The North-Western Italian experience with anti IL-5 therapy and comparison with regulatory trials

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Abstract

Background: The severe forms of asthma represent a major burden, because of severity of symptoms, costs and impact on everyday life. Recently, Mepolizumab (MEP) was approved and marketed for the treatment of hypereosinophilic severe asthma. This anti-IL-5 monoclonal antibody reduced exacerbation rates and oral corticosteroid (OCS) use in well selected patients. The aim of this study was to evaluate the characteristics of patients receiving MEP in a real-life setting. Thus, we describe a retrospective analysis of patients treated with MEP in six centres in North Western Italy, including those who participated in the main regulatory trials.

Methods: The baseline data, before prescription, from six North Western Italy severe asthma clinics, between June 1st 2017 and December 31st 2017, were evaluated. The collected real-life data were then compared with those of SIRIUS, MENSA, DREAM and MUSCA trials.

Results: Sixty-five patients were included (45% female; mean age 56 years; age range 19–84). Main observed differences with regulatory trials could be observed in eosinophils blood count at baseline, where the mean of our real-life patients (653 cells/μL) was overall higher than the one of all trials (240 cells/μL, 296 cells/μL, 253 cells/μL; \( p < 0.0001 \)). The incidence of polyposis was also significantly higher in our sample (72% vs. 24%, 49%, 10%, 19%; \( p < 0.0001 \)). The daily average dose of OCS was lower in our real-life patients (9 mg), if compared with SIRIUS (13.7 mg), MENSA (13.2) and MUSCA (13), and similar to the data published in DREAM (10.8).

Conclusions: The comparison of real-life patients’ characteristics with regulatory trials, displayed several apparent discrepancies. The demographic and clinical aspects were similar in all groups, whereas other features (eosinophil count, pulmonary function FEV1%) differed. These data, for the first time, could represent a basis for a more accurate prescription of the drug.

Keywords: Severe asthma, Uncontrolled asthma, Eosinophilic asthma, Mepolizumab, IL-5, Real-life

Background

Asthma is a common chronic respiratory disease, which prevalence ranges between 1 and 18%, with slight variations among Countries, and according to selection criteria and methodology [1]. The severe form affects about 5–10% of asthmatic patients. According to guidelines of the American Thoracic Society and European Respiratory Society (ATS/ERS) [2], a “severe” patient needs a maximal therapy (step 4–5 GINA) [3] with the chronic use of systemic steroids, usually oral corticosteroids (OCS). To provide a different therapeutic approach to the more severe forms of asthma, biological treatments targeting the known pathogenic mechanisms have been hypothesized and realized. The first commercialized biological treatment was Omalizumab (an anti-IgE antibody) [4]. Recently, an IL-5 antagonist was commercialized, mepolizumab (MEP), directed to circulating IL-5. Its effectiveness in hypereosinophilic asthma is now well ascertained [5]. In clinical trials MEP displayed a favourable efficacy in reducing exacerbations, OCS intake, and in enhancing the quality of life (QoL). It
appeared that a careful selection of patients is needed to achieve the best results. In fact, in the earliest trial MEP was given to a non-selected population of patients with moderate persistent asthma and variable levels of eosinophils. No significant clinical result emerged for asthma control and specific bronchial hyperresponsiveness [6, 7]. Subsequently, other big trials including patients with at least 150–300 eosinophils/mmc were performed, with favourable results [8–11]. Following the commercial release of MEP, we attempted to strictly evaluate the characteristics of the treated patients in a real-life setting, as compared to regulatory trials. In this retrospective we provide a description of the characteristics of patients treated with MEP in six centres in the North-Western Italy, including those who participated in the main clinical trials.

