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Pharmacokinetics and pharmacodynamics of monoclonal antibodies for asthma treatment

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ABSTRACT

Introduction: Asthma is a chronic inflammatory airway disease. It occurs in a "severe" form in about 8-10% of asthmatic patients. In the last decade the development of biological drugs (e.g. monoclonal antibodies) allowed to efficiently approach severe asthma. The current therapeutic targets available are mainly those related to TH2 inflammation.

Areas covered: The main pharmacokinetic and pharmacodynamic characteristics of the monoclonal antibodies against IL-5, IL-5Ra, IL4-IL13 and IgE, that are currently marketed or understood for severe asthma are discussed in this paper.

Expert opinion: The currently available biological drugs represent an excellent therapeutic add-on to traditional drugs, especially in replacing systemic corticosteroid therapies. The different pharmacokinetic and pharmacodynamic characteristics of the drugs, despite sometime sharing the

same target, would allow a better personalization of the therapy, tailoring the treatment to the characteristics of the patient.

Key Words: severe asthma, pharmacokinetic, pharmacodynamics, monoclonal antibodies, biological drugs, precision medicine, personalized medicine

ABBREVIATIONS:

ADCC: antibody-dependent cell-mediated cytotoxicity

AUC_{∞}: area under the serum concentration-time curve

ICS: inhaled corticosteroids

Cmax: Maximum plasma concentrations

IV: intravenous

LABA : long-acting beta2-agonists

mAB : monoclonal antibody

PD: pharmacodynamic

PK: pharmacokinetic

SC: subcutaneous

TH: T Helper lymphocyte

Article highlights:

1. Monoclonal antibodies are an efficient therapy in patients with severe asthma
2. Biological drugs currently marketable can be used in patients with an allergic or an eosinophilic phenotype of asthma
3. The pharmacokinetic and pharmacodynamic aspect of these drugs makes them different from each other despite, in some cases, the biological target is the same
4. The point of inoculum of these drugs modifies the pharmacokinetics mechanisms, therefore it is necessary to use the one suggested by clinical trials to guarantee a correct absorption
5. Although these drugs have different routes of administration, they have proved equally effective, despite this modifying PK and PD

1. INTRODUCTION

Asthma is a chronic airways disease, with high incidence and prevalence, usually sustained by a bronchial inflammatory process. It is estimated that about 235 million of people suffer from asthma, and the prevalence of this disease is still rising worldwide [1,2]. About 10% of asthmatic subjects have a severe uncontrolled form of the disease [3]. These patients, according to ATS/ERS guidelines, though receiving the highest dose of inhaled therapies, principally based on inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA), are not controlled and must take other drugs to try to control the disease [4]. People with uncontrolled severe asthma have a higher risk of exacerbations, morbidity and mortality, not to mention the direct and indirect economic burden on the healthcare system [5]. In recent years some biological drugs have been developed to provide a therapeutic response to a part of patients who do not respond adequately to traditional therapies. Nowadays these drugs are mainly targeted to those patients with prevalent T Helper (TH)2-type inflammation [6,7], that is, for historical and cultural reasons, the better known.

2. THERAPEUTIC TARGETS OF mABs

Currently many biological agents with different biological targets are under clinical experimentation, but only drugs directed on IgE and eosinophils have been marketed. Both mechanisms represent different faces of the same type of asthma, namely the TH2-dominant phenotype. Frequently, type 2-immunity is activated by the exposure to allergens and it develops by

the differentiation of naïve T CD4+ cells, associated with IgE production, increase in peripheral eosinophils and allergen-triggered mast cell activation. The principal cytokines involved in type 2 immune response are interleukin (IL) 4, IL-5, IL-9, and IL-13 [8-10]. Since the role of those cytokines/receptors are well recognized, these molecules have been the main therapeutic targets.

