy end points were evaluated in the ITT population, which was defined as patients who were randomized and received at least 1 dose of trial therapy, and the safety end points were evaluated in the per-protocol population, defined as the actual therapy received. All patients received at least 1 dose of the trial regimen, and as a result, all patients were included in the ITT population.[13]

Statistical Analysis: MANDARA Trial

Based on the primary end point of remission at weeks 36 and 48, investigators assumed that benralizumab and mepolizumab would each have a remission rate of 32%. Based on this and a prespecified noninferiority margin of −25%, a total of 140 patients would provide approximately 90% power to demonstrate noninferiority at the 2.5% 1-sided significance level. For benralizumab to be considered noninferior to mepolizumab, the lower 95% CI for the difference between benralizumab and mepolizumab needs to be above the noninferiority margin of −25%. The trial investigators justified the chosen noninferiority margin of −25% "because of the small population with a rare disease."[14]

The primary end point was analyzed using a logistic regression model that included the covariates of the treatment arm, baseline dose of prednisone, baseline BVAS, and region to calculate the adjusted percentage of patients achieving the end point and the risk difference in relapse rates with the associated 2-sided 95% CI.[14] The trial investigators prespecified that if this analysis demonstrated noninferiority, a formal test of superiority between benralizumab and mepolizumab would be performed.[14]

For the secondary end points, the time to first EGPA relapse was analyzed using a Cox proportional hazards model, and the annualized relapse rate was evaluated using a negative binomial model. The accrued duration of remission, the average of daily OCS dose during weeks 48 to 52, and percentage reduction from baseline in average prednisolone or prednisone dose at weeks 48 to 52 was analyzed using a proportional odds model.[14] Remission achieved within the 24 weeks and sustained for remainder of the double-blind treatment period was analyzed using a logistic regression model. Treatment arm, baseline dose of prednisone, baseline BVAS and region were included as covariates in all the models. For all categorical end points, the adjusted percentage of patients achieving the end point was estimated and reported, and the percentage was adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

The type I error rate was not controlled for any of the secondary analyses in the MANDARA trial.[14]

For time to event analyses, patients were censored if they withdrew from the trial on the date of withdrawal or at the completion of the trial.[14]

Patients with missing remission data due to withdrawal from the trial were assumed to not be in remission from the data of withdrawal until the end of the trial treatment period.[14] For missing BVAS scores, the next visit BVAS score was imputed. Patients with a missing or nonevaluable ACQ-6 score at the end of week 52 were considered to be nonresponders. It was unclear how missing data for the other trial end points was handled in the analysis.[14]

The supportive remission end point was defined as a BVAS of 0 and OCS dose of 7.5 mg/day or less and used for the end points of proportion of patients who achieve remission at both week 36 and week 48, total accrued duration of remission, and proportion of patients who achieved remission within the first 24 weeks and remained in remission for remainder of treatment period.[14]

BVAS, VDI, ACQ-6, pulmonary function testing, SNOT-22, SSQ, and the SF-36 (acute; PCS, MCS, and domain scores) were assessed as change from baseline over the 52-week treatment period and were analyzed using a mixed effects model repeated measures analysis with treatment arm, baseline dose of prednisone, baseline BVAS, and region as covariates.[14] Safety end points were reported descriptively.

Based on the relevant subgroups identified for this review, only ANCA positivity was evaluated.[14] As such, this subgroup analysis is reported in the Results section.

The efficacy end points were evaluated in the full analysis set, which was defined as all patients who were randomized and received at least 1 dose of trial therapy.[14] The safety end points were evaluated in the safety analysis set, defined patients who received at least 1 dose of trial therapy and were analyzed based on the actual therapy received.

Critical Appraisal

Internal Validity

Study Design

Both trials were randomized, double-blind, multicentre trials. The methods for randomization were acceptable in both trials. In addition, methods were put in place to maintain blinding of participants, personnel, and outcome assessors throughout the trial.[13,14] The MIRRA trial used an identical-appearing placebo,[13] and the MANDARA trial used a double-dummy process where patients randomized to benralizumab also received placebo that was identical-appearing to mepolizumab, and patients randomized to mepolizumab also received placebo that was identical-appearing to benralizumab.[14] Also, blinded investigators did not have access to blood eosinophil counts during the trial.[13,14] There did not appear to be evidence of unblinding based on differential adherence or use of concomitant medications in the MANDARA trial; however, there was potential for unblinding in the MIRRA trial given the differential impact of mepolizumab compared to placebo on the OCS dose.[13,14]

The MANDARA trial used a noninferiority design to compare benralizumab to mepolizumab. The noninferiority margin for the primary end point of achievement of remission at weeks 36 and 48 was prespecified as a difference of −25%,[14] meaning, for benralizumab to be considered noninferior to mepolizumab, the lower bound of the CI could not be less than −25%. The justification given for this

noninferiority margin was "because of the small population of patients with this rare disease."[14] However, no further justification was provided, and it is unclear as to whether −25% would be considered the largest clinically acceptable difference between benralizumab and mepolizumab.

Selection and Disposition of Patients

In both trials, patients were randomized 1:1 to achieve prognostic balance between the treatment arms, and allocation concealment was maintained through an unblinded delegate at each trial site.[13,14] There were some imbalances in baseline characteristics between treatment arms. In the MIRRA trial, patients randomized to placebo were more likely to have a baseline BVAS greater than 0 (71% vs. 54%), more likely have refractory disease (59% vs. 50%), less likely to be taking immunosuppressive therapy at baseline (46% vs. 60%), and less likely to have cardiomyopathy (10% vs. 19%) compared to patients randomized to mepolizumab.[13] In the MANDARA trial, patients randomized to mepolizumab were more likely to have biopsy evidence of eosinophilic vasculitis inflammation (47% vs. 29%), more likely to have neuropathy (64% vs. 54%), and less likely to have nonfixed pulmonary infiltrates (61% vs. 70%) compared to patients randomized to benralizumab.[14] However, it is likely that the prognostic differences between treatment arms was due to the small overall sample sizes of the trials and not due to problems with the randomization process, and it is unclear whether these imbalances would have any impact on the results of the trials.

Details of patient disposition were reported and reasons for discontinuation from the study were provided. In the MIRRA trial, 9 patients (13%) discontinued placebo, and 5 patients (7%) discontinued mepolizumab during the trial.[13] However, 63 patients (93%) in the placebo group and 65 patients (96%) in the mepolizumab group completed week-52 assessments, and all patients were included in the efficacy analyses.[13] In the MANDARA trial, 69 patients (99%) in the benralizumab group and 67 patients (96%) in the mepolizumab group completed the 52-week double-blind trial period, and all patients were included in the efficacy analyses.[14] However, it was unclear how missing data were handled in a number of the end point evaluations for both the MIRRA and MANDARA trials.[13,14]

Outcome Measures

In general, the outcomes assessed in the MIRRA and MANDARA trials were clinically relevant and important to patients and clinicians. The primary end points in the MIRRA trial were accrued weeks of remission over the 52-week trial period and the proportion of patients in remission at weeks 36 and 48, and the primary end point for the MANDARA trial was the proportion of patients in remission at weeks 36 and 48.[13,14] For the primary analysis of these end points, remission was defined as a BVAS of 0 and a dose of prednisone or prednisolone of 4.0 mg/day or less over the 52-week trial period. In addition, supportive analyses were conducted using the European Alliance of Associations for Rheumatology–recommended definition of a BVAS of 0 and a prednisone or prednisolone dose of 7.5 mg/day or less.[25] Given that the European Alliance of Associations for Rheumatology definition was created before the availability of OCS-sparing agents such as mepolizumab, the more stringent definition of 4.0 mg/day or less of prednisone or prednisolone, in addition to a BVAS of 0, is acceptable.[9]

Relapse was clearly defined in both trials as an increase of prednisone or prednisolone to more than 4.0 mg/day, initiation of or increase in immunosuppressive therapy, hospitalization due to active vasculitis (BVAS of

more than 0), active asthma signs or symptoms with a corresponding worsening in the score of the ACQ-6, or active nasal or sinus disease with corresponding worsening in at least 1 of the SNOT-22 items.[13,14]

Both the MIRRA and MANDARA trials used instruments, including the BVAS, VDI, ACQ-6, and SNOT-22, to evaluate the impact of treatment on vasculitis, asthma control, and sinonasal symptoms.[13,14] In addition, the SF-36v2 was used to evaluate HRQoL in patients in the MANDARA trial.[14] However, with the exception of the BVAS, no evidence was identified evaluating the psychometric properties of these instruments in patients with EGPA. As such, the validity, reliability, responsiveness, and interpretability in relation to a minimum clinically important difference are unknown in patients with EGPA.

Although the MIRRA trial protocol lists the change in SF-36 from baseline to 52 weeks as an end point, the results of this end point were not provided in the trial publication or supplemental data, indicating a risk of bias due to selective reporting.[13]

Statistical Analysis

The ITT populations were used for the efficacy analyses in both trials and were defined as patients who were randomized and received at least 1 dose of trial medication.[13,14] All patients in each trial received at least 1 dose of trial medication and were therefore included in the efficacy analyses.[13,14]

The statistical analysis in the MIRRA trial was generally acceptable. Statistical comparisons for the primary and secondary end points were controlled for type I error; however, the other end points were not controlled for type I error.[13] In addition, the CIs around the point estimates for total accrued weeks of remission, remission at weeks 36 and 48, remission within 24 weeks and sustained until week 52, and percentage reduction in OCS dose at weeks 48 to 52 were wide; as a result, the true benefit of mepolizumab is uncertain.[13] Lastly, the results of the analysis for change from baseline in FEV_1, FVC, ACQ-6, SNOT-22, BVAS, and VDI were only available graphically; as such, it is not possible to assess whether any potential differences between mepolizumab and placebo were clinically important.[13]

The statistical tests used to compare outcomes in the MANDARA trial were acceptable. The secondary and other end points in the MANDARA trial were not controlled for type I error, and this is important to note because 1 comparison between benralizumab and mepolizumab was statistically different (proportion of patients with 100% reduction of OCS at weeks 48 and 52).[14] Similarly to the results of the MIRRA trial, the CIs around the point estimates for remission at weeks 36 and 48, and remission within 24 weeks and sustained until week 52 were wide; as a result, the true difference between benralizumab of mepolizumab is uncertain.[14] Given that EGPA is a rare disease, the sample sizes for the MIRRA and MANDARA trials were small, which increases the uncertainty of comparisons between mepolizumab and placebo and between benralizumab and mepolizumab.

