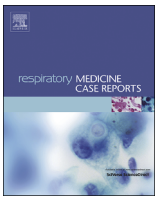
Respiratory Medicine Case Reports 41 (2023) 101795

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Two years follow-up of relapsing eosinophilic pneumonia with concomitant severe asthma successfully treated with benralizumab: A case report and brief review of the literature

G. Angeletti *, M. Mazzolini, A. Rocca

Department of Respiratory Medicine, Bellaria Hospital, Bologna, Italy

A B S T R A C T

Relapsing eosinophilic pneumonia and severe eosinophilic asthma are rare and disabling diseases, which share common inflammatory backgrounds and often require long-term systemic steroid therapy. Benralizumab is a humanized antibody targeting IL-5 receptor that reduces corticosteroid dependence and flares up in severe eosinophilic asthma on long term. In this case report, successful treatment of eosinophilic pneumonia and severe eosinophilic asthma with benralizumab is described after a 2-year follow up, showing the promising results of this therapy for eosinophilic pneumonia management.

1. Introduction

Eosinophils are cells involved in various biologic processes, such as response to several parasitic, bacterial, and viral infections and in disease pathology [1]. Eosinophilic lung diseases are a group of diffuse parenchymal lung diseases, characterized by the prominent infiltration of the lung interstitium and the alveolar spaces by polymorphonuclear eosinophils (with conservation of the lung architecture), frequent severe impairment of lung function at presentation and by a dramatic response to systemic corticosteroid therapy. In most cases, eosinophilic lung diseases can be treated without serious sequelae. Idiopathic chronic eosinophilic pneumonia (ICEP) is characterized by onset of cough, dyspnea, malaise, and weight loss over a few weeks, as well as diffuse pulmonary infiltrates. ICEP occurs predominantly in patients with high levels of T2 inflammation and two-thirds of patients with ICEP have a prior history of asthma. About 50% of patients have a relapse during tapering or after discontinuation of corticosteroid treatment, increasing the risk of becoming steroid-dependents [2,3]. Given the serious side effects of steroid therapy, other therapies like biotechnological drugs are being explored [4,5]. Eosinophil-associated diseases share a common pathogenetic background, represented by eosinophil-led inflammation and overexpression of interleukin 5 (IL-5). Three monoclonal antibodies targeting IL-5 are currently available: mepolizumab and reslizumab block circulating IL-5 preventing the binding to its receptor, while benralizumab binds to IL-5 receptor α, all with excellent results in eosinophilic asthma [6]. Mepolizumab has been approved in several countries for the treatment of both hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis. Benralizumab induces rapid and sustained depletion in blood and tissue eosinophils and shows potential to treat eosinophilic diseases, but further studies are needed [7]. We hereby report a case of relapsing chronic eosinophilic pneumonia (CEP) and concomitant severe eosinophilic asthma successfully treated with benralizumab at two years.

* Corresponding author.
E-mail address: giulia.angeletti@ausl.bologna.it (G. Angeletti).

https://doi.org/10.1016/j.rmcr.2022.101795
Received 8 August 2022; Accepted 12 December 2022
Available online 13 December 2022

2. Case presentation

The patient was a 52 years old female - BMI: 23 Kg/m2, former smoker (stop in 2007, 10 pk/y), without significant work or environmental exposures, no domestic animals, regular physical activity. She reported a history of sinusitis in childhood, and was diagnosed asthma in 2007; the prescribed therapy of a medium dose of inhaled corticosteroid plus long acting β2 agonists bronchodilator (ICS-LABA) well controlled the asthma until 2016.

In September 2016, asthma became uncontrolled, the patient developed fatigue and dyspnoea, and was prescribed a chest radiography and a chest CT-scan. The latter showed pulmonary infiltrates and ground glass opacities mainly in the upper lobes (see Fig. 1A). Blood tests run on the patient showed marked eosinophilia.The patient was subsequently treated with prednisone 0.5 mg/kg gradually tapered from February 2017 to August 2017 by a territorial pulmonologist suspecting an eosinophilic pneumonia.

