CLINICAL REPORT

Pattern and Severity of Psoriasiform Eruptions in Patients with Inflammatory Bowel Diseases, Arthritis or Skin Inflammatory Disorders Treated with TNF-alpha Inhibitors

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Psoriasiform eruptions are a classical adverse skin reaction of tumour necrosis factor (TNF)-α inhibitors. The aim of this study was to identify the association between the severity or pattern of psoriasiform reactions and the underlying disease. A retrospective study was conducted between January 2012 and May 2015. Adult patients who developed psoriasiform eruptions whilst being treated with TNFα inhibitors were included. For each patient, 3 independent blinded dermatologists graded twice the severity of the lesions according to 6 clinical psoriasiform eruption types. Inter- and intra-individual kappa tests were performed to evaluate the robustness of the scoring system. The association between severity score levels or the pattern of reactions and the underlying disease was assessed. The severity scoring system showed good inter- and intra-observer reproducibility. Women patients treated with TNFα inhibitors for inflammatory bowel diseases showed a higher risk of developing severe reactions with scalp and skin-fold involvement.

Key words: TNF-α inhibitors; psoriasiform eruption; inflammatory bowel disease; arthritis; psoriasis; tumour necrosis factor.

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Treatment with tumour necrosis factor (TNF)-α inhibitors has profoundly changed the course of inflammatory diseases, such as inflammatory bowel diseases (IBD), inflammatory rheumatism (IR) and psoriasis (1). While TNFα inhibitor therapies are generally well tolerated, their use has been associated with a wide range of adverse events, including cutaneous events. Psoriasiform eruptions are the most common inflammatory skin adverse events reported so far. Their prevalence ranges from 0.6% to 5.3% in patients treated with these therapies (2–8). Psoriasiform eruptions have been observed with all the TNFα inhibitors (7, 9, 10) and are characterized by various clinical presentations, including palmoplantar keratoderma or pustulosis, and skin-fold or scalp lesions, which lead to diagnostic difficulties. Severe manifestations, such as alopecia, generalized psoriasiform plaques or pustulosis, can lead to treatment discontinuation with a potential risk of flare-up of the underlying disease (9–12). Therefore, we sought to identify a potential association between the severity or the pattern of the psoriasiform reactions under treatment with TNFα inhibitors and the underlying disease using a new validated severity scoring system.

PATIENTS AND METHODS

Population and study sample

We conducted a retrospective single-centre study between January 2012 and May 2015 in the department of dermatology at the University Hospital in Bordeaux. All patients aged 18 years or over were referred to our clinic in the first 3 months after the onset of the psoriasiform eruption. Patients were referred from the gastroenterology, rheumatology, dermatology and internal medicine departments. Each patient completed a standardized questionnaire including demographic and clinical characteristics, underlying inflammatory conditions, type and dose of TNFα inhibitors initiated, concomitant therapies and delay between administration of TNFα inhibitors and the onset of psoriasiform eruptions. Written informed consent was obtained from all patients.

Clinical features of psoriasiform eruptions

Psoriasiform eruptions were defined as a cutaneous eruption occurring during treatment with TNFα inhibitors in a patient with no personal history of similar lesions. The absence or presence of each of the 6 following patterns was noted: palmoplantar keratoderma (PPK), palmoplantar pustulosis (PPP), psoriasiform plaques, skin-fold involvement, scalp involvement and generalized pustulosis.

Scoring system and statistical analysis

Three experienced dermatologists (A, B, C) independently rated the photographs of the psoriasiform lesions twice with a 15-day interval. For each patient, the 6 patterns were assessed with a 3-grade severity score (0 for no lesion, 1 for mild involvement and 2 for severe involvement) (**Fig. 1**). Intra- and inter-observer reproducibility of ratings between each pair of dermatologists was estimated using kappa statistics (A and B, A and C, B and C) (13). A kappa statistic with equal-spacing weights was used to estimate the degree of agreement between the pairs of dermatologists. The 5-level nomenclature proposed by Landis & Koch (14) was used to interpret the level of agreement.

