Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: A report of 21 cases

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Received 6 September 2011; received in revised form 19 October 2011; accepted 19 October 2011

KEYWORDS
Adalimumab; Crohn’s disease; Inflammatory bowel disease; Infliximab; Psoriasis; Ulcerative colitis

Abstract

Aim: Anti-tumor necrosis factor (TNF)-alpha agents are widely used for the treatment of both inflammatory bowel disease (IBD) and psoriasis. Psoriatic skin lesions induced by anti-TNF have been described in patients with IBD. We report a case series of psoriasis induced by anti-TNF agents in IBD patients.

Methods: Systematic analysis of cases of psoriasis induced by anti-TNF in an IBD patient cohort in tertiary hospitals of Madrid.

Abbreviations

ADA, Adalimumab; CD, Crohn’s disease; CI, confidence interval; IBD, inflammatory bowel disease; IFX, infliximab; TNF, tumor necrosis factor; UC, ulcerative colitis.

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Psoriasis by anti-TNF in inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory process that includes Crohn’s disease (CD), ulcerative colitis (UC) and IBD type unclassified. Although its etiology is unknown, the immune mechanism plays an essential role in its chronic development and progression.1 Tumor necrosis factor alpha (TNFα) is a cytokine with a critical role in the pathogenesis of several inflammatory diseases such as IBD or psoriasis.2 Because of this, anti-TNF agents are among the therapeutic options available for IBD.3 Currently, the anti-TNF agents that are most commonly used in the treatment of patients with IBD are infliximab (IFX) and adalimumab (ADA). Their use has led to a very significant advance in the treatment of not only IBD, but also in the treatment of other chronic inflammatory diseases such as psoriasis or psoriatic arthritis.4 Paradoxically, the onset of psoriatic lesions has been observed in patients on anti-TNF treatment due to other diseases. The cause of this side effect has not been clearly identified yet.5 This study analyzes a case series of psoriasis induced by anti-TNF treatment in a large multicenter cohort of IBD patients in the Madrid region, Spain.

2. Methods

We retrospectively identified all cases of psoriasis observed in a multicenter cohort of patients diagnosed with IBD under IFX or ADA treatment, followed in 12 University Hospitals in the Madrid region, Spain.6 The study was approved by the Ethics Committee of the steering center (Hospital Universitario de Fuenlabrada).

In each case, psoriasis was diagnosed by the gastroenterologist and confirmed by a dermatologist who carried out a biopsy of the lesions only in those patients in whom it was considered necessary.

Information extracted from the clinical records included demographic data, type of IBD, years from diagnosis, disease location and behavior according to the Montreal classification in Crohn’s disease patients,7 anti-TNF treatment, concomitant treatments, personal and family history of psoriasis, time of onset of psoriasis, site of lesions, psoriasis phenotypes, management after psoriasis diagnosis and response to that management.

Definition of response: we defined a complete response as the disappearance of all psoriasis lesions; a partial response was defined as an improvement in lesions without complete resolution; no response was defined as the absence of improvement with the treatment performed.

2.1. Statistical analysis

Statistical analysis (SPSS; SPSS Inc., Chicago, IL, USA) included descriptive statistical analysis. Qualitative variables were expressed as percentages, with confidence intervals (CI), and quantitative variables as expressed as the mean and standard deviation or median and interquartile range, according to the presence or absence of a normal distribution. The Kolmogorov–Smirnov test was used to evaluate normality in continuous variables.

3. Results

3.1. Patients characteristics

A total of 1294 patients with IBD, 1087 (84%) CD and 207 (16%) with UC, had been treated with anti TNF-alpha agents, IFX or ADA, until January 2011. Of the 1087 patients with CD 648 (59.6%) were on IFX therapy, 371 (34.1%) were on ADA and 68 (6.3%) patients were treated with both IFX and ADA, sequentially. Of the 207 patients with UC 160 (77.3%) were on IFX therapy, 41 (19.8%) on ADA and 6 (2.9%) received both drugs sequentially. Twenty-one of them developed drug-induced psoriasis (cumulative incidence 1.62%; 95% CI 1.06%–2.47%). Fourteen (67%) patients were in treatment with IFX and seven (33%) with ADA. The mean age in patients with psoriasis due to TNF-alpha was 39 ± 10 years, 15 (71%) were females and 10 (47.6%) were smokers. Seventeen patients (81%) with IBD had CD and four (19%) were UC patients. Clinical data of the included patients are shown in Table 1.

The median duration under anti-TNF at the onset of skin lesions was 12 months (interquartile range 36–4). In all cases except in one patient who developed psoriasis after the third...
induction dose of IFX, skin lesions occurred during maintenance therapy (after a mean of 13±8 doses of the anti-TNF drug). The median of follow-up since the onset of psoriasis was 14 months (interquartile range 16.5–9). IFX induction therapy used a standard regimen of 3 intravenous infusions at the dose of 5 mg/kg at 0, 2 and 6 weeks; ADA induction therapy dose regimen was a 160 mg subcutaneous injection, followed by 80 mg 2 weeks later. All patients on maintenance therapy with ADA received the same dose: 40 mg every other week. Two patients on IFX treatment required dose escalation, one with ADA received the same dose: 40 mg every other week. 80 mg two weeks later. All patients on maintenance therapy (after a mean of 13±8 doses of the anti-TNF drug).