3. OMALIZUMAB (Xolair ™,anti IgE)

The oldest, and therefore deeply studied biological drug in the field of severe asthma is omalizumab. It's a recombinant humanized antibody with a human framework and complementary-determining region obtained from an anti-IgE murine antibody [11]. It is derived from recombinant DNA which selectively binds to immunoglobulin E (IgE human).

3.1) PHARMACOKINETIC (PK) CHARACTERISTICS OF OMALIZUMAB

Omalizumab is marketed in pre-filled syringes with variable dosages and frequency of administration, depending on weight and IgE levels [12]. The absorption of the anti-IgE molecule results to be rather slow, with a peak of absorption within 7-8 days after administration and an average bioavailability of about 62% [13]. The pharmacokinetics of omalizumab results to be linear at doses above 0.5 mg/Kg. With the subsequent administrations, the area under the serum concentration-time curve (AUC) of omalizumab increases. Once a steady state has been reached the AUC after 14 days results to be greater up to six times compared to the first administration [14]. Specific studies on severe asthmatic people have shown that omalizumab have an apparent volume of distribution of about 78 ± 32 mL/Kg [15]. Although omalizumab form complexes with IgE, it has been observed that these do not exceed the molecular weight of one million Daltons neither *in vitro* nor *in vivo*. The clearance of the omalizumab involves IgG clearance processes as well as through specific bonds and formation of complexes with its target ligand, the IgE [15]. The hepatic elimination of IgG includes degradation in the reticuloendothelial system and endothelial cells.

Unchanged IgG is also excreted into the biliary fluid. In asthmatic patients it was shown an average elimination half-life of about 26 days, with a clearance of 2.4 ± 1.1 mL/Kg/day [13,15,16].

3.2) PHARMADYNAMIC (PD) CHARACTERISTICS OF OMALIZUMAB

The administration of Omalizumab decreases the concentration of free IgE level, thus preventing the binding of IgE to high (Fc∑RI) and low-affinity (Fc∑RII/CD23) receptors, interrupting the activation of mast cells and basophils degranulation [11]. Once linked to IgE, Omalizumab, creates small sizes immune complexes, that turn out to be soluble, biologically inert, unable to fix the complement and to precipitate in the kidney [11]. Furthermore Omalizumab, due to the its action reduction of free IgE, promotes a down-regulation of Fc∑RI on mast cells and basophils, leading to a reduction in responsivity of these cells to antigens [17]. Several studies demonstrated that basophils histamine release, in people traded with omalizumab, decrease of about 90% compared with non-treated patients [18]. Clinical studies demonstrated that serum levels of free IgE decreased in a dose-dependent manner within one hour of the first administration and remained stable between doses [19].

4. MEPOLIZUMAB (Nucala ™, anti IL-5)

Mepolizumab is a humanized mAb belonging to the $IgG_{1/k}$ class whose target is IL-5, a cytokine with a crucial role in eosinophils development, maturation and action [20]. This molecule is indicated in subjects with severe uncontrolled asthma and high blood eosinophils levels. The first route of administration in clinical trials was the intravenous one, with different doses (75 mg, 250 mg and 750 mg). Subsequently the subcutaneous (SC) administration was chosen at the fix dose of 100 mg, regardless of weight or other factors, due to the fact that endpoints obtained with SC and intravenous (IV) administration were overlapping [21]. As the subcutaneous administration has proved to be as effective as the intravenous one, due to a greater simplicity of use and a less

invasive, the drug has been commercialized in this formulation. Furthermore, in the case of mepolizumab, the subcutaneous formulation also proved to be safer with lower side effects than the EV [22].

4.1) PHARMACOKINETIC (PK) CHARACTERISTICS OF MEPOLIZUMAB

The pharmacokinetic of Mepolzumab was assessed in various studies: animal models, humans, healthy and asthmatic patients. We summarize herein the main studies on human model both in healthy asthmatic subjects.

