IBD REVIEWS REVIEW ARTICLE

Dermatological manifestations associated to the use of anti-tumor necrosis factor therapy

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Abstract

Anti-tumor necrosis factor (anti-TNF) drugs such as infliximab, adalimumab, and certolizumab pegol have been largely used for the treatment of inflammatory bowel diseases (IBD) for the past two decades. These biological agents showed efficacy and good safety profile in Crohn's disease patients as well as in ulcerative colitis. The anti-TNF drugs have demonstrated good results not only just in the induction of remission but also in the long-term maintenance. Nevertheless, the occurrence of autoimmune processes related to anti-TNF agents is not rare. In this group, cutaneous inflammatory manifestations have increasingly been reported, most frequently describing the occurrence of psoriasis and psoriasiform eruptions presenting as a paradoxical reaction. Besides, a wide spectrum of inflammatory dermatological conditions has been associated to the use of anti-TNF drugs, such as vasculitis, lichenoid and acneiform eruptions, sarcoidosis, multiform erythema, toxic epidermal necrolysis, atopic dermatitis exacerbation, and alopecia. The precise explanation for this phenomenon remains unknown, but different explanations have been postulated. We made a retrospective study to understand when and how these skin lesions occur. It's important to point out that in the vast majority of cases, skin lesions are mild and suspension or switching of treatment is unnecessary. (IBD Rev. 2018;4:99-105)

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Introduction

Both inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are a huge challenge for the treating physician as these are life-long incurable conditions with a significant impact on quality of life and personal burden often causing a reduction in work capacity and restrictions of leisure time[1,2]. Among different potential therapeutic approaches, current and evolving biologic therapies include the blockade of key inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α)[3,4].

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Anti-TNF-α biologic therapies induce a fast clinical response, promote mucosal healing, have a steroid-sparing effect, improve quality of life, and reduce hospitalization rates[4,5]. However, anti-TNF-α agents have been associated with important side effects, some of which only became apparent postmarketing[6-8].

In this context, the number of cases of the cutaneous lesions induced or exacerbated by anti-TNF-α biologic therapies described in IBD patients has increased with many publications coming out lately[9,10]. Further clinical investigations are needed to explore the frequency, clinical aspects, and outcome findings of the skin reactions following the initiation of anti-TNF-α therapy. The purpose of this study is to report the skin reactions associated with the administration of infliximab, adalimumab, and certolizumab pegol in a cohort of IBD patients. Frequency, clinical aspects and outcomes are reported.

Casuistry and methods

We have made a retrospective analysis of charts of 1476 patients seen between 1998 and 2016, with IBD from a specialized institute (Instituto Steinwurz de Saude do Intestino). During that period of time, 297 patients received either infliximab, adalimumab, or certolizumab pegol, or even more than one, in different periods of time. From the overall number of patients, 218 received infliximab, 154 received adalimumab, and 18 received certolizumab pegol, taking into account that the sum is >297, since many of them switched medications due to loss of response or other indication, and therefore, could be included in several lists. We have searched for patients with skin lesions that occurred by the time of the anti-TNF-α treatment that could possibly be associated with the medication. We then collected data among those patients, related with the type of anti-TNF used by the time of the dermatologic lesion occurrence, which kind of skin affection was diagnosed, when it happened along the treatment, and what was the final result of that finding.

Results

From the 297 patients that received anti-TNF-α therapy, 20 (6.7%) of them developed skin lesions probably related with the treatment. Among those patients, we found 6 (30%) case of psoriasis, 4 (20%) of herpes, 3 (15%) of atopic dermatitis, and 2 (10%) of vasculitis as being the most common findings (Table 1 and Figs. 1-11).

We have excluded acneiform lesions since they are a very frequent occurrence among patients overall and probably not related with the medication.

From the 20 patients that developed cutaneous lesions, 12 were on infliximab treatment, 8 on adalimumab, and none on certolizumab pegol. The average time since the beginning of the anti-TNF treatment and the occurrence of the skin lesions was 3 years for both infliximab and adalimumab. All the patients were referred to a dermatologist and received proper treatment, and in only 2 cases change of medication was needed. All the others improved with dermatological management and could keep receiving the same anti-TNF drug.