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3.2. De novo psoriasis

Eighteen patients developed de novo psoriasis (cumulative incidence 1.39%; 95% CI 0.88%–2.19%). Three patients (14.3%) had a history of psoriasis before treatment which reappeared with the anti-TNF therapy as plaque psoriasis. Three of these cases were managed successfully with topical agents without discontinuation of anti-TNF. Three patients (14.3% of the total patients) who developed psoriasis during ADA treatment had been treated previously with IFX without cutaneous side effects. ADA was discontinued only in one of them, while the other 2 patients were treated with topical steroids with complete response. No patient was on treatment with any of the drugs that are known to induce psoriasis (lythium, betablockers, anti-malarial drugs, and NSAID).

3.3. Location of the lesions

The most frequent sites were the limbs (62%) followed by the trunk (48%) and scalp (43%). Sixty-two percent of patients had more than one site of skin lesions. Psoriasis phenotypes were plaque psoriasis (57%), scalp psoriasis (14%), palmoplantar pustulosis (14%), generalized pustular psoriasis (5%), guttate (5%) and inverse (5%).

3.4. Management

Discontinuation of anti-TNF agent was the initial management in 4 (19%) patients and led to complete regression of lesions in only 1 of them, with no further recurrence of psoriasis after reintroduction of the anti-TNF therapy. The other 3 patients presented partial response and anti-TNF was permanently discontinued in two of them. The other patient, who had palmoplantar psoriasis, was treated with topical steroids and the anti-TNF was reintroduced after clinical response with the reappearance of mild palmoplantar psoriasis which was successfully controlled with topical therapy.

Seventeen patients (81%) were managed with topical steroids alone or in combination with other topical drugs for the treatment of psoriasis. Two of them (11.8%) were treated with concomitant UVA therapy. Seven patients (41.2%) presented a complete response to topical therapy and 9 (52.9%) had partial response. Only one patient (5.9%) did not respond to this strategy and then the anti-TNF was discontinued with complete response. The duration of therapy before response was 1–3 weeks.

Two patients were switched between anti-TNF agents (1 to infliximab and 1 to adalimumab) due to a partial response. With the second anti-TNF, both patients suffered a mild recurrence of psoriasis, with a complete response to topical treatment. In 9 patients (43%), skin biopsy was considered necessary by the dermatologist, with confirmation of psoriasis in all cases.

4. Discussion

Anti-TNF drugs are effective in patients with chronic inflammatory diseases such as IBD or psoriasis. Psoriasis is a cutaneous autoimmune disease characterized by hyperproliferation and abnormal differentiation of keratinocytes mediated by abnormal T-cell cytokine production. The incidence of psoriasis is increased in IBD patients regarding general population, with an Odds Ratio of 1.8 (95% CI: 1.4–2.4) having been described in patients with CD.

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onset of psoriatic lesions due to anti-TNF therapy are the migration of T-cells to the skin induced by interferon alpha produced by plasmacytoid dendritic cells, the activation of auto-reactive T-cells or certain infectious agents such as Streptococcus.

This paradoxical effect of the anti-TNF treatment has been described with all anti-TNF drugs and in the different diseases in which they are employed as treatment. The lesions reappear after switching the anti-TNF agent in almost all cases; this fact seems to indicate the existence of a class effect of anti-TNF agents in inducing psoriatic lesions. The prevalence of psoriasis during anti-TNF treatment in different clinical entities has been estimated at 0.6–5.3%, with an incidence of 1.04 (95% CI: 0.97–1.54) per 1000 person-years of de novo psoriasis in patients with rheumatoid arthritis. In IBD, a prevalence of 1.6–2% of psoriasis in patients on anti-TNF treatment has been reported in the literature. In our series, the cumulative incidence of psoriasis was 1.62% (1.39% incidence of de novo psoriasis), which is similar to the incidence reported in previous series, and because of the tight follow-up that patients on anti-TNF therapy receive, the probability of missing cases is low, in our opinion.

A greater absolute frequency of psoriasis cases has been reported with the use of IFX than with ADA in the treatment of IBD, as has also occurred in our experience, though this is probably due to the subsequent introduction of ADA in the treatment of IBD. Nevertheless, a significantly higher incidence of psoriasis has been reported in rheumatological diseases in patients treated with ADA versus IFX or etanercept. On the other hand, psoriasis caused by anti-TNF drugs has been reported more frequently in women (58–68%, 71% in our series), though the greater incidence of autoimmune diseases in women may skew this observation. Some authors have suggested that there is a genetic susceptibility, though the majority of patients do not have a family history. In our series, only 3 (14.3%) patients had a family history of a first or second-degree relative with psoriasis. The age of onset of psoriatic lesions is highly variable in both literature and our own experience: the mean age of our patients is 39 years old, although some pediatric cases have been reported. The timing of onset is highly variable, from days to months after having initiated the treatment with anti-TNF. An earlier onset has been reported in IBD than in patients with rheumatological disease, and in patients with ADA. Our data also show a wider distribution of the time of onset of lesions, which is clearly more frequent during maintenance therapy. A high ANA-titer could be a predisposing factor for the development of skin lesions, included psoriasis, in IBD patients under anti-TNF therapy, although more data are needed. We did not find any risk factor for the development of psoriatic lesions under anti-TNF therapy because of the limited number of cases, but this point should be evaluated in future studies prospectively designed.

