

Oral corticosteroid-sparing effects of mepolizumab in severe eosinophilic asthma: evidence from randomized controlled trials and real-world studies

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Abstract: Oral corticosteroids (OCS) have long been a mainstay of treatment for asthma exacerbations and chronic severe asthma. However, it is increasingly recognized that both long-term and short-term OCS use are directly associated with a wide range of serious adverse effects, and as such OCS-sparing treatment alternatives are now widely recommended for patients with severe asthma. While several international guidelines recommend these treatments, guidance on OCS tapering, and which patients are most likely to tolerate OCS reduction and/or discontinuation, is still lacking. Several biologics have demonstrated efficacy in patients with OCS-dependent asthma. One OCS-sparing treatment is the anti-interleukin-5 monoclonal antibody mepolizumab, which is approved for the treatment of severe eosinophilic asthma. In addition to improved exacerbation rates, asthma control, quality of life, and lung function among patients with severe eosinophilic asthma, mepolizumab also has an OCS-sparing effect, which has been demonstrated in randomized controlled trials and real-world studies. Both physicians and patients express concerns about the adverse effects of OCS, and additional data from the randomized, controlled SIRIUS trial (NCT01691508) highlight the high level of concern among patients regarding OCS-related burden. In this article, we discuss current guidance on OCS-sparing strategies for patients with severe asthma, provide a summary of the available evidence of the OCS-sparing effect of mepolizumab, and highlight patient and physician perspectives on the use of OCS and OCS-sparing treatments in severe asthma.

Keywords: biologics, eosinophilic asthma, mepolizumab, oral corticosteroids, oral corticosteroid-sparing, tapering

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Introduction

Asthma is a common, heterogeneous respiratory disease, usually characterized by chronic airway inflammation.^{1,2} The goal of asthma treatment is to minimize the manifestations of asthma by appropriate therapeutic intervention, which hinges on the intrinsic severity of disease activity, the degree of control achieved, and the ease of controlling disease manifestations.^{3,4} Difficult-to-treat asthma is defined as asthma that is uncontrolled despite prescription of medium- or high-dose

inhaled corticosteroid (ICS) with a second controller [usually long-acting β_2 -agonist (LABA)] or with maintenance oral corticosteroids (OCS), or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.² Severe asthma, which affects around 3–10% of the general asthma population, is a subset of difficult-to-treat asthma defined as asthma uncontrolled despite adherence to maximal, optimized high-dose ICS/LABA therapy and management of contributory factors, or that worsens when

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high-dose treatment is decreased.^{2,5} Compared with mild or moderate asthma, patients with severe asthma have more exacerbations and comorbidities,⁶ which are associated with an elevated risk of morbidity and mortality.^{7,8} Historically, guidelines have recommended escalation to maintenance OCS treatment for severe asthma, if control is not achieved with standard of care.⁹ Reports suggest 20–60% of patients with severe or uncontrolled asthma use long-term OCS therapy, with use more likely in those with the greatest number of exacerbations.^{10,11} Short-term OCS therapy use (i.e. for < 30 days)¹² is more variable, with reports of use in 23–93% of patients with severe or difficult-to-treat asthma, and patients with increasing disease severity were more likely to receive short-term OCS therapy.¹⁰

Maintenance OCS use is associated with a wide range of well-recognized and serious short- and long-term adverse events (AEs), including weight gain, diabetes, osteoporosis, cataracts, hypertension, and adrenal suppression as well as increased risk of mortality.^{2,10,13–22} Psychological AEs, such as depression and anxiety, have also been reported by patients on OCS therapy.²³ Increasing OCS exposure has a statistically significant dose-dependent relationship with the risk of developing either acute or chronic OCS-related complications.^{14,20,24} This risk is also present with OCS exposures as low as ≤ 1 mg/day,^{22,25,26} with each OCS prescription adding a cumulative burden on current and future health, regardless of dose and duration.²⁷ This is particularly pertinent for patients with severe asthma as OCS can also be used to treat comorbidities such as chronic rhinosinusitis with nasal polyps;²⁸ as such, multiple different specialists may be prescribing short-term OCS therapy. Indeed, even short-term OCS use is associated with sleep disturbance and an increased risk of infections, bone fractures, and thromboembolism,¹² and OCS bursts (OCS use for ≤ 14 days) are associated with increased risk of gastrointestinal bleeding, sepsis, and heart failure within a month after treatment initiation.²⁹ Notably, the benefit of reducing long-term OCS may often be countered by an increased need for short-term OCS,³⁰ as any reduction in OCS use must be balanced with the risk of asthma exacerbations requiring rescue therapy. Overall, OCS use is a major contributor to the substantial risk among patients with severe asthma, worsening prognosis and potentially reducing life expectancy.^{23,31,32} As such, the development of strategies to decrease

OCS exposure in patients with severe asthma has been a high priority for several decades, with replacement of OCS with alternative treatments, such as ICS, identified as a goal as early as 1973.^{2,25,33,34}

Several biologic therapies developed for the treatment of severe asthma have been shown to have OCS-sparing effects.^{35–39} One such therapy is mepolizumab, a humanized monoclonal antibody approved in multiple regions worldwide for the treatment of severe eosinophilic asthma,^{40,41} an endophenotype of severe asthma characterized by eosinophilic inflammation and frequent exacerbations.⁴² Mepolizumab is also approved for the treatment of eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and chronic rhinosinusitis with nasal polyps.^{41,43} Mepolizumab binds to and inactivates interleukin 5 (IL-5), thereby blocking the proliferation, activation, and survival of eosinophils, and is associated with a range of clinical benefits in patients with severe eosinophilic asthma.⁴⁴ Notably, prednisolone treatment has also been associated with reduced expression of IL-5 mRNA in bronchial biopsies from patients with asthma.⁴⁵ As such, both OCS and mepolizumab have an anti-IL-5 effect.^{44,46} Here, we discuss current guidance on OCS-sparing strategies for patients with severe asthma, provide a summary of evidence of the OCS-sparing effect of mepolizumab, and highlight patient and physician perspectives on the use of OCS and OCS-sparing treatments in severe asthma.

Current clinical guidelines and patient views on the role of OCS and biologic therapies in severe asthma management

Current guidelines support the need to consider alternative treatment strategies to the use of OCS for patients with severe asthma, and anti-IL-5 therapies, anti-immunoglobulin E (IgE) therapy, and/or anti-IL-4/13 therapies are widely recommended (Table 1). From a patient's perspective, the 2018 OCS Stewardship Statement underscores the urgent need to educate patients and healthcare providers about OCS-associated risks and protect patients from potential OCS overexposure, by suggesting OCS-sparing strategies.²¹ Together with the consistent recommendations in asthma guidelines to reduce OCS use, the Stewardship Statement demonstrates the growing appreciation of the detrimental effects

Table 1. Guideline recommendations for OCS and biologic use for adults with severe asthma.

