Treatment of Granulomatous Cheilitis With Infliximab

Olivia Barry, MB; Jane Barry, MB; Sinead Langan, MB; Michelle Murphy, MB; James Fitzgibbon, MB, FCAP, FRCPATH; James F. Lyons, MB, FRCPI; South Infirmary Victoria Hospital (Drs O. Barry, J. Barry, Langan, Murphy, and Lyons) and Mercy University Hospital (Dr Fitzgibbon), Cork, Ireland

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 24-year-old woman presented with a 5-year history of painless, nonpruritic swelling of her lips (Figure 1). The swelling was initially intermittent but became progressive and persistent. It began on her upper lip and gradually extended to the lower lip and right inner cheek. She was otherwise well and reported no gastrointestinal or respiratory symptoms. Physical examination showed a rubbery, infiltrated, erythematous swelling of both lips; an erythematous plaque on the right cheek; and a cobblestonelike appearance on the right buccal mucosa. The findings of a routine blood workup, including the serum angiotensin-converting enzyme level, were normal. The results of a Mantoux test were negative. A chest x-ray film did not show any signs of lymphadenopathy. Patch tests, including standard, metal, bakery, and dental batteries, revealed no abnormalities. The findings of colonoscopy were unremarkable. A punch biopsy specimen of the buccal mucosa showed noncaseating granulomatous inflammation, confirming the clinical impression of granulomatous cheilitis (Figure 2).

Figure 1. Before infliximab therapy, a rubbery, infiltrated, erythematous swelling of both lips is evident.

Figure 2. A punch biopsy specimen of the buccal mucosa showing noncaseating granulomatous inflammation (hematoxylin-eosin, original magnification ×200).

Several treatment options were tried over a 5-year period. A 6-month course of oral minocycline hydrochloride (100 mg) proved to be of little benefit. Erythromycin stearate therapy (500 mg twice daily) was administered over the next 6 months but did not result in any reduction in lip swelling. Five weeks of topical tacrolimus therapy was of no benefit either, and 5 months of treatment with the antileprosy agent clofazimine (200 mg) was ineffective as well. Some improvement was observed with 1 month of oral corticosteroid therapy (prednisolone, 40 mg/d); however, the patient reported a flare in her condition when the dosage was reduced. She also responded initially to intralesional corticosteroid therapy (triamcinolone, 30 mg). Because of the considerable swelling of her lips, there were concerns as to whether she could tolerate the administration of triamcinolone acetonide (5 mg) with only local anesthesia, so she underwent the procedure under general anesthesia. There was some re-
duction in the macrocheilia after the first treatment, but this was not sustained despite 3 more injections at 2-week intervals. The patient’s condition was having a devastating effect on her life. She was no longer socializing, and concerns were raised about her psychological state. An alternative treatment option was needed, preferably one that could achieve rapid results.

**SOLUTION**

It has been suggested that there is an association between granulomatous cheilitis and Crohn disease. Increased tumor necrosis factor α (TNF-α) production is believed to play a role in the mucosal damage that is characteristic in both conditions. Thalidomide has been used to treat granulomatous cheilitis. It exerts a specific inhibitory action on TNF-α, which is the key chemokine in most types of acute and chronic inflammation. This treatment was discussed with our patient, but in view of the potential adverse effects, most notably teratogenicity and peripheral neuropathy, it was not considered an appropriate therapeutic option. Infliximab is a chimeric monoclonal antibody that is directed specifically against TNF-α. In vitro, it binds membrane-bound TNF-α, thus facilitating cell destruction by means of antibody-dependent cell toxicity or a complement-dependent mechanism. The use of infliximab has been shown to be very successful in the treatment of Crohn disease and to have an acceptable safety profile; therefore, we elected to treat our patient with infliximab.

Infliximab therapy (3 mg/kg) was initiated at 0, 2, 6, and 9 weeks, which is the regimen that is recommended for the treatment of rheumatoid arthritis. A dramatic clinical response was achieved after the second infusion (Figure 3). Our patient did not experience any adverse effects and is currently antinuclear antibody negative. However, she did demonstrate a tendency for relapse before the next infusion, and we therefore increased the dosage to 5 mg/kg, which is the amount that is recommended for the treatment of Crohn disease. Hydrocortisone was administered intravenously (200 mg) before the next infusion, because it is thought to reduce the likelihood of the development of an adverse reaction to the infusion and of antibodies to infliximab. At present, our patient requires maintenance infliximab infusions at 8-week intervals and has had 9 infusions to date. Her normal lip architecture is fully restored. Whereas long-term treatment is required in Crohn disease, we hope that we will be able to gradually discontinue our patient’s treatment.

**COMMENT**

Granulomatous cheilitis is characterized by a chronic relapsing, remitting course of painless swelling of one or both lips. During the first episode, the edema typically subsides completely, but after recurrent attacks, the swelling may persist and increase. The resultant cosmetic deformity can have a significant psychological impact on a young patient. We describe the effectiveness of infliximab therapy in a case of granulomatous cheilitis that was resistant to conventional therapy.

A new class of biologic agents is being developed, and there is little doubt that they will revolutionize the treatment of inflammatory disorders. Etanercept is a recombinant TNF-soluble receptor that competitively inhibits TNF binding to cell surface TNF receptors, preventing TNF-mediated cellular responses. It is currently used to treat rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. It was also successfully used to treat a patient with a 24-year history of recurrent aphthous stomatitis. However, trials with etanercept have failed to prove its efficacy in the treatment of Crohn disease. Possible explanations include its relatively poor TNF-α binding compared with that of infliximab as well as the unavailability of functional drug in intestinal tissues.

Infliximab is a chimeric monoclonal antibody that binds soluble bioactive TNF-α and neutralizes its pro-inflammatory effects. It is now licensed for the treatment of rheumatoid arthritis in patients who do not have an adequate response to methotrexate therapy alone. It is also used to treat moderate to severe Crohn disease and has been reported to be helpful in reducing joint inflammation in patients with juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, uveitis, psoriasis, and sarcoidosis that is refractory to conventional therapies. Recently, a case of Crohn disease with severe orolaryngeal involvement was reported to have been treated successfully with infliximab. Because there is an association between Crohn disease and granulomatous cheilitis, we thought that a therapeutic trial of infliximab was a rational approach in the present case. This treatment has proved successful. Our patient has resumed social activities and has returned to college. She currently requires maintenance infliximab infusions at 5 mg/kg, in keeping with the current treatment of Crohn disease. We hope to taper the dosage of her infliximab therapy in the future, in conjunction with her clinical response.

To our knowledge, this case represents the first report of the treatment of granulomatous cheilitis with infliximab. We suggest the use of infliximab as a therapeutic option in the management of a difficult condition.
Accepted for Publication: December 29, 2004.
Correspondence: Olivia Barry, MB, Department of Dermatology, South Infirmary Victoria Hospital, Old Blackrock Road, Cork, Ireland (oliviamebarry@yahoo.com).
Financial Disclosure: None.

REFERENCES


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