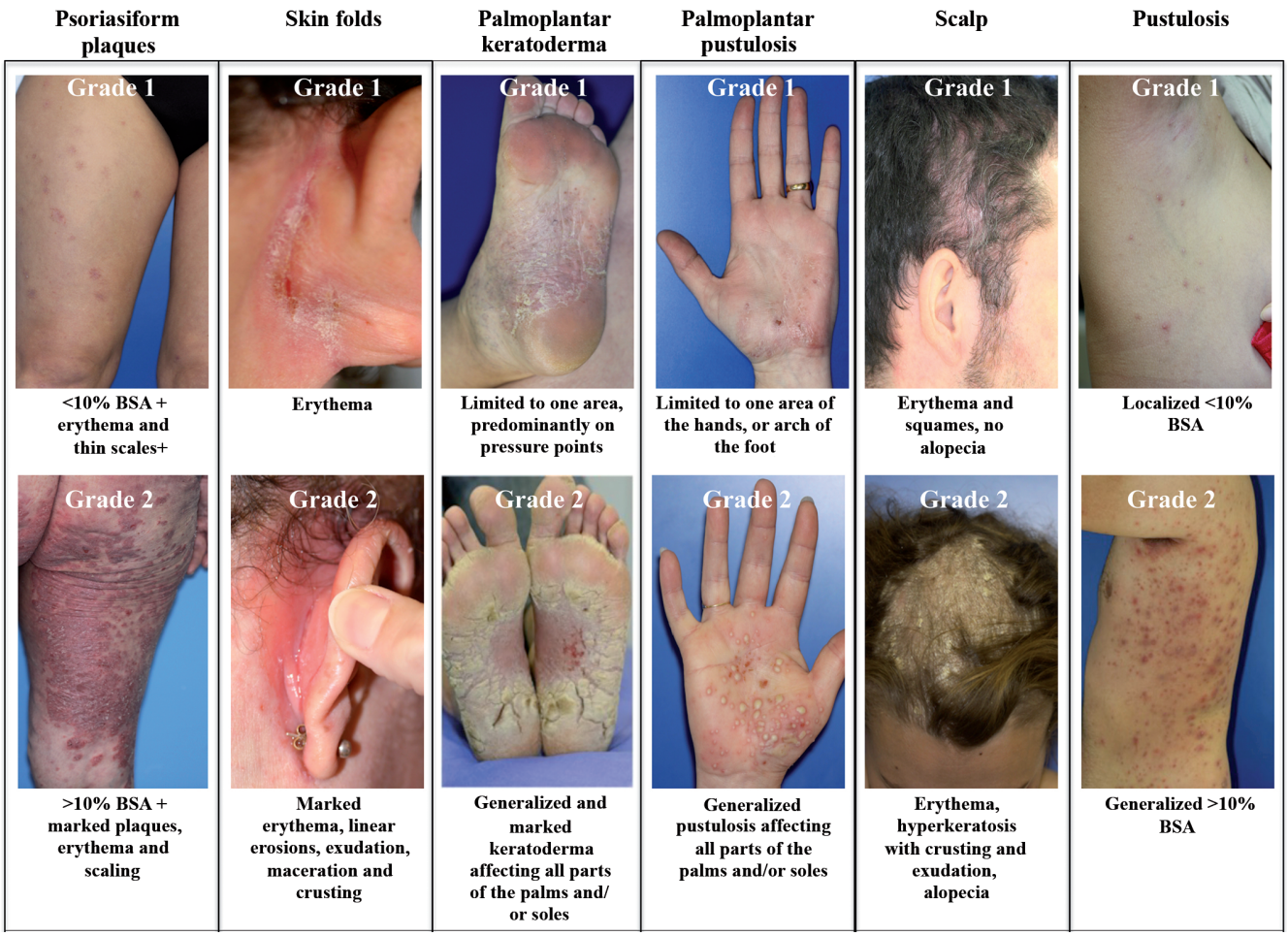

Fig. 1. Psoriasiform eruptions: The 6 identified patterns were rated with a 3-grade severity score (0: no lesion, 1 point: grade 1, 2 points: grade 2). A global severity score was obtained by summing the scores of all types of psoriasiform reactions.

