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ORIGINAL RESEARCH ARTICLE

Clinical experience of combination therapy of infliximab and total glucosides of paeony for severe psoriasis with liver disorder history

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ABSTRACT

Severe psoriasis patients are reported to have a higher risk of liver abnormalities. Treatment option for severe psoriasis patients with liver disorder history remains a great challenge. Hepatic toxicity and long-term safety are the major concerns. Hence, it is necessary to look for safer and more effective treatment for those patients. This retrospective review evaluated the safety and efficacy of combination therapy of infliximab and total glucosides of paeony (TGP) in treating 13 severe psoriasis patients with liver disorder history. Patients with severe psoriasis, comprising eight men and five women with a mean age of 37.3 ± 12.3, were observed. The patients experienced a mean course of psoriasis of 11.2 ± 7.1 years. The mean psoriasis area and severity index (PASI) score was 29.3 ± 12.9. All patients have the history of liver disorder. In our study, these patients were treated with infliximab at a dose of 5 mg/kg and TGP at a dose of 1.8 g/day. No liver test abnormalities were seen during combination therapy. After treatment, 61.5% patients showed PASI 50 response at week 2, and 81.8% patients have PASI 75 response at week 6. The mean time for achieving PASI 75 and PASI 90 improvement was 4.2 weeks and 9.6 weeks, respectively. Our observation demonstrates that combined therapy of infliximab and TGP is effective and safe in the treatment of severe psoriasis, especially for patients with liver disorder history.

Keywords*: psoriasis; infliximab; total glucosides of paeony; liver disorder; treatment*

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Introduction

Psoriasis is a chronic inflammatory skin disease characterized by proliferation of keratinocytes and infiltration of inflammatory cells into both dermis and epidermis. The prevalence of psoriasis is about 2% of the world's population[1]. Psoriasis is proved to be associated with a series of comorbidities especially in severe forms, including the metabolic syndrome, cardiovascular disease and liver abnormalities[2]. Recent studies indicate that drug-induced hepatitis and non-alcoholic fatty liver disease (NAFLD) may account for liver test abnormalities in severe psoriasis patients[3,4]. Considering the risk of abnormal liver function, treatment options need to be chosen carefully in severe psoriasis patients with liver disorder history.

Conventional systemic agents such as methotrexate (MTX) and acitretin are not recommended in treating those patients, for potential liver toxicities. While biological agent such as infliximab may be an appropriate option for patients with liver disorder history, it is still important to be cautious about the risk of HBV reactivation and other adverse effects[5,6]. Though the incidence of liver injury is relatively low, the existing several cases suggest that liver injury has a strong correlation with anti-TNF-α medications[7,8]. In addition, it is suggested that some patients lack a complete response to infliximab treatment. Hence, the application of combined medication is necessary to improve safety and efficacy.

Total glucosides of paeony (TGP), extracted from roots of *Paeonia lactiflora* Pall, has been approved by State Food and Drug Administration as an anti-inflammatory and disease-modifying drug in China. TGP has been widely used as disease-modifying antirheumatic drugs (DMARDs) in the

treatment of rheumatoid arthritis and psoriasis with good efficacy and fewer side effects[9]. In addition, it is well known that TGP has protective effects on liver function[10]. A double-blind, randomized, placebo-controlled trial reflected that TGP combined with acitretin is effective and safe in treating moderate-to-severe plaque psoriasis[11]. However, up to now, there have been no studies involved in the combination therapy of infliximab and TGP in treating psoriasis.

Thus, in this paper, we aim to share our experience about the efficacy and safety of combination therapy of infliximab and TGP in severe psoriasis patients with liver disorder history.

Methods

We retrospectively reviewed the medical records of severe psoriatic patients with liver disorder history who were treated with infliximab from 2013 to 2015 at the Institute of Dermatology, Chinese Academy of Medical Sciences & Peking Union Medical College (Nanjing, Jiangsu Province, China). All patients were diagnosed as severe psoriasis, as their psoriasis area and severity index (PASI) scores were all >10. The patients all had history of liver function disorder because of the use of conventional systemic therapies. The clinical data collected included age, gender, weight, history of smoking and drinking, course of disease, comorbidities and prior medication use. All patients were provided written informed consent before the treatment of infliximab.