Recommendations for OCS use		Recommendations for biologic use	
	Biologic	Patient demographic	Recommendation
ERS/ATS 2020 ⁴⁷	Mepolizumab Benralizumab Reslizumab	Patients with severe uncontrolled eosinophilic asthma and those with severe corticosteroid-dependent asthma	Anti-IL-5 strategy recommended as add-on therapy (conditional recommendation ^a)
	Dupilumab	Patients with severe eosinophilic asthma and those with severe corticosteroid-dependent asthma regardless of eosinophil levels	Recommended as add-on therapy (conditional recommendation ^a)
	Omalizumab	Patients with severe allergic asthma	Blood eosinophil count and FeNO should be used to identify patients most likely to benefit from anti-IgE treatment (conditional recommendation)
EAACI 2021 ⁴⁸	Mepolizumab	Patients with uncontrolled severe eosinophilic asthma ^b in spite of controller treatment	Recommended as an add-on therapy to decrease or withdraw OCS (strong recommendation)
	Reslizumab	Patients with uncontrolled severe eosinophilic asthma ^c in spite of controller treatment	No recommendation
	Benralizumab	Patients with uncontrolled severe eosinophilic asthma ^d in spite of optimal controller treatment	Recommended as an add-on therapy to decrease or withdraw OCS (strong recommendation)
	Dupilumab	Patients with uncontrolled severe eosinophilic asthma ^e in spite of optimal controller treatment	Recommended as an add-on therapy to decrease or withdraw OCS in patients on maintenance OCS and high-dose ICS in combination with a second controller (strong recommendation)
	Omalizumab	Patients with uncontrolled severe allergic asthma ^f and adults with severe eosinophilic asthma ^g in spite of controller treatment	Recommended as an add-on therapy to decrease the use of rescue medication (conditional recommendation)
	OCS dose reduction is described as an important asthma-related outcome		

(Continued)

Table 1. (Continued)

Recommendations for OCS use		Recommendations for biologic use	
	Biologic	Patient demographic	Recommendation
NHLBI 2020 ^{a,g,h}	Asthma biologics (e.g. anti-IgE, anti-IL-5, anti-IL-5R, anti-IL-4/IL-13)	Patients on step 5 or 6 ⁱ treatment for asthma	Should be considered (no specific recommendations)
GINA 2021 ²	<p>Anti-IL-5/5-receptor therapy</p> <p>Anti-IL-4 receptor therapy</p> <p>Anti-IgE therapy</p>	<p>Patients with severe eosinophilic asthma that is uncontrolled with step 4–5 treatment</p> <p>Patients with severe eosinophilic asthma that is uncontrolled with step 4–5 treatment</p> <p>Patients with moderate or severe allergic asthma that is uncontrolled with step 4–5 treatment</p>	<p>Recommended as step 5 add-on therapy</p> <p>Recommended as step 5 add-on therapy</p> <p>Recommended as step 5 add-on therapy</p>

AEs, adverse events; ATS, American Thoracic Society; EAACI, European Academy of Allergy and Clinical Immunology; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; NHLBI, National Heart, Lung, and Blood Institute; OCS, oral corticosteroid; ppb, parts per billion; SABA, short-acting beta₂-agonist.

^aPanel were uncertain that the desirable consequences of the intervention outweighed the undesirable consequences based on low-quality evidence or the study populations not uniformly meeting ERS/ATS severe asthma criteria.

^bDetermined by a blood eosinophil count \geq 300 cells/ μ l in the past 12 months, or \geq 150 cells/ μ l at treatment initiation.

^cDefined as inadequately controlled asthma, receiving \geq medium dose of ICS with/without another controller, including OCS, and \geq 1 blood eosinophil count \geq 400 cells/ μ l during a 2-4-week screening.

^dUncontrolled by high-dose ICS + LABA with a baseline blood eosinophil count $>$ 300 cells/ μ l ($>$ 150 cells/ μ l for OCS-dependent patients).

^eUncontrolled by medium-/high-dose ICS plus up to two additional controllers (including OCS), with T2 inflammation characterized by blood eosinophil count $>$ 150 cells/ μ l and/or FeNO levels $>$ 20 ppb.

^fWith a total IgE level of 30–700 IU/ml (US) and 30–1500 IU/ml (EU) \pm one perennial aeroallergen.

^gWith FeNO \geq 24 ppb and blood eosinophil count \geq 260 cells/ μ l.

^hThe systematic review that informed the report did not include studies that examined the role of asthma biologics.

ⁱStep 5: Daily medium-high dose ICS-LABA + LAMA and as-needed SABA; step 6: Daily high-dose ICS-LABA + oral systemic corticosteroids + as-needed SABA.

of both short- and long-term OCS use in patients with severe asthma. As such, strategies to minimize OCS use should be pursued as a high priority.

Strategies for and goals of OCS tapering

While there is broad consensus on the need to minimize OCS use in patients with severe asthma, guidance on the strategies for, and goals of, OCS tapering in this population is lacking. In a recent Delphi world expert consensus, experts agreed that OCS tapering should be attempted in all patients with asthma who are receiving maintenance OCS therapy.⁵⁰ Furthermore, there was almost 80% agreement that OCS cessation should be implemented when there is no evidence of adrenal insufficiency.⁵⁰ The schedule and speed of OCS tapering should be determined by the needs of each individual patient, and based on factors such as duration of previous maintenance OCS, and history and future risk of AEs.⁵⁰ However, the minimum target dose for such tapering remains unclear. The European Academy of Allergy and Clinical Immunology (EAACI) guidelines and the Delphi consensus recommend a minimally important reduction of 50% in OCS dose and failure to achieve this may warrant switching strategies.^{48,50} We suggest that, while not every patient will be able to omit OCS use completely, any reduction in dose or frequency of use should be a treatment goal for patients with severe asthma, with the aim of reducing the daily dose to around physiological levels (i.e. prednisolone equivalent of ≤ 5.0 mg/day).⁵¹ Notably, biologics should play an important role in OCS tapering.⁵⁰

Evidence supporting the OCS-sparing effect of mepolizumab in patients with severe eosinophilic asthma

Mepolizumab has been approved for the treatment of severe eosinophilic asthma since 2015.⁴¹ A wealth of data have now accumulated from randomized controlled trials, supported by a growing body of evidence from real-world studies, which together demonstrate the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma, as well as its OCS-sparing effect (Table 2).

Clinical trial data

SIRIUS (NCT01691508) was the first randomized trial to use a biologic (mepolizumab) to target OCS reduction by reducing eosinophil counts in severe eosinophilic asthma.³⁵ To determine the true minimum OCS dose required for disease control, patients' OCS dose was reduced during an optimization phase before randomization. Following randomization to either mepolizumab 100 mg subcutaneous or placebo, OCS doses were tapered based on a prespecified algorithm if asthma control was maintained and there were no symptoms of adrenal insufficiency. The trial showed significantly greater reductions in maintenance OCS dose in patients receiving mepolizumab *versus* those receiving placebo, independent of patient weight (Table 2), with median daily OCS dose falling by 69% (10.0–3.1mg) at week 24 in the 66 patients in the mepolizumab group who reached week 20–24 of the study (Figure 1). Furthermore, patients treated with mepolizumab had fewer exacerbations and significant improvements in asthma control and quality of life *versus* those on placebo, even with the clinically relevant reduction in OCS dose (Table 2). Notably, the median percentage reduction in daily OCS dose in the SIRIUS placebo arm was 0%. This reduction was in contrast to VENTURE (dupilumab; 50%) and ZONDA (benralizumab; 25%) suggesting a placebo effect in those trials, which needs to be accounted for when considering the reduction in the active treatment arm of these studies.^{37,38} These data demonstrate the effectiveness of the SIRIUS optimization phase in reducing OCS to the lowest effective dose. SIRIUS demonstrated that significant and clinically relevant OCS reductions were possible with mepolizumab not only without a loss of asthma control but with concomitant clinical improvements. Overall, 54% of patients on mepolizumab had a clinically meaningful reduction in their OCS dose ($\geq 50\%$ ^{48,50}) and 14% were able to discontinue OCS therapy in this short-term trial with only a 16-week period of dose reduction;³⁵ however, longer and larger trials were needed to determine the plausibility and long-term effects of complete OCS withdrawal.