In November 2017, asthma became uncontrolled again: CT-scan was repeated and showed phlogistic confluent parenchymal opacities with air bronchogram, mainly at the apices bilaterally (see Fig. 1B); at the same time, blood samples showed a new increase in eosinophil count (780/microliter/11.5%). Any infectious, neoplastic or drug driven disease was excluded. The patient was prescribed high dose ICS-LABA and underwent fibrobronchoscopy with bronchioloalveolar lavage (BAL); microbiological studies for microorganisms and parasites resulted in negative. Cell cytofluorometry reported increased cellularity compared to the normal, with a marked increase in eosinophil granulocytes (46%). A diagnosis of chronic recurrent eosinophilic pneumonia was becoming a concrete

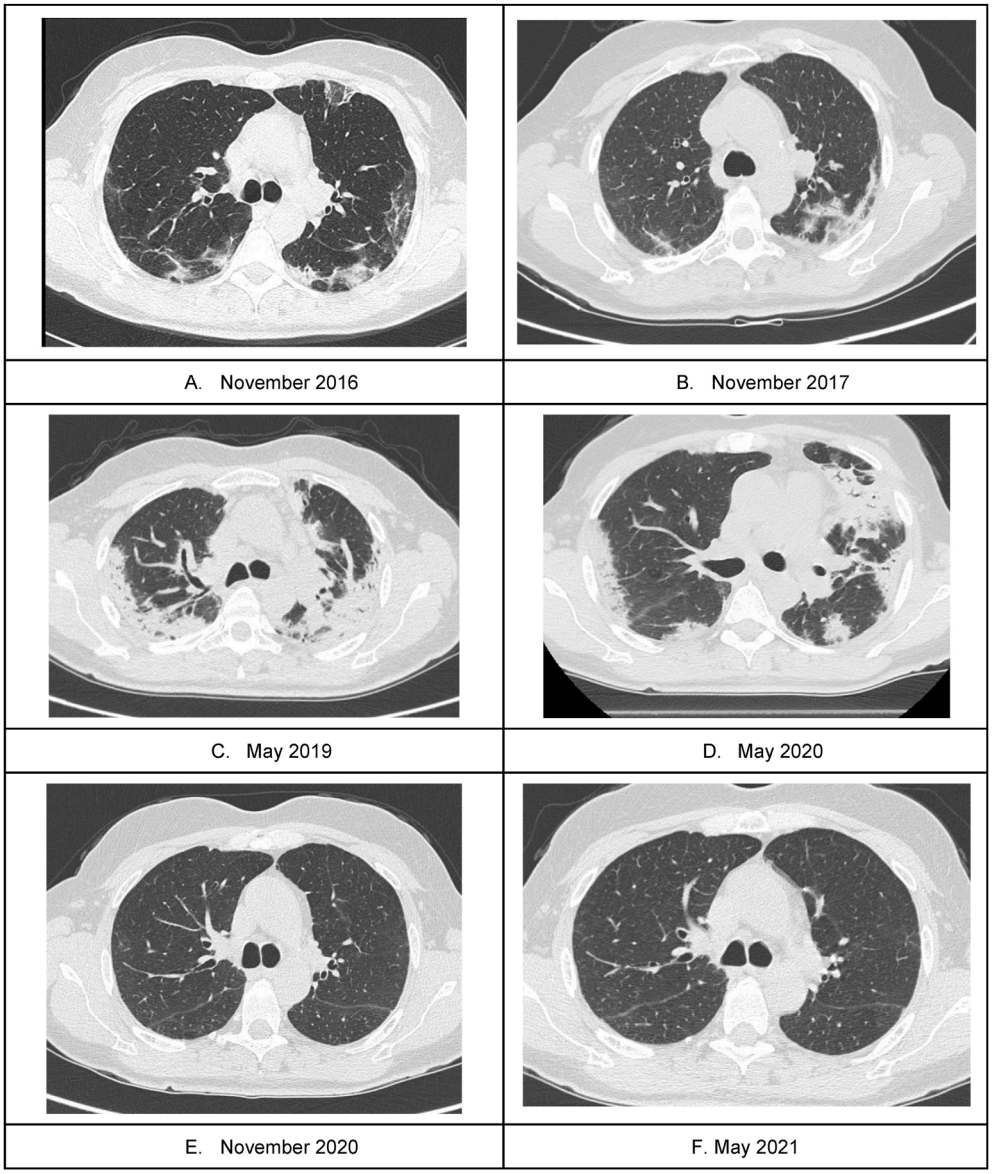


Fig. 1. Progressive worsening of the ICEP (A to D) until introduction of benralizumab and subsequent regression of the radiological signs (e and F).

possibility in light of the aforementioned results. In December 2017, the patient was evaluated for vasculitis by a rheumatologist but no signs were detected, and the subject also tested negative for antineutrophil cytoplasmic antibodies (ANCA). The patient was then prescribed a therapy with prednisone 25 mg with tapered over three months, that was discontinued in March 2018. The subject achieved clinical stability and maintained it until the beginning of 2019.

