Cutaneous Reactions to Adalimumab Administration

MR Downes, S Prendiville, C Kiely, P Lenane, N Mulligan
Departments of Histopathology and Dermatology, Mater Misericordiae University Hospital, Eccles St, Dublin 7

Abstract
Patients receiving antitumour necrosis factor-α treatment may develop cutaneous reactions. This human monoclonal antibody is used in the treatment of chronic inflammatory diseases, including arthritis and inflammatory bowel disease. A variety of side effects have been documented ranging from infection and vasculitis through to systemic lupus erythematosus and psoriasis. We report on two arthritic patients treated with adalimumab (Humira, Abbott Laboratories, IL, USA) who developed new onset rashes that resolved with discontinuation of therapy. The frequency of these cutaneous reactions has not been fully established and may benefit from a centralised registry.

Introduction
Tumour necrosis factor-α (TNF-α) is a pleiotropic proinflammatory cytokine, which in the skin, is produced by Langerhans cells, keratinocytes and melanocytes. It has been implicated in the pathogenesis of chronic inflammatory diseases including arthritis, psoriasis and inflammatory bowel disease. As a result, a number of anti TNF-α antibodies have been developed as a therapeutic strategy. Adalimumab (Humira, Abbott Laboratories, IL, USA) is a recombinant, fully human IgG1 monoclonal antibody that neutralises the effect of this circulating cytokine. Various studies have demonstrated that adalimumab is a well-tolerated and safe treatment for autoimmune conditions. However, reports have appeared in the literature of cutaneous side effects associated with the administration of adalimumab. The commonest described have been skin infections and hypersensitivity reactions at injection site.

Additionally, multiple case reports pertaining to the onset of lupus, vasculitis, granuloma annulare, interstitial granulomatous dermatitis and bullous disease have emerged. We identified two patients in our institution who developed rashes after adalimumab therapy. Both received 40mg subcutaneously on alternate weeks and were reviewed and biopsied by the dermatology service. The biopsies were reported by a single pathologist and the cases were subject to clinico-pathological correlation at multidisciplinary team review.

Case Report
Case 1
29 year old male with seronegative arthritis who commenced adalimumab in Oct 2009. He noticed a rash within one month (arms and back) and underwent a biopsy in April 2010. Histology showed a non-infective, granulomatous dermatitis. Adalimumab therapy was stopped and the rash resolved.

Case 2
62 year old male with seropositive arthritis started adalimumab in March 2010 and developed a rash within one month (legs, chest and back). A biopsy from the leg showed a leucocytoclastic vasculitis with neutrophilic infiltration into the overlying reticular dermis. No further adalimumab was administered and the lesions spontaneously resolved.

Figure 1: Case 1- panel a,b: Haematoxylin and eosin (H&E) stained sections showing dermal, non-caseating granulomas at 4X (a) and 20X (b) magnification. Case 2- panel c,d: H&E stained sections showing neutrophilic infiltration of the deep reticular dermis (c) with a leucocytoclastic vasculitis in the panniculus (d). Both 10X magnification.
Discussion

Previous studies of anti TNF-α drugs have not shown a difference in the spectrum of cutaneous complications seen with adalimumab compared to other TNF-α inhibitors. The most frequent adverse effect is a localised reaction at the injection site. A recent, large prospective study looking at dermatological conditions in arthritic patients receiving TNF-α blocking therapy demonstrated that 25% of patients required a dermatological consultation versus 13% in the control group, naïve to TNF-α blocking therapy, with eventual withdrawal of the drug in 20% of cases. Vasculitis is a known extra-articular manifestation of RA, however there have been case reports linking anti TNF-α inhibitors therapy with the de novo appearance of cutaneous vasculitis. Granulomatous/intersitial dermatitis have been associated with various systemic disorders, most commonly rheumatoid arthritis, lupus and systemic vasculitis. It has been postulated that the deposition of immune complexes in the vasculature is the inciting event.

A variety of skin lesions can occur in patients receiving anti TNF-α therapy and vigilance on the part of the clinician is necessary to identify their nature. Patients should be referred to a dermatologist for assessment and biopsy of the lesion/rash in order to rule out an infectious aetiology (e.g. reactivation of tuberculosis) and to classify the disease process. Long-term observation of patients receiving anti TNF-α therapy is indicated to identify the frequency of these side effects and the establishment of a national database would facilitate epidemiological study and provide insight into the possible pathogenesis of these cutaneous effects.

Correspondence: MR Downes
Department of Histopathology, Mater Misericordiae University Hospital,
Eccles St, Dublin 7
Email: michelle.downes@ucd.ie

References
