

ORIGINAL ARTICLE

Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study

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Keywords

Anti-TNF α , cutaneous side effect, chronic inflammatory joint diseases

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Abstract

Background Anti-tumour necrosis factors (anti-TNF) are more and more used, but the rate of skin adverse events is not known.

Objective The aim was to assess the number of skin infections and other dermatoses in patients treated with anti-TNF α .

Patients and methods One hundred eighty-seven patients suffering from rheumatoid arthritis or ankylosing spondylitis underwent a dermatological exam. Patients with anti-TNF were compared with those without this treatment in a prospective transversal study.

Results Among them, 59 patients were treated with anti-TNF α and steroids were prescribed in 100 cases. There was no difference in the prevalence of skin infections or eczema or tumours. Skin drug reactions were observed in six patients. Infections by dermatophytes appear very frequent, approaching 70% in both groups.

Conclusions This study shows that skin infections (or other skin diseases) are not more frequent in these patients. No differences were observed in infections (bacterial fungal, parasital or viral), tumours, psoriasis or the manifestations of atopic dermatitis. Nonetheless, a long-term survey might be interesting, especially about skin tumours.

Introduction

Tumour necrosis factor (TNF) alpha promotes the inflammatory response that underlies many autoimmune disorders including rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease and psoriasis. It can be inhibited using the monoclonal antibodies infliximab and adalimumab, or the circulating receptor fusion protein etanercept.

The advent of these and other biological therapies (also known as biotherapies) revolutionized the treatment of cutaneous psoriasis and offered great promise in the management of systemic disorders. In the nearly 10 years since anti-TNF alpha was first used in rheumatology, it has

transformed the functional prognosis and the quality of life of patients with chronic inflammatory rheumatoid conditions such as RA and AS.

However, numerous side effects, some of them serious, have been reported. Those consistent with immunosuppression include severe infections (tuberculosis), increased risk of lymphoma and solid tumours and the development of antinuclear autoantibodies responsible for lupus. With regard to cutaneous side effects, the medical literature contains many isolated observations, but only one large study – a report of non-serious skin-related events among patients receiving anti-TNF alpha for RA.¹

The principal objective of the present cross-sectional exploratory investigation was to elucidate differences in

cutaneous events between patients with RA or AS given anti-TNF alpha, and those not. Events of interest included infections (bacterial, fungal, viral and parasitic), atopic dermatitis, xerosis, eczema, toxidermia, precancerous lesions and cancers.

Patients and methods

We performed a prospective transversal study. Patients were recruited primarily from the rheumatology department at Brest university hospital (177 patients); seven were rheumatology patients at Quimper Hospital, and three attended the internal medicine department of the hospital des armées Clermont Tonnerre in Brest. The population comprised four groups: Group 1: confirmed RA not receiving anti-TNF alpha (95 patients) Group 2: confirmed RA receiving anti-TNF alpha (41 patients) Group 3: confirmed AS not receiving anti-TNF alpha (33 patients) Group 4: confirmed AS receiving anti-TNF alpha (18 patients). All confirmed RA were seropositive.

Data collection

All subjects underwent a single, systematic cutaneous examination. It was carried out on the day of infliximab perfusion or durinf a follow up consultation with patients given anti-TNF alpha, or during hospitalization for unspecified reasons in patients not given anti-TNF alpha. A questionnaire was performed by the same dermatologist for all patients except for five patients from Quimper, who were examined by another dermatologist but with the same questionnaire. Subjects were required to have been receiving adalimumab or etanercept for at least 1 month, or to have had three or more infliximab perfusions.

Statistical analysis

Data from all 187 patients included in the study were taken into account in the statistical analysis. The sample size was calculated to address the principal objective with a P-value of 0.05. Patients receiving and not receiving anti-TNF alpha were initially compared using Pearson’s chi-squared test or, when the patient population was too small, Fisher’s exact test. The test was carried out for the two groups (with or without anti-TNF alpha) then separately for each disorder. Because corticotherapy may influence cutaneous signs, a stratified analysis was conducted by 5-mg increments in

the daily corticoid dose using the Mantel-Haenszel odds ratio and the Mantel-Haenszel chi-squared test. Data were analysed with SPSS software.