ANCA status was evaluated as a prespecified subgroup in the MANDARA trial; however, it was evaluated in post hoc subgroup analysis in the MIRRA trial.[14,22]

External Validity

Patient Selection

The trial inclusion and exclusion criteria were generally clinically relevant; however, patients with severe active EGPA (defined as having organ-threatening or life-threatening EGPA within 3 months before screening) were excluded from the trial, as were patients who had EGPA for less than 6 months. In addition, the proportion of patients with ANCA positivity at screening was approximately 10% in each trial, which is less than the ANCA positivity reported in observational studies of patients with EGPA, which have ranged from 30% to 50%.[7,34,35] Also, the presentation of EGPA appears to be different based on ANCA status; patients with MPO-ANCA positivity were more likely to have cutaneous symptoms, kidney involvement, alveolar hemorrhage, and peripheral neuropathy, whereas patients with MPO-ANCA negativity were more likely to have cardiomyopathy, gastrointestinal disease, and pulmonary infiltrates.[36] As such, patients may respond differently to treatment based on ANCA status, and the results from the subgroup analyses based on ANCA status were limited by the post hoc analysis in the MIRRA trial and the serious imprecision for the comparisons.

Patients under the age of 18 years were not included in the trial, so no conclusions can be drawn in pediatric patients with EGPA, although EGPA in pediatric patients is noted to be rare.[15] In addition, all patients were required to be receiving OCSs at baseline. As a result, it is unclear whether the results of the MIRRA and MANDARA trials would apply to patients who are not taking OCSs due to harms, for example. Lastly, patients were required to have asthma for inclusion in both trials, thereby excluding the up to 10% of patients with EGPA who do not have asthma.[7,9] It is unclear whether the response to mepolizumab in patients with EGPA without asthma would be similar to those with asthma.

Treatment Regimen and Length of Follow-Up

Both trials evaluated mepolizumab 300 mg SC once every 4 weeks, and the duration of both trials was 52 weeks. The MANDARA trial has an open-label extension phase that is currently ongoing; however, only benralizumab is being evaluated. Given that EGPA is a lifelong condition, the efficacy and safety of mepolizumab after 52 weeks in patients with relapsing or refractory EGPA is unclear.

Outcome Measures

Longer-term end points that are important to patients and clinicians, such as prevention of organ damage and survival, were not evaluated in either the MIRRA or MANDARA trials. As such, the longer-term benefit of mepolizumab on these end points is unclear.

Results of the Included Trials

Baseline Characteristics

Baseline demographic and disease characteristics for both trials are listed in Table 6. The mean age was 49 years (standard deviation [SD] = 12) in the mepolizumab group and 48 years (SD = 14) in the placebo group in the MIRRA trial, and 52 years (SD = 14) in the MANDARA trial. The majority of patients were female (59% in the MIRRA trial and 60% in the MANDARA trial), and the average duration since diagnosis was 5 years.

Approximately 10% of patients in each trial were ANCA-positive, and the baseline mean absolute eosinophil count ranged from 0.2 × 10^9/L to 0.4 × 10^9/L.

Patient Disposition

A total of 151 patients were screened and 136 underwent randomization (n = 68 in each arm) in the MIRRA trial. Of those randomized, 59 patients (87%) in the placebo arm and 63 patients (93%) in the mepolizumab arm completed the trial regimen; 63 patients (93%) completed the week 52 assessments and 61 patients (90%) completed follow-up in the placebo arm, and 65 patients (96%) in the mepolizumab arm completed the week 52 assessments and follow-up.

For the MANDARA trial, 157 patients were screened and 140 were randomized (n = 70 in each arm). Of the patients randomized, 69 patients (99%) in the benralizumab arm and 67 patients (96%) in the mepolizumab arm completed the double-blind treatment phase. One patient (1%) in the benralizumab arm and 2 patients (3%) in the mepolizumab arm withdrew from the trial.

Concomitant Therapy

All patients were taking prednisolone or prednisone as per the inclusion criteria of the MIRRA trial. The median daily dose was 12.0 mg (range, 7.5 to 40.0 mg) in the mepolizumab group and 11.0 mg (range, 7.5 to 50.0 mg) in the placebo group at baseline. In addition, 41 patients (60%) in the mepolizumab arm and 31 patients (46%) in the placebo arm were taking an immunosuppressive therapy.

In the MANDARA trial, all patients were taking prednisolone or prednisone as per the inclusion criteria. The median daily dose was 10.0 mg (range, 5.0 to 30.0 mg) in the benralizumab arm and 10.0 mg (range, 7.5 to 40.0 mg) in the mepolizumab arm at baseline. A total of 26 patients (37%) in the benralizumab group and 24 patients (34%) in the mepolizumab group were taking an immunosuppressant at baseline.

Table 6: Baseline Patient Characteristics — MIRRA and MANDARA Trials

Characteristic	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Age in years, mean (SD)	49 (12)	48 (14)	52.0 (13.9)	52.7 (14.4)
Sex, n (%)				
Men	26 (38)	30 (44)	25 (36)	31 (44)
Women	42 (62)	38 (56)	45 (64)	39 (56)
ANCA-positive status at screening (MPO or PR3), n (%)	7 (10)	6 (9)	7 (10)	7 (10)
Mean absolute eosinophil count	0.2 × 10^9/L	0.2 × 10^9/L	0.3 × 10^9/L	0.4 × 10^9/L
BVAS > 0, n (%)	37 (54)	48 (71)	34 (49)	33 (47)
VDI score, mean (SD)	NR	NR	4.0 (1.8)	4.0 (1.8)
Prednisolone or prednisone dose, mg/day				
Median	12.0	11.0	10.0	10.0

Characteristic	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Range	7.5 to 40.0	7.5 to 50.0	5.0 to 30.0	7.5 to 40.0
Immunosuppressive therapy since diagnosis, n (%)	56 (82)	49 (72)	NR	NR
Immunosuppressive therapy at baseline, n (%)[a]	41 (60)	31 (46)	26 (37)	24 (34)
Azathioprine	20 (29)	10 (15)	15 (21)	13 (19)
Methotrexate	13 (19)	11 (16)	7 (10)	5 (7)
Methotrexate Sodium	NR	NR	1 (1)	1 (1)
Mycophenolic acid	6 (9)	6 (9)	NR	NR
Cyclosporine	0	3 (4)	NR	NR
Hydroxyurea/hydroxycarbamide	0	2 (3)	NR	NR
Hydroxychloroquine	NR	NR	0	1 (1)
Leflunomide	1 (1)	1 (1)	NR	NR
Mycophenolate mofetil	1 (1)	0	4 (6)	3 (4)
EGPA diagnostic disease characteristics, n (%)				
Asthma with eosinophilia	68 (100)	68 (100)	70 (100)	70 (100)
Biopsy evidence	25 (37)	31 (46)	20 (29)	33 (47)
Neuropathy	32 (47)	24 (35)	38 (54)	45 (64)
Nonfixed pulmonary infiltrates	50 (74)	48 (71)	49 (70)	43 (61)
Sinonasal abnormality	64 (94)	64 (94)	63 (90)	66 (94)
Cardiomyopathy	13 (19)	7 (10)	17 (24)	13 (19)
Glomerulonephritis	1 (1)	0	4 (6)	2 (3)
Alveolar hemorrhage	3 (4)	1 (1)	NR	NR
Palpable purpura	9 (13)	8 (12)	7 (10)	10 (14)
ANCA-positive status	13 (19)	13 (19)	NR	NR
Relapsing disease, n (%)	51 (75)	49 (72)	45 (64)	48 (69)
Refractory disease, n (%)	34 (50)	40 (59)	42 (60)	42 (60)
Relapsing and refractory, n (%)	NR	NR	18 (26)	20 (29)
Years since diagnosis of EGPA, mean (SD)	5.2 (4.4)	5.9 (4.9)	5.4 (5.4)	4.9 (5.9)

ANCA = antineutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; EGPA = eosinophilic granulomatosis with polyangiitis; MPO = myeloperoxidase; NR = not reported; PR3 = proteinase 3; SD = standard deviation; VDI = Vasculitis Damage Index.

[a]Patients could receive more than 1 immunosuppressant at baseline.

Sources: Wechsler et al., 2017;[13] Wechsler et al., 2024.[14]

Efficacy Results

Only those efficacy outcomes identified as relevant in the review protocol are reported in this section. A summary of the efficacy results from the MIRRA and MANDARA trials is listed in Table 7.

