



Biologicals for severe asthma: what we can learn from real-life experiences?

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Purpose of review

Severe asthma is a serious disease affecting about 5–10% of asthmatic patients. Often patients with this kind of asthma requires periodical courses or daily intake of oral corticosteroids, to control symptoms. In the last few years several biological drugs have been developed with the aim to decrease exacerbations and reduce or suspend intake of systemic steroids in severe asthmatic patients. Clinical trials demonstrated the efficacy and the safety of biological antibodies in asthma, but it is already known that randomized controlled trials alone are not sufficient to provide complete information on a drug.

Recent findings

After marketing of monoclonal antibodies has been developed several real-life studies with the aim to observe how drugs, tested only on trial patients, are able to provide adequate effectiveness even on 'real' patients; indeed, it is well known that the latter differ in some characteristics from the patients of the trials.

Summary

The results of this analysis confirm the good efficacy of the biologics similarly in real-life patients, also ensuring a promising safety even in periods of observation longer than those of the randomized controlled trials.

Keywords

biological antibodies, personalized medicine, precision medicine, real life, severe asthma

INTRODUCTION

Asthma is a common airway disease, whose worldwide prevalence reaches 300 million people, with an estimated increase of around 50% in next 10 years, making it, therefore, the most frequent chronic respiratory disease (<http://ginasthma.org/2017-gina-report-global-strat>; accessed on 24 September 2019). The mean incidence of this disease, in Caucasian population, is 10%, with peaking in Anglo-Saxon-speaking countries, such as the UK and New Zealand, with a 15% of incidence [1]. Although asthma is a disease that in most cases can be controlled by inhaled therapies, in a variable percentage, from 5 to 10% of affected patients, these therapies are not sufficient to achieve control and patients need to improve their therapy with other drugs, often including oral corticosteroids (OCS) [2]. According to American Thoracic Society and European Respiratory Society document [3], these patients can be defined as severely uncontrolled. In the last few years, different biological drugs (monoclonal antibodies, MABs) were developed and marketed with different aims, the most relevant, considered as principal endpoints of clinical trials, were both the reduction of daily OCS intake in

steroid-dependent patients or annual courses of OCS in the nondependents, the reduction of exacerbations, the improvement of quality of life (QoL) and maintaining the control of the disease. In addition, the contribution of these drugs in improving respiratory function has also been evaluated in clinical trials. A deepest knowledge of the mechanisms involved in the pathogenesis of asthma allowed to develop drugs principally directed to type 2 inflammation, that is characterized by the expression of T-helper 2 cytokines as interleukin (IL) 4, IL-5, IL-13 and by the action of innate lymphoid cells (ILC)2 [4^a,5] and eosinophils.

The effect of these MABs against cytokines was extensively assessed in randomized controlled clinical trials (RCTs) where patients, treated with

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Curr Opin Allergy Clin Immunol 2019, 19:000–000

DOI:10.1097/ACI.0000000000000600

KEY POINTS

- Severe asthma is a disease not only with a high clinical but also socioeconomic impact, and the development of new biological drugs has made it possible to provide a therapeutic response to many patients.
- Although they must be tested in randomized controlled clinical trials, the drugs, once marketed, are often used by patients who would not always be randomizable in the trials.
- Real-life trials are, therefore, essential in order to assess, after marketing, how active a drug is also on the 'uncontrolled' population of trials.
- The five drugs available for asthma seem to have excellent results even in real-life trials, proving to be able to reduce exacerbations, OCS intake, and improve control of the disease.
- Further trials in real life will be necessary to verify the efficacy and long-term safety, and also to evaluate how much to continue the therapy, and what happens at the suspension of the drug after long periods of administration.

experimental drugs, were preventively chosen according to more or less strict inclusion and exclusion criteria.

Although RCTs remain the most widely used and robust method to study new drugs, they could be limited by the fact that the inclusion and exclusion criteria are often too 'limiting' [6]. Indeed, several studies demonstrated that people treated in real life differ from those enrolled in trials [7,8], and other studies reported that the screening failure exceeded 70% in several RCTs [9]. Therefore, the studies carried out in real life are central, in order to confirm the efficacy and safety of previously studied drugs.

