

Successful Desensitization of Three Patients with Hypersensitivity Reactions to Omalizumab

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Abstract: *Background:* Omalizumab is prescribed as a step-up therapy for patients with moderate to severe allergic asthma uncontrolled on high-dose inhaled corticosteroids and long acting beta agonists. However, hypersensitivity reactions may lead to its discontinuation and subsequent worsening or loss of asthma control. No successful desensitization protocols to omalizumab have been previously reported.

Objective: We aimed to determine the efficacy and safety of a novel one-day outpatient omalizumab desensitization protocol for patients with hypersensitivity reactions to omalizumab.

Methods: We retrospectively assessed the efficacy of omalizumab desensitization protocol performed in a university allergy-immunology clinic from July 2009 to July 2010.

Results: We successfully desensitized 3 patients with moderate-severe asthma to omalizumab. After desensitization all patients had improvement in asthma control and were able to discontinue or decrease chronic systemic steroid therapy.

Conclusions: This novel outpatient omalizumab desensitization protocol was a safe and effective approach for the treatment of omalizumab hypersensitivity in patients with moderate to severe allergic asthma who required omalizumab therapy.

Keywords: Asthma, omalizumab, hypersensitivity, desensitization.

INTRODUCTION

Omalizumab (Xolair™) is a recombinant IgG1 monoclonal antibody that binds free IgE resulting in 96% decrease in free IgE level and subsequent down regulation of Fc epsilon receptors on the surface of mast cells and basophils. Currently, it is indicated for treatment of moderate to severe allergic asthma that cannot be controlled with high dose inhaled corticosteroids and long-acting beta agonists. Omalizumab has been shown to decrease inhaled corticosteroid use, asthma exacerbations, and asthma emergency room visits [1-3]. Additionally, the successful use of omalizumab has been reported for treatment of a number of IgE mediated diseases such as allergic rhinitis, eczema and chronic urticaria [1, 4-8].

Omalizumab is contraindicated in patients who developed anaphylaxis to omalizumab. Approximately 0.1-0.2% of patients have experienced anaphylaxis which has occurred as early as after the first dose of omalizumab and as late as one year after beginning regularly administered treatment. The mechanism of hypersensitivity reactions to omalizumab remains unknown. Current theories include IgE binding to one of the excipients (e.g. polysorbate) or to glycosylation products of the Chinese Hamster ovary cell line from which part of the monoclonal antibody is produced [9]. The time range of onset of anaphylaxis has ranged from

minutes to days after injection [9]. The majority of reactions (68%) occurred during first three injections; however, some reactions have occurred as late as 39 doses into treatment [10]. Therefore, hypersensitivity reactions to omalizumab present a serious obstacle to medical treatment in a small but significant group of severe asthma patients. To our knowledge there have been no previously published successful desensitization protocols to omalizumab.

METHODS

We present a case series of three patients who were successfully desensitized to omalizumab. The electronic medical record was reviewed to determine if patients were allergic to omalizumab and if they had undergone an elective desensitization for a hypersensitivity reaction. This study was approved by the Institutional Review Board at our facility. Informed consent was obtained from all patients prior to undergoing desensitization. All patients were desensitized from July 2009 to July 2010 in the outpatient University Allergy-Immunology Clinic that specializes in the treatment of allergic drug reactions as well as asthma, including severe asthma in collaboration with the severe asthma program of the University Asthma Institute. The patients 2 and 3 were referred to our clinic specifically for desensitization while the patient 1 was co-managed with pulmonologists from the severe asthma program. The patient 1 is our only patient, out of approximately forty patients treated with omalizumab in our clinic, who had a reaction to omalizumab. Table 1 lists the desensitization protocols used. All patients were pre-medicated with fexofenadine 180 mg and ranitidine 150 mg one hour prior to desensitization.

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Three different dilutions of omalizumab in saline were used for desensitization. Each dose of omalizumab was given 30 minutes apart. Target doses were split in half with a plan for weekly or biweekly injections dependent on a total dose. For example, if a regular dosing schedule was every 4 weeks, the target dose for desensitization was one half of the regular dose administered every 2 weeks. Additionally, all patients had spirometry performed prior to desensitization and peak flow performed prior to each omalizumab dose. Outcomes were measured by the success rate of desensitization, subsequent tolerability of omalizumab treatment at 12 months after desensitization, and overall improvement of asthma control.

Table 1. Desensitization Protocols

Dose	Stock Solution (S.S.) Con.	Patient 1	Patient 2	Patient 3
	(mg/ml)	Dose (mg) (Every 30 Minutes)		
1	1.5mg/1.2ml	0.0625	0.0625	0.0625
2	1.5mg/1.2ml	0.625	0.625	0.625
3	15mg/1.2ml	1.25	1.25	1.25
4	15mg/1.2ml	2.5	2.5	2.5
5	15mg/1.2ml	5	5	5
6	15mg/1.2ml	10	10	10
7	150mg/1.2ml	20	20	20
8	150mg/1.2ml	37	40	37
9	150mg/1.2ml	37	55	37
10	150mg/1.2ml	n/a*	55**	37
Cumulative Dose (mg)		113.38	189.38	150.38

*- Patient 1 required 9 doses to be desensitized.

