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REVIEW ARTICLE

Induction or exacerbation of psoriatic lesions during anti-TNF-α therapy for inflammatory bowel disease: A systematic literature review based on 222 cases☆

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Abstract

Background: Paradoxical cases of psoriatic lesions induced or exacerbated by anti-tumor necrosis factor (TNF)-α therapy have been reported more frequently in recent years, but data related to inflammatory bowel disease (IBD) are rare. A systematic literature review was performed to provide information about this adverse effect in patients with IBD who receive anti-TNF therapy.
Methods: Published studies were identified by a search of Medline, Embase, Cochrane, SciELO, and LILACS databases.
Results: A total of 47 studies (222 patients) fulfilled the inclusion criteria and were selected for analysis. Clinical and therapeutic aspects varied considerably among these reports. Of the 222 patients, 78.38% were diagnosed with Crohn's disease, and 48.20% were female. The mean patient age was 26.50 years, and 70.72% of patients had no history of psoriasis. Patients developed psoriasiform lesions (55.86%) more often than other types of psoriatic lesions, and infliximab was the anti-TNF-α therapy that caused the cutaneous reaction in most patients (69.37%). Complete remission of cutaneous lesions was observed in 63.96% of the cases.

☆ Research was performed at the Division of Coloproctology, Department of Surgery, School of Medical Sciences, University of the State of São Paulo (UNESP), Botucatu, SP, Brazil.

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Conclusions: We found that psoriatic lesions occurred predominantly in adult patients with Crohn's disease who received infliximab and had no previous history of psoriasis. Most patients can be managed conservatively without discontinuing anti-TNF-α therapy.

Contents

1. Introduction

In the last few years, tumor necrosis factor-alpha (TNF-α) antagonists such as infliximab and adalimumab have revolutionized the treatment of inflammatory bowel disease (IBD)[1] and psoriasis.[2] However, as the use of these biologic agents has increased, reactivation of latent infections,[3] cutaneous reactions (eczematous, neoplastic, granulomatous, and psoriatic lesions),[4,5] and other side effects[6] have been documented. These adverse cutaneous events include an increasing number of paradoxical cases of psoriatic lesions (typical psoriasis and psoriasiform lesions).[7] Because some patients may present with severe manifestations that require discontinuing the use of biologic agents and subsequently risk aggravating the underlying disease, physicians who treat these patients should understand the clinical manifestations of this side effect and therapeutic approaches.[4,5]

This paradoxical phenomenon has been described in the literature.[7] However, studies reporting psoriatic lesions induced or exacerbated by TNF-α antagonists are largely heterogeneous regarding the therapeutic agent involved, underlying disease, treatment duration, personal and family history of psoriasis, type of cutaneous eruption, and therapeutic approaches and outcomes.[4] Furthermore, in the largest study available on this topic, patients with IBD comprised only 19.80% of the study population, whereas rheumatologic patients comprised 73.91%.[7]

We therefore conducted a systematic literature review to better understand the induction or exacerbation of psoriatic lesions (typical psoriasis or psoriasiform lesions) by TNF-α antagonists in patients with IBD. We also discuss the possible pathogenesis of this phenomenon.

2. Methods

2.1. Strategy for article search and selection

We performed a systematic literature review by searching the Medline (PubMed), Embase, Cochrane, SciELO, and LILACS databases for articles published from January 2004 to October 2011 (the final literature review was performed on October 30, 2011). To identify all relevant articles published in English (clinical trials, case series and reports, and letters to the editor) about psoriasis or psoriasiform lesions induced or exacerbated by TNF-α antagonists (infliximab, adalimumab, and certolizumab) in patients with IBD, we used the following search terms: "adalimumab", "anti-TNF-α", "biological", "certolizumab", "Crohn", "inflammatory bowel disease", "IBD", "infliximab", "TNF inhibitor", "tumor necrosis factor alpha inhibitor", and "ulcerative colitis" combined with the terms "adverse event", "cutaneous adverse effects", "exacerbated", "guttate", "new-onset", "paradoxical", "plaque", "pustular" "psoriasis", "side effect", and "skin reactions". Relevant secondary references including abstracts published in the annals of national and international congresses were also included. Additionally, the reference lists of these articles were examined to identify additional studies. Repeated studies were considered only as a search source. Studies were selected based on their titles (and abstracts if they were available) and

retrieved for more detailed analysis. Theoretical review articles that did not include additional cases were excluded, as were studies that did not present information about IBD separately from other diseases. Principles of the PICO strategy[8] were adopted to ensure quality.