AVAILABLE MONOCLONAL ANTIBODIES IN SEVERE ASTHMA

As previously mentioned, severe asthma research focused its attention on the mechanisms underlying the disease. Particularly patients could be endotyped according to the inflammation characteristics in type 2 (T2) [10,11] and nontype 2 inflammation [12,13]. Type 2 endotype is the better known and several mechanisms has been demonstrated to be involved in the development of asthma, particularly IL-5, IL-4 and IL-13, innate lymphoid cells (ILC)2 [14] and the IgE-mediated form of this disease. If in T2 inflammation, different drugs have been developed and marketed, although the same is not true for non-T2 asthma that, at present, can benefit of few therapeutic options.

Until today, there are five biological drugs available for severe asthmatic patients, Omalizumab (OMA), Mepolizumab (MEP), Reslizumab (RES) and Benralizumab (BEN), and Dupilumab (DUP).

Omalizumab

OMA is a humanized recombinant antibody with a murine region, able to bind IgE with high affinity, thus impeding the activation of mast cells and interrupting basophil degranulation [15]. Since first clinical trials, the primary endpoint of OMA was the reduction of exacerbations, confirmed in the RCT described by Busse *et al.* [16], with a decrease both in the stable steroid phase [0.28 vs. 0.54 ($P=0.006$) and 14.6 vs. 23.3% ($P=0.009$), respectively] and during the steroid reduction phase [0.39 vs. 0.66 ($P=0.003$) and 21.3 vs. 32.3% ($P=0.004$), respectively], and in the subsequent trial with a reduction of 58% of exacerbations in stable-steroid phase ($P<0.001$) and 52% in steroid-reduction one ($P<0.001$) compared with placebo [17]. Also an improvement in control of the disease and in QoL was demonstrated [18]. Also subsequent studies demonstrate the efficacy of OMA in the reduction of exacerbations, as described by Hanania *et al.* [19] where the ratio of reduction of exacerbations in treated vs. placebo resulted 0.66 vs. 0.88 ($P=0.006$). As for exacerbations, OMA was also evaluated as OCS-sparing agent, with favourable results [20].

Mepolizumab

The first developed and commercialized drug against IL-5 was MEP. It is a MAb belonging to the IgG1/k class [21,22]. Indeed, the first trials did not achieve the endpoint of reduction of exacerbations [23]. The desired result was subsequently achieved once the patients had been carefully selected: severe asthma with an eosinophilic count greater than 300 cells/ μ l [24]. As for OMA, also MEP was tested for the reduction of exacerbations. The DREAM study showed a decrease of exacerbations in active arm, compared with placebo, of 48% [95% confidence interval (CI) 31–61%; $P<0.0001$] in those who has been treated with 75 mg intravenously, 39% (19–54%; $P=0.0005$) in 250 mg intravenous group, 52% (36–64%; $P<0.0001$) in 750 mg intravenous group [25]. Similar results were reported in the MENSA trial, where MEP was administered both subcutaneously and intravenously with a decrease, respectively, of 47% (95% CI 28–60) in intravenous administration and 53% (95% CI 36–65) in the subcutaneous route [26]. The effect of MEP on OCS intake was evaluated in the SIRIUS trial where reduction of OCS was 2.39 times greater in

active patients as compared with the placebo group (95% CI 1.25–4.56; $P=0.008$) [27]. Further analyses were conducted in the MUSCA trial, where MEP demonstrated its efficacy in improving the QoL in treated patients [28].

Reslizumab

RES, another MAb against IL-5, differs from MEP because it belongs to the IgG4/k class, and its formulation is available only in intravenous form [29]. As previously observed with OMA and MEP, RES also demonstrated an efficacy in severe asthmatic patients, in reducing exacerbations [study 1: rate ratio (RR) 0.50 (95% CI 0.37–0.67); study 2: 0.41 (0.28–0.59); both $P<0.0001$] [30], improving FEV1 [difference vs. placebo (reslizumab 0.3 and 3.0 mg/kg), 115 ml (95% CI 16–215; $P=0.0237$) and 160 ml (95% CI 60–259; $P=.0018$)] [31]. Unlike MEP, RES failed the trials with subcutaneous administration, maintaining, therefore, the only intravenous administration. A second difference between these two drugs is that MEP prescription is linked to a minimum historical value of at least 300 eosinophils/ μ l, whereas for RES, the cut off value is 400/ μ l.