Discussion

IBD is frequently associated with a variety of extraintestinal manifestations. While most series report arthropathy as the most common one, it is closely followed by cutaneous conditions, such as erythema nodosum and pyoderma gangrenosum and possibly also psoriasis[9,11]. However, not all associated inflammatory skin conditions can be attributed to CD and UC. Data from the rheumatology and dermatology literature, where anti-TNF agents have been most extensively prescribed, suggest that cutaneous reactions are related to the anti-TNF therapy itself. The most widely known and reported problems are palmoplantar pustular and to a lesser extent plaque-type psoriasis lesions. More recently, case reports and one retrospective case series in CD and UC patients receiving

Table 1. Dermatological lesions induced by TNF-α therapy in patients with IBD

Sex	Primary disease	Therapy	Clinical latency (years)	Dermatologic lesion
F	CD	Adalimumab	4	Scabious/pityriasis
F	CD	Adalimumab	6	Alopecia areata
F	CD	Infliximab	7	Atopic dermatitis
F	CD	Infliximab	2	Vasculitis
F	CD	Adalimumab	9	Onychomycosis
F	CD	Infliximab	6	Herpes
F	CD	Infliximab	3	Psoriasis
F	CD	Infliximab	4	Vasculitis
M	CD	Infliximab	5	Pilonidal cyst
F	CD	Infliximab	3	Skin abscess/piodermitis
M	CD	Adalimumab	2	Psoriasis
F	CD	Infliximab	1	Atopic dermatitis
F	CD	Adalimumab	2	Psoriasis
M	UC	Infliximab	1	Herpes
M	UC	Adalimumab	2	Herpes
M	CD	Adalimumab	2	Guttate psoriasis /ungueal
M	CD	Infliximab	1	Psoriasis
F	CD	Infliximab	1	Herpes
M	CD	Infliximab	2	Psoriasis
F	CD	Adalimumab	3	Seborrheic + atopic dermatitis

M: male; F: female; UC: ulcerative colitis; CD: Crohn's disease; TNF-α: anti-tumor necrosis factor-alpha.

anti-TNF therapy with infliximab, adalimumab, or certolizumab drew attention to this problem among gastroenterologists as well[12]. However, their frequency, outcome, and impact on management in IBD are still largely unknown and cannot necessarily be extrapolated from case reports or data in other indications. Taking this raising matter into account, our study tried to investigate the frequency and management of those dermatological lesions induced by or developed during anti-TNF treatment for patients with IBD.

In a prospective study[13], 22.9% of the patients presented non-infectious dermatological adverse events, including new-onset skin lesions in 6.8%, during anti-TNF treatment for IBD. Around 80% of the patients had CD[13]. As the current hypotheses on the mechanisms of action for different anti-TNF induced skin manifestations, there are two main hypotheses suggesting the immunopathogenesis pathway of psoriasiform skin lesions[14]. One theory is that Th17 cell enhancement and T-reg cell downregulation following TNF inhibition leads to increased Th17 cytokine interleukin (IL)-22 productions. IL-22 would then act on keratinocytes and create a pro-inflammatory loop. The pathogenesis of CD is mediated by Th1 and Th17 cells and their differentiation, too. A gene variant of IL23R was

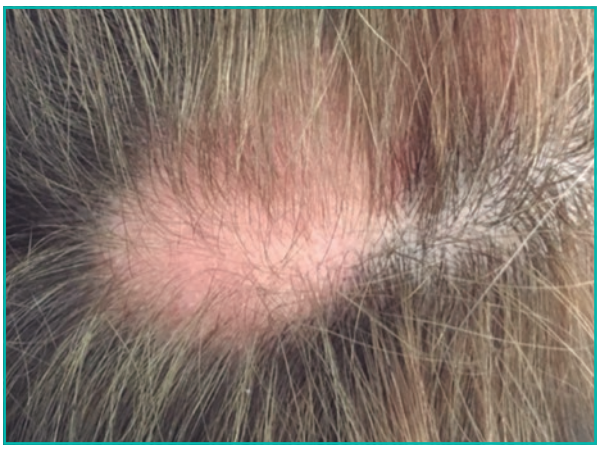

Figure 1. Alopecia areata in a 57 years old. Female after 6 years of treatment with adalimumab.

