

## A ROLE FOR B-CELL-DEPLETING AGENTS IN TREATING PSORIATIC SKIN LESIONS INDUCED BY TUMOR NECROSIS FACTOR-ALPHA ANTAGONISTS: A CASE REPORT AND LITERATURE REVIEW

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**Abstract** - Despite recent advances in understanding the pathological pathways, clinical pattern and management opportunities for new-onset psoriasis as a paradoxical adverse event in patients receiving TNF inhibitors for their immune-mediated disorder, there is a subset of patients who are either partial responders or non-responders, whatever the therapeutic scenario. We present the case of new-onset psoriasis and severe alopecia development in a case study of long-standing rheumatoid arthritis (RA) treated with adalimumab (ADA) and leflunomide. Since skin lesions and alopecia are resistant to the classic protocol (topical treatment, ADA discontinuation) and RA becomes highly active, rituximab (RTX) was started. Dramatic improvement in joint disease, total remission of alopecia and partial remission of pustular psoriasis were described after the first RTX cycle. Although B-cell-depleting agents result in controversial effects on psoriatic skin lesions, this is the first case of ADA-induced psoriasis and alopecia that improved under RTX, suggesting a possible role in treating such a patient population.

**Key words:** new-onset psoriasis; TNF- $\alpha$  antagonists; rituximab; adalimumab

### INTRODUCTION

Paradoxical psoriasis, either new-onset or worsening of pre-existent lesions, remains of particular interest in patients receiving tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors for their inflammatory immune-mediated rheumatic pathology (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, idiopathic juvenile arthritis) or non-rheumatic pathology (e.g. inflammatory bowel disease), since current therapeutic guidelines recommend them and such agents are remarkably effective for moderate-

to-severe plaque psoriasis, (Collamer and Battafarano, 2010, Pham et al., 2011).

Although it appears that *de novo* psoriasis is a temporary condition, side effect described during after application of TNF inhibitors (infliximab, adalimumab, etanercept) can be controlled in over 90% of cases with the addition of topical agents and immunosuppressive medication, with or without discontinuation of responsible TNF- $\alpha$  blocker, (Pham et al., 2011, Viguier, 2010). Management recommendations are critical with persistent lesions.

## CASE REPORT

We present the case of a 34-year-old woman treated with adalimumab (ADA), a totally humanized anti-TNF- $\alpha$  monoclonal antibody, for her long-standing seropositive (rheumatoid factor, anti-CCP-antibody) erosive rheumatoid arthritis (RA) after developing a suboptimal response with sequential non-biologic DMARDs (methotrexate, sulfasalazine and leflunomide). She had no personal or familial history of psoriasis, skin rash or allergic reactions.

Twenty-six months after the initiation of ADA (40 mg every other week) given in conjunction with leflunomide (20 mg daily), our patient unexpectedly developed multiple lesions of psoriasis, comprising typical palmoplantar pustular lesions, extensive plaque-type psoriasiform eruption on the abdomen, trunk and extremities and severe diffuse alopecia and erythematous scaly plaques on the scalp. Conventional histopathological analysis of paraffin embedded hematoxylin-eosin-stained biopsy specimens obtained from punch biopsy of the skin and scalp confirmed the diagnosis based on acanthosis with parakeratosis, elongation of the dermal papillae, intraepidermal pustules and neutrophils into the stratum corneum, all findings being consistent with pustular psoriasis.

Despite the severe flare-up of paradoxical psoriasis, her RA was in remission according for the new 2011 *American College of Rheumatology / European League Against Rheumatism* definition, for about five months; moreover, no specific immune abnormality such as rheumatoid factor, anti-cyclic citrullinated peptide antibodies, total antinuclear and anti-double stranded DNA antibodies, as well as anti-ADA antibodies, was detectable. Both skin psoriasis and alopecia failed to respond to classic treatment (topical steroids, vitamin D derivatives, emollients), although they modestly subsided with the discontinuation of ADA, while plaque-type lesions significantly improved following this therapeutic scenario.

