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Case Report

Allergy to Montelukast Sodium Treated Effectively by Protracted Oral Desensitization: First case report

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Antileukotrienes such as Montelukast Sodium play a significant role in asthma control. IgE mediated hypersensitivity reactions to Montelukast is very rarely reported. To explore the efficacy of oral desensitization in Montelukast hypersensitivity. A 30 year old Saudi woman with uncontrolled asthma despite maximum pharmacological therapy presented to allergy clinic with recurrent symptoms of lip swelling, maculopapular skin rash and shortness of breath a few minutes after taking Montelukast 10 mg orally. Eventually, she was diagnosed as a case of hypersensitivity reaction type I to Montelukast. As a consequence of her uncontrolled asthma symptoms and as no other alternative Antileukotrine was available, it was decided to start an oral desensitization with Montelukast. Phase I desensitization was conducted in the clinic by gradually increasing doses of oral Montelukast starting from 0.001 mg up to 1 mg. Phase II desensitization was conducted at home with increasing doses starting from 1mg up to 10 mg/day. Patient was followed by frequent clinic visits, emails and phone calls. Desensitization phases I was successful over a period of 3 hours with minimal reactions. Desensitization phase II was prolonged due to the occurrence of several allergy symptoms of shortness of breath, dizziness and itching, which were controlled partially with oral antihistamines, prednisolone and maintaining the same dose until clear. Finally, after 12 weeks, the patient was able to tolerate pharmaceutical doses of Montelukast at 10 mg safely and managed to gain a better asthma control. To our knowledge, this is the first case report of effective oral Montelukast desensitization in an asthmatic patient with hypersensitivity type 1 to Montelukast. Although such allergic reaction to antileukotrienes is rare, it should be recognized by healthcare providers. If no alternative therapy is available to control asthma symptoms, oral desensitization could stand as a valid effective therapeutic option.

Keywords: Montelukast sodium, Oral Desensitization, asthma

INTRODUCTION

Montelukast Sodium is a selective leukotriene receptor antagonist (LTRAs) that inhibits the leukotriene receptor. It is widely prescribed as an orally active asthma treating agent. Usually, it is well tolerated by almost all asthmatics with rare adverse reactions (Bateman et al., 2011).

One of these adverse reactions is hypersensitivity which is reported in few cases (Bateman et al., 2011).

The mechanism of hypersensitivity to Montelukast is mainly a type I hypersensitivity (IgE antibody mediated) (Minciullo et al., 2004). Literature review revealed at least three main patterns of type I hypersensitivity to Montelukast: 1) generalized urticarial rash (Minciullo et al., 2004). 2) angioedema (Sabbagh and Sheikh-Taha, 2009). 3) anaphylaxis (Gernard, 2009). Churg-strauss

Vasculitis also has been documented as a complication to Montelukast (Kaliterna et al., 2009).

The confirmation of clinically suspected type I hypersensitivity to a drug is mainly based on detailed clinical history by the constellation of exposure, timing, and clinical features (Marc et al., 2003). *In vivo* (skin tests) and/or *in vitro* IgE tests (specific serum IgE antibodies) to drugs can also be used (Mirakian et al., 2008). Unfortunately, there is no standard skin test to Montelukast as the literatures elucidate.

In most cases with drug allergy, the management is usually based on medications such as antihistamines and corticosteroids; avoidance of the component which caused the reaction, and switching to other alternatives (Cernadas et al., 2010). However, when there are no other alternatives available in the market and therapy is mandatory with this drug, the use of an oral desensitization procedure with gradually increasing doses would be a good plan (Cernadas et al., 2010). Subsequently, the re-use of therapeutic doses can be achieved safely (Mirakian et al., 2008).⁷ Desensitization procedure needs a close up monitoring of the patient for any side effect or allergic reaction which may need immediate action (Mirakian et al., 2008).

The aim of this case report is to sort out this patient problem with Montelukast type I hypersensitivity, to evaluate the response to the desensitization procedure to Montelukast and to document this for the first time in the literature.