Such long-term data were obtained from the COSMOS (NCT01842607) 52-week, open-label extension (OLE) trial,⁵² which enrolled patients with severe eosinophilic asthma who had

Table 2. Design and outcomes of OCS-sparing mepolizumab clinical trials and real-world studies.

Trial/study	Trial/study design	Inclusion criteria for patient population	Patient characteristics at baseline	OCS reduction	Other efficacy outcomes	Safety
Clinical trials						
SIRIUS (N = 135) ³⁵	24-week, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial	Aged ≥ 12 years with asthma; receiving high-dose ICS with a second controller; 6-month history of maintenance treatment with SCS; before study entry: blood eosinophil count ≥ 150 cells/ μ l ^a or ≥ 300 cells/ μ l ^e	Mean age Placebo: 50 years Mepolizumab: 50 years Female Placebo: 45% Mepolizumab: 64% Median daily OCS dose Placebo: 12.5 mg Mepolizumab: 10.0 mg	↓ daily OCS dose ^a OR (95% CI): 2.39 (1.25–4.56); p = 0.008 ≥ 50% ↓ median daily OCS dose ^a ↑ 64% OR (95% CI): 2.26 (1.10–4.65); p = 0.03 % ↓ median daily OCS dose ^a ↑ 50%; p = 0.007 Subgroup analysis according to weight Patients with ≥ 50% ↓ daily OCS dose ^a ≤ 75 kg: ↑ 69% ^b ≥ 75 kg: ↑ 60% ^b	Rate of clinically significant exacerbations/patient/year ^{a,i} 1.44 versus 2.12 (↓ 32%) ^h [RR (95% CI): 0.68 (0.47–0.99)]; p = 0.04 Mean ACO-5 score ^{a,j} ↓ 0.52 points; p = 0.004 Mean SGRQ score ^{a,j} ↓ 5.8 points; p = 0.02 Mean prebronchodilator FEV₁ ^{a,i} ↑ 114 mL; p = 0.15	Any on-treatment AE 83% versus 92% On-treatment serious AE 1% versus 18% AEs leading to treatment discontinuation 4% versus 5%
COSMOS (N = 651) ³²	52-week, multicenter, open-label, phase IIb study	Patients completing the MENSA or SIRIUS studies SIRIUS inclusion criteria See above MENSA inclusion criteria Aged 12–82 years with asthma; receiving high-dose ICS with a second controller; ≥ 2 exacerbations requiring SCS treatment; blood eosinophil count ≥ 150 cells/ μ l ^k or ≥ 300 cells/ μ l ^e	Mean age Previous placebo: 50 years Previous mepolizumab: 52 years Female Previous placebo: 53% Previous mepolizumab: 57%	↓ daily median OCS dose For patients with previous placebo who completed COSMOS (n = 58) SIRIUS: 12.3 mg → 10.0 mg (↓ 19%) ^h COSMOS: → 5.0 mg (↓ 59%) ^h For patients with previous mepolizumab who completed COSMOS (n = 57) SIRIUS: 10.0 mg → 2.5 mg (↓ 75%) ^h COSMOS: → ↓ maintained Patients with OCS discontinuation ⁱ For patients with previous placebo who completed COSMOS (n = 58): 10% → 28% For patients with previous mepolizumab who completed COSMOS (n = 57): 20% → 32%	Patients with on-treatment exacerbations For patients with previous placebo: 51% For patients with previous mepolizumab: 46% Mean ACO-5 score ^m Patients with previous placebo: ↓ 0.30 (1.00) points Patients with previous mepolizumab: ↑ 0.04 (0.96) points Mean prebronchodilator FEV₁ ^m Patients with previous placebo: ↑ 100 mL Patients with previous mepolizumab: ↓ 13 mL	Any on-treatment AE Patients with previous placebo: 84% Patients with previous mepolizumab: 86% On-treatment serious AE Patients with previous placebo: 15% Patients with previous mepolizumab: 14% AEs leading to treatment discontinuation Patients with previous placebo: < 1% Patients with previous mepolizumab: 3%
COSMEX (N = 339) ³³	Multicenter, open-label, 172-week, phase IIb study	Life-threatening or seriously debilitating asthma; receiving ICS; previously demonstrated a protocol-defined clinical benefit from mepolizumab in MENSA, SIRIUS, or COSMOS	Mean age Continued mepolizumab: 53 years Interrupted ^b mepolizumab: 61% Female Continued mepolizumab: 50% Interrupted ^b mepolizumab: 59%	Patients with OCS discontinuation ⁿ Weeks 124–128: 17/38 (45%) Weeks 228–232: 7/12 (58%) Median daily OCS dose ^r Mepolizumab group (n = 7) SIRIUS: 12.5 mg → 2.2 mg (↓ 82%) ^h in weeks 20–24 COSMOS: → 1.3 mg (↓ 90%) ^h in weeks 72–76 COSMEX: → 0.0 mg (↓ 100%) ^h in weeks 228–232	Rate of exacerbations/year ^r (n = 95) MENSA: 3.67 → 0.95 (↓ 77%) ^h at week 32 COSMOS: → 1.05 (↓ 71%) ^h at week 84 COSMEX: → 0.86 (↓ 77%) ^h at week 136 → 0.98 (↓ 73%) ^h at week 188	On-treatment AEs 93% On-treatment serious AEs 25% AEs leading to treatment discontinuation 1%
Real-world studies						
IBM® MarketScan® Commercial claims database study (N = 527) ³⁴	Retrospective cohort study using data from the IBM® MarketScan® Commercial claims database	≥ 12 years of age with asthma; received first mepolizumab dose between November 2015 and September 2017; continuous enrollment with medical and pharmacy benefits during baseline and follow-up periods; ≥ 2 mepolizumab administrations in the first 6 months of follow-up period	Mean age 49 years Female 61% Patients with ≥ 1 OCS claim 93%	Patients with ≥ 1 OCS claim ^v ↓ 15%; p < 0.001 Patients with no OCS use ^v 20.3% versus 28%; p < 0.001 6.6% Mean number of OCS claims per patient ^v 3.9 versus 5.5 (↓ 29%) ^h ; p < 0.001 Mean number of OCS bursts ^{vw} 1.2 versus 1.9 (↓ 37%) ^h ; p < 0.001 Patients with OCS bursts ^{vw} 54% versus 69% (↓ 22%) ^h ; p < 0.001 Patients with OCS use ≥ 5 mg/day 28% versus 42% (↓ 35%) ^h ; p < 0.001	Patients with any asthma exacerbation ^v 59% versus 83% (↓ 28%) ^h ; p < 0.001 Rate of any exacerbations per patient ^v 1.2 versus 2.2 (↓ 46%) ^h ; p < 0.001	Not reported

(Continued)

Table 2. (Continued)