Figure 2. Alopecia areata in a 36 years old, male after 12 months of treatment with infliximab.

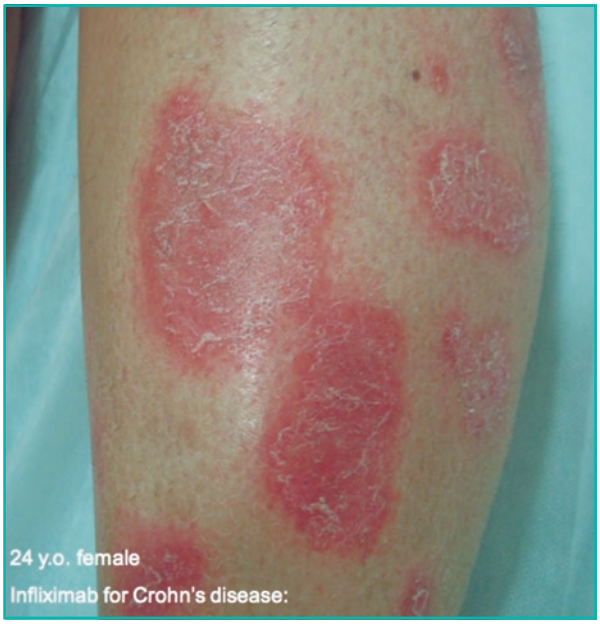

Figure 3. Psoriasis in a 24 years old, female after 5 months of treatment with infliximab.

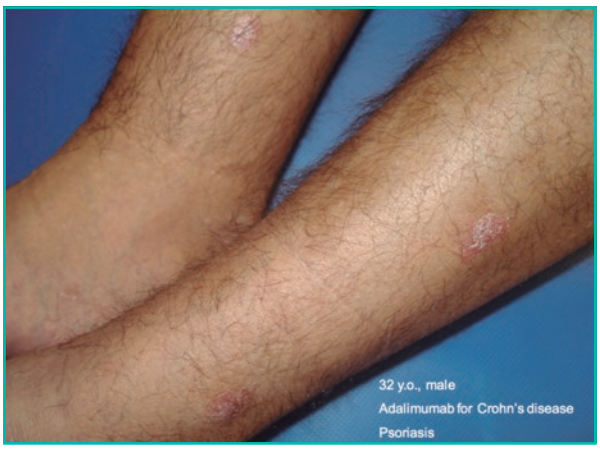

Figure 4. Psoriasis in a 32 years old, male after treatment adalimumab.

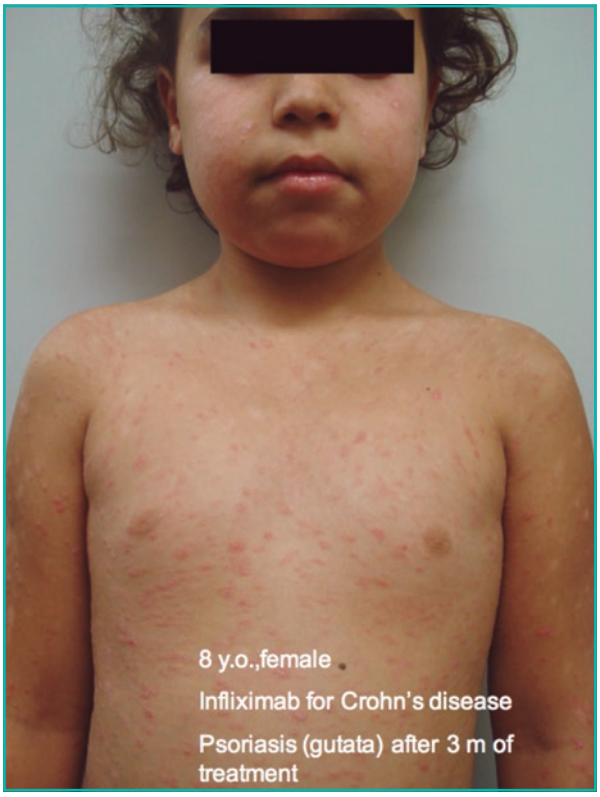

Figure 5. Psoriasis (gutata) in a 8 years old, female after 3 months of treatment with infliximab.

