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ORIGINAL RESEARCH

Sustained Effectiveness of Benralizumab in Naïve and Biologics-Experienced Severe Eosinophilic Asthma Patients: Results from the ANANKE Study

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Purpose: Severe eosinophilic asthma (SEA) patients often present overlapping inflammatory features rendering them eligible for multiple biologic therapies; switching biologic treatment is a strategy adopted to optimize asthma control when patients show partial or no response to previous biologics.

Patients and Methods: ANANKE is a retrospective, multicenter Italian study (NCT04272463). Here, we outline the characteristics and long-term clinical outcomes in naïve-to-biologics and biologics-experienced patients treated with benralizumab for up to 96 weeks. Bio-experienced patients were split into omalizumab and mepolizumab subsets according to the type of biologic previously used.

Results: A total of 124 (76.5%) naïve and 38 (23.5%) bio-experienced patients were evaluated at index date; 13 patients (34.2%) switched from mepolizumab, 21 patients (55.3%) switched from omalizumab, and four patients (10.5%) received both biologics. The mepolizumab subset was characterized by the longest SEA duration (median of 4.6 years), the highest prevalence of chronic rhinosinusitis with nasal polyposis (CRSwNP) (76.5%), and the greatest oral corticosteroid (OCS) daily dosage (median of 25 mg prednisone equivalent). The omalizumab group showed the highest severe annual exacerbation rate (AER) (1.70). At 96 weeks, treatment with benralizumab reduced any and severe AER by more than 87% and 94%, respectively, across all groups. Lung function was overall preserved, with major improvements observed in the mepolizumab group, which also revealed a 100% drop of the median OCS dose. Asthma Control Test (ACT) score improved in the naïve group while its increment was more variable in bio-experienced patients; among these, a marked difference was noticed between omalizumab and mepolizumab subsets (median ACT score of 23.5 and 18, respectively).

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Conclusion: Benralizumab promotes durable and profound clinical benefits in naïve and bio-experienced groups, indicating that a nearly complete depletion of eosinophils is highly beneficial in the control of SEA, independently of previous biologic use.
Keywords: benralizumab, asthma, eosinophils, switch, long-term

Background

Severe eosinophilic asthma (SEA) is a complex chronic disease of the lungs in which the inflammatory process is driven predominantly by eosinophils. Severe exacerbations and inadequate lung function contribute to the poor quality of life that SEA patients experience.[1–3] In addition to the typical increase in blood and sputum eosinophil counts,[4] mainly sustained by interleukin (IL)5,[5,6] SEA patients can also present other clinical features, such as atopy and increased levels of multiple inflammatory biomarkers (eg, fractional exhaled nitric oxide [FeNO], IL4, IL13), which are governed by distinct but overlapping T2 inflammatory pathways.[7] Oral corticosteroids (OCS) suppress the ongoing T2 inflammation in a non-specific manner, hence are highly efficacious in reducing asthma symptoms. Based on the several adverse events that OCS can cause, their use is strongly condemned by international guidelines, which endorse their use as a "last resort" only.[8] In the last decades, the advance of several biologic drugs targeting selected T2 inflammatory players encouraged the minimization of OCS treatment and emphasized the use of a personalized approach, in an effort to distinguish not only the SA phenotype but also the underlying individual endotype.

To date, there are six monoclonal antibodies (mAbs) authorized for the treatment of severe asthma (SA): while omalizumab is intended to treat allergic SA patients,[9] mepolizumab, reslizumab, and benralizumab are indicated for SEA,[10–12] dupilumab is approved for T2 SA,[13] and tezepelumab use has been recently authorized in a broader SA population.[14] Patients showing overlapping T2 features can be eligible for multiple biologics; choosing the right treatment for these patients is difficult as no head-to-head randomized controlled trials have been conducted to compare the different mAbs in terms of efficacy and safety. Only a few real-life studies have investigated the effects of mepolizumab and benralizumab, reporting either no clinically relevant differences[15] or a higher number of patients treated with benralizumab in terms of disease clinical remission.[16] Although most patients largely benefit from the prescribed biologic agent, the extent of the response can vary.[17] Therefore, a thorough characterization of the patient searching for specific clinical characteristics, comorbidities, and/or biomarkers that could predict the most effective biologic is recommended.[8,18] Chronic rhinosinusitis with nasal polyps (CRSwNP) has been linked to an enhanced response to benralizumab in reducing annual exacerbation rate (AER)[19,20] and improving lung function;[21,22] dupilumab represents the first choice in patients with high FeNO[23] but should be avoided if blood eosinophil count (BEC) is higher than 1,500 cells/mm;[3,8] the presence of atopy could favor the choice of omalizumab, although it does not preclude beneficial effects from other biologics in patients with overlapping T2 features.[24–28]

Despite the efforts to select the most effective biologic to treat SA, the rate of patients undergoing a biologic switch because of poorly controlled asthma is significant. A recent real-world analysis examining the patterns of biologics use and switch among 3,531 patients showed that the initial biologic was maintained in most cases (79% of patients), while it was either stopped or switched in 10.2% and 10.8% of patients, respectively.[29] Higher percentages of patients who switched biologic have been observed in smaller studies (up to 43.3%).[30,31] These results underline the importance of routinely examining the patient and re-assess their response to the biologic treatment. As recommended by Global Strategy for Asthma Management (GINA) guidelines, the therapy should be stopped if patients do not respond and a biologic switch should be considered by the practitioner.[8]

Among all available biologics, benralizumab is the only mAb that ensures an extensive eosinophil apoptosis through enhanced antibody-dependent cell cytotoxicity (ADCC), activated via the simultaneous binding of IL5 receptor alpha (IL5Rα) and FcγIIIRa receptor, predominantly expressed by eosinophils and natural killer (NK) cells, respectively.[32] A recent study described a series of immunological modifications taking place in SEA patients treated with benralizumab, including increased NK cell proliferation, maturation and cytotoxic activity, and modulation of T cell subsets. These findings further elucidated the benralizumab unique mode of action, proving its ability to restore immune functions to levels comparable to those seen in untreated healthy controls.[33] ANANKE (NCT04272463)[34,35] is a large retrospective study evaluating the characteristics of Italian SEA patients treated with benralizumab and their clinical response. A number of post hoc analyses have been conducted so far; among these, Caruso et al examined the differences between

patients who received benralizumab as the first-choice biologic (naïve patients) and patients switching to benralizumab after they received other biologics (bio-experienced patients).[36] The results revealed that benralizumab was highly efficacious in both naïve and bio-experienced groups; clinical outcomes were comparable even though bio-experienced patients were characterized by higher severe AER and a protracted duration of SEA compared to naïve patients. More recently, we confirmed the durable effectiveness of benralizumab in reducing any and severe AER by more than 90% in both naïve and bio-experienced patients, up to 96 weeks of treatment.[37]

In light of what has been previously reported, we conducted a post hoc analysis to further describe the outcomes of long-term response to benralizumab in patients with severe eosinophilic asthma, irrespective from previous biologics treatment (naïve and bio-experienced). Moreover, bio-experienced patients were split into two subsets according to the biologic(s) previously received (omalizumab and/or mepolizumab); these were added to the comparative analysis to evaluate if and how the biologic(s) previously used influenced the response to benralizumab.