Trial/study	Trial/study design	Inclusion criteria for patient population	Patient characteristics at baseline	OCS reduction	Other efficacy outcomes	Safety
nATU French study (N = 146) ⁵⁵	Retrospective, observational study of data from hospital medical records in France as part of the nATU	Severe eosinophilic asthma (without features of EGPA); received ≥ 1 mepolizumab injection at a nATU participating center	<p>Mean age 58 years</p> <p>Female 45%</p> <p>Patients with current OCS use: 93%</p> <p>Mean daily OCS dose 20.6 mg</p>	<p>Patients with mOCS use^a 12 months: 41% (↓ 56%^b) 24 months: 34% (↓ 63%^b)</p> <p>Mean OCS dose^c 12 months: 8.3 mg (↓ 60%^b) 24 months: 7.8 mg (↓ 62%^b)</p> <p>Patients with OCS discontinuation^d 12 months: 59% 24 months: 65%</p>	<p>Rate of exacerbations/patient/year^e 12 months: 0.8 versus 5.8 (↓ 86%^b) 24 months: ↓ sustained</p> <p>Mean % predicted prebronchodilator FEV₁ and mean FEV₁/FVC ratio^f Steadily increased during the first 10 months of treatment before stabilizing</p> <p>Mean ACT score^g 3 months: ↑ 7.2 points 24 months: ↑ sustained</p>	<p>Pharmacovigilance events 276 events reported by 100 patients; 173 were identified as AEs possibly related to mepolizumab</p> <p>Nonserious AEs 159 events reported in 99 patients</p> <p>Serious AEs Eight patients reported 14 events that were possibly drug-related</p> <p>AEs leading to treatment discontinuation in 41 patients</p>
Australian mepolizumab registry (N = 309) ⁵⁶	Prospective observational study Data were collected prior to mepolizumab treatment initiation (baseline) and during the follow-up ^h period	Severe eosinophilic asthma; undergoing mepolizumab therapy; treatment with daily OCS ⁱ or a cumulative dose of ≥ 0.5 g ^e	<p>Mean age 60 years</p> <p>Female 58%</p> <p>Patients with mOCS use 48%</p> <p>Patients with ≥ 1 OCS burst^{e,z} 96%</p> <p>Patients with any OCS use 97%</p> <p>Cumulative dose of ≥ 1 g^e 68%</p>	<p>Patients receiving mOCS therapy^y 12 months: 55% (↓ 46%^b); p < 0.001</p> <p>Patients with OCS bursts^{z,ab} 12 months: 50% (↓ 48%^b); p < 0.001</p> <p>Patients with any OCS use^y 12 months: 67% (↓ 31%^b); p < 0.001</p> <p>Median daily OCS dose^y 12 months: 2.0 mg versus 10 mg (↓ 80%^b); p < 0.001</p> <p>Patients with OCS discontinuation almost half</p>	<p>Not reported</p>	<p>Not reported</p>
Greek study (N = 70) ⁵⁷	Prospective, multicenter, observational study Data were collected prior to mepolizumab initiation (baseline) and during the follow-up ^h period	Severe eosinophilic asthma newly initiating mepolizumab	<p>Mean age 55 years</p> <p>Female 69%</p> <p>Median daily mOCS dose 10 mg</p>	<p>Patients with OCS discontinuation^y 4 months: 20% 8 months: 30%</p> <p>Median daily OCS dose^y 4.5 mg versus 10.1 mg (↓ 56%^b); p < 0.0001</p>	<p>Rate of exacerbations/year^v 1.2 versus 4.3 (↓ 70%^b); p < 0.0001</p> <p>Mean ACT score^v ↑ 4.9 points p < 0.0001</p> <p>Mean FEV₁, % predicted^v 74.3% versus 67.3% (↑ 10.4%^b); p < 0.0001</p> <p>Mean FEV₁/FVC^v 67.0% versus 63.5% (↑ 5.2%^b); p < 0.01</p>	<p>AEs 27%</p> <p>Severe AEs none</p> <p>AEs leading to treatment discontinuation < 1% (one patient)</p>
UK study (N = 99) ⁵⁸	Retrospective study using data from a regional tertiary asthma center Data were collected prior to mepolizumab initiation (baseline) and at routine visits during the follow-up ^h period	Severe asthma ^{a,h} ; had ≥ 16 weeks of mepolizumab therapy; had ≥ 4 exacerbations ^{a,ab} and/or were receiving mOCS ⁱ ; blood eosinophil count ≥ 300 cells/ μ l ^e	<p>Mean age 54 years</p> <p>Female 53%</p> <p>Patients with mOCS use 69%</p> <p>Median daily mOCS dose 10 mg</p>	<p>Median daily OCS dose^v 0 mg versus 10 mg (↓ 100%^b); p < 0.001</p> <p>Patients with OCS discontinuation^y 57%</p> <p>Patients with ≥ 50% ↓ in mOCS dose^y 75%</p>	<p>Rate of exacerbations/year^v 1.9 versus 4.0 (↓ 54%^b); p < 0.001</p> <p>Mean ACO-6^v 2.2 versus 2.7 (↓ 19%^b); p < 0.001</p> <p>Mean FEV₁, % predicted^v 63.2% versus 64.7% (↓ 2%^b); p = 0.438</p>	<p>Not reported</p>

(Continued)

Table 2. (Continued)

