Anti-tumour necrosis factor alpha therapy and increased risk of *de novo* psoriasis: is it really a paradoxical side effect?

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Abstract

Objective

Tumour necrosis factor (TNF) alpha inhibitors (infliximab, etanercept, adalimumab) revolutionised the treatment of autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD) and plaque psoriasis. During these treatments, cutaneous adverse effects may occur like eczema, lupus, alopecia areata or psoriasis, which represents a paradoxical adverse effect. The aim of this study was to collect and to analyse characteristics and outcomes of psoriasis induced by anti-TNF alpha treatments.

Methods

A search in the French Pharmacovigilance Database was performed between January 2002 and September 2009 using the following terms "infliximab", "etanercept", "adalimumab" combined with the term "psoriasis".
A literature review was performed utilising PubMed Database and Google scholar using permutations of the following terms "infliximab", "etanercept", "adalimumab", "tumour necrosis factor-α inhibitor" combined with "psoriasis", "palmoplantar pustular psoriasis", palmoplantar pustulosis". Certolizumab pegol and golimumab were approved only recently and so were not included in the search.

Results

We found 57 cases in the French Pharmacovigilance Database and 184 cases in the literature. It appeared that the eruptions are most often pustular lesions and occur mainly on palms and/or soles (33.3% in the French Pharmacovigilance Database and 42.9% in the literature), while palmoplantar pustular psoriasis represents only 1.7% of the psoriatic patients. The three anti-TNF-alpha are involved in the psoriasis induction. Half the cases appeared with infliximab. The patients affected by this adverse effect are mostly women aged between 40–50 years old.
The time of onset of psoriasis is highly variable. Those patients treated for their psoriasis with TNF-alpha inhibitor developed a psoriasis induced by the treatment with a different localisation and a different morphology from the initial psoriasis while other patients had a recurrence of this side effect with two different TNF-alpha antagonists, then the psoriasis developed with the 2nd anti-TNF alpha is of the same type as the psoriasis developed with the first molecule.

Conclusion

This suggests that psoriasis occurring during anti-TNF-alpha therapy are de novo psoriasis and not an aggravation of a pre-existing psoriasis. To this day several hypotheses have been proposed to explain the mechanism of action. The occurrence of this adverse effect may call into question the continuation of the treatment which is nevertheless effective.

Key words

anti-TNF-α, psoriasis, palmoplantar pustulosis, paradoxical adverse effect

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Introduction

Tumour necrosis factor alpha (TNF-α) antagonists appeared in the 90s and revolutionised the therapeutic field. These molecules neutralise the action of TNF-α, a cytokine which plays a key role in inflammation. In the past ten years, the therapeutic approach in the treatment of autoimmune disease has changed for the treatment of illnesses such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD) and plaque psoriasis. For the treatment of these diseases there are five authorised drugs: four monoclonal antibodies (infliximab, adalimumab, certolizumab pegol and golimumab) and a soluble TNF-α receptor (etanercept). These treatments significantly improve the quality of life of patients by controlling their disease and reducing the symptoms. However, psoriasis is a "paradoxical" adverse effect, that is the emergence of a disease caused by the therapeutic class which is normally used to cure or improve symptoms of it. Other cutaneous adverse effects, which are not paradoxical, include eczema, lupus or alopecia areata. The aim of this study was to collect and to analyse the characteristics and the outcomes of psoriasis induced by TNF-α antagonists.

Methods

A search in the French Pharmacovigilance Database was performed between January 2002 and September 2009 using the following terms "infliximab", "etanercept", "adalimumab" combined with the term "psoriasis".

A literature review was carried out utilising PubMed Database and Google scholar using permutations of the following terms "infliximab", "etanercept", "adalimumab", "tumour necrosis factor-α inhibitor" combined with "psoriasis", "palmoplantar pustular psoriasis", palmoplantar pustulosis". Certolizumab pegol and golimumab were approved only recently and so were not included in the search.

No time or other limits were placed in the search. All relevant references including clinical trial data, case reports, letters, review articles were analysed.