Materials and Methods

Study Design

ANANKE (NCT04272463) is an Italian multi-center, observational, retrospective study.[34] The centers participating in the ANANKE study are listed in Supplementary File 1. Briefly, benralizumab was administered to SEA patients in accordance with clinical practice or as part of the Italian Sampling Programme; their enrolment occurred at least 3 months after the index date (when benralizumab treatment was started). Differently from the initial design, the observation period of the study was extended up to 96 weeks; as a consequence, patients agreed to participate in the extended study period and signed the related privacy and informed consent forms. After initiation of benralizumab treatment, data were collected at weeks 4, 16, 24, 48, and 96. ANANKE was performed in agreement with the ethical principles outlined in the Declaration of Helsinki as well as with the regulations and policies governing the clinical practice in Italy. Ethics committees/institutional review boards of all sites involved in the study approved the study.

Patient Population

Inclusion and exclusion criteria have been previously detailed.[35] Briefly, enrolled patients were adults (≥18 years old), diagnosed with SEA and requiring treatment with high doses of background medications (inhaled corticosteroids [ICS] and a long-acting b2-agonist [LABA]), with or without additional asthma controllers. Participants were required to have initiated Benralizumab therapy at least 3 months prior to enrollment, with at least one benralizumab injection received, and their hospital medical charts had to be available from 12 months before the index date. Patients were excluded from the ANANKE study if they took part in other studies dictating a particular patient management method that differed from the site's normal clinical practice after the enrollment visit.

Eligible patients satisfied all inclusion, exclusion, and amendment criteria. Evaluable patients were all eligible patients with BEC data available at index date.

Outcomes

Data were gathered from hospital medical records and entered into the electronic case report form (eCRF) as per clinical practice.

The primary endpoint was the description of patients' characteristics at index date (ie, when benralizumab treatment was started). Specifically, the data at index date were gathered throughout the 12 months before the start of benralizumab treatment and consisted of age, gender, body mass index (BMI), tobacco usage, age at asthma diagnosis, duration of asthma and duration of SEA, diagnosis of atopy (in presence of a positive skin prick test (SPT) for an allergen, either perennial and/or seasonal), diagnosis of concomitant illnesses (comorbidities associated with either asthma or OCS use, and any other conditions deemed meaningful by the treating clinician), BEC, and blood level of serum immunoglobulin E (IgE), respiratory parameters, control of asthma symptoms (measured with the Asthma Control Test [ACT]), use of asthma treatments (background and chronic therapies, including OCS, and any biologics used during the 12 months prior to benralizumab initiation), any and severe AER. Any AER accounted for all the clinically significant asthma

exacerbations determined by a physician, while severe AER included all exacerbations that further deteriorated asthma symptoms, requiring either: a) systemic corticosteroids, administered for at least 3 days, or a transient increment in the dosage of maintenance OCS; b) a visit to the emergency department (shorter than 24 hours) during which systemic corticosteroids were administered; or c) hospitalization (longer than 24 hours).

In addition, a range of secondary endpoints was evaluated during benralizumab treatment (ie, between the index date and 96 weeks), and included outcomes recorded at multiple time points (4, 16, 24, and 48 weeks) when available. Changes in the following clinical and laboratory outcomes were evaluated over time:

1. BEC (to confirm benralizumab performance);
2. AER (any and severe), proportion of patients eliminating any and severe exacerbations;
3. ACT score, the proportion of patients reaching ACT score ≥20 (well-controlled asthma);
4. Respiratory parameters (forced expiratory volume in the first second [FEV_1], forced vital capacity [FVC], measured both pre- and post-bronchodilator [BD]);
5. Treatment with OCS and their dosage (expressed as prednisone-equivalent mg per day), proportion of patients reducing or permanently interrupting OCS; and
6. Discontinuation to benralizumab treatment.

Both primary and secondary outcomes were analyzed in naïve patients (not treated with any biologic for asthma before index date) and bio-experienced patients (previously treated with one or more biologics for asthma before the index date). Within the bio-experienced patients, two subsets were considered for analysis based on the type of biologic received before benralizumab: the first group included patients who previously received omalizumab only (omalizumab group), the second group consisted of patients who were previously treated with mepolizumab, including patients who firstly received omalizumab and then switched to mepolizumab before receiving benralizumab. These groups were included in the post hoc analyses and compared with naïve and bio-experienced patients.

Statistical Analysis

Statistical analyses were extensively described by Menzella et al.[35] Briefly, descriptive analyses were performed; no formal hypothesis was explicitly determined due to the study's observational nature. Data are expressed as mean ± standard deviation (SD) or absolute numbers and frequencies. Median (IQR) was used instead of mean ± SD if data distribution was highly variable.

Demographic and clinical characteristics at the index date were assessed in evaluable patients (naïve and bio-experienced patients, N=124 and N=38, respectively); secondary endpoints were assessed in evaluable patients for secondary analyses at 48 (naïve and bio-experienced patients, N=110 and N=35, respectively) and 96 weeks (naïve and bio-experienced patients, N=86 and N=27, respectively).

SAS for Windows Version 9.4 and SAS Enterprise Guide 7.12 (SAS Institute, Cary, NC, USA) were used to conduct statistical analyses.

Results

Patient Distribution

As previously described, 218 patients diagnosed with SEA were enrolled in the ANANKE study.[35] Based the inclusion and exclusion criteria, 167 (76.6%) patients were eligible for evaluation during the extended period. Reasons for non-eligibility were: benralizumab initiation did not take place at least 3 months before enrollment; absence of signed informed consent and privacy forms (including amendments related to the extended observation period); patients did not receive ICS and LABA before starting benralizumab treatment.

Because five patients were missing BEC values, the number of evaluable patients at index date was 162; of these, 124 (76.5%) were naïve and 38 (23.5%) were already treated with biologics before switching to benralizumab (bio-experienced). Among the latter group, 13 patients (34.2%) received mepolizumab, 21 patients (55.3%) received omalizumab, and four

patients (10.5%) received omalizumab as first treatment, which was followed by mepolizumab. Because of the low number of patients undergoing double switching (from omalizumab to mepolizumab, and then from mepolizumab to benralizumab, N=4), these patients were combined with the 13 patients who received mepolizumab only and formed the mepolizumab group (N=17, representing 44.7% of all bio-experienced patients).

Among evaluable patients at index date, 145 participants were judged evaluable for secondary analyses at 48 weeks. Among these, there were 110 (67.9%) naïve patients and 35 (21.6%) bio-experienced patients (with 20 [57.1%] and 15 [42.9%] patients in the omalizumab and mepolizumab groups, respectively). At 96 weeks, 113 patients were judged evaluable for secondary analysis, with 86 (53.0%) naïve patients and 27 (16.7%) bio-experienced patients (with 17 [62.9%] and 10 [37.0%] patients in the omalizumab and mepolizumab groups, respectively).

Characteristics of Patients at Index Date According to Previous Biologics Use

The ANANKE patient population eligible for extended analysis presented characteristics compatible with the late onset, eosinophilic-driven SA phenotype.[37] The key features of naïve and bio-experienced patients at index date (ie, collected during the 12 months before benralizumab initiation) have already been reported; in general, asthma clinical control appeared worse in bio-experienced patients in terms of severe AER, OCS dosage, and OCS-related comorbidities (Table 1).[37] The characteristics of bio-experienced patients divided into omalizumab and mepolizumab subsets are detailed below.