Trial/study	Trial/study design	Inclusion criteria for patient population	Patient characteristics at baseline	OCS reduction	Other efficacy outcomes	Safety
Italian study (Bagnasco <i>et al.</i>) (N=138) ⁵⁹	Retrospective study of data from 11 severe asthma centers. Data were collected prior to mepolizumab initiation (baseline) and during the follow-up ^v period.	Severe uncontrolled asthma ^{ai} ; had ≥ 12 months of mepolizumab therapy; received maximum dose of inhaled treatments and minimum OCS dose required to maintain symptom control; blood eosinophil count > 300 cells/ μ l ^e or > 150 cells/ μ l ^{ad}	Mean age 58 years Female 57% Mean daily mOCS dose 10.1 mg	Patients with OCS-dependence^v 28% versus 80% (↓ 65% ^{ae} ; p<0.0001) Mean daily OCS dose^v 2.0 mg versus 10.1 mg (↓ 80%); p<0.0001 Subgroup analysis according to baseline blood eosinophil count Mean daily OCS dose^v < 500 cells/ μ l: 2.6 mg versus 10.5 mg (↓ 75% ^h) > 500 cells/ μ l: 1.8 mg versus 10.0 mg (↓ 82% ^h)	Rate of exacerbations/year^v 0.7 versus 3.8 (↓ 82% ^{af}); p<0.0001 Mean FEV₁ % predicted^v 75% versus 69% (↑ 8% ^h); p<0.0001 Mean FEV₁/FVC^v 0.69 versus 0.65 (↑ 6%); p=0.002 Mean ACT^v 22 versus 17 (↑ 23% ^{aj}); p<0.0001	AEs 10%
Italian study (Sposato <i>et al.</i>) (N=134) ⁶⁰	Retrospective study using data from 20 severe asthma centers. Data were collected prior to mepolizumab initiation (baseline) and during the follow-up ^{ah} period.	Severe asthma ^{ai} ; ≥ 6 months of mepolizumab therapy; received maximum dose of inhaled treatments ^{ai} ; blood eosinophil count > 300 cells/ μ l ^e or > 150 cells/ μ l ^{ad}	Mean age 58 years Female 54% Patients with mOCS use 74%	Patients with OCS-dependence^v 43% versus 74% (↓ 42% ^h); p<0.0001 Patients with ↓ in OCS dose^v 46%	Mean number of exacerbations^v 1.9 versus 3.8 (↓ 50% ^h); p<0.0001 Mean FEV₁^v 780 ml versus 720 ml (↑ 8% ^h); p<0.0001 Mean ACT^v 20.5 versus 14.2 (↑ 31% ^h); p<0.0001	Not reported
REDES Spanish study (N=318) ⁶¹	Retrospective, multicenter, observational study. Data collected from asthma units in Spain during the baseline ^e and follow-up ^v periods.	≥ 18 years of age; severe uncontrolled eosinophilic asthma; ≥ 12 months of data following mepolizumab initiation ^{ai} ; medical records spanning the baseline period	Mean age 57 years Female 69% Median daily mOCS dose 10.0 mg Patients with mOCS use 31%	Median daily mOCS dose^v 2.3 mg versus 10.0 mg (↓ 60% ^h) Patients with daily mOCS use ≥ 7.5 mg ^v 29% versus 57% (↓ 49% ^h) Patients with mOCS discontinuation^v 48%	Rate of clinically significant exacerbations/year^{iv} 1.0 versus 4.5 (↓ 78%); p<0.001 Mean FEV₁ % predicted^v 82.3% versus 76.3% (↑ 7% ^h) Mean ACT^v 20.8 versus 14.1 (↑ 32% ^h); p<0.0001	Treatment-related AE 3% Treatment-related serious AE None
REALITI-A study, early initiators (N=368) ⁶²	Global, prospective, single-arm, observational cohort study. Data collected for baseline ^{ae} and follow-up ^{ah} periods.	≥ 18 years of age with asthma; newly prescribed mepolizumab treatment in the real world (physician decision); relevant medical records during the baseline period ^{dk}	Mean age 53 years Female 62% Patients with mOCS use 48% Median daily mOCS dose 10.0 mg Patients with baseline blood eosinophil count < 150 cells/ μ l: 14% ≥ 150 to < 300 cells/ μ l: 13% ≥ 300 cells/ μ l: 73%	Median daily OCS dose^v 5.0 mg versus 10.0 mg (↓ 50% ^h) Patients with OCS discontinuation^{ai} , 34% Subgroup analysis according to baseline blood eosinophil count Median daily OCS dose^v < 150 cells/ μ l: 6.5 mg versus 12.8 mg (↓ 49% ^h) ≥ 150 to < 300 cells/ μ l: 5.0 mg versus 11.3 mg (↓ 56% ^h) ≥ 300 cells/ μ l: 2.5 mg versus 9.8 mg (↓ 74% ^h)	Rate of clinically significant asthma exacerbations^{iv} 4.63 versus 1.43 (↓ 69% ^h) [RR (95% CI): 0.31 (0.27–0.35)]; p<0.001 On-treatment treatment-related serious AEs < 1% AEs leading to treatment discontinuation 2%	On-treatment treatment-related AEs 14% On-treatment treatment-related serious AEs < 1% AEs leading to treatment discontinuation 2%
REALITI-A study, full population at 1 year (N=822) ^{63,64}			Age 54 years Female 63% Patients with mOCS use 39% Subgroup analysis according to mOCS use at baseline Patients with mOCS use < 10 mg/day: 47% ≥ 10 mg/day: 53%	Median daily OCS dose^v < 10 mg/day mOCS at baseline: 5.0 mg versus 0.36 mg (↓ 93% ^h) ≥ 10 mg/day mOCS at baseline: 12.9 mg versus 5.0 mg (↓ 61% ^h) Patients with OCS discontinuation^{ai} ≥ 10 mg/day mOCS at baseline: 49% ≥ 10 mg/day mOCS at baseline: 36%	Rate of clinically significant exacerbations/year^{iv} 4.3 versus 1.2 (↓ 71% ^h) [RR (95% CI): 0.29 (0.26–0.32)]	On-treatment treatment-related AEs No mOCS at baseline: 9% mOCS use at baseline: 13% On-treatment treatment-related serious AEs < 1% in both no mOCS at baseline & mOCS use at baseline groups

(Continued)

Table 2. (Continued)

Trial/study	Trial/study design	Inclusion criteria for patient population	Patient characteristics at baseline	OCS reduction	Other efficacy outcomes	Safety
Systematic review of studies reporting acute exacerbation and/or hospitalization data (N = 1457) ⁶⁵	Systematic review and meta-analysis including 13 observational studies Data collected before mepolizumab treatment (baseline) and during the follow-up ⁿ period	Severe eosinophilic asthma; exposed to mepolizumab	Mean age 50 years Female 58%	Patients with OCS use^v 6 months: 38% versus 61% (↓ 38%) OR (95% CI): 0.29 (0.17–0.50) 12 months: 26% versus 59% (↓ 56%) OR (95% CI): 0.19 (0.10–0.37) OCS dose^v 6 months: ↓ 9.0 mg SMD 0.90 12 months: ↓ 7.7 mg SMD 0.77	Mean number of exacerbations/patient/year^v 6 months: ↓ 2.92 SMD 1.39 12 months: ↓ 2.73 SMD 1.23 Mean ACO score^v 6 months: ↓ 1.3 points SMD 1.15 12 months: ↓ 1.0 points SMD 0.84 Mean ACT^v 6–12 months ↑ 6.52 points SMD 1.83 Mean FEV₁^v 1–3 months: ↑ 230 ml SMD 0.29 6–12 months: ↑ 230 ml SMD 0.30	AEs Reported for individual studies only

ACO, Asthma Control Questionnaire; ACT, Asthma Control Test; AE, adverse event; ATS, American Thoracic Society; CI, confidence interval; EGPA, eosinophilic granulomatosis with polyangiitis; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; mOCS, maintenance OCS; nATU, nominative autorisation temporaire d'utilisation [temporary use authorization]; OCS, oral corticosteroid; OR, odds ratio; RR, rate ratio; SC, subcutaneous; SCS, systemic corticosteroids; SD, standard deviation; SMD, standardized mean difference.

^aOCS dose reduced weekly until exacerbation or ≥ 0.5-point increase in ACO-5 score.

^bOCS dose reduced according to a prespecified schedule by 1.25–10 mg per day every 4 weeks.

^c5–35 mg per day (prednisone equivalent).

^dDuring the optimization phase.

^eDuring the previous year.

^fAt week 20–24 versus the dose determined during the optimization phase.

^gMepolizumab versus placebo.

^hRelative change.

ⁱClinically significant exacerbations were defined as the worsening of asthma requiring systemic corticosteroids for ≥ 3 days (or a doubling (or more) of the existing mOCS dose for ≥ 3 days if patients were on mOCS) or an ED visit or hospital admission.

^kAt week 24 versus baseline.

^lAt screening.

^mBetween commencing COSMOS and week 48 and 52 of COSMOS.

ⁿAt week 52 of COSMOS versus baseline.

^oLife-threatening asthma was defined as ≥ 1 of: history of ≥ 1 intubation during their lifetime, ≥ 1 hospitalization for asthma exacerbation in the 12 months before MENSA or SIRIUS screening, ≥ 3 exacerbations in the 12 months before MENSA screening, an optimized OCS dose (prednisone equivalent) of ≥ 10 mg at SIRIUS randomization. Seriously debilitating asthma was defined as percent predicted FEV₁ of ≤ 80% at randomization for MENSA or SIRIUS and either an ACO-5 score ≥ 3 or an SGRO total score ≥ 80 at MENSA or SIRIUS randomization.

^p≥ 500 µg/day fluticasone propionate equivalent for the previous 8 months.

^qInterrupted subjects were those who had not received mepolizumab in the ≥ 90 days between the end of COSMOS and COSMEX enrollment.

^rIn patients with continuous reporting across SIRIUS, COSMOS, and COSMEX by the week specified.

^sIn the seven patients, 232 weeks of continuous reporting with mepolizumab 100 mg SC across SIRIUS, COSMOS and COSMEX with ≤ 12 weeks between the last dose in COSMOS and the first dose in COSMEX.

^tIn 95 patients with ≥ 188 weeks of continuous reporting across MENSA, COSMOS, and COSMEX.