2.2. Data extraction and analysis

Two authors independently extracted data from each article, and disagreements were resolved by consensus. Each study was individually reviewed to identify data concerning age, gender, personal and family history of psoriasis, biological medication administered, duration of clinical latency, lesion type (typical psoriasis or psoriasiform lesions), performance of cutaneous biopsy, therapeutic approaches and outcomes, and clinical IBD development. Nonspecific or unavailable information was designated as unknown or unstated data. The selected data were compiled in Microsoft Excel. Because this information did not provide sufficient data evidence or meta-analysis data, a simple descriptive analysis was performed.

3. Results

Using the inclusion and exclusion criteria, 47 publications were identified (42 peer-reviewed papers and five meeting abstracts) with a total of 222 patients with IBD who experienced induction or exacerbation of psoriatic lesions during anti-TNF-α therapy.[9–55] The number of reported cases has increased over the years (Fig. 1). However, the reporting of various aspects of the cases was inconsistent across studies. For example, gender, age, duration of clinical latency, histopathological evaluation, therapeutic approach, and clinical outcomes were not described in all studies. The main demographic and clinical characteristics of the 222 IBD patients are summarized in Tables 1 and 2.

3.1. Demographic aspects

In this review, 107 patients (48.20%) were female, and the mean patient age was 26.50 years. Most patients did not report a personal and/or family history of psoriasis (70.72%), and most received anti-TNF-α therapy for the treatment of

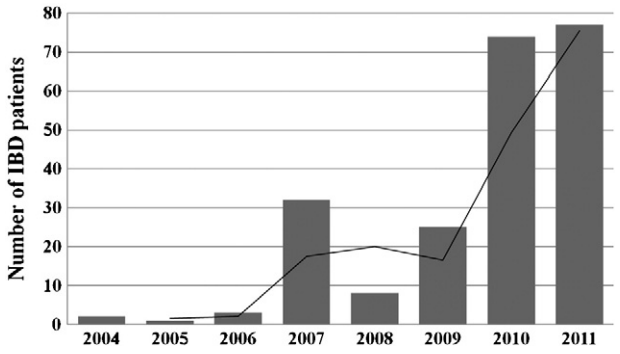

Figure 1 Number of patients with inflammatory bowel disease (IBD) who experienced psoriatic lesions induced or exacerbated by anti-TNF-alpha therapy annually, based on analysis of studies published through October 2011.

Table 1 Summary of demographic characteristics of 222 inflammatory bowel disease patients with psoriatic lesions induced or exacerbated by tumor necrosis factor-alpha antagonists published until October 2011.

Variables	Patients (No. = 222)
Primary disease, no. (%)	
CD	174 (78.38)
UC	25 (11.26)
IBD [a]	23 (10.36)
Disease associated, no. (%)	4.0 (1.80)
Gender, no. (%)	
Female	107 (48.20)
Male	85 (38.29)
Unknown	30 (13.51)
Median age (years)	26.50 (8–54)
Unknown, no. (%)	35 (15.76)
Previous history of PS, no. (%)	
No (*de novo* or induced PS)	157 (70.72)
Personal (exacerbated pre-existing PS)	20 (9.00)
Familiar	14 (6.31)
Unknown	31 (13.96)

UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease; PS, psoriasis.

[a] Ulcerative colitis or Crohn's disease.

Table 2 Summary of main findings of 222 inflammatory bowel disease patients with psoriatic lesions induced or exacerbated by tumor necrosis factor-alpha antagonists published until October 2011.

Variables	Patients (No. = 222)
Anti-TNF-α involved, no. (%)	
Infliximab	154 (69.37)
Adalimumab	50 (22.52)
Certolizumab	6.0 (2.70)
Anti-TNF-α [a]	12 (5.41)
Clinical latency (months)	13.79 (0.5–105)
Unknown, [b] no. (%)	40 (18.01)
Type of cutaneous lesion, no. (%)	
Psoriasiform lesions	124 (55.86)
Plaque-type PS	46 (20.72)
Pustular-type PS	8.0 (3.60)
More than one form of PS	8.0 (3.60)
Guttate-type PS	3.0 (1.35)
Diffuse-type PS	3.0 (1.35)
Other	10 (4.50)
Unknown	20 (9.00)
Cutaneous biopsy, no. (%)	
Yes	75 (33.78)
No	76 (34.23)
Unknown	71 (31.98)

Anti-TNF-α, tumor necrosis factor-alpha antagonists; PS, psoriasis.

[a] Infliximab or adalimumab.
[b] Some studies have reported only the number of doses administered.