Results

Study population

A total of 187 patients were included in the study: 136 with RA and 51 with AS. The population comprised 134 women and 53 men aged between 15 and 92 years; their mean age was 56.2 years and their median age 56 years. Fifty-nine patients were given anti-TNF alpha: 46 infliximab, 9 etanercept and 11 adalimumab. Eight patients had received several different anti-TNF alpha agents before recruitment. Of the 136 RA patients, 113 were women and 23 men; their ages ranged from 18 to 92 years (mean 60.5 years, median 61 years). The duration of their condition ranged from 6 months to 43 years. Forty-one patients had been treated with anti-TNF alpha. Associated treatments were leflunomide in 21 cases, methotrexate in 72 (mean dose of 4.2 tablets per week), salazopyrine in 15, hydroxychloroquine in 12, gold salts in 2, and non-steroidal anti-inflammatory drugs (NSAIDs) in 51. Twenty-one of 51 AS patients were women and 30 were men; their ages ranged from 15 to 72 years (mean 44.6 years, median 44 years). Durations of disease ranged from 4 months to 45 years. Associated treatments were NSAIDs in 35 cases, salazopyrine in 11, methotrexate in 6 (mean dose 5.2 tablets per week), corticotherapy in 4 and gold salts in 1.

Cutaneous infection overall

Information was gathered on viral infections (herpes, shingles), fungal infections and bacterial infections. Anti-TNF alpha had no statistically significant effect on the total incidence of cutaneous infections in either disease group. The findings did not change when corticotherapy was taken into account (Tables 1 and 2). Ninety-one patients with RA (67%) presented with at least one site of dermatophyte infection. Fingernails were affected in three cases: one patient was given anti-TNF alpha and two were not given anti-TNF alpha. Toenails were affected in 48 patients: 16 were given anti-TNF alpha

Table 1 Prevalence of infections according to anti-TNF alpha status

Infection	No anti-TNF alpha (n = 128)	Anti-TNF alpha (n = 59)	P-value (Fisher's exact test)
Absent	46	18	0.46
Present	82	41	

Table 2 Prevalence of infection according to disorder, anti-TNF alpha status and corticotherapy

Disorder and therapy	Infection	No corticotherapy	Corticotherapy	P-value (Pearson's χ^2)	P-value (Fisher's exact test)
Group 1 (n = 95)	+	14	50	0.16	
	–	11	20		
Group 2 (n = 41)	+	12	21	0.95	
	–	3	5		
Group 3 (n = 33)	+	17	2		0.49
	–	14	0		
Group 4 (n = 18)	+	8	0		0.47
	–	8	2		

Groups: 1 = RA without anti-TNF alpha; 2 = RA with anti-TNF alpha; 3 = AS without anti-TNF alpha; 4 = AS with anti-TNF alpha.

and 32 were not given anti-TNF alpha. There were 74 cases of interdigitoplantar intertrigo: 20 in RA patients were given anti-TNF alpha, and 54 were in the untreated individuals. Thirty-five RA patients presented with dermatophyte infection at multiple sites.

Twenty-two patients with AS (43%) presented with at least one dermatophyte infection: of 21 with interdigitoplantar intertrigo, seven were receiving anti-TNF alpha, as were seven patients whose toenails were affected.

Anti-TNF alpha had no statistically significant effect on the incidence of dermatophyte infections in either disease group. The findings did not change when corticotherapy was taken into account (Table 3).

No statistically significant differences were observed in viral infections (including herpes – chicken pox/shingles – see Table 4, and papillomavirus), bacterial infections or parasitic infections. The findings did not change when corticotherapy was taken into account.

Psoriasis

Of 12 AS patients (65%) found to have cutaneous psoriasis affecting the scalp or nails, only one had received anti-TNF alpha. Of the six RA patients with psoriasis, two had been given anti-TNF alpha (Table 5). The incidence of psoriasis among patients not given anti-TNF alpha was five times that in the treated group. No psoriasis occurred among AS patients given corticotherapy, compared with 6.25% among patients not taking corticotherapy ($P \geq 0.05$).

Cancerous and precancerous lesions

Among patients given anti-TNF alpha therapy, one case of basocellular carcinoma of the back was seen in a 23-year-old man with AS; a 54-year-old woman with RA had actinic keratosis of the face. Other keratotic pre-epitheliomatous lesions and epithelial cutaneous carcinomas were observed in patients not given anti-TNF alpha (Table 6).