associated with all cases of severe psoriasiform lesions in the study by Tillack, et al.[15]. Patients with these lesions had a 100% response rate to the IL12/23 monoclonal antibody ustekinumab and also reported IL23R polymorphism in their pediatric study[15]. The Th17, although not part of the traditional Th1/Th2 paradigm, might be involved in the

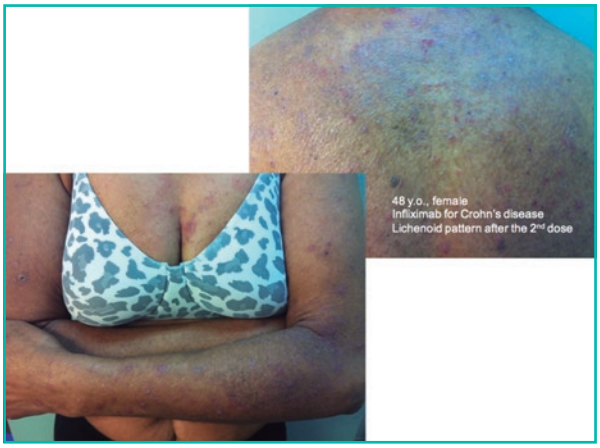

Figure 6. Lichenoid pattern in a 48 years old, female after treatment with infliximab.

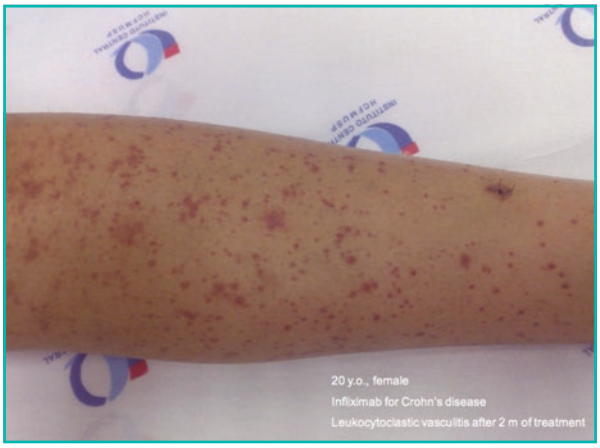

Figure 7. Leukocytoclastic vasculitis in a 20 years old, female after treatment with infliximab.

exacerbation of atopic dermatitis and inflammatory disorders of the skin[16].

According to a study performed by Hellström, et al.[13], the most frequent skin lesions related with the use of anti-TNF drugs are located on the face and arms[13]. It's very important to point out that in case the face is affected, it causes a great impact on the patient's life. It's not an easy task to differentiate cutaneous manifestations due to the anti-TNF use, from those related to other problems such as secondary from the disease itself or infections. This is particularly important since the treatment is completely different but even when the lesions are drug-related, the treatment usually does not need to be discontinued.

