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DRUG SAFETY EVALUATION



Safety of humanized monoclonal antibodies against IL-5 in asthma: focus on reslizumab

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ABSTRACT

Introduction: Reslizumab, a humanized mAb against IL-5, reduces the number of eosinophils in the blood and lungs. Based on efficacy and safety data from pivotal RCTs, reslizumab had been approved for use as an add-on maintenance treatment of severe asthma with an eosinophilic phenotype in adults who have a history of exacerbations despite receiving their current asthma medicines.

Areas covered: Current literature on reslizumab has been reviewed with a specific focus on its safety profile in the treatment of severe asthma.

Expert opinion: Large pivotal and supportive trials reinforce the view that reslizumab is well tolerated, with an acceptable safety profile in patients exposed for longer than 2 years. However, no or few data concerning safety in special populations such as smokers, those with immune- and cellular senescence, patients with comorbidities and those receiving multi-drug treatments are available as yet. Furthermore, we need to fully elucidate some fundamental issues such as the risk of anaphylaxis and the long-term risk-benefit ratio of the impact of depletion of eosinophils and the potential risk of malignancies induced by a treatment with this anti-IL-5 agent.

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1. Introduction

Reslizumab is a humanized monoclonal antibody (mAb) of IgG4 subtype against interleukin (IL)-5 that has been developed to block IL-5 bioactivity and reduce biologically available IL-5, making it clinically beneficial in blocking pathologic inflammatory processes [1] (Box 1). IL-5 is a proinflammatory cytokine involved in the maturation, recruitment, and activation of eosinophils and a high expression of IL-5 is often associated with eosinophilia in atopic diseases and hypereosinophilic syndrome [2]. On the other hand, asthma is associated with tissue eosinophilia in 40–60% of patients [3], and the intensity of eosinophilia has been correlated with asthma severity [4]. A Cochrane meta-analysis that has included 4 studies with 1656 participants has shown that the serum eosinophil counts were significantly reduced in the reslizumab-treated group (mean difference vs. placebo: −476.83, 95% CI −499.32 to −454.34) [5]. This study only included eosinophilic participants.

The efficacy of reslizumab was established in a series of phase III randomized controlled trials (RCTs), collectively known as the BREATHE program. Based on efficacy and safety data from these RCTs, reslizumab had been approved for use as an add-on maintenance treatment of severe asthma with an eosinophilic phenotype in adults who have a history of exacerbations despite receiving their current asthma medicines in the USA, Canada, and European Union in addition to Norway, Liechtenstein, and Iceland [1]. Furthermore, reslizumab has been included in the most recent iteration of the Global

Initiative for Asthma strategy document for the treatment of severe refractory eosinophilic asthma [6].

2. Biology of IL-5

IL-5 is a hematopoietic cytokine that is produced by a large number of cell types, including CD4⁺ Th2 lymphocytes, eosinophils, basophils, mast cells, CD34⁺ progenitor cells, and invariant natural killer T cells [2]. IL-5 is also produced by Group 2 innate lymphoid cells, which are the major innate sources of this interleukin [7].

IL-5 masterminds most of the eosinophil functions from expansion to maturation, survival, and activation. In particular, it plays a leading role in promoting expansion of the eosinophil lineage from committed progenitors in the bone marrow [2]. Importantly, while IL-5 promotes expansion of eosinophil numbers and activation, it does not contribute to the trafficking of eosinophils into specific tissues. In fact, additional cytokines and chemokines are instrumental in directing eosinophil migration into inflamed tissues [2]. Furthermore, in humans, factors other than IL-5 contribute to the differentiation and survival of eosinophils in the bone marrow and pulmonary mucosa. Thus, inhibiting IL-5 alone may not be adequate to eliminate tissue eosinophils rapidly [2]. IL-5 also plays a role in the development, metabolism, and function of basophils and mast cell, owing to the common expression of several crucial receptors in these cells [8]. While IL-5 does not affect basophil

Box 1. Drug summary.