Table 3 Dermatophyte infection according to disorder and anti-TNF alpha status

Therapy	Dermatophyte infection	No dermatophyte infection
TNF– (n = 128)	77	51
TNF+ (n = 59)	36	23

Table 4 Herpes virus infection by disorder and anti-TNF alpha status

Therapy	HSV–	HSV+
Anti TNF– (n = 128)	124	4
Anti TNF+ (n = 59)	57	2

Table 5 Psoriasis by disorder and anti-TNF alpha status

	Psoriasis	No anti-TNF alpha	Anti-TNF alpha	P-value (Fisher's exact test)
No corticotherapy (n = 87)	+	10	1	0.08
	–	47	30	
Corticotherapy (n = 100)	+	5	2	1
	–	67	26	

Table 6 Neoplastic and preneoplastic lesions by disorder and anti-TNF alpha status

Therapy	Neoplastic and preneoplastic lesions	No neoplastic and preneoplastic lesions
Anti TNF– (n = 128)	12	116
Anti TNF+ (n = 59)	2	57

Skin drug reactions

Skin drug reactions were observed in six patients receiving anti-TNF alpha (10.2%). One case of eczematoid eruption

Table 7 Atopic dermatitis, xerosis or eczema (ADXE) by disorder and anti-TNF alpha status

Therapy	ADXE	No ADXE
Anti TNF- (n = 128)	36	92
Anti TNF+ (n = 59)	18	41

ADXE, atopic dermatitis, xerosis, eczema.

Table 8 Atopic dermatitis, xerosis or eczema (ADXE) by disorder, anti-TNF alpha status and corticotherapy

		No anti-TNF alpha (n = 128)	Anti-TNF alpha (n = 59)	P-value (Fisher's exact test)
No corticotherapy	+	17	11	0.639
	-	39	20	
Corticotherapy	+	19	7	1
	-	53	21	

in a patient given infliximab resolved after the introduction of etanercept. The other cases involved knotty erythema with the fifth and sixth perfusions of infliximab, a maculo-papulous rash with infliximab, a maculo-erythematous rash with infliximab, an eruption at the etanercept injection site that regressed despite continuation of the treatment, and erythematous plaques at the adalimumab injection site that also improved despite continuation. Two cases were first diagnosed on the day of inclusion in this study.

Atopic dermatitis, xerosis, eczema

Manifestations of atopic dermatitis, xerosis or eczema were seen in 41 RA patients (30%) and 11 of those with AS (21.5%). The average ages of the patients concerned were 62.8 and 46.8 years, respectively. Administration of anti-TNF alpha had no statistically significant effect (Table 7). Stratification by corticotherapy did not change the result (Table 8).

Others

No cases of lupus or neutrophilic dermatosis neither autoimmune skin disease were seen in this study population.

Discussion

TNF alpha plays a role in innate immunity and protection against bacterial, viral and parasitic infection. It is

therefore not surprising that data collected by the US Food and Drug Administration between 1998 and 2002 show a significant increase in fungal and mycobacterial granulomatous infections among patients given anti-TNF alpha, particularly during the first 72 days of infliximab or etanercept administration.²

The principal objective of the present study was to look at differences in cutaneous infections between patients given and not given anti-TNF alpha. In accordance with the literature, the sample size was sufficient to allow a P-value of 0.05.³⁻⁵ In a large retrospective study involving nearly 1218 patients, the incidence of infection among the group with RA was twice that among patients without RA; 2.99% of infections were of soft tissue.³

In the present investigation, the overall rate of infection was, at nearly 64.5%, high, principally due to the high levels of dermatophyte infections. Among RA patients, dermatophyte infection was found in 65% of those not given anti-TNF alpha and 70% of those who were treated. A Turkish study reported dermatophyte infections in only 32% of RA patients.⁶

There is only one exploratory study in the literature reporting the number of cutaneous events occurring during anti-TNF alpha therapy.¹ It compared 289 RA patients starting anti-TNF alpha with 72 age-matched controls. The majority of events were cutaneous, but only 17 dermatophyte infections occurred among patients given anti-TNF alpha (5.8%). The difference in findings can be explained in several ways. In the study by Flendrie *et al.*,¹ only cutaneous events that warranted a dermatologic consultation were recorded, whereas here, patients underwent a systematic dermatologic examination. Furthermore, the great majority of interdigitoplantar intertrigo and fingernail infections are asymptomatic and rarely prompt a dermatologic consultation, despite the fact that they often precede more serious cutaneous or articular infections.