MATERIAL AND METHOD

Case History

This is a 30-years-old Saudi woman diagnosed with asthma, controlled on Budesonide/Formoterol turbobaler, one puff BID plus Montelukast 10 mg once daily. Her asthma started since childhood and her chest symptoms started to become more recurrent when she was 6 years old. Her chest symptoms include a shortness of breath, cough, wheeze and yellowish sputum. These symptoms become worse in early morning, after flu and during winter. Her chest symptoms continue throughout the year.

Systemic review showed no (haemoptysis, fever, rigors, heartburn, orthopnea, hyperventilation nor paroxysmal nocturnal dyspnea). No history of smoking nor hypertension. On examination, vital signs were normal. No use of accessory respiratory muscles. Also, there was no (eye pallor, cyanosis, clubbing, decreased air entry, basal crepitations nor lower limb swelling). Chest x-ray was negative.

She is also a known case of chronic rhinitis which had started since puberty, controlled on Mometasone Furoate nasal spray, once daily. Her rhinitis was complicated into rhinitis medicamentosa due to the frequent use of

Xylometazoline nasal drops. She is also a case of mild atopic dermatitis, subclinical hypothyroidism and vitamin D deficiency.

Unfortunately, five month after using Montelukast, she developed a recurrent itching and skin rash which disappeared after stopping Montelukast. Reexposure to Montelukast within two months caused an immediate lip swelling, skin rash and shortness of breath. Montelukast was stopped and Chlorpheniramine Maleate, 4 mg tablet was prescribed to control her allergic symptoms.

Subsequently, her asthma symptoms control deteriorated after stopping the Montelukast. An alternative manufacturer for Montelukast such as (Romilast®). Zafirlukast is a good option to try but unfortunately it's not available in the market of Saudi. Then, she was referred from her family physician to the allergy clinic for a proper asthma control.

At the private allergy clinic at King Abdulaziz University Hospital (KAUH) in Jeddah, her clinical data was reevaluated and detailed history was taken. Asthma in this patient was classified by severity as sever persistent according to the British Thoracic Society guideline (BTS) (British Guideline on the Management of Asthma, 2012). Also it was classified by control as uncontrolled according to the Global Initiative for Asthma guideline (GINA) (Bateman et al., 2011). Skin prick test to common food and inhalant allergens was negative.

Anti-asthma medications were used in a stepwise approach at (step 4) as the maximal dose according to (GINA) guideline (Bateman et al., 2011). Budesonide/Formoterol turbobaler were prescribed as two puffs BID plus if needed. Theophylline half tablet nocte, Prednisolone 5 mg tablets course, and Mometasone Furoate nasal spray once daily. Other drugs added were: thyroxin tablet 25 mcg OD and one alpha tablet 0.25 mg OD.

Next visit within two weeks showed that her total serum IgE was high at 505 IU/ml, negative IgE antibody screen to common inhalant allergens (Phadiatop®), normal total Eosinophil count at 0.12 K/ul, negative RAST to common twenty food and twenty inhalant allergens.

However inspite of high IgE level, the diagnosis of allergic asthma isn't clear in this patient and it was classified as non-allergic type. That's why anti IgE Omalizumab was not an option plus it's commercial impact and the frequent subcutaneous injections which was not accepted by the patient.

She was diagnosed with uncontrolled, non allergic asthma and rhinitis with type I hypersensitivity to Montelukast. Type I IgE hypersensitivity to Montelukast was verified by the clear correlation of typical symptoms immediately after exposure. Since there is no single standardized diagnostic test to confirm Montelukast hypersensitivity, it is mainly diagnosed by the constellation of exposure, timing, and clinical features including the pattern of organ manifestations.