Data about age, gender, underlying disease, scheduled therapy, type of psoriasis, time from TNF-α antagonist initiation to psoriasis onset or exacerbation, previous history of psoriasis in the patient or family and outcome were collected. Missing data were noted as not described (ND). A simple descriptive analysis was performed.

Results

French Pharmacovigilance database

Fifty-seven patients were identified, changes in characteristics of patients according to scheduled TNF-α inhibitor are shown in Table I. There were 21 men (36.8%) and 36 women (63.2%). The mean age was 43.9 years (range: 17–80). The most common primary diseases were the ankylosing spondylitis (38.6%) and the rheumatoid arthritis (29.2%). The mean time to onset of psoriasis was 14.5 months (range: 0–84). Thirty-eight patients (66.7%) had no personal history of psoriasis. Information about family history of psoriasis was missing in most of the cases. The lesions improved in 24 cases and a symptomatic treatment was started in 35 cases.

Nineteen patients (33.3%) developed pustular lesions on the palms and/or soles consistent with psoriasis. There were 13 women and 6 men with an age range from 27 to 69 years. The mean age was 47.4 years. Seven patients were taking infliximab, 2 etanercept and 10 adalimumab. Six patients were treated for ankylosing spondylitis, 3 were treated for Crohn's disease, 8 were treated for rheumatoid arthritis, 2 were treated for psoriatic arthritis, 1 was treated for psoriasis. The mean time from TNF-α antagonist initiation to onset or exacerbation of psoriasis was 15.1 months (range 1 month to 6 years). Only three patients presented a previous history of psoriasis. Eight patients had an improvement of their lesions. Five of these patients stopped anti-TNF-α therapy and three had a topical treatment. The most commonly employed treatment was topical corticosteroid.

Half of the cases of psoriasis were found in patients using infliximab but the majority of the cases of palmoplantar pustular psoriasis appeared in patients using adalimumab.

Table I. Characteristics of cases of psoriasis-induced by anti-TNF-α treatment in the French Pharmacovigilance Database.

	Infliximab		Etanercept		Adalimumab		Total	
	n	%	n	%	n	%	n	%
Cases	30	52.6%	10	17.5%	17	29.8%	57	100.0%
Men	15	50.0%	1	10.0%	5	29.4%	21	36.8%
Women	15	50.0%	9	90.0%	12	70.6%	36	63.2%
Age, mean (range), years	41.9 (17-68)		53.8 (36-80)		41.6 (24-69)		43.9 (17-80)	
Underlying disease								
RA	5	16.7%	4	40.0%	8	47.1%	14	24.6%
AS	13	43.3%	2	20.0%	7	41.2%	22	38.6%
Psoriasis	2	6.7%	1	10.0%	1	5.9%	4	7.0%
CD	12	40.0%	–	–	2	11.8%	17	29.2%
PsA	3	3.3%	2	20.0%	1	5.9%	6	10.5%
Other*	2	6.7%	–	–	1	5.9%	3	5.3%
ND	–	–	1	10.0%	–	–	1	1.7%
Cutaneaous eruption								
Pustular palmoplantar	7	23.3%	2	20.0%	10	58.8%	19	33.3%
Plaque psoriasis	3	10.0%	3	30.0%	3	17.6%	9	15.8%
Guttate psoriasis	2	6.7%	–	–	2	11.8%	4	7.0%
Generalised pustular psoriasis	2	6.7%	–	–	1	5.9%	3	5.3%
Inverse psoriasis	1	3.3%	–	–	–	–	1	1.7%
Scalp psoriasis	2	6.7%	–	–	2	11.8%	4	7.0%
ND	13	43.3%	5	50.0%	6	35.3%	24	42.1%
Latency, mean (range), months	18.5 (0-84)		11.1 (0-30)		8.8 (1-30)		14.5 (0-84)	
Personal history of psoriasis								
Yes	11	36.7%	4	40.0%	3	17.6%	18	31.6%
No	19	63.3%	5	50.0%	14	82.3%	38	66.7%
ND	–	–	1	10.0%	–	–	1	1.7%
Evolution of the lesions								
Improvement	9	30.0%	5	50.0%	10	58.8%	24	42.1%
No change	4	13.3%	3	30.0%	4	23.5%	11	19.3%
ND	17	56.7%	2	20.0%	3	17.6%	22	38.6 %
Symptomatic treatment								
Yes	17	56.7%	6	60.0%	12	70.6%	35	61.4%
No	–	–	–	-	–	–	–	–
ND	13	43.3%	4	40.0%	5	29.4%	22	38.6%
Discontinuation								
Yes	12	40.0%	5	50.0%	12	70.6%	29	50.9%
No	10	33.3%	5	50.0%	5	29.4%	20	35.1%
ND	8	26.7%	–	–	–	–	8	14.0%