The average age of patients in the Flendrie study was between 45 and 50 years, and the mean duration of RA was 2.3 years, compared with 60.5 and 15.5 years, respectively, here. Our patients are probably less functionally able and more likely to have articular deformations that necessitate orthopedic footwear, and movement restrictions that reduce their ability to take the hygiene measures necessary to prevent maceration and fungal and other infections. Lastly, 75% of our patients were receiving corticotherapy vs. only 39% of Flendrie's population. This again puts our population at greater risk of cutaneous infections, particularly interdigitoplantar intertrigo.⁷

Concerning AS patients, in the present series, the prevalence of dermatophyte infection was lower among patients given anti-TNF alpha than in the untreated

group. This can be explained by measures taken to make patients aware of the risk, the absence of foot deformation, and the greater mobility of these young patients – with all that implies in terms of foot hygiene.

The literature contains several cases of severe infections with herpes virus (chicken pox and shingles) among patients treated with anti-TNF alpha for various indications, including RA,^{8–12} pyoderma gangrenosum¹⁰ and Crohn's disease.¹¹ Ito *et al.* explain this apparent vulnerability to viral infections in terms of the lack of TNF alpha's inhibitory effect on replication of varicella-zoster virus (VZV), and suppression of antigenic expression.¹² However, neither our study nor that by Flendrie *et al.*¹ detected an increase in viral infections [herpes simplex virus (HSV) and VZV]. Given the high frequency of HSV and VZV infection in the general population, a very large sample would probably be necessary to identify any increase in prevalence associated with anti-TNF alpha.

Cutaneous carcinomas do not require systematic declaration for pharmacovigilance purposes because of their high frequency and relatively benign prognosis. The English language data are contradictory in cutaneous carcinoma in this area. A study by Lebwohl *et al.* in 1442 RA patients given etanercept found no significant increase in tumour incidence compared with untreated controls. The risk of tumours appeared to be greatest in the first 72 days of treatment.¹³ Chakravarty *et al.* looked at a population of 15 589 RA patients and reported a significant increase in epithelial cutaneous cancers dependent on corticotherapy, anti-TNF alpha and methotrexate or leflunomide.¹⁴

The pathophysiological mechanism of action of anti-TNF alpha in the development of tumours is not fully understood. However, TNF alpha knockout mice develop a resistance to the papillomavirus, which suggests that anti-TNF alpha may promote cancer.¹⁵ TNF alpha inhibits nuclear factor-kappa B, which involves the production of many proapoptotic cytokines. Anti-TNF alpha would be expected to lead to under-production of metalloproteinases and cytokines implicated in the development of tumours and metastases.¹⁶ Only one basocellular carcinoma was noted here, on the back of a patient with clear skin particularly exposed to the sun, and with many lentigines. However, the youth of this patient (aged 23 years) suggests that anti-TNF alpha may play a role.

Infliximab and the etanercept are likely to become increasingly popular for the treatment of cutaneous psoriasis following demonstrations of their effectiveness in terms of a significant improvement in quality of life as measured by the Dermatology Quality of Life Index (DLQI) and a significant fall in the Psoriasis Activity Severity Index (PASI) 75.^{17–20} To date, no information is available comparing the different anti-TNF alpha agents.

Paradoxically, recent months have seen publication of several cases of psoriasis, psoriasis-like reactions and aggravation of existing psoriasis among patients receiving anti-TNF alpha therapy.²¹ Sfrikakis *et al.* report a series of four cases of palmoplantar pustulosis and one of psoriasis of the scalp in patients given infliximab, etanercept or adalimumab.²² The pathophysiology of these eruptions is unknown. In the present study, 65% of the cases of psoriasis involved AS, and 82.5% of patients with psoriasis had not received anti-TNF alpha, which is in accord with generally accepted data.

Moderate atopic dermatitis is seen in patients with a Th2-type immunologic profile characterized by increased production of interleukins 4, 5, 6, 10 and 13 after interaction between lymphocyte B antigen presenter and specific lymphocyte T. Logic suggests that the prevalence of atopic dermatitis and eczema should be reduced among RA patients, who have a Th1-type immunologic profile, and should be unaffected among people with AS and an intermediate Th1/Th2 immunologic profile. This is confirmed by two large studies: Hilliquin *et al.*²³ reported a significantly lower prevalence of atopy among RA patients and suggested that atopy may protect against the development of severe RA. Rudwaleit *et al.*²⁴ showed a higher prevalence of atopy in patients with AS and controls than among RA patients. No significant increase in the prevalence of atopic symptoms was seen among patients given anti-TNF alpha here, but the patient population was too small to allow firm conclusions to be drawn.

