

Reslizumab in Eosinophilic Asthma: A Review

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Abstract Reslizumab (Cinqaero[®]; Cinqair[®]) is a humanized monoclonal antibody against interleukin-5 (IL-5), a cytokine mediator of eosinophilic airway inflammation. Reslizumab is indicated as an add-on treatment for severe eosinophilic asthma in adults, on the basis of data from the BREATH phase III clinical trial programme. In three double-blind BREATH studies of up to 52 weeks' duration, adding intravenous reslizumab (3 mg/kg, once every 4 weeks) to the current asthma therapy of patients (aged 12–75 years) with eosinophilic asthma inadequately controlled with inhaled corticosteroids resulted in significant reductions in clinical asthma exacerbation frequency and significant improvements in lung function, asthma control and health-related quality of life relative to adding placebo. Pooled data from the two trials of 52 weeks' duration

indicated similar benefits with reslizumab across various patient subgroups, including patients with severe eosinophilic asthma. Reslizumab was generally well tolerated, with very few recipients experiencing severe or serious treatment-related adverse events. Moreover, in an open-label extension study, continued use of reslizumab for up to 2 years was associated with durable lung function benefit, without any new tolerability concerns. Thus, intravenous reslizumab extends the valuable add-on treatment options for adults with severe eosinophilic asthma inadequately controlled with standard therapies.

Reslizumab: clinical considerations in severe eosinophilic asthma

Humanized monoclonal antibody against IL-5

Reduces blood and sputum eosinophil counts

Reduces the likelihood of clinical asthma exacerbation and improves lung function, asthma control and HR-QOL in patients with inadequately-controlled eosinophilic asthma, including those with severe disease

Generally well tolerated

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1 Introduction

Eosinophilic asthma is an asthma subphenotype most common in individuals with adult-onset asthma [1]. It is characterized by the presence of eosinophils in the lungs (as indicated by eosinophilia in induced sputum or

bronchial biopsies, both estimable from peripheral blood eosinophilia) and is often associated with considerable morbidity and poor quality of life despite standard therapies [1, 2]. However, the recent introduction of biological agents targeting interleukin-5 (IL-5), a cytokine pivotal in the differentiation, maturation and survival of eosinophils and thus eosinophilic airway inflammation, has provided much needed treatment options for these patients [1–3]. One such agent is reslizumab (Cinqaero® [4]; Cinqair® [5]), a monoclonal antibody against IL-5 that is indicated as an add-on therapy for adults with severe eosinophilic asthma in various countries, including the USA [5] and those of the EU [4]. This article focuses on data relevant to the use of reslizumab in this indication and, wherever possible, the recommended intravenous regimen of 3 mg/kg once every 4 weeks (q4w).

2 Pharmacodynamic Properties of Reslizumab

Reslizumab is a potent IL-5 antagonist. It binds to IL-5 with high affinity (dissociation constant of 81 pmol/L at 37 °C in vitro) [6], occupying a specific region of the cytokine required for its interaction with the IL-5 receptor complex at the eosinophil surface [7]. In vitro, the concentration of reslizumab required to inhibit IL-5 from binding to its receptor by 50% was 0.5 nmol/L [6]. By inhibiting such binding, reslizumab blocks IL-5 signalling, with a consequent reduction in eosinophil production, activity and survival; however, the exact mechanism(s) underlying its clinical benefit in patients with eosinophilic asthma (Sect. 4) has yet to be determined [4, 5].