Patients were treated with omalizumab for 35.3 months (15.9–92.0) before receiving benralizumab, while patients in the mepolizumab group (including four patients who were treated with omalizumab prior to mepolizumab) received the anti IL5

Table 1 Socio-Demographic and Clinical Characteristics of Naïve and Bio-Experienced Patients, Including Omalizumab and Mepolizumab Subsets, Collected Before Initiating Benralizumab Treatment

Characteristics at Index Date	Naïve (N=124)	Bio-Experienced (N=38)	Omalizumab (N=21)	Mepolizumab (N=17) (Including Four Patients Switched from Omalizumab)
Age (years)	56.6 ± 12.3	54.3 ± 13.7	59.1 ± 10.5	48.3 ± 15.0
Gender (female)	82 (66.1)	17 (44.7)	8 (38.1)	9 (52.9)
BMI classes				
Underweight/Normal	47 (37.9)	11 (28.9)	4 (19.0)	7 (41.2)
Overweight	46 (37.1)	16 (42.1)	11 (52.4)	5 (29.4)
Obese	19 (15.3)	7 (18.4)	5 (23.8)	2 (11.8)
Unknown	12 (9.7)	4 (10.5)	1 (4.8)	3 (17.6)
Smoking status				
Current smokers	4 (3.2)	1 (2.6)	0 (0.0)	1 (5.9)
Past smokers	31 (25.0)	13 (34.2)	8 (38.1)	5 (29.4)
Unknown	4 (3.2)	3 (7.9)	1 (4.8)	2 (11.8)
Asthma duration (years) (N=123, 38, 21, 17)	13.5 (8.1–26.4)	14.0 (8.5–20.5)	20.3 (9.4–30.1)	10.2 (6.5–14.8)
SEA duration (years) (N=120, 38, 21, 17)	1.6 (1.0–3.0)	3.5 (1.6–6.5)	2.1 (1.1–4.5)	4.6 (2.5–9.2)
Patients positive to ≥ 1 allergen	56 (45.2)	21 (55.3)	12 (57.1)	9 (52.9)
BEC (cells/mm^3)	605 (440–915)	550 (300–756)	550 (400–770)	550 (230–700)
Total serum IgE (IU/mL) (N=69, 22, 13, 9)	161 (73–474)	308 (128–620)	326 (78–520)	215 (172–774)
Duration of previous biologic treatment (months)	N/A	21.0 (10.6–52.9)	35.3 (15.9–92.0)	15.4 (10.6–27.4)

(*Continued*)

Table 1 (Continued).

Characteristics at Index Date	Naïve (N=124)	Bio-Experienced (N=38)	Omalizumab (N=21)	Mepolizumab (N=17) (Including Four Patients Switched from Omalizumab)
Any comorbidities	107 (86.3)	34 (89.5)	17 (81.0)	17 (100.0)
≥1 any asthma-related	71 (57.3)	20 (52.6)	9 (42.9)	11 (64.7)
CRSwNP (current or past)	68 (54.8)	18 (47.4)	5 (23.8)	13 (76.5)
CRSsNP	32 (25.8)	11 (28.9)	6 (28.6)	5 (29.4)
≥1 current OCS-related	44 (35.5)	20 (52.6)	11 (52.4)	9 (52.9)
≥1 other ongoing	20 (16.1)	7 (18.4)	4 (19.0)	3 (17.6)
OCS users (for asthma treatment)	30 (24.2)	11 (28.9)	4 (19.0)	7 (41.2)
OCS daily dose (mg) (N=28, 11, 4, 7)	8.1 (5.0–21.3)	10.0 (5.0–25.0)	5.0 (5.0–7.5)	25.0 (10.0–25.0)
Exacerbations				
Patients with ≥1, any (N=117, 37, 20, 17)	109 (93.2)	35 (94.6)	20 (100.0)	15 (88.2)
Patients with ≥1, severe (N=117, 37, 20, 17)	39 (33.3)	18 (48.6)	11 (55.0)	7 (41.2)
AER, any (N=117, 37, 20, 17)	4.15	3.95	3.80	4.12
AER, severe (N=117, 37, 20, 17)	0.81	1.51	1.70	1.29
Lung function				
Pre-BD FEV_1 (L) (N=82, 29, 18, 11)	1.8 (1.4–2.5)	2.1 (1.4–2.4)	2.0 (1.4–2.4)	2.2 (1.0–2.7)
Pre-BD FEV_1 predicted (%) (N=83, 30, 18, 12)	72.0 (54.0–85.0)	71.0 (48.0–84.0)	71.0 (48.0–81.0)	71.5 (39.5–89.0)
Post-BD FEV_1 (L) (N=58, 14, 7, 7)	2.0 (1.4–2.7)	2.1 (1.4–3.0)	2.8 (1.3–3.4)	1.9 (1.4–3.0)
Post-BD FEV_1 predicted (%) (N=56, 14, 7, 7)	73.0 (60.0–91.5)	66.5 (47.0–110)	90.0 (50.0–117)	49.0 (42.0–97.0)
Pre-BD FVC (L) (N=80, 28, 18, 10)	2.7 (2.2–3.4)	3.0 (2.5–3.7)	3.2 (2.7–3.9)	2.9 (2.4–3.3)
Post-BD FVC (L) (N=56, 12, 7, 5)	3.0 (2.3–3.8)	3.3 (2.4–4.4)	3.7 (2.4–5.0)	2.9 (2.3–3.2)
ACT score (N=90, 30, 16, 14)	14.0 (12.0–18.0)	14.0 (12.0–17.0)	15.0 (12.5–17.0)	12.5 (10.0–15.0)

Notes: Data were collected at index date and are expressed as N (%), mean ± SD, or median (IQR). Unless otherwise specified, N=124 patients were evaluated in the naïve group, N=38 patients in the bio-experienced group, N=21 patients in the omalizumab group, and N=17 patients in the mepolizumab group.
Abbreviations: N, number of patients; SEA, severe eosinophilic asthma; BEC, blood eosinophil count; IgE, immunoglobulin E; CRSwNP, chronic rhinosinusitis with nasal polyposis; CRSsNP, chronic rhinosinusitis without nasal polyps; OCS, oral corticosteroids; AER, annual exacerbation rate; Pre-BD FEV_1, pre-bronchodilator forced expiratory volume in 1 second; Pre-BD FVC, pre-bronchodilator forced vital capacity; Post-BD FEV_1, post-bronchodilator forced expiratory volume in 1 second; Post-BD FVC, post-bronchodilator forced vital capacity; ACT, asthma control test.

mAb for a total period of 15.4 months (10.6–27.4). Overall, there was a median gap of 2.3 months (1.3–4.9) between the end of the previous biologic treatment and the start of benralizumab. In general, the mepolizumab group was characterized by a lower age compared with all the other groups (48.3 years ± 15.0); patients in this subset also showed a greater proportion of females and a lower proportion of overweight patients compared with the omalizumab group (females: 52.9% versus 38.1%; overweight: 29.4% versus 52.4%). Although asthma duration was shorter in the mepolizumab group (10.2 years, 6.5–14.8) compared with the other groups, this subset also featured the longest SEA duration (4.6 years, 2.5–9.2).

All mepolizumab-switched patients had at least one comorbidity, with CRSwNP being the most frequent asthma-related condition, affecting 13 out of 17 patients (76.5%). On the other hand, patients in the omalizumab group were predominantly positive for at least one allergen (57.1% of patients displayed allergen-specific IgE) and showed the highest median amount of total IgE levels (326 IU/mL, 78–520). As previously mentioned,[36,37] OCS-related comorbidities were more prevalent in bio-experienced than naïve patients, with no difference between omalizumab and mepolizumab-treated subsets (52.4% and 52.9%, respectively), despite the mepolizumab group showing the highest proportion of OCS users (41.2%) and OCS daily dose (25.0 mg, 10.0–25.0).