One of the main pharmacokinetic trial, was conducted in an open-label, single-dose, randomized, parallel group 12-week study (study SB-240563/018) [23], where 60 healthy people were enrolled and treated. Different arms of treatment were planned: one received 250 intravenously as a 30-minute infusion (n = 12), other groups received the drug subcutaneously in three different body site (abdomen, arm or thigh; n = 12 each site) and the last group received an intramuscular injection in the lateral thigh (n = 12). The bioavailability of mepolizumab, through SC route of administration resulted 64% in the abdomen, 75% in the arm and 71% on thigh, as compared with the one of the intramuscular route that was 81% [2,24]. Maximum plasma concentrations (Cmax) was observed after 0.5-4.8 hours from the beginning of the infusion. Although the time taken to reach the Cmax was longer (2-14 days) in the SC than the IV administration, mepolizumab was found to be equally well absorbed in both routes of administrations. Consistently with what is known for endogenous IgG1 antibodies in humans [25,26], the half-life of mepolizumab was approximately 20 days, regardless of the route of administration [27].

Several trials are also available, conducted in asthmatic patients. A first study was a multicentre, double-blind, randomized, placebo-controlled, dose escalation study, performed on patients (n = 38) with a mild atopic asthma, where mepolizumab was administrated intravenously one time at the dose of 0.05 mg/kg, 0.5 mg/kg, 2.5 mg/kg, or 10 mg/kg, than compared with placebo. After the

administration, the concentration of Mepolizumab decreased with a mean early $t_{1/2}$ of about two days. The terminal $t_{1/2}$ was documented after about 20 days (14-30 days). The observations done on Cmax and AUC suggested a linear pharmacokinetic profile of the drug [28]. Pouliquen and colleagues described the results of a multi-center, randomized, open-label, parallel-group, repeat-dose study where mepolizumab was administered to 70 subjects (66 completed) with asthma and blood eosinophils count of at least 300 cells/μL. Three SC dose of drug (12.5, 125, and 250 mg) were administered subcutaneously and compared to 75 mg intravenously [29]. In this trial the terminal half-life estimated was of 22 days for SC and 28 for IV administration. Regarding t_{max} , the median time was assessed at 6-8 days after SC dosing compared with 0.5 hours in IV dosing. Bioavailability was found to be the same for all SC dosage (74%). The pharmacokinetic profiles resulted to be more variable at the dose of 12.5 mg than in the other groups. The SC formulation was also evaluated in a trial where 250 mg was administered for three times. Doses 1 and 2 were given 6 weeks apart; dose 3 was given 2 weeks after dose 2. Due to the known half-life of about 20 days, plasma accumulation was observed after third dose. The recorded AUC and Cmax resulted higher after dose 3 than dose 1 (65% and 80%) [30]. Further data were provided by Ortega et al. where mepolizumab was given subcutaneously at different sites, and compared with intramuscular and IV route. The best SC bioavailability was recorded in arm 75% (66–86), AUC resulted 1,238 (±228) mg d/mL. The half-life was protracted, in a range of 11 to 26 days and independent of dosing route and clearance from 1.9 to 3.3 mL/day/kg [31].

4.2) PHARMACODYNAMIC (PD) CHARACTERISTICS OF MEPOLIZUMAB

As it happened for pharmacokinetics studies, also pharmacodynamic one were performed in healthy and asthmatic patients. In the above mentioned trial [23] about 60 people treated with mepolizumab at different dose and different administration routes, the peripheral blood eosinophils count described a substantial decrease of at least 50% from baseline [23]. In mild-moderate