Remission

In the MIRRA trial (n = 136), the accrued weeks of remission was 1 of the primary end points. Over the 52-week trial, 19 (28%) patients in the mepolizumab group and 2 (3%) in the placebo group had remission for at least 24 weeks (OR = 5.91; 95% CI, 2.68 to 13.03; P < 0.001); the absolute between-group difference and CI were not reported.[13] A total of 32 patients (47%) in the mepolizumab group and 55 patients (81%) in the placebo group had 0 weeks of remission over the 52-week trial period. Total accrued weeks of remission was a secondary end point in the MANDARA trial. A total of 41 patients (59%) in the benralizumab group and 37 patients (53%) in the mepolizumab group had at least 24 weeks of accrued remission over the 52-week trial period (OR = 1.36; 95% CI; 0.77 to 2.62); the absolute between-group difference and CI were not reported. A total of 9 patients (13%) in the benralizumab group and 15 patients (21%) in the mepolizumab group had 0 weeks of remission.[14]

The second primary end point in the MIRRA trial was remission at both weeks 36 and 48, and 22 patients (32%) in the mepolizumab group and 2 patients (3%) in the placebo group experienced this end point (OR = 16.74; 95% CI, 3.61 to 77.56, P < 0.001); the absolute between-group difference and CI were not reported.[13] The primary end point in the MANDARA trial (n = 140) was remission at both weeks 36 and 48; 59% (adjusted percentage) of patients in the benralizumab group and 56% (adjusted percentage) in the mepolizumab group met this end point (RD = 3%; 95% CI, −13 to 18%; noninferiority P < 0.05; superiority P = 0.73).[14] The prespecified noninferiority margin of −25% was not included in the lower bound of the CI; as a result, benralizumab considered was noninferior to mepolizumab.[14]

For the secondary end point of remission (defined as BVAS = 0 and a prednisone or prednisolone dose of 4.0 mg or less per day) within the first 24 weeks that was sustained until week 52, 13 patients (19%) in the mepolizumab group and 1 patient (1%) in the placebo group in the MIRRA trial experienced this end point (OR = 19.65; 95% CI, 2.30 to 167.93); the absolute between-group difference and CI were not reported. In the MANDARA trial, 42% of the benralizumab group and 36% of the mepolizumab group met this end point (absolute difference [AD] = 6%; 95% CI, −9 to 20%).[13,14]

Similar results were seen with the remission end points when the definition of remission was changed to the more permissive definition of a BVAS of 0 and a daily dose of prednisone or prednisolone of 7.5 mg or less, as are listed in Table 7.[13,14]

Relapse

In the analysis of time to first relapse, a total of 38 patients (56%) in the mepolizumab group and 56 patients (82%) in the placebo group experienced an EGPA relapse during the MIRRA trial (hazard ratio [HR] = 0.32; 95% CI, 0.21 to 0.50), whereas 21 patients (30%) in each of the benralizumab and mepolizumab groups experienced a relapse in the MANDARA trial (HR = 0.98; 95% CI, 0.53 to 1.82).[13,14] The median time to first relapse was not reported in either trial. Absolute between-group differences in the proportion of patients who experienced a relapse at relevant time points were also not reported.

The annualized relapse rate in the MIRRA trial was 1.14 per year in the mepolizumab group compared to 2.27 per year in the placebo group (rate ratio [RR] = 0.50; 95% CI, 0.36 to 0.70).[13] Annualized relapse in the

MANDARA trial was 0.50 per year in the benralizumab group and 0.49 per year in the mepolizumab group (RR = 1.03; 95% CI, 0.56 to 1.90).[14]

In the analysis of time to major relapse, a total of 22% of patients in the mepolizumab group and 35% in the placebo group experienced a major relapse in the MIRRA trial (HR = 0.51; 95% CI, 0.26 to 0.98). The median time to first major relapse and absolute between-group differences at relevant time points were not reported. The time to first major relapse was not evaluable in the MANDARA trial because 0 patients in the benralizumab group experienced a major relapse (3 patients [4%] in the mepolizumab group experienced a major relapse).[13,14]

Change in OCS Dose

In the MIRRA trial, patients in the mepolizumab group had lower average daily doses of prednisolone or prednisone during weeks 48 through 52 than did those in the placebo group (OR = 0.20; 95% CI, 0.09 to 0.41; P < 0.001).[13] Thirty patients (44%) in the mepolizumab group were able to taper the OCS dose to 4.0 mg or less per day, as compared with 5 (7%) receiving placebo. In addition, 12 patients (18%) in the mepolizumab group were able to discontinue their OCS completely compared with 2 patients (3%) in the placebo group.[13]

In the MANDARA trial, the mean daily OCS dose was 2.98 mg in the benralizumab group and 3.43 mg in the mepolizumab group.[14] A total of 29 patients (41%) in the benralizumab arm and 19 patients (27%) in the mepolizumab arm were receiving 0 mg/day of OCS in weeks 48 to 52, and 49 (70%) of patients in both the benralizumab group and the mepolizumab group were receiving 4.0 mg/day or less of OCS.[14]

For the protocol-identified outcomes of minimizing damage, prevention of asthma exacerbations or asthma control, and HRQoL, results were only available graphically in the MIRRA trial without details regarding sample sizes for each comparison, between-group differences, or results of the statistical comparisons.[13] Similarly, results were only available graphically for change in BVAS, prevention of asthma exacerbations or asthma control, and HRQoL from the MANDARA trial.[14] As such, it is unclear whether any comparisons between mepolizumab and placebo (MIRRA trial) and benralizumab and mepolizumab (MANDARA trial) showed a clinically important difference.

Table 7: Efficacy Results From the MIRRA and MANDARA Trials

	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Remission: BVAS = 0 and OCS dose 4.0 mg/day or less				
Total accrued weeks of remission, n (%)				
0 weeks	32 (47)	55 (81)	9 (13)	15 (21)
More than 0 weeks to less than 12 weeks	8 (12)	8 (12)	12 (17)	10 (14)
12 weeks to less than 24 weeks	9 (13)	3 (4)	8 (11)	8 (11)
24 weeks to less than 36 weeks	10 (15)	0	21 (30)	19 (27)
36 weeks or more	9 (13)	2 (3)	20 (29)	18 (26)

	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
OR (95% CI)	5.91 (2.68 to 13.03) P < 0.001		1.36 (0.75 to 2.48)[a] P = NR	
Remission at weeks 36 and 48, n (%)	22 (32)	2 (3)	41 (59)[b]	40 (56)[b]
Comparison	OR = 16.74 (95% CI, 3.61 to 77.56) P < 0.001		RD = 3 (95% CI, −13 to 18) P = 0.73	
Remission within 24 weeks, sustained until week 52, n (%)	13 (19)	1 (1)	42%[b]	36%[b]
Comparison (95% CI)	OR = 19.65 (2.30 to 167.93) P = 0.007		RD = 6 (−9 to 20) P = NR	
Relapse				
Time to first EGPA relapse, n with event (%)	38 (56)	56 (82)	21 (30)	21 (30)
HR (95% CI)	0.32 (0.21 to 0.50) P < 0.001		0.98 (0.53 to 1.82)[a] P = NR	
Annualized relapse rate	1.14	2.27	0.50	0.49
RR (95% CI)	0.50 (0.36 to 0.70)[a] P < 0.001		1.03 (0.56 to 1.90)[a] P = NR	
Time to first major relapse, n with event (%)	15 (22)	24 (35)	0	3 (4)
HR (95% CI)	0.51 (0.26 to 0.98)[a] P = 0.04		NR	
Annualized relapse rate for major relapse	0.12	0.21	0	0.05
RR (95% CI)	0.56 (0.28 to 1.14)[a] P = 0.11		NR	
OCS end points				
Average OCS dose during weeks 48 to 52, n (%)				
0 mg/day	12 (18)	2 (3)	29 (41)	19 (27)
More than 0 mg/day to 4.0 mg/day	18 (26)	3 (4)	20 (29)	30 (43)
More than 4.0 mg/day to 7.5 mg/day	10 (15)	18 (26)	14 (20)	13 (19)
More than 7.5 mg/day	28 (41)	45 (66)	7 (10)	8 (11)
OR (95% CI)	0.20 (0.09 to 0.41) P < 0.001		1.42 (0.77 to 2.62)[a] P = NR	
Mean (SD) Daily OCS dose, mg	9.2 (NR)	13.5 (NR)	2.98 (NR)	3.43 (NR)
Percentage reduction from baseline in average OCS dose at weeks 48 to 52, n (%)				
No reduction or withdrawal from treatment	14 (21)	33 (49)	3 (4)	7 (10)
Less than 25% reduction	8 (12)	9 (13)	0	2 (3)

	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
25% to less than 50% reduction	8 (12)	11 (16)	7 (10)	9 (13)
50% to less than 75% reduction	16 (24)	11 (16)	20 (29)	17 (24)
75% to less than 100% reduction	10 (15)	3 (4)	11 (16)	17 (24)
100% reduction	12 (18)	1 (1)	29 (41)	18 (26)
OR (95% CI)	4.32 (2.28 to 8.19)[a] P < 0.001		1.80 (0.98 to 3.28)[a] P = NR	
Reduction of 50% or more	38 (56)	15 (22)	60 (86)	52 (74)
RD (95% CI)	NR		12 (−1 to 25)[a] P = NR	
100% reduction	12 (18)	1 (1)	29 (41)	18 (26)
RD (95% CI)	NR		16 (1 to 31)[a] P = NR	
Remission: BVAS = 0 and OCS dose 7.5 mg/day or less				
Total accrued weeks of remission, n (%)				
0 weeks	15 (22)	36 (53)	2 (3)	4 (6)
More than 0 weeks to less than 12 weeks	15 (22)	19 (28)	2 (3)	3 (4)
12 weeks to less than 24 weeks	7 (10)	0	5 (7)	4 (6)
24 weeks to less than 36 weeks	9 (13)	7 (10)	16 (23)	15 (21)
36 weeks or more	22 (32)	6 (9)	45 (64)	44 (63)
OR (95% CI)	5.31 (2.63 to 10.74) P < 0.001		1.12 (0.55 to 2.29)[a] P = NR	
Remission at weeks 36 and 48, n (%)	28 (41)	7 (10)	(79)[b]	(74)[b]
Comparison (95% CI)	OR = 7.19 (2.60 to 19.87) P < 0.001		RD = 5 (−7 to 18)[a] P = NR	
Remission within 24 weeks, sustained until week 52, n (%)	16 (24)	2 (3)	NR	NR
OR (95% CI)	11.39 (2.35 to 55.24) P = 0.003		NR	

BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; EGPA = eosinophilic granulomatosis with polyangiitis; HR = hazard ratio; NR = not reported; OCS = oral corticosteroid; OR = odds ratio; RD = risk difference; RR = rate ratio; SD = standard deviation.