An identical median BEC of 550 cells/mm^3 was observed in both omalizumab and mepolizumab groups. Of note, BEC might have been measured before the start of mepolizumab treatment in some patients (characteristics at index date

were measured throughout the 12 months before the start of benralizumab treatment and some patients were treated with mepolizumab only for a few months before switching to benralizumab). As expected, the omalizumab group displayed the highest level of total serum IgE (326.0 IU/mL).

During the year before the start of benralizumab treatment, all patients in the omalizumab group had one or more exacerbations of any severity and 55% of patients had at least one or more severe exacerbations (versus 88.2% and 41.2% of patients in the mepolizumab group). Any AER was slightly lower in the omalizumab compared with the mepolizumab group (3.80 vs 4.12); on the contrary omalizumab-switched patients featured the highest severe AER (1.70) among all groups considered.

Poor respiratory function and control of asthma were confirmed in all groups; the mepolizumab group displayed the lowest values of post-BD FEV_1 (1.9, 1.4–3.0), indicating the highest degree of airway obstruction, and the lowest values of ACT scores (12.5, 10.0–15.0).

Benralizumab Reduced Exacerbations Irrespective of Previous Biologics Use

We have already shown the remarkable effectiveness of benralizumab in decreasing exacerbations in naïve and bio-experienced groups.[36,37] Here, additional data are reported to describe the reduction in any and severe AER in omalizumab and mepolizumab groups after 96 weeks of treatment with benralizumab. As shown in Figure 1A, similarly to naïve and bio-experienced groups, the two switched groups had a consistent and sustained decrease in any AER, with reductions ranging from 86.2% (mepolizumab group) to 93.9% (omalizumab group) at 96 weeks. The most profound effects were related to severe AER, which declined in all

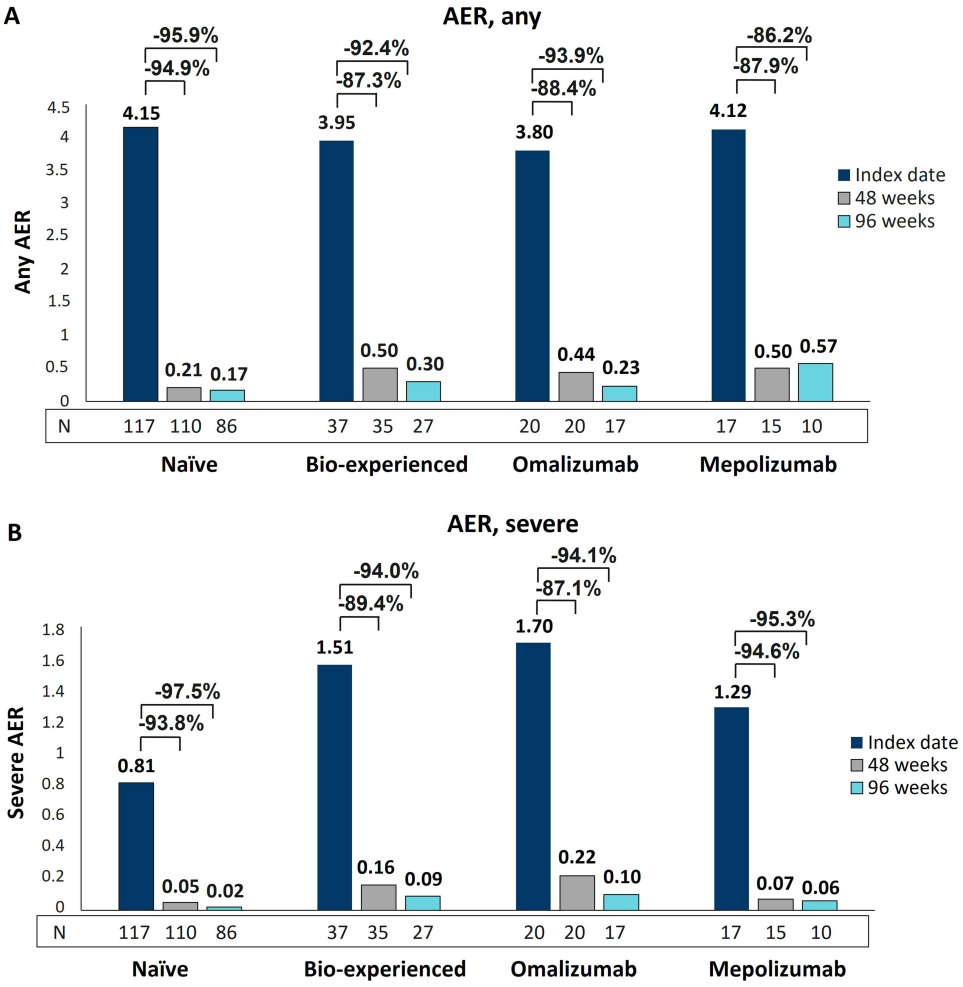


Figure 1 AER reduction during benralizumab treatment in naïve, bio-experienced, omalizumab, and mepolizumab groups. Any (**A**) and severe (**B**) AER are shown at index date and after 48 and 96 weeks of treatment with benralizumab.

Table 2 Proportion of Patients Free from Severe Exacerbations Before and During Benralizumab Treatment in Naïve, Bio-Experienced, Omalizumab, and Mepolizumab Groups

	Naïve (N=117, 110, 86)	Bio-Experienced (N=37, 35, 27)	Omalizumab (N=20, 20, 17)	Mepolizumab (N=17, 15, 10)
Patients without severe exacerbations at index date, N (%)	78 (66.7)	19 (51.4)	9 (45.0)	10 (58.8)
Patients without severe exacerbations at 48 weeks, N (%)	106 (96.4)	30 (85.7)	16 (80.0)	14 (93.3)
Patients without severe exacerbations at 96 weeks, N (%)	84 (97.7)	23 (85.2)	14 (82.4)	9 (90.0)

Notes: Data were collected at index date and at 48 and 96 weeks of benralizumab treatment; data are expressed as N (%).
Abbreviation: N, number of patients.

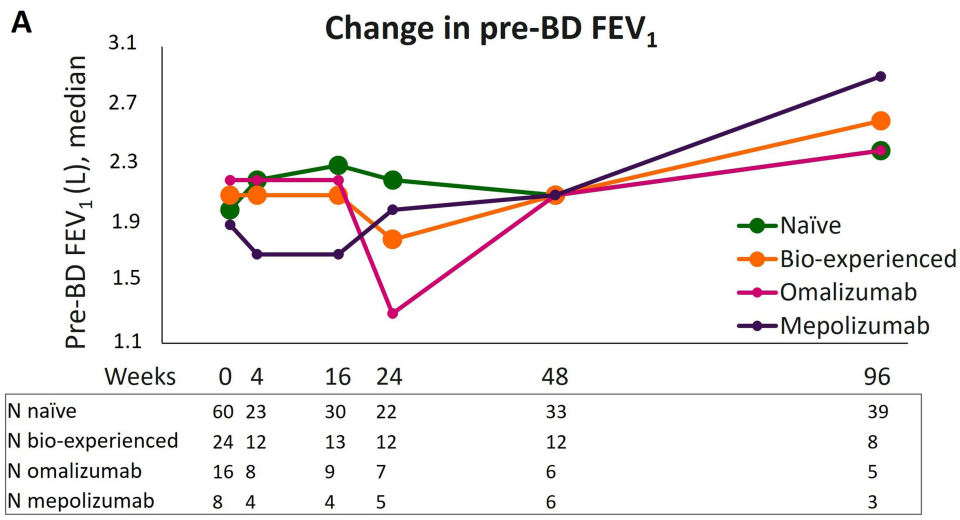
groups in a progressive manner and at a nearly identical extent (from 94.1% in the omalizumab group to 97.5% in naïve patients at 96 weeks) (Figure 1B). As shown in Table 2, the percentage of patients free from severe exacerbations at 48 weeks increased in all groups, and the results were maintained at 96 weeks. In more detail, 66.7% of naïve patients were already free from severe exacerbations at the index date and almost all of them (97.7%) did not experience severe exacerbations for up to 96 weeks (+31% patients free from severe exacerbations). Similar increases were observed in the bio-experienced group and the subset of mepolizumab-treated patients (+33.8% and +31.2% patients respectively, at 96 weeks). The omalizumab group was characterized by the lowest proportion of patients without severe exacerbations at index date (45%), nevertheless, their percentage increased up to 82.4% at 96 weeks (+37.4% patients).