*Other: Synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome, uveitis, Gougerot-Sjögren syndrome, Behçet disease, Shulman syndrome, TNF receptor associated periodic (TRAPS) syndrome, non classified arthritis, juvenile rheumatoid arthritis, seronegative arthritis.
RA: rheumatoid arthritis; AS: ankylosing spondylitis; CD: Crohn's disease; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; ND: not described.

Literature

We identified 184 cases with 174 patients whose changes in characteristics of patients according to scheduled TNF -α inhibitor are shown in Table II (1-56). There were 106 women (60.9%) and 63 men (36.2%) whose average age was 45.7 years (range: 13-77). Five cases were not stated. The underlying disease was a rheumatoid arthritis in 80 cases (46.0%), ankylosing spondylitis in 37 cases (21.3%). The mean time to onset of psoriasis was 9.2 months (range: 0-62). Only 37 patients (20.1%) had a personal history of psoriasis, while 130 patients (70.6%) had no previous history of psoriasis and 111 patients (60.3%) had no family history of psoriasis. The lesions improved in 87 cases (47.3%) and resolved in 37 cases (20.1%). A symptomatic treatment was employed in 105 cases (57.1%) and the treatment was discontinued in 78 cases (42.4%).

Half of the cases of psoriasis were found with infliximab. Most of the lesions are palmoplantar pustular which mostly appeared with infliximab but in percentage the majority of the cases of palmoplantar pustular psoriasis appeared in patients using adalimumab.

Among the 37 patients (20.1%) with a previous history of psoriasis, 14 were treated for their psoriasis with a TNF-α inhibitor. Among these 14 patients, we observed that the psoriasis developed during the anti-TNF-α therapy was mostly a guttate psoriasis, even though these patients had no history of guttate lesions (Table III). We thus observed *de novo* psoriasis in most cases.

Among the 174 patients, 9 patients had a recurrence of this adverse effect with a second anti-TNF-α treatment. In 7 of these patients, the recurrent psoriasis was the same type as the psoriasis which had first developed, signing its iatrogenic appearance.

Comparison of our two data sources

Data of the French Pharmacovigilance Database presented the same characteristics as those of the international literature (Table IV). However there is a disparity in the indications of molecules that reflect different professional practices and/or different dates of issue of market authorisation.

Discussion

We found 57 cases of psoriasis induced by anti-TNF-α therapy in the French Pharmacovigilance Database and 184 cases in the literature. The prevalence of this adverse effect is 5% (54). It appears that the eruptions are more often pustular lesions and occur mainly on palms and/or soles, although this form of psoriasis is rare in the population. In the general population, the prevalence of palmoplantar pustulosis is very low (0.01–0.05%) (57), but in our population of patients treated by anti-TNF-α treatment in the French Pharmacovigilance Database and in the literature, it represents a large percentage. The three molecules we studied are involved in the genesis of this adverse effect. Most cases are described with infliximab. This can be explained by the fact that infliximab has been on the market the longest and is the most prescribed. In 2007, 864000 patients were treated worldwide with infliximab, 460000 patients were treated with etanercept and 153000 patients were treated with adalimumab (58). Actually, in a study of 9882 patients treated with anti-TNF-α, Harrison *et al*. think that patients treated with adalimumab have a 4-fold increased risk compared

Table II. Characteristics of cases of psoriasis-induced by anti-TNF-α treatment in the literature.