asthmatic patients, Leckie and colleagues described the results with an administration of 2.5 and 10 mg/Kg intravenously. The blood eosinophil count decreased by 73% from baseline on 8th day, and by 87% on day 29 in patients treated with 10 mg/Kg, as compared to 32% and 34% in the placebo arm [28]. People treated with 10 mg/Kg also showed a reduction in blood ($p<0.001$) and sputum ($p<0.01$) eosinophils count post an allergen challenge, compared with placebo. Less apparent results were observed with 2.5 mg/Kg. A subsequent double-blind, randomized, placebo-controlled study, involved the administration of a single IV dose of 0.5mg/kg (n = 4), 2.5mg/kg (n = 4) or 10mg/kg (n = 4), or placebo (n = 6). This study confirmed a reduction of blood eosinophils count higher in people treated with mepolizumab (max decrease estimated 85%; IC_{50} of 0.45 mg/mL) [32]. Pouliquen REF also confirmed the reduction of blood eosinophils with all dosages and routes of administration, although the 12.5 mg dose was less effective. Overall, a significant and prompt reduction in peripheral eosinophils appeared since the third day, with a marginal reduction between 7 and the end of the study day (84 day) [29]. Eosinophils levels decreased not only in blood but also in sputum, starting from day 7 to the end of treatment period (day 84) in all groups, with the largest decreases in the SC 125 and 250 mg. Despite the effect of mepolizumab on peripheral eosinophil count is well ascertained, what happens in other organs is not well defined. A reduction has been observed both in bronchial mucosa (biopsies), where a median decrease of 55% from baseline was recorded at the ninth week of EV administration ($p = 0.009$ vs placebo), and in bone marrow samples where eosinophils showed a median reduction of 52%, again at the ninth week of treatment ($p = 0.003$ vs placebo). On the other hand, no statistically significant decrease in eosinophils could be demonstrated in bronchoalveolar lavage fluid (BALF) in patients treated with mepolizumab compared with placebo group ($p=0.4$), despite the median reduction from baseline was 79% [33].

5. BENRALIZUMAB (Fasenra ™ anti IL-5Ra)

Benralizumab is a humanized mAB of the $IgG_{1/k}$ class which binds D1 domain of IL-5Ra, or CD125 [34,35] that is expressed on eosinophils and basophils surface [20, 36]. This molecule is not fucosylated: this increases its affinity for the FcγRIIIa receptor, and achieves an antibody-dependent cell-mediated cytotoxicity (ADCC) [20,37]. Similarly to mepolizumab, also benralizumab the eligible patients are severe asthmatic people with high levels of eosinophils (> 300 cell/γL).

5.1) PHARMACOKINETIC (PK) CHARACTERISTICS OF BENRALIZUMAB

The PK characteristics of benralizumab was firstly investigated by Busse and colleagues, in a phase I, multicentre, open-label, sequential dose-escalation study, where the drug was administered in mild atopic asthmatic patients (age 18-45 years). The drug was given according to a dose-incremental design: cohort 1, 0.03 mg/kg; cohort 2, 0.1 mg/kg; cohort 3, 0.3 mg/kg; cohort 4, 1 mg/kg; and cohort 5, 3 mg/kg. Two additional cohorts were also added (cohort 6, 0.003 mg/kg; cohort 7, 0.0003 mg/kg), with the aim to identify the minimum effective dose. The results about mean C_{max}, at the doses of 0.03 and 3 mg/kg resulted approximatively dose-proportional (1 mg/mL to 82 mg/mL), as well as the AUC_{∞} (5 mg*d/mL to 775 mg*d/mL) [38]. As for other mAbs, also benralizumab, in its clearance, behaves like typical human IgG antibodies, with a mean elimination half-life of around 18 day, at the doses of 0.03 and 3 mg/kg. The data held by the researchers also showed a clearance of about 4 mL/kg/day, with a faster clearance and a shorter half-life in 0.03 mg/Kg group. The large volume of distribution, established between (52– 93 mL/Kg), suggested a possible drug binding to receptors IL-5Ra expressed by blood cells and/or its penetration into the extravascular tissue [34-38]. Pharmacokinetic effects observed in a Phase II safety study, where benralizumab was administered at three different doses (25, 100 and 200 mg) subcutaneously, showed a C_{max} between 1.2 and 14 μg/mL and an AUC_{∞} between 0.12 ± 0.071 and 1.2 ± 0.11 mg day/mL [40,41].

