Clinical and Experimental Rheumatology 2010; 28: 408-410.

Exacerbation of psoriatic skin lesions in patients with psoriatic arthritis receiving anti-tumour necrosis factor-alpha therapy: description of 3 cases and review of the literature

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Received on January 31, 2009; accepted in revised form on January 19, 2010.

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Key words: Adverse drug reaction, psoriatic arthritis, tumour necrosis factor alpha antagonists

Competing interests: Dr Rustin has been a member of the Medical Advisory Board for Wyeth and Schering-Plough and has given invited lectures; the other co-authors have declared no competing interests.

ABSTRACT

The use of tumour necrosis factor alpha (TNF-α) blockade to treat patients with both psoriasis and psoriatic arthritis (PsA) is now well established. However, paradoxical case reports of new-onset or exacerbation of psoriasis during all TNF-α blockers therapy have been published. We now review the literature and add a description of three PsA patients whose arthritis had responded well to TNF blockade but in whom major exacerbation of their psoriatic skin lesions occurred.

Introduction

The use of tumour necrosis factor alpha (TNF-α) blockade to treat patients with both psoriasis and psoriatic arthritis (PsA) is now well established (1). The treatment seems logical since studies have shown that synovial fluid of PsA patients contains highly increased levels of tumour necrosis factor (TNF)-α and other pro-inflammatory cytokines (1). Furthermore, TNF-α is known to play a key role in sustaining the psoriatic inflammatory process in skin as well as in joints (2). The two monoclonal anti-TNF-α antibodies (infliximab and adalimumab) and the soluble p75 TNF-α receptor (etanercept) have been shown to be beneficial in PsA. However, paradoxical case reports of new-onset or exacerbation of psoriasis during all TNF-α blockers therapy have been published (Table I) (3-11). We now review the literature and add a description of three PsA patients whose arthritis had responded well to TNF blockade but in whom major exacerbation of their psoriatic skin lesions occurred.

Case reports

Case 1

A 43-year-old woman with a 21-year history of polyarticular PsA was started on sulphasalazine (1 g twice daily) at the beginning of the disease and methotrexate (up to 20 mg weekly) 4 years later with insufficient clinical response. Twenty-one months latter, subcutaneous etanercept 25 mg twice weekly was added with excellent clinical benefit on her joint inflammation, which allowed her to stop taking anti-inflammatory drugs. However, there was scarcely any improvement in her psoriasis, with persisting erythematous lesions on both arms. Thirty-two months after the first injection of etanercept she had a major exacerbation of erythematous, scaly, pruritic plaques of psoriasis on her arms. In contrast, her arthritis remained in remission. She did not smoke or take any other medication. The psoriatic lesions did not improve with topical calcipotriol alone or in combination with potent topical corticosteroids. No clinical or serological evidence of infection was found and her medication was stable. Etanercept has not yet been stopped because of the good response of the arthritis.

Case 2

A 45-year-old woman with psoriasis since she was 5 years old and PsA since aged 20, who had had bilateral total knee and left hip replacements, was started on subcutaneous etanercept 25 mg twice weekly due to poor control of her joint symptoms with methotrexate (20 mg weekly), prednisolone (5 mg daily) and rofecoxib (25 mg twice daily). Her psoriasis had been virtually asymptomatic for many years. Forty-one months later, etanercept was discontinued due to a failing response of her arthritis and recurrent cutaneous and respiratory infections. Treatment was switched to subcutaneous adalimumab 40 mg every other week, and suspended 10 months later due to its inability to control her joint symptoms and a notable exacerbation of her psoriasis involving most (>80%) of the skin over her upper arms, trunk and back. Etanercept was restarted with reasonable control of her psoriasis, limited to discrete patches on the arms, but still no improvement in her articular inflammation. Concomitant medications at the time included methotrexate (20 mg weekly), prednisone (5 mg daily) and celecoxib (100 mg daily). Eleven months later she was admitted in the hospital for a generalised flare of joint disease. Etanercept and celecoxib were stopped and she was started on infliximab infusions (3 mg/kg every 6 weeks) and diclofenac (75 mg twice daily). Nine months later, her psoriasis flared again markedly, with large plaques of

Table I. Characteristics of the patients who developed exacerbation of psoriasis during anti-TNF treatment.