Methods
This is a retrospective analysis of patients from six severe asthma clinics of North West Italy (IRCCS Policlinico San Martino Genoa, Santa Corona Hospital Pietra Ligure, AO Mauriziano, AOU Città della Salute e della Scienza Turin, Humanitas University Milan, and Fondazione Poliambulanza Brescia), which were the first clinics to have the product available. All patients meet the ATS/ERS criteria for uncontrolled severe asthma [2] and the conditions to be treated. All patients receiving MEP in the aforementioned period were the first clinics to have the product available.

Statistical analysis
All patients receiving MEP in the aforementioned period were included in the analysis. Arithmetic mean and standard deviation were used for the descriptive statistics. To compare data of our patients with those of the four mentioned clinical randomised, double-blind, placebo-controlled studies [8–11], a weighted average was used due to the difference in sample sizes. To compare our data with those of the main clinical trials with MEP we used a t-test one sample and a Z-test one proportion when indicated. A p value of ≤0.05 was considered to be significant.

Results
General description
Starting from June 1st, 2017 to December 31st, 2017, 65 severe hypereosinophilic asthmatic patients were treated. All patients were classified as step 4/5 GINA [3], remaining uncontrolled despite the maximal therapy [2]. The mean age was 56 ± 11.5 (range 19–84) (Table 1). Seven patients (11%) had their asthma symptoms before adolescence. Mean age of onset of asthma was 38 ± 16.5 (range 2–68), with a mean duration of the disease, before MEP treatment of 18.2 years (±14.4). Females accounted for 45% of the whole population. 17/65 patients (26%) were former or current smokers.

The control of the disease was evaluated with validated asthma control test (ACT) at baseline with a mean value of 16.6 ± 4.7 (range 6–25). Also lung function test prior to MEP evidenced a mean forced expiratory volume at the first second (FEV₁) of 73 ± 18%. Fifty-three out of 65 patients (82.5%) were receiving daily OCS therapy at the time of inclusion, with a mean dose of 9.2 mg (±9.2) of prednisolone (different molecules were converted in prednisolone equivalent). The mean eosinophils level at baseline, before treatment, was 653 cells/mmc (range 150–1987), with a mean historical value in the previous year of 1046 cells/mmc (range 320–6000). Nasal polyps were documented (by fiberoptic rhinoscopy and/or computerized tomography) in 47 (72%) subjects. 7/65 (11%) patients

| Table 1 | The current observed population receiving MEP | SD or percentage |
| --- | --- | --- |
| Number of patients | 65 | – |
| Female/Male | 29/36 | 45% female |
| Age range | 19–84 | – |
| Age mean | 56 | ±11.5 |
| Current smoker | 17 | 26% |
| Duration of asthma (years) | 18.2 | ± 14.4 |
| Historical eosinophilic count | 1046 | ± 885 |
| Blood eosinophil count at baseline | 653 | ±381 |
| Mean exacerbations previous 12 months | 3.0 | ±1.8 |
| Hospitalized patients previous 12 months | 20 | 31% |
| Mean OCS dose at baseline (mg) | 9.2 | ±9.2 |
| Mean FEV₁ at baseline (%) | 73 | ±18.1 |
| ACT | 16.6 | ±4.7 |
| Concomitant nasal polyposis | 47 | 72% |
come from the previous regulatory trials conducted at our centres.

