SKIN

BRIEF ARTICLE

Omalizumab-Induced Arthralgias in a Patient with Chronic Idiopathic Urticaria

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ABSTRACT

Background: Omalizumab (Xolair) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to the high-affinity IgE receptor on the surface of mast cells and basophils, limiting release of mediators of the allergic response. It is the first monoclonal antibody approved for the treatment of refractory chronic idiopathic urticaria in patients over the age of 12 and has been shown to result in clinically significant improvement of itching and wheal formation in these patients. Rarely, inflammatory arthralgias can be a severe side effect of omalizumab.
Clinical Case: We report a case of a 38-year-old female patient with chronic idiopathic urticaria who responded well on a therapeutic dosage of omalizumab, but subsequently developed severe inflammatory arthralgias. We decreased her dosage and added methotrexate for complete resolution of her urticarial and arthritic symptoms.
Conclusion: In patients with concern for medication-induced inflammatory arthralgias, physicians should consider reducing or discontinuing omalizumab with consideration of patient goals for the treatment of chronic idiopathic urticaria. This article highlights the occurrence of inflammatory arthralgias as a side effect of omalizumab and the importance of eliciting patient goals and preferences for treatment and proposes a solution to manage these arthralgias while appropriately treating symptoms in patients with chronic idiopathic urticaria.

INTRODUCTION

Omalizumab (Xolair) is a recombinant anti-IgE monoclonal antibody immunomodulator that has shown to be effective in relieving symptoms and improving quality of life in patients with refractory chronic idiopathic urticaria (CIU).[1-3] Arthralgias are an adverse effect reported in <10% of patients on omalizumab according to safety and tolerability reviews.[4,5] Few reports of omalizumab-induced arthralgias in patients with chronic urticaria currently exist in the literature. We present the case of a 38-year-old female who developed inflammatory arthralgias on omalizumab for the treatment of chronic idiopathic urticaria.

CASE REPORT

A 38-year-old female with known CIU previously trialed on optimized antihistamine (fexofenadine and cetirizine), methotrexate, and prednisone presented with persistent urticarial eruptions. She reported decreased quality of life due to chronic pruritis and

associated burning, mobility limitations, and concern with cosmesis. She was started on omalizumab 300 mg every 4 weeks with minimal response after 8 weeks. At that point, the dose was increased to 450 mg every 4 weeks with 180 mg daily of fexofenadine and cetirizine 10 mg three times with complete resolution of her symptoms.

After 4 weeks of the increased dose, the patient reported sudden onset severe proximal joint pain 1-2 days after her injection along with occasional swelling of the arms and legs. The joint pain was the worst in the morning and improved with movement throughout the day. The dosage of the omalizumab was then decreased to 300mg monthly due to concerns of an inflammatory arthritis. Rheumatoid factor and anti-CCP antibodies were within normal limits, and a referral to rheumatology was placed.

Two months later, the patient reported reduction of her arthralgias by an estimated 40% but developed worsening cutaneous symptoms associated with a tingling and burning sensation. Methotrexate 15 mg weekly and folic acid 1mg daily supplementation were then added to the patient's regimen with complete resolution of both urticarial and arthritic symptoms.

DISCUSSION

Omalizumab has been FDA-approved for the use of CIU since 2014. For patients who fail or cannot tolerate H1 antihistamines as the preferred treatment of chronic urticaria, this medication is generally preferred as the next best option. Meta-analysis determined the most effective dose to be 300mg every 4 weeks with significant improvement to itching and wheal formation when compared to placebo.[1,6] Efficacy of omalizumab was found to be dose dependent, and higher doses of omalizumab are indicated in patients who do not respond to 300mg dosage.[6] Musculoskeletal adverse effects, including arthralgia, occurred mainly on the 300mg dosage compared to 150mg or 75mg.[1] Additionally, combination therapy of omalizumab and antihistamines have been shown to have synergistic effects on efficacy.[7]

Multiple reviews have shown that use of omalizumab has been associated with complaints of arthralgia in >1% of patients,[4,5] as well as in 2.9% during clinical trials for treatment of CIU.[8] However very few cases of inflammatory arthralgias related to omalizumab are reported in the literature. Inflammatory arthritis is characterized by symmetrical stiffness and pain of the joints often more than 30 minutes in duration that is worst in the morning and improves with activity. Typical joints affected include the shoulders and knees as seen in our patient, as well as the hands, wrists, elbows, ankles, and feet. Seronegative inflammatory arthritis exists in those who are negative for both anti-cyclic citrullinated peptide antibody and rheumatoid factor. In the case of our patient, use of omalizumab was correlated with the onset of a seronegative inflammatory arthritis, the mechanism of which is currently unknown.

The symptoms of a seronegative inflammatory arthritis may mimic those of rheumatoid arthritis (RA), which may be concerning for those with a personal or family history of autoimmune disease. While there are no current studies in the literature on induction of RA by omalizumab, other medications have been shown to induce RA, including interferon-alpha in 0.2% (n=987).[9] Medication-induced inflammatory arthritis is not uncommon in the literature.[10] However, there are very few cases reported in the literature on the induction of inflammatory

arthritis by omalizumab.[11-12] Most report relief of arthralgias upon discontinuation of omalizumab, with the exception of one patient in Di Bona et al. whose symptoms improved, but did not subside after stopping the medication.[12] According to the manufacturer, the rare occurrence of arthritis will likely onset in the first 1-5 days after the first or subsequent doses of omalizumab.[8] However, two reports showed a presentation of arthritis after months to 1 year of treatment which resolved with discontinuation.[11,12] This suggests that the onset of arthritis is not time-limited and should therefore be monitored on follow-up visits.

As seen with our patient, CIU is often physically and mentally debilitating, and initiation of omalizumab for management suggests refractory disease on multiple trials of antihistamines up to 4 times their licensed dose.[1] It is important to elicit patients' preferences and goals regarding treatment. In this case, the patient was clear in her preference to focus on the elimination of her urticaria over the concerns of arthralgias from omalizumab. However, it is still important to address the onset of medication side-effects, even if such symptoms are not widely reported in the literature. Physicians treating patients with CIU who develop inflammatory arthralgias on omalizumab should have a thorough discussion with their patient about goals of care as well as benefits and risks of medication continuation. Such patients would likely also benefit from rheumatology evaluation, especially if the decision is made to continue omalizumab. Physicians should consider reducing dosage or stopping omalizumab in alignment with patient preferences. In patients with refractory CIU, adding a moderate dose of methotrexate to treatment with a decreased dose of omalizumab may help ameliorate symptoms of arthritis while maintaining improved outcomes for CIU. Follow up labs should be ordered for rheumatoid factor and anti-cyclic citrullinated peptide antibody to assess for the onset of rheumatic disease.

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