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CASE REPORT



# Long-term outcomes of combination biologic therapy in uncontrolled severe asthma: a case study

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**ABSTRACT**

**Introduction:** Treatment with biologics has significantly reduced the social and economic burden of severe asthma. However, some patients may still feature a suboptimal control of their symptoms while on therapy. In this subset of asthmatic patients, a benefit from a dual biologic therapy has sporadically been reported in literature. Our aim is to add our experience to the limited body of evidence supporting combination biologic therapies.

**Case study:** Here we present the case of a 68-year-old nonsmoker female, with an allergic and eosinophilic corticosteroid-dependent severe asthma. She displayed well controlled comorbidities and good adherence to the inhaled therapy. Omalizumab was started in 2008 with an initial remarkable clinical improvement. After nine years of biologic therapy, she reported a gradual worsening of her symptoms and exacerbations. Mepolizumab was then added in 2019.

**Results:** The addition of Mepolizumab resulted in a meaningful amelioration of her quality of life, asthma control, number of exacerbations and 6-minute-walking-distance at 3-year follow-up. The average Prednisone dosage was tapered from 25 mg to 20 mg daily. No adverse events were observed since the introduction of the second biologic.

**Conclusion:** Our experience indicates that Mepolizumab may be beneficial and safe as an add-on biologic in a patient whose allergic and eosinophilic asthma remains uncontrolled despite treatment with an anti-IgE strategy. Further studies on a larger number of patients are required to demonstrate whether the positive outcomes published so far are replicable on a larger scale.

**Abbreviations.** ICS-LABA: Inhaled Corticosteroid and Long-Acting Beta2-Agonist; IL-5: Interleukin-5; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; FeNO: Fractional exhaled nitric oxide; 6MWT: 6-minute-walking-test; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire

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Severe asthma; biologic therapy; eosinophilic asthma; allergic asthma; uncontrolled asthma

## Introduction

Helping severe asthmatic patients improve their symptom control and quality of life may still nowadays represent a challenge to the clinician, despite significant advances in the understanding of its pathophysiology and consequent therapeutic empowerment (1).

Current guidelines on the management of severe asthma suggest phenotyping the asthmatic patient by dosing serum total IgE, peripheral eosinophils and by measuring the fraction of exhaled nitric oxide. This recommendation follows the well-known notion of the predominant role of type 2 inflammation in the pathophysiology of asthma. As a matter of fact, type 2 inflammatory signaling pathways are the only targets of currently approved biologic drugs (2).

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody used as an add-on option for patients with severe allergic asthma uncontrolled on high dose inhaled corticosteroid and long-acting beta-agonist (ICS-LABA). Whereas an anti-interleukin-5 (IL-5) strategy (Mepolizumab, Benralizumab, Reslizumab) is recommended in adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma. In particular, Mepolizumab, a monoclonal antibody that targets IL-5, is effective in reducing exacerbations and hospitalizations in patients

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with severe eosinophilic asthma, as well as reducing maintenance oral corticosteroids dose in patients with corticosteroid-dependent severe asthma (3).

Although add-on biologic drugs have significantly improved the outcome of asthmatic patients, their use may not be sufficient in achieving optimal symptom control. The complex interplay among multiple inflammatory signaling pathways, as well as the possibility of a coexistence or else a gradual shift from one endophenotype to another, might explain the suboptimal response in this group of patients (4). The logical consequence is that these patients, despite displaying a more complex disease, may also have multiple therapeutic targets that require a combination of biologics. However, the use of combination biologic therapies in asthmatic patients has not been thoroughly investigated, and no guidelines worldwide recommend its use. We report here the successful use of a combination of Omalizumab and Mepolizumab in increasing the quality of life and exercise capacity, reducing the number of exacerbations and burden of respiratory symptoms in an asthmatic patient. Of interest, to the best of our knowledge this represents the longest follow-up ever published of a dual biologic therapy for uncontrolled severe asthma.