Intravenous reslizumab regimens reduced blood eosinophil counts in patients with asthma in randomized trials ($n = 32$ –496) [8–12]. For instance, in three large phase III studies in patients with poorly-controlled asthma and elevated eosinophil counts (≥ 400 cells/ μ L) [Sect. 4], the recommended reslizumab regimen (i.e. 3 mg/kg administered q4w via intravenous infusion) was associated with significant ($p < 0.0001$) mean reductions in blood eosinophil count relative to placebo over 16 [8, 9] and 52 [8] weeks of therapy. Reductions from baseline in this measure were evident in reslizumab recipients from the first assessment (i.e. generally 4 weeks after the first dose [8, 9], but days 2–3 in a subset of patients [5]) and were inversely related to reslizumab concentrations in the serum [5]. Where reported [8], patients who had finished or withdrawn from reslizumab treatment had blood eosinophil counts return towards baseline within ≈ 120 days of the last reslizumab dose. Significant ($p = 0.0068$ vs. placebo) reductions in sputum eosinophil counts were also observed with the recommended reslizumab regimen over 15 weeks in patients with eosinophilic asthma [11].

Data from various animal allergy models are consistent with these findings, with reslizumab reducing pulmonary eosinophilia (an effect that lasted for up to 6 months after a single dose in monkeys) as well as airway hypersensitivity; moreover, unlike corticosteroids (CS), reslizumab did not appear to have any immunosuppressive effects [6, 13].

Some reslizumab recipients may develop antibodies against the drug [i.e. anti-drug antibodies (ADAs)] [4, 5, 8–10, 12]. For instance, anti-reslizumab antibodies were detected in 5% of 983 patients with asthma receiving reslizumab 3 mg/kg in 16- or 52-week placebo-controlled phase III trials, and the incidence of anti-reslizumab antibodies did not increase over up to 36 months in an open-label phase III extension study (5% of 1014 patients) [4]. Moreover, these antibodies are of low titre, often transient and do not appear to affect the clinical pharmacodynamics, systemic exposure, efficacy or tolerability of the drug [4, 5]. Neutralizing and product-specific IgE antibodies were not assessed [5].

3 Pharmacokinetic Properties of Reslizumab

The pharmacokinetics of reslizumab appear to be dose-proportional [4, 12], and serum concentrations of the drug usually peak at the end of the intravenous infusion, declining thereafter in a biphasic manner [4, 5]. Exposure to reslizumab (peak and overall) varies by 20–30% between individuals [4, 5], and the drug accumulates approximately twofold in the serum following multiple doses [5]. Weight-based dosing is recommended for intravenous reslizumab (Sect. 6) [4, 5], so that consistent steady-state exposure to the drug can be achieved across patients with a wide range of bodyweights, as supported by a population pharmacokinetic study [14].

Reslizumab has a small volume of distribution (≈ 5 L) and, like other monoclonal antibodies, is likely degraded into small peptides and amino acids via enzymatic proteolysis [4, 5]. Clearance of the drug is ≈ 7 mL/h [4, 5] and is expected to be linear and non-target mediated [4]; the half-life of reslizumab is ≈ 24 days [4, 5].

To date, no trials have evaluated reslizumab pharmacokinetics specifically in patients with renal or hepatic impairment [5], although it is not anticipated that the drug will be eliminated via the urine or that hepatic function will impact its pharmacokinetics [4]. Indeed, the pharmacokinetics of reslizumab were not significantly altered by mild or moderate renal impairment [4, 5], mild hepatic impairment [4, 5] or by age, gender or race [5] in population pharmacokinetic analyses.

In vitro studies suggest that CYP1A2, CYP2B6 and CYP3A4 activity is unlikely to be impacted by

reslizumab [4, 5]. Moreover, although the clinical drug interaction potential of reslizumab has not yet been formally assessed, the pharmacokinetics of the drug were not impacted by concomitant leukotriene antagonist or systemic CS use in a population pharmacokinetic analysis [4].

4 Therapeutic Efficacy of Reslizumab

This section focuses on the clinical efficacy of adding intravenous reslizumab 3 mg/kg q4w to background therapy in patients with inadequately-controlled, moderate to severe asthma and elevated blood eosinophil levels, as evaluated in three randomized, double-blind, placebo-controlled studies of the phase III trial programme, BREATH. These three studies were primarily designed to assess lung function over 16 weeks (study 3081) [9] or asthma exacerbations over 52 weeks (studies 3082 and 3083) [8].