Drug name	Reslizumab
Phase	Approved for use in the USA, Canada, EU, Norway, Liechtenstein, and Iceland
Indication	Add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICSs plus another medicinal product
Mechanism of action	Humanized mAb that binds specifically to IL-5 and inhibits IL-5-induced cell proliferation
Route of administration	Intravenous, subcutaneous (route under investigation, not approved yet)
Molecular formula	Not available
Pivotal studies	3082 and 3083 [38], 3081 [39], 3084 [40], 3085 [42]

histamine release or degranulation directly, it does serve to prime the basophil and thereby amplify histamine release by these cells [9].

Several lines of experimental evidence support the possible role of IL-5 in the pathogenesis of asthma. IL-5 expression is elevated in bronchoalveolar lavage fluid and bronchial biopsies from asthmatic patients with eosinophilic pulmonary inflammation [10] and inhalation of IL-5 by patients with asthma causes sputum eosinophilia and airway hyperresponsiveness [11]. Furthermore, inhaled bronchial provocation with allergen causes an increase in IL-5 mRNA [12].

Clinical studies in humans have documented the close correlation between airway IL-5 expression, eosinophilia, and asthma symptoms [13]. Since eosinophils rapidly undergo apoptosis in the absence of IL-5, targeting IL-5 was identified as a potential treatment approach to prevent or blunt eosinophil-mediated inflammation [14].

3. The consequences of eosinophil deficiency

It would be reasonable to consider the eosinophils as multifaceted leukocytes that contribute to various physiological and pathological processes depending on their location and activation status [15].

The available evidence suggests that reduction of eosinophils appears to have no characteristic deleterious effects on normal health [16]. Appropriate studies in mice [17] and in nonhuman primates [18] using anti-IL-5 mAbs to deplete eosinophils showed that the lack of circulating eosinophils did not elicit any adverse effect on the health and longevity of these animals, even when the antibody intervention was maintained for extended periods of time, up to 6 months [18]. Furthermore, several experiments using mAbs to IL-5 in mice infected with *Trichinella spiralis* and *Schistosoma mansoni* had not shown altered parasite immunity to reinfection [19,20].

However, several studies suggest that eosinophils, whose function has long been restricted to an effector activity in parasitic infections or allergic diseases, likely play a role in innate defense and antitumor surveillance, acting synergistically with other effectors [21]. Activated eosinophils initiate substantial changes in the tumor microenvironment, including macrophage polarization and normalization of the tumor vasculature, which are known to facilitate T cell infiltration and promote tumor rejection, but the precise mechanism of tumor

vessel normalization is still not clear [22]. Other possible mechanisms by which eosinophils and their mediators may promote tumor regression been suggested [23]. Eosinophils could exhibit antitumor activity through direct tumor cell cytotoxicity mediated by reactive oxygen species (ROS), granzyme, tumor necrosis factor- α , eosinophil cationic proteins (eosinophil cationic protein, eosinophil peroxidase, major basic protein), and IL-18. Interferon- γ produced by eosinophils favors M1 (classically activated) polarization of tumor-associated macrophages. Eosinophils could also exert antitumor activity indirectly through the attraction of CD8+ T cells via the production of C-C motif chemokine ligand 5 (CCL5), C-X-C motif chemokine 9 (CXCL9), and CXCL10. Intriguingly, an inverse association between allergic diseases or IgE and certain tumors has been suggested [22]. Tumor antigen-specific IgE has been shown to trigger eosinophils-mediated tumor cell death by cytotoxic mechanisms [24]. Actually, eosinophils from allergic donors induce higher levels of tumor cell apoptosis compared with eosinophils from nonallergic donors [25], which suggest that the allergic state favors antitumor processes. Therefore, one of the protective roles of IgE/atopy in cancer could be mediated in part by hypereosinophilia associated with several allergic disorders [24].

Eosinophils can also be recruited by danger signals released by pathogen infections or tissue injury, inducing host defense against parasitic, fungal, bacterial, and viral infection or promoting tissue repair and remodeling [26].

With advancing technology and accumulating knowledge, the understanding of eosinophils has changed from a simple postmitotic cell with limited functional capacity in parasite infection and allergy to a cell type that is actively involved in orchestrating a variety of mucosal and non-mucosal immune responses at baseline and during a variety of disease responses [27].