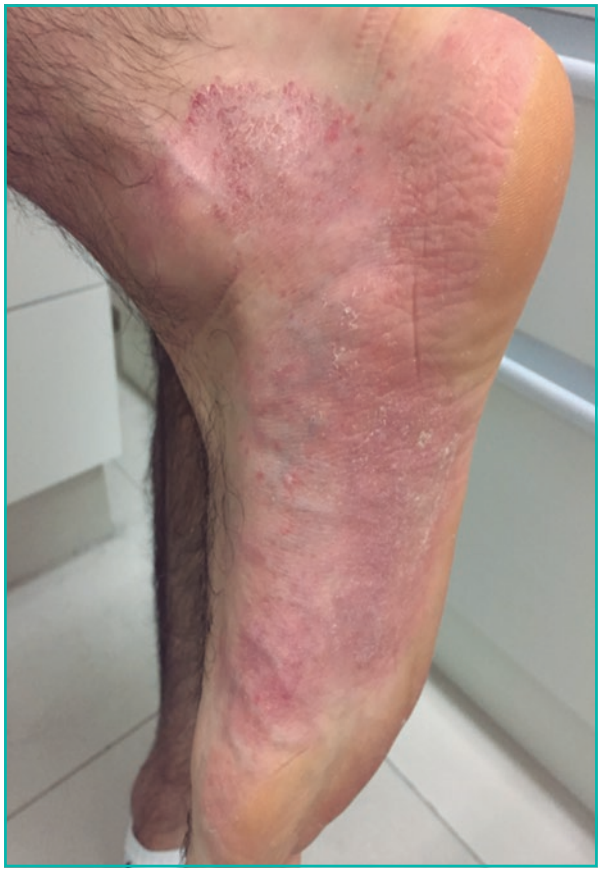

Figure 8. Psoriasis in a 54-year-old male, after treatment with infliximab.

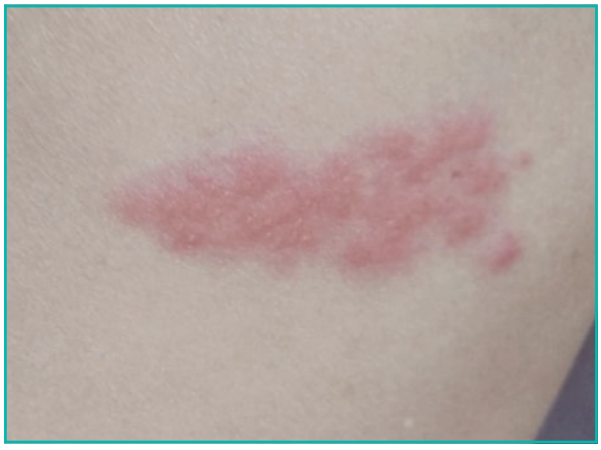

Figure 9. Herpes in a 32 years old, after treatment with infliximab.

Baumgart, et al.[9] published a study of 50 patients with IBD, 92% with CD and 8% with UC where 62% of them developed dermatological lesions during anti-TNF treatment in a 12 months period of follow-up. The most common were dermatitis, acne, and psoriasiform

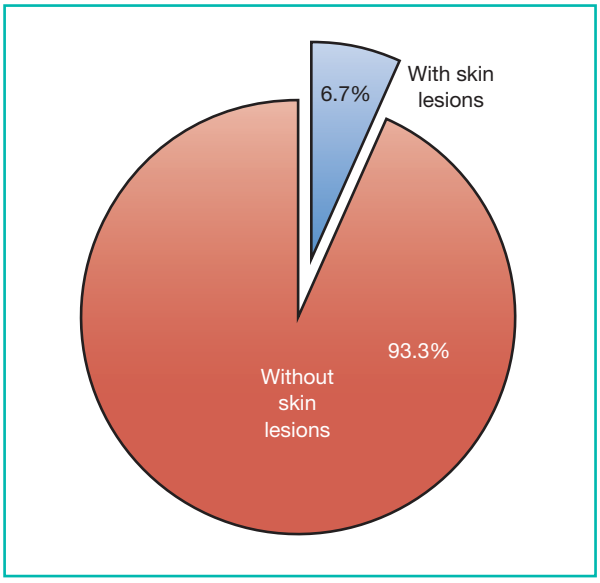

Figure 10. Skin lesions in patients with IBD on use of anti-tumor necrosis factor.