A pooled analysis took into consideration six different studies to characterize pharmacokinetic and pharmacodynamics characteristics of benralizumab [42]. The resulting pharmacokinetic model was

a two-compartment model with first-order elimination from the central compartment and with a first-order absorption from the dosing site regarding the SC administration [39]. The calculated mean systemic clearance was 0.321 L/day, which turned out to be within the therapeutic range of mAbs [43]. The estimated volume of distribution of the central and the peripheral compartments results 3.16 and 2.83 L. In SC administration route the absorption of benralizumab results slow, with a constant rate of 0.252/day with a mean absorption time of 3.97 days. Bioavailability turned out to be 52.6% [42].

5.2) PHARMACODYNAMIC (PD) CHARACTERISTICS OF BENRALIZUMAB

In the trial by Busse et al. benralizumab reduced the blood eosinophil counts, at dosages higher than 0.3 mg/kg within 24 hours after the administration. The reduction of eosinophil count persisted for at least 12 weeks [38]. In the mentioned phase II safety trial peripheral blood eosinophils count was reduced in all active groups starting from the seventh day, and the reduction was maintained for at least 161 days, this ensuring an acceptable security profile [40,41]. The effect of benralizumab on airways eosinophil population was evaluated in a Phase I study, assessing sputum, bone marrow and peripheral samples. The trial involved mild-to-moderate asthmatic people with sputum eosinophilia higher than 2.5% despite ICS treatment. The study design involved a single IV administration of 1 mg/Kg benralizumab or placebo (cohort 1) or three monthly SC doses of benralizumab 100 or 200 mg or placebo every 28 days (cohort 2). Both in the IV or SC administration airway mucosa eosinophil count was reduced, the median decrease from baseline was respectively 61.9% and 95.8%, and 18.7% and 89.9% in sputum sample. Furthermore people treated with benralizumab had a significant suppression of peripheral and bone marrow eosinophils. A similar observation was reported for basophils presenting IL-5Ra [44].

6. RESLIZUMAB (anti IL-5)

Reslizumab is an anti-IL-5 mAb, differently by the other anti IL-5 it belongs to the $IgG_{4/k}$ class, and it is prescribed in asthmatic patients with eosinophilic disorders [20]. Its formulation is only intravenous and weight-adjusted. Clinical trials where reslizumab was administered subcutaneously did not reach primary endpoint (exacerbations and OCS sparing) so IV administration route is the only available, at the moment (NCT02452190, NCT02501629) [45]. This route and the characteristics of product permit to weight-adjust the dose of drug as detailed below.

6.1) PHARMACOKINETIC (PK) CHARACTERISTICS OF RESLIZUMAB

The pharmacokinetic properties of reslizumab were measured in a trial with three groups of patients, healthy (n = 130), asthmatic (n = 438) and with nasal polyps (n = 236), with I.V 3.0 mg/kg of the drug. After infusion, the peak of drug concentration in serum was assessed, and resulted to decline in a biphasic manner. The calculated volume of distribution, settled in above 5 L, suggests a little extravascular distribution of the drug. AUC was calculated in 27.2 to 33.1 mg·h/mL. Reslizumab shows a clearance of about 7 mL/h, resulting in a linear and non-target mediate mechanism. The estimated half-life of reslizumab is 24 days. Usually, liver and kidney are not directly involved in the degradation/excretion of mAbs, thus it is unlikely that liver or kidney failure could modify the PK of the drug, and no dosage adjustment is required [46,48].

