

The Use of Benralizumab in the Treatment of Near Fatal Asthma: A New

Approach

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To the editor,

Systemic corticosteroids (SCS) have an important role in the management of acute asthma, but their use can be associated with side effects. Central serous retinopathy (CSR) is a rare ophthalmic complication associated with partial or complete visual loss that precludes further SCS(1). Here we report for the first time, the use of benralizumab, a monoclonal antibody against interleukin-5 receptor alpha subunit (anti-IL5ra), as treatment for an acute asthma attack, when SCS is contraindicated.

Background: Mr C is a 52-year-old never smoker, diagnosed with asthma at age 36. Of note, the past medical history included CSR, with complete visual loss, following a trial of oral dexamethasone (dose equivalent to prednisolone 30mg/per day for 12 days) for nasal polyposis in 2016. Near complete recovery of visual acuity took 4-months and he was advised to never use SCS again for fear of risk of recurrent CSR(2) and potential irrecoverable visual loss(3). His asthma had been well controlled with budesonide/formoterol 200/6 µg 2 puffs twice a day, with a best peak expiratory flow rate (PEFR) of 450L/min, at 87% of predicted PEFR (520L/min).

On the 24th of November 2019, Mr C developed a virus induced asthma attack, presenting to his local emergency department, with features consistent of a near fatal asthma attack including: a PEFR of 80L/min (<20% predicted), tachycardia (HR 115 beats per minute) and hypercapnia (pCO₂ 6.7kPa/50.4mmHg). Bloods showed a normal C reactive protein, with a peripheral blood eosinophil count (PBEC) of 530 cells/uL. Initial treatment included hourly short acting beta-2 agonists, short acting muscarinic receptor antagonists and supplemental oxygen therapy. Immediate advice was sought regarding the use of SCS and following discussion with the ophthalmologist and consultation with the patient, SCS was not given. Following this instruction, intravenous (IV) magnesium (Mg²⁺), IV aminophylline and oral montelukast and carbocysteine were also started. Despite these treatments, minimal symptomatic improvement occurred and he was transferred to the tertiary respiratory centre on the 8th day of his hospital admission. On the 14th day, IV aminophylline was reduced, due to an

apparent improvement of PEFr to 270L/min (60% best PEFr), but restarted once again when the PEFr deteriorated. Throughout the admission, he continued to have an elevated PBEC, with a peak at 840 cells/uL on the 16th day when his sputum eosinophil count was 44% and exhaled nitric oxide was 28ppb. We postulated that the persistent eosinophilic inflammation was the likely driver for his incomplete recovery and proposed an alternative method of eosinophil suppression. On the 17th day of admission, Mr C was offered benralizumab, an anti-IL5ra monoclonal antibody, licensed for the use of preventing asthma attacks in stable disease(4). This was authorised and approved by the local Hospital Medicines Board following an individual patient request.

Progress: Serial physiological, symptomatic and inflammatory data monitoring was performed. At 1, 2, 4 and 6 hours after 30mg of subcutaneous benralizumab, the PBEC was 630, 180, 20 and 40 cells/ μ L respectively (see top panel, figure 1). Within 6 hours of treatment, he achieved a clinically significant improvement of his visual analogue scale scores for breathlessness, wheeze and cough (see figure 2). Within 19 hours of benralizumab administration, there was marked improvement of post-bronchodilator lung function (see bottom panel, figure 1) with a PEFr increase from 270L/min to 370 L/min (37% improvement) and a FEV₁ from 1.34L to 2.26L (69% improvement). Within 24hours of benralizumab administration, supplemental oxygen was ceased and he was discharged from hospital on the 19th day of hospital admission, 43 hours following benralizumab administration, with a PEFr of 380L/min (84% best predicted), PBEC of 10cells/uL and sputum eosinophil count of 0%.

Following discharge, on the 6th day following benralizumab administration, Mr C continued to improve in all his indices of physiology and symptoms. His FEV₁ reached 2.91L (92% predicted), with a PEFr of 520L/min, better than his best in the preceding 5 years. He also noticed significant improvement in his sense of smell and taste. He continued to improve reaching an FEV₁ of 3.31L (104% predicted), at 2 weeks following the benralizumab administration. Mr C volunteered the following perspective to the clinical research team: *“My asthma has always been well controlled with my inhalers. I took tablet steroids once to help with nasal polyps, which led to almost complete loss of vision. I was told to avoid*

steroids at all costs to prevent permanent eye damage. After a virus brought on my first ever asthma attack, I was petrified about possibly needing steroid tablets again. I felt stuck and I was not improving after 2 weeks in hospital. I felt better within 12 hours of the injection and was walking around the hospital within 24 hours. When I got home, I was surprised to be able to smell coffee again. In the month since coming out of hospital, my breathing is the best it has ever been. I am very reassured that medicines have improved such that I may now have another option if this happens again.”