Benralizumab

Regarding BEN, its mechanism, despite it is aimed at asthmatic patients with blood hypereosinophilia ($>300/\mu$ l), it does not directly bind circulating IL-5, but block its receptor alpha, promoting cell's apoptosis [32]. As for the above-mentioned biologics BEN is also supported by clinical trials proving its efficacy in reducing exacerbations both in Q4W regimen [rate 0.60 (95% CI 0.48–0.74), rate ratio 0.64 (95% CI 0.49–0.85), $P=0.0018$, $n=241$] and Q8W regimen [rate 0.66 (95% CI 0.54–0.82), rate ratio 0.72 (95% CI 0.54–0.95), $P=0.0188$, $n=239$] compared with placebo [rate 0.93 (95% CI 0.77–1.12), $n=248$] [33].

Dupilumab

Dupilumab is a fully humanized Mab that is able to block both IL-4 and IL-13, with its action on IL-4 receptor α [22]. Even in the case of DUP, principal clinical trials observe the effect of the drug, in patients with severe uncontrolled asthma, with the aim to reduce exacerbations and OCS intake. Rabe *et al.* described a reduction of 70.1% of OCS dose in systemic steroid-dependent patients with 48% of enrolled patients able to reach a discontinuation of OCS therapy [34]. Exacerbation reduction has been described in another trial, enrolling 1902 patients, in which a reduction has been

demonstrated both in patients treated with 200 and 300 mg, compared with placebo [35].

REAL-LIFE STUDIES

Omalizumab

Due to its early availability as the unique biologic anti IgE Mab for severe asthma, for more than 10 years, OMA was widely investigated in a number of real-life studies [36–38]. This great amount of data reinforced and clarified the evidence coming from the RCTs, which demonstrated the drug safety and efficacy but could not satisfy a number of open questions [7]. In fact, because of their short duration and experimental setting quite far from the daily clinical practice, RCTs did not provide extensive data concerning: long-term effects of omalizumab (safety and efficacy), especially after discontinuation; its impact on asthma comorbidities; adherence rate and reasons for drop-out; patient selection and identification of nonresponders. In the last years, many omalizumab-related clinical outcomes were specifically investigated by real-life studies [36,38]. Despite some differences between the study populations in the real-life setting and in RCTs (patients in real-life are significantly older, show a significantly lower baseline FEV1%, a higher total serum IgE title and the number of current smokers is highly variable) [7], the real-life evidence confirms the main clinical outcomes observed in RCTs: the reduction of exacerbation rate, a better symptoms control and the improvement in lung function after at least 4 months' treatment [36,38]. Other real-life evidence show that pretreatment FeNO values and blood eosinophils levels could be taken as predictors of persistent reversal of airway obstruction [39].

A smaller number of real-life studies specifically addressed the steroid-sparing effect of omalizumab. Overall, the patients interested by reduction/discontinuation of OCSs on average reduced by 58% at 12 months, by 53.1% at 23–32 months, and by 83.1% in the period of further observation. The mean daily intake decreased from 55.1% at 5–9 months to 68.6% at 12 months, to 63.6% at 23–32 months [36].

The relevance of patients' reported outcomes has recently increased in the frame of treatment evaluation, even under the regulatory perspective. Some specific tools including Asthma Control Questionnaire (ACQ), Brief Illness Perception Questionnaire, and Euro QoL five-dimensional three-level questionnaire (EQ-5D-3L) have been analysed in longitudinal studies, which demonstrated that omalizumab significantly improves illness perception and QoL after 12 months of treatment [40,41].

Although chronic rhinosinusitis with nasal polyps is one of the most relevant comorbidities of severe asthma, few and small studies specifically investigated the effectiveness of OMA in such populations [7,42,43]. Furthermore, the efficacy of OMA in asthma seems to be independent of the presence of nasal polyposis.

Some specific OMA-related outcomes require further investigations: the optimal duration of omalizumab therapy and the persistence of asthma control after treatment withdrawal still remains controversial. Data in real life are extremely limited; a recent study conducted on 49 patients reported a persisting effect for at least 4 years after discontinuation of a 6 years' long omalizumab treatment in 60% of patients [44²²]. Finally, predictors of omalizumab efficacy need to be better defined. In fact, lack of efficacy in patients matching the prescription criteria represents one of the most common reasons for treatment discontinuation in real-life studies [45]; furthermore, the relevance of blood eosinophils, still considered the most accurate biomarkers, has been recently questioned [46,47].

