Rapid onset of effect of benralizumab on respiratory symptoms in a patient with eosinophilic granulomatosis with polyangiitis

Angelo Coppola *, Krisstopher Richard Flores, Francesca De Filippis

UOC Malattie dell’Apparato Respiratorio, Ospedale “Regina Apostolorum”, Albano Laziale, RM, Italy

ARTICLE INFO
Keywords: EGPA Churg Strauss syndrome Benralizumab Eosinophils Anti IL-5Ra

ABSTRACT
A 63 years old woman affected by severe eosinophilic asthma associated with EGPA presented refractory respiratory symptoms, resistant to high dose oral corticosteroid treatment. A significant hyper-eosinophilia was present at the blood test, and the ACT score was steadily low, despite the maximal dose of inhalation therapy. The CT chest scan showed a persistent diffuse bronchial wall thickening, pulmonary infiltration and paranasal sinusitis. We report here the rapid onset of effect of benralizumab 30 mg in a monthly subcutaneous injection in reducing patient’s symptom, inducing regression of CT scan abnormalities, determining a steroid sparing effect and improving lung function tests after 3 months of therapy. A fast and stable reduction of peripheral eosinophilia associated with an increase in ACT score were also documented after the first dose of benralizumab.

1. Introduction
Eosinophilic granulomatosis with polyangiitis - EGPA, formerly known as the Churg–Strauss syndrome, is a primary small vessel vasculitis characterized by asthma, sinusitis, pulmonary infiltrates, neuropathy, and multiorgan eosinophilic vasculitis [1].

Eosinophils seem to play a pathogenic role in EGPA, inducing vascular infiltration, eosinophilic granulomatosis with polyangiitis and tissue inflammation by releasing several mediators [2].

Glucocorticoids are considered the cornerstone of treatment for EGPA’s patients and most of them remain steroid - dependent despite the use of cyclophosphamide or other immunosuppressant treatment as INF- alpha, infliximab, rituximab which can be used in steroid resistant cases. Relapses are common and a variable percentage of patients does not achieve satisfactory control of the disease [3].

Mepolizumab, a fully humanized anti IL-5 monoclonal antibody that binds to free IL-5 with specificity and affinity, has been tested as an effective steroid sparing agent able to reduce in patients with refractory EGPA the frequency of exacerbation at different dose administration [4].

Some evidence supported also the use of Benralizumab, a fully humanized afucosylated anti IL – 5 receptor antibody, in treatment of eosinophilic condition other than asthma [5]. Is been recently showed a decrease in MPO – ANCA after administration of benralizumab in a patient with EGPA associated with an improvement of respiratory symptoms of bronchial asthma [6].

We report here the successful use of Benralizumab in reducing respiratory symptoms in a severe asthmatic patient with EGPA according to ACR classification criteria.

2. Case report
A 63 years old woman presented with a 5 year history of refractory respiratory symptoms as weezing, exertional dyspnea, cough and phlegm with marked hyper-eosinophilia, recurrent pneumonia and chronic sinusitis. She had been initially characterized as a step 4 GINA asthmatic patients and was treated with inhaled corticosteroid (budesonide) and beta agonist (formoterol) at maximum dose associated with antibiotics (amoxicilline/clavulanic acid, ciprfloxacine, claritromicine) during exacerbation of respiratory symptoms.

The serum IgE level was increased (185 IU/mL – N < 85 IU/mL) associated with negative results for perennial or seasonal inhalant allergens. For the persistent hyper-eosinophilia (2,74 cell/μL, 31,5%) she received multiple hematological evaluation to exclude a primitive bone marrow disease or any clonality. She had no travel history or known helminthic infestation but she was equally tested with negative results.

In the last year she developed a progressive peripheral neuropathy involving left peroneal nerves, recurrent fever associated with frequent exacerbation of respiratory symptoms which required a persistent use of...
oral corticosteroid in a variable dose (5–25 mg/day).

The first determination of c and p ANCA was negative but was repeated in presence of peripheral neuropathy with a positivity of c ANCA at dilution of 1:40 and a negative ENA screen. Proteinuria was also documented (418 mg/24h).

On physical examination, chest auscultation revealed slight diffuse expiratory wheezing and a vesicular murmur reduction with frequent occurrence of bronchi.

The Computed Tomography (CT) showed diffuse bronchial wall thickening, pulmonary infiltration and paranasal sinusitis (Fig. 1).

Her peripheral arterial blood oxygen saturation was 95% and gas analysis showed pCO2 44 mmHg, pO2 74 mmHg, pH 7.45. At the nocturnal oxymetry was found a mild desaturation with time < 90% of 9.2% and minimal SpO2 87%.

Pulmonary Function Tests - PFTs documented a reduction of expiratory flow in MEF 25–75% (Table 1). ACT score was 9. The inhalation technique was checked without presenting critical error.

Electrocardiogram and echocardiography were normal. Nasal scraping confirm an eosinophilic infiltration.