In line with the benralizumab mechanism of action (MoA), we confirmed the nearly complete depletion of blood eosinophils, which took place independently of previous biologics use (all groups showed a median BEC of 0 cells/mm^3, maintained up to 96 weeks, data not shown).

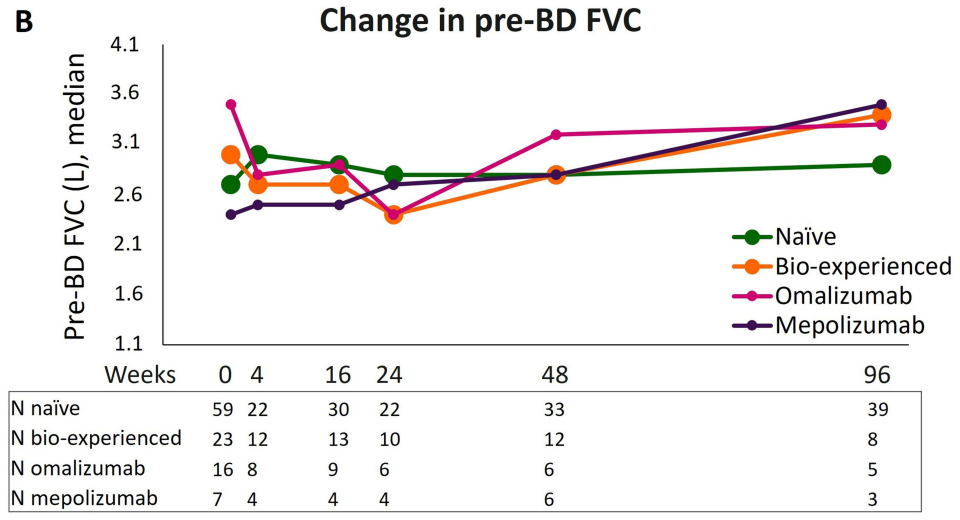
Benralizumab Preserved Lung Function in Both Naïve and Bio-Experienced Groups with Pronounced Outcomes in the Mepolizumab Group

Changes in pre-BD FEV_1 and FVC induced by benralizumab in naive and bio-experienced groups, including the subsets of omalizumab and mepolizumab-treated patients, are shown in Figure 2; median values related to the graphs are reported separately in Supplementary Table 1A and 1B. Both naïve and bio-experienced groups had net and comparable increments in pre-BD parameters measured from the start of benralizumab treatment to 96 weeks (median increases in pre-BD FEV_1: +0.4 L and +0.5 L; median increases in pre-BD FVC: +0.2 L and +0.4 L, in naïve and bio-experienced patients, respectively). Although pre-BD FEV_1 was ameliorated in both omalizumab and mepolizumab groups at 96 weeks, a more pronounced and steadier increase in both FEV_1 and FVC was noticed in patients previously treated with mepolizumab. As a matter of fact, among all groups evaluated, this subset showed the greatest improvements at 96 weeks (median increase in pre-BD FEV_1: +1.0 L and median increase in pre-BD FVC: +1.1 L). On the contrary, the worse response was observed in omalizumab-switched patients: both pre-BD measures profoundly decreased at 24 weeks compared with values at the index date; at 96 weeks, FEV_1 improved by +0.2 L and a small decrease in FVC was registered (−0.2 L).

Post-BD FEV_1 and FVC were generally preserved in all groups, with the most evident increments displayed once again by patients in the mepolizumab group at 96 weeks (Supplementary Figure 1, Supplementary Table 2A and 2B). Notably, the mepolizumab group displayed lower pre-BD FEV_1 and FVC values (Figure 2A and B), as well as lower post-BD parameters (Table 1) compared with omalizumab-treated patients at index date, implying a more compromised respiratory function in this subset.



Weeks	0	4	16	24	48	96
N naïve	60	23	30	22	33	39
N bio-experienced	24	12	13	12	12	8
N omalizumab	16	8	9	7	6	5
N mepolizumab	8	4	4	5	6	3



Weeks	0	4	16	24	48	96
N naïve	59	22	30	22	33	39
N bio-experienced	23	12	13	10	12	8
N omalizumab	16	8	9	6	6	5
N mepolizumab	7	4	4	4	6	3

Figure 2 Change in pre-BD respiratory parameters during benralizumab treatment in naïve, bio-experienced, omalizumab, and mepolizumab groups. Median pre-BD FEV_1 (**A**) and pre-BD FVC (**B**) are shown at various time points (index date and 4, 16, 24, 48, and 96 weeks of treatment with benralizumab).

Benralizumab Ensured a Long-Term Reduction in OCS Use in Naïve and Bio-Experienced Groups with Prevalent Effects in the Mepolizumab Group

As shown in Figure 3, the median dose of OCS used by both naïve and bio-experienced groups was 0.0 mg/day (0–5) at 48 weeks. At 96 weeks, while the median OCS daily dose persisted at 0.0 mg in naïve patients, it slightly increased to 1.9 mg in bio-experienced patients. Such a result was not caused by an actual increase in the prescribed dose of OCS, but rather by missing data from one patient who stopped OCS at 48 weeks (the bio-experienced patients decreased from N=9 to N=8 at 96 weeks). In general, bio-experienced patients had a variable response to benralizumab treatment: when examining omalizumab and mepolizumab groups separately, clear differences were noticed between the two subsets. Patients previously treated with omalizumab had a modest decrease in median OCS dose (from 5 mg to 3.8 mg, 24% reduction measured at both 48 and 96 weeks, data from N=3), while a median OCS reduction of 100% was observed in the mepolizumab group (data from N=6 and N=5 at 48 and 96 weeks, respectively), despite the highest OCS starting dose (25 mg at index date).