[a]Analyses were not controlled for type I error.[13,14]

[b]Adjusted percentage: Adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

Comparisons between mepolizumab and placebo in the MIRRA trial were adjusted for baseline dose of prednisolone or prednisone, baseline BVAS, and geographic region (North America, Europe, or Japan).[13]

Comparisons between benralizumab and mepolizumab in the MANDARA trial were adjusted for baseline dose of oral glucocorticoid, baseline BVAS, and region (North America, Japan, and rest of world).[14]

Sources: Wechsler et al., 2017;[13] Wechsler et al., 2024.[14]

Organ Damage

Figure 1 displays the LS mean change from baseline in BVAS score in patients who were randomized to mepolizumab and patients randomized to placebo, and Figure 2 shows the LS mean change from baseline in BVAS score for benralizumab and mepolizumab.[13,14] LS mean change from baseline in BVAS score appeared similar between mepolizumab and placebo as well as between benralizumab and mepolizumab.

The LS mean change from baseline to 52 weeks in the VDI score was 0.13 points in the benralizumab group and 0.10 points in the mepolizumab group (LS mean difference = 0.03; 95% CI, −0.10 to 0.16 points) in the MANDARA trial.[14] The LS mean change from baseline to 52 weeks in VDI in the MIRRA trial is provided in Figure 1.[13]

Asthma Exacerbations/Asthma Control

The LS mean change from baseline to 52 weeks in FEV_1, FVC, and the ACQ-6 score in the MIRRA trial is provided in Figure 1. Mepolizumab was consistently associated with a numerically larger reduction in ACQ-6 score compared with placebo, but it is unclear whether the difference was clinically important.[13]

The LS mean change from baseline to 52 weeks in FEV_1 and ACQ-6 score in the MANDARA trial are provided in Figures 3 and 4, respectively. Based on the figures, changes in FEV_1 and ACQ-6 scores were similar between benralizumab and mepolizumab.[14]

Health-Related Quality of Life

Figure 1 shows the results in change from baseline to week 52 in SNOT-22 score from the MIRRA trial, and Figure 5 shows the results from the MANDARA trial. Patients who received mepolizumab had a numerically greater reduction in SNOT-22 score compared to placebo; however, this difference was not statistically significant at week 52.[13] The magnitude of the difference was not reported. Change in SNOT-22 score from baseline was similar between benralizumab and mepolizumab in the MANDARA trial.[14]

Change in SF-36v2 PCS, MCS, and domain scores from baseline to 52 weeks were evaluated in the MANDARA trial; however, only the changes in PCS and MCS scores were reported in the supplement to the MANDARA trial (Figure 6).[14] Changes in the PCS and MCS scores were similar between benralizumab and mepolizumab.

Figure 1: Results From the MIRRA Trial for Change in FEV_1, FVC, ACQ-6, SNOT-22, VDI, and BVAS[13]

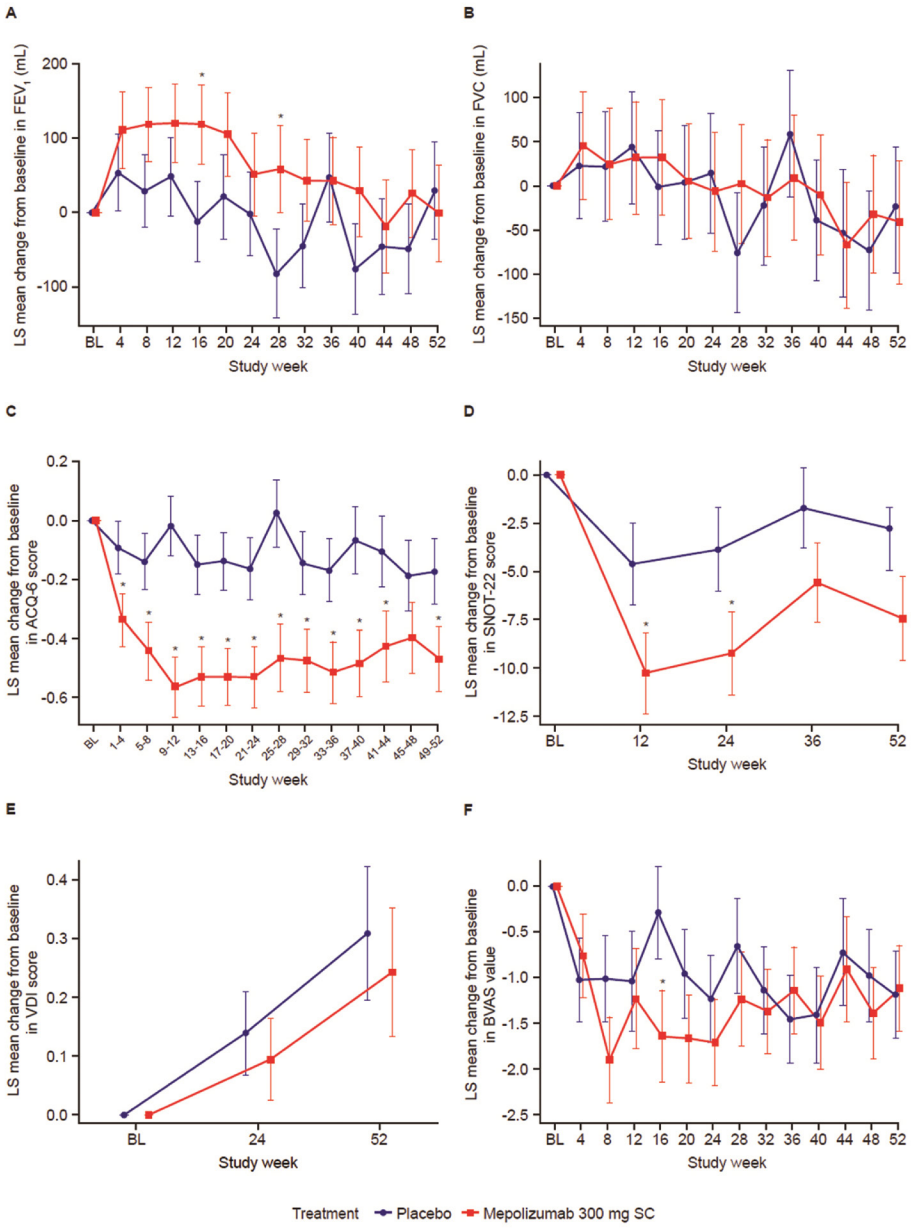

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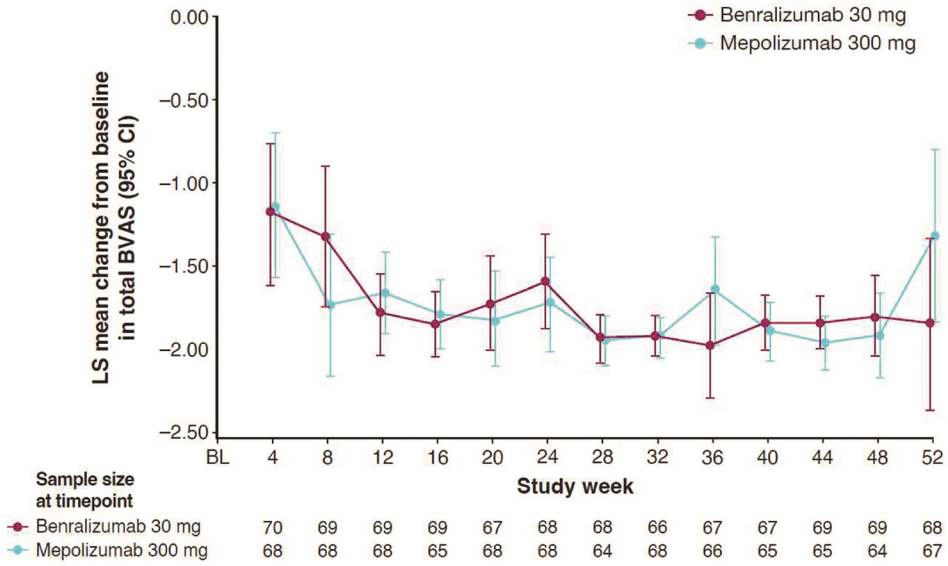
Figure 2: LS Mean Change From Baseline in BVAS From the MANDARA Trial[14]



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Cardiovascular Events

Cardiovascular events were not evaluated as an efficacy end point in the MIRRA trial; however, they were captured as harms events and are listed in Table 8.[13] Cardiovascular events were not evaluated in the MANDARA trial.

