

## 1.1. Adalimumab and pustular psoriasis

### Introduction

Adalimumab (Humira<sup>®</sup>) is a fully human recombinant monoclonal immunoglobulin G1 antibody expressed in Chinese hamster ovary cells that inhibits the action of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by binding specifically to TNF- $\alpha$  and neutralizing the biological function of TNF- $\alpha$  by blocking its interaction with the p55 and p75 cell surface TNF receptors [1]. Adalimumab was granted marketing authorization on 8 September 2003 in Europe [1].

Therapeutic indications include rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. In RA adalimumab is used either as monotherapy or in combination with methotrexate in patients with an inadequate response to classic disease-modifying antirheumatic drugs. Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, or have a contraindication for other systemic therapy including cyclosporine, methotrexate or PUVA [1].

The SmPC of adalimumab mentions psoriasis as an uncommon adverse drug reaction, but pustular psoriasis is not mentioned [1].

This report describes pustular psoriasis in association with the use of adalimumab.

### Reports

Excluding one duplicate report by the marketing authorization holder, the Netherlands Pharmacovigilance Centre Lareb received five reports of patients with RA with pustular psoriasis in association with the use of adalimumab (Humira<sup>®</sup>) until April 2, 2009.

Table 1. Reports of pustular psoriasis with the use of adalimumab.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 62472, F, 77	adalimumab 40 mg once every 2 weeks, rheumatoid arthritis	alfacalcidol 0.25 $\mu$ g, methotrexate 2.5 mg, folic acid 0.5 mg	psoriasis pustular (palmaris et plantaris)	42 months, action taken with adalimumab and outcome unknown
B 68024 and 70659, M, 64	adalimumab, rheumatoid arthritis	omeprazole 20 mg, salazopyrine 2000 mg	extensive pustular psoriasis on the hands, feet and legs	13.5 months, adalimumab was withdrawn, 1 month later the patient had not yet recovered
C 78505, F, 39	adalimumab 40 mg once every 2 weeks, rheumatoid arthritis		psoriasis pustular plantaris palmaris	3.5 months, adalimumab was withdrawn, patient not yet recovered. Patient is treated with cutaneous tar preparations, corticosteroids, PUVA and acitretin

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
D 81015, F, 77	adalimumab 40 mg, rheumatoid arthritis	Folic acid 10 mg/week, methotrexate 7.5 mg	psoriasis pustular	1 month, adalimumab was withdrawn, patient was treated with methotrexate, tar, acitretin and recovered with sequel
E 78316 F, unknown age	adalimumab 40 mg, rheumatoid arthritis		acute severe pustular psoriasis	months, adalimumab was withdrawn, the patient was hospitalized and treated with prednisolone, ciclosporin and methotrexate. The pustular psoriasis improved.

## Other sources of information

### Literature

Pustular psoriasis is a rare and serious form of psoriasis consisting of widespread pustules on an erythematous background and systemic symptoms. Cutaneous lesions characteristic of psoriasis vulgaris may be present before, during, or after an acute pustular episode [2]. Palmoplantar psoriasis is a subtype of localized psoriasis that affects the palms of the hands and the soles of the feet. When it occurs without other psoriatic lesions, some consider it as a separate entity of unknown origin.

Among hypersensitivity reactions during TNF- $\alpha$  inhibitors like local reactions at the injection site, urticaria and other drug eruptions, also paradoxically, the development or exacerbation of psoriasis or psoriasis-like lesions have been reported [3,4,5]. This also includes pustular psoriasis, which most often is localized to the palms and soles [6] In literature, (pustular) psoriasis is described as a class-effect of TNF-inhibitors [7,8,9].

Heymann in a review article on TNF-inhibitors and pustular psoriasis concludes that the majority of reported cases appeared in patients without a history of psoriasis, for whom the drug was administered for other conditions, most commonly RA [4]. Most cases, but not all, appear in women and there appears to be a predilection for the palms and soles.