	Infliximab		Etanercept		Adalimumab		Total	
	n	%	n	%	n	%	n	%
Cases	94	51.1%	50	27.2%	40	21.7%	184	100.0%
Men	39	41.5%	13	26.0%	12	30.0%	63	36.2%
Women	55	58.5%	35	70.0%	25	62.5%	106	60.9%
ND	–	–	2	4.0%	3	7.5%	5	2.9%
Age, mean (range), years	43.7 (19-78)		47.2 (13-77)		48.7 (19-77)		45.7 (13-78)	
Underlying disease								
RA	30	32.6%	25	56.8%	25	65.8%	80	46.0%
AS	26	28.3%	6	13.6%	5	13.1%	37	21.3%
Psoriasis	1	1.1%	10	22.7%	3	7.9%	14	8.0%
IBD	25	27.2%	–	–	4	10.5%	29	16.7%
PsA	4	4.3%	3	6.8%	3	7.9%	9	5.2%
Other*	7	7.6%	3	6.8%	4	10.5%	14	8.0%
Cutaneaous eruption								
Pustular palmoplantar	42	44.7%	16	32.0%	21	52.5%	79	42.9%
Plaque psoriasis	16	17.0%	11	22.0%	9	22.5%	27	14.7%
Guttate psoriasis	9	9.6%	9	18.0%	2	5.0%	20	10.9%
Generalised pustular psoriasis	9	9.6%	1	2.0%	4	8.0%	14	7.6%
Inverse psoriasis	1	1.1%	1	2.0%	–	–	2	1.1%
ND	32	34.0%	15	30.0%	7	17.5%	54	29.3%
Latency, mean (range), months	9.9 (0.5-48)		7.4 (0-48)		10.2 (0.25-62)		9.2 (0-62)	
Personal history of psoriasis								
Yes	8	8.5%	21	42.0%	8	20.0%	37	20.1%
No	74	78.7%	28	56.0%	28	70.0%	130	70.7%
ND	12	12.8%	1	2.0%	4	10.0%	17	9.2%
Familial history of psoriasis								
Yes	4	4.2%	2	4.0%	5	12.5%	11	6.0%
No	60	63.8%	30	60.0%	21	52.5%	111	60.3%
ND	30	31.9%	18	36.0%	14	35.0%	62	33.7%
Evolution of the lesions								
Improvement	68	72.3%	31	62.0%	25	62.5%	124	67.4%
No change	6	6.4%	6	12.0%	4	10.0%	16	8.7%
ND	20	21.3%	13	26.0%	11	27.5%	44	23.9%
Symptomatic treatment								
Yes	57	60.6%	29	58.0%	19	47.5%	105	57.1%
No	8	8.5%	2	4.0%	4	10.0%	14	7.6%
ND	29	30.8%	19	38.0%	17	42.5%	65	35.3%
Discontinuation								
Yes	39	41.5%	22	44.0%	17	42.5%	78	42.4%
No	50	53.2%	22	44.0%	15	37.5%	87	47.3%
ND	5	5.3%	6	12.0%	8	20.0%	19	10.3%

*Other: Synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome, uveitis, Gougerot-Sjögren syndrome, Behçet disease, Shulman syndrome, TNF receptor associated periodic (TRAPS) syndrome, non classified arthritis, juvenile rheumatoid arthritis, seronegative arthritis.
RA: rheumatoid arthritis; AS: ankylosing spondylitis; CD: Crohn's disease; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; ND: not described.