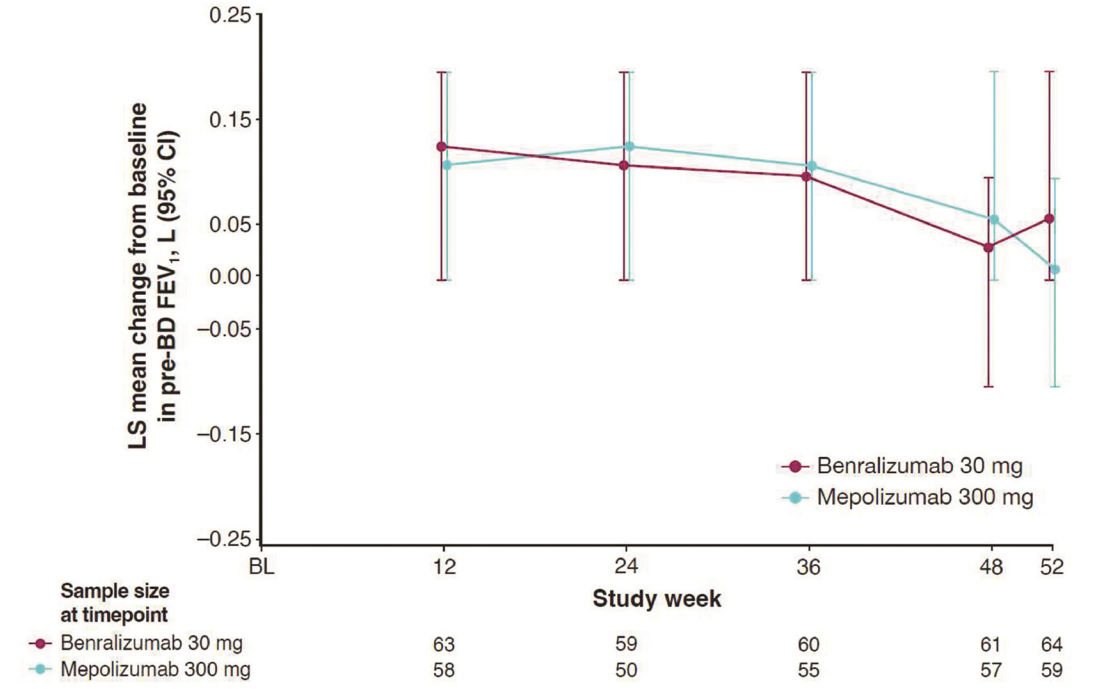
Survival

Survival was not evaluated in the MIRRA or MANDARA trials; however, deaths were captured as harms in both trials and are listed in Table 8.[13,14]

Subgroup Analyses

The patients included in the MIRRA and MANDARA trials were aged 18 years or older, and as a result, the preplanned subgroup of age (less than 6 years, 6 to 17 years, 18 years and older) from the systematic review protocol was not evaluated. In addition, because patients with severe EGPA (defined as presence of organ-threatening or life-threatening EGPA) were excluded from the MIRRA and MANDARA trials, we were unable to evaluate the preplanned subgroup of severe versus nonsevere EGPA.

Figure 3: LS Mean Change From Baseline in FEV_1 From the MANDARA Trial[14]



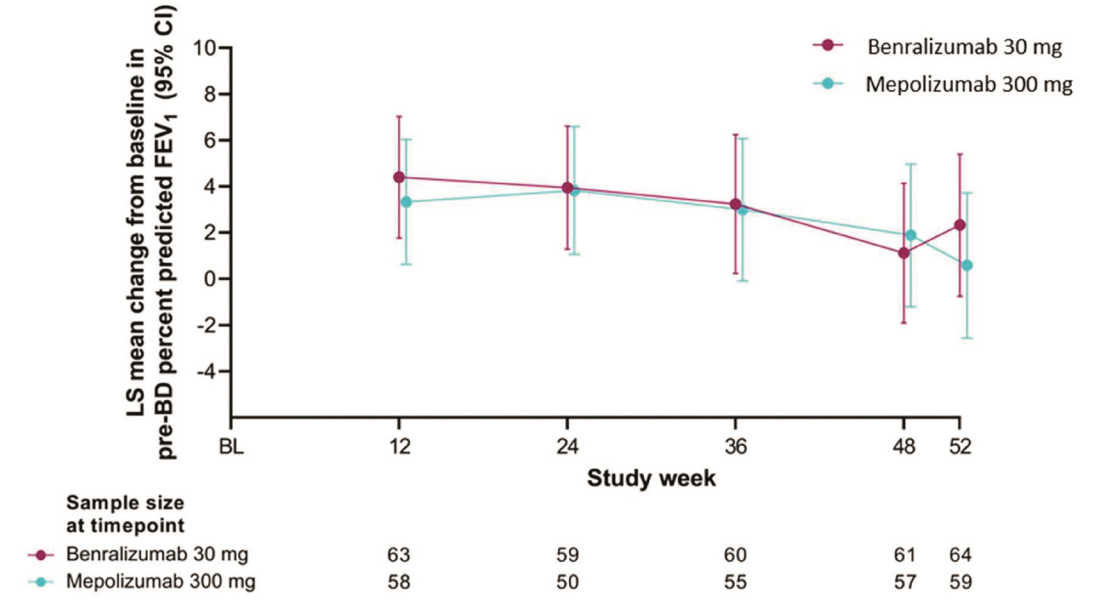


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Figure 4: LS Mean Change From Baseline in ACQ-6 Score From the MANDARA Trial[14]

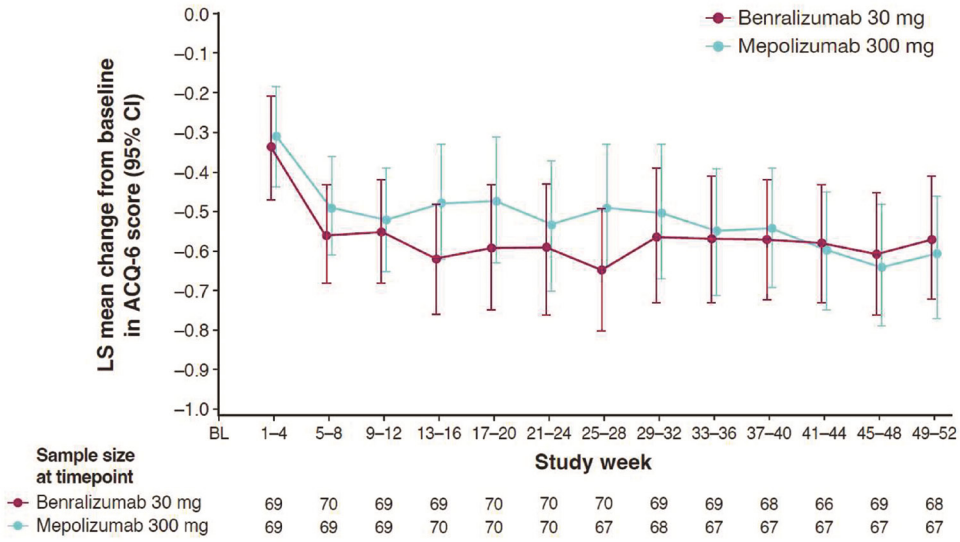

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Figure 5: LS Mean Change From Baseline in SNOT-22 Score From the MANDARA Trial[14]

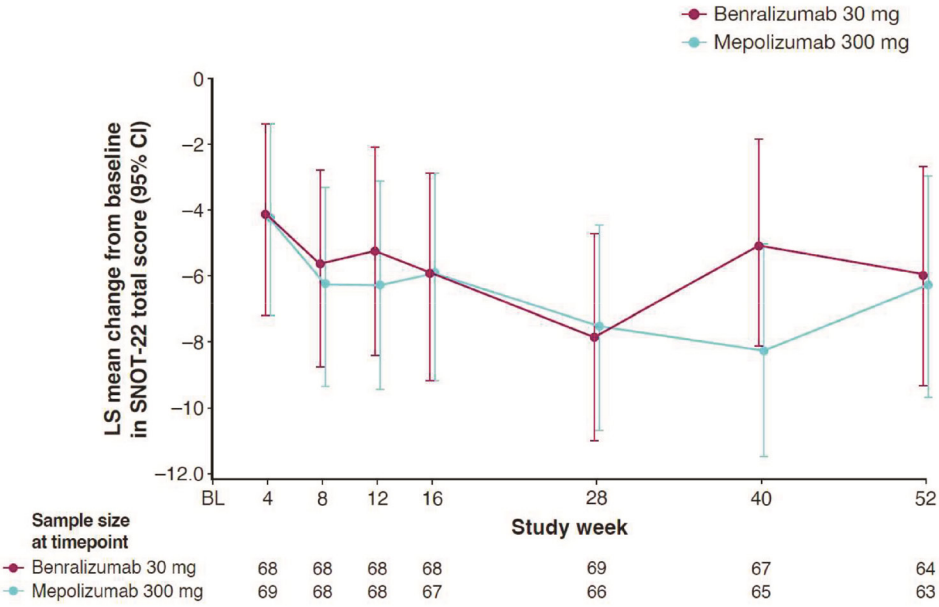

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Figure 6: LS Mean Change From Baseline in SF-36v2 PCS Scores From the MANDARA Trial[14]