A global severity score was obtained by summing the scores of all types of psoriasiform reaction in each patient. The distribution of each psoriasiform clinical subtype in each group of patients according to the underlying disease treated with TNFα inhibitors was compared using the 2-sided χ^2 test or Fisher's exact test, as required. Severity scores between IBD patients and others were determined using a 2-sided Student's *t*-test. The type and severity scores of each psoriasiform reaction were then compared with the underlying disease.

RESULTS

Patient characteristics

Patient characteristics are presented in **Table I**. A total of 83 patients were included in the study: 36 males and 47 females. Mean age was 39 years (range 18–75 years). Forty-three patients (51.8%) were followed for IBD (31 Crohn's disease, 12 ulcerative colitis), 40 (48.2%) for IR (24 ankylosing spondylitis, 11 rheumatoid arthritis, 6 psoriatic arthritis), and 7 (8.4%) for psoriasis. TNFα inhibitors were prescribed off-label for 9 patients (10.8%). Twenty-three patients (27.7%) had a personal and/or familial history of psoriasis. Mean body mass index (BMI) was 24.8 (range 17–36), 33 patients (39.8%) smoked, 13 (15.7%) had hypertension and 7 (8.4%) had dyslipidaemia.

Overall, 43 patients (51.8%) were receiving infliximab, 22 (26.5%) adalimumab, 16 (19.3%) etanercept and 2 golimumab (2.4%). The mean time elapsed from initiation of anti-TNFα therapy to onset of skin lesions was 26.5 months for infliximab (range 0–148), 7.2 months for adalimumab (range 2–22), 15 months for etanercept (range 0–108) and 6 months for golimumab (range 4–8). Overall, 59 patients (71.1%) developed psoriasiform plaques, 35 (42.2%) presented skin-fold lesions, 16 (19.3%) PPP, 14 (16.9%) PPK, 26 (31.3%) scalp lesions and 13 (15.7%) generalized pustulosis.

Statistical analysis

First, a severity scoring system was designed and validated, based on photographs of the patients (Fig. 1). The weighted kappa statistic values were found to be 0.79 between dermatologists A and B, 0.66 between dermatologists A and C, and 0.69 between dermatologists B and C. The intra-observer kappa coefficient showed

Table I. Demographic and clinical characteristics of the patients (*n* = 83)

Patient's characteristics	
Age, year, mean (range)	39 (18–75)
Sex, % F/M	56.6/43.4
Body mass index, mean (range)	24.8 (17–36)
Personal or family history of psoriasis, yes, *n* (%)	23 (27.7)
Personal history of atopy/drug reaction, yes, *n* (%)	18 (21.7)/17 (20.5)
Risk factors, *n* (%)	
Smokers	33 (39.8)
Hypertension	13 (15.7)
Dyslipidaemia	7 (8.4)
Underlying disease, *n* (%)	
Inflammatory bowel disease	
Crohn's disease	31 (37.3)
Ulcerative colitis	12 (14.5)
Inflammatory rheumatism	
Ankylosing spondylitis)	24 (28.9)
Rheumatoid arthritis	11 (13.3)
Psoriatic arthritis	6 (7.2)
Cutaneous psoriasis	7 (8.4)
Other	9 (10.8)
Psoriasiform eruption subtype, *n* (%)	
Psoriasiform plaques	59 (71.1)
Skin-fold eruption	35 (42.2)
Scalp lesions	26 (31.3)
Palmoplantar keratodermia	14 (16.9)
Palmoplantar pustulosis	16 (19.3)
Generalized pustulosis	13 (15.7)
TNFα inhibitors, *n* (%)	
Infliximab	43 (51.8)
Adalimumab	22 (26.5)
Etanercept	16 (19.3)
Golimumab	2 (2.4)
Concomitant therapies, yes, *n* (%)	43 (51.8)
Delay between anti-tumour necrosis factor-α and psoriasiform eruption, months, mean (range)	18.5 (0–148)
Infliximab	26.5 (0–148)
Adalimumab	7.2 (2–22)
Etanercept	15 (0–108)
Golimumab	6 (4–8)

"substantial agreement" or "almost perfect agreement" in all clinical subtypes (0.73–0.92), except for the generalized pustulosis subtype, for which agreement was moderate to fair (0.34–0.64).