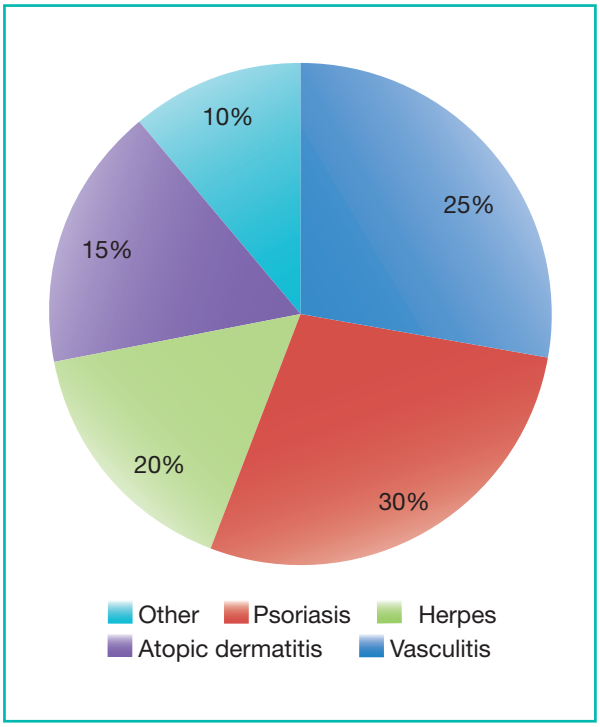

Figure 11. Types of dermatological lesions induced by anti-tumor necrosis factor-α therapy in patients with IBD.

lesions followed by rosacea and herpes. Despite no significant differences between many aspects studied, a slight difference was found in favor of combined therapy with immunosuppressive drugs, and long-term disease, in association with the of development of skin lesions[9].

In a retrospective cohort study, Cleynen, et al.[17] evaluated patients treated with anti-TNF antibodies who did and did not develop skin lesions. Data were included for 917 consecutive patients with IBD who initiated anti-TNF therapy. Patients were followed for a median of 3.5 years. The researchers found that skin lesions associated with anti-TNF therapy use developed in 29% of patients. Lesions, especially psoriasiform lesions, typically developed at flexural regions, genitalia, and the scalp. Lesions developed in 26 and 31% of men and women, respectively. Patients with and without lesions had similar median cumulative doses (2864 and 2927 mg/y, respectively) and trough levels (4.2 and 4.0 µg/mL, respectively) of infliximab. Apart from 28 patients (11%), all patients were managed successfully without needing to stop therapy due to lesions[17].

We have found skin lesions in just 6.0% of the patients on the use of anti-TNF medication, which represents a very small number when compared with the data from Belgium[17]. The most frequent lesions were the same that means psoriasiform lesions. We found 5 cases, 2 with the use of infliximab and 3 with the use of adalimumab. Perhaps the large difference between the two cohorts occurred because we did not actively search for dermatological lesions. We have just referred patients who complained about skin symptoms to the dermatologist.

The occurrence of alopecia areata in the setting of TNF-therapy has been previously reported[18,19]. A direct causal effect cannot be excluded although an epiphenomenon must be considered. In our casuistry, two patients developed alopecia areata, one male on use of infliximab and the other, a female, on adalimumab.

In 2012, our group[10] first published the possible paradoxical effect of infliximab in inducing psoriasis in patients treated with anti-TNF-α for CD. Denadai, et al.[20] published, in 2013, a review of 47 studies (222 patients) that fulfilled

the inclusion criteria and were selected for analysis to determine the incidence of psoriasiform lesions in patients on anti-TNF treatment. Of the 222 patients, 78.38% were diagnosed with CD, 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. We found that psoriatic lesions occurred predominantly in adult patients with CD who received infliximab and had no previous history of psoriasis. Most patients could be managed conservatively without discontinuing anti-TNF-α therapy[20,21].

The incidence of psoriasis in patients with IBD is higher than in the general population, and the IL23R and IL12B genes act as susceptibility variants for IBD and psoriasis, which may account for the increasing rate of psoriatic lesions in IBD patients treated with anti-TNF-alpha agents. Therefore, assessment by a dermatologist would be essential to define the specific types of anti-TNF-alpha-related psoriasis and further exclude differential diagnoses such as acute exanthematous pustulosis and cutaneous infections[22].

Conclusion

Dermatological lesions may occur in patients with IBDs on use of anti-TNF drugs, probably related with the treatment. They are possibly more frequent than we usually see since patients sometimes do not complaint to the gastroenterologist and for that reason would be advisable to be more proactive in search of skin related symptoms. Fortunately, most of the patients do not require changes in the IBD treatment and can be easily managed by the dermatologist.