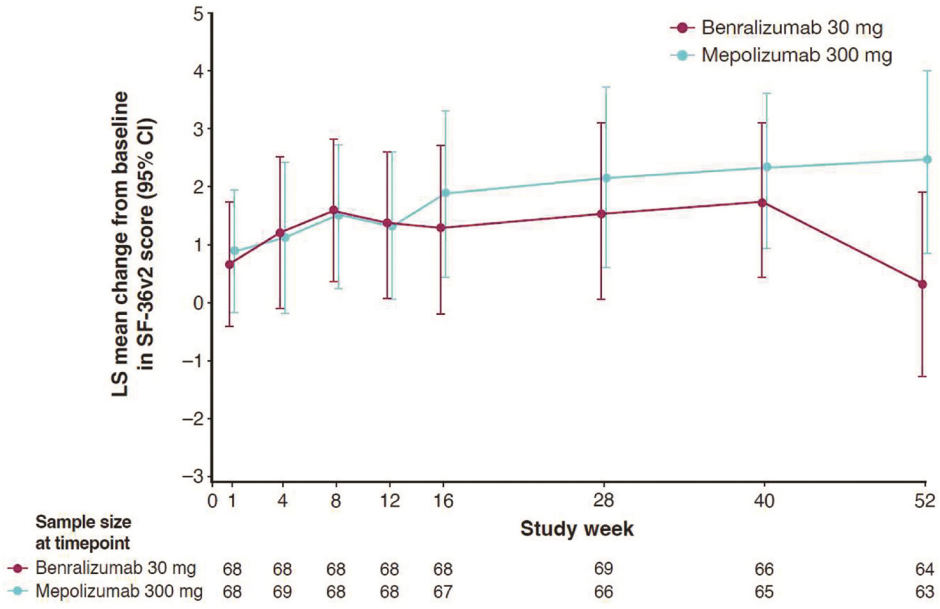

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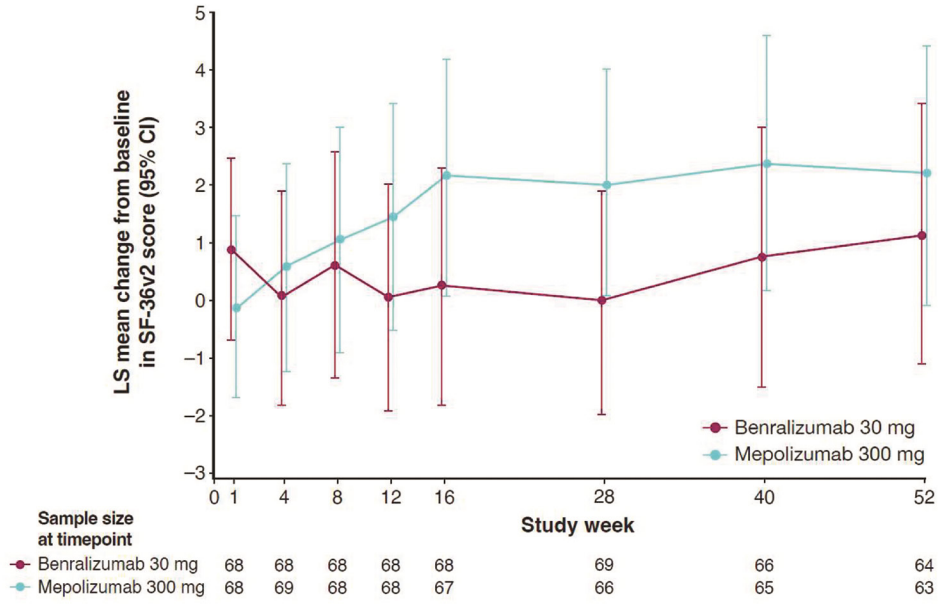
Figure 7: LS Mean Change From Baseline in SF-36v2 MCS Scores From the MANDARA Trial[14]



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Terrier et al. conducted a post hoc subgroup analysis based on ANCA history in patients from the MIRRA trial.[22] In patients with a history of ANCA positivity, those in the mepolizumab arm had a greater accrued duration of remission compared to patients in the placebo arm (OR = 21.06; 95% CI, 2.65 to 167.18), and patients with a history of ANCA negativity in the mepolizumab group also had a greater accrued duration of remission compared to patients who received placebo (OR = 4.91; 95% CI, 2.04 to 11.81).[22] The proportion of patients who achieved remission at weeks 36 and 48 could not be evaluated in ANCA-positive patients because none of the patients in the placebo group achieved remission. However, for those with a history of ANCA negativity, patients in the mepolizumab group had increased odds of achieving remission at 36 and 48 weeks compared to people in the placebo group (OR = 9.01; 95% CI, 1.87 to 43.43).[22] Absolute between-group differences at were not reported. These results are highly uncertain given the wide CIs around the point estimates and the fact that these subgroup analyses were post hoc.

Response to benralizumab compared to mepolizumab was also evaluated based on ANCA status in the MANDARA trial.[14] In patients with ANCA positivity, there was no statistical difference in likelihood of remission at weeks 36 and 48 in patients randomized to benralizumab compared to patients randomized to mepolizumab (RD = 1.87; 95% CI, −27.65 to 31.39). In patients with ANCA negativity, results were similar (RD = 3.22; 95% CI, −14.75 to 21.20).[14] The results are highly uncertain given the imprecision of the CIs around the point estimate.

Harms Results

Only those harms identified in the review protocol are reported herein. Table 8 lists the AEs reported in the MIRRA and MANDARA trials.

Adverse Events

In the MIRRA trial, a total of 66 patients in the mepolizumab arm (97%) experienced an AE, and of these patients, 35 (51%) were considered by the investigator to be related to the trial drug, whereas 64 patients in the placebo arm (94%) experienced an AE, and 24 (35%) were considered by the investigator to be related to the trial drug.[13] The most common AE was headache, reported by 32% of patients in the mepolizumab group and 18% of patients in the placebo group. In addition, arthralgia was reported by 22% of the patients in the mepolizumab arm and 18% of patients in the placebo arm.[13]

In the MANDARA trial, 63 patients (90%) in the benralizumab group and 67 patients (96%) in the mepolizumab group experienced in AE.[14] The most common AE was COVID-19 infection (21% in the benralizumab group and 27% in the mepolizumab group), headache (17% in the benralizumab group and 16% in the mepolizumab group), and arthralgia (17% in the benralizumab group and 11% in the mepolizumab group).[14]

Serious Adverse Events

SAEs occurred in 12 patients (18%) in the mepolizumab arm and 18 patients (26%) in the placebo arm in the MIRRA trial.[13] It is possible that the number of SAEs was numerically larger in patients randomized to placebo because events related to worsening EGPA were captured as SAEs. For example, the most

common SAE reported was exacerbation or worsening of asthma, which occurred in 3% of patients in the mepolizumab group and 6% of patients in the placebo group.

A total of 4 patients (6%) in the benralizumab group and 9 patients (13%) in the mepolizumab group experienced a SAE in the MANDARA trial.[14] Two patients (3%) in the mepolizumab group were diagnosed with prostate cancer during the trial, resulting in discontinuation of mepolizumab.[14]

Table 8: Proportion of Patients With Adverse Events

Adverse event	MIRRA trial[13]		MANDARA trial[14]	
	Mepolizumab (n = 68)	Placebo (n = 68)	Benralizumab (n = 70)	Mepolizumab (n = 70)
Any event, n (%)	66 (97)	64 (94)	63 (90)	67 (96)
Event leading to trial-drug discontinuation or trial withdrawal	2 (3)	1 (1)	0	2 (3)
Death	1 (1)	0	0	0
Serious adverse event				
Any event, n (%)	12 (18)	18 (26)	4 (6)	9 (13)
Systemic or local-site reaction				
Systemic reaction, n (%)	4 (6)	1 (1)	NR	NR
Local-site reaction, n (%)	10 (15)	9 (13)	NR	NR
Cardiovascular events				
Arrhythmia, n (%)	2 (3)	3 (4)	NR	NR
Stroke or TIA, n (%)	1 (1)	0	NR	NR
Congestive heart failure, n (%)	0	1 (1)	NR	NR
Myocardial infarction or unstable angina, n (%)	1 (1)	1 (1)	NR	NR

NR = not reported; TIA = transient ischemic attack.
Sources: Wechsler et al., 2017;[13] Wechsler et al., 2024.[14]

Withdrawals Due to Adverse Events

AEs leading to discontinuation occurred in 2 patients (3%) in the mepolizumab arm and 1 patient (1%) in the placebo arm in the MIRRA trial, and 0 patients in the benralizumab group and 2 patients (3%) in the mepolizumab group in the MANDARA trial.[13,14] As described above, 2 patients discontinued treatment due to the diagnosis of prostate cancer during the MANDARA trial.[14]

Deaths

One death was reported in the mepolizumab arm in the MIRRA trial.[13] There were no deaths in the MANDARA trial.[14]

Harms of Special Interest

Allergic reactions: Allergic reactions were not reported in the MIRRA or MANDALA trials.

Injection-site reactions: The frequency of local-site reactions was similar between the mepolizumab arm (15% of patients experienced a local-site reaction) and the placebo arm (13% of patients experienced a local-site reaction) in the MIRRA trial.[13] Injection-site reactions were not reported in the MANDARA trial.

Severe infections: Severe infections were not reported in the MIRRA trial, however, upper respiratory tract infection occurred in 21% of patients in the mepolizumab group and 16% of patients in the placebo group in the MIRRA trial.

In the MANDARA trial, 1 person (1%) in each of the benralizumab and mepolizumab groups experienced a SAE due to COVID-19 infection; in the mepolizumab group, 1 (1%) person experienced a SAE due to a urinary tract infection and 1 person (1%) experienced a SAE due to a wound infection.[14]

Helminth infections: Helminth infections were not identified in the MIRRA or MANDARA trials.[13,14]

Shingles: Shingles (herpes zoster) was not identified in the MIRRA trial. In the MANDARA trial, 0 patients in the benralizumab group and 3 patients (4%) in the mepolizumab group developed shingles.[14]

ENT adverse events: In the MIRRA trial, nasopharyngitis occurred in 18% of patients in the mepolizumab group and 24% of patients in the placebo group.[13] In addition, sinusitis occurred in 21% of patients in the mepolizumab group and in 16% of patients in the placebo group.[13]

In the MANDARA trial, 6 patients (9%) in the benralizumab group and 10 patients (14%) in the mepolizumab group experienced nasopharyngitis, and 5 patients (7%) in the benralizumab group and 8 patients (11%) in the mepolizumab group experienced sinusitis.[14]

Indirect Evidence

A total of 41 references were identified from the ITC search. After title and abstract screening, none met the selection criteria for full-text review. No ITCs were included.

Economic Evidence

CADTH Analyses

As this review is part of the CADTH nonsponsored reimbursement review program, in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for mepolizumab with or without OCSs and/or immunosuppressive therapies for the treatment of patients with EGPA. As a result, the economic review consisted of a cost comparison between mepolizumab with or without OCSs and/or immunosuppressive therapies and appropriate comparators for the treatment of adult patients with EGPA.

The comparators presented in the following table have been deemed to be appropriate based on feedback received from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice were noted, the dose specified by clinical experts was used. Pricing for comparator products was based on publicly available list prices.

Clinical expert feedback obtained by CADTH indicated there are 3 distinct comparator classes: OCS (i.e., prednisone), immunosuppressive therapies (i.e., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and rituximab), and biologics (i.e., benralizumab). While rituximab is categorized as an immunosuppressive therapy, insights from clinical experts suggest that it is not typically used in combination with mepolizumab. Instead, rituximab may be used independently to induce remission in patients with severe active EGPA.[9,13] Results of the cost comparison demonstrate that, whether used as a standalone treatment or as part of a combination therapy, mepolizumab is more costly than an OCS, immunosuppressive therapies, and benralizumab. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 1.