The reported frequency of reactions to perfusions and injections of anti-TNF alpha varies from author to author between 5%²¹ and 22%.²⁵ Immune reactions (anaphylactic shock, Quincke's oedema and urticaria) can be distinguished from non-immune reactions (erythema, oedema, heat and irritation during the perfusion) that may be attenuated by the concomitant perfusion of corticoids and antihistamines.^{21,26} Local reactions at the injection site occur in more than 37% of patients given etanercept and 5% of those treated with adalimumab. Polymorphic reactions of unknown pathophysiology including oedema, contusion, heat and pain occur during the first month of treatment and do not necessitate discontinuation.⁷ One case of discoidal lupus and one of extensive necrotic purpura originating at injection sites have been reported.²⁷ Among six cases of cutaneous reactions to anti-TNF alpha here, two patients had to stop their treatment, two successfully switched anti-TNF alpha, and two continued their treatment with no further problems.

In spite of the lack of an effect of anti-TNF alpha on the prevalence of infections among patients with AS and RA – even those given concomitant corticotherapy – the

prevalence of dermatophyte infection was very high. The risk was particularly great in older people (mean age, 60.5 years), those immunocompromised by anti-rheumatic treatment, those with a long history of RA (mean, 15.5 years) and those whose condition was severe. We consider it essential to insist on tracking patients and systematically treating these infections, which have the potential to cause serious complications such as erysipelas and, importantly, septic arthritis.

Dermatology patients who will benefit most from anti-TNF alpha are not those with chronic inflammatory rheumatic conditions, even if they often have psoriasis. For as yet unexplained reasons, the most prominent side effect of methotrexate in patients with inflammatory rheumatism is pulmonary fibrosis, whereas those with psoriasis are more prone to hepatopathy. People with psoriasis often benefit from interventions such as phototherapy (UVB and PUVA) and cyclosporine, which increase the risk of cutaneous carcinogenesis regardless of anti-TNF alpha administration. Corticotherapy is rarely used in the treatment of psoriasis. Cutaneous carcinogenesis is more likely than cutaneous infections to increase among these patients, and more information will emerge about the side effects of anti-TNF alpha monotherapy.

Finally, the known increase in lymphomas among patients with RA and psoriasis warrants prudence and careful monitoring.²⁵

Some limitations and biases of this study should be acknowledged. The design is prospective but cross-sectional and therefore takes no account of the time between initiation of anti-TNF alpha and the emergence of cutaneous effects. The population studied comprised hospitalized patients – who are older than a general sample, and more likely to be handicapped. Patients were also under a heavy therapeutic burden because of the severity of their condition and therefore at increased risk of cutaneous infection.

Our work is the first exploratory study of its size involving systematic dermatologic examination of all patients, not just those who requested a consultation. Two recent studies reported systematically cutaneous side-effects in patients with rheumatic diseases during application of TNF alpha antagonists.^{28,29} They reported a broad variety of cutaneous reactions. A meta-analysis on patients with infliximab and adalimumab (but not etanercept) from nine trials was in favour of an increased risk of malignancies and serious infections, which were not restricted to the skin³⁰ but its conclusions are discussed.³¹ The prospective multicentre studies necessary to evaluate in detail cutaneous events among patients with psoriasis will probably come as prescriptions of biotherapies increase. They are necessary because we need to know if there is a true risk or not.

Conclusions

This cross-sectional exploratory study in 187 patients with RA or AS looked at the effect of treatment with anti-TNF alpha agents on the prevalence of cutaneous events. No differences were observed in infections (bacterial, fungal, parasitic or viral), tumours, psoriasis or the manifestations of atopic dermatitis. That a very large proportion of subjects (approaching 70%) had dermatophyte infections probably reflects the thorough dermatologic examination they all received and underscores the need for systematic tracking and treatment of interdigitoplantar intertrigo at every consultation in order to avert serious infectious complications, both articular and cutaneous, in these already weakened individuals.