According to the ACR criteria, on the basis of the presence of asthma, eosinophilia >10%, peripheral neuropathy, paranasal sinus abnormalities and pulmonary infiltrates, was diagnosed EGPA supported also by the presence of positive ANCA test. The patient started treatment with Prednisone at the dose of 25 mg/day with a good control of peripheral symptoms, reduction in proteinuria and persistent aperic state, but without achieving a satisfactory control of respiratory symptom and only a partial reduction in peripheral eosinophilia (1,54 cell/μL, 15.7%) under steroid treatment. Moreover, the patient showed a progressive worsening of respiratory symptoms characterized by cough,

Table 1
Time course of the benralizumab treatment. Symptoms reduction, fewer peripheral eosinophils and improvement in lung function were observed after 3 month of treatment with benralizumab. FEV1 – Forced expiratory capacity in 1 second; FVC – Forced vital capacity; MEF 25/50/75 - Maximum expiratory flow at 25/50/75%; TLC – Total lung capacity; RV – Residual volume; ACT – Asthma control test.

|                     | Before benralizumab | After benralizumab for 3 months |
|---------------------|---------------------|-------------------------------|
| FEV1 (L)            | 2.23                | 2.55                          |
| %                   | 95%                 | 109%                          |
| FVC (L)             | 2.78                | 2.98                          |
| %                   | 103%                | 107%                          |
| MEF 25 (L)          | 0.67                | 1.24                          |
| %                   | 52%                 | 98%                           |
| MEF 50 (L)          | 2.37                | 3.11                          |
| %                   | 65%                 | 86%                           |
| MEF 75 (L)          | 5.26                | 5.33                          |
| %                   | 99%                 | 100%                          |
| TLC (L)             | 5.54                | 5.54                          |
| %                   | 109%                | 109%                          |
| RV (L)              | 2.68                | 2.56                          |
| %                   | 134%                | 129%                          |
| Peripheral Eosinophils (count/μL) | 2.74 | 0.04 |
| %                   | 31.5                | 0.5                           |
| ACT score           | 9                   | 20                            |
| Prednisone dose     | 25 mg/day           | 5 mg/day                       |

Fig. 1. A) Computed Tomography shows bilateral sinusitis (A–B) and diffuse bronchial wall thickening associated with pulmonary infiltration (C). The CT scan after 3 months of treatment with benralizumab showed a quite completely regression of bronchial wall thickening and pulmonary infiltration (D).

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wheezing and exertional dyspnea.

According with the condition of hyper-eosinophilia (Table 1), because respiratory symptoms were not controlled, in December 2018, considering the Orphan Drug Designation (ODD) for the treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) granted by US regulators, we started therapy with Benralizumab 30 mg in monthly subcutaneous injection after acquiring informed consent by the patient. Respiratory symptoms significantly improved after the first infusion with an increase in ACT score from 9 to 19 in one month. After 3 months of treatment we observed an improvement in respiratory function test, a persistent improvement in ACT score at 20 and a reduction of flogistic area in CT scan (Fig. 1). Eosinophil count was progressively reduced (Table 1) and oral steroid was progressively reduced at the dose of 5 mg/day which is still now the therapeutic dosage of the patient after 1 year without exacerbation.

3. Discussion & conclusion

Benralizumab is a fully humanized afucosylated anti IL-5 receptor antibody which binds with high affinity the α-chain of human IL-5R, blocking its activation and signal transduction. Moreover, afucosylation enhances antibody-dependent cell mediated cytotoxicity (ADCC) function, increasing the ability of benralizumab to reduce the number of circulating eosinophils, as well as those resident in different tissues, implicated in the inflammatory response [7]. This unique mechanism of action may represent a therapeutic opportunity for the patients with EGPA. Is been demonstrated the decrease in MPO-ANCA after administration of benralizumab in patients affected by EGPA with an improvement of symptoms of bronchial asthma [5].

The clinical data presented in this case, showed that benralizumab has been able to induce in a patient affected by EGPA according to the ACR criteria, a rapid and stable depletion of blood eosinophil associated with a consistent reduction of respiratory symptoms and a progressive improvement in pulmonary function test and CT abnormalities. Moreover after 3 month of treatment we have documented a steroid sparing effect because the patients reduce prednisone from 25 mg each day to 5 mg each day with a complete control of systemic symptoms and fever, without receiving any immunosuppressant agent.

Benralizumab has a different mechanism of action compared to other anti-IL-5 mAbs, because of its ability to reduce eosinophils count by enhancing ADCC, determining a potential advantage of this biologic drugs in the treatment of EGPA.

At the moment is ongoing the clinical trial NCT03010436 which is exploring the Efficacy and Safety of Benralizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis (EGPA).

We reported here an effective clinical response on respiratory symptoms in a patient with EGPA and we observed a rapid and maintained effect, starting from the first dose associated with a depletion of peripheral eosinophils, but further study and more data are needed.

Declaration of competing interest

“I declare on behalf of my co-authors and myself that we do not have any conflict of interest to declare”.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101050.

Statement confirming consent

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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