Skin cancer in psoriatic arthritis treated with anti-TNF therapy

SIR, Psoriasis is a common and distressing skin condition. Up to 10% of patients with extensive psoriasis have an associated arthritis [1]. In July 2006, anti-TNF agents were approved by NICE for the management of both conditions [2]. The guidelines produced by NICE state that these drugs may increase the likelihood of skin cancer in the subgroup of patients who have had previous UV therapy for psoriasis [2]. We present the cases of two brothers treated for psoriatic arthritis with anti-TNF therapy.

Both had previously received UV therapy and immunosuppressive therapy and both went on to develop skin cancer. A 54-year-old man developed Bowen’s disease, penile squamous cell carcinoma and superficial basal cell carcinomas. As a young adult he had received extensive PUVA treatment for psoriasis and after developing psoriatic arthropathy was treated with methotrexate and anti-TNF therapy. Between the age of 5 and 14 he had repeated episodes of nephrotic syndrome requiring treatment with prednisolone and cyclophosphamide.


In 1968, at the age of 15, he developed severe psoriasis responsive only to repeated courses of the then newly available PUVA (psoralen plus UVA radiation) therapy. Between 1973 and 1993 he received PUVA once a week. During treatment no genital protection was used although he had never received UV therapy directly to the genital area.

Two years after the onset of psoriasis he developed peripheral inflammatory arthritis. Having tried gold, sulphasalazine and steroid therapy with little success, in 1995 he was started on methotrexate therapy, which he has been on ever since. His joint disease continued to progress and in July 2003 he was commenced on infliximab (at a dose of 3 mg/kg administered by intermittent intravenous infusion). Initially both his psoriasis and psoriatic arthropathy responded well; however, his joint disease relapsed and in November 2004 his therapy was switched to etanercept (25 mg twice weekly administered subcutaneously). A failure to improve after 6 months led to etanercept being withdrawn and he continued with methotrexate monotherapy (at a dose of 22.5 mg weekly).

Six months after commencing anti-TNF therapy he developed an actinic keratosis on his nasolabial fold and biopsy confirmed Bowen’s disease of his trunk and left upper cheek. Reactivation of viral infections, especially papillomas was also noted. Two months after stopping anti-TNF treatment a lesion on his glans penis was removed: histological examination demonstrated a moderately differentiated squamous cell carcinoma. He has subsequently developed multiple superficial basal cell carcinomas on his trunk which have been treated with imiquimod.

A 66-year-old man, the elder brother of the above patient, developed psoriasis and inflammatory arthritis at the age of 17. His psoriasis was not as severe as his younger brother’s, and although treated initially with a short course of UVB therapy, he was never exposed to UVA or PUVA. The mainstay of his psoriasis treatment was topical therapy.

After an initial severe episode of synovitis at the onset of his psoriasis, his joint symptoms were quiescent until the age of 60 when he developed extensive peripheral inflammatory arthritis and was commenced on methotrexate (with the dose gradually being increased to 25 mg/week). This failed to control his arthritis. The addition of azathioprine (100 mg twice daily) and subsequently of cyclosporine (2.5 mg/kg) was associated with side effects (the development of blood dyscrasias and hypertension, respectively) and these drugs were subsequently discontinued.

In January 2004 he was commenced on infliximab (at a dose of 3 mg/kg administered by intermittent intravenous infusion) to which his skin and joint symptoms responded well. However, 6 months later the development of a serum sickness type illness led to the discontinuation of infliximab, and the commencement of adalimumab (40 mg fortnightly administered subcutaneously). However, in July 2005 he developed a nodular pigmented basal cell carcinoma which was removed from his left deltoid area.

The development of biological agents targeting pro-inflammatory cytokine pathways has revolutionized the management of many chronic inflammatory diseases. Careful post-marketing surveillance programmes have been established to assess the long-term risks associated with anti-TNF agents. Current evidence does not suggest an increased risk of non-haematological malignancies [3]. However, to date clinical experience with these drugs has largely been in rheumatoid arthritis (RA) [4, 5]. It is not yet clear whether the safety profile seen in RA is applicable to psoriatic arthritis [3].

Little has been documented about the development of skin cancer in patients treated with anti-TNF agents for psoriatic arthritis. Reports of the rapid development of squamous cell carcinoma in rheumatoid arthritis patients treated with anti-TNF exist in the literature [6, 7]. Patients with psoriasis, especially those in whom psoriasis develops early may represent a particularly susceptible group.

As anti-TNF’s drugs are more widely used in patients with psoriasis the potential for an increased risk of skin cancer should be recognized. Heightened awareness amongst patients will allow them to report newly developing skin lesions at an early stage and increased awareness on the part of general practitioners and rheumatologists should allow rapid referral for dermatological assessment when new skin lesions develop.

CDB and KR have received funding and honoraria from Wyeth and UCB-Celltech.

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Accepted 6 July 2007

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Rheumatology 2007;46:1623–1624
doi:10.1093/rheumatology/kem162
Advance Access publication 27 June 2007

Response to Dr Gotzche and Dr Bjarnason

Sir, Dr Gotzche and Dr Bjarnason raise several questions regarding the design and reporting of our study. Their comments are largely based upon inaccurate assumptions and inferences regarding these protocols and data analyses. Specific responses are listed subsequently:

• These are two separate trials with results presented side-by-side in the manuscript, not data pooled from two studies. In no place in our manuscript do we refer to the primary efficacy or safety results as pooled, and the results are described and presented as being from Study 1 or from Study 2 throughout the manuscript.

• Regarding the non-inferiority design, we state in the statistical methods subsection that the primary hypothesis was a non-inferiority hypothesis between the two active treatment groups, with the non-inferiority bounds defined. This design was pre-specified and filed with regulatory authorities. We acknowledge that it may have been clearer to also state that these were non-inferiority studies in the initial sentence of the study design subsection.

• We disagree with the characterization that the use of non-inferiority trials is limited only to scenarios in which the use of...