Therefore, further research is needed to investigate the real consequences of totally lacking eosinophils or to have a reduced number of eosinophils because of the use of biological drugs in real-life settings.

4. Classification of adverse side effects caused by biologics

Therapeutic mAbs are biological agents and as such they are structurally immunogenic, which involves the production of specific antidrug antibodies (ADAs) [28], and can cause a great variety of adverse side effects [29]. In particular, ADAs might be expected to diminish the effectiveness of mAbs as a therapeutic drug, and perhaps have other metabolic consequences [28]. Patients developing high levels of ADAs are more likely to show acute hypersensitivity reactions [30].

Based on the peculiar features of these agents, Pichler [31] proposed a classification of the adverse side effects of biological agents that was related but clearly distinct from the classification of side effects observed with chemicals and drugs. This classification differentiates five distinct types, namely clinical reactions because of high cytokine levels (type α), hypersensitivity because of an immune reaction against the biological agent (β), immune or cytokine imbalance syndromes (γ), symptoms because of cross-reactivity (δ), and symptoms not directly affecting the immune system (ϵ).

Numerous biological agents have been associated with hypersensitivity reactions, including anaphylaxis. Two forms of hypersensitivity reactions have been identified: acute and delayed. They appear to be related to the presence of antibodies to the mAb (against murine or human components) but many reactions do not appear to be anaphylactic (IgE-mediated) [29]. Non-IgE ADAs, mostly represented by IgG, may lead to infusion reactions through complement activation or, as clearly shown in animal models, involving FcγRIII (CD16), basophils, macrophages, and neutrophils [32]. Humanized or fully human mAbs have a low immunogenicity, as immunological tolerance exists to the constant part of the immunoglobulin. Nevertheless, the antigen-binding site of the mAb can still elicit an immune response [29].

5. Safety of reslizumab

Although this scientific background may suggest that targeting IL-5 with reslizumab may induce a risk of even serious adverse events, in general, reslizumab appears to be safe and well tolerated in patients exposed for longer than 2 years [33].

5.1. Preclinical findings

The results of preclinical studies had already been largely encouraging about the safety of this anti-IL-5 agent. In fact, conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development have revealed no special hazard for humans [34].

In particular, safety pharmacology data indicated that intravenous reslizumab given at dose levels of 25 mg/kg in cynomolgus monkeys did not elicit deleterious effects on parameters related to organ functions (cardiovascular, respiratory, neurological, ophthalmic, renal, and gastrointestinal) [33]. Furthermore, no carcinogenicity was observed in a 6-month bioassay in which reslizumab was administered intravenously once every 2 weeks for 26 consecutive weeks (14 total doses) to Tg.rasH2 mice at doses up to 516 mg/kg. In a fertility study, administration of reslizumab to parental CD-1 mice at doses up to 50 mg/kg (approximately six times the maximum recommended human dose on an area under the curve basis) had no effects on male or female mating or fertility [33].

However, we must highlight that although reslizumab is a humanized protein and therefore expected to have antigenic properties in animals, which indeed was observed in some animals (formation of antibodies to reslizumab), no dedicated studies on immunotoxicity have been conducted [35].

5.2. Early clinical studies

In an initial small study in which reslizumab was administered at a single intravenous dose ranging between 0.03 and 1.0 mg/kg, the most common adverse events reported were headache and fatigue [36]. However, these occurred with the same frequency in the placebo group and consequently, they were not considered treatment related. In one subject treated with reslizumab at 1.0 mg/kg, ADAs were detected in serum.

In a 15-week, phase II, randomized, double-blind, placebo-controlled clinical study that evaluated the effect of 3 mg/kg intravenously reslizumab every 4 weeks per 4 doses (study

Res-5-0010), adverse events were generally mild or moderate in severity [37]. Nasopharyngitis was the most common adverse event (21% in the reslizumab group and 9% in the placebo group), but it occurred mainly in patients that also had nasal polyps at baseline. No clinically meaningful changes in laboratory values or vital signs were observed. Serious adverse events occurred in two patients in the reslizumab group (pneumonia and worsening of asthma).