6.2) PHARMACODINAMIC (PD) CHARACTERISTICS OF RESLIZUMAB

The in vitro studies showed that reslizumab has a great affinity for IL-5 (Kd = 20 pmol/l) that it efficiently inhibits the binding of IL-5 to Ba/F3 cells (IC50 = 0.5 nmol/l), and it is also able to block the proliferation of human erythroleukemic TF-1 cells mediated by IL-5 [49]. The biological inhibition of IL-5 is consequent to the binding of the drug to the small region ERRR (glutamic acid, arginine, arginine, arginine) [50]. In animal model trials on guinea pigs, sensitized with ovalbumin, reslizumab at doses of 0.03 and 0.3 mg/kg administered intraperitoneally, was shown to suppress the airway hyperactivity, in concomitance with a reduction of pulmonary

eosinophilia [46]. The administration of 0.3 mg/kg of reslizumab in severe asthmatic patients with persistent symptoms, induced a reduction in blood eosinophils count ranging between 52.3% at 48 hours of administration to 18.9% after 30 days [51]. Increasing the dosage to 1.0 mg/kg eosinophils reduction the effect was more pronounced and higher up to day 30. Thus, Reslizumab was able to reduce eosinophil count in blood but also in sputum. A recent study, where reslizumab (3.0 mg/kg), after a 12 months of wash out period, was administered to 10 prednisone-dependent asthmatics, with previous failure of mepolizumab. In this study Reslizumab decreased both sputum by 91.2% ($P = 0.003$) and blood eosinophils by 87.4% ($P = 0.004$) as compared to placebo. In this trial, out of 10 of patients with persistent high eosinophils level despite mepolizumab, 6 achieved a <3% reduction with reslizumab [52].

(Table 1)

7. DUPILUMAB

Dupilumab is a fully humanized anti IL-4 receptor α monoclonal antibody, able to blocks both IL-4 and IL-13 [53]. The studied and next to marketing route of administration is the subcutaneous one, with the dose of 300 mg (150 mg/ml) every two weeks. PK and PD data about this antibody have been studied more in the subject with atopic dermatitis (for which the drug is already on the market) than the one with asthma.

7.1) PHARMACOKINETIC (PK) CHARACTERISTICS OF DUPILUMAB

After a single administration of dupilumab (SC), at the dose of 75-600 mg, Tmax recorded was 3-7 days with a bioavailability of 64%. The observed primarily distribution of dupilumab in vascular system allow to calculate a volume of distribution of about 4.6L. The mean ±SD steady-state trough concentrations ranged from 73.3±40.0 mcg/mL to 79.9±41.4 mcg/mL for 300 mg dose. Dupilumab, at higher concentrations is eliminated principally thought a non-

saturable proteolytic pathway, instead at low concentrations by a non-linear saturable IL-4R α target-mediated system [54].

7.2) PHARMACODINAMIC (PD) CHARACTERISTICS OF DUPILUMAB

In clinical trials, dupilumab has been able to reduce concentrations of type 2 immunity biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17) [54]. The action of dupilumab allow also to reduce fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, allergen specific IgE, TARC, and periostin in asthma subjects in about 2 weeks, and total IgE concentration but in a longer time, with a median percent reduction from baseline in total IgE concentrations of 52% at Week 24 [55] and 70% at Week 52 [56]. For FeNO, the mean percent reduction from baseline at Week 2 was 35% [55] and 24% [56].

8. CONCLUSIONS

The development and marketing of biological agents as therapeutic add-on in severe asthma allowed to provide a clinical and therapeutic advancement for patients with uncontrolled asthma. Clinical trials has proved that all these drugs, though through different mechanisms, have been shown to have a good profile of effectiveness and safety [21,57-70]. (Table 2)

In the context of anti IL-5 drugs, and TH2-high asthma, eosinophils maintain a central role in the pathogenesis of the disease. Certainly, the peripheral differential blood count is the most simple and feasible parameter to decide the prescription status of the anti-IL5 drugs. Nonetheless, it should be remembered that eosinophils are mainly marginated in specific organs (i.e. lungs), where they exert their biological action. Therefore it would be correct to evaluate the effect of drugs also at this level, particularly in low/not responder patients. Indeed in the above mentioned manuscript by Mukherjee, despite the low number of patients treated, it seems that a better response could be assessed in whom where the drug reduce more relevantly sputum eosinophils [52]. It is interesting to underline

that the different action of these drugs (two blocking the cytokine and one its receptor), lead to a common result but in a different way. Acting directly on the cytokine means modulate its action on eosinophils, usually normalizing the number at the peripheral level, as regards the benralizumab, having as its goal the receptor and a pro apoptotic action, we are going to eliminate this population. A direct action on the cell was found to be faster than that on the cytokine, but with the unknown factor of the suppression of a cell population.