Authors/Reference	Age yrs/Sex	Disease	Anti-TNF	Months after treatment initiation
Mourão AF *et al*. (our work)	43/F	PsA	ETA	32 m
	45/F	PsA	ETA	41 m
			ADA	10 m
			INF	9 m
	23/M	PsA	ETA	4 m
Kary S *et al*. (4)	49/F	RA	ETA	1 m
	49/F	RA	ETA	8 m
Borrás-Blasco J *et al*. (6)	38/F	PsA	ADA	6 w
Lee H-H *et al*. (10)	39/M	NC	ADA	6 m
	63/M	RA	ETA	2 w

RA: rheumatoid artritis; PsA: psoriatic arthritis; ETA: etanercept; ADA: adalimumab; INF: infliximab; NC: nonclassified; m: months; w: weeks.

psoriasis on her chest and back, involving more than 20% of body surface area and marked nail dystrophy. In contrast, her joint symptoms remain well controlled on infliximab.

Case 3

A 23-year-old man first presented in 1973 with psoriasis affecting his scalp and over the next 17 years the psoriasis became more widespread, was no longer responsive to topical treatments and he developed extensive psoriatic finger nail dystrophy with onycholysis and pitting. In 2001 he was treated with acitretin but because of a worsening eczematous eruption on his limbs secondary to this drug with no concomitant improvement in the psoriasis, the acitretin was discontinued. In view of progressive worsening of the psoriasis and painful onycholysis affecting his dominant thumb, which was interfering with his professional guitar playing, methotrexate was commenced in 2002. At a dose of 17.5mg weekly the psoriasis cleared but in 2003 he developed synovitis affecting the PIP joint of the left thumb. This was diagnosed as PsA and over the following year he developed synovitis affecting other finger joints, which partially responded to intra-articular injections of triamcinolone. During 2005 and 2006 he had either no or minimal psoriasis and the dominant problem was waxing and waning activity of the psoriatic arthritis affecting the PIP finger joints of both hands. By October 2007 this had become so severe that subcutaneous etanercept 25 mg twice weekly was commenced with continuation of methotrexate 17.5 mg weekly. Within 8 weeks there had been a dramatic improvement in the pain and swelling of the finger joints but over the subsequent 4 months he developed new plaques psoriasis on his limbs and trunk which became progressively more extensive and inflammatory. An objective score of the Psoriasis Area and Severity (PASI) increased from 0.3 to 12.6 despite continuing both the etanercept and methotrexate. There were no other obvious exacerbating factors such as new medications or infection. It is planned to discontinue the etanercept and substitute adalimumab

Literature review and discussion

We report 3 cases of major exacerbations of psoriasis in patients who were treated with anti-TNF-α agents for PsA and whose joint symptoms remained very well controlled. Table I shows the data from previous publications in which a similar complication arose.

Psoriasis is probably a multifactorial disease and its underlying physiopathologic mechanisms are still unclear. TNF-α is a well-documented contributor to the psoriatic skin lesion and the inhibition of this cytokine effectively treats psoriasis in most patients (12, 13). As psoriatic inflammation is reduced by TNF-α antagonists some protection against an exacerbation of pre-existing psoriasis might have been expected. However, an increasing number of cases of new-onset or exacerbations of psoriasis in patients treated with these agents for different rheumatologic conditions have been published, raising the hypothesis that TNF-α antagonists may induce or exacerbate psoriasis in predisposed patients (3-11). The latency period for the exacerbation of psoriasis is quite variable and may sometimes be delayed up to a few years after exposure, as it occurred in our first patient (nearly 3 years).