5.3. Pivotal and supportive trials

The phase III BREATH program that evaluated reslizumab treatment in four separate trials involving patients with elevated eosinophils, whose symptoms were inadequately controlled with ICSs with or without another controller medication, has allowed a more solid assessment of the safety of reslizumab. However, it is likely that reporting of adverse events in each trial was mostly selective, either by the adverse events severity levels or by the occurrence threshold selected for presentation. Therefore, the reported prevalence of certain adverse events (Table 1) should be interpreted with caution.

Castro and colleagues described the results of two large, multicenter, double-blind, randomized, placebo-controlled, 52-week phase III trials (studies 3082 and 3083) that enrolled 953 patients who had at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months, had to have at least one blood eosinophil count of 400/μL, and were receiving at least medium-dose ICS with or without a second controller [38]. The overall safety profile of reslizumab was similar to that of placebo. Nasopharyngitis, upper respiratory tract infections, sinusitis, influenza, and headache were the adverse events that occurred in more than 5% of patients treated with reslizumab. Notably, serious adverse events were more frequent in the placebo group. Infections and infestations were equally balanced between patients receiving placebo or reslizumab and no helminthic infestations were reported. Infusion-site reactions (e.g. pain, rash, and hematoma) were

Table 1. Overall adverse events [*n* (%)] reported in clinical trials 3081 [39,40], 3082 and 3083 [38,39], and in the open-label extension study 3085 [42]. Only adverse events that affected at least 5% of patients in any of these trials have been considered.

Adverse event	Reslizumab (<i>n</i> = 1151)	Placebo (<i>n</i> = 1060)
Asthma	339 (29.5)	419 (39.5)
Upper respiratory tract infection	101 (8.8)	86 (8.1)
Nasopharyngitis	160 (13.9)	161 (15.3)
Sinusitis	64 (5.6)	64 (6.0)
Headache	102 (8.9)	87 (8.2)
Influenza	18 (1.6)	23 (2.2)
Bronchitis	44 (3.8)	62 (5.8)
Back pain	25 (2.2)	21 (2.0)
Urinary tract infection	49 (4.3)	43 (4.1)
Oropharyngeal pain	13 (1.1)	8 (0.8)
Rhinitis allergic	44 (3.8)	25 (2.4)
Nausea	12 (1.0)	10 (0.9)
Cough	11 (1.0)	13 (1.2)
Pharyngitis	10 (0.9)	13 (1.2)
Dyspnea	10 (0.9)	12 (1.1)
Fatigue	6 (0.5)	11 (1.0)
Dizziness	5 (0.4)	13 (1.2)

N: total number of a specific adverse event that affected at least 5% of patients in any of the examined trials; %: percentage with respect to the total number of adverse events that affected at least 5% of patients in any of the examined trials.

uncommon (less than 2%). Two patients in the reslizumab group had anaphylactic reactions, but they were negative for ADAs. About 3% of reslizumab-treated patients had at least one positive ADA response but generally ADA responses were of low titer and transient. The safety profile of ADA-positive patients did not differ from that noted in the overall population. Malignant neoplasms were uncommon.

Headache, nasopharyngitis, upper respiratory tract infection, and sinusitis were the most common adverse events reported by Bjerner and colleagues, who randomized 311 patients with asthma inadequately controlled by at least using medium-dose ICS and with a blood eosinophil count ≥ 400 cells/ μ l to receive reslizumab 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks (study 3081) [39]. The percentages of patients who reported treatment-related adverse events were 8% in the placebo group, 6% in the 0.3 mg/kg reslizumab group, and 12% in the 3.0 mg/kg reslizumab group, respectively. No serious adverse events were considered related to the study drug. One patient was withdrawn from the reslizumab 3.0 mg/kg group for mild myalgia. ADA responses were detected in 12% and 11% of patients in the reslizumab 0.3 and 3.0 mg/kg groups, respectively, but they were of low titer, and the majority of patients were positive at only one time point.