The available studies demonstrate that the different pharmacokinetic asset depends on the administration route, therefore the more appropriate administration is of relevance for each drug [71]. Furthermore, in a world where medicine is becoming increasingly personalized, where drugs are modelled on the immunological characteristics of patients, the pharmacokinetic and pharmacodynamic characteristics of biological drugs could play an important role in choosing one drug over another. To choose a drug at the moment we are rightly referring to the mechanism of action, but in the future could be also useful to consider also its pharmacokinetic and pharmacodynamic pattern in order to perform a medicine of precision [72].

In addition, drugs that act on TH2 phenotype mechanisms will be able soon to respond to those patients when standard of care therapies are not sufficient. Finally, as a perspective, in allergic asthma the use of allergen-specific immunotherapy in combination with biologicals could be also considered, to expand the field of treatments of severe asthma [73].

9. EXPERT OPINION

Starting with omalizumab then with mepolizumab currently with benralizumab and reslizumab and soon with dupilumab, additional therapeutic proposals are available for asthmatic allergic and hypereosinophilic patients, where the standard of care is ineffective. The pharmacokinetic and pharmacodynamic studies, so far performed, allowed to better define the mechanisms of action and characteristics of these drugs. However, not all drugs currently marketed have unravelled all doubts. Further observations are needed, particularly in real life, to evaluate the behaviour of such

molecules in relation, for instance, to the administration of other drugs [74]. A further point to be clarified is the one of the prescribing overlap, both among drugs with the same therapeutic target (anti IL-5 and IL-5r), and in allergic patients but with high blood eosinophils level.

No direct head to head comparison with the mentioned drugs is available, however some data suggest that omalizumab is effective, regardless of eosinophil count [57], and that mepolizumab can control hypereosinophilic patients who had a poor response to omalizumab [75]. Benralizumab probably requires a separate discussion, since the different mechanism of action that involves also basophils CALIMA [63] and SIROCCO [64]. This latter molecule showed an efficacy substantially independent from IgE concentration [76]. No direct data are available in reslizumab trials. Dupilumab demonstrated its efficacy in allergic diseases as atopic dermatitis and also atopic patients. Due to the fact that all these drugs seems to be effective in some cases both in eosinophilic than in allergic patients, specific clinical trials will be needed in this group of patients with common prescription characteristics.

Additionally, administration route could be a factor able to modify PK and PD and consequently, at least hypothetically, able to differentiate action of these drugs. Indeed, a IV administration could offer the advantage of avoiding presystemic degradation, allowing therefore to obtain a greater concentration of drug [46,77]. However, it is true that the route of administration SC proved to be equally effective and able to reduce the eosinophilic count, improving the symptoms of the patients, in the same way as with EV.

The path of biological drugs for the control of severe asthma is certainly right but needs further investigation to better understand the mechanisms of these drugs. A greater understanding would also be very useful for targeting therapy, making it more and more personalized and precise, sewing it on the patient.