The onset of psoriatic lesions during anti-TNF treatment can follow 3 primary patterns: psoriasiform eruption with typical histopathological features of a drug reaction, showing lichenoid or interface dermatitis; exacerbation of pre-existing psoriasis and de novo psoriasis. Palmoplantar pustulosis is an infrequent variant (~20%) in sporadic psoriasis. This variety appears to be more frequent in patients who are treated with anti-TNF drugs for IBD than for other diseases. In our series, only 3 patients (14.3%) had palmoplantar pustulosis that significantly differs from what has been previously reported (40–70%) in small series. In the largest series published in this regard, Rahier et al. report that 35% of patients had palmoplantar involvement. It is possible that the frequency of palmoplantar involvement in anti-TNF-induced psoriasis is not as high as previously reported, and this frequency is closer to that described in sporadic psoriasis. This form of psoriasis shows variations that are distinct from plaque psoriasis: a clear predominance in women (90%, 67% in our series) and smokers (95%, 100% in our series). Conversely, the remaining forms of psoriasis show a distribution of 51% of women and 25% of smokers at diagnosis (72% women and 39% smokers in our series). One of the possible explanations for this preponderance may be the different expression of TNF-α in the eccrine palmoplantar sweat gland and duct among patients with this form of psoriasis and plaque psoriasis. Palmoplantar pustulosis also has been associated with metal allergies and, histologically, shows an increase in mastocytes and eosinophils that is not seen in plaque psoriasis.

The evaluation by a dermatologist is recommended in order to confirm the diagnosis and to initiate the most appropriate treatment. Performing a biopsy helps to confirm the diagnosis by observing the histological characteristics of idiopathic psoriasis with an increased proliferation of keratinocytes, with large increases in cell turnover and an abnormal expression of keratins in the skin. Several therapeutic options are available depending on the severity of the lesions. Topical steroids are the treatment of choice when cutaneous involvement is mild. Treatment with the anti-TNF drug should probably be maintained given that discontinuation may exacerbate IBD and the majority of patients respond adequately to topical treatment. The majority of our patients were treated topically without discontinuation of the anti-TNF drug and had a partial or complete response with the exception of one patient in whom the anti-TNF drug was discontinued due to lack of a response with resolution of psoriatic lesions. Initial treatment with topical corticosteroids alone or concomitantly with other topical drugs (keratolytics, vitamin D analogs) or phototherapy (narrow band ultraviolet-B treatment or soak PUVA) appears to be a reasonable initial approach. If there is no response with this treatment, the risk-to-benefit of discontinuing the anti-TNF drug should be evaluated. If the psoriatic lesions are severe, covering more than 5% of the body surface area, or in the case of pustulosis, discontinuing the biological agent, together with topical or systemic treatment for psoriasis (methotrexate, retinoids, and cyclosporine) is an adequate measure. If the lesions, despite not being severe, alter the patient’s daily life, temporary suspension of the biological agent with subsequent reintroduction with strict clinical monitoring may be an option.

Similar to that which has been reported in previous series, changing the anti-TNF drug in 2 of our patients caused reappearance of the psoriatic lesions, though their intensity was mild and there was a good response to treatment.

Given the ever increasing use of anti-TNF drugs in patients with IBD, it is important to keep in mind the appearance of psoriatic lesions among the other side effects. In our experience, this paradoxical effect occurs more frequently during maintenance therapy, with the appearance of plaques on the extremities as the most frequent presentation. Though the literature refers to a predominance of palmoplantar
pustulosis, this has not been seen in our study. With the exception of the most severe or extensive forms, topical treatment of the lesions is the treatment of choice for psoriasis in these patients and the withdrawal of the anti-TNF agent is seldom needed. In all cases, we should evaluate the potential damage of psoriasis versus the current benefit that anti-TNF treatment offers in controlling IBD activity, while trying not to lose prematurely the benefit of these drugs when faced with a paradoxical effect that can be managed in the majority of cases with topical treatment without discontinuing the biological agent.

Conflicts of interest

Alicia Algaba is receiving a grant from Merck, Sharp & Dohme ( MSD). Maria Chaparro has served as speaker and has received research funding from MSD and Abbott. Javier P. Gisbert has served as speaker, consultant and advisory board member for and has received research funding from MSD and Abbott. Fernando Bermejo has served as advisory board member for MSD and has received research funding from Abbott.

Acknowledgments

None.

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