References

- 1 Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; **7**: 666–676.
- 2 Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; **1**: 1261–1265.
- 3 Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002; **46**: 2287–2293.
- 4 Hernandez-Cruz B, Cardiel MH, Villa AR, Alcocer-Varela J. Development, recurrence, and severity of infections in Mexican patients with rheumatoid arthritis. A nested case-control study. *J Rheumatol* 1998; **25**: 1900–1907.
- 5 Vandenbroucke JP, Kaaks R, Valkenburg HA et al. Frequency of infections among rheumatoid arthritis patients, before and after disease onset. *Arthritis Rheum* 1987; **30**: 810–813.
- 6 Bicer A, Tursen U, Cimen OB et al. Prevalence of dermatophytosis in patients with rheumatoid arthritis. *Rheumatol Int* 2003; **23**: 37–40.
- 7 VIDAL. 2005: 81^{ème} édition. Issy Les Moulineaux. 2791 pages.
- 8 Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology (Oxford)* 2003; **42**: 326–335.
- 9 Van der Klooster JM, Bosman RJ, Oudemans-van Straaten HM, van der Spoel JI, Wester JP, Zandstra DF. Disseminated tuberculosis, pulmonary aspergillosis and cutaneous heRA es simplex infection in a patient with infliximab and methotrexate. *Intensive Care Med* 2003; **29**: 2327–2329.

- 10 Tai YJ, Kelly R. Pyoderma gangrenosum complicated by herpetic simplex virus infection. *Australas J Dermatol* 2005; **46**: 161–164.
- 11 Baumgart DC, Dignass AU. Shingles following infliximab infusion. *Ann Rheum Dis* 2002; **61**: 661.
- 12 Ito M, Nakano T, Kamiya T et al. Effects of tumor necrosis factor alpha on replication of varicella-zoster virus. *Antiviral Res* 1991; **15**: 183–192.
- 13 Lebwohl M, Blum R, Berkowitz E et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. *Arch Dermatol* 2005; **141**: 861–864.
- 14 Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis and TNF alpha. *J Rheumatol* 2005; **32**: 2130–2135.
- 15 Scott KA, Moore RJ, Arnott CH et al. An anti-tumor necrosis factor-alpha antibody inhibits the development of experimental skin tumors. *Mol Cancer Ther* 2003; **2**: 445–451.
- 16 Burge D. Etanercept and squamous cell carcinoma. *J Am Acad Dermatol* 2003; **49**: 358–359.
- 17 Feldman SR, Gordon KB, Bala M et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. *Br J Dermatol* 2005; **152**: 954–960.
- 18 Gottlieb AB, Evans R, Li S et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51**: 534–542.
- 19 Gottlieb AB, Matheson RT, Lowe N et al. A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003; **139**: 1627–1632; discussion 1632.
- 20 Leonardi CL, Powers JL, Matheson RT et al. Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **20**: 2014–2022.
- 21 Thielen AM, Kuenzli S, A.Surat JH. Cutaneous adverse events of biological therapy for psoriasis: review of the literature. *Dermatology* 2005; **211**: 209–217.
- 22 Sfrikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. *Arthritis Rheum* 2005; **52**: 2513–2518.
- 23 Hilliquin P, Allanore Y, Coste J, Renoux M, Kahan A, Menkes CJ. Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case-control study. *Rheumatology (Oxford)* 2000; **39**: 1020–1026.
- 24 Rudwaleit M, Andermann B, Alten R et al. Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**: 968–974.
- 25 Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. *Arch Dermatol* 2003; **139**: 1425–1429.
- 26 Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. *J Dermatolog Treat* 2004; **15**: 280–294.
- 27 Misery L, Perrot JL, Gentil-Perret A, Pallot-Prades B, Cambazard F, Alexandre C. Dermatological complications of etanercept therapy for rheumatoid arthritis. *Br J Dermatol* 2002; **146**: 334–335.
- 28 Lee HH, Song IH, Friedrich M et al. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor- α antagonists. *Br J Dermatol* 2007; **156**: 486–491.
- 29 Lebas D, Staumont-Sallé D, Solau-Gervais E, Flipo RM, Delaporte E. Manifestations cutanées observées au cours d'un traitement par anti-TNF alpha: 11 observations. *Ann Dermatol Venereol* 2007; **34**: 337–342.
- 30 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295**: 2275–2285.
- 31 Corona R, Bigby M. What are the risks of serious infections and malignancies for patients treated with anti-tumor necrosis factor antibodies? *Arch Dermatol* 2007; **143**: 405–406.