Comparison with the clinical trials (Table 2)
The mean age in our real-life sample was 56 years, with a statistically significant difference compared to MUSCA (51 years; \( p < 0.0005 \)), DREAM (46 years; \( p < 0.0001 \)), MENSA and SIRIUS (50; \( p < 0.0001 \)). Concerning gender, MEP was given to 29/56 women (45%) in the DREAM study (387/621, 58% \( p = 0.04 \)). Concerning smoking habit, in our sample 17/65 (26%) were current or former smokers at baseline. If in DREAM, MENSA and MUSCA study the percentage of smoking people was rather similar to which observed in our sample, the same cannot be said about the SIRIUS study, where the percentage of smoking people was broadly distributed with a mean value of 1046 (range 320–6000) cells/μl and 653 (range 150–325) cells/μl, respectively. Also in this case, the observed values were different from those of clinical trials, where the weighted averages were 58.7 (±17.7) in SIRIUS, 61 (±17.9) in MENSA, 60 (±16.0) in DREAM and 55 (±14.5) in MUSCA, all value with a statistically difference < 0.0001. The range of eosinophils, in the previous and current years, was broadly distributed with a mean value of 1046 (range 320–6000) cells/μl and 653 (range 150–325) cells/μl, respectively. Matching these results with those of previous clinical trials, a mean value of 653 (±381) cells/μl was recorded in our cohort, whereas in the four randomized trials the concentration of eosinophils at baseline (SIRIUS 240 cells/μl, MENSA 296 cells/μl, DREAM 253 cells/μl and 325 for MUSCA) was lower, all with a statistically significant difference (\( p < 0.0001 \)). Comparing our data with that of the MUSCA study, where eosinophils were

| Table 2 | Comparison among groups. Real-life population and regulatory studies. The significant difference for the available parameters are indicated in boldface |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | CURRENT POPULATION | SIRIUS (11) | MENSA(10) | DREAM (8) | MUSCA (9) |
| Age     | Mean ± SD (range)  | 56 ± 11.5 (19–84) | 50 (n.p.) (16–74) | 50 (n.p.) (12–82) | 46 ± 11.2 (n.p.) | 51 ± 13.4 (n.p.) |
| Female %| \( P \)-value       | \(< 0.0001 \) | \(< 0.0001 \) | \(< 0.0001 \) | \(< 0.0001 \) |
| Duration of asthma (years) | Mean ± SD | 18.2 ± 14.4 | 18.27 ± 13.1 | 19.9 ± 13.8 | 19.1 ± 45.8 | 19.5 ± 4.8 |
| Smoker | \( P \)-value       | n.s. | n.s. | n.s. | n.s. |
| FEV1%  | Mean ± SD | 73 ± 18.1 | 58.7 ± 17.7 | 61 ± 17.9 | 60 ± 16 | 55 ± 14.5 |
| Eosinophils baseline (cells/μl) | Mean ± SD | 653 ± 381 | 240 ± 1126 | 296 ± 992 | 253 ± 1022 | 325 (n.p.) |
| Exacerbations/12 months | Mean ± SD | 3 (1.8) | 3.1 (3.1) | 3.6 (2.6) | 3.58 (3.03) | 2.8 (1.7) |
| ER access/12 months | \( P \)-value | n.s. | \( 0.0047 \) | \( 0.0087 \) | n.s. |
| OCS dose at baseline | Median (range) | 9 (0–50) | 13.7 (5–35) | 13.2 (1–80) | 10.8 (8–20) | 13 (±10.9) |
| Nasal polyposis | \( P \)-value | \(< 0.0001 \) | \(< 0.0001 \) | \(< 0.0001 \) | \( 0.0043 \) | \(< 0.0001 \) |

\(^{a}\)Geometric mean, \( n.p. \) not provided, \(^{b}\)comparison in % of patients, n.s not significant
categorized in two ranges, we observed a statistically significant difference in both groups (98% vs 86%, \( p = 0.0043 \) in \( \geq 150 \) cells/\( \mu L \); 91% vs. 64%, \( p < 0.0001 \) in \( \geq 300 \) cells/\( \mu L \)). The mean exacerbation rate of our population was 3.0 (±1.8), not different from of SIRIUS (±3.1; \( p = 0.5644 \)), MUSCA (±1.7; \( p = 0.4561 \)), and lower than in MENSA (3.6 ± 2.6; \( p = 0.0047 \)) and DREAM (3.58 ± 3.03; \( p = 0.0087 \)). The percentage of subjects hospitalized or requiring emergency room visit, was higher in our sample (31%) as compared to SIRIUS (17%; \( p = 0.005 \)) and MENSA (19%; \( p = 0.024 \)), similar in MUSCA (32%; \( p = 0.94 \)) and lower in the DREAM trial (24%; \( p = 0.26 \)).