Mepolizumab

The real-life MEP experience firstly confirmed the difference between patients treated in RCTs and in real life: eosinophils baseline value, lung function tests (FEV1 and FVC), presence of comorbidities (i.e. nasal polyps) resulted higher in real life than in RCTs [48²³]. The earliest observation included a relatively small number of patients [49], then increased to 61 [50], and finally to 138 patients treated for 12 months with the drug. These patients confirmed or even improved the findings of clinical trials, with a decrease of exacerbations rate of 81% compared with pre-MEP value. In this study, the effect of the drug as a possible sparing of OCS was also evaluated. As already shown in the SIRIUS study [27], MEP could reduce the daily dose of OCS (from 10.1 to 2.0 mg/day) and, in most patients (72%), complete discontinuation was achieved [51²⁴]. Also in this clinical report, a higher presence of nasal polyps in real patients, despite without a significant reduction after 12 months of therapy. In real-life studies, one of the most interesting evaluation is the observation of what happens in patients previously unsuccessfully treated with other MABs. This assessment was described in a recent clinical trial, OSMO, where the primary end-point, the change of Asthma Control Questionnaire (ACQ-5), was achieved, confirming a positive effect of MEP on the QoL of treated patients [50]. Real-life experience instead take into consideration the effect of drug in the reduction of exacerbations, OCS intake, and improvement of FEV1. A reduction of 81% of

exacerbations, 82% of hospitalization, and 70% of the number of OCS-dependent patient were described by authors [52]. Also in this case, MEP did not result particularly effective on nasal polyps, despite the evaluation of variation of number, sizes, and characteristics of polyps were not analysed in detail. Furthermore, this study allowed to evaluate the safety profile of the drug also performing a switch from a MAB to another one in a shorter time compared with the usual required by RCTs, safeguarding a comforting safety profile. As for OMA, also with MEP, one of the main question is the duration of therapy. Differently by OMA, MEP has a lower marketing history, so very few data are available on this aspect. In literature, there is only one case report about a patient where MEP was discontinued after 4 years and 11 months of therapy. In this single case, the patient had, after 2 months, a serious exacerbation requiring hospitalization. Interestingly, after re-starting MEP, the patient become controlled again [53]. Despite the numerous real-life work, because of the fact that MEP is a recently marketed drug, similar studies will be needed to confirm its effectiveness, safety and deepen the point on suspension, with longer observation time than only 1 year.

Reslizumab and benralizumab

Literature is poor about real-life experiences about these two drugs. The only available data concern a group of 13 patients treated for at least 1 month with BEN, whose eosinophils count decreased from 814.7 ± 292.3 to 51.3 ± 97.5 cells/ μ l and an increase of ACT score from 15.31 ± 2.78 to 21.15 ± 3.58 [54].

Dupilumab

Due to the very recent authorization of DUP in severe asthma, only few data in real life about this drug are available. The only data is the one about a case report of a patient treated with DUP because of a severe asthma, that immediately showed an improvement of symptoms and a good control of the disease, despite that authors reported an eosinophilic pneumonia occurred during the therapy [55]. As already pointed out in the case of BEN and RES, also in the case of DUP, numerous other real life observations will be necessary in order to monitor the effectiveness and safety of a very promising drug but with poor data in real life.

Experience from real life

We described herein the results obtained in RCT trials and in the real-life experience with the currently commercialized MABs for severe asthma. As