A few possible explanations have been described by other authors for the paradoxical induction or exacerbation of psoriasis as an adverse effect of TNF-α antagonists treatment. The strongest evidence comes from the work of Nestle *et al*., who identifies dermal plasmacytoid dendritic cells (PDCs) and PDC-derived interferon α (INF-α) as being important upstream initiators of psoriasis development (14). TNF-α regulates INF-α production, and inhibition of TNF-α sustains INF-α production by PDCs. Based on this evidence, deGannes *et al*. proposed that TNF-α inhibition might induce locally sustained INF-α production in patients developing psoriasis while undergoing this therapy (9). Another possible explanation might be the overall increased susceptibility to bacterial infections caused by TNF-α inhibition. The effect of TNF-α blockade, in addition to other precipitating factors, seems to result in dysregulation of T cells in the epidermis and increased keratinocyte proliferation, with subsequent development of psoriasis (5). Furthermore, injury and infection have been considered possible triggers to induce pathogenic INF-α production by PDCs in individuals genetically predisposed to psoriasis (15). However, the precise pathogenesis of this paradoxical adverse reaction remains elusive.

Several reports referred new onset psoriasis in patients with other chronic inflammatory diseases treated with anti-TNF-α agents, namely rheumatoid arthritis (3-5, 7-11). The mechanisms underlying new onset psoriasis in these patients seem to be the same as exacerbation of psoriasis in patients with psoriatic arthritis under anti-TNF-α treatment.

The interval of time between initiation of anti-TNF-α treatment and exacerbation of psoriasis was generally longer in our patients (4 to 32 months) compared to the earlier published reports (2 weeks to 8 months) (4, 6, 10, 11). Although the question of whether the exacerbation of psoriasis in our patients was related to some other unknown etiology remains, there were no physiologic factors that predisposed patients to develop an exacerbation of psoriatic skin lesions. The excellent joint response to the anti-TNF-α agents particularly in 2 of our 3 cases, encouraged us to persevere with these agents in spite of the exacerbation of the psoriatic skin lesions. Only one of our patients (case 2) was taking a nonsteroidal anti-inflammatory drug (rofecoxib) when the psoriasis flared. Nonsteroidal anti-inflammatory drugs are also known to be associated with the development of psoriasis or its exacerbation (16). In spite of this, she had stopped all medications when started on infliximab, and yet she still developed exacerbation of psoriasis, implicating this agent in causing the skin flare. Moreover, this patient had been taking rofecoxib for nearly 4 years with no adverse effect on the skin. In this case the dose of infliximab was lower than the dose we normally use for psoriasis (5mg/kg) which may also have contributed to the escape of the psoriasis. There was a clear temporal link between anti-TNF-α agents administration and cutaneous lesions in the other two cases. The flare of psoriasis in the third patient was severe enough to consider discontinuing the medication.

Sari *et al*. carried out a medline search for patients who developed psoriasis during therapy with TNF-α inhibitors and concluded that exacerbation of psoriasis was more commonly reported with etanercept, whereas new-onset psoriasis and psoriasiform skin eruptions were reported more frequently with infliximab and adalimumab (7). In contrast, in our second patient, it is notable to notice that the skin exacerbation always occurred while being treated with the mononuclear antibodies to TNF-α (infliximab and adalimumab) but not during treatment with etanercept. Also notable is that the exacerbation of psoriasis occurred in the three patients receiving concomitant immunosuppressive drugs, such as methotrexate and sulphasalazine that have been also found effective in treating psoriasis (17).

We have no formal histopathological confirmation of the skin lesions and we do not have Psoriasis Area and Severity Index (PASI) available. However, the 3 patients were seen by experienced dermatologists who had no doubt about the diagnosis and the skin changes we describe here were extremely striking and would have shown a major change in PASI.

In accordance with previous authors, our report supports the idea of a link between TNF-α inhibition and exacerbation of psoriasis in predisposed patients re-iterating the need for long-term follow-up in patients treated with anti-TNF-α agents. Further work is needed to elucidate the mechanisms underlying this undesirable side effect.

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