Table 9: CADTH Cost Comparison Table for EGPA

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost ($)
Mepolizumab (Nucala)	**100 mg/mL**	**Vial of powder for SC injection**	**2,207.7400[a]**	**300 mg once every 4 weeks**	**236.54**	**86,338**
		Prefilled syringe for SC injection				
		Prefilled autoinjector for SC injection				
Prednisone (generic)	5 mg	Tab	0.0220	2 mg to 60 mg daily[b]	0.07	24
	50 mg		0.1735			
Mepolizumab in combination with OCS (prednisone)					236.61	86,362
Mepolizumab in combination with immunosuppressive therapies (excluding rituximab)					236.86 to 239.51	86,456 to 87,422
OCS						
Prednisone (generic)	5 mg	Tab	0.0220	2 mg to 60 mg daily	0.02 to 0.26	8 to 96
	50 mg		0.1735			
Immunosuppressive therapies						
Azathioprine (generic)	50 mg	Tab	0.5185	2 mg/kg daily, maximum dose of 200 mg	1.56	568
Cyclophosphamide (Procytox)	25 mg	Tab	0.3545	2 mg/kg daily, maximum dose of 200 mg	1.43	523
	50 mg		0.4773			
Methotrexate (generic)	2.5 mg	Tab	0.2513	20 mg to 25 mg every week	0.32[c]	118[c]

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost ($)
Mycophenolate mofetil (generic)	250 mg	Tab	0.3712	1,000 mg twice daily	2.97	1,084
	500 mg		0.7423			
Rituximab (generic)	10 mg/mL	10 mL vial	29.7000	500 mg every 14 days	106.07	38,716
Rituximab (Truxima)	100 mg/mL	10 mL vial pack	297.0000			
	500 mg/mL	50 mL vial pack	1,485.0000			
Immunosuppressive therapies					0.32 to 106.07	118 to 38,716
Biologics						
Benralizumab[d] (Fasenra)	30 mg/mL	Prefilled syringe for SC injection	4,115.5400[a]	30 mg every 4 weeks for first 3 doses, then once every 8 weeks	88.68	32,367
		Prefilled pen for SC injection	4,036.8000[a]			

EGPA = eosinophilic granulomatosis with polyangiitis; OCS = oral corticosteroid; SC = subcutaneous.

Note: Assumes mean patient weight of 60 kg and body surface area of 1.80m^2 as highlighted by Mendel et al. 2021 and validated by clinical expert feedback.[10,37] All prices are from the Ontario Drug Benefit Formulary (Accessed April 2024),[38] unless otherwise indicated, and do not include dispensing fees. Dosing is based on product monographs and was validated by clinical expert feedback obtained by CADTH.

[a]Prices obtained from the Ontario Exceptional Access Program (EAP).[39]

[b]Clinical experts indicated that, when used in combination with mepolizumab, patients typically receive 12 mg of prednisone.

[c]Costs calculated using an average weekly patient dose of 22.5 mg.

[d]Benralizumab is not a relevant comparator because it is not funded by any participating drug plan for this indication, is not a publicly reimbursed treatment used off-label in Canadian practice and has not previously received a recommendation in favour of reimbursement for EGPA. Benralizumab is accessed off-label by some patients with EGPA through private insurance, and as such, is considered a therapeutic alternative but not a relevant comparator. The price of benralizumab was obtained from the EAP, where benralizumab is reimbursed for severe eosinophilic asthma. The annual cost of benralizumab is calculated based on the recommended dosage for severe eosinophilic asthma (30 mg every 4 weeks for the first 3 doses, then once every 8 weeks). It should be noted that when patients with EGPA access benralizumab off-label through private insurance, the dosing schedule is likely to be 30 mg every 4 weeks.

Issues for Consideration

- Drug plan input highlighted that as mepolizumab (Nucala) is a biologic, it is expected that biosimilars would be introduced in the future. This could result in reduced drug acquisition costs.
- Relative to SoC (i.e., an OCS with or without immunosuppressive therapies), clinical expert input indicated that mepolizumab is anticipated to reduce hospitalizations, outpatient visits, monitoring costs, and disease management costs. Clinical expert input further noted that mepolizumab's ability to reduce reliance on an OCS would minimize AEs and reduce the need for laboratory monitoring when compared to SoC.
- Clinical expert feedback indicated that there would be no anticipated differences in health care utilization between mepolizumab and benralizumab.
- No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on April 2, 2024.

Discussion

Summary of Available Evidence

Two trials were identified for this review: the MIRRA trial — a randomized, double-blind, placebo-controlled, phase III trial of mepolizumab (n = 68) versus placebo (n = 68) in patients with relapsing or refractory EGPA — and the MANDARA trial — a randomized, double-blind, double-dummy, noninferiority trial comparing benralizumab (n = 70) to mepolizumab (n = 70).[13,14] The MIRRA and MANDARA trials were similarly designed, with similar eligibility criteria, the same dose of mepolizumab, the same definitions for end points, and the same double-blind treatment phase (52 weeks).[13,14] The MIRRA and MANDARA trial populations were more likely to be female, and the mean age ranged from 48 years to 52 years. Patients had an average duration of EGPA of 5 years. The median daily prednisone or prednisolone dose at baseline ranged from 10 mg to 12 mg. More patients in the MIRRA trial were taking immunosuppressive therapy at baseline (60% in the mepolizumab group and 46% in the placebo group) compared to the MANDARA trial (37% in the benralizumab group and 34% in the mepolizumab group).

There were no studies identified that evaluated mepolizumab for EGPA in patients under the age of 18 years. In addition, patients with severe EGPA, defined as organ-threatening or life-threatening EGPA within 3 months before randomization, were excluded from both trials.[13,14]

Interpretation of Results

Efficacy

Based on feedback from patients and clinicians, prevention of organ involvement and tissue damage by preventing relapses is an important goal for patients with EGPA. In addition, patients often require high-dose IV steroids, long-term OCSs, as well as immunosuppressants including cyclophosphamide and azathioprine. As a result, another important goal for patients with EGPA is to minimize the harms associated with OCSs and immunosuppressants.

In the MIRRA trial, patients randomized to mepolizumab 300 mg SC once every 4 weeks had a greater total accrued weeks of EGPA remission, were more likely to achieve remission at 36 and 48 weeks, and were more likely to achieve remission at 24 weeks that was sustained to week 52 compared to patients randomized to placebo.[13] In addition, the hazard of EGPA relapse and major EGPA relapse was longer in the mepolizumab group compared to the placebo group. Lastly, the patients randomized to mepolizumab experienced a greater reduction in OCSs at weeks 48 to 52 from baseline and were taking a lower dose of OCSs during weeks 48 to 52 compared to patients randomized to placebo.[13]

In the MANDARA trial, benralizumab 30 mg SC once every 4 weeks was noninferior but not superior to mepolizumab 300 mg SC once every 4 weeks for remission at weeks 36 and 48, based on a noninferiority margin of −25%.[14] In addition, benralizumab and mepolizumab were similar in terms of the duration of accrued remission, reduction in OCS dose from baseline, annualized relapse rate, or time to first major relapse, and both treatment groups experienced benefit during the trial.[14] As an observation, more patients who were randomized to mepolizumab in the MANDARA trial experienced an increased likelihood of EGPA

remission at weeks 36 and 48, an increased duration of accrued remission, a greater reduction in OCS dose from baseline, and a reduction in relapse compared to the patients randomized to mepolizumab in the MIRRA trial. This could be due to differences in trial design; for example, an active-controlled versus placebo-controlled trial or the more aggressive OCS tapering plan in the MANDARA trial, changes in clinical practice over time, and the impact of isolation and social distancing during the COVID-19 pandemic.[13,14]

Limitations of both trials included the relatively small sample sizes, which contributed to imbalance in some prognostic factors at baseline between the treatment and control groups, as well as wide CIs around point estimates, indicating a wide range of potential effects of mepolizumab in patients with EGPA.[13,14] In addition, all patients were receiving an OCS at baseline; as a result, the efficacy of mepolizumab in patients who are not taking an OCS is unclear. Also, in the MANDARA trial, the prespecified noninferiority margin for the primary end point of remission at 36 and 48 weeks was −25%; however, the clinical relevance of the margin is unclear.[14] Also, the statistical comparisons for the secondary and other end points were not controlled for type I error. Both cardiovascular end points and survival were identified as outcomes of interest for this review; however, they were not evaluated as efficacy end points in either trial.[13,14] Lastly, both trials were 52 weeks in duration; therefore, the duration of mepolizumab efficacy beyond this time period is unclear.[13,14]

Harms

In the MIRRA trial, a total of 66 patients in the mepolizumab arm (97%) experienced an AE, and 64 patients in the placebo arm (94%) experienced an AE.[13] The most common AE was headache, reported by 32% of patients in the mepolizumab group and 18% of patients in the placebo group. In addition, arthralgia was reported by 22% of the patients in the mepolizumab arm and 18% of patients in the placebo arm.[13] In the MANDARA trial, 63 patients (90%) in the benralizumab group and 67 patients (96%) in the mepolizumab group experienced in AE.[14] The most common AE was COVID-19 infection (21% in the benralizumab group and 27% in the mepolizumab group), headache (17% in the benralizumab group and 16% in the mepolizumab group), and arthralgia (17% in the benralizumab group and 11% in the mepolizumab group).[14]

SAEs occurred in 12 patients (18%) in the mepolizumab arm and 18 patients (26%) in the placebo arm in the MIRRA trial.[13] It is possible that the number of SAEs was numerically larger in patients randomized to placebo because events related to worsening EGPA were captured as SAEs. A total of 4 patients (6%) in the benralizumab group and 9 patients (13%) in the mepolizumab group experienced a SAE in the MANDARA trial.[14] Two patients (3%) in the mepolizumab group were diagnosed with prostate cancer during the trial, resulting in discontinuation of mepolizumab; however, this was not considered to be related to treatment.[14]

Given the duration of both the MIRRA and MANDARA trials of 52 weeks, potential long-term harms with mepolizumab are unclear. In addition, harms of special interest identified in the review protocol, including allergic reactions and helminth infections, were not reported in either trial.[13,14]

Cost

- The annual patient cost of mepolizumab monotherapy is $86,338. When used in combination with OCSs, the annual patient cost of mepolizumab is $86,363. When used in combination with immunosuppressive therapies, the annual patient cost of mepolizumab ranges between $86,456

(mepolizumab + methotrexate) and $87,422 (mepolizumab + mycophenolate mofetil). Whether used as a standalone treatment or as part of a combination therapy, mepolizumab is more costly than OCSs (annual cost: $8 to $96), immunosuppressive therapies (annual cost: $118 to $38,716), and benralizumab (annual cost: $32,367).