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Declaration of interest

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Drug	Dose	References	Bioavailability	AUC	Cmax	CL	Vss	T1/2
Omalizumab	0.5 mg/kg s.c	[13,14]	62%	n.a.	n.a.	2.4 ± 1.1 mL/Kg/day	78 ± 32 mL/Kg	26 days
Mepolizumab	250 mg s.c	[21]	75%	1,238 ± 228 µg d/mL	34.1–38.2±7.3–12.1mg/mL	1.9 to 3.3 mL/day/kg	55 to 85 mL/kg	11 - 26days
Benralizumab	0.03–3 mg/kg i.v. 25–200 mg s.c.	[38] [40]	n.a. 52.6%	5 ± 2–775 ± 110 µg∗d/mL 0.12 ± 0.071–1.2 ± 0.11 mg day/mL	1± 0.3–82 ± 18µg/mL 1.2–14 µg/mL	7 ± 3–4 ± 0.6 mL/kg/day	65 ± 28–71 ± 18 mL/kg	7 ± 2–16 ± 3 days
Reslizumab	3.0mg/kg i.v.	[48]	n.a.	27.2 to 33.1 mg·h/mL	86.7 to 105.33 µg/mL	≈ 7 mL/h	≈ 5 L	≈ 24 days
Dupilumab	75-600 mg s.c.	[54]	64%	73.3±40.0 mcg/mL to 79.9±41.4 mcg/mL	n.a.	0.126 L/day	4.6 L	3 – 7 days

Legenda: AUC = area under the serum concentration–time curve, Cmax = maximum plasma concentrations, CL = clearance; Vss = volume of distribution at steady state; T ½ = elimination half life: n.a.= not available

Table 1

Table 2 . Main results about efficacy and safety of MAbs in severe asthma			
Authors	**Exacerbations**	**Other endpoints**	**Common and serious adverse events**
OMALIZUMAB			
[57-59]	⇩ Exacerbations v.s. placebo	Lower emergency visit rate (0.24 vs 0.43, P=0.038) ICS dose reduction ≥50% (median 75% vs 50%, p<0.001) and discontinuation (39.6% vs 19.1%, p<0.001), ICS dose reduction ≥50% (median 79% vs 55%, p<0 .001) and discontinuation (43% vs 19%, p < 0.01)	Lower respiratory tract infections, nasopharyngitis, headache, sinusitis, influenza, cough, upper respiratory tract infection, injection site reactions Serious asthma exacerbations requiring hospitalization, urticarial, depression, appendicitis, flu-like syndrome, suspected eosinophilic granuloma of the skull, intestinal villous adenoma with dysplasia, infectious mononucleosis, squamous cell carcinoma of the face
MEPOLIZUMAB			
[21, 60-62]	⇩ Exacerbations (53% s.c. MENSA, 32% SIRIUS, 48% DREAM)	⇧ FEV_1 (98 ml s.c. MENSA), no change in DREAM ACQ-5 improve MENSA, SIRIUS, no variation in DREAM	Nasopharyngitis, upper respiratory tract infection and headache Incidence of 7 % in intra-venous group, 8 % in subcutaneous, 14 % placebo
RESLIZUMAB			
[65-68]	⇩ Exacerbations (61%, 73%)	Improve QoL	Worsening of asthma symptoms, upper respiratory tract infections, nasopharyngitis, 2 anaphylactic reactions, pneumonia, worsening of asthma
BENRALIZUMAB			
[63,64]	⇩Exacerbations (45 % in Q4W, 51 % in Q8W), (36 % in Q4W 28 % in Q8W)	⇧FEV1 (106 ml Q4W, 159 ml Q8W), (125 ml Q4W, 116 ml Q8W)	Nasopharyngitis, worsening of asthma, headache, dizziness, cough, pyrexia, bronchitis, anxiety, hyperhidrosis, injection site reaction ,allergic granulomatous angioitis, panic attack, paraesthesia, injection-site erythema, urticarial, herpes zoster, chest pain, pyrexia, tachycardia and anxiety, uterine leiomyoma, erythema nodosum, thyroid storm
DUPILUMAB			
[69,70]	⇩ asthma exacerbation (46%)	⇧FEV_1 (+130 ml) change of ACQ5 score	conjunctivitis, injection site reactions, and local herpes simplex infections, Nasopharyngitis, urinary tract infection, upper respiratory tract

		Decrease OCS dose	infection Hypereosinophilia