World Journal of Clinical Cases

Online Submissions: http://www.wjgnet.com/esps/
wjcc@wjgnet.com
doi:10.12998/wjcc.v1.i2.74

World J Clin Cases 2013 May 16; 1(2): 74-78
ISSN 2307-8960 (online)

MINIREVIEW

Biological therapy for dermatological manifestations of inflammatory bowel disease

Maddalena Zippi, Roberta Pica, Daniela De Nitto, Paolo Paoluzi

Maddalena Zippi, Roberta Pica, Daniela De Nitto, Unit of Gastroenterology and Digestive Endoscopy, Sandro Pertini Hospital, 00157 Rome, Italy
Paolo Paoluzi, Department of Internal Medicine and Medical Specialties, La Sapienza University, 00161 Rome, Italy
Author contributions: Zippi M made a substantial contribution to the study conception and design; De Nitto D and Zippi M were involved in the acquisition, analysis and interpretation of data; Pica R and Zippi M were involved in drafting the article and revising it critically for important intellectual content; Paoluzi P gave the final approval of the version to be published.
Correspondence to: Maddalena Zippi, MD, Unit of Gastroenterology and Digestive Endoscopy, Sandro Pertini Hospital, Via dei Monti Tiburtini 385, 00157 Rome, Italy. maddyzip@yahoo.it
Telephone: +39-6-41735005 Fax: +39-6-41735005
Received: January 6, 2013 Revised: March 22, 2013
Accepted: March 28, 2013
Published online: May 16, 2013

Abstract

Ulcerative colitis and Crohn's disease are the two forms of inflammatory bowel disease (IBD). The advent of biological drugs has significantly changed the management of these conditions. Skin manifestations are not uncommon in IBD. Among the reactive lesions (immune-mediated extraintestinal manifestations), erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major cutaneous ills associated with IBD, while psoriasis is the dermatological comorbidity disease observed more often. In particular, in the last few years, anti-tumor necrosis factor (TNF)-α agents have been successfully used to treat psoriasis, especially these kinds of lesions that may occur during the treatment with biological therapies. The entity of the paradoxical manifestations has been relatively under reported as most lesions are limited and a causal relationship with the treatment is often poorly understood. The reason for this apparent side-effect of the therapy still remains unclear. Although side effects may occur, their clinical benefits are undoubted. This article reviews the therapeutic effects of the two most widely used anti-TNF-α molecules, infliximab (a fusion protein dimer of the human TNF-α receptor) and adalimumab (a fully human monoclonal antibody to TNF-α), for the treatment of the major cutaneous manifestations associated with IBD (EN, PG and psoriasis).

Key words: Biological therapies; Erythema nodosum; Inflammatory bowel disease; Psoriasis; Pyoderma gangrenosum

Core tip: Ulcerative colitis and Crohn's disease are the best known forms of inflammatory bowel disease (IBD) and are considered immune-mediated disorders of unknown etiology that primarily affect the gastrointestinal tract. In addition, other organ systems can be involved, such as skin. Erythema nodosum, pyoderma gangrenosum and psoriasis are the dermatological comorbidities often associated with it. The anti-tumor necrosis factor (TNF)-α drugs (infliximab and adalimumab) have significantly changed the management of these conditions. In this brief review, we provide an overview on the prevalence and clinical aspects of the more commonly reported skin manifestations of IBD and the role of TNF-α inhibitors in their treatment.

Zippi M, Pica R, De Nitto D, Paoluzi P. Biological therapy for dermatological manifestations of inflammatory bowel disease. *World J Clin Cases* 2013; 1(2): 74-78 Available from: URL: http://www.wjgnet.com/2307-8960/full/v1/i2/74.htm DOI: http://dx.doi.org/10.12998/wjcc.v1.i2.74

INTRODUCTION

Extraintestinal manifestations (EIMs) are commonly seen in association with inflammatory bowel disease (IBD). The reported prevalence of EIMs in IBD ranges from

25% to 40%[1]. EIMs can involve any organ or system, with the musculoskeletal and the dermatological ones being the most common. Major skin involvement has been described in 2% to 34% of patients with IBD[2]. Erythema nodosum (EN) and pyoderma gangrenosum (PG) are the two major skin manifestations associated with IBD, defined as reactive lesions (immune-mediated EIMs), while psoriasis is the dermatological associated disease observed more frequently.