Benralizumab successfully eliminated OCS use in 60% and 63.6% of naïve patients and 55.6% and 50% of patients in the bio-experienced group at 48 and 96 weeks (Table 3). Among bio-experienced patients, one out of three patients

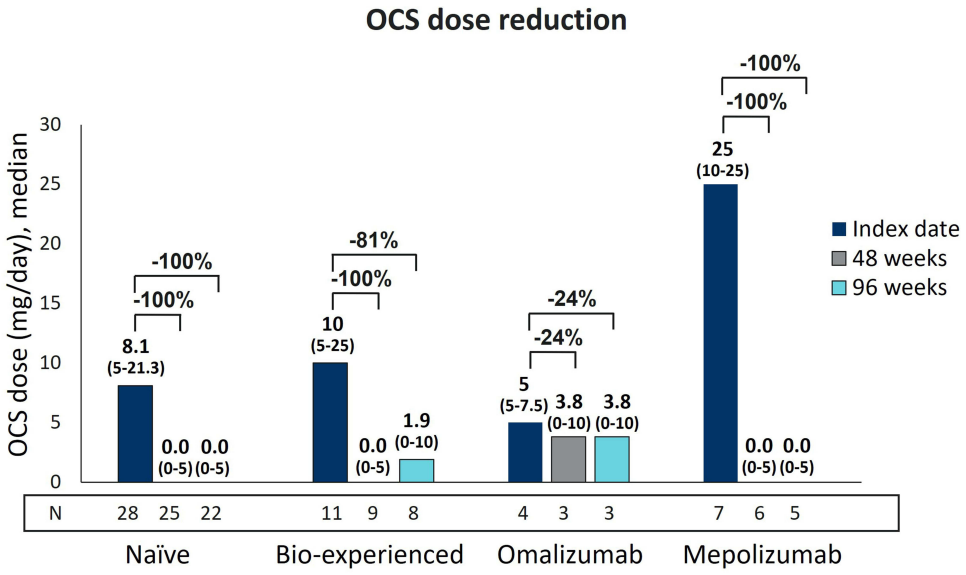


Figure 3 Long-term OCS reduction during benralizumab treatment in naïve, bio-experienced, omalizumab, and mepolizumab groups. OCS daily dose (mg of prednisone equivalent), expressed as median (IQR), is shown at index date and after 48 and 96 weeks of treatment with benralizumab.

(33.3%) previously treated with omalizumab remained free from OCS use, whereas the number of patients interrupting OCS in the mepolizumab group were four (66.7%) and three (60%) at 48 and 96 weeks, respectively (96-week data are missing from one patient who interrupted OCS at 48 weeks).

Benralizumab Induced a Superior Improvement in Asthma Control in Naïve and Omalizumab-Switched Patients

Change in asthma control was monitored via ACT during benralizumab treatment. As shown in Figure 4A and Supplementary Table 3A, ACT score quickly increased after only 4 weeks of treatment with benralizumab (ie, after a single injection), reaching median values equal to or greater than 20 in all groups. The rapid improvement in asthma control was maintained in naïve and bio-experienced groups, who obtained median ACT scores of 23 and 22, respectively, at 96 weeks. Within bio-experienced patients, the omalizumab group had a sharp increase in median ACT score that was maintained and reached a median score of 23.5 at 96 weeks. Although patients in the mepolizumab group also featured a rapid increment of asthma control (median ACT score=20 at 4 weeks), their ACT score was more variable and generally lower compared to the other groups.

The percentage of patients achieving an ACT score ≥20 (patients with well-controlled asthma, Figure 4B and Supplementary Table 3B) were also analyzed. Naïve and omalizumab groups had the highest percentages of patients with well-controlled asthma up to 96 weeks (80.3% and 80.0%, respectively), with a smaller percentage displayed by mepolizumab-treated patients (50%).

Discontinuation from Benralizumab Treatment

Of the eligible patients that were treated with benralizumab up to 96 weeks, six naïve (6.8%) and six bio-experienced patients (22.2%) (two and four patients in the omalizumab and mepolizumab groups, respectively) interrupted benralizumab. Efficacy failure was the primary reason leading to discontinuation across all groups (data not shown).

Discussion

A new post hoc analysis has been conducted from the real-life ANANKE study, in which the clinical characteristics and outcomes in naïve and bio-experienced SEA patients treated with benralizumab were described for up to 96 weeks. The findings here support earlier research with a shorter treatment duration (median of 9.8 months)[36] and demonstrate the

Table 3 Proportion of Patients Achieving OCS Dose Reduction and/or Interruption During Benralizumab Treatment in Naïve, Bio-Experienced, Omalizumab, and Mepolizumab Groups After 48 and 96 Weeks

OCS Reduction from Index Date	Naive at 48 Weeks N (%) (N=25)	Naive at 96 Weeks N (%) (N=22)	Bio-Experienced at 48 Weeks N (%) (N=9)	Bio-Experienced at 96 Weeks N (%) (N=8)	Omalizumab at 48 Weeks N (%) (N=3)	Omalizumab at 96 Weeks N (%) (N=3)	Mepolizumab at 48 Weeks N (%) (N=6)	Mepolizumab at 96 Weeks N (%) (N=5)
Interruption	13 (52.0)	14 (63.6)	5 (55.6)	4 (50.0)	1 (33.3)	1 (33.3)	4 (66.7)	3 (60.0)
Any reduction (including interruption)	15 (60.0)	15 (68.2)	6 (66.7)	5 (62.5)	2 (66.7)	2 (66.7)	4 (66.7)	3 (60.0)
≥90% dose reduction	13 (52.0)	14 (63.6)	5 (55.6)	4 (50.0)	1 (33.3)	1 (33.3)	4 (66.7)	3 (60.0)
≥75% dose reduction	13 (52.0)	14 (63.6)	5 (55.6)	4 (50.0)	1 (33.3)	1 (33.3)	4 (66.7)	3 (60.0)
≥25% dose reduction	15 (60.0)	15 (68.2)	5 (55.6)	4 (50.0)	1 (33.3)	1 (33.3)	4 (66.7)	3 (60.0)
No reduction	10 (40.0)	7 (31.8)	3 (33.3)	3 (37.5)	1 (33.3)	1 (33.3)	2 (33.3)	2 (40.0)

Notes: OCS dosage is expressed as daily mg (prednisone equivalent). Data are expressed as N (%).
Abbreviations: N, number of patients; OCS, oral corticosteroids.

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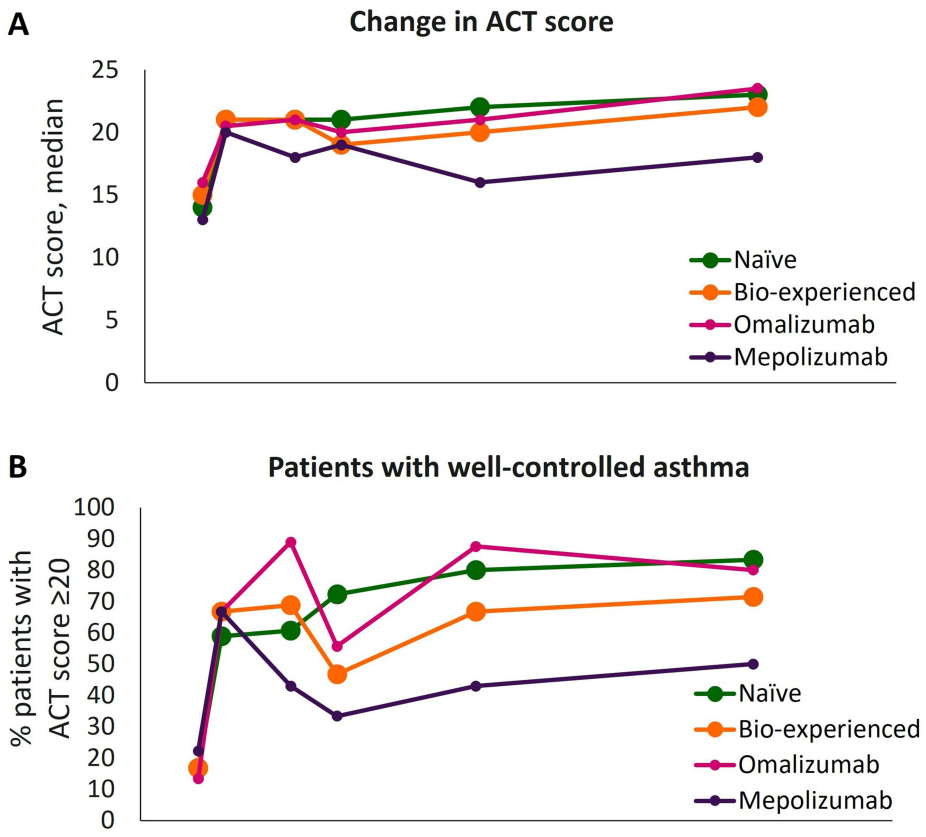