The use of OCS is a main determinant in severe asthma. Among our real-life patients, 53 had a daily prescription of OCS (5–50 mg of prednisone or equivalent, mean value 9.2 mg). Only in the DREAM study the daily dose was similar to our patients, (10.76 mg; \( p = 0.1715 \)), in SIRIUS (13.7 mg; \( p = 0.0002 \)), MENSA (13.2 mg; \( p = 0.0007 \)) and MUSCA (13 mg; \( p = 0.0014 \)) trials. The daily dose was on average higher than in our sample. Finally, ACT was somewhere used to evaluate the QoL, but this aspect was difficult to compare, since different instruments were used in the different studies. When the presence of nasal polyps was assessed by endoscopy [14], in the real-life population the percentage of patients with nasal polyps was surprisingly highest than in the reference trials: 72% in real life, 49% in MENSA (\( p = 0.0003 \)), 19% in MUSCA (\( p < 0.0001 \)) and 10% in DREAM (\( p < 0.0001 \)). No data were available from the SIRIUS study. This may be explained by the strict inclusion criteria of the regulatory trials that were not applied to our real-life patients. Also, it has to be considered that the association of polyposis, asthma and hypereosinophilia is quite frequent, and usually underdiagnosed [15].

Discussion

Our clinics began to use MEP in the real-life setting, since the drug was approved and released by the local regulatory agency. Thus, we attempted to evaluate the characteristics of eligible patients, and to compare the data to those obtained from the major regulatory-oriented trials. The data herein collected in real-life setting confirm that eosinophilic asthma is predominantly a disease of adulthood (late onset asthma) [16], as compared with the early onset form that is most frequently characterized by an allergic-mediated pattern. At variance with omalizumab, where FEV1 below 80% of predicted was mandatory to start the add-on treatment in severe uncontrolled asthma [17], no limitation in lung function was recommended to prescribe MEP [18].

With the commercialization of MEP severe uncontrolled hypereosinophilic asthma certainly achieved more expanded therapeutic improvement. The clinical data about efficacy (reduction of exacerbations, decrease in OCS use, improved QoL) together with the safety profile are promising. It is true that, in comparison with the regulatory trials, in real life, the high level of blood eosinophils count is essential to decide for the IL-5 antagonism strategy. The possibility of decreasing the OCS burden would be regarded as a relevant socio-economical advantage [19]. Nevertheless, this observational trial evidenced some discrepancies between real life patients and clinical trials. The age at first administration and gender are probably not relevant, whereas the presence of eosinophils blood count at baseline or the presence of nasal polyposis are of importance. Also, it seems from the real-life observation that a more precise judgement would require at least 1 year of treatment.

One of the main endpoints of all biological drugs remains, in severe asthma, the reduction of the use of OCS or inhaled corticosteroids [19] and in this context, the use of MEP produced a significant reduction in OCS usage. Although randomized controlled trials (RTCs) play a pivotal role in the experimental development plan of a drug [20–23], and its subsequent clinical use, often the characteristics of the patients enrolled in the registration clinical trials do not reflect what happens in real-life.

Conclusions

We report herein the characteristics of a real-life patient population compared to the “formal” trials, showing some apparent discrepancies among the populations. In general, the demographic and clinical aspects were similar among the patient groups, but the groups themselves displayed some differences that could be taken into account for a more refined definition of the appropriate prescription.

Abbreviations

ACT: Asthma Control Test; FEV1: Forced expiratory volume at the first second; MEP: Mepolizumab; OCS: Oral Corticosteroids; QoL: Quality of life

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Consent for publications

“Not applicable”

Availability of data and materials

All data generated or analysed during this study are included in this. Giovanni Passalacqua is the final responsible for the data collected among centres. The data reported by other trials are available in literature.