Patients eligible for these trials were aged 12–75 years, had asthma that was inadequately-controlled by at least medium-dose inhaled CS (with or without another controller medication, which included oral CS in the exacerbation studies [8]) and had at least one blood eosinophil count of $\geq 400/\mu\text{L}$ (shown to best correspond with the presence of airway eosinophilia) during the 2- to 4-week screening period [8, 9]. The two 52-week exacerbation trials also required patients to have experienced one or more asthma exacerbations that needed systemic CS in the last year, and have $\geq 12\%$ reversibility of forced expiratory volume in 1 s (FEV_1) [8]; the 16-week study had no exacerbation or FEV_1 requirements and excluded patients on maintenance oral CS [9].

Across the three trials [8, 9], patients had a mean time since asthma diagnosis of 19–20 years, a mean (prebronchodilation [8]) FEV_1 of 1.9–2.2 L, a mean blood eosinophil count of 614–660/ μL and used a mean of 2–3 puffs/day of rescue medication; the majority of patients (78–86%) were receiving a long-acting beta-adrenoceptor agonist (LABA). Over half (56%) of the patients had experienced an asthma exacerbation in the year preceding the 16-week trial [9], and a mean of approximately two asthma exacerbations were experienced by participants of the 52-week trials during the equivalent period [8]. Patients had a mean/median age of 44–49 years [8, 9], with most (95%) being aged ≥ 18 years where specified [9]; only 39 patients were aged 12–17 years across the studies [4, 5]. Reslizumab was administered at a dosage of 0.3 [9] or 3 [8, 9] mg/kg q4w, in addition to background asthma treatment, in these trials, with 3 mg/kg q4w (the recommended dosage) being the focus of discussion. Some data are from abstracts [15–19].

4.1 Exacerbations

Adding intravenous reslizumab (3 mg/kg q4w) to background asthma therapy was effective in reducing the rate of clinical asthma exacerbations in patients with eosinophilic asthma inadequately-controlled with inhaled CS-based therapy in studies 3082 and 3083 (Table 1) [8]. Over 52 weeks' treatment, reslizumab significantly reduced the rate of such exacerbations by up to 59% compared with placebo (primary endpoint), with most of this benefit being driven by significant reductions (of up to 61%) in the rate of exacerbations requiring ≥ 3 days of systemic CS. The rate of exacerbations requiring hospitalization or an emergency department visit was low and did not significantly differ between the treatment groups (Table 1). Notably, reslizumab recipients had a significantly ($p < 0.0001$) longer time to first clinical asthma exacerbation than placebo recipients in both studies [8]. The pooled analysis of these two trials supported their individual findings (Table 1) [8].

4.2 Lung Function

Adding intravenous reslizumab to the background asthma regimen of patients with inadequately-controlled eosinophilic asthma was effective in improving lung function. Recipients of reslizumab 3 mg/kg q4w experienced significant increases in FEV_1 of 0.1–0.2 L relative to placebo recipients over 16 weeks of therapy in study 3081 (primary endpoint) [9], studies 3082 and 3083, and a pooled analysis of the latter two trials [8] (Table 2). Benefit was noted after the first 4 weeks of reslizumab therapy in all studies ($p \leq 0.05$ vs. placebo) [8, 9], and was maintained to week 52 (Table 2) [8].

In terms of other lung function parameters, forced vital capacity (FVC) and forced expiratory flow at 25–75% FVC were improved to a clinically relevant extent with reslizumab relative to placebo at 16 weeks where reported, although only the between-group difference in FVC reached statistical significance (0.13 L; $p < 0.02$) [9].