Six months later, when our patient returned to the rheumatology outpatients department with ac-

tive RA (disease activity score DAS28 being 6.7), moderate palmoplantar pustular psoriasis and refractory scalp psoriasis with alopecia, a second line biologic modifier was introduced.

Surprisingly, after the first cycle of rituximab (1 000 mg, 2 weeks), not only did the articular disease significantly improve (DAS28 of 3.2, with the EULAR response more than 1.2), but also the skin disease. Partial remission of pustular psoriasis was achieved as soon as the first administration and persisted through the following six months; a dramatic effect on the alopecia with total healing was also reported (Fig. 1).

## DISCUSSION

While the pathogenic pathways underlying psoriasis induced by anti-TNF agents are still unclear, several paradigms have been proposed including an imbalance between TNF- $\alpha$  and type 1 interferon- $\alpha$ , reduction in TNF- $\alpha$ -driven apoptosis, enhancement of CXCR3 expression, T-cell activation, and TNF- $\alpha$  receptor polymorphism (Collamer and Batafarano, 2010, Pham et al., 2011).

Despite recent advances in understanding pathogenic pathways, clinical pattern and management opportunities for new-onset psoriasis as a paradoxical adverse event in patients receiving TNF inhibitors for their immune-mediated rheumatic or non-rheumatic disorder, there is a subset of patients who are either partial responders or non-responders, whatever the therapeutic scenario.

Rituximab, a B-cell-depleting monoclonal antibody targeting CD20, is a novel agent approved for an expanding range of rheumatic disorders, particularly moderate-to-severe RA (1 000 mg for two weeks, every six months), in patients who fail to respond or develop toxicity to anti-TNFs.

Data emphasizing the behavior of either articular or skin involvement in psoriatic disease following rituximab are extremely limited and controversial. Several anecdotal reports have demonstrated mod-



**Fig. 1.** Palmoplantar pustular psoriasis, scalp psoriasis and alopecia induced by adalimumab: baseline (A), after first infusion (B) and six months after the first cycle of rituximab

est efficacy for arthritis, primarily in patients not previously exposed to TNF- $\alpha$  inhibitors, along with modest improvement and significant inhibition of inflammatory biomarkers expression in skin lesions, (Viguier, 2010, Cohen, 2008, Mease, 2011); nevertheless, development of psoriasis after B-cell ablation has also been reported. (Dass et al., 2007)

A wide spectrum of psoriasis associated with biological drugs has been described during the last years (Collamer and Battafarano, 2010, Pham et al., 2011, Viguier, 2010), particularly in patients without a personal history of psoriasis. Although several authors recommend topical agents and/or discontinuation of the inducing drug, others agree with the change to another anti-TNF- $\alpha$  inhibitor (Collamer and Battafarano, 2010, Pham et al., 2011, Viguier, 2010).

A systematic analysis of cases of psoriasis induced by anti-TNF in our database showed that only 10 out of 250 patients receiving biologic therapy for their rheumatic disorder developed paradoxical psoriasis (2 with infliximab, 4 with adalimumab and 4 with etanercept) (cumulative incidence of 2.5%). Different phenotypes of psoriasis were reported in our cohort, ranging from plaque psoriasis on the extremities and trunk (8 cases), palmoplantar pustulosis (2 cases), scalp psoriasis (1 case) and guttate lesions (2 cases); lesions developed as early as 7 days, but also after 62 months of anti-TNF therapy. Furthermore, a relatively good outcome guided by specific dermatological treatment with or without discontinuation of the responsible agent and/or switching to a second one TNF inhibitor was demonstrated in the majority of cases (9 patients).

To our knowledge this is the first report of a patient diagnosed with ADA-induced psoriasis successfully treated with rituximab; moreover, the role of rituximab in treating non-scarring ADA-related alopecia should also be mentioned, given that total healing was reported after the second infusion.

### CONCLUSION

There is a need for new drugs in refractory cases of *de novo* psoriasis with TNF- $\alpha$  inhibitors, and rituximab is such a candidate. Rituximab could be an attractive alternative for RA developing *de novo* psoriasis with TNF inhibitors, supplementary studies being necessary to confirm the efficacy on this paradoxical skin lesion and non-scarring alopecia induced by ADA.

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