Crohn's disease (78.38%). In two patients (0.90%), IBD was associated with spondyloarthritis, and in two others (0.90%), IBD was associated with ankylosing spondylitis.[18,26,51]

3.2. TNF-α inhibitors

Three anti-TNF-α agents (infliximab, adalimumab, and certolizumab) were responsible for the induction or exacerbation of psoriatic lesions in patients with IBD, and 154 cases (69.37%) were related to infliximab infusions. The mean latency time between initiation of anti-TNF-α therapy and onset of the psoriatic lesions was 13.79 months; however, latency was up to 105 months in some cases.[52]

3.3. Clinical manifestations

Clinical presentation varied; psoriasiform lesions were the most common form of psoriasis (55.86%), followed by typical plaque-type lesions (20.72%), and pustular-type lesions (3.60%). Six patients (2.70%) concomitantly presented with alopecia,[40,41,55] one patient (0.45%) presented with palmoplantar pustulosis,[49] and another patient (0.45%) presented with palmoplantar pustulosis and psoriatic arthritis.[47]

3.4. Histopathological evaluation

Histopathological findings (epithelial hyperplasia with acanthosis and hyperkeratosis, parakeratosis, lymphocytic infiltration of the epidermis, and dilated capillaries) confirmed the diagnosis of psoriasis in 75 of the patients included in this review. Less frequently, histopathological evaluations showed a lichenoid aspect or spongiosis.[29,31,38,44,51,55]

3.5. Therapeutic approach

In 142 patients (63.96%), there was complete remission of cutaneous lesions with different therapeutic approaches (Tables 3 and 4). Topical corticosteroid treatment was the antipsoriatic therapy used most often (72.52%). Anti-TNF-α therapy was withdrawn in 86 patients (38.74%), resulting in the complete resolution of 71 cases (31.98%). In 87 patients (39.19%) for whom anti-TNF-α therapy was not suspended, 64 cases (28.83%) showed complete resolution of the lesions. In 29 patients (13.06%), the anti-TNF-α agent that triggered the psoriatic lesions was replaced with another anti-TNF-α agent, with recurrence or aggravation of psoriatic lesions in most cases (9.46%).

3.6. Management of the IBD following withdrawal of TNF-α antagonist

In the studies[16,18,27,33,37,41,44,42,45,47,48] describing IBD development after discontinuation of TNF-α antagonists, gastrointestinal symptoms were controlled after the reintroduction of infliximab[16] or with the introduction of adalimumab,[27,42,47,48] certolizumab,[37] azathioprine,[41] methotrexate,[33,45] mesalazine and corticosteroids,[47] or methotrexate and corticosteroids,[44] demonstrating the considerable heterogeneity of approaches used after discontinuation of anti-TNF-α therapy. Psoriatic lesions recurred in cases in which etanercept (used to treat associated spondyloarthritis)[18] and adalimumab[27,42,48] were given.

Table 3 Summary of antipsoriatic therapeutic approaches adopted in the 222 inflammatory bowel disease patients with psoriatic lesions induced or exacerbated by tumor necrosis factor-alpha antagonists published until October 2011.

Therapeutic approaches	Patients (No. = 222)
Antipsoriatic therapy, [a] no. (%)	
Topical corticosteroid	161 (72.52)
Vitamin D analogues	62 (27.93)
Phototherapy	24 (10.81)
Methotrexate	9.0 (4.05)
Systemic corticosteroid	5.0 (2.25)
Cyclosporine	3.0 (1.35)
Azathioprine + systemic corticosteroid	2.0 (0.90)
Azathioprine + mycophenolate mofetil	2.0 (0.90)
6-Mercaptopurine	1.0 (0.45)
Unknown	43 (19.37)

[a] Isolated or associated.

4. Discussion

Recognition of the role played by the proinflammatory cytokine TNF-α in the pathogenesis of autoimmune inflammatory diseases (e.g., rheumatoid arthritis, IBD, and psoriasis)[56]

Table 4 Summary of therapeutic approaches and clinical outcomes in the 222 inflammatory bowel disease patients with psoriatic lesions induced or exacerbated by tumor necrosis factor-alpha antagonists published until October 2011.

Management	Patients (No. = 222)
Anti-TNF-α stopped, [a] no. (%)	
Yes	86 (38.74)
No	87 (39.19)
Unknown	20 (9.00)
Anti-TNF-α switched, no. (%)	29 (13.06)
Clinical response related to anti-TNF-α, no. (%)	
Completely resolved off anti-TNF-α	71 (31.98)
Partially resolved off anti-TNF-α	10 (4.50)
No resolution off anti-TNF-α	2.0 (0.90)
Unknown	3.0 (1.35)
Completely resolved on anti-TNF-α	64 (28.83)
Partially resolved on anti-TNF-α	7.0 (3.15)
No resolution on anti-TNF-α	2.0 (0.90)
Unknown	4.0 (1.80)
Resolved with anti-TNF-α switched	7.0 (3.15)
Recurrence or aggravation with anti-TNF-α switched	21 (9.46)
Unknown	1.0 (0.45)

Anti-TNF-α, tumor necrosis factor-alpha antagonists.