Longer term, the lung function benefits of reslizumab were maintained for up to 2 years with continued use of the drug (3 mg/kg q4w) in an open-label extension study [15]. The study enrolled 1,052 patients who had participated in any of the phase III trials discussed in this section, including 480 who had received placebo (i.e. were reslizumab naive). As may be expected, lung function was more favourable at the start of the extension in patients who had received reslizumab than in those who had received placebo in the prior trials; however, reslizumab-naïve patients experienced FEV_1 improvements by week 4 of active treatment and FEV_1 was maintained throughout the extension in all patients (no quantitative data reported) [15].

Table 1 Efficacy of intravenous reslizumab (3 mg/kg once every 4 weeks) in reducing asthma exacerbations when added to background therapy in patients aged 12–75 years with eosinophilic asthma in two 52-week phase III trials and their pooled analysis [8]

Trial	Treatment (pt no.)	Number of clinical asthma exacerbations per pt per year (rate ratio vs. placebo; 95% CI)		
		All ^a	Requiring systemic CS for ≥ 3 days	Requiring hospitalization or ER visit
Study 3082	Reslizumab (245)	0.90 (0.5; 0.37–0.67)*	0.72 (0.45; 0.33–0.62)*	0.14 (0.66; 0.32–1.36)
	Placebo (244)	1.80	1.60	0.21
Study 3083	Reslizumab (232)	0.86 (0.41; 0.28–0.59)*	0.65 (0.39; 0.26–0.58)*	0.03 (0.69; 0.29–1.65)
	Placebo (232)	2.11	1.66	0.05
Pooled analysis				
Overall population	Reslizumab (477)	0.84 (0.46; 0.37–0.58)*	0.66 (0.43; 0.33–0.55)*	0.08 (0.66; 0.38–1.16)
	Placebo (476)	1.81	1.54	0.12
Severe asthma subgroup ^b	Reslizumab (383)	0.85 (NR) ^c		
	Placebo (380)	1.95		

All asthma exacerbations were adjudicated by an independent review committee

CS corticosteroid, ER emergency department, NR not reported, pt patient

* $p < 0.0001$ vs. placebo

^a Primary endpoint

^b Pts requiring medium- to high-dose inhaled CS plus another controller, with or without oral CS. Data obtained from the EU summary of product characteristics [4]

^c Between-group difference was significant (no further details reported)

Table 2 Efficacy of intravenous reslizumab (3 mg/kg every 4 weeks) in improving lung function, when added to background therapy, in patients aged 12–75 years with eosinophilic asthma in three phase III trials and a pooled analysis

Trial	Treatment [no. of pts]	Mean FEV ₁ at BL [L]	Mean change from BL in FEV ₁ [L] (difference vs. placebo; 95% CI)	
			Over 16 weeks	Over 52 weeks
Study 3081 [9] ^a	Reslizumab (106)	2.19	0.29 (0.16; 0.06, 0.26)* ^b	
	Placebo (105)	2.22	0.13 ^b	
Study 3082 [8]	Reslizumab (245)	1.89	0.25 (0.14; 0.08, 0.198)**	0.24 (0.13; 0.06, 0.19)**
	Placebo (244)	1.93	0.11	0.11
Study 3083 [8]	Reslizumab (232)	2.13	0.19 (0.09; 0.003, 0.155)*	0.20 (0.09; 0.003, 0.153)*
	Placebo (232)	2.00	0.09	0.11
Pooled (3082 + 3083) [8]	Reslizumab (477)	NR	0.23 (0.12; 0.07, 0.16)**	0.22 (0.11; 0.07, 0.15)**
	Placebo (476)	NR	0.11	0.12

BL baseline, FEV₁ forced expiratory volume in 1 s, NR not reported, pts patients

* $p < 0.01$, ** $p < 0.0001$ vs. placebo

^a This study also contained a reslizumab 0.3 mg/kg q4w arm ($n = 104$)

^b Primary endpoint

4.3 Other Outcomes

Reslizumab improved both asthma symptoms and their control in each of the three phase III studies, as measured using the Asthma Symptom Utility Index (ASUI) and Asthma Control Questionnaire (ACQ). Significant ($p < 0.02$) mean improvements from baseline in ASUI and