## Case study

A 54-year-old nonsmoker female was referred to the Severe Asthma Clinic of the Respiratory Medicine Unit of the San Paolo Hospital, Milan in 2008 for an uncontrolled severe eosinophilic and allergic asthma, diagnosed in her twenties. She reported increasingly frequent respiratory symptoms, a significant limitation to the activities of daily living, four exacerbations a year (two of which requiring hospitalization). Her therapeutic regimen included Fluticasone/Formoterol 250/10 mcg two inhalations twice daily, Tiotropium 2.5 mcg two inhalations daily, Salbutamol 100 mcg 10 inhalations daily, Prednisone 25 mg daily, Cetirizine 10 mg daily. Pulmonary function tests showed a severe bronchial airflow obstruction, with a forced expiratory volume in 1 s ($FEV_1$) of 0.63 L – 27% predicted and a forced vital capacity (FVC) of 1.39 L – 50% predicted; the total IgE serum level was 114 IU/mL, and the peripheral eosinophil count was 1009/μL. Comorbidities included nasal polyposis, type 2 diabetes mellitus and osteoporosis. Her documented allergies included dust mites, non-steroidal anti-inflammatory drugs, beta-lactam antibiotics and ranitidine; previous therapies with Theophylline and Montelukast led to intolerance as well. After a thorough assessment of the patient's phenotype, control of comorbidities and therapeutic compliance, biological therapy with Omalizumab 300 mg every 4 weeks was started in May 2008.

After 9 years of biologic therapy, with an initial significant improvement of her quality of life (albeit, without success in tapering off Prednisone) the patient reported a slight – yet persistent – progression of her symptoms' severity and increased number of exacerbations. Since the authors did not interpret her worsening as a therapeutic failure, but rather as a reduction of its efficacy, and given the patient's firm refusal of interrupting/changing a biologic therapy that had remarkably ameliorated her life, it was decided to add Mepolizumab 100 mg every 4 weeks to her ongoing therapeutic regimen in April 2019.

Pulmonary function tests, exercise capacity (through the 6-min-walking-test), peripheral blood eosinophil count, total serum IgE concentration were assessed before and after the introduction of Mepolizumab at each follow-up visit every 3–6 months. The Asthma Quality of Life Questionnaire and the Asthma Control Test were regularly administered as well (Table 1).

## Results

As shown in Table 1, after 3 years of dual biologic therapy, there was a significant clinical improvement, especially in terms of exercise capacity (160 m vs 280 m), quality of life (AQLQ from 3.5 to 5.1) and number of yearly exacerbations (four vs two). From a functional standpoint, there was a mild yet significant increase of the FEV1 (1.08 L – 50% vs 1.32 L – 64%). The peripheral blood eosinophil count fell from 2330 to 200 cells/μL, with approximately stable total serum IgE levels. After an initial successful reduction of the Prednisone dosage at 6 months, a stable daily dose of 20 mg proved to be necessary to prevent asthma flare ups. On the other hand, the use of Salbutamol was markedly reduced (15 vs 2 puffs daily). There were no reported adverse events at the time of first administration as well as during follow-up.

## Discussion

The main findings of this report are: (1) a dual anti-IgE plus anti-IL-5 biologic strategy in a patient with allergic and eosinophilic severe asthma, still uncontrolled while on biologic monotherapy, significantly improved the quality of life, exercise capacity and number of exacerbations at 3 year follow-up, without any further hospitalization; (2) combination therapy proved to be safe and well tolerated; (3) the addition of Mepolizumab allowed a slight tapering of the steroid daily dose, without ever reaching its discontinuation.

**Table 1.** Patient's characteristics at baseline (prior to the introduction of the second biologic) and at follow-up.*

| | T0 (04/2019) | *T*+6 months (10/2019) | *T*+24 months (04/2021) | *T*+36 months (04/2022) |
|---|---|---|---|---|
| WBC, cells/μL | 11810 | 8450 | 7575 | 8970 |
| Eosinophils, cells/μL | 2330 | 300 | 250 | 200 |
| Eosinophils, % | 20 | 0.4 | 3.3 | 2.2 |
| Total IgE, IU/mL | 189 | 107.5 | 82.7 | 161 |
| FEV1, L | 1.08 | 1.55 | 1.32 | 1.32 |
| FEV1, % predicted | 50 | 72 | 63 | 64 |
| FVC, L | 2.0 | 2.25 | 2.08 | 2.1 |
| FVC, % predicted | 73 | 82 | 77 | 77 |
| FEV1/FVC, % predicted | 68 | 87 | 81 | 91 |
| FeNO, ppb | 13 | N/A | N/A | 10 |
| 6MWT distance, m | 160 | 240 | N/A | 280 |
| 6MWT mean SpO2 | 94% | 97% | N/A | 97% |
| 6MWT duration, minutes | 3 | N/A | N/A | 6 |
| ACT | 11 | 14 | 15 | 15 |
| AQLQ | 3.5 | 4.4 | N/A | 5.1 |
| HADS | A10D5 | N/A | N/A | A9D3 |
| Number of exacerbations/ year | 4 | 2 | 2 | 2 |
| Number of exacerbations with hospitalization/ year | 1 | 1 | 0 | 0 |
| Prednisone average daily dose, mg | 25 | 12.5 | 20 | 20 |
| SABA usage, puffs daily | 15 | 6 | 3 | 2 |
| Inhaled Therapy | Fluticasone/ Formoterol 250/10 mcg 2 puffs bid + Tiotropium 5 mcg daily | Fluticasone/ Formoterol 250/10 mcg 2 puffs bid + Tiotropium 5 mcg daily | Fluticasone/ Formoterol 250/10 mcg 2 puffs bid + Tiotropium 5 mcg daily | Fluticasone/ Formoterol 250/10 mcg 2 puffs bid + Tiotropium 5 mcg daily |