All patients were treated with infliximab at a dose of 5 mg/kg in a scheduled or episodic therapy. Scheduled therapy was defined as patients receive infliximab infused at 0, 2 and 6 weeks, followed by scheduled infusions every 8 weeks. Episodic therapy was aimed for the induction of clinical remission, thus receiving infusions if necessary. All patients were also treated with TGP at a dose of 1.8 g/day. The numbers of infliximab infusions and adverse events were collected from the medical records. For the evaluation of the severity of psoriasis and the response to infliximab therapy, PASI was calculated before the first treatment of infliximab and at 2, 4 and 6 weeks, as well as at each follow-up visit. PASI 50, PASI 75 and PASI 90 refer to 50%, 75% and 90% reduction in the PASI scores compared to the baseline, respectively, and have been recognized as the significant endpoint in the assessment of psoriasis[12]. Clinical laboratory tests such as blood and urine routine tests, hepatic and renal function and other biological tests were also performed and data were collected. Chest X-ray and tuberculosis examination were included.

Statistical analyses

Statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). All continuous variables were expressed as mean ± standard deviation (SD), and discrete variables were described as sample number and percentage.

Results

Thirteen patients were enrolled in the study (**Table 1**). All patients were negative for HIV or active infections such as hepatitis, pneumonia or tuberculosis; the patients also had no history of malignant tumors, and were not pregnant or lactating. They all had the history of liver function damage because of the use of conventional systemic therapy, and the hepatic enzymes returned to normal by liver-protecting treatment before using infliximab. The backgrounds of their liver diseases are reported in **Table 2**. Eight men and five women with a mean age of 37.3 ± 12.3 years (range 18–60 years) were enrolled. The mean weight was 68.8 ± 9.0 kg. The patients experienced a mean course of psoriasis of 11.2 ± 7.1 years. The mean PASI score before therapy was 29.3 ± 12.9 (range 14.4–52.0). Of all the patients in this study, one (7.7%) had psoriatic arthritis and nine (69.2%) patients had nail involvement. Two (15.4%) active smokers were also included in these patients. Last but not least, all the patients' previous treatments before infliximab therapy are reported in **Table 1**.

Of all 13 patients, eight received scheduled therapy and the remaining five received episodic the-

Table 1. Clinical characteristics of patients in the study

Characteristics	Psoriasis (*n* = 13)
Male/Female, *n* (%)	8(61.5%)/5(38.5%)
Age, years (mean ± SD)	37.3 ± 12.3
Weight, kg (mean ± SD)	68.8 ± 9.0
Psoriasis duration, years (mean ± SD)	11.2 ± 7.1
Psoriatic arthritis, *n* (%)	1 (7.7%)
Nail involvement, *n* (%)	9 (69.2%)
Active smoker, *n* (%)	2 (15.4%)
Chronic hepatitis, *n* (%)	0
Psoriasis medication history, *n* (%):	
Acitretin	10 (77.0%)
Tripterygium wilfordii	9 (69.2%)
Methotrexate	2 (15.4%)
Cyclosporine	1 (7.7%)
Etanercept	1 (7.7%)

Table 2. Clinical characteristics of liver disorder history

Characteristics	Psoriasis (n = 13)
Liver injury-related drugs, n (%):	
Acitretin	8
Tripterygium wilfordii	3
Methotrexate	2
Liver injury type, n (%):	
Hepatocellular	7
Cholestatic	4
Mixed	2
Treatment of liver disorder:	
Withdraw	10
Stronger Neo-Minophagen C	3
Hepatitis:	
HBV	0
HCV	0

rapy. All patients received at least one infusion of infliximab, and the detailed information is included in the flowchart (**Figure 1**). As for TGP therapy, 11 patients received combination therapy of infliximab and TGP from the first infusion of infliximab, while the remaining two patients started the treatment of TGP when they experienced adverse events.

As for liver function monitoring, one patient had positive biological detection of liver abnormalities during monotherapy of infliximab. No liver test abnormalities were seen during the combination therapy of infliximab and TGP.