7-item ACQ scores were seen with reslizumab versus placebo over 16 [8, 9] and 52 [8] weeks, with these benefits evident from week 4, where reported [8]; shorter versions of the ACQ (i.e. 5- and 6-item ACQ) generally supported these findings [8, 9]. In addition, significantly ($p = 0.0002$) more reslizumab than placebo recipients achieved a minimal clinically important improvement (MCII) (i.e. a 0.5-

point reduction) in ACQ score from baseline to end of treatment period in each of the two 52-week trials (76 vs. 63% in study 3082; 77 vs. 61% in study 3083) [8], but not in the 16-week study (quantitative data not reported) [9].

Use of rescue medication was significantly reduced with reslizumab relative to placebo over 16 weeks in study 3081 (mean changes from baseline were -0.9 vs. -0.3 puffs/day; $p = 0.0151$) [9], whereas the between-group difference for this measure was not significant at 16 or 52 weeks in studies 3082 or 3083 [8]. However, a pooled analysis of the latter two trials indicated that reslizumab recipients received fewer new prescriptions for rescue systemic CS (mean of 0.5 vs. 1.0 per patient; $p < 0.0001$) and had a lower total rescue systemic CS burden (254 vs. 611 mg/patient; $p < 0.0001$) than placebo recipients during these studies [16].

Reslizumab also improved health-related quality of life (HR-QOL), as measured by the Asthma Quality of Life Questionnaire (AQLQ). The AQLQ total score significantly ($p < 0.05$) improved from baseline with reslizumab versus placebo over 16 weeks in each of the three trials [8, 9], with this benefit maintained to week 52 in studies 3082 and 3083 ($p < 0.01$) [8]. Moreover, a MCII (i.e. ≥ 0.5 -point increase from baseline to endpoint) in this score was achieved by significantly more reslizumab than placebo recipients in each of the three trials (64–74 vs. 48–65%; all $p \leq 0.03$) [8, 9]. Longer term, the HR-QOL benefits seen with reslizumab in the three phase III trials were maintained for up to ≈ 2 years with continued use of the drug (3 mg/kg q4w) in the extension study; patients who were reslizumab-naïve at the start of the extension experienced HR-QOL improvements consistent with those seen with the drug in the parent studies [17].

4.4 Severe Asthma and Other Subgroups

According to the pooled analysis of the 52-week trials, adding reslizumab to the current asthma therapy of patients with severe eosinophilic asthma significantly reduced the clinical asthma exacerbation rate (by 56%) compared with adding placebo (Table 1) [4]. This severe asthma population also had improvements in lung function with reslizumab versus placebo (mean change from baseline in FEV₁ differed between treatment groups by a mean of 0.14 and 0.13 L at weeks 16 and 52), as well as asthma control (ACQ) and HR-QOL (AQLQ) [4]. Moreover, patients with refractory or non-refractory disease had reductions in asthma exacerbations of 59 and 49% with reslizumab (vs. placebo; no further details reported) [4].

In another subanalysis of these pooled data, patients with baseline blood eosinophil counts of ≥ 500 or ≥ 700 cells/ μ L had significant reductions in clinical exacerbation rates with reslizumab (of 51 and 59% vs. placebo) consistent with

those seen with the drug in the overall population (i.e. blood eosinophil count ≥ 400 cells/ μ L; Sect. 4.1) [8]. Likewise, in the 16-week trial, reslizumab improved lung function to a similar extent, regardless of baseline blood eosinophil count (≥ 400 to < 500 cells/ μ L or ≥ 500 cells/ μ L) [9].