^u12 months pre-mepolizumab treatment.

^v12 months post-mepolizumab treatment.

^wFollow-up versus baseline.

^x≥ 20 mg prednisone equivalent for a duration of 3–28 days.

^y3-, 6-, and 12-month following mepolizumab treatment initiation.

^zFor ≥ 6 weeks.

^{aa}Defined as short-term OCS exposure assumed as 250 mg.

^{ab}According to the definition provided by the International ERS/ATS guidelines on definition, evaluation, and treatment of severe asthma.⁵

^{ac}Exacerbations were defined as a worsening in asthma control that required ≥ 3 days of OCS (or a doubling or more of OCS dose if already taking mOCS).

^{ad}Criteria set out by the National Institute for Health and Care Excellence, UK.

^{ae}At mepolizumab initiation.

^{af}Study publication reports 66%; relative reduction calculated for Table 2.

^{ag}Study publication reports 81%; relative reduction calculated for Table 2.

^{ah}Study publication reports 34%; relative reduction calculated for Table 2.

^{ai}Approximately 11 months following mepolizumab initiation.

^{aj}In accordance with the 2016 Global Initiative for Asthma report.

^{ak}Regardless of mepolizumab treatment continuation at the point of data collection.

^{al}1 year prior to study enrollment plus a variable length run-in period between study enrollment and mepolizumab treatment initiation.

^{am}Up to week 56 following mepolizumab treatment initiation.

^{an}While-on-treatment and for treatment discontinuation.

^{ao}Between 3–36 months following mepolizumab treatment initiation.

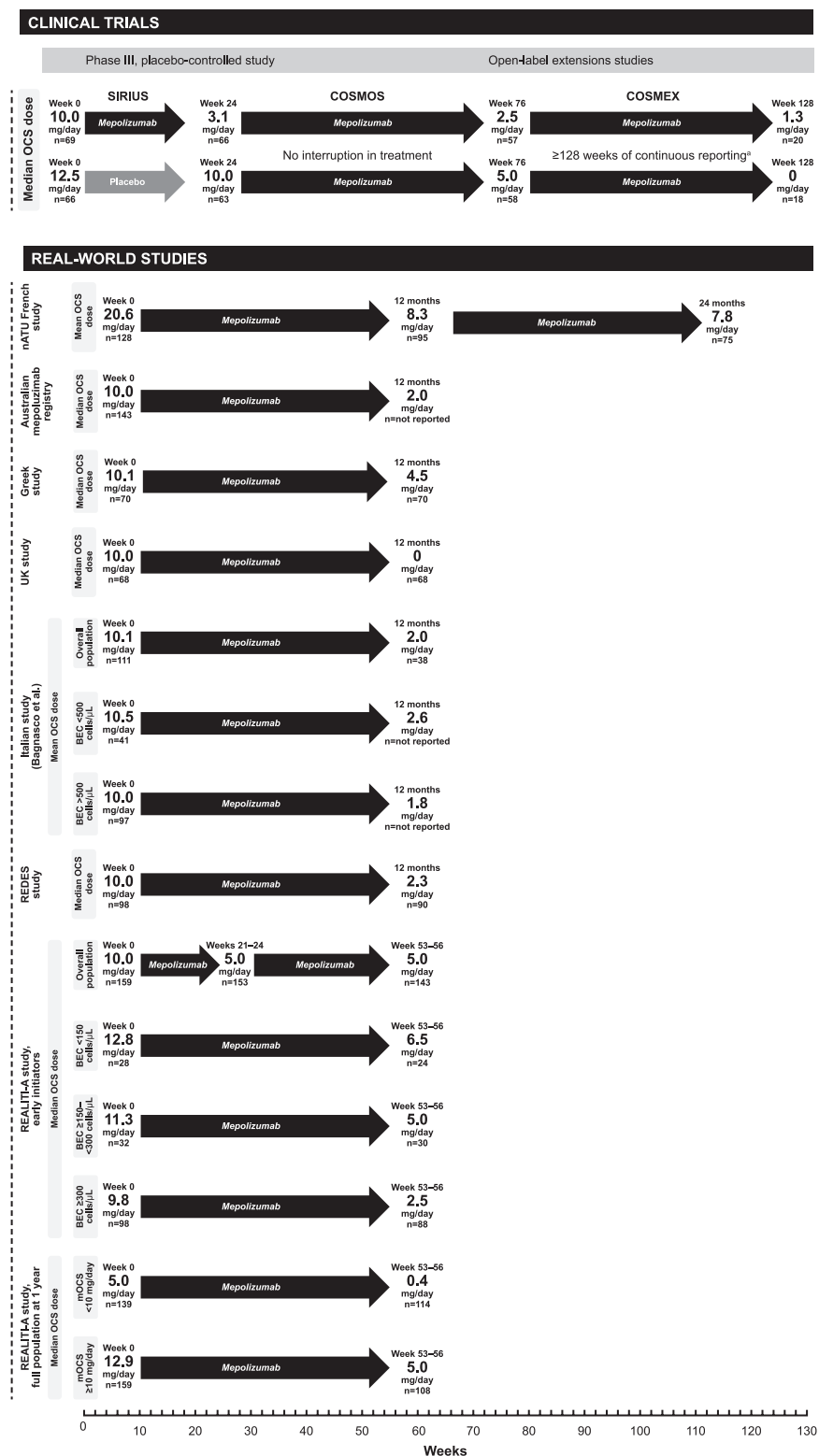


Figure 1. OCS dose reductions in clinical trials and real-world studies.

BEC, blood eosinophil count; mOCS, maintenance OCS; nATU, nominative autorisation temporaire d'utilisation [temporary use authorization]; OCS, oral corticosteroid.

^aOf 73 patients enrolled from the SIRIUS feeder study, 38 patients had \leq 12 weeks gap in treatment between COSMOS and COSMEX and data available up to week 128.

previously received mepolizumab or placebo in the MENSA⁶⁶ or SIRIUS³⁵ trials (Table 2). In contrast to the protocol-defined OCS reduction schedule in SIRIUS, OCS tapering in COSMOS was at the discretion of the physician. The median daily OCS dose achieved with mepolizumab during SIRIUS was further reduced among patients who completed the open-label period of COSMOS (Figure 1). In addition, by weeks 48 to 52 of COSMOS, a further 18% of patients previously on placebo and 12% of patients previously on mepolizumab were no longer receiving OCS treatment *versus* the beginning of the COSMOS trial (Table 2). These results further supported a clinically meaningful mepolizumab-induced OCS dose reduction in SIRIUS, indicated a durable and stable effect over time, and highlighted that OCS discontinuation is not possible in all patients. Importantly, as OCS reduction was based on physician judgment and as the trial was open label, the dose reductions seen may better reflect what could be achieved in clinical practice *versus* those seen during SIRIUS.

Further evidence on the long-term OCS-sparing effects of mepolizumab was obtained from the 172-week OLE COSMEX (NCT02135692) trial. COSMEX enrolled patients from COSMOS who had been assessed as having protocol-defined life-threatening or seriously debilitating asthma before entry into their first mepolizumab trial (Table 2) and patients remained in COSMEX until they could begin commercially available mepolizumab in their participating country.⁵³ As such, the duration of follow-up varied. While the main aim of this trial was to assess the long-term safety and efficacy of mepolizumab in patients with the most severe eosinophilic asthma, daily OCS use was assessed as a secondary endpoint. Among 38 patients (placebo, $n = 18$; mepolizumab, $n = 20$ in the initial SIRIUS study) with ≥ 128 weeks of continuous reporting across SIRIUS, COSMOS, and COSMEX and ≤ 12 weeks between their last COSMOS dose and first COSMEX dose, there was a sustained reduction in daily OCS dose (Table 2 and Figure 1). In addition, 17/38 (45%) patients were able to discontinue OCS use during COSMEX. These data support the use of mepolizumab as a long-term, effective OCS-sparing treatment choice and suggest that there is potential for a slow progressive tapering of OCS therapy with long-term mepolizumab, even in those with the most severe asthma.