The advent of biological therapies [tumor necrosis factor (TNF)-α inhibitors] has changed the course of these EIMs. In particular, there are three TNF-α inhibitors commercially available: etanercept (Enbrel®, Immunex Corporation, Thousand Oaks, CA), a fusion protein dimer of the human TNF-α receptor; infliximab (Remicade®, Centocor Incorporated, Horsham, PA), a chimeric mouse-human monoclonal antibody to TNF-α; and adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL), a fully human monoclonal antibody to TNF-α. All these drugs specifically bind to TNF-α, blocking its biological activity[3], with important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production[4]. The aim of this brief review is to investigate the role of biological therapy in these kind of dermatological manifestations associated with IBD.

EN

EN is the most common cutaneous lesion. It is usually easily recognized on account of its characteristic features; in fact, a biopsy is helpful only in atypical cases. EN lesions are frequently palpable and appear as raised, tender, red or violet subcutaneous nodules 1-5 cm in diameter. EN commonly affects the extensor surfaces of the extremities, particularly the anterior tibial areas, but the arms and the trunk can also be affected. The differential diagnosis of EN includes other types of panniculitis, like cutaneous infections and subcutaneous lymphomas[5].

The prevalence of EN in IBD and Crohn's disease (CD), respectively, ranged from 4.2% to 7.5% and seems to be higher in CD than in ulcerative colitis (UC)[6-8]. The occurrence of lesions is closely related to intestinal disease activity and their treatment is based on that of the underlying IBD. In a study of 792 patients affected by IBD, every case of EN (48 patients) responded to medical treatment of the IBD[9].

Reading the literature, we have found only two cases of EN successfully treated with anti-TNF-α therapy; a case of a child with CD refractory to treatment with corticosteroids and immunomodulators had a rapid and sustained response to the anti-TNF-α antibody infliximab[10] and a case of a refractory chronic EN successfully treated with adalimumab[11]. On the other hand, a case of an EN as paradoxical occurrence has been reported after infliximab infusion given for ankylosing spondylitis in a patient without IBD[12].

PG

PG typically presents with ulcerated lesions with violaceous undetermined borders that are covered with pus or necrotic debris[13]. These ulcers can be solitary or multiple, unilateral or bilateral, and can range in size from several centimeters to an entire limb[14]. PG usually occurs on the extensor surface of the legs but can appear anywhere on the skin, like on the abdominal wall adjacent to a post-surgical stoma[15]. While EN usually correlates with IBD activity, PG correlation with IBD activity is controversial. In fact, PG does not always respond to treatment of underlying bowel disease and response to bowel resection is unpredictable[16]. In recent publications, PG is reported in 0.6%-2.1% of UC and CD patients[6,7], even though it seems more prevalent in UC.

Rapid healing of these lesions should be the therapeutic aim because PG can be a debilitating skin disorder. Usually, systemic corticosteroids and cyclosporin are the most commonly drugs used. Biological therapy is reserved only for specific cases. In fact, infliximab has been reported to be successful in treating severe or refractory lesions[5]. A multicenter retrospective study of medically refractory PG patients reports a positive response to infliximab[17]. The mechanism of action is in line with the putative involvement of immune-mediated factors in the pathogenesis of PG concerning suppression of inflammatory processes. In the study by Tan *et al*[18], two patients with refractory Crohn's fistula and PG had a rapid improvement shortly after the first infusion with infliximab. Sapienza *et al*[19] also reported a good response of PG lesions in four patients with CD treated with infliximab.

The authors supposed that the rapid response to infliximab in these patients was the result of blunted T cell activation early in the inflammatory cascade leading to a decrease in neutrophil infiltration[19]. The largest study on the treatment of PG with IFX was published by Brooklyn *et al*[20]. This was a multicenter, randomized, placebo-controlled trial of 30 patients, including 19 patients with IBD. IFX 5 mg/kg or placebo was given at week 0. At week 2 (the primary end point), significantly more patients in the IFX group had improved compared to placebo (46% *vs* 6%, $P = 0.025$); the response was based upon reduction on size, depth and degree of the lesions. At week 2, subjects in both arms were then offered an open-label for IFX. Overall, 29 patients received IFX with the majority of them showing a beneficial clinical response at week 6 (response 69%, remission 31%). The response rate was over 90% in patients with short duration of PG (< 12 wk) and less than 50% in those with disease present for more than 3 mo. In addition, there was no difference in response between PG patients with IBD and those without[20].