Clinical exacerbation rates were significantly reduced with reslizumab versus placebo irrespective of the patient's exacerbation history [8], nasal polyp status (in patients with concomitant chronic sinusitis) [18], background asthma regimen (oral CS; or inhaled CS, with or without a LABA) [8] or asthma onset age [20] in additional subgroup analyses of the pooled data (background regimen analysis was prespecified). However, the significant ($p < 0.02$) clinical exacerbation rate reductions with reslizumab versus placebo appeared to be more pronounced in patients with chronic rhinosinusitis and nasal polyps (83 vs. 70% in patients with chronic rhinosinusitis with vs. without nasal polyps) [18], a background asthma regimen that included oral CS (68 vs. 55 and 49% with inhaled CS, with or without LABA) [8], or with late-onset asthma (i.e. age of onset ≥ 40 years) [75 vs. 42% in patients with age onset < 40 years; $p = 0.0083$ for interaction] [20]. Lung function (FEV₁) benefits were also evident with reslizumab regardless of asthma onset age [20] or background asthma regimen [8], although where specified, the difference versus placebo did not always reach significance in the smallest subgroups [i.e. patients receiving oral CS ($n = 142$) or inhaled CS without LABA ($n = 170$)] [8].

Each of these outcomes (i.e. clinical exacerbation rate and lung function) were improved with reslizumab versus placebo in the pooled analysis regardless of whether patients were aged ≥ 65 or 18–64 years, although these benefits were numerically greater in the older subgroup [19]. The efficacy of reslizumab in patients aged 12 to < 18 years could not be determined because of the small sample size [4, 5].

5 Tolerability of Reslizumab

Reslizumab, administered intravenously q4w in addition to background therapy, was generally well tolerated for up to 52 weeks in patients with eosinophilic asthma in the phase III clinical trials discussed in Sect. 4 [8, 9]. Wherever possible, this section focuses on data for reslizumab 3 mg/kg from pooled analyses [21] of asthma trials [including key phase 3 studies (Sect. 4), a phase 3 trial in patients not selected by blood eosinophil count (Sect. 7) [10], and a phase 2 study [11]].

In a pooled analysis of placebo-controlled asthma studies, the tolerability profile of reslizumab ($n = 1028$) over up to 52 weeks' treatment was generally similar to that of placebo ($n = 730$) in terms of the proportion of

patients who experienced treatment-related adverse events (AEs) (12 vs. 13%) or discontinued therapy because of AEs (5% in each group) [21]. Treatment-related AEs were generally mild or moderate, with very few reslizumab or placebo recipients (<1%) experiencing treatment-related AEs that were severe or serious [21]. The most common treatment-related AE in both groups was headache (2% incidence each); all other treatment-related AEs occurred in <1% of reslizumab and placebo recipients, including myalgia (0.29 vs. 0.27%) and increased blood creatine phosphokinase (CPK) [0.58 vs. 0.27%] [21]. Elevations in blood CPK with reslizumab were asymptomatic, transient and were not a cause of therapy discontinuation [4].

Reslizumab continued to be generally well tolerated for up to 2 years in an open-label extension of phase III trials (Sect. 4) [15]. Few patients ($\leq 2\%$) withdrew from reslizumab therapy because of AEs during the extension, regardless of whether they had received reslizumab or placebo in the preceding trial; headache (2% overall incidence) was the most common treatment-related AE.

5.1 Adverse Events of Special Interest

Anaphylaxis may occur with reslizumab, with information pertaining to this risk featuring in a boxed warning in the US prescribing information [5]. In the pooled analysis, serious treatment-related anaphylactic reactions occurred in 0.3% of reslizumab recipients (all of whom were ADA-negative) and no placebo recipients; all cases developed during, or within 20 min after, infusion of reslizumab (second or twelfth dose), led to discontinuation of the drug, and resolved completely in the clinic with standard treatment [21]. As anaphylaxis can be life-threatening, recipients of reslizumab should be monitored during [4] and/or for an appropriate period after [4, 5] the infusion; reslizumab should be immediately and permanently discontinued if anaphylaxis [4, 5] or other (severe systemic [5]) hypersensitivity reactions [4] occur. Reslizumab is contraindicated in patients with hypersensitivity to reslizumab or any of its excipients [4, 5].