Real-world data

Initial real-world evidence on the OCS-sparing effect of mepolizumab came from a retrospective cohort study conducted between 2015 and 2017 [GSK ID: 209642 (HO-19-19597)],⁵⁴ which assessed outcomes in the 12 months following *versus* the 12 months before mepolizumab initiation (Table 2). The OCS-sparing effect of mepolizumab was demonstrated by a reduced proportion of patients with ≥ 1 OCS claim, a lower mean number of OCS bursts, and a lower proportion of patients with chronic OCS use (Table 2). Furthermore, the proportion of patients discontinuing OCS increased by 14% between pretreatment and follow-up ($p < 0.001$) (Table 2).

Reductions in OCS use were also shown in a retrospective, observational study conducted in 2015–2016 in France [nATU; GSK ID: 207943 (HO-17-18317)].⁵⁵ Data from patients with severe eosinophilic asthma were collected for 24 months following mepolizumab initiation. Notably, while 93% of patients were using OCS at baseline, there was a 62% reduction in the proportion of patients using OCS following 24 months of mepolizumab treatment (Table 2). Patients who still required OCS during follow-up needed lower doses at month 24 *versus* baseline (mean: 7.8 mg/day *versus* 20.6 mg/day)⁵⁵ and these lower OCS doses were consistent with those reported for corticosteroid replacement for adrenal insufficiency.⁶⁷ As seen in the clinical trials, reductions in OCS use were accompanied by improvements in exacerbation rate, lung function, and asthma control (Table 2).

Several other regional real-world studies, conducted across Australia, Greece, United Kingdom, Italy, and Spain also showed the OCS-sparing effect of mepolizumab in patients with severe eosinophilic asthma (Table 2).^{56–61} In addition, the Australian study identified baseline predictors of OCS discontinuation after 6 months of mepolizumab treatment. These were lower body mass index (BMI) [odds ratio (95% confidence interval): 0.93 (0.87–0.98); $p = 0.009$], late-onset asthma [1.03 (1.01–1.05); $p = 0.010$], and a lower Asthma Control Test score [1.11 (1.01–1.22); $p = 0.028$].⁵⁶

REALITI-A is the largest 24-month, prospective, international, observational study (GSK ID: 204710), which collected data from routine health-care visits from patients with asthma enrolled

between December 2016 and October 2019.⁶² The data from the early trial initiators ($N=368$) showed a 50% reduction in the median daily maintenance OCS dose following mepolizumab treatment at 1 year (Figure 1); similar reductions were also seen across baseline blood eosinophil subgroups (Figure 1 and Table 2). Using data from the full study population at 1 year ($N=822$), a subgroup analysis by baseline maintenance OCS dose thresholds showed that, following mepolizumab treatment, a 93% reduction in median daily OCS dose was observed in patients with a baseline maintenance OCS dose < 10 mg/day, with 49% of these patients discontinuing OCS use (Figure 1 and Table 2).

Together these studies demonstrated that the OCS-sparing effects of mepolizumab seen in clinical trials were extended to a real-world clinical setting. Indeed, a recent systematic literature review of 13 real-world studies showed that patients were much less likely to require OCS following 6 or 12 months of mepolizumab treatment; OCS doses were significantly decreased after 6 (9.0 mg reduction) and 12 months (7.7 mg reduction) of treatment (Table 2).⁶⁵ Further information on the use of biomarkers to predict the likelihood of OCS reduction in individual patients is needed; additional work should focus on facilitating tailored and optimized OCS tapering among patients with severe asthma.

Lessons from OCS-sparing trials and real-world data

Phase III, controlled studies assessing formal OCS reduction with mepolizumab are limited to SIRIUS; however, a much greater wealth of data spanning a longer time period are available from extension and real-world studies. The real-world data have been collated in clinically relevant settings in which OCS reductions are likely to have been tailored to individual patients rather than being conducted based on formal algorithms. Together with the data from SIRIUS, the real-world studies to date have demonstrated sustained OCS-sparing effects with mepolizumab that span a range of patients with differing clinical characteristics and disease severities, providing important information for clinicians managing patients with severe disease. The studies also demonstrate that complete OCS discontinuation is not possible in all patients, but clinically meaningful reductions can often be achieved. While it is recognized

that adrenal insufficiency can contribute to the need for maintenance of OCS therapy among patients with severe asthma,⁵⁰ further information on the characteristics of those without adrenal insufficiency who are most likely to be able to discontinue OCS would be clinically useful. The Australian mepolizumab registry study⁵⁶ associated lower BMI and optimized asthma control with a greater likelihood of discontinuing OCS use in clinical practice, although these characteristics may also indicate less severe disease where OCS treatment is less widely utilized. However, the characteristics of patients most likely to tolerate OCS discontinuation require further investigation. Importantly, as mepolizumab was the first approved anti-eosinophilic biologic with proven OCS-sparing capabilities, it is likely that in real-world practice, patients with the most severe disease and the longest duration of OCS therapy would have been initiated on mepolizumab. This should be considered when interpreting these real-world outcomes.

OCS-sparing treatments at the patient and physician level

To date, there has been little focus on the direct impact of OCS reductions on a patient level. Furthermore, the concerns of healthcare professionals relating to OCS use, such as maintaining asthma control and reducing AE burden, are also important considerations. Additional data from SIRIUS provide insights into the burden of worry associated with OCS use among patients and the burden of OCS-related AEs in this population.

OCS use from the patient's perspective

The real-world benefit of OCS reduction on patient's perception on quality of life has been demonstrated in patients who have discontinued OCS use following biologic treatment; these improvements in quality of life were paralleled by progressive mood improvements over time.⁶⁸ During SIRIUS, patients completed a Steroid Perception Questionnaire (Supplementary materials), which assessed the levels of concern ('worry') regarding daily OCS use. Responses showed that a high proportion of patients were 'very worried' or 'extremely worried' about OCS side effects, including cataracts, bone fracture, and weight gain, both prior to and following 24 weeks of treatment (Table 3), emphasizing the importance of minimizing OCS use at a patient level. In addition, at baseline,

Table 3. High level of worry responses^a in the Steroid Perception Questionnaire at baseline and week 24 (ITT population).

Worry relating to steroid side effect, <i>n</i> (%)	Baseline		Week 24	
	Mepolizumab 100 mg SC (<i>n</i> = 69)	Placebo (<i>n</i> = 66)	Mepolizumab 100 mg SC (<i>n</i> = 69)	Placebo (<i>n</i> = 66) ^b
Cataracts or eye problems	40 (58.0)	25 (37.9)	36 (52.2)	29 (45.3)
Weak/easy to break bones	35 (50.7)	29 (43.9)	34 (49.3)	30 (46.9)
Weight gain	30 (43.5)	33 (50.0)	29 (42.0)	28 (43.8)
Diabetes	25 (36.2)	25 (37.9)	27 (39.1)	29 (45.3)
Muscle weakness	27 (39.1)	17 (25.8)	25 (36.2)	21 (32.8)
High blood pressure	23 (33.3)	18 (27.3)	22 (31.9)	22 (34.4)
Thinning skin/stretch marks	27 (39.1)	13 (19.7)	27 (39.1)	19 (29.7)
Bleeding stomach or intestines	19 (27.5)	18 (27.3)	20 (29.0)	22 (34.4)
Change in mood	20 (29.0)	17 (25.8)	17 (24.6)	20 (31.3)
Trouble sleeping	20 (29.0)	15 (22.7)	14 (20.3)	18 (28.1)
Infection	19 (27.5)	15 (22.7)	20 (29.0)	22 (34.4)

ITT, intent-to-treat; SC, subcutaneous.

