

THE ONSET OF PSORIASIS DURING THE TREATMENT OF INFLAMMATORY BOWEL DISEASES WITH INFLIXIMAB: should biological therapy be suspended?

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ABSTRACT – *Context* - Several paradoxical cases of infliximab-induced or-exacerbated psoriatic lesions have been described in the recent years. There is disagreement regarding the need to discontinue infliximab in order to achieve the resolution of these adverse cutaneous reactions specifically in inflammatory bowel disease (IBD) patients. *Objective* - To systematically review the literature to collect information on IBD patients that showed this adverse cutaneous reaction, focusing mainly on the therapeutic approach. *Methods* - A systematic literature review was performed utilizing Medline, Embase, SciELO and Lilacs databases. Published studies were identified, reviewed and the data were extracted. *Results* - Thirty-four studies (69 IBD patients) met inclusion criteria for review. There was inconsistency in reporting of some clinical and therapeutic aspects. Most patients included had Crohn's disease (89.86%), was female (47.83%), had an average age of 27.11 years, and no reported history of psoriasis (84.05%). The patients developed primarily plaque-type psoriasis (40.58%). There was complete remission of psoriatic lesions in 86.96% of IBD patients, existing differences in the therapeutic approaches; cessation of infliximab therapy led to resolution in 47.83% of cases and 43.48% of patients were able to continue infliximab therapy. *Conclusion* - As increasing numbers of IBD patients with psoriasis induced or exacerbated by infliximab, physicians should be aware of its clinical manifestations so that appropriate diagnosis and treatment are properly established. The decision whether to continue or discontinue infliximab should be individualized.

HEADINGS – Inflammatory bowel disease. Infliximab. Psoriasis. Biological therapy.

INTRODUCTION

Infliximab is a chimeric IgG1 monoclonal antibody (75% human and 25% murine) that inhibits the tumor necrosis factor-alpha (anti-TNF- α). It has been efficient in the treatment of inflammatory bowel diseases (IBD) for more than a decade⁽²⁰⁾; however, since 2004, the number of paradoxical cases of psoriasis induced or exacerbated by infliximab described in IBD patients have increased^(6, 10, 14, 32, 37), since TNF- α inhibition determines therapeutic benefits in psoriasis⁽⁴⁾.

With this regard, there is disagreement in the literature as to the need to suspend biological therapy in order to achieve complete resolution of these cutaneous lesions (psoriasis), specifically in IBD patients. Some authors^(6, 14) agree to its withdrawal while others^(10, 32, 37) report that the biological must be maintained.

Due to risk for IBD deterioration after suspension of the TNF- α inhibitory molecule, the authors of the present study aimed at presenting a systematic litera-

ture review on this intriguing phenomenon (psoriasis induced or exacerbated by infliximab) specifically in patients with IBD, mainly focusing on its therapeutic aspects.

METHODS

Search strategy

A systematic literature review was performed using the Medline (PubMed), Embase, SciELO and Lilacs databases from January 2004 to September 2011 so as to collect all relevant articles in English specifically addressing IBD patients who developed psoriasis after receiving infliximab by searching up the following terms “anti-TNF- α ”, “biological”, “Crohn” “inflammatory bowel disease”, “infliximab”, “TNF inhibitor”, “tumor necrosis factor alpha inhibitor” and “ulcerative colitis” combined with terms “adverse event”, “exacerbated”, “guttate”, “new-onset”, “plaque”, “pustular” and “psoriasis”.

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Study selection, data extraction and analysis

The identified studies were selected for analysis based on their titles and abstracts whenever they were available. The studies that did not contain specific information on IBD patients who developed psoriasis during infliximab therapy were excluded. Each study included was individually reviewed in order to collect data concerning age, gender, personal and family history of psoriasis, biological medication administered, clinical latency, cutaneous lesion type, cutaneous biopsy performance, therapeutic approaches and outcomes. Two authors were responsible for data extraction independently and disagreements were resolved by consensus. Considering that such information does not provide sufficient data evidence or meta-analysis data, a critical and descriptive analysis was performed.