There are also warnings relating to malignancies with reslizumab [5]. Lung adenocarcinoma, considered by the investigator to be treatment related, occurred in one reslizumab recipient; however, it was diagnosed after <10 days of reslizumab exposure and was thus not considered drug related by the manufacturer [22]. Treatment-emergent malignancies occurred in six reslizumab recipients (0.6%) and two placebo recipients (0.3%) in this analysis, with an additional 15 reslizumab recipients developing malignancies during the open-label extension study [21]. Malignancies were considered unlikely to be drug related, with

those occurring in reslizumab recipients being diverse in nature and not of any particular tissue type. Excluding non-melanoma skin cancers, the malignancies in reslizumab recipients involved tissues such as the colon, breast, prostate or lung, which are also the most common tissues of malignancy in the general adult population [21].

Although the potential for infections is a concern with immunomodulator therapy, reslizumab was associated with a numerically lower incidence of infections than placebo in the pooled analysis (41 vs. 53%) [21]. No helminth infections were reported in this analysis [21] or over up to 2 years in the open-label extension [15]; however, existing helminth infections should be treated prior to starting reslizumab therapy, as immune responses to some of them may involve eosinophils [4, 5]. If helminth infection occurs during treatment with reslizumab and does not respond to appropriate therapy, reslizumab should be temporarily discontinued [4, 5].

6 Dosage and Administration of Reslizumab

Reslizumab is indicated in the EU as an add-on therapy for adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled CS plus another medication for maintenance treatment [4], and in the USA as an add-on maintenance treatment for adults (aged ≥ 18 years) with severe asthma with an eosinophilic phenotype [5]. The recommended dosage is 3 mg/kg administered q4w via intravenous infusion (over 20–50 min) [4, 5]. Once reslizumab therapy has been initiated, CS should not be abruptly discontinued; CS dosages can be reduced gradually, if appropriate [5]. Reslizumab should not be used for the treatment of other eosinophilic conditions [5], acute asthma symptoms [5] or exacerbations [4, 5], acute bronchospasm [5] or status asthmaticus [5]. Local prescribing information should be consulted for detailed information regarding preparation/administration instructions, drug interactions and other warnings and precautions.

7 Current Status of Reslizumab in Eosinophilic Asthma

Asthma is a chronic, heterogeneous and potentially serious inflammatory disease of the airways [2]. Treatment is stepwise, with initial regimens being selected on the basis of the patient's current asthma severity and then modified as necessary, according to the level of asthma control [23, 24]. Although many patients are able to achieve control of their symptoms with a standard combination of an inhaled LABA and CS, some require the addition of other controller medications (e.g. theophylline, leukotriene receptor antagonists, long-acting muscarinic antagonists

and/or oral CS) [23, 24]. However, for patients with severe asthma who may continue to experience frequent exacerbations and hospitalizations despite such standard therapies, the era of more personalized asthma therapy offers hope, with various targeted biological agents effective in some of the more severe asthma patients.

The biological agents currently approved for the treatment of asthma are humanized monoclonal antibodies that target specific proteins with roles in asthma pathogenesis, including IgE (omalizumab) and more recently IL-5 (mepolizumab and reslizumab) [25]; all are administered via injection or intravenous infusion and are indicated as add-ons to standard treatment regimens. Unlike omalizumab, which is approved for severe [26] (or moderate to severe [27]) persistent allergic asthma despite standard therapies [26, 27], the anti-IL-5 agents are indicated specifically for uncontrolled severe eosinophilic asthma.