N naïve	72	17	61	55	60	61
N bio-experienced	24	9	16	15	15	14
N omalizumab	15	6	9	9	8	10
N mepolizumab	9	3	7	6	7	4

Figure 4 Improvement in asthma control during benralizumab treatment in naïve, bio-experienced, omalizumab, and mepolizumab groups. Median change in ACT score (**A**) and percentage of patients achieving a well-controlled asthma (ACT score ≥20) (**B**) are shown at various time points (index date and 4, 16, 24, 48, and 96 weeks of treatment with benralizumab).

sustained response of benralizumab in patients characterized by an eosinophilic-driven SA phenotype which failed to respond to previous biologics. Novel data have also been generated by analyzing bio-experienced patients split into omalizumab and mepolizumab groups. A total of four patients switched from omalizumab to mepolizumab prior to receiving benralizumab; because of the small number of patients undergoing a double biologic switch, these were combined with patients in the mepolizumab group. Within our bio-experienced group, no patients previously received dupilumab because this biologic became reimbursable in Italy after the ANANKE population was enrolled.[35,38]

Clinical characteristics of naïve and bio-experienced groups have already been discussed.[35,37] Briefly, the eosinophilic-driven nature of SA was confirmed in all patients, with the bio-experienced group showing poorer clinical characteristics compared with naïve patients in terms of severe AER, OCS dosage, and OCS-related comorbidities. When examining the two bio-experienced subsets, we noticed that severe AER was greater in omalizumab-switched patients, while patients in the mepolizumab group showed a higher level of airway obstruction (as indicated by the lowest values of post-BD FEV_1 and FVC) and higher frequency of CRSwNP. Although both benralizumab and mepolizumab induce an enhanced response in the presence of CRSwNP,[19,39] our data suggest that mepolizumab may not guarantee a durable optimal control of asthma in comorbid patients, whereas benralizumab could be more efficacious. An accurate phenotyping of the comorbid patient is crucial to assist the physician in selecting the biologic treatment.[40] Patients in the mepolizumab group were also characterized by a higher OCS usage compared with patients who switched from omalizumab (25 mg versus 5 mg). In line with this result, a high OCS dose is known to correlate with worse outcomes to mepolizumab treatment,[39] but a superior response is expected

in response to benralizumab in the eosinophilic-driven phenotype;[19] interestingly, patients who take a high dose of OCS while receiving mepolizumab have recently been found to have a higher change of undergoing a biologic switch.[41]

Despite having different characteristics at index date, all groups considerably benefitted from benralizumab treatment, as demonstrated by the sustained improvements described across all clinical outcomes. The most impressive results are represented by the prolonged drop in any (>86%) and severe AER (≥94%), along with the substantial increase in patients with zero severe exacerbations at 96 weeks (at least 82% patients free from severe exacerbations). This dramatic decline in exacerbations coincided with a persistent BEC value of 0.0 cells/mm^3 across all groups, highlighting how a broad depletion of eosinophils is necessary to achieve such a result in the context of eosinophilic-driven asthma, as already postulated by other groups.[42,43] Previous long-term studies also showed a consistent exacerbations decrease in patients switching from mepolizumab to benralizumab, from zero OCS-requiring exacerbations at 48 months (N=6)[31] to a 66.7% AER reduction after a median period of 31 months (AER decreased from 6 to 2);[41] exacerbations were also decreased after shorter treatment periods.[44,45] Similarly, patients switching from omalizumab showed a robust and significant reduction in exacerbation rate after receiving benralizumab (reduction greater than 50%[28] and 90%).[44]

Lung function was analyzed at several time points and found to be either preserved or improved in all groups after 96 weeks of treatment. Although bio-experienced patients had a decline in both pre-BD FEV_1 and FVC at 24 weeks, these parameters substantially increased at 96 weeks (+0.5 L and +0.4 L, respectively), exceeding the improvement registered in naïve patients (+0.4 L and +0.2 L, respectively). When evaluating omalizumab and mepolizumab subsets, a drop of both pre-BD parameters at 24 weeks was noticed specifically in the omalizumab group, while the mepolizumab group exhibited a striking improvement at 96 weeks. The superior respiratory response observed in mepolizumab-treated patients could be due to the poorer lung function shown by this group at index date, which may have allowed for a more pronounced response; likewise, the modest airway obstruction initially measured in omalizumab-switched patients could explain the slow and variable FEV_1 increase in this subset. Nonetheless, given the remarkable decrease in AER, a recovery of respiratory parameters was expected in all groups.[46,47] Once again, we can deduct that the lung function was preserved thanks to benralizumab-mediated extensive and long-lasting reduction in eosinophils, not only in peripheral blood but also in the tissues.[48] As a matter of fact, benralizumab has been demonstrated to lower the number of tissue eosinophils,[49] with a superior effect in decreasing sputum eosinophils when compared with mepolizumab.[50] In addition, according to the novel findings reported by Bergantini et al, benralizumab induced profound changes in CD3+ T cell number and NK cell activation, and these were positively correlated with improvements in FEV_1 and FVC measured in their SEA patient population.[33] Therefore, this differentiating action of benralizumab is likely to explain the greater effectiveness on respiratory parameters in patients who were treated with other biologics.

In the literature, wide improvements in respiratory function were shown in patients switching to benralizumab,[28,41,44] although in the 48 months-long study by Numata et al, after an initial increase in FEV_1 at 24 months, a decrease of this parameter to baseline values was recorded in both naïve and mepolizumab-switched patients after 36 and 48 months of benralizumab treatment.[31] Additional studies with observation periods longer than 2 years and evaluating more patients would be necessary to corroborate the findings presented here. The OCS-sparing effect of benralizumab is another essential component to evaluate its efficacy in treating SEA patients. The long-term OCS dose reduction shown in this study exceeds the results previously communicated by Caruso et al, in which naïve and bio-experienced patients reached median daily OCS doses of 4.5 mg and 8.6 mg, respectively, after a median period of 9.8 months (reductions of 61.9% and 49.1%, respectively).[36] Indeed, at 48 and 96 weeks, naïve patients maintained a median OCS dose of 0 mg/daily, while bio-experienced patients had a slight increase in median OCS dose from 0 to 1.9 mg/daily. As already explained above, such a modest increment was not caused by an actual increase in OCS dosage but rather by the low number of bio-experienced patients, which further decreased at 96 weeks. In this context, it is important to emphasize that, while omalizumab-treated patients could not eliminate OCS use, patients in the mepolizumab group retained a median OCS daily dose of 0.0 mg up to 96 weeks despite receiving the highest dose at the index date (25 mg/daily). Similarly, Caminati et al also reported a durable elimination in median OCS daily dose in their mepolizumab-switched population,[41] but no OCS dose reduction was found in the long-term study by Numata et al.[31] Beyond the predictable conflicting results emerging from real-world studies, our findings suggest that the specific MoA of benralizumab may play a role for reaching a sustained OCS reduction of interruption. Bergantini et al recently found that higher or more frequent OCS courses may paradoxically further impair the immunological imbalance found in SEA patients