Then, we estimated the association between the global score of our scoring system and the underlying disease treated with TNFα inhibitors. Patients with IBD (whatever the associated disease) had a higher global score compared with those with IR or skin inflammatory diseases but without IBD involvement ($p = 0.0001$, 95% CI (–2.5512; –0.8583)). No statistically significant differences were observed between the mean elapsed time from the initiation of the anti-TNFα to the onset of the skin eruption between patients followed for IBD and patients followed for IR. Patients with IBD developed predominantly scalp and skin-fold lesions compared with those followed for other inflammatory disorders ($p = 0.009$, odds ratio (OR) 6.1486, 95% confidence interval (95% CI) (1.4192; 38.3955) and $p = 0.002$ OR 6.92, 95% CI (1.7533; 34.5866), respectively. In addition, female (F) patients had a higher global score than males (M) (mean global score: F 3.46, M 2.52) $p = 0.03$, 95% CI (0.0865; 1.8075). Female patients, who represent 70% of the patients followed for IBD in our cohort, experienced higher frequencies of severe (grade 2) scalp or skin-fold eruptions than males (severe scalp eruptions: F 90%, M 10%; skin-fold eruptions: F: 60%, M 40%).

DISCUSSION

Psoriasiform eruptions occurring during treatment with TNFα inhibitors have become a well-known adverse skin event of these biologics since their first description in 2004 (15). We first evaluated a scoring system based on 6 different patterns of psoriasiform eruptions. The intra- and inter-observer reproducibility of this score for each psoriasiform clinical subtype showed substantial intra- and inter-observer agreement, except for generalized pustulosis, which represents a minor proportion of the patients. This scoring system clearly revealed that female patients with IBD who were receiving treatment with TNFα inhibitors experienced more severe psoriasiform eruptions compared with those with other inflammatory diseases. Furthermore, they experienced predominantly scalp (sometimes evolving to severe alopecia) and skin-fold involvement compared with those without digestive involvement. Three cohort studies that recently evaluated adverse skin events and psoriasiform eruptions in patients with IBD also demonstrated this pattern, although patients without IBD were not included (6, 16, 17). The incidence rate was higher in female patients. We hypothesize that these IBD female patients may have predisposing factors for the adverse events of TNFα a inhibitors owing to a pathomechanism that needs more in-depth studies. In accordance with our hypothesis, Tillack et al. (18) recently reported 11 patients with psoriasiform eruptions, 9 with scalp involvement and 3 with severe alopecia, all of whom were treated successfully with ustekinumab, an anti-IL12/IL23, based on genetic and biological analyses showing the involvement of Th1 and Th17 cells. Another pathophysiological hypothesis that would explain the occurrence of psoriasiform eruption under treatment with TNFα inhibitors is the involvement of the type I interferon pathway as previously demonstrated (19–24). The analysis of genetic variants involving the type I IFN response in women with severe psoriasiform eruptions might therefore be of interest for future investigations. Indeed, recent evidence supports a role of the X chromosome in shaping autoimmune responses (25).

Our study has some limitations. It is a retrospective single-centre study, and the quality of the data depends on the completeness of the medical records and the clinical photographs. We cannot rule out that only patients with mild-to-severe psoriasiform eruptions were referred to the dermatology department and included in the study. In addition, while our analysis demonstrated a clear correlation between IBD and scalp and skin-fold involvement, our cohort was too small to determine the absence of a significant correlation between the treatment used, such as infliximab, which is the most widely prescribed anti-

TNFα therapy for patients with IBD, and the severity of the psoriasiform eruption or a specific clinical subtype. A larger prospective study will be necessary to answer this specific question.

In conclusion, patients with IBD being treated with TNFα inhibitors display a higher risk of developing more severe psoriasiform eruptions with predominant scalp and skin-fold eruptions than those with other inflammatory disorders. This risk should be taken into account when starting a TNFα inhibitor in this subset of patients.

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