TABLE 1. Summary of data on 69 inflammatory bowel disease patients who developed psoriasis after administration of infliximab published until September 2011

Characteristics	Patients (n = 69)
Primary disease, n (%)	
CD	62 (89.86)
UC	5.0 (7.25)
IBD *	2.0 (2.89)
Gender, n (%)	
Female	33 (47.83)
Male	32 (46.38)
Unknown	4.0 (5.80)
Median age (years)	27.11 (8–54)
Unknown, n (%)	6.0 (8.70)
Previous history of PS, n (%)	
No (de novo or induced PS)	58 (84.05)
Personal (exacerbated pre-existing PS)	3.0 (4.35)
Familiar	4.0 (5.80)
Unknown	4.0 (5.80)
Clinical latency (months)	14.15 (0.5–42)
Unknown **, n (%)	3.0 (4.35)
Type of skin lesion, n (%)	
Plaque-type PS	28 (40.58)
Pustular-type PS	6.0 (8.70)
Psoriasiform lesions	5.0 (7.25)
More than one form of PS	6.0 (8.70)
Guttate-type PS	2.0 (2.90)
Diffuse-type PS	2.0 (2.90)
Other	6.0 (8.70)
Unknown	14 (20.29)

UC = ulcerative colitis;

CD = Crohn disease;

IBD = inflammatory bowel disease;

PS = Psoriasis;

* = Ulcerative colitis or Crohn disease;

** = Some studies have reported only the number of doses administered

RESULTS

In the evaluated period and based on the previously described reviewing methodology, 69 patients with psoriasis induced or exacerbated during IBD therapy were found^(1-3, 5, 7-9, 11, 12, 15-18, 21-23, 25-31, 33-36, 38-44). The cases were described in 34 publications (33 peer-reviewed and one abstract of congress). Some information, such as gender, age, latency time between infliximab administration and the onset of psoriasis, cutaneous biopsy performance, therapeutic approach and clinical outcomes, was not described in all studies. A summary with the main demographic and clinical characteristics of the 69 IBD patients found is included in Table 1.

Demographics

Most of the patients who developed psoriasis received infliximab in order to control Crohn's disease (89.86%). They were females (47.83%), with a mean age of 27.11 years and did not report a personal and/or family history of psoriasis (84.05%). In three patients, pre-existing psoriasis was exacerbated^(25, 26), and in three others, there was a positive family history of psoriasis^(12, 29, 30).

TABLE 2. Summary of therapeutic approaches and clinical outcomes in the 69 inflammatory bowel disease patients who developed psoriasis after administration of infliximab published until September 2011

Management	Patients (n = 69)
Antipsoriatic therapy *, n (%)	
Topical corticosteroid	51 (73.91)
Phototherapy	7.0 (10.14)
SCE	4.0 (5.78)
Metotrexato	3.0 (4.35)
SCE + AZA	2.0 (2.90)
Cyclosporine	2.0 (2.90)
MM + AZA	1.0 (1.45)
6-Mercaptopurine	1.0 (1.45)
Unknown	11 (15.94)
IFX stopped, n (%)	
Yes	35 (50.72)
No	30 (43.48)
Unknown	4.0 (5.78)
Clinical outcomes related to IFX, n (%)	
Completely resolved off IFX	33 (47.83)
Partially resolved off IFX	-
No resolution off IFX	2.0 (2.90)
Completely resolved on IFX	27 (39.13)
Partially resolved on IFX	3.0 (4.35)
No resolution on IFX	-

AZA = azathioprine;

IFX = infliximab;

MM = mycophenolate mofetil;

SCE = systemic corticosteroid;

* = Isolated or associated

Biological therapy

The mean time of clinical latency between the beginning of infliximab infusions and the onset of psoriasis was of 14.15 months. In addition to infliximab, some patients also developed psoriasis with the administration of adalimumab^(5, 8, 17) and etanercept (used for associated spondyloarthritis)⁽⁵⁾.