Authors’ contributions

DB, MM, GP have equally contributed in the design of the study, the evaluation and collection of data and to the manuscript drafting. All authors contributed to the clinical work, data analysis, read and approved the final manuscript and its submission.

Ethics approval and consent to participate

All the procedures herein described were performed as per standard of care. The study was observational, with approved and commercialized drugs. No approval or registration was required according to the Italian laws.
Competing interests
The authors declare that they have no competing interests.

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References
1. Bagnasco D, Ferrando M, Bernardi S, Passalacqua G, Canonica GW. The path to personalized medicine in asthma. Expert Rev Respir Med. 2016;10(9):957–65.
2. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73.
3. GINA guidelines of asthma. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 02nd March 2018.
4. Israel E, Redd HL. Severe and difficult-to-treat asthma in adults. N Engl J Med. 2017;377:965–76.
5. Bagnasco D, Ferrando M, Varrielli G, Puggioni F, Passalacqua G, Canonica GW. Anti-interleukin 5 (IL-5) and IL-5ra biological drugs: efficacy, safety, and future perspectives in severe eosinophilic asthma. Front Med (Lausanne). 2017;4:135.
6. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. International Mepolizumab study group. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med. 2007;176:1062–71.
7. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O’Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. Lancet. 2002;359(9294):2144–8.
8. Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651–9.
9. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med. 2017;5(6):390–400.
10. Ortega HG, Liu MC, Pavord ID, Brusselle GG, Fitzgerald JM, Chetta A, et al. MENS investigatars. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198–207.
11. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW. SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371:1189–97.
12. http://www.gazzettaufficiale.it/eli/id/2017/02/28/17A01570/sg;jsessionid=-GDAkHfACp3aDv-1A99QwQ__.ntc-as2-guri2a. Accessed 19th March 2018.
13. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values. Eur Respir J. 2012;40:324–43.
14. Langdon C, Mullol J. Nasal polyposis in patients with asthma: prevalence, impact, and management challenges. J Asthma Allergy. 2016;9:45–53.
15. O’Sullivan JA, Bochner B. Eosinophils and eosinophil-associated diseases: An update. J Allergy Clin Immunol. 2018;141:505–17.
16. De Ferrari L, Chiappori A, Bagnasco D, Riccio AM, Passalacqua G, Canonica GW. Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma? Expert Rev Respir Med. 2016;10:38–49.
17. De Ferrari L, Chiappori A, Bagnasco D, Riccio AM, Passalacqua G, Canonica GW. Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma? Expert Rev Respir Med. 2016;10:38–49.
18. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/003860/WC500198037.pdf. Last access 04th April 2018.
19. Heffler E, Nascimento Girardi Madeira L, Ferrando M, Puggioni F, Racca F, Malvezzi L, et al. Inhaled corticosteroids and adverse effects in patients with asthma. J Allergy Clin Immunol Pract. 2018;3:pii: S2213–2198(18)30052–7.
20. Price D, Chisholm A, van der Molen T, Reche N, Hillyer EV, Bousquet J. Reassessing the evidence hierarchy in asthma: evaluating comparative effectiveness. Curr Allergy Asthma Rep. 2011;11:526–38.
21. Caminati M, Senna G, Guerriero M, Dama AR, Chieco-Bianchi F, Stefanuzzi G, et al. Mornalizumab for severe allergic asthma in clinical trials and real-life studies: what we know and what we should address. Pulm Pharmacol Ther. 2015;31:28–35.
22. Ware J, Hamel MB. Pragmatic trials and guides to better patient care? N Engl J Med. 2011;364:1685–7.
23. Travers J, Marsh S, Williams M, Weatherall M, Caldwell B, Shinchiffe P, Aldington S, Brasley R. External validity of randomised controlled trials in asthma: what do the results of the trials apply? Thorax. 2007;6.