Between May 2019 and December 2019 the patient had three more relapses; after being discussed at the multidisciplinary meeting of pulmonary interstitial diseases, the diagnosis of Relapsing Chronic Eosinophilic Pneumonia was confirmed at this point (see Fig. 1C). In February 2020 the disease relapsed again and the patient was referred to our outpatient clinic, where she refused additional treatment with benralizumab. At the end of May 2020, the patient had a new recurrence with a significant aggravation of asthma (see Fig. 1D) and biologic therapy with benralizumab was consequently started on June 3rd, 2020 (30 mg every 4 weeks for 3 doses and then once every 8 weeks) with prednisone 0.5 mg/kg/die (25 mg). In July 2020, the patient had a clinical and functional improvement compared to May 2020, with an asthma control test of 25/25, so slow tapering from steroid therapy was initiated (see Table 1). The blood cell count of August 2020 revealed 0 eosinophils (0/microliter/0%t).

At the follow-up visit in October 2020, the patient reported complete well-being and as physical examination and lung function were normal, steroid therapy was completely suspended at the end of October 2020 without any sign or symptom of adrenal suppression.

A CT scan performed in November 2020 showed almost total resolution of the parenchymal opacities (see Fig. 1E).

Clinical, functional and radiological stability was maintained after steroid suspension at 6 and 9 months (see Fig. 1F). The patient underwent a hematological evaluation in February 2021, and it showed no signs of hematologic disease; the subject also tested negative to the analysis for rearrangement of FIP1L1-PDGFRA.

At a follow up visit in April 2021, the patient reported a recent paucisymptomatic SARS-CoV2 infection. Chest CT-scan in May 2021 (one year from the last asthma-CEP exacerbation and 6 months from steroid suspension) revealed no significant alterations.

In June 2022, 2 years after the last asthma-CEP flare up, the patient still had no respiratory symptoms, excellent asthma control, normal lung function, negative chest X Ray and no eosinophils detected in blood test.

3. Discussion

Relapsing eosinophilic pneumonia is a rare disease usually associated with asthma but while there is extensive literature about the efficacy of benralizumab on severe eosinophilic asthma [6], only a few case reports describe effects of benralizumab on CEP. Patients affected by asthma and CEP respond well to systemic steroids, but relapses are very frequent during tapering or discontinuing steroids. No alternative therapy for CEP has been established, but long-term adverse events generated by steroids can cause serious health issues [4]. Benralizumab, a monoclonal antibody against the alpha-chain of IL-5 receptor, almost completely depletes eosinophils through enhanced antibody-dependent natural killer cell-mediated cytotoxicity. This drug reduces exacerbations, shows systemic corticosteroid-sparing effect and improves lung function in patients with severe eosinophilic asthma [6,8]. IL-5 seems to have a role in the pathogenesis of CEP, and its histopathology is characterized by interstitial and alveolar exudates with eosinophils [9], so benralizumab may be a potential treatment option. In a 2019 case report, benralizumab was used to treat relapsing CEP with an apparently positive response, but no information about the duration of the positive effect of the monoclonal antibody was provided [10]. In a 2020 review, benralizumab showed promising results in the treatment of asthma associated with a variety of eosinophilic diseases, including eosinophilic pneumonia [11]. CEP requires careful examination in order to exclude other causes of pneumonia, being its radiological presentation subject to high variability. In a recent review focused on eosinophilic pneumonia diagnosed through BAL between 2014 and 2020 a total of 53 cases were identified; of these cases, 12 patients were receiving treatment with either mepolizumab or benralizumab. As these patients started the biological therapy, all of them showed improvement and did not require additional steroid therapy [12]. Similarly, four recent case reports reveal that even a single dose of benralizumab may have a positive impact on eosinophilic pneumonia [13–16]. In two of these case reports, benralizumab was given on a single dose and discontinued with persistence of positive effects at 2 months [13] and 6 months [14], respectively (see Table 2). In the other two cases, the drug was administered to treat uncontrolled asthma associated with CEP and not discontinued, with promising results on both pathologies at 12 months [15,16]. Anti IL-5r was also used off-label on a pediatric patient with relapsing eosinophilic pneumonia with typical presentation (fever, reverse butterfly pattern, BAL eosinophilia), with positive outcomes [17]. To the best of our knowledge, there is only one case that reports using benralizumab in a patient with CEP treated with multiple doses of the monoclonal antibody over 30 months, but the subject did not suffer of severe asthma. Moreover, tapering of steroids is not reported and CEP diagnosis was not confirmed either by consensus meeting or biopsy [18,19]. Finally, while there is extensive knowledge and trial based schemes on gradual reduction of steroids with substitution with benralizumab therapy in severe asthma [20], a significant lack

Table 1
Progressive tapering of steroid therapy.