to etanercept and a 3-fold increased risk compared to infliximab treated patients (59). We did not find any case of psoriasis induced by DMARDs (disease-modifying anti-rheumatic drugs), indicating therefore, that TNF-α antagonists play a role in causing this eruption. Furthermore, the underlying disease was effectively controlled at the onset of psoriasis, strongly suggesting the involvement of the therapeutical blockade of the cytokine in this paradoxical effect (60). Patients who present this adverse effect are mostly women aged between 40-50 years with rheumatoid arthritis or ankylosing spondylitis. This female predominance could also be related to the fact that rheumatoid arthritis affects mostly women. In fact, in psoriatic disease, male and female are equally represented but men and women differ in their susceptibility to ankylosing spondylitis with about 2.5 men affected for every woman with the disease; unlike in Crohn's disease where the ratio of females to males is approximately 1:2. Smoking is a risk factor of psoriasis, including the palmoplantar psutulosis but in most cases, we have no information about the smoking status of patients. The time of onset is highly variable (from the first injection to 7 years) but most cases occur during the first month of treatment. The majority of patients had no history (personal or familial) of psoriasis, suggesting rather a *de novo* apparition. It is interesting to note that patients treated for their psoriasis with anti-TNF-α therapy developed a psoriasis with a different localisation and a different morphology from the initial lesions. Some patients had a recurrence of this side effect with two different TNF-α antagonists, then the psoriasis developed with the 2nd anti-TNF-α is of the same type than the psoriasis developed with the first molecule. This suggests that psoriasis occurring during anti-TNF-α therapy is *de novo* psoriasis and not an aggravation of a pre-existing psoriasis. A majority of lesions improve after the discontinuation and/or the establishment of symptomatic treatment (most frequently topical corticosteroid). In some patients, patch skin tests were performed, which were negative. Collamer *et al*. proposed an algorithm treatment for the management of this adverse effect (47, 61). The mechanism of this paradoxical effect still remains unclear, but several hypotheses have been proposed to explain this phenomenon. The most described hypothesis, and which we consider most likely, is the one involving the interferon alpha (IFN-α). The TNF-α inhibits the synthesis of plasmacytoid dendritic cells, which release IFN-α, and the production of IFN-α by these plasmacytoid dendritic cells. Therefore, the blockade of TNF-α may lead to an overexpression of IFN-α which causes psoriatic lesions (45, 51, 56, 62). The effect of TNF-α blockade could conduce to activation of autoreactive T cells in the epidermis which increase the keratinocyte proliferation and result in a development of psoriasis (15, 42, 46, 48, 62). The TNF-α antogonists could also increase the expression of chemokine receptors, such as CXCR3, which promote infiltration of autoreactive T lymphocytes to the skin. (15, 30, 63).

Table III. Primary psoriasis and psoriasis induced by anti-TNF-α treatment.

	Primary disease	TNF-α inhibitor	Psoriasis induced by anti-TNF-α	Ref.
1	10 plaques psoriasis with 3 psoriatic arthritis	9 Etanercept 1 Adalimumab	6 guttate psoriasis 1 pustular psoriasis 1 exacerbation of the lesions 2 palmoplantar pustular psoriasis	2 21 23 47
2	Generalised pustular psoriasis well controlled by the anti TNF-α No history of guttate psoriasis	Etanercept	Guttate psoriasis	21
3	Psoriasis + psoriatic arthritis	Infliximab	Guttate papules + scaly plaques over the trunk and extremities, with clustering over the lower back	30
4	1 Pustular psoriasis of the scalp 1 Pustular psoriasis confined on palms and soles involving elbows, posterior scalp and knees	2 Adalimumab	Generalised pustular psoriasis Exacerbation of psoriatic skin lesions on palms and soles	48 49

Table IV. Comparison between the French Pharmacovigilance database and the literature.