** - Patient 2 did not receive dose 10 (see Results section).

RESULTS

Patient 1 is a 32 yo female with severe persistent asthma since childhood. Her baseline spirometry demonstrated a moderate obstructive pattern with significant reversibility (FEV1 = 67% with 52% bronchodilator (BD) response). She has a history of multiple ICU admissions and exacerbations requiring oral steroids. An allergy evaluation revealed both seasonal and perennial allergen sensitivity and the baseline IgE level was 172 IU/ml. She was started on omalizumab with significant improvement in asthma control.

After one and a half years of therapy, she developed a systemic reaction to omalizumab. Three hours after omalizumab injection, she developed cough, shortness of breath, and tachycardia. There was no urticaria, angioedema, or gastrointestinal symptoms. She had a drop in FEV1 compared to previous testing (89% → 78%). She was given methylprednisolone, albuterol and diphenhydramine with improvement. Pulmonary function testing later that day revealed an improved FEV1. Her asthma exacerbation resolved after several days on systemic steroids.

Three months later the patient had skin prick testing performed with full strength omalizumab and Quintip testing

device which was negative. She was then administered 75mg omalizumab which she tolerated well. The following day she received 150mg (for the total dose of 225mg) and within minutes developed eye itching, shortness of breath and a drop in FEV1 (83%→58%). She was treated with epinephrine, diphenhydramine, and methylprednisolone with improvement. A day later she developed urticaria. Her symptoms resolved after one week with improvement in FEV1 (93%).

The patient stopped omalizumab therapy for one year and during that time her asthma became poorly controlled requiring treatment with monthly IM triamcinolone injections, daily oral prednisone and high dose inhaled steroid/LABA therapy.

The patient was then evaluated for desensitization to omalizumab. The protocol designed for desensitization is listed in Table 1. Her target dose (225mg every two weeks) was split in half with a plan for weekly injections. Approximately half way through her desensitization she developed shortness of breath, coughing, and nausea. Pulmonary function testing was unchanged. Flexible laryngoscopy was performed and revealed significant paradoxical vocal cord motion. The symptoms resolved with breathing exercises and the protocol was completed without further complications. She continues on weekly omalizumab without any signs of allergic reaction. She has been able to wean off systemic steroids and her asthma has become well controlled.

Patient 2 is a 21 yo female with severe cough and shortness of breath caused by overlap syndrome of eosinophilic bronchitis (diagnosed with lung biopsy) and asthma as well as vocal cord dysfunction (VCD). Her spirometry has been normal at baseline (FEV1 >100%) but during one exacerbation she had obstructive pattern (FEV1= 68% with 48% BD response and decreased FEV1/FVC ratio). The lung biopsy revealed bronchial mucosa with basement membrane thickening, submucosal scarring and rare eosinophils while on high-dose prednisone. Her baseline exhaled nitric oxide level was 40-60 ppb which would go up to 260 ppb during exacerbations. Her allergy skin testing was remarkable for both perennial and seasonal allergy sensitization. Her IgE level was 740 IU/ml.

Her symptoms were controlled only with high doses of daily prednisone (40-80mg). She has tried steroid sparing medications, such as interferon alpha and imatinib, which were not helpful. She was treated with azathioprine with some improvement but not complete resolution of her symptoms.

She was then started on omalizumab with significant improvement in her chronic cough, nasal congestion, and post-nasal drip. Three months into her treatment, 20 minutes after receiving her omalizumab dose, she developed nasal congestion and eye swelling. Despite treatment with diphenhydramine, her symptoms progressed and she had to go to the emergency department for facial and tongue swelling, throat tightness, and wheezing where she was treated with epinephrine and methylprednisolone and discharged home.

A few months later she was evaluated for omalizumab desensitization and a desensitization protocol was created.

Her dose of 375mg was split in half with a plan for weekly administration. After the 4th dose, she developed some pruritus without rash which resolved without treatment. After the 8th dose, her peak flow dropped from 400 and 280 and she stated she felt "wheezy." She was clear to auscultation. Spirometry was performed and there was no significant change in FEV1. She was then administered a 9th dose and developed mild eye pruritus and conjunctival injection requiring treatment with diphenhydramine. Her FeNO increased from 48ppb prior to desensitization to 69ppb post-desensitization. Dose 10 was not administered.

Two weeks later she received the target dose of 187.5mg of omalizumab. One hour after administration, she developed clear nasal discharge as well as chest, throat, and ocular pruritus. On exam, she had chest erythema but no obvious hives or any signs of respiratory distress. She was observed and her symptoms resolved spontaneously.

She continues to receive omalizumab weekly without any signs of an allergic reaction. Her cough and shortness improved and she was able to decrease prednisone to 10 mg daily.