Month	Dose of prednisone/die
June 2020	25 mg
July 2020	18,75 mg
August 2020	12,5 mg
September 2020	5 mg
October 2020	5 mg every other day

Table 2
Literature on chronic eosinophilic pneumonia treated with benralizumab.

Author, year	Type of publication	CEP diagnosis confirmed by	Population	Concomitant asthma	Intervention	Additional steroid weaning scheme	Need for additional systemic steroid after intervention	Duration of follow-up
Askin 2021	population-based review	BAL	12 subjects 5 males, 7 females	unknown	benralizumab or mepolizumab unknown dose	unknown	no	unknown
Garcia-Saucedo 2019	case report	BAL	Female, 31 y	no	benralizumab 30 mg every 28 days	unknown	no	7 days
Isomoto 2020	case report	transbronchial lung biopsy	Female, 58 y	yes, severe	benralizumab 30 mg single administration	no additional steroids at intervention	no	2 months
Izumo 2020	case report	criobiopsy	Female, 43 y	no	benralizumab 30 mg single administration	no additional steroids at intervention	no	6 months
Ben-david 2021	case report	BAL	Male, 16 y	no	benralizumab 30 mg every 4 weeks for 3 doses and then once every 8 weeks	oral steroids <5 mg/alternate day) for 4 months than stop	no	8 months
Takano 2021	case report	BAL	Female, 83 y	yes, severe	benralizumab 30 mg every 4 weeks for 3 doses and then once every 8 weeks	prednisolone 7.5 mg, unknown weaning scheme	no	10 months
Yazawa 2021	case report	BAL + transbronchial lung biopsy	Female, 70 y	yes, not severe	benralizumab 30 mg unknown scheme	no additional steroids at intervention	no	12 months
Ricketti 2021	case report	BAL	Male, 57y	yes, not severe	benralizumab 30 mg every 4 weeks for 3 doses and then once every 8 weeks.	unknown initial dose, tapering in 3 weeks.	no	30 months

of information about timing and duration of tapering of steroids for asthma and relapsing CEP is still present, and this case report could provide a first insight on this topic.

4. Conclusion

Although long-term safety of benralizumab in patients with CEP is still to be explored, a therapy based on this drug has showed to have considerably fewer side effects than systemic corticosteroids, and may potentially be used long term for the treatment of CEP to prevent relapses of the condition. This is the first case report using benralizumab in a patient with relapsing CEP and severe asthma, treated with multiple doses of the monoclonal antibody over 24 months. As shown by the presented results, this monoclonal antibody may be a promising treatment option for CEP and asthma, especially in patients with frequent relapses or relapses caused by corticosteroid dose reduction.

Author contribution

Angeletti Giulia: writing original draft; writing review and editing (equal), conceptualization (supporting).

Massimiliano Mazzolini: conceptualization (lead); writing review and editing (equal); validation (supporting); supervision (supporting).

Alberto Rocca: supervision (lead); validation (lead).

Declaration of competing interest

The authors have no conflict of interest to declare.

References

[1] M.E. Wechsler, A. Munitz, S.J. Ackerman, et al., Eosinophils in health and disease: a state-of-the-art review, Mayo Clin. Proc. 96 (10) (2021) 2694–2707, https://doi.org/10.1016/j.mayocp.2021.04.025.
[2] V. Cottin, Eosinophilic lung diseases, Clin. Chest Med. 37 (3) (2016) 535–556, https://doi.org/10.1016/j.ccm.2016.04.015.
[3] Y. Suzuki, T. Suda, Eosinophilic pneumonia: a review of the previous literature, causes, diagnosis, and management, Allergol. Int. 68 (4) (2019) 413–419,