	FPD (n=57)	Literature (n=184)
Anti-TNF-α therapy		
Infliximab	52.6%	51.1%
Etanercept	17.5%	27.2%
Adalimumab	29.8%	21.7%
Patients		
Men	36.8%	36.2%
Women	63.2%	60.9%
ND	–	2.9%
Age, mean (range), years	43.9 (17-80)	45.7 (13-78)
Underlying disease		
RA	24.6%	46.0%
AS	38.6%	21.3%
Psoriasis	7.0%	8.0%
IBD	29.2%	16.7%
PsA	10.5%	5.2%
Other*	5.3%	8.0%
ND	1.7%	–
Cutaneous eruption		
Pustular palmoplantar	33.3%	42.9%
Plaque psoriasis	15.8%	14.7%
Guttate psoriasis	7.0%	10.9%
Generalised pustular psoriasis	5.3%	7.6%
Inverse psoriasis	1.7%	1.1%
Scalp psoriasis	7.0%	–
ND	42.1%	29.3%
Latency, mean (range), months	14.5 (0-84)	9.2 (0-62)
Personal history of psoriasis		
Yes	31.6%	20.1%
No	66.7%	70.7%
ND	1.7%	9.2%
Familial history of psoriasis		
Yes	–	6.0%
No	–	60.3%
ND	–	33.7%
Evolution of the lesions		
Improvement	42.1%	67.4%
No change	19.3%	8.7%
ND	38.6%	23.9%
Symptomatic treatment		
Yes	61.4%	57.1%
No	–	7.6%
ND	38.6%	35.3%
Discontinuation		
Yes	50.9%	42.4%
No	35.1%	47.3%
ND	14.0%	10.3%

*Other: Synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome, uveitis, Gougerot-Sjögren syndrome, Behçet disease, Shulman syndrome, TNF receptor associated periodic (TRAPS) syndrome, non classified arthritis, juvenile rheumatoid arthritis, seronegative arthritis.
RA: rheumatoid arthritis; AS: ankylosing spondylitis; CD: Crohn's disease; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; ND: not described. FPD: French Pharmacovigilance Database.

Some authors have suggested that the lesions are not psoriasis but is a reaction due to drug hypersensitivity like an atypical presentation of acute generalised exanthematous pustulosis, which can mimic palmoplantar pustular psoriasis (15, 58, 59, 64). In this study, biopsy results were available in only a few cases. But it is difficult to differentiate between palmoplantar pustulosis and palmolantar pustular psoriasis because these two eruptions are similar in morphology and in histology (57). Another hypothesis proposed that the psoriatic lesions are a bacterial infection, particularly in the context of the palmoplantar pustular psoriasis. This infection may be caused by the inhibition of the TNF-α (45, 59, 65). In addition, TNF-α seems to play a role in the eccrine sweat glands. Patients who develop palmoplantar pustular psoriasis have a lower expression of TNF-α in the eccrine sweat glands than the healthy subjects. The administration of anti-TNF-α antagonists may therefore lead to psoriatic lesions (16, 27, 35, 63). The patients with psoriasis could have been misdiagnosed and they actually had psoriatic arthritis (which can precede skin disease in 10% of cases) rather than rheumatoid arthritis or ankylosing spondylitis (15, 31, 59, 64-66). The palmoplantar lesions may in fact be a manifestation of keratoderma blenorrhagicum occurring after exposition to *Chlamydia trachomatis* (44, 65, 66, 67). The palmoplantar pustular psoriasis could have different genetic aspect from the plaque psoriasis. Polymorphism in the TNF-β gene has been reported to be associated with palmoplantar pustular psoriasis rather than the TNF-α gene which is associated with plaque psoriasis (15, 35, 68, 69).

Palmoplantar pustular psoriasis might be a dermatological entity generated by anti-TNF-α and not a true psoriasis.

This adverse effect seems to be a class effect. Cases of psoriasis with certolizumab pegol have been published (70, 71). We did not find any case of psoriasis during golimumab treatment but palmoplantar pustular psoriasis is mentioned in the adverse event section of the summary of product characteristics (72).

Conclusion

Analysis of the French Pharmacovigilance Database and literature show that psoriasis induced by anti-TNF-α therapy is predominantly palmoplantar pustulosis and that there are mostly *de novo* lesions rather than an exacerbation of previous eruptions. This adverse effect especially in severe cases may call into question the continuation of this efficacy treatment. Several hypotheses have been proposed to explain this event: IFN-α overexpression caused by the TNF-α inhibition or hypersensitivity to anti-TNF-α treatment, an entity erroneously described as psoriasis.

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