

Cytokine release hypersensitivity reaction after the first dose of benralizumab for severe eosinophilic asthma

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Benralizumab is a humanized IgG1 monoclonal antibody (mAb) that specifically binds to the alpha interleukin-5 (IL-5) receptor, blocking the signaling pathway that activates eosinophils. Furthermore, through its constant Fc region, it has the capability to bind to the FC γ RIII receptor of natural killer (NK) cells and other immune cells, leading to the apoptosis of eosinophils through degranulation of these immune cells¹. Here, we present a case of cytokine release hypersensitivity reaction (CRHR) induced by benralizumab therapy in a patient with severe eosinophilic asthma.

Our patient is a 71-year-old female with severe persistent uncontrolled eosinophilic asthma on inhaled high dose corticosteroids, long acting beta-agonist, long acting muscarinic-antagonist, and frequent courses of systemic corticosteroids every two months on average. She had no prior history of adverse drug reactions. Due to the lack of adequate asthma control, treatment with benralizumab was indicated. Two hours after receiving her first subcutaneous dose (30 mg), she developed diffuse, generalized myalgia, chills, nausea, tachycardia and dyspnea, no rashes were noted. The patient was admitted to the emergency department for observation, Vital signs included a heart rate of 110 beats per minute, blood pressure of 164/96 mmHg, oral temperature of 37.4°C, respiratory rate of 18 breaths per minute, and an oxygen saturation of 94%. At the time, laboratory analysis showed an elevated IL-6 (11.5 pg/ml; reference <1.8 pg/ml) and the diagnosis of CRHR was done. She received fluids and systemic intravenous corticosteroids, and her symptoms subsided five hours after admission. No evidence of organ dysfunction resulted from this reaction. Baseline IL-6 measurement three months after the event was <2.0 pg/ml. She declined a drug challenge with benralizumab and an alternative treatment plan was proposed. Even though we had a low suspicion for an IgE-mediated reaction, we performed skin testing, which was negative for omalizumab, benralizumab, mepolizumab, and dupilumab; intradermal

concentrations included 1:100,000 to 1:10 (mild irritant reaction to dupilumab 1:10). The patient tolerated an open two-step drug challenge with dupilumab and is currently well controlled (200 mg subcutaneous every 14 days) without adverse reactions to the medication.

CRHRs are defined as systemic inflammatory responses that can be triggered by several different types of infections and drugs, especially cancer immunotherapeutics including checkpoint inhibitors^{2,3}. Their pathophysiological mechanisms are not completely understood, but the hypothesized mechanisms include massive release of certain cytokines (specifically IL-6, IL-10 and IFN- γ) by T cells. These cytokines cause a chain reaction of activation of the immune system causing clinical manifestations ranging from fever and other flu-like symptoms (myalgia, arthralgia, fatigue and malaise) to more severe manifestations including renal and/or liver failure, coagulopathy and respiratory failure, often requiring mechanical ventilation³.

Elevation of IL-6 levels is a hallmark of CRHR⁴, however, no clear cut-off value for the normal ranges exist. Jakubovic and colleagues explored IL-6 as a biomarker for breakout reactions during drug desensitization to biologic agents using a conservative (<17.5 pg/ml) and liberal (<1.8 pg/ml) threshold and found that IL-6 levels correlate with clinical features suggestive of CRHR⁵. Jakubovic et al has previously demonstrated that CRHRs are associated with changes in temperature, heart rate and oxygen saturation and the changes are correlated to the extent of the IL-6 elevation⁵. In this case report, the patient presented with tachycardia and a ten-fold elevation of IL-6 compared to baseline which is consistent with a diagnosis of CRHR.

Algorithms for the management of patients with suspected hypersensitivity reactions to mAbs have been described, using skin testing and further drug challenge can improve and guide management⁶. After a CRHR, the need to reintroduce the same culprit drug must be assessed against the potential benefits and side effects of desensitization, and against the use of an

alternative agent⁷. Our patient declined further doses of benralizumab due to the reaction after the first dose. Thus, an alternative agent was selected. In this case, the patient tolerated a drug challenge with dupilumab without further adverse reactions.

To our knowledge, this is the first reported case of a benralizumab-induced cytokine release hypersensitivity reaction in a patient with severe uncontrolled eosinophilic asthma. The diagnosis and further management of cytokine release hypersensitivity reactions needs to be individualized and IL-6 cut off levels should be established by drug hypersensitivity guidelines.

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