This patient was already on maximum anti-asthma

Table 1. Desensitization Phase I

Min.	Dilution	Conc. mg/ml	Dose mg	Volume (ml)	Symptoms
0	3	0.004	0.01	2.5	No symptoms
15	3	0.004	0.02	5	No symptoms
30	2	0.4	0.04	0.1	Shortness of breath and dizziness. Period prolonged to 30 minute to take the next dose plus given antihistamine
60	2	0.4	0.08	0.2	Mild dizziness
15	2	0.4	0.16	0.4	No symptoms
30	2	0.4	0.32	0.8	No symptoms
45	1	4	0.64	0.16	No symptoms
60	1	4	0.8	0.2	No symptoms
14	1	4	1	0.25	No symptoms

medications except antileukotrienes. Because no other alternatives were available to Montelukast and there was an obligatory need for the use of Montelukast for enhanced asthma control, desensitization to Montelukast was determined as an acceptable and safe tool of drug allergy treatment (Mirakian et al., 2008; Cernadas et al., 2010).

Intervention

Since oral desensitization to Montelukast in this case will be carried out for the first time, the chosen desensitization protocol will depend on simulation to other protocols of oral desensitization to other drugs which was conducted successfully. Several protocols of oral desensitization to drugs were collected and evaluated. Examples of desensitization protocols, like the ultra-rush protocol, continuous subcutaneous insulin infusion (CSII) (Hasselmann et al., 2012; Pföhler et al., 2008). The protocol of oral desensitization through gradually increasing doses of Montelukast was opted for because it is safer to the patient.

The desensitization procedure and its potential risks were discussed with the patient and her family, and then an informed verbal consent was obtained from the patient. Oral suspension was prepared at the allergy private clinic at KAUH. Montelukast sachet 4 mg was dissolved in distilled water at a concentration of 4 mg per ml. Oral desensitization to Montelukast was planned over two phases (Tayeb et al., 2008).

Phase I desensitization took place at the allergy clinic at KAUH over 3 hours. Desensitization was initiated at 7:00 pm on Tuesday, 7th of February 2012 by using a very low oral dose of Montelukast as 0.01 mg, at a concentration of 0.004 mg per ml diluted 3 times. The doses were increased gradually every 15 minutes and reached a dose of 1 mg (Table 1). Throughout Phase I desensitization procedure, her vital signs were measured every 15 minutes and were within normal range.

The subsequent doses were taken at home in Phase II desensitization starting from 1 mg to a target dosage of 10 mg of oral Montelukast/day. She was instructed to continue on the same dose for 3 days if any mild reactions developed, and to take oral antihistamine Chlorpheniramine Maleate 4 mg as needed. However, she was advised to prolong the period with the previous tolerated dose during the appearance of allergic symptoms as shown in (Table 2). She was also prescribed a self injectable epinephrine as an emergency treatment in case of any systemic reaction or anaphylaxis that might occur, and to seek emergency care immediately (Topal et al., 2012). A close follow up by clinic visits, e-mails and phone calls was reserved for serious issues (Bawakid et al., 2011).

Allergic reactions that appeared first in phase I included shortness of breath and dizziness after taking the Montelukast suspension dose of 0.04 mg which was recovered after single dose of oral antihistamine Chlorpheniramine Maleate 4 mg. Another allergic reaction of mild dizziness developed at dose 0.08 mg, and recovered after a single dose of oral antihistamine also.

Such allergic reactions re-occurred at phase II at home at doses of 1 mg, 4 mg, 7 mg and the last one at 8.5 mg. Allergic reactions took a protracted course (up to 82 days) to disappear. Medications advised were: Prednisolone 5 mg tablets as needed, Theoped tablets nocte, Chlorpheniramine Maleate 4 mg tablet as needed, Budesonide/Formoterol turbobhaler one puff as needed and Mometasone Furoate nasal spray once daily.

The total duration of Phase II desensitization process at home was 82 days as shown in (Table 2). When the Montelukast doses reached 10 mg/day with no serious side effect, the dose was repeated for three days then the patient was advised to take the Montelukast tablets in the form of 10 mg. She was seen in a follow-up visit after the end of Phase II desensitization. Asthma symptoms were much better and the desensitization process was maintained at this dose.