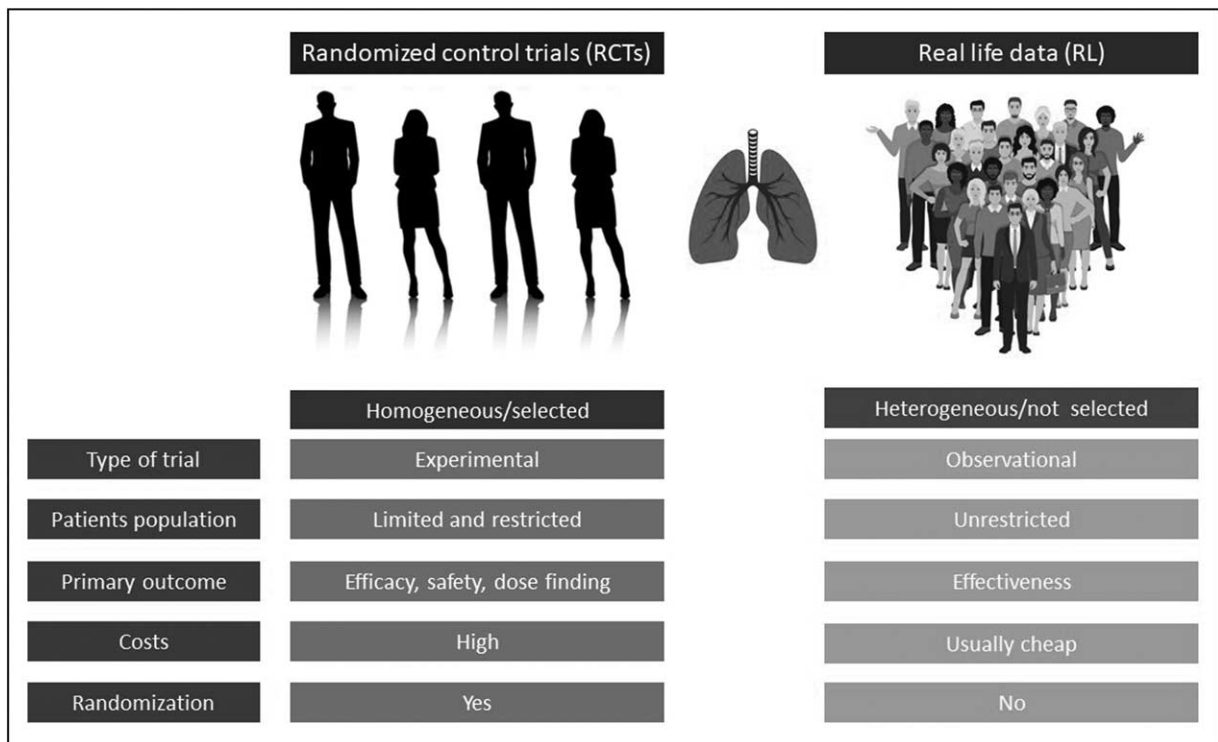


FIGURE 1. Principal characteristics of randomized controlled trials compared with the one of real-life.

already described for other diseases, also in severe asthma there is a discrepancy in term of results and patients' characteristics between trials and real life. In some studies, particularly those concerning MEP in real life, the results related to the administration of the drug were found to be even better than what shown in the respective RCTs.

The importance of trials in real life can also be observed in terms of drug safety. We know that the main differences between RCTs and real life are related to the criteria of inclusion and exclusion from randomized trials, sometimes quite restrictive. In real life, the patients treated, subject to the local criteria of prescription (e.g. number of IgE, and eosinophils), are treated although they may be affected by comorbidities, sometimes even severe. The experience in real life shows us, at least with regard to the drugs described in this manuscript, how safety is also maintained in patients with numerous and severe associated diseases. Studies in real life will also be necessary with regard to the duration of the treatment. The time limit for RCTs, which is absolutely adequate for this type of study, is insufficient if the objective is the long-term effect of the drug and especially if we want to observe if the patients are controlled over time even after discontinuation. At the moment, at least for anti-IL-5 drugs, given the short duration of the marketing there are only a few data, albeit very

interesting, limited to case reports. The real life will, therefore, not only allow us to observe patients treated for long periods of time, obtaining data on safety, effectiveness but also on what happens to the suspension after a long period of treatment (Fig. 1).

CONCLUSION

In conclusion, the RL studies are very important for the observation of the products marketed and previously evaluated only in clinical trials. As far as severe asthma is concerned, currently five drugs are on the market that have guaranteed promising results in the control of the disease, in reducing the exacerbations, in reducing OCS intake, and in improving the QoL of the treated patients. As far as OMA is concerned, numerous data on its efficacy and safety in real patients are available in the literature, despite the short period of commercialization, MEP also has a rich literature on efficacy, safety, effect in patients previously treated with other biologicals without success and a case of suspension after years of administration. Further studies, with a longer observation period, will be necessary in order to confirm and deepen the excellent results described so far. As far as RES, DUP, and BEN are concerned, the data in real life are few, also because of their more recent commercialization compared with OMA and MEP.

Acknowledgements

CIPRO (Centro Interprofessionale Pneumologico di Ricerca ed Organizzazione) Genoa. E.C., L.D.F., A.M.R., E.T. and A.M. for their help in drafting manuscript.

Authorship: All the signing authors contributed to data collection, analysis, and clinical work. All approved the final version and its submission.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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