Discussion: To the best of our knowledge this is the first report of the use of benralizumab as an alternative to SCS at the time of an acute asthma attack. Novak et al (5) have previously shown that benralizumab is a potential adjunct to SCS in the acute setting. CSR is a rare complication and in this clinical situation, both specialist ophthalmology opinion and patient choice precluded the use of SCS as part of routine clinical care. We found that benralizumab, suppressed PBEC by 90% within 4hours, an effect comparable to SCS (6). The prompt clinical improvement supports our hypothesis that T-helper 2 eosinophil-mediated inflammation was the primary driver of symptoms and raises the possibility that rapid onset biological treatment targeting this pathway may be a future non-corticosteroid treatment of eosinophilic acute attacks (NCT04098718).

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Figure 1. Serial measurements of peripheral blood eosinophil count (Fig 1A) and peak expiratory flow rate (Fig 1B, pre-bronchodilator (red) and post (blue) bronchodilator). Vertical dashed line indicated time of benralizumab administration. Vertical solid line indicates time of hospital discharge.

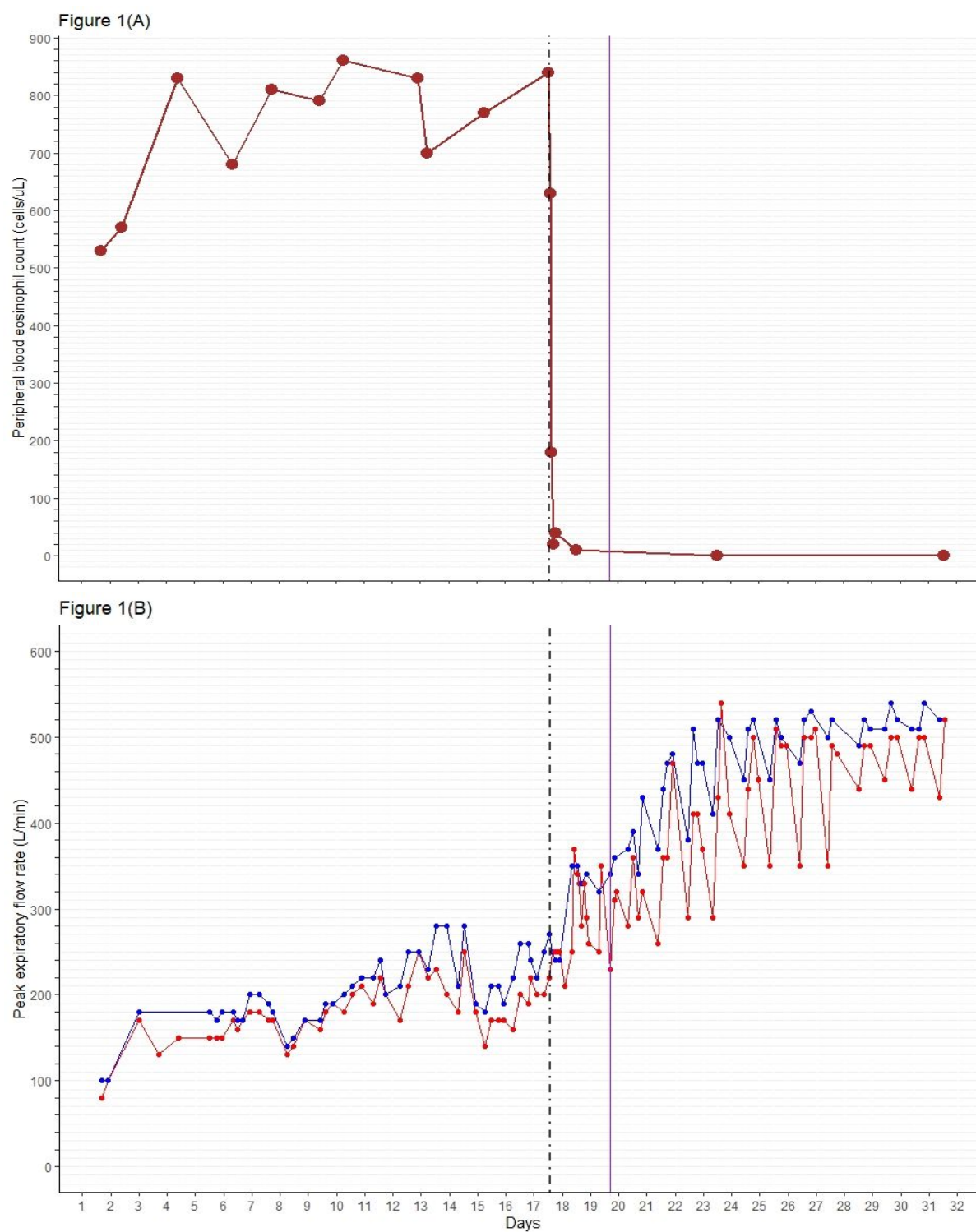


Figure 2. Percentage improvement of visual analogue scale for symptoms of cough, dyspnoea and wheeze following benralizumab administration. Vertical dashed line indicated time of benralizumab administration. Vertical solid line indicates time of hospital discharge.