Clinical presentation

Clinical presentation varied among the IBD patients who developed psoriasis during infliximab infusions, and there was predominance of plaque-type psoriasis (40.58%), followed by the pustular type (8.70%), and psoriasiform eruptions (7.25%).

Cutaneous biopsy

In this review, the histopathological findings (lymphocytic infiltrate in the epidermis, epithelial hyperplasia with acanthosis and hyperkeratosis, parakeratosis, and dilated capillaries) in the 42 IBD patients submitted to cutaneous biopsy confirmed the clinical hypotheses of psoriasis^(1, 2, 7, 23, 27, 34, 38, 39, 41, 44).

Treatment

The majority of patients (86.66%) showed complete remission of cutaneous lesions; however, therapeutic approaches varied (Table 2). Topical corticosteroids were the main anti-psoriatic therapy used (73.91%). Infliximab was suspended, which resulted in psoriasis resolution in 47.83% of cases while cutaneous lesions receded even with subsequent infliximab infusions in 43.48% of cases.

DISCUSSION

Although the first case of infliximab-induced psoriasis was described in a 46-year old patient with Crohn's disease⁽⁴²⁾, the majority (73.91%) of subsequent reports have occurred in rheumatologic patients⁽⁶⁾. According to the present review, 69 cases^(1-3, 5, 7-9, 11, 12, 15-18, 21-23, 25-31, 33-36, 38-44) of psoriasis induced or exacerbated by infliximab were reported in IBD patients. Some studies^(10, 13, 24, 32, 37, 45) did not participate in this descriptive analysis because it was not possible to extract data on IBD patients only under infliximab therapy and/or because they did not contain information on such patients' clinical development.

Regardless of the base disease, the cases of psoriasis induced or exacerbated by anti-TNF- α seem to predominate in females (65%), at any age (mean of 44.9 years) and without a history of psoriasis (85%)⁽⁶⁾, similarly to the IBD patients included in the present review. Also, without considering underlying diseases, the predominant form of psoriasis was the pustular type (56%)⁽⁶⁾, which differs from the IBD patients in this and in other reviews including a smaller number of patients^(6, 14), who primarily showed the plaque-type psoriasis.

The clinical latency period between anti-TNF- α administration and psoriasis development is extremely variable⁽⁶⁾. It is of 9.5 months in patients with different base diseases⁽⁷⁾ and of 14.15 months in the IBD patients presented in this review.

In other studies^(6, 7, 14, 44) most cases were described in patients treated with infliximab (the object of this study). However, as there are cases involving different TNF- α inhibitors (infliximab, adalimumab, etanercept, and certolizumab^(6, 7, 10, 14, 44), such side effect has been described as a reaction to the pharmacological class, and not specifically to one drug^(3, 15, 18).

The pathogenesis of this paradoxical phenomenon (psoriasis subsequent to infliximab therapy) is still not completely known, and it is believed that plasmacytoid dendritic cells (natural IFN- α producers) are capable of inducing psoriasis through IFN- α production^(6, 18, 22). Since such plasmacytoid cells are usually downregulated by TNF- α , its inhibition by the biological may determine increased and uncontrolled IFN- α production and consequently induce or exacerbate psoriasis^(6, 18, 22).

Although in some patients, the diagnosis of psoriasis induced or exacerbated by infliximab was based only on the clinical aspect of cutaneous lesions, it has been described that patients must be evaluated by a dermatologist with the purpose to confirm the psoriasis hypothesis (correlating clinical manifestations with histopathological findings⁽³⁵⁾) and discard similar cutaneous diseases (e.g., acute exanthematous pustulosis) and other psoriasis-triggering factors (e.g., infections and other medications)^(6, 7).