Further follow up visits were arranged for any late

Table 2. Desensitization Phase II

Day	Dose mg	Symptoms
1 - 17	1	Dyspnea, swelling of eye lids, itching, hoarseness and tiredness relieved by Symbicort and antihistamine
18 - 20	1.5	No symptoms
21 - 23	2	No symptoms
24 - 26	2.5	No symptoms
27 - 29	3	No symptoms
30 - 32	3.5	No symptoms
33 - 46	4	Congested throat, yellow sputum, shortness of breath, fever relieved with Prednisolone, Mucolytic, Theophylline
47 - 49	4.5	No symptoms
50 - 52	5	No symptoms
53 - 55	5.5	No symptoms
56 - 58	6	No symptoms
59 - 61	6.5	No symptoms
62 - 64	7	Mild shortness of breath relieved by Symbicort
65 - 67	7.5	No symptoms
68 - 70	8	No symptoms
71 - 73	8.5	Mild itch relieved by antihistamine
74 - 76	9	No symptoms
77 - 79	9.5	No symptoms
80 - 82	10	No symptoms

reactions, and the final dose of Montelukast after successful desensitization was adjusted. The patient was told to comply strictly with the daily Montelukast, as any missed dose may lead to loss of tolerance and the need to repeat the desensitization process from the start.

There was a close monitoring throughout the desensitization procedure by patient visits to the clinic, phone calls and emails for reporting any side effects, answering any questions, giving advices and appropriate responses. Patient visit to the clinic was after one, three and six month. This contact was a very helpful way with many rewards to the patient and the team. Moreover, this helped create a closer relationship between the treating physician and the patient, improve the patient compliance, answer the patient concerns quickly, reassure the patient if any adverse reaction appears and involves the patient in supervising her own health care (Topal et al., 2012).

RESULT

Desensitization phases I was successful over a period of 3 hours with minimal reactions while phase II was prolonged due to the occurrence of several allergy symptoms. After 12 weeks, the patient was able to tolerate pharmaceutical doses of Montelukast at 10 mg safely and asthma symptoms were controlled.

Our case had a successful first attempt of oral Montelukast desensitization. Apart from very mild symptoms that were resolved with oral medications, the desensitization protocol was completed successfully.

DISCUSSION

Although the prevalence of type I hypersensitivity to oral Montelukast has been rarely reported, it can still happen as in this case report. Therefore, health care providers must keep in mind the possibility of Montelukast allergy when initiating such therapy. Physicians who prescribe Montelukast must be aware of anaphylaxis as the most serious complication even if its prevalence is rare (Gernard, 2009).

There are few readily available alternatives for asthmatics who are intolerant to Montelukast in the international markets. They include agents such as Montelukast Sodium (Romilast®), an alternative manufacturing company for Montelukast.

Desensitization to Montelukast poses potential risks, and is not recommended as a first-choice treatment for all patients with allergic reactions to the drug. The procedure is beneficial in selected patients who had allergic reactions to this medication, when other alternative are not available, or in patients who cannot be treated with other antileukotrine drugs (Cernadas et al., 2010).

Montelukast desensitization protocols are not available as this is the first case report, that's why a slow protracted oral desensitization protocol has been selected as a safe and effective regimen. That is why it remains difficult to reach the exact success and failure rates of this protocol. Continued monitoring of patients, both during and following desensitization, is important as hypersensitivity to the drug may recur (Mirakian et al., 2008).

Electronic communications have been proven to be effective in facilitating communication among care providers and patients, thereby allowing for greater continuity of care and more timely interventions. E-mail communications for close follow up can be a very helpful tool for a 24 hours monitoring of patients progress without the need to come to the clinic (Tayeb et al., 2008).

CONCLUSION

Type I hypersensitivity to Montelukast can occur but rarely; results from the present study confirm the efficacy and the safety of slow protracted oral desensitization to Montelukast.

It's crucial to do Montelukast desensitization after trying all the other tools because of anaphylaxis risk with desensitization procedure. It's vital to exclude all the diseases which could be similar to asthma. The desensitization procedure can be carried out in an outpatient setting under close medical supervision after careful counseling and detailed discussions with the patient prior to initiating therapy (Hugh, 2004). The new intervention in this case report is the use of a slow protracted protocol desensitization process. To our knowledge, this is the first case report in literature. Montelukast is well tolerated with a safety profile that is similar in adult and pediatric populations (Michael, 2009).

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