References

1. Alarhayem A, Achebe E, Logue AJ. Psychosocial support of the inflammatory bowel disease patient. Surg Clin North Am. 2015;95:1281-93, 7-8.
2. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12:720-7.
3. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:644-59, quiz 660.
4. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol. 2015;12:537-45.
5. Lopez A, Ford AC, Colombel JF, et al. Efficacy of tumour necrosis factor antagonists on remission, colectomy and hospitalisations in ulcerative colitis: meta-analysis of placebo-controlled trials. Dig Liver Dis. 2015;47:356-64.
6. Sehgal P, Colombel JF, Narula N. Adverse events during anti-TNFα therapies in IBD (Excluding infections and malignancies): when to stop, continue, or switch therapies. Inflamm Bowel Dis. 2016;22:1239-45.
7. Wang F, Lin X, Zhao Q, Li J. Adverse symptoms with anti-TNF-alpha therapy in inflammatory bowel disease: systematic review and duration-response meta-analysis. Eur J Clin Pharm. 2015;71:911-9.
8. Feuerstein JD, Cheifetz AS. Miscellaneous adverse events with biologic agents (excludes infection and malignancy). Gastroenterol Clin North Am. 2014;43:543-63.
9. Baumgart DC, Grittner U, Steingräber A, Azzaro M, Philipp S. Frequency, phenotype, outcome, and therapeutic impact of skin reactions following initiation of adalimumab therapy: experience from a consecutive cohort of inflammatory bowel disease patients. Inflamm Bowel Dis. 2011;17:2512-20.
10. Steinwurz F, Denadai R, Saad-Hossne R, et al. Infliximab-induced psoriasis during therapy for Crohn's disease. J Crohns Colitis. 2012;6:610-6.
11. Fréling E, Baumann C, Cuny JF, et al. Cumulative incidence of, risk factors for, and outcome of dermatological complications of anti-TNF therapy in inflammatory bowel disease: a 14-year experience. Am J Gastroenterol. 2015;110:1186-96.
12. Rahier JF, Buche S, Peyrin-Biroulet L, et al. Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. Clin Gastroenterol Hepatol. 2010;8:1048-55.
13. Hellström AE, Färkkilä M, Kolho KL. Infliximab-induced skin manifestations in patients with inflammatory bowel disease. Scand J Gastroenterol. 2016;51:563-71.
14. Mocci G, Marzo M, Papa A, Armuzzi A, Guidi L. Dermatological adverse reactions during anti-TNF treatments: focus on inflammatory bowel disease. J Crohns Colitis. 2013;7:769-79.
15. Tillack C, Ehmann LM, Friedrich M, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing th1 cells and IL-17A/IL-22-expressing th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut. 2014;63:567-77.
16. Asarch A, Barak O, Loo DS, Gottlieb AB. Th17 cells: a new therapeutic target in inflammatory dermatoses. J Dermatolog Treat. 2008;19:318-26.
17. Cleynen I, Van Moerkercke W, Billiet T, et al. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. Ann Intern Med. 2016;164:10-22.
18. Sladden MJ, Clarke PJ, Mitchell B. Infliximab-induced acne: report of a third case. Br J Dermatol. 2008;158:172.
19. Toda-Brito H, Lopes L, Soares-Almeida L, Filipe P. Adalimumab-induced psoriatic alopecia/alopecia areata-like reaction in a patient with Crohn's disease. Dermatol Online J. 2015;21:13030/qt79j1d2jv.
20. Denadai R, Teixeira FV, Steinwurz F, Romiti R, Saad-Hossne R. Induction or exacerbation of psoriatic lesions during anti-TNF-α therapy for inflammatory bowel disease: a systematic literature review based on 222 cases. J Crohns Colitis. 2013;7:517-24.
21. Denadai R, Teixeira FV, Saad-Hossne R. The onset of psoriasis during the treatment of inflammatory bowel diseases with infliximab: should biological therapy be suspended? Arq Gastroenterol. 2012;49:172-6.
22. Romiti R, Araujo KM, Steinwurz F, Denadai R. Anti-tumor necrosis factor α-related psoriatic lesions in children with inflammatory bowel disease: case report and systematic literature review. Pediatr Dermatol. 2016;33:e174-8.