In the literature, various therapeutic approaches have been described for the cases of psoriasis subsequent to infliximab administration. Regardless of the base disease, anti-TNF- α interruption or replacement culminated in the resolution of cutaneous lesions in 24% and 15% of cases, respectively^(6, 8). In other reviews^(6, 14), such strategy (interruption or replacement of the inhibitory molecule) has been more successful especially in IBD patients; resolution of cutaneous lesions after anti-TNF- α discontinuation was observed in 46%-88% of cases^(6, 14) while only 34% of patients showed resolution of cutaneous lesions without suspension of the biological⁽⁶⁾. However, these data must be cautiously interpreted because anti-TNF- α withdrawal can determine the aggravation of intestinal manifestations^(3, 8, 17, 31, 38, 40).

Based on the present review^(1-3, 5, 7-9, 11, 12, 15-18, 21-23, 25-31, 33-36, 38-44), the IBD patients developing psoriasis during infliximab therapy must be treated by the conventional psoriasis approach (topical corticosteroids, phototherapy, vitamin-D analogs, methotrexate and/or cyclosporine) without the need to suspend infliximab. The discontinuation of infliximab infusions must be considered, especially in generalized, recalcitrant cases of psoriasis with important impact on quality of life. After the resolution of skin lesions, the reintroduction of biological therapy must be considered. In cases where it is necessary to suspend the biological, but IBD is aggressive, and infliximab withdrawal may lead to clinical deterioration, the adoption of alternative therapeutic forms (e.g., antibiotics, mesalazine, or azathioprine) for IBD control, or infliximab replacement for another inhibitory molecule must be considered. Although the administration of systemic corticosteroids has been used in some cases^(2, 23, 41, 44), its introduction must be carefully analyzed due to the existing risk for psoriasis rebound⁽¹⁹⁾.

CONCLUSIONS

As the number of IBD patients showing psoriasis after receiving infliximab increases, physicians dealing with such patients must be aware of their clinical manifestations so that an accurate diagnosis can be made and adequate therapy can be instituted. The decision about continuing or suspending biological therapy must be individualized and based on the response to the antipsoriatic approach

(standard therapy), psoriasis severity, possibility of using alternative therapeutic forms for IBD and potential deleterious effect on IBD.

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RESUMO – *Contexto* - Inúmeros casos paradoxais de lesões psoriásicas induzidas ou exacerbadas por infliximabe têm sido descritos nos últimos anos, existindo discordância quanto à necessidade de interromper o infliximabe, para se conseguir a resolução destas reações adversas cutâneas especificamente em pacientes com doença inflamatória intestinal (DII). *Objetivo* - Revisar sistematicamente a literatura para coletar informações sobre pacientes com DII, que apresentaram essa reação adversa cutânea, focando principalmente na abordagem terapêutica. *Métodos* - Uma revisão sistemática da literatura foi realizada utilizando as bases de dados Medline, Embase, SciELO e Lilacs. Os estudos publicados foram identificados, analisados e os dados extraídos. *Resultados* - Trinta e quatro estudos (69 pacientes com DII) preencheram os critérios de inclusão para a revisão, existindo inconsistência no relato de alguns aspectos clínicos e terapêuticos. A maioria dos pacientes incluídos tinha doença de Crohn (89,86%), era do sexo feminino (47,83%), tinha idade média de 27,11 anos, e sem antecedentes de psoríase (84,05%). Os pacientes desenvolveram principalmente a psoríase tipo placa (40,58%). Houve remissão completa das lesões psoriásicas em 86,96% dos pacientes com DII, existindo diferenças nas abordagens terapêuticas; interrupção do infliximabe determinou a resolução em 47,83% dos casos e 43,48% dos pacientes continuaram recebendo o tratamento com infliximabe. *Conclusão* - Uma vez que cresce o número de pacientes com DII com psoríase induzida ou agravada por infliximabe, os médicos devem estar cientes de suas manifestações clínicas, para que o diagnóstico e tratamento adequados sejam devidamente estabelecidos. A decisão sobre continuar ou interromper o infliximabe deve ser individualizada.

DESCRIPTORIOS – Doença inflamatória intestinal. Infliximabe. Psoríase. Terapia biológica.

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