In the literature there is a case of a young women with CD and PG who was successfully treated with Adalimumab[21]. She was a 38-year-old woman with fistulizing CD (enterogastric fistula) that manifested as diffuse abdominal pain and bloody diarrhea, accompanied by arthralgia and PG. The patient was treated with high doses of parenteral methylprednisolone, methotrexate and IFX without any improvement. A positive response to adalimumab therapy was observed: after 2 mo of therapy, the ulcerative skin

lesion healed completely and after 5 mo the enterogastric fistula was closed[21].

On the other hand, three cases of PG as a paradoxical occurrence have been reported after infliximab infusion[22-24]. A 38-year-old woman developed severe PG while receiving treatment with infliximab and azathioprine for active lymphocytic ileitis, in whom the ulcer was finally resolved when treatment with adalimumab was initiated[22]. A 40-year-old woman with UC, developed PG following the second infusion of IFX. In this case, infliximab was discontinued and cyclosporine was initiated with remission of the skin lesion[23]. Finally, a case of a PG has been reported during infliximab infusion given for rheumatoid arthritis in a patient without IBD[24].

Psoriasis

Psoriasis is a chronic skin condition characterized by erythematous papules and plaques. Psoriasis seems to be more common in CD patients than in the general population[25]. Danese *et al*[26] found that psoriasis occurs in 7%-11% of the IBD population, compared to 1%-2% of the general population. Yates *et al*[27] in their study found that psoriasis was more prevalent in CD (11.2%) than in UC (5.7%). Psoriatic lesions have a high concentration of TNF-α, similar to lesions seen in CD, suggesting some immunological overlap. In fact, the association of IBD with psoriasis is believed to be both genetically and immunologically related[28].

Evidence in favor of infliximab and adalimumab for psoriasis has been derived from clinical studies managed by dermatologists. Gottlieb *et al*[29] analyze the efficacy and safety of infliximab as induction therapy for patients with severe plaque psoriasis. In this multicenter, double-blind, placebo-controlled trial, 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of either 3 or 5 mg/kg of infliximab or placebo given at weeks 0, 2 and 6. The primary end-point was the proportion of patients who achieved at least 75% improvement in the psoriasis area and severity index score from baseline at week 10. Infliximab treatment resulted in a rapid and significant improvement in the signs and symptoms of psoriasis. At week 10, 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab (5 mg/kg) achieved a 75% or greater improvement from baseline in the psoriasis area and severity index score compared with 6% of patients treated with placebo ($P < 0.001$)[29]. A subsequent follow-up study by Reich *et al*[30], conducted on 378 patients with moderate to severe plaque psoriasis, demonstrated that 1 year of IFX was effective in both induction and maintenance regimens[30]. In the literature, six cases of patients with plaque psoriasis unresponsive to previous therapies, including infliximab and etanercept, in whom adalimumab (given at 40 mg/wk for 20 wk) resulted in clinical improvement are also described[31].

In the last years, paradoxical cases of psoriatic lesions induced or exacerbated by anti-TNF-α therapy have been reported more frequently, an observation that does not seem to relate to the age of the patient or to the duration of treatment[32-34]. Psoriasiform eczema, eczema and xerosis were the most commonly observed type of skin paradoxical inflammation[35].

The role played by the cytokine network in psoriasis is crucial in understanding the complex mechanisms that underlie the paradox anti-TNF-α-induced psoriasis. Recently, in the pathogenesis of this condition, interferon (IFN)-γ has been called into question[36,37]. This cytokine (IFN-γ), in combination with molecules such as TGF-β, IL-15 and IL-20, can enhance the proliferation of keratinocytes and inhibit their apoptosis[38]. For these kinds of reactions topical therapy with corticosteroids, keratolytics (salicylic acid, urea), emollients, vitamin D analogues and ultraviolet (UV) therapy (UVA or narrow band UVB) are usually used. A class effect is suggested in patients with psoriatic lesions that do not improve with topical therapy and develop recurrent lesions after being switched to anti-TNF-α therapies. Uncontrolled skin lesions led to discontinuation of anti TNF agents in about 34% of patients[39].

We herein report two recent systematic reviews. Denadai *et al*[40] included thirty-four studies in their first study. Sixty-nine patients with IBD were analyzed. Most patients had CD (89.86%), were female (47.83%), had an average age of 27.11 years and no reported history of psoriasis (84.05%). The most common type of psoriatic lesion that developed was plaque-type psoriasis (40.58%). There was a complete remission of psoriatic lesions in 86.96% of IBD patients despite 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[40].