Corren and colleagues described a supportive 16-week, randomized, double-blind, placebo-controlled, multicenter phase III trial in which the use of reslizumab (3 mg/kg intravenously every 4 weeks per four doses) was explored in 492 uncontrolled asthmatics with a wide range of blood eosinophil levels (study 3084) [40]. Reslizumab was generally well tolerated. Upper respiratory tract infection and sinusitis were the most frequent ($\geq 3\%$) adverse events in the reslizumab group. One patient had anaphylaxis associated with reslizumab with symptoms of wheezing, shortness of breath, and flushing that occurred shortly after infusion, without hemodynamic compromise. One patient in the reslizumab group had colon cancer. Five percent of patients treated with reslizumab were classified as ADA-positive during treatment. Most ADA responses were low titer and transient.

A meta-analysis that used the results of these pivotal trials and also those of the study Res-5-0010 representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group) showed that reslizumab and placebo were similar in terms of the incidence of withdrawn due to adverse events and incidence of upper respiratory adverse events such as upper respiratory tract infection, nasopharyngitis, and sinusitis [41].

However, the most reassuring data regarding the safety profile of reslizumab were produced by the open-label extension of three phase III reslizumab studies (studies 3081, 3082, and 3083) in which 1051 patients received reslizumab 3 mg/kg intravenously once every 4 weeks for up to 2 years (study 3085) [42]. Continuous exposure in these controlled studies was ≥ 12 months for 740 patients and ≥ 24 months for 249 patients. Few patients ($\leq 2\%$) withdrew from reslizumab therapy because of adverse events during the extension, regardless of whether they had received reslizumab or placebo in the preceding trial. Treatment-related adverse events were reported in 10% and 7% of reslizumab-naïve and reslizumab-

experienced patients, respectively. The overall pattern of adverse events in this trial was similar to the preceding pivotal studies. In fact, nasopharyngitis, upper respiratory tract infection, sinusitis, and headache were the most common adverse events, occurring in $>5\%$ of patients. However, headache was the only adverse event assessed by investigators to be treatment related that occurred in $>1\%$ of patients (incidence 2%). There was neither specific pattern of infections nor reports of helminthic parasitic or suspected opportunistic infections indicating a specific risk due to reslizumab treatment. Fifteen adult patients had malignancies of diverse and common tissue types, without evidence of clustering. The most frequent sites of malignancy were breast, melanoma (including *in situ*), and basal cell carcinoma of the skin, reported by three patients each. In any case, five of the patients with malignancies reported during this study had previous medical history of malignancies and two had a recurrence of their previous malignancy. Local infusion-related adverse events (e.g. pain at site of administration) were rare ($<1\%$). No anaphylaxis cases were reported. During the study, 5% of patients in the reslizumab-naïve and reslizumab-experienced groups showed treatment-emergent ADA response. ADA was frequently observed at 1 time point only, and in general the titer was low. There were no clinically relevant changes in laboratory test results or vital signs.

5.4. Adverse events of special interest

Anaphylaxis, malignancies and musculoskeletal/creatine phosphokinase (CPK) abnormalities are designated as adverse events of special interest based on potential effects of the anti-IL-5 mechanism of action and on individual study results [43,44].

Approximately 0.3% of patients of a cohort that included patients from the studies Res-5-0010, 3081, 3082, 3083, and 3084 (1028 patients treated with reslizumab 3.0 mg/kg and 103 with reslizumab 0.3 mg/kg), reported anaphylaxis that was always ADA negative [43,44]. These events occurred within 20 min of the infusion as early as the second dose. Manifestations included dyspnea, decreased oxygen saturation, wheezing, vomiting, and skin, mucosal involvement, including urticarial, and no reaction involving hemodynamic or pulmonary compromise. They fully resolved after standard treatment. Due to the overlap in signs and symptoms, it was not possible to distinguish between anaphylaxis, other hypersensitivity reactions, or an infusion reaction in all cases [44].

Placebo-controlled clinical studies demonstrated that 0.6% of patients receiving 3 mg/kg of reslizumab developed at least one malignant neoplasm compared with 0.3% of those in the placebo group. The malignancies observed in the reslizumab-treated patients were diverse in nature and without clustering of a particular tissue type. Most patients were diagnosed within 6 months of their exposure to reslizumab [44] suggesting that these malignancies were preexisting conditions. There was no malignancy in the reslizumab 0.3 mg/kg treatment group [44]. However, this treatment group was small and had an observation period of only 16 weeks [44].