by worsening NK cell dysfunction: this could be counterbalanced by benralizumab through the binding of FcγIIIRa receptors expressed on the NK cells surface, leading to a substantial restoration of NK cells maturation and activity comparable to non-asthmatic individuals.[33] Previous studies focusing on omalizumab-switched patients reported either a median reduction to 0.0 mg/day,[28] or a decline in OCS cycles.[44] The dissimilarities in OCS reduction seen in patients switching from mepolizumab across our and previous studies are of difficult interpretation; although benralizumab has been shown to decrease OCS dosage independently of OCS duration in the PONENTE study,[51] we cannot exclude that this variable could have negatively influenced OCS reduction in omalizumab-switched patients. Prolonged OCS treatment may cause OCS-related comorbidities[52] and adrenal gland dysfunction; if adrenal insufficiency occurs, treatment with low-dose OCS is required independently of asthma symptoms.[53] However, data on the duration of OCS treatment are not available in our and other studies, thus we can only presume that patients in the omalizumab group may have been treated with OCS for a longer period.

Both naïve and bio-experienced populations achieved asthma control already at 4 weeks after benralizumab initiation. The median ACT score rapidly increased, reaching its maximum after 96 weeks in all groups except mepolizumab-switched patients, even though this subset showed superior improvements in both respiratory function and OCS dose reduction. Unlike the mepolizumab group, omalizumab-switched patients displayed a robust improvement in asthma control, demonstrated by a median ACT score ≥20 maintained at all time points and peaking at 96 weeks. The limited change in ACT score seen in the mepolizumab group may have been caused by the modest number of patients with available ACT data. Interestingly, similar data have been shown in the 1-year study conducted by Gómez-Bastero Fernández et al, in which patients switching from omalizumab achieved a great asthma control (mean ACT score increased from 13.5 ± 5.1 to 22.9 ± 2.1), while patients switching from mepolizumab reached an inferior mean ACT score of 17.8 ± 4.7 (from an initial value of 12.4 ± 4.6).[44]

Based on the effectiveness of benralizumab in omalizumab-switched patients across a range of clinical outcomes, as demonstrated in our and previous studies,[28,44] the eosinophilic-driven pheno-endotype of asthma appears to be often neglected in atopic patients, where the IgE-driven pathophysiological mechanism is usually considered predominant. However, asthma is a dynamic disease and T2 biomarkers have been found to fluctuate over time in SA patients even before they received a biological therapy.[54] Therefore, eosinophilic inflammation may prevail and aggravate asthma symptoms in atopic SEA patients independently of IgE levels.[24,42,43] That is the reason why BEC should be closely monitored in atopic patients and, ultimately, benralizumab should be the first choice for treating atopic SEA patients when they present an eosinophilic-driven asthma phenotype.

Switching asthma therapy from mepolizumab to benralizumab has become frequent in clinical practice, as indicated by the growing number of studies demonstrating a positive and durable response to benralizumab following mepolizumab failure.[31,41,44,45] A possible explanation for mepolizumab failure is represented by the limited effect in reducing tissue eosinophil number compared with benralizumab:[49,50] even a high dose of mepolizumab (750 mg) could decrease airway eosinophils by only 55%.[55] As demonstrated in the phenotyping Mepolizumab EXacerbations in severe eosinophilic asthma (MEX) study, a large proportion of eosinophilic exacerbations occurred in SEA patients despite being on stable treatment with mepolizumab;[56] on the contrary, exacerbations have been found to be mostly non-eosinophilic in benralizumab-treated patients.[50] Moreover, as mentioned above, benralizumab induces a deep modulation of the immune system that goes beyond the mere apoptosis of eosinophils by leading to full recovery of NK cell maturation and activity.[33] Overall, these data reinforce the hypothesis that benralizumab action within the tissue is extensive and outperforms the limited reduction of tissue eosinophils mediated by mepolizumab, thus justifying patients' enhanced clinical response during benralizumab treatment.

Although BEC is widely used to guide the biologic choice and predict treatment efficacy, its level should be evaluated along with other clinical characteristics, which are known to be components of the eosinophilic phenotype.[3] The following aspects should also be considered:

1. correlation between BEC and number/severity of exacerbations;
2. correlation between BEC and respiratory parameters;
3. use of OCS in-between exacerbations, and response to OCS; and
4. presence and clinical relevance of sensitivity to perennial allergens.

Our study's observational retrospective design is its principal limitation. The ANANKE study has been conducted in real life; as such, the inclusion criteria (mainly related to benralizumab eligibility according to the Italian clinical practice) allowed the enrolment of a broad SEA population and determined some unavoidable heterogeneity in patients' characteristics. In addition, since clinical characteristics at index date were gathered throughout the 12 months before benralizumab initiation, data may have been potentially skewed by the extended collection period.

Similarly to our study, some discrepancies between omalizumab and mepolizumab subsets at baseline were noticed in other real-life studies.[44] Whether the initial biologic therapy determined such differences would warrant further investigations.

The lack of statistical analysis represents a considerable disadvantage of this study, as it precludes the quantitative and universal interpretation of the results. The analysis of variables was descriptive only because the primary endpoint of the ANANKE study is to describe the clinical profile of patients eligible for treatment with benralizumab in a real-world setting. As such, no formal hypotheses could be pre-specified and statistically tested.

Taking into account these limitations, the findings presented here will serve the scientific community by providing an update on the clinical outcomes observed in SEA patients switched to benralizumab after a partial response to previous biologics.

Conclusions

In this post hoc analysis, benralizumab induced a substantial and durable clinical response in both naïve and bio-experienced patients. The magnitude of the observed effects may be also due to the newly proposed MoA of benralizumab, involving improved NK cell maturation and anti-eosinophilic activity.[32,33] Given the dramatic decline in AER and the broad improvement in lung function in both groups, it seems reasonable to recognize these two clinical outcomes as "treatable traits" of benralizumab in the context of eosinophilic asthma. Overall, our data not only endorse the switch to benralizumab whenever patients experience a sub-optimal response from either omalizumab and/or mepolizumab but encourage choosing benralizumab as first-line biologic to treat SEA patients whenever the eosinophilic-driven nature of asthma has been ascertained.

Abbreviations

ACT, asthma control test; ADCC, antibody-dependent cellular cytotoxicity; AER, annual exacerbation rate; BEC, blood eosinophil count; BMI, body mass index; eCRF, electronic case report form; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL5, interleukin 5; IL5Rα, interleukin 5 receptor alpha; IQR, interquartile range; LABA, long-acting β2-agonist; mAb, monoclonal antibody; MoA, mechanism of action; N, number of patients; NK, natural killer; OCS, oral corticosteroids; pre/post-BD FEV_1, pre/post-bronchodilator forced expiratory volume in 1 second; pre/post-BD FVC, pre/post-bronchodilator-forced vital capacity; SA, severe asthma; SD, standard deviation; SEA, severe eosinophilic asthma.

Data Sharing Statement

Upon reasonable request, the corresponding author will provide the datasets used and/or analysed during the current work.

Ethics Approval and Informed Consent

The ANANKE study was carried out in agreement with the ethical standards outlined in the Declaration of Helsinki as well as laws and policies governing the Italian medical ethics and practice. Before participating in the study, each patient gave informed consent and signed updated informed consent and privacy forms related to the extended period of observation. Ethics committees/institutional review boards granted ethical approval at each site involved in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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