[a] Isolated or associated.

led to the development of TNF-α antagonists, which enabled important advances in the treatment of these disabling chronic diseases.[57] However, paradoxical cases of psoriatic lesions induced or exacerbated by anti-TNF-α agents have increasingly been reported worldwide.[7]

Although the first case of infliximab-induced psoriasis was described in a patient with Crohn's disease,[9] most of the evidence concerning this phenomenon was obtained from the rheumatologic literature.[58] An increasing number of IBD patients have developed this cutaneous reaction, as described in subsequent reviews,[7,21,23,52,59] and the latest review[52] included 120 IBD patients. In the present review, 102 additional cases were included and analyzed for a total of 222 IBD patients with this reaction.[9–55] Five studies[60–64] were not included in this review, because it was not possible to extract only the data regarding the clinical development of patients with IBD.

The present review showed that this adverse event was more frequently reported in adult patients who did not have a personal or family history of psoriasis, which is consistent with the results of previous studies.[7,58,59] Pustular psoriasis was the most frequently described form of psoriasis (56%) in a recent review[7] that included patients with several underlying diseases; however, among IBD patients, plaque-type psoriasis was the most common form (61%). In contrast, psoriasiform lesions were the most frequently reported cutaneous lesions (55.86%) in our study. Because there is no clear definition of psoriasiform lesion, many lesions classified as psoriasiform may actually be the classic type of psoriasis.

The review[7] that analyzed the largest number of cases (207 patients with different underlying diseases) reported that the latency between anti-TNF-α administration and onset of psoriatic lesions was extremely variable, similar to what was observed in the present review. These cases involved different TNF-α inhibitors (infliximab, adalimumab, certolizumab, and etanercept); therefore, this paradoxical effect is a reaction to a pharmacologic class of drugs rather than a reaction to a specific drug.[39,43] The present review and previous reviews[7,21,23,52,59] found that more cases involved infliximab than any other anti-TNF-α agent, most likely because this was the first biological agent available on the market.[52,59]

The incidence of psoriasis among IBD patients can reach 11%, whereas it is only 1.5% in the general population.[65,66] In addition, the same genes (interleukin [IL]23R, IL12B, and tyrosine kinase 2) predispose for both IBD and psoriasis,[67] which may account for the high rate of psoriatic lesions in IBD patients treated with anti-TNF-α agents.[65–67] However, several aspects of this phenomenon provide evidence for the idea that it is a side effect of anti-TNF-α agents. These include the absence of a personal or family history of psoriasis in most reported cases, the increasing number of reported cases, the temporal relationship between anti-TNF-α treatment and the appearance of cutaneous lesions, and the clinical improvement observed after discontinuation of therapy and subsequent recurrence of psoriatic lesions after switching to another anti-TNF-α agent.

The mechanism underlying the induction or exacerbation of psoriatic lesions by anti-TNF-α antagonists is not clear.[7,47,48] The most widely accepted hypothesis is based on an interaction between increased interferon-alpha (IFN-α) levels and reduction in TNF-α levels.[7,31,41] Plasmacytoid dendritic cells appear to induce psoriasis through IFN-α production. These cells infiltrate the skin and produce IFN-α during the initial phase of psoriasis.[68,69] Plasmacytoid cells are normally downregulated by TNF-α, which inhibits the maturation of their hematopoietic precursors.[39] Therefore, TNF-α inhibition with the biological agent may result in uncontrolled IFN-α production, thereby inducing or exacerbating psoriasis.[39,41] Changed lymphocytes can also participate in this process through the expression of the CXCR3 receptor.[31,70]

Several studies[31,70,72] have reported findings that support the role of IFN-α in the onset of psoriatic lesions during anti-TNF-α therapy. One study[31] reported high levels of the protein MxA (marker for IFN signaling) in the inflammatory cells of skin samples of psoriasis induced by anti-TNF-α. Another study[70] reported higher levels of IFN-α in the psoriatic lesions of patients receiving anti-TNF-α therapy compared with spontaneous psoriasis lesions. Furthermore, there are cases of psoriasis that developed or worsened after injection of recombinant IFN-α[71] or topical application of imiquimod (a potent IFN-α inducer).[72]