^aResponses were 'very worried' or 'extremely worried'.

^bSixty-four patients had data available at week 24.

112/134 (84%) patients reported that they were worried about the side effects of long-term OCS use and 85/134 (63%) patients had talked with their physician regarding their concerns surrounding OCS use. These findings align with recent literature reviews that highlighted a wide range of OCS-related side effects, even with brief exposure to OCS, and these side effects worried patients.^{22,69} Furthermore, patients had low levels of satisfaction with the information provided by healthcare professionals regarding OCS-related side effects. Overall, these factors contributed to high levels of poor OCS treatment adherence.⁶⁹

OCS use from the physician's perspective

Of great clinical interest are the trial outcomes assessing patients who were able to reduce their OCS usage by $\geq 50\%$ or discontinue completely *versus* those who continued OCS alongside their study treatment. These data will provide information for physicians regarding the likelihood of patients tolerating OCS reduction or discontinuation.

In the SIRIUS trial, evaluation of asthma control in patients who were not able to decrease OCS was difficult to assess, as reducing OCS dose was dependent on maintaining asthma control. Nonetheless, between weeks 0 and 4, during which time OCS use was stable, an improvement in asthma control was achieved with mepolizumab *versus* placebo (least squares mean change in ACQ-5 score: -0.47 *versus* 0.02 ; treatment difference: -0.49 ; $p < 0.001$) and this improvement was maintained for the duration of the study. Further analysis of clinical trial outcomes according to OCS reduction will be useful and may provide valuable clinical information regarding the effect of OCS tapering on disease control.

On-treatment AEs potentially related to OCS use were reported in 27/135 (20%) patients during SIRIUS (Table 4). Information on the timing of these AEs in relation to OCS dose reduction and whether they led to discontinuation was not available; collation of these details would be useful in any future work. One of the most common steroid-related medical conditions experienced by

Table 4. Summary of on-treatment AEs potentially associated with OCS toxicity in the SIRIUS trial (ITT population).

Preferred term, n (%)	Mepolizumab 100 mg SC (n=69)	Placebo (n=66)
Any event	17 (25)	10 (15)
Insomnia	3 (4)	1 (2)
Anxiety	2 (3)	0 (0)
Cataract	1 (1)	1 (2)
Contusion	1 (1)	1 (2)
Gastritis erosive	2 (3)	0 (0)
Hypertension	1 (1)	1 (2)
Oral candidiasis	0 (0)	2 (3)
Sleep disorder	2 (3)	0 (0)
Affective disorder	1 (1)	0 (0)
Blood glucose increased	0 (0)	1 (2)
Candida infection	0 (0)	1 (2)
Cushingoid	1 (1)	0 (0)
Depressive symptoms	1 (1)	0 (0)
Foot fracture	1 (1)	0 (0)
Genital infection fungal	0 (0)	1 (2)
Hyperglycemia	1 (1)	0 (0)
Mood altered	0 (0)	1 (2)
Osteonecrosis	1 (1)	0 (0)
Stress fracture	1 (1)	0 (0)
Tibia fracture	1 (1)	0 (0)
Vulvovaginal mycotic infection	0 (0)	1 (2)

AE, adverse event; ITT, intent-to-treat; OCS, oral corticosteroid; SC, subcutaneous.

patients at enrollment into the SIRIUS study included weight gain. Despite this, patients experienced minimal mean change in weight in the mepolizumab (0.2 kg) or placebo (−0.6 kg) groups from baseline to week 24. These data highlight the concern surrounding OCS use among patients with severe asthma and add to the existing reports of AE burden associated with OCS use.^{2,10,13–21} Together, this evidence supports the goal of reducing, or discontinuing where possible, OCS treatment in this population and

further emphasizes the need for OCS-sparing treatment alternatives such as mepolizumab.

Future directions and important unanswered questions

While the success of OCS tapering and the associated benefits have been demonstrated in mepolizumab trials and real-world settings, there are some important avenues of further investigation to ensure that reducing OCS use is widely achievable. Importantly, OCS tapering should be attempted in all patients with asthma receiving maintenance OCS therapy and any attempted reduction in OCS should be tailored to individual patients to ensure safety and optimize effectiveness.⁵⁰ However, as evidenced in the SIRIUS study,³⁵ OCS discontinuation is not always achievable. As such, information regarding the clinical characteristics of patients most likely to tolerate OCS dose reduction would be useful. There is some evidence that patients with high baseline doses of OCS and those who have received OCS treatment for ≥ 1 year achieve smaller OCS dose reductions than patients who are not in these categories.⁷⁰ Furthermore, clinical factors such as adrenal insufficiency, suboptimal treatment guideline adherence, the presence of eosinophilic granulomatosis with polyangiitis, under-recognition of the cumulative burden of OCS, and the lack of a standardized approach for OCS tapering can hamper OCS reduction.^{47,50,71} Likewise, patients with a non-type 2 asthma endotype may be refractory to OCS treatment and are unlikely to benefit from biologics that target components of the type 2 pathway.⁷² It would be interesting to assess the size of the impact of adrenal insufficiency on the OCS-sparing effect of mepolizumab in real-world populations. The development of treatment guidelines that shepherd tailored and effective OCS dose tapering^{73,74} after biologic therapy initiation is a priority and more formal algorithms that assess adrenal insufficiency as part of the OCS reduction protocol have been developed.⁷¹ However, even with prolonged attempts to reduce OCS, it is apparent that not all biologic add-on therapy in severe asthma is effective in enabling a dose reduction in OCS therapy.^{35,37,75}

It will also be important to determine whether any OCS reductions achieved during biologic therapy use are sufficient to prevent or at least decrease the incidence of OCS-related AEs; studies to evaluate this are beginning.⁷⁶ Finally, it will

be important to determine whether the OCS-sparing effect of mepolizumab extends to other eosinophilic diseases, such as eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and chronic rhinosinusitis with nasal polyps, in which the clinical benefits of mepolizumab have already been shown.

Conclusions

In both randomized clinical trials and real-world studies, mepolizumab therapy resulted in clinically significant reductions in maintenance OCS use that were associated with clinical benefits in patients with severe eosinophilic asthma. Use of mepolizumab to reduce OCS dose may mitigate the major adverse health consequences associated with OCS use in patients with severe asthma. The OCS-sparing effect of mepolizumab should be considered when selecting treatment options for patients with severe asthma. While treatment guidelines provide recommendations for tapering OCS dose in patients with severe asthma, the potential adverse effects experienced during tapering must be monitored and further guidance on tapering strategies should be developed as a priority.

Declarations

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Not applicable.

Consent for publication

Not applicable.

Author contributions

Thomas B. Casale: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

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Arnaud Bourdin: Formal analysis; Methodology; Writing – review & editing.

Peter Howarth: Formal analysis; Methodology; Writing – review & editing.

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Availability of data and materials

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Supplemental material

Supplemental material for this article is available online.

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