*Data at 1 year follow-up (April 2020) are missing due to the intercurrent COVID-19 pandemic, during which patients were followed-up only by telephone interviews. WBC: White blood cells; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; FeNO: Fractional exhaled nitric oxide; 6MWT: 6-min-walking-test; ACT: Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; HADS: Hospital Anxiety and Depression Scale; SABA: Short-acting beta agonist.

Our case report adds to the sparse body of published evidence that dual biologic therapy may be safe and beneficial in patients whose allergic and eosinophilic asthma remains poorly controlled despite the use of one biologic (5–10). Dedaj et al. describe a similar successful case of dual biologic therapy in a patient affected by eosinophilic severe asthma with elevated total IgE still uncontrolled while on Omalizumab, in whom the addition of Mepolizumab led to a significant tapering of the oral corticosteroid daily dose (7). Thomes et al. report comparable outcomes in three patients receiving a dual biologic therapy, with a reduction in the number of exacerbations, tapering of oral corticosteroid dose and improved control of respiratory symptoms (9).

## Conclusion

In conclusion, the positive outcomes reported so far on the use of dual biologic therapies in selected groups of asthmatic patients may be a valuable option and should prompt further investigation in the field, with a larger number of patients and longer follow-up.

## Declarations

### Ethics approval, consent to participate and for publication

Written informed consent was obtained from the patient for publication of this case report.

### Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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No source of funding was available for this study.

### Authors' contributions

**Andrea Baccelli**: Conceptualization, Data curation, Methodology, Investigation, Writing - original draft, review & editing. **Marcelina Koćwin:** Data curation, Investigation, Writing - review & editing. **Elena M Parazzini**: Conceptualization, Investigation, Writing - review & editing. **Rocco F Rinaldo**: Conceptualization, Methodology, Writing - review & editing. **Stefano Centanni**: Conceptualization, Methodology, Supervision, Writing - review & editing.

## References

1. Oppenheimer J, Slade DJ, Hahn BA, Zografos L, Gilsenan A, Richardson D, McSorley D, Lima R, Molfino NA,

Averell CM. Real-world evidence: patient views on asthma in respiratory specialist clinics in America. Ann Allergy Asthma Immunol. 2021;126(4):385–393.e2. doi:10.1016/j.anai.2020.12.015.

2. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeyer L, Khurana S, Knight S, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2020;55(1):1900588. doi:10.1183/13993003.00588-2019.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org.
4. Pavord I, Bahmer T, Braido F, Cosío BG, Humbert M, Idzko M, Adamek L. Severe T2-high asthma in the biologics era: European experts' opinion. Eur Respir Rev. 2019;28(152):190054. doi:10.1183/16000617.0054-2019.
5. Caskey JR, Kaufman D. Dual biologic therapy in a patient with severe asthma and other allergic disorders. BMJ Case Rep. 2021;14(5):e242211. doi:10.1136/bcr-2021-242211.
6. Fox HM, Rotolo SM. Combination anti-IgE and anti-IL5 therapy in a pediatric patient with severe persistent asthma. J Pediatr Pharmacol Ther. 2021;26(3):306–310. doi:10.5863/1551-6776-26.3.306.
7. Dedaj R, Unsel L. Case study: a combination of mepolizumab and omaluzimab injections for severe asthma. J Asthma. 2019;56(5):473–474. doi:10.1080/02770903.2018.1471706.
8. Ortega G, Tongchinsub P, Carr T. Combination biologic therapy for severe persistent asthma. Ann Allergy Asthma Immunol. 2019;123(3):309–311. doi:10.1016/j.anai.2019.06.013.
9. Thomes R, Darveaux J. Combination biologic therapy in severe asthma: a case series. Ann Allergy Asthma Immunol. 2018;121(5). doi:10.1016/j.anai.2018.09.297.
10. Altman MC, Lenington J, Bronson S, Ayars AG. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract. 2017;5(4):1137–1139. doi:10.1016/J.JAIP.2017.01.013.