The time between anti-TNF-α administration and development of psoriatic lesions varies widely,[7] suggesting that an environmental trigger may also be involved.[52] In addition, TNF-α antagonists have been administered to more than 2 million patients worldwide[57] and cases of this adverse cutaneous reaction are numerous, indicating that this phenomenon may be related to a genetic predisposition.[7,36] Genetic studies may be useful to identify genetically susceptible patients and elucidate the immunopathogenic mechanism.[7]

Patients who have psoriatic lesions while undergoing anti-TNF-α therapy must be evaluated by a dermatologist.[42,54] A detailed evaluation (clinical history, physical examination, and cutaneous biopsy, if necessary)[23,42] can eliminate acute exanthematous pustulosis and other cutaneous diseases to confirm the diagnosis of psoriasis.[23,39] Although psoriatic lesions in 34.23% of the IBD patients in this review were clinically diagnosed, the authors of the present review and others[7,23,39] emphasize that it is important to correlate clinical manifestations with histopathological findings,[39] especially in cases where lesions are present in sites that are not common for psoriasis (e.g., face or flexor areas) or if the skin lesions do not show the characteristics of psoriasis. Additionally, infections, mechanical stressors, trauma (including emotional trauma), and medications that trigger or exacerbate psoriasis (e.g., beta-blockers, antimalarial drugs[73]) must also be excluded.[7,23,45]

To date, no guidelines exist for treating cutaneous side effects of TNF-α antagonists.[54] A wide range of therapeutic approaches have been used to treat IBD patients who develop psoriatic lesions during anti-TNF-α therapy, and there is disagreement as to whether discontinuation of the biological agent is needed to achieve complete resolution of the lesions. Regardless of the underlying disease, discontinuation of anti-TNF-α therapy has culminated in the complete resolution of cutaneous lesions in 24% of cases.[7] Two reviews[7,59] reported that discontinuing anti-TNF-α therapy has been particularly successful in IBD patients, and complete regression of cutaneous lesions was observed in 46% of patients, whereas complete regression of cutaneous lesions was observed in only 17% of patients who continued treatment with the anti-TNF-α agent.[7] However, decisions must be cautious because only 18

to 41 IBD patients were evaluated in these reviews.[7,59] As the number of reported cases increases, therapeutic approaches and outcomes must be re-evaluated. With the inclusion of a larger number of patients in the present review, we found that the most common approach has been to continue anti-TNF-α therapy despite adverse cutaneous reactions. Furthermore, aggravation or recurrence of the psoriatic lesions was common despite switching anti-TNF-α agents.

Based on the evidence that discontinuation of biological therapy can aggravate gastrointestinal manifestations[16,18,27,33,37,41,44,42,45,47,48] and the analysis of the 47 articles (222 patients)[9–55]included in this review, we believe that most IBD patients with anti-TNF-α-related psoriatic lesions should be treated using a conventional approach (topical corticosteroids, emollients, keratolytic therapy, vitamin D analogs, phototherapy, methotrexate and/or cyclosporine) while continuing the biological therapy. However, discontinuation of anti-TNF-α therapy should be considered, particularly in generalized, recalcitrant cases and when quality of life is severely impaired. After resolution of the cutaneous lesions, reintroduction of biological therapy must be considered.

Patients with aggressive IBD who require discontinuation of biological therapy may experience clinical deterioration. Therefore, continuing biological therapy is recommended along with standard treatment for psoriasis. However, alternative therapies for IBD (e.g., antibiotics, mesalazine, and azathioprine) should be considered. Although replacing the anti-TNF-α antagonist with another agent of the same class has been successful in 31.5% of the analyzed cases, further studies are still required to better characterize the efficacy and safety of this approach.[38,52,64]

Our review has some limitations, such as its retrospective design, lack of complete data in some studies, and heterogeneity of the studies included. It is important that prospective cohort studies are designed to clarify the incidence and prevalence of this adverse reaction and establish guidelines for its diagnosis and treatment.

5. Conclusion

Although psoriatic lesions that are induced or exacerbated by anti-TNF-α therapy in patients with IBD have been reported, their immunopathogenic mechanisms have not yet been elucidated. This cutaneous adverse reaction occurs predominantly in adults with Crohn's disease receiving infliximab therapy who have no personal or family history of psoriasis. For most patients, the therapeutic approach should be based on standard antipsoriatic therapy, without discontinuing or switching the anti-TNF-α agent.

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None.

Conflict of interest

Flavio Steinwurz is a speaker and consulting physician for MSD and Abbott. Ricardo Romiti is a speaker and consulting physician for Abbott, MSD, Pfizer, and Janssen-Cilag.

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