Reslizumab is the latest anti-IL-5 agent to be introduced and, like mepolizumab, is recommended as an add-on treatment for severe eosinophilic asthma in the most recent Global Initiative for Asthma guidelines [24]. The drug was approved for the treatment of severe eosinophilic asthma on the basis of the BREATH phase III trial programme; in particular, three double-blind BREATH trials of 16–52 weeks' duration that selected patients with ≥ 400 eosinophils/ μL (corresponds with presence of airway eosinophilia). In these placebo-controlled studies, adding intravenous reslizumab (3 mg/kg q4w) to the asthma therapy of patients (aged 12–75 years) with eosinophilic asthma inadequately controlled with inhaled CS reduced rates of clinical asthma exacerbation (Sect. 4.1) and improved lung function (Sect. 4.2), asthma control and HR-QOL (Sect. 4.3). Reslizumab consistently provided benefit across various patient subgroups, including patients with severe eosinophilic asthma (Sect. 4.4), and was generally well tolerated (Sect. 5). Moreover, in an extension study, lung function and HR-QOL benefits were seen for up to 2 years with continued reslizumab use (Sects. 4.2 and 4.3), with no new tolerability issues (Sect. 5).

Although the pivotal BREATH trials were conducted in patients with moderate to severe eosinophilic asthma, reslizumab was approved specifically for use in severe cases, as the available treatment options are limited [21].

Notably, in a separate double-blind BREATH trial in which patients with poorly-controlled asthma were not selected on the basis of eosinophil count, reslizumab 3 mg/kg did not significantly improve lung function versus placebo over 16 weeks in the overall population, but did in the subgroup of patients with ≥ 400 eosinophils/ μL at baseline [10], a finding that further supports the approved use of reslizumab (Sect. 6). A similar phenomenon occurred in the assessment of mepolizumab (the first and only other anti-IL-5 antibody commercially available at present) [28].

Given the chronic nature of asthma, longer-term trials and clinical practice experience with reslizumab would be beneficial to confirm the durability of its clinical benefit and to further assess the rare, but serious, AEs of anaphylaxis and malignancies (Sect. 5.1). Moreover, there are currently no studies directly comparing reslizumab with mepolizumab as add-on therapies for severe eosinophilic asthma. Thus, at present, choosing which of these agents to use in this setting may involve consideration of the efficacy data currently available for the individual agents, as well as factors such as route of administration (which is intravenous infusion q4w for reslizumab [4, 5] and subcutaneous injection q4w for mepolizumab [29, 30], the latter of which some patients may find more convenient). Patient age may also influence the choice between reslizumab and mepolizumab in some regions, as although both drugs are approved for use in adults in the EU [4, 29], the approved patient age range for reslizumab (≥ 18 years) [5] and mepolizumab (≥ 12 years) [4] currently differs in the USA; data for reslizumab in patients aged 12–18 years in the pivotal BREATH trials were considered inconclusive (Sect. 4.4) [4, 5].

With the growing availability of biological agents for severe asthma, there is an increasing need to determine which patients are the most likely to respond to each therapy, and which biomarkers would be the easiest and most specific to identify such patients [2, 31]. Given their relatively high costs (e.g. $\approx$ £500 per 100 mg of reslizumab in the UK [32]), identifying likely responders may make these agents more cost effective. Indeed, in a recent cost-utility model, mepolizumab plus standard treatment in adults with severe asthma exceeded willingness-to-pay thresholds versus standard treatment alone, although its cost effectiveness shifted towards the thresholds when limited to mepolizumab responders [33]. Further cost-effectiveness studies for targeted therapies, including reslizumab, would therefore be of interest, particularly as around half of all asthma costs are accounted for by the few (5–10%) patients with severe asthma, for reasons such as impromptu emergency visits/consultations, hospitalizations and drug costs [31, 34].

In conclusion, intravenous reslizumab extends the valuable add-on treatment options for adults with severe eosinophilic asthma inadequately controlled with standard therapies.

Data selection sources: Database(s): EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data [searches last updated 31 March 2017]. Records were limited to those in English language.

Search terms: Reslizumab, Cinquil, Cinqaero, Cinqair, severe, poorly controlled, inadequately controlled, uncontrolled, asthma

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Compliance with Ethical Standards

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