In a prospective cohort study Flendrie *et al.* [10] focused on dermatologic complications in patients with 289 RA receiving anti-TNF- $\alpha$  therapy (follow-up period 2,3 years) with infliximab, etanercept, or adalimumab. They were compared with a group of 289 RA patients naïve to anti-TNF- $\alpha$  therapy. A significant greater number of dermatologic consultations (25%) was found, compared with the control group (13%), resulting in withdrawal of TNF- $\alpha$  therapy in 6,5% of patients.

De Gannes *et al.* observed new-onset psoriasis (n=13) or severe exacerbation of psoriasis (n=2) in 15 patients with a variety of rheumatologic conditions, during treatment with etanercept (n=6), infliximab (n=5), adalimumab (n=4) [8].

Wollina *et al.* reviewed 114 patients from the literature with (pustular) psoriasis and included six new patients (three women and three men) who developed pustular lesions during treatment with TNF- $\alpha$  inhibitors [9]. Palmoplantar pustular psoriasis occurred in 37 of the cases. A positive personal or family history of psoriasis was present in 25, respectively 8 patients. Timing of the

occurrence of skin lesions varied considerable among the patients ranging from after a single application up to 63 months after initiation of therapy [9].

Beuthien *et al* [5] describe the case of a 63-year-old female with a history of rheumatoid arthritis in which adalimumab was added to her regimen of methotrexate and leflunomide. Within a few hours of the sixth injection of adalimumab (at approximately week 12), she developed papulopustular lesions at the injection site on the thigh and on the palms and soles. This was followed by desquamation at these sites. There was no mucous membrane involvement. Adalimumab was discontinued and the eruption improved.

On the other hand, TNF- $\alpha$  inhibitors have been reported to be successful in pustular psoriasis; for example adalimumab effectively controlled recalcitrant generalized pustular psoriasis in an adolescent [4].

### Databases

On April 02, 2009, the association of pustular psoriasis with the use of adalimumab was disproportionally present in the Lareb database with a ROR of 674 (95% CI = 192.5 - 2360.4). The WHO database contained 141 cases of psoriasis (ROR 7.9, 95% CI = 6.6 - 9.4) but did not specify cases of pustular psoriasis.

On April 15, 2009, the Eudravigilance database contained 41 reports of pustular psoriasis in adalimumab users. The reaction was rated serious in all but two cases, and included 18 male patients and 22 female patients. Gender was not specified in one case; age ranged from 28 to 77 years. No reactions led to decease or life-threatening disorders. Hospitalisation was necessary in fifteen cases, in three reports the reaction led to disability.

### Mechanism

According to Collamer *et al.* the pathogenesis of psoriasis as an adverse drug reaction on TNF- $\alpha$  inhibitors appears to involve a disruption in cytokine balance following TNF inhibition, resulting in the up-regulation of plasmacytoid dendritic cells and the subsequent production of unopposed interferon-alpha, following a triggering event in predisposed individuals [11]. De Gannes *et al.* propose that cross regulation between TNF and type 1 interferon (IFN) may have a role in the pathogenesis of this reaction. This may result in pustular cutaneous inflammation. [8].

### Discussion and conclusion

In total there are only ten reports of pustular psoriasis in the Lareb database. Five reports of pustular psoriasis concern the use of adalimumab (not including one duplicate report), all patients with RA. RA can be considered a prototype for the diseases characterized by neutrophilic inflammation, a feature it shares with psoriasis. This supports the role of dysregulation in cytokine balance, induced by TNF- $\alpha$  inhibitors. In the Lareb data base, there are also two reports of pustular psoriasis concerning the use of etanercept. In the SmPC of etanercept psoriasis is mentioned, but not pustular psoriasis [12]. Furthermore pustular psoriasis has been reported once with the use of metoprolol and amitriptyline. The association between adalimumab and pustular psoriasis is disproportionally present in the Lareb database and is also extensively described in the literature. Although psoriasis is mentioned in the SmPC, (palmoplantar) pustular psoriasis as a specific subtype of psoriasis should also be explicitly mentioned.

### References

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*This signal has been raised on July 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbg-meb.nl/cbg/en/default.htm](http://www.cbg-meb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*