Subsequently, in another systematic review, Denadai *et al*[41] included 47 studies (222 IBD patients). Of the 222 patients, 78.38% were diagnosed with CD and 48.20% were female. The mean patient age was 26.5 years and 70.72% of patients had no history of psoriasis. Patients developed psoriasiform lesions (55.86%) and infliximab was the anti-TNF-α therapy that caused the cutaneous reaction in most of them (69.37%). The majority of patients were managed conservatively without discontinuing anti-TNF-α therapy and complete remission of cutaneous lesions was observed in 63.96% of cases[41].

CONCLUSION

Early recognition of dermatological manifestations associated with IBD is very important for their treatment. The advent of biological response modifiers (anti-TNF-α inhibitors) represents a new and efficacious approach that is able to modify the clinical course of such patients. The diagnosis of the cutaneous manifestations of IBD generally is based on their characteristic features and biopsy is reserved only for atypical cases.

Treatment of EN is usually based on the underlying IBD (CD or UC) and is performed using systemic steroids. PG is initially treated with systemic steroids, oral

calcineurin inhibitors and then with infliximab or adalimumab.

The anti-TNF treatment can induce paradoxical inflammation of the skin which is generally considered a class-drug effect and it is usually reversible upon drug switching or discontinuation. In most cases, psoriatic lesions are the more commonly seen paradoxical inflammation of the skin. In fact, in recent years, an increasing number of cases of onset psoriasis related to anti-TNF therapy in IBD patients has been reported. Psoriasis appearing during anti-TNF-α therapy is considered a class effect of TNF-α blocking agents rather than a drug-specific adverse event[42]. Plaque psoriasis on the extremities and the trunk were the most frequent presentations. The mechanism underlying this paradoxical phenomenon is controversial but it is well known that the increased production of IFN-γ, a key element in the induction of psoriasis, after TNF-α blockage might play a major role[42]. Reading the literature, we found that actually there is no consensus as to whether to continue or discontinue the anti-TNF-α therapy in these cases. In our opinion, the decision should be individualized. Topical steroid treatment is often effective in most patients. Anti-TNF discontinuance may be reserved for patients with severe psoriasis or for the ones that do not respond to topical therapy.

In conclusion, since the introduction of the biological agents, antibodies to cytokine TNF-α, the treatment of IBD and their EIMs such as cutaneous ones has changed dramatically. Although side effects may occur, their clinical benefit remains undoubted.

REFERENCES

1 **Bernstein CN**, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001; **96**: 1116-1122 [PMID: 11316157 DOI: 10.1111/j.1572-0241.2001.03756.x]

2 **Tavarela Veloso F**. Review article: skin complications associated with inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; **20** Suppl 4: 50-53 [PMID: 15352894 DOI: 10.1111/j.1365-2036.2004.02055.x]

3 **Mpofu S**, Fatima F, Moots RJ. Anti-TNF-alpha therapies: they are all the same (aren't they?). *Rheumatology* (Oxford) 2005; **44**: 271-273 [PMID: 15561736 DOI: 10.1093/rheumatology/keh483]

4 **Andrisani G**, Guidi L, Papa A, Armuzzi A. Anti-TNF alpha therapy in the management of extraintestinal manifestation of inflammatory bowel disease. *Eur Rev Med Pharmacol Sci* 2012; **16**: 890-901 [PMID: 22953637]

5 **Larsen S**, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med* 2010; **42**: 97-114 [PMID: 20166813 DOI: 10.3109/07853890903559724]

6 **Freeman HJ**. Erythema nodosum and pyoderma gangrenosum in 50 patients with Crohn's disease. *Can J Gastroenterol* 2005; **19**: 603-606 [PMID: 16247522]

7 **Nguyen GC**, Torres EA, Regueiro M, Bromfield G, Bitton A, Stempak J, Dassopoulos T, Schumm P, Gregory FJ, Griffiths AM, Hanauer SB, Hanson J, Harris ML, Kane SV, Orkwis HK, Lahaie R, Oliva-Hemker M, Pare P, Wild GE, Rioux JD, Yang H, Duerr RH, Cho JH, Steinhart AH, Brant SR, Silverberg MS. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol* 2006; **101**: 1012-1023 [PMID: 16696785 DOI: 10.1111/j.1572-0241.2006.00504.x]