During clinical trials, patients randomized to reslizumab had elevated baseline CPK levels compared with patients receiving placebo (14% vs. 9%, respectively) [33]. Transient CPK elevation

was reportedly higher in patients receiving reslizumab compared with those receiving placebo (20% vs. 18%). CPK elevations greater than 10 times the upper limit of normal were reported in 0.8% of the reslizumab group and in 0.4% of the placebo group; however, these elevations were asymptomatic and did not result in treatment discontinuation [33]. In fact, none of the CPK elevations progressed to rhabdomyolysis with acute renal failure, and many experienced a return of their CPK to baseline with continued reslizumab therapy [44].

Myalgia was reported in 1% of the reslizumab group and in 0.5% of the placebo group [33]. Musculoskeletal adverse events, including chest pain, neck pain, muscle spasms, extremity pain, and muscle fatigue, were reported on the day of infusion in 2.2% of reslizumab-treated patients and in 1.5% of those who received placebo [32]. In general, these events were mild, transient, and did not recur with continuing reslizumab treatment [44]. Pharmacokinetics/pharmacodynamics analyses suggest a relationship between reslizumab exposure and musculoskeletal adverse events. However, this relationship was mainly due to five overweight/obese female patients with high reslizumab concentrations and nonspecific complaints of back pain and foot pain [44].

6. Conclusion

Large pivotal and supportive trials reinforce the view that reslizumab is well tolerated, with an acceptable safety profile in patients exposed for longer than 2 years. For this reason, the opinion of the National Institute for Health and Care Excellence (NICE) Committee is that the overall pattern of adverse events in the reslizumab clinical trials was consistent with what would be expected in a moderate to severe, predominantly adult asthma population [44].

7. Expert opinion

We completely agree on the opinion that the safety profile of biological agents is, just as much as their efficacy, one of the fundamental criteria justifying their clinical broad use [32]. The current alternative to biological agents is the use of systemic corticosteroids and, in effect, treatment with systemic corticosteroids in some patients with severe asthma helps to improve asthma control and reduce exacerbation rates through their anti-inflammatory effect [6]. Unfortunately, corticosteroids produce considerable side effects with increasing doses and especially when delivered systemically, and patients with low eosinophil counts are less responsive to corticosteroids treatment [45]. It has been suggested that each prescription for oral corticosteroids (OCSs) can result in a cumulative burden on current and future health, regardless of dose and duration, suggesting that even OCS bursts might be deleterious to health [45].

Data from phase II/III RCTs have documented that reslizumab not only reduces asthma exacerbation rates and statistically improves pre-bronchodilator lung function [1], but also is well tolerated.

Indisputably RCTs are the most strong form of medical evidence, and their data are the basis of regulatory approval of new therapies and their incorporation in clinical guidelines. However, RCTs usually exclude patients with comorbidities, the most

challenging patient groups for healthcare providers to manage [46]. RCTs are also often designed with intermediate measures as endpoints, and thus do not provide the information most desired by physicians, patients, and other medical decision makers [46]. Additionally, short follow-up times do not allow appreciation of survival or longer-term outcome measures [46].

With regard to reslizumab, no or few data concerning safety in special populations such as smokers, those with immune- and cellular senescence, patients with comorbidities and those receiving multidrug treatments are available as yet (Table 2). Numerically larger improvements with reslizumab have been observed in a small sample of old people (≥ 65 years) compared with the younger adults [47], but this anti-IL-5 agent has not been studied in patients with hepatic impairment and in those with severe renal impairment or end stage renal disease. Furthermore, there are limited safety data in non-white ethnic populations. Therefore, it is questionable whether data generated by RCTs can be extrapolated to a larger, 'real life' population of patients.

However, regardless of these concerns, we believe that we need to fully elucidate two fundamental issues, the risk of anaphylaxis and the long-term risk-benefit ratio of the impact of depletion of eosinophils induced by a treatment with this anti-IL-5 agent. Closely related to the impact of depletion of eosinophils, there might be risk of malignancies.