Patient 3 is a 41 yo female with severe, persistent asthma. Her baseline spirometry revealed a moderate obstructive pattern with significant reversibility (FEV 1= 75% with 16 % BD response). Allergy testing revealed sensitivity to cat, dog and alternaria. Her IgE level was 78 IU/ml. She was treated with high dose inhaled corticosteroids combined with long acting beta-agonists and required daily prednisone use to control her asthma. She was started on omalizumab and was able to discontinue daily oral corticosteroids. However, she developed urticaria after 3 months of omalizumab therapy. Urticaria would occur immediately after each injection and would last for 2-3 days. The reactions persisted after several omalizumab injections and omalizumab was discontinued.

She was evaluated in our office and desensitized to omalizumab using a 10 step protocol (Table 1). Her dose of 300mg monthly was split in half with a plan for biweekly administration of 150mg. She developed some mild chest tightness mid-way through the protocol which resolved with albuterol. She completed the remainder of the protocol without complications. She again developed some mild increased shortness of breath after her second injection of omalizumab post-desensitization which lasted for 2 days and was treated with albuterol only. She has been continued on biweekly treatments without any further reactions. Her asthma has improved and she has been weaned off prednisone.

DISCUSSION

Desensitization is a procedure in which patients receive incremental doses of a drug to which they have previously experienced a hypersensitivity reaction until the therapeutic target dosage is achieved.

Desensitization results in temporary tolerance of mast cells and basophils to the specific drug in question. The mechanism by which this desensitized state is induced is not fully understood. *In vitro* studies have demonstrated that sub-threshold doses of antigen given prior to activating doses

can render mast cells and basophils unresponsive to activation by that specific antigen, but still reactive to other activating stimuli [11,12]. Sub-threshold doses of antigen might result in monomeric binding to the IgE receptor leading to internalization of the antigen-receptor complex without cross-linking such that the cell does not become activated [13]. IgG specific to the antigen increases after desensitization therapy [14]. The rising IgG titer may neutralize drug epitopes and serve a blocking function for an IgE-dependent reaction. At a molecular level, the transcription factor STAT 6 was shown to be necessary for desensitization in a mouse model of rapid antigen desensitization [15].

Successful desensitization protocols to other monoclonal antibodies have been published but to our knowledge not to omalizumab [16]. Desensitization to omalizumab has been reported once in the literature by Dreyfus and Randolph [17] who performed omalizumab desensitization in a 32 yo female with chronic idiopathic urticaria and asthma. They postulated her reaction was anaphylactoid given normal tryptase levels. Their patient experienced continued pruritus and erythema after desensitization which resolved with pretreatment with ibuprofen. Unfortunately, she developed a serum sickness-like reaction after the seventh dose post-desensitization and therapy was discontinued.

We provide our experience with the successful desensitization of three patients with severe, steroid dependent asthma with hypersensitivity reactions to omalizumab. All three of our patients had mild to moderate reactions during desensitization but were able to complete desensitization procedure and continue omalizumab therapy without adverse reactions for 12 months after desensitization. After successful desensitization all patients experienced significant improvement in their asthma control and were able to discontinue or taper oral steroids. We elected to split the target desensitization dose in half and administer omalizumab more frequently in order to prevent the loss of desensitized state. To our knowledge, these are the only successful cases of omalizumab desensitization reported to date.

One potential limitation of our study is that 2 out of 3 patients did not receive skin testing to omalizumab prior to desensitization. We elected to proceed with desensitization if the history was strongly suggestive of immediate hypersensitivity reaction. The skin testing had not been performed due to the lack of standardization and it would not have changed our clinical approach to desensitization, as demonstrated in the patient 1 who developed a hypersensitivity reaction despite the negative skin prick test to omalizumab. However, we believe that it would be beneficial to standardize skin testing procedures in the future by testing multiple patients, both with prick and intradermal testing methods, in order to determine the sensitivity and specificity as well as positive and negative predictive values of the skin testing. Another limitation is that no patients had tryptase checked after their reactions, which if elevated, may have provided additional evidence of mast cell degranulation. An additional limitation is that we did not perform skin testing to polysorbate, an excipient in omalizumab, which has been shown to cause hypersensitivity reactions [18].

Two of our patients had underlying VCD which may have contributed to both their initial reaction and their reaction to desensitization. The patient 1 developed shortness of breath and cough after omalizumab administration and it is possible that some of her symptoms may have been related to VCD. Objective criteria that indicate she had a hypersensitivity reaction included two documented drops in FEV1 that improved with albuterol and the development of urticaria. During desensitization she developed shortness of breath with no change in the spirometry and a documented VCD flare by laryngoscopy indicating VCD as the etiology of her shortness of breath during desensitization. Patient 2 also has VCD and had a likely VCD attack during desensitization indicated by her shortness of breath but lack of wheezing, normal spirometry, and resolution without treatment. That said, a VCD flare would not explain the angioedema and wheezing she developed after omalizumab administration prior to desensitization. Patient 3 had signs and symptoms consistent with an allergic reaction. Another limitation of our study is the small sample size.

In conclusion, desensitization represents an important therapeutic option for treatment of patients with hypersensitivity reactions to omalizumab. This can lead to significant improvement in asthma control and quality of life as well as decreased need for treatment with systemic steroids.

ACKNOWLEDGEMENT

None declared.

CONFLICT OF INTEREST

Dr. Petrov has research grant support from Genentech.

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