8 **Barreiro-de Acosta M**, Domínguez-Muñoz JE, Núñez-Pardo de Vera MC, Lozano-León A, Lorenzo A, Peña S. Relationship between clinical features of Crohn's disease and the risk of developing extraintestinal manifestations. *Eur J Gastroenterol Hepatol* 2007; **19**: 73-78 [PMID: 17206080 DOI: 10.1097/01.meg.0000243883.47938.aa]

9 **Veloso FT**, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol* 1996; **23**: 29-34 [PMID: 8835896 DOI: 10.1097/00004836-199607000-00009]

10 **Kugathasan S**, Miranda A, Nocton J, Drolet BA, Raasch C, Binion DG. Dermatologic manifestations of Crohn disease in children: response to infliximab. *J Pediatr Gastroenterol Nutr* 2003; **37**: 150-154 [PMID: 12883301 DOI: 10.1097/00005176-200308000-00013]

11 **Ortego-Centeno N**, Callejas-Rubio JL, Sanchez-Cano D, Caballero-Morales T. Refractory chronic erythema nodosum successfully treated with adalimumab. *J Eur Acad Dermatol Venereol* 2007; **21**: 408-410 [PMID: 17309478 DOI: 10.1111/j.1468-3083.2006.01893.x]

12 **Rosen T**, Martinelli P. Erythema nodosum associated with infliximab therapy. *Dermatol Online J* 2008; **14**: 3 [PMID: 18627725]

13 **Evans PE**, Pardi DS. Extraintestinal manifestations of inflammatory bowel disease: focus on the musculoskeletal, dermatologic, and ocular manifestations. *MedGenMed* 2007; **9**: 55 [PMID: 17435655]

14 **Levine JS**, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Hepatol* (NY) 2011; **7**: 235-241 [PMID: 21857821]

15 **Lebwohl M**, Lebwohl O. Cutaneous manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 1998; **4**: 142-148 [PMID: 9589299 DOI: 10.1002/ibd.3780040209]

16 **Levitt MD**, Ritchie JK, Lennard-Jones JE, Phillips RK. Pyoderma gangrenosum in inflammatory bowel disease. *Br J Surg* 1991; **78**: 676-678 [PMID: 2070231 DOI: 10.1002/bjs.1800780613]

17 **Barrie A**, Regueiro M. Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2007; **13**: 1424-1429 [PMID: 17567879 DOI: 10.1002/ibd.20196]

18 **Tan MH**, Gordon M, Lebwohl O, George J, Lebwohl MG. Improvement of Pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. *Arch Dermatol* 2001; **137**: 930-933 [PMID: 11453813]

19 **Sapienza MS**, Cohen S, Dimarino AJ. Treatment of pyoderma gangrenosum with infliximab in Crohn's disease. *Dig Dis Sci* 2004; **49**: 1454-1457 [PMID: 15481318 DOI: 10.1023/B:DDAS.0000042245.20042.4f]

20 **Brooklyn TN**, Dunnill MG, Shetty A, Bowden JJ, Williams JD, Griffiths CE, Forbes A, Greenwood R, Probert CS. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006; **55**: 505-509 [PMID: 16188920 DOI: 10.1136/gut.2005.074815]

21 **Zold E**, Nagy A, Devenyi K, Zeher M, Barta Z. Successful use of adalimumab for treating fistulizing Crohn's disease with pyoderma gangrenosum: Two birds with one stone. *World J Gastroenterol* 2009; **15**: 2293-2295 [PMID: 19437575 DOI: 10.3748/wjg.15.2293]

22 **Fonder MA**, Cummins DL, Ehst BD, Anhalt GJ, Meyerle JH. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J Burns Wounds* 2006; **5**: e8 [PMID: 17149453]

23 **Brunasso AM**, Laimer M, Massone C. Paradoxical reactions to targeted biological treatments: A way to treat and trigger? *Acta Derm Venereol* 2010; **90**: 183-185 [PMID: 20169304 DOI: 10.2340/00015555-0777]

24 **Vandevyvere K**, Luyten FP, Verschueren P, Lories R, Segaert S, Westhovens R. Pyoderma gangrenosum developing during therapy with TNF-alpha antagonists in a patient with rheumatoid arthritis. *Clin Rheumatol* 2007; **26**: 2205-2206 [PMID: 17876646 DOI: 10.1007/s10067-007-0733-8]

25 **Najarian DJ**, Gottlieb AB. Connections between psoriasis and Crohn's disease. *J Am Acad Dermatol* 2003; **48**: 805-821; quiz 822-824 [PMID: 12789169 DOI: 10.1067/mjd.2003.540]