- As such, mepolizumab monotherapy results in incremental costs compared with OCSs ($86,314), immunosuppressive therapies ($47,662 to $86,221), and benralizumab ($53,972). When used alongside OCSs or in combination with immunosuppressive therapies, the incremental cost of mepolizumab compared with OCSs or immunosuppressive therapies alone amounts to $86,338. This cost comparison is based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

Evidence from the MIRRA trial demonstrated an increased likelihood of EGPA remission at weeks 36 and 48, an increased duration of accrued remission, a greater reduction in OCS dose from baseline, and a reduction in EGPA relapse in patients randomized to mepolizumab 300 mg SC once every 4 weeks compared to placebo. Results from the MANDARA trial demonstrated that benralizumab 30 mg SC once every 4 weeks was noninferior but not superior to mepolizumab 300 mg SC once every 4 weeks for likelihood of EGPA remission at weeks 36 and 48. In addition, results were similar between benralizumab and mepolizumab for duration of accrued remission, reduction in OCS dose from baseline, annualized relapse rate, or time to first major relapse. However, the comparisons were associated with wide CIs, increasing the uncertainty due to the large range of possible effects. More patients who were randomized to mepolizumab in the MANDARA trial experienced an increased likelihood of EGPA remission at weeks 36 and 48, an increased duration of accrued remission, a greater reduction in OCS dose from baseline, and a reduction in relapse compared to the patients randomized to mepolizumab in the MIRRA trial. This could be due to differences in trial design, for example, an active-controlled versus placebo-controlled trial or the more aggressive OCS tapering plan in the MANDARA trial, changes in clinical practice over time, and the impact of isolation and social distancing during the COVID-19 pandemic.[13,14] Lastly, most patients experienced at least 1 AE, however, SAEs and discontinuation due to AEs were rare. Uncertainties remain for pediatric patients with EGPA, as no relevant evidence was identified that included patients under 18 years of age.

The results of the cost comparison of drug acquisition costs demonstrate that, when compared to OCSs, immunosuppressive therapies, or benralizumab, the reimbursement of mepolizumab with or without OCSs and/or immunosuppressive therapies is expected to increase treatment costs. This increase translates to incremental costs ranging from $47,662 to $86,314, per patient per year.

Based on the clinical review conclusions, mepolizumab in combination with SoC likely results in improved duration of accrued remission, improved reduction in relapse rate, and improved reduction in OCS use compared with SoC alone. Given that mepolizumab in combination with SoC is associated with incremental costs and incremental benefit compared with SoC alone, a cost-effectiveness analysis would be required to determine the cost-effectiveness of mepolizumab relative to SoC alone. As this was not available, the cost-

effectiveness of mepolizumab in combination with SoC relative to SoC alone for the treatment of patients with EGPA could not be determined.

The clinical review further concluded that benralizumab was noninferior and not superior to mepolizumab with regard to duration of accrued remission, reduction of relapse rate, and reduction in OCS use. Benralizumab is less costly than mepolizumab. Neither is publicly funded for this indication.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: January 10, 2024

Alerts: Weekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type

Limits:

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 10: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1. (mepolizumab* or Nucala* or Bosatria* or bat 2606 or bat2606 or sb 240563 or sb240563 or 90Z2UF0E52).ti,ab,kf,ot,hw,rn,nm.
2. Churg-Strauss Syndrome/
3. ((Strauss adj2 Churg) or (allergic adj2 granulomat*) or (eosinophilic adj2 granulomat* adj3 (vasculit* or polyangiit* or polyangit* or angiit* or angit*)) or (allergic adj2 (angiit* or angit*)) or eosinophilic GPA or EGPA).ti,ab,kf.
4. or/2-3
5. 1 and 4
6. 5 use medall
7. *mepolizumab/ or (mepolizumab* or Nucala* or Bosatria* or bat 2606 or bat2606 or sb 240563 or sb240563).ti,ab,kf,dq.
8. Churg Strauss syndrome/
9. ((Strauss adj2 Churg) or (allergic adj2 granulomat*) or (eosinophilic adj2 granulomat* adj3 (vasculit* or polyangiit* or polyangit* or angiit* or angit*)) or (allergic adj2 (angiit* or angit*)) or eosinophilic GPA or EGPA).ti,ab,kf,dq.
10. or/8-9
11. 7 and 10
12. 11 use oemezd
13. 12 not (conference review or conference abstract).pt.
14. 6 or 13

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

Search terms – mepolizumab, eosinophilic granulomatosis with polyangiitis (EGPA)

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

Search terms – mepolizumab, eosinophilic granulomatosis with polyangiitis (EGPA)

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

Search terms – mepolizumab, eosinophilic granulomatosis with polyangiitis (EGPA)

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms – mepolizumab, eosinophilic granulomatosis with polyangiitis (EGPA)

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

Search terms – mepolizumab, eosinophilic granulomatosis with polyangiitis (EGPA)

Grey Literature

Search dates: January 4 to 8, 2024

Keywords: mepolizumab and eosinophilic granulomatosis with polyangiitis (EGPA)

Limits: Publication years: none

Updated: Search updated before the completion of stakeholder feedback period

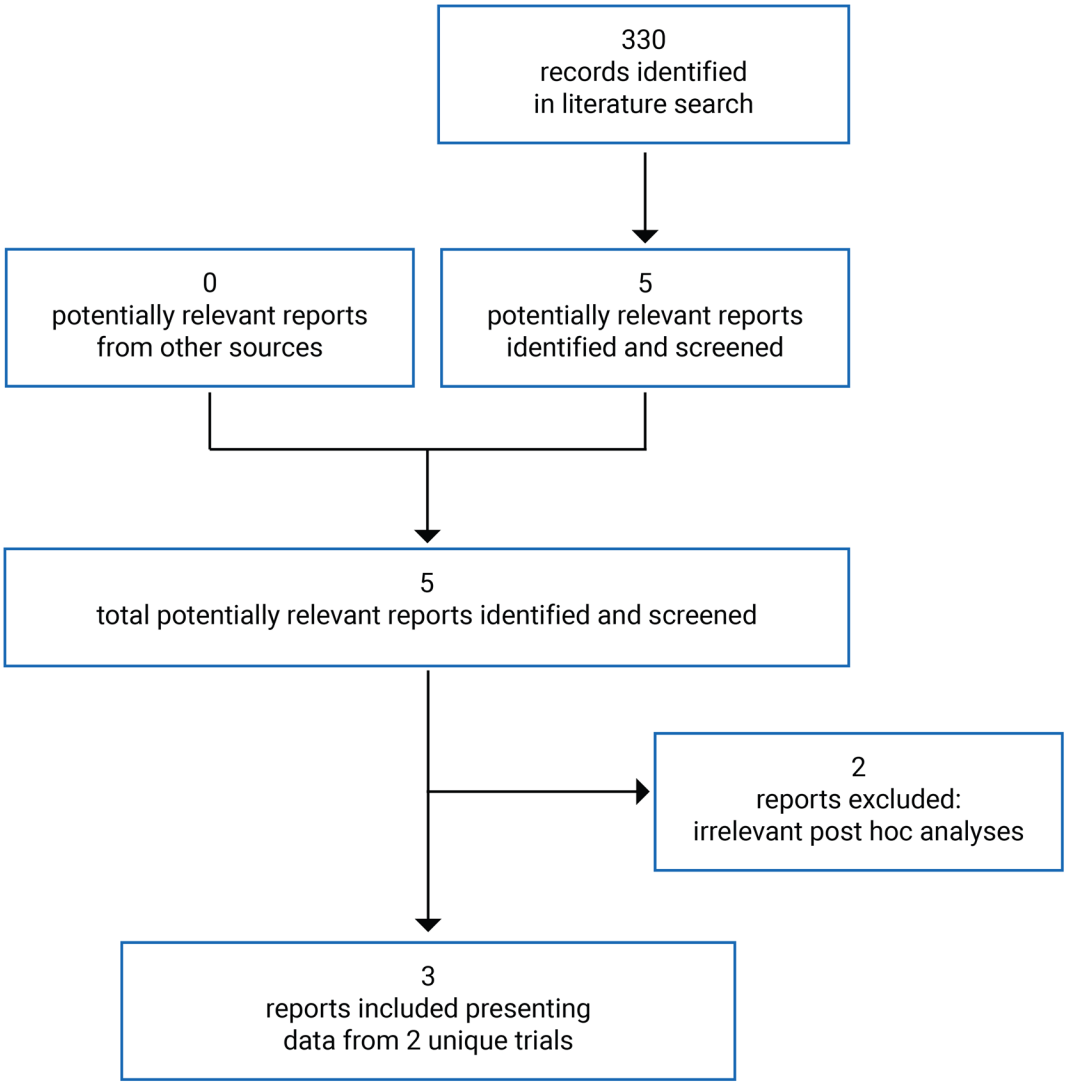
Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews

- Clinical Trials Registries
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 2: Study Selection

Figure 8: Flow Diagram for Inclusion and Exclusion of Studies



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