The root causes of the anaphylactic events have not been adequately investigated, although hypersensitivity reactions may be more common in patients with eosinophilic asthma than in the general population [48]. It has been highlighted that product-related factors in reslizumab might impact immunogenicity and affect the incidence of anaphylaxis [48]. These factors include glycosylation, and residual nucleic acids and host cell proteins from the cell substrate used to manufacture reslizumab. The contribution of host cell-derived impurities to reslizumab anaphylaxis is still unclear. Although anaphylaxis is a known risk for mAbs, it is rare to observe. It is noteworthy that the four patients with treatment-related anaphylaxis tested antidrug-IgG negative, but were not tested for product specific IgE. For this reason, a product-specific IgE ELISA is currently under development [48]. In the meantime, reslizumab carries a boxed warning for anaphylaxis.

Reslizumab is an effective treatment of most subjects with severe refractory eosinophilic asthma, but we do not know if it provides long-term safe control of their disease. In fact, the real long-term consequences of eosinopenia are still not known. In particular, we must highlight that recent work showed that eosinophils are also able to contribute to the resolution of acute inflammation. Actually, eosinophils did not contribute to the

Table 2. Further research topics needed to be investigated to define the safety profile of reslizumab.

- Safety in special populations
 - Smokers
 - Subjects with immune- and cellular senescence
 - Patients with comorbidities
 - Patients receiving multidrug treatments
 - Patients with hepatic impairment
 - Patients with severe renal impairment or end stage renal disease
 - Non-white ethnic populations
- Risk of anaphylaxis
- Long-term risk-benefit ratio of the impact of depletion of eosinophils
- Potential risk of malignancies

development of airway hyperresponsiveness in a murine model in response to repeated allergen challenges and instead they were necessary for the resolution of such inflammation [49]. These findings provide a novel perspective on eosinophil functions and suggest that there might be multiple facets (and perhaps subtypes) to this otherwise inflammatory granulocyte [50]. There is a clear need to understand if there is only a subgroup of patients in which the anti-IL-5 treatment-induced eosinopenia is really useful over time regardless of the number of eosinophils in blood and sputum, while in other patients it could even be harmful.

Rebound eosinophilia after stopping treatment with anti-IL-5 therapy is another concern because of *in vitro* observations of upregulation of the IL-5R in eosinophils [51], and clinical documentation of increased eosinophils in some patients with the hypereosinophilic syndrome after treatment with reslizumab [52]. However, a resolution of rebound eosinophilia was achieved by repeated monthly dosing with reslizumab, although the response to treatment was attenuated with each subsequent dose [52]. In any case, an increase in plasma IL-5 levels and IL-5Ra expression by blood eosinophils after anti-IL-5 treatment in a variety of eosinophilic diseases led to concerns that there could, theoretically, be a rebound worsening of tissue inflammation when anti-IL-5 therapy is discontinued [51]. This finding raises the question of whether treatment with reslizumab, as well as that with other anti-IL-5 agents, should be continued forever or if patients are different regarding the possible risk of rebound. If this is the case, it will become imperative to understand to whom and, especially when, the drug can be suspended.

An inverse association between allergic diseases and certain tumors with a protective role of atopy in cancer because of hypereosinophilia associated with several allergic disorders has been suggested [24]. Ikutani and colleagues [53] demonstrated that genetic blockade or neutralization of IL-5 impaired eosinophil recruitment into the lung and resulted in increased tumor metastasis. Conversely, exogenous IL-5 treatment resulted in suppressed tumor metastasis and augmented eosinophil infiltration. In any case, the precise impact of eosinophils on malignant disease is unclear. There is evidence that eosinophils in tumor microenvironment can promote tumor initiation and progression through the release of ROS, angiogenic factors, metalloproteinase-9, and the induction of epithelial-to-mesenchymal transition [23]. Actually, certain hematologic malignancies are associated with hypereosinophilia or tissue eosinophilia [54]. The information available on reslizumab is reassuring, suggesting that malignancies were preexisting conditions. Nevertheless, we believe that close long-term monitoring of patients treated with reslizumab also in the real life will be appropriate in order to exclude that the blockade of IL-5 facilitates the onset of malignancies.

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