https://doi.org/10.1016/j.alit.2019.05.006.
[4] J.R. Curtis, A.O. Westfall, J. Allison, et al., Population-based assessment of adverse events associated with long-term glucocorticoid use, Arthritis Rheum. 55 (3) (2006) 420–426, https://doi.org/10.1002/art.21984.
[5] B. Olivieri, E. Tinazzi, M. Caminati, C. Lunardi, Biologics for the treatment of allergic conditions: eosinophil disorders, Immunol. Allergy Clin.North Am. 40 (4) (2020) 649–665, https://doi.org/10.1016/j.iac.2020.07.001.
[6] I. Agache, J. Beltran, C. Akdis, et al., Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma, Allergy 75 (5) (2020) 1023–1042, https://doi.org/10.1111/all.14221.
[7] Q. Delcros, M. Groh, M. Nasser, J. Kahn, V. Cottin, Steroid alternatives for managing eosinophilic lung diseases, Expert Opin. Orphan. Drugs 9 (7–10) (2021) 205–218, https://doi.org/10.1080/21678707.2021.2003777.
[8] P. Nair, S. Wenzel, K.F. Rabe, et al., Oral glucocorticoid-sparing effect of benralizumab in severe asthma, N. Engl. J. Med. 376 (25) (2017) 2448–2458, https://doi.org/10.1056/NEJMoa1703501.
[9] M. Laviolette, D.L. Gossage, G. Gauvreau, et al., Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia [published correction appears in J Allergy Clin Immunol. 2014 Apr;133(4):1232], J. Allergy Clin. Immunol. 132 (5) (2013) 1086–1096 https://doi.org/10.1016/j.jaci.2013.05.020, *e*5.
[10] J. Garcia-Saucedo, I. Carrillo-Martin, M. Sanchez-Valenzuela, G. Motoa, A. Lee, A. Gonzalez-Estrada, M401 Benralizumab for unresponsive steroid-dependent chronic eosinophilic pneumonia, Ann. Allergy Asthma Immunol. 123 (5) (2019) S134, https://doi.org/10.1016/j.anai.2019.08.436.
[11] M. Toyoshima, K. Koda, T. Nozue, T. Suda, Benralizumab for severe asthma associated with extra-airway eosinophilic diseases, Airway pharmacol Treatment (September 7, 2020) https://doi.org/10.1183/13993003.congress-2020.2222, Published online.
[12] c Askin, m Morris, When steroids fail: a population-based review of biologic therapies in the management of recalcitrant eosinophilic pneumonia, Chest 160 (4) (2021) A1273, https://doi.org/10.1016/j.chest.2021.07.1160.
[13] K. Isomoto, T. Baba, A. Sekine, N. Aiko, T. Ogura, Promising effects of benralizumab on chronic eosinophilic pneumonia, Intern. Med. 59 (9) (2020) 1195–1198, https://doi.org/10.2169/internalmedicine.3606-19.
[14] T. Izumo, N. Kuse, N. Awano, et al., Rapid and sustained effects of a single dose of benralizumab on chronic eosinophilic pneumonia, Respir. Med. Case Rep. 30 (2020), 101062 https://doi.org/10.1016/j.rmcr.2020.101062, 2020 Apr 22.
[15] S. Yazawa, M. Toyoshima, K. Koda, T. Suda, Benralizumab as initial treatment for chronic eosinophilic pneumonia, Allergol. Int. 70 (1) (2021) 140–142, https://doi.org/10.1016/j.alit.2020.07.005.
[16] T. Takano, Y. Inutsuka, S. Nakamura, N. Ando, M. Komori, Benralizumab use in chronic eosinophilic pneumonia with eosinophilic bronchiolitis and chronic airway infection, Respirol. Case Rep. 9 (8) (2021), e00810 https://doi.org/10.1002/rcr2.810, 2021 Jul 20.
[17] Y. Ben-David, L. Bentur, M. Gur, et al., Reverse butterfly pattern image with eosinophilia: effective treatment with benralizumab-A case report, Pediatr. Pulmonol. 56 (8) (2021) 2736–2739, https://doi.org/10.1002/ppul.25511.
[18] P.A. Ricketti, A.J. Ricketti, Relapsing chronic eosinophilic pneumonia treated successfully with benralizumab, Ann. Allergy Asthma Immunol. 126 (6) (2021) 726–727, https://doi.org/10.1016/j.anai.2021.02.016.
[19] L. Richeldi, N. Launders, F. Martinez, et al., The characterisation of interstitial lung disease multidisciplinary team meetings: a global study, 00209-2018. ERJ Open Res. 5 (2) (2019) https://doi.org/10.1183/23120541.00209-2018, 2019 Apr 1.
[20] A. Menzies-Gow, J. Corren, E.H. Bel, et al., Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial, ERJ Open Res. 5 (3) (2019) https://doi.org/10.1183/23120541.00009-2019, 00009-2019. Published 2019 Sep. 25.