Responses to biological therapies in eosinophilic severe asthma

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To the Editor:

A number of severe asthma (SA) subjects remain uncontrolled despite high doses of inhaled corticosteroids (CS) and a second controller [1,2]. Biological therapies, by reducing severe asthma exacerbations (SAE) and improving lung function, open promising and hopeful expectations. Currently indicated in SA are Omalizumab that blocks IgE, Mepolizumab and Reslizumab directed against free-serum-IL-5, Benralizumab that depletes eosinophils by blocking IL-5-receptor, and Dupilumab that blocks IL-4/IL-13 axis. All are more effective in T2 and eosinophilic asthma but even in such phenotypes, there is an unpredictable variability in individual response. So, it is recommended to re-evaluate patients in the first year of treatment and only continue it if the response is adequate [3]. The National Institute for Health and Care Excellence (NICE) defines an adequate response as reduction by more than half in either, SAE number or CS dose needed to maintain control [3].

We report the behavior to biological therapies in two patients with SA [1,2]. Given their similar asthma characterization we aprioristically presumed comparable responses.
Subject-1: 51-years-old female, diagnosed of asthma and rhinosinusal polyps for 30-years. She suffers from adrenal insufficiency for 3-years and requires Metilprednisolone (5mg) daily. She had 3 episodes of eosinophilic pneumonia. Total serum IgE 78-422 kU/L and blood eosinophilia ranges 100-300/μL. Asthma Control Test (ACT) scores ranges 11-25.

Subject-2: 51-years-old male, diagnosed of asthma and rhinosinusal polyps for 15-years. Total serum IgE ranges 202-330 kU/L, Sputum eosinophilia 5%-75% and blood eosinophils 300-800/μL. ACT scores ranges 8-25.

None of them is obese (body mass indexes: 29 and 28). Their tests for dyspnea and anxiety are always negative. Both are sensitized to perennial allergens (subject-1 to Cupressus pollen and animal danders and Subject-2 to D. pteronyssinus), have documented bronchial reversibility and tolerate NSAIDs. They receive Fluticasone (1000μg), Formoterol (40μg) and Tiotropium (5μg). Their treatment adhesion is good.

We calculated annual-averaged SAE by multiplying SAEs number by 12 and dividing it by the number of months in which they were recorded. Treatment periods’ duration was different for each patient depending upon clinical decisions (Figure-1). In both, Omalizumab for more than 1-year failed to reduce SAE (from 4/yr to 6.67/yr in subject-1 and from 6.0/yr to 7.2/yr in subject-2).

Following Omalizumab end, Subject-1 suffered an episode of eosinophilic pneumonia. Since she started Mepolizumab (100mg/4w) in October/2017, she is symptom-free, no SAE and her FEV1 mean values have increased in 340 mL.
Six months after Omalizumab cessation, Subject-2 initiated Mepolizumab at 100mg/4w. After the first 4 months, SAEs reappeared with their usual cadence. According to Literature [4], we decided together with the patient, the Ethics Commission and the Pharmacy Department, to increase Mepolizumab to 200mg/2w. During the following 10 months, SAE rate dropped to 4.8/yr (33%) but the patient complained from muscle pain that interfered with his activity. In August/2018, we stopped Mepolizumab and started intravenous (iv), weight-adjusted Reslizumab (30mg/4w). The initially milder muscle symptoms disappeared and SAE rate dropped to 2.4 (66%). However, since anti-IL-5 therapies started, his FEV1 mean values dropped in 237 mL and Exhaled Nitric Oxide (ENO) mean values increased from 70ppb to 106ppb. Moreover, SAEs became less sensitive to systemic-CS requiring longer treatments with them (from 5 to 10 days).

Despite conventional treatment, both subjects, with high eosinophils and SAE rate, were candidates to anti-IL-5 therapies but their behavior to Mepolizumab radically differed. Mepolizumab was absolutely successful in subject-1 who is symptom-free over 1-year and her lung function has increased. After an initial 4-months improvement with Mepolizumab, subject-2 returned to his usual cadency of SAEs. In premarketing trials, doses of iv-Mepolizumab of 750mg and 75mg similarly reduced SAEs and blood eosinophils. Nevertheless, the iv-75mg dose was significantly less effective in reducing sputum eosinophils [5] and was the equivalent to the subcutaneous(sc)-100mg dose finally marketed [6]. It is possible that the administration of antibody at suboptimal doses lead to immune-complex formation that would constitute a local reservoir of IL-5 perpetuating bronchial eosinophilic inflammation [7]. Therefore, we increased sc-Mepolizumab to 200mg/2w and then, SAEs dropped in 33% but he had disabling muscular symptoms.
Intravenous-Reslizumab also blocks free IL-5, but its dose is adjusted for body weight, allowing dispensation of higher doses. Since both, dosing and route of administration can modify clinical response to anti-IL-5 therapies [4,7] we changed high-dose-Mepolizumab by iv-Reslizumab. After 8 months of treatment, SAE fell 66% but for us, the response is unsatisfactory as both, ENO and FEV1 mean values worsened since anti-IL-5 therapy beginning, and daily disturbing symptoms of asthma reappeared.

It is speculated that respiratory epithelium can be so damaged in some SA subjects that in response to stimuli it releases epithelial-derived alarmins (thymic stromal lymphopoietin, IL-33, IL-25) that can promote local eosinopoiesis making systemic anti-IL-5 therapies ineffective [7]. In next future, we will try to control subject-2 asthma by completely blocking eosinophils with Benralizumab.

ENO values were much higher in Subject-2 and could account for the different response to anti-IL-5 therapies. However Subject-1 was on daily oral corticosteroids and ENO is highly sensitive to them. Since ENO production is T2 cells-related, Dupilumab by blocking IL-4/IL-13 axis could be an alternative in Subject-2 although we ignore the effect of the initial Dupilumab-induced eosinophils increase [8]. Also hypothetically, we could associate both therapies: Dupilumab and Benralizumab.

In real-life, leaving aside the inclusion criteria managed in clinical trials, we are far from profiling the indicators that predict SA patients’ response to biological therapies. Blood eosinophils, ENO values or SAE rate are weak markers that do not regard either, asthma heterogeneity or the not necessarily parallel change in its different faces (functional, clinical, inflammatory) as happened to subject-2 who despite reducing SEA had functional deterioration. No available data allows us to presume the superiority of
any anti-asthma biological therapy so that we need to empirically obtain such information from real-life practice what means a great debt to our patients. According to Drazen [9], it is essential to have independent comparative studies made by well-established public institutions in which therapies are supplied cost-free by laboratories. Only then, we certainly will be aware of prescribing our patients with the most accurate treatment. To finish, the lower sensitivity of Subject-2 SAE to CS, may be thought in the context of the anti-IL-5-therapies induced eosinopenia and should lead us to revisit the role of oral-CS treatment [10].

Disclosures:

Dr. MARIA J reports personal fees from GSK outside the submitted work.

E. Arroabarren has nothing to disclose.

MJ Zavala has nothing to disclose.

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References


Evolution of annualized SAE rate (Fig. 1a), FEV₁ mean values (Fig. 1b), ACT (Fig.1c), and ENO mean values (Fig. 1d) for each time period:

Before starting treatment with Omalizumab

During treatment with Omalizumab

After treatment with Omalizumab

During treatment with Mepolizumab at 100mg/4W

Only for subject-2

During treatment with Mepolizumab at 200mg/2w

During treatment with Reslizumab