26 **Danese S**, Semeraro S, Papa A, Roberto I, Scaldaferri F, Fedeli G, Gasbarrini G, Gasbarrini A. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol* 2005; **11**: 7227-7236 [PMID: 16437620]

27 **Yates VM**, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. *Br J Dermatol* 1982; **106**: 323-330 [PMID: 7066192 DOI: 10.1111/j.1365-2133.1982.tb01731.x]

28 **Georgiou S**, Pasmatzi E, Monastirli A, Tsambaos D. Cutaneous manifestations of inflammatory bowel disease. *Hosp Chron* 2006; **1**: 158-168

29 **Gottlieb AB**, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, Bala M, Marano CW, Menter A. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51**: 534-542 [PMID: 15389187 DOI: 10.1016/j.jaad.2004.02.021]

30 **Reich K**, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**: 1367-1374 [PMID: 16226614 DOI: 10.1016/S0140-6736(05)67566-6]

31 **Pitarch G**, Sanchez-Carazo JL, Mahiques L, Perez-Ferriols MA, Fortea JM. Treatment of psoriasis with adalimumab. *Clin Exp Dermatol* 2007; **32**: 18-22 [PMID: 17305904]

32 **Fiorino G**, Allez M, Malesci A, Danese S. Review article: anti TNF-alpha induced psoriasis in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2009; **29**: 921-927 [PMID: 19210297 DOI: 10.1111/j.1365-2036.2009.03955.x]

33 **Guerra I**, Gisbert JP. Onset of psoriasis in patients with inflammatory bowel disease treated with anti-TNF agents. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 41-48 [PMID: 23265148 DOI: 10.1586/egh.12.64]

34 **Guerra I**, Algaba A, Pérez-Calle JL, Chaparro M, Marín-Jiménez I, García-Castellanos R, González-Lama Y, López-Sanromán A, Manceñido N, Martínez-Montiel P, Quintanilla E, Taxonera C, Villafruela M, Romero-Maté A, López-Serrano P, Gisbert JP, Bermejo F. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. *J Crohns Colitis* 2012; **6**: 518-523 [PMID: 22398059 DOI: 10.1016/j.crohns.2011.10.007]

35 **Cleynen I**, Vermeire S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 496-503 [PMID: 22751454 DOI: 10.1038/nrgastro.2012.125]

36 **Eriksen KW**, Lovato P, Skov L, Krejsgaard T, Kaltoft K, Geisler C, Ødum N. Increased sensitivity to interferon-alpha in psoriatic T cells. *J Invest Dermatol* 2005; **125**: 936-944 [PMID: 16297193]

37 **Palucka AK**, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of TNF and IFN-alpha in autoimmune diseases. *Proc Natl Acad Sci USA* 2005; **102**: 3372-3377 [PMID: 15728381 DOI: 10.1073/pnas.0408506102]

38 **Qin JZ**, Chaturvedi V, Denning MF, Choubey D, Diaz MO, Nickoloff BJ. Role of NF-kappaB in the apoptotic-resistant phenotype of keratinocytes. *J Biol Chem* 1999; **274**: 37957-37964 [PMID: 10608863 DOI: 10.1074/jbc.274.53.37957]

39 **Rahier JF**, Buche S, Peyrin-Biroulet L, Bouhnik Y, Duclos B, Louis E, Papay P, Allez M, Cosnes J, Cortot A, Laharie D, Reimund JM, Lémann M, Delaporte E, Colombel JF. Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol* 2010; **8**: 1048-1055 [PMID: 20728573 DOI: 10.1016/j.cgh.2010.07.022]

40 **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**: 172-176 [PMID: 22767007 DOI: 10.1590/S0004-28032012000200014]

41 **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* 2012; Epub ahead of print [PMID: 22960136 DOI: 10.1016/j.crohns.2012.08.007]

42 **de Gannes GC**, Ghoreishi M, Pope J, Russell A, Bell D, Adams S, Shojania K, Martinka M, Dutz JP. Psoriasis and pustular dermatitis triggered by TNF-{alpha} inhibitors in patients with rheumatologic conditions. *Arch Dermatol* 2007; **143**: 223-231 [PMID: 17310002 DOI: 10.1001/archderm.143.2.223]

P- Reviewers Guan YS, Rehman HU, Zhang Q, Papanas N
S- Editor Huang XZ **L- Editor** Roemmele A **E- Editor** Zheng XM