The PASI 50, PASI 75 and PASI 90 responses of all these patients after each infliximab therapy are summarized in **Table 3**. At week two, eight had at least 50% (PASI 50) improvement, five had a 75% (PASI 75) improvement and one had at least 90% (PASI 90) improvement compared with baseline. At week six, the PASI 50, PASI 75 and PASI 90 responses were for 10, 9 and 7 of the remaining 11 patients, respectively. Except for the only patient with no response to the therapy, all the other 12 patients maintained at least 75% improvement compared with baseline after the last infusion. Moreover, we also calculated the mean time to achieve PASI 75 and PASI 90 improvements among all patients.

Of all 13 patients, we have observed two patients with different circumstances during the combination therapy. These two interesting cases are described as follows:

Case 1: A 31-year-old man had three years of history of plaque-type psoriasis. When the patient presented at our department, physical examinations

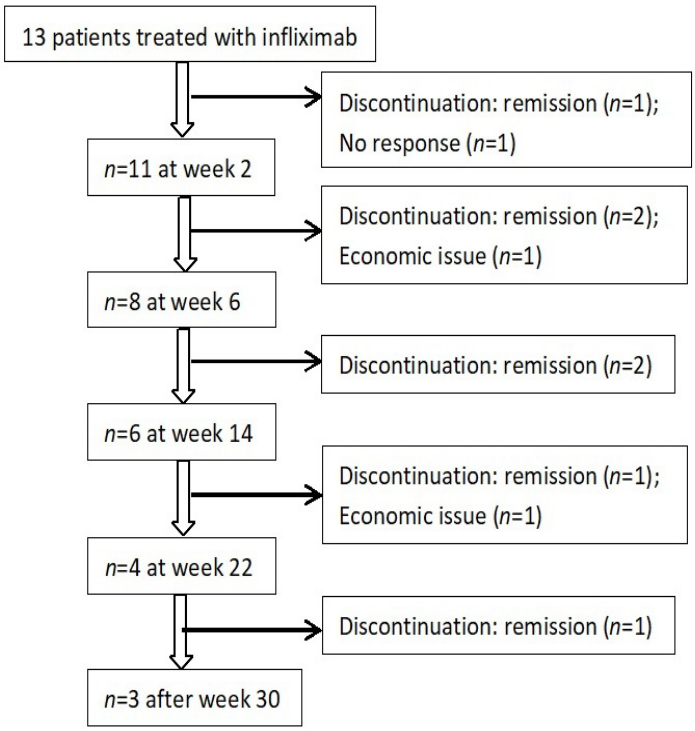

Figure 1. Flowchart of psoriasis patients treated with infliximab in our study

Table 3. Clinical response after infliximab treatments

Week	Patients (*n*)	PASI 50 (*n*)	PASI 75 (*n*)	PASI 90 (*n*)
2	13	8	5	1
4	11	9	8	6
6	11	10	9	7
10	8	8	7	7
14	8	8	7	7
22	6	6	6	6
Mean time of achieving PASI 75 improvement: 4.2 weeks				
Mean time of achieving PASI 90 improvement: 9.6 weeks				

revealed generalized symmetric distribution of erythematous scaly plaques involving more than 70% of the body surface, and the PASI score was nearly 52 (**Figure 2**). There was nothing abnormal from the blood and urine routine tests and biochemical test. Although the HBeAb, HBcAb and HBsAb were all positive, the level of HBV DNA in serum and hepatic enzymes were all normal. Then, he was treated with infliximab (5 mg/kg) combined with topical moisturizer. Within one week after the first treatment, the plaques and papules were resolved, the effusion lesions were significantly reduced and the PASI score dropped to 30. He missed the second treatment two weeks later for the slight elevation of the level of hepatic enzymes, so he was treated with TGP. Two weeks later, hepatic enzymes became normal, but the lesions relapsed. Then, he continued the treatment with infliximab at the week 4, 8 and 16 combined with TGP, and the improvement continued. All lesions cleared up after his eight-week treatment (**Figure 2**). Before each treatment, we performed blood and urine routine tests, biochemical test, the level of HBV DNA and T-Spot, and no adverse event occurred.

Case 2: A 48-year-old man had a 10-year history of plaque-type psoriasis. He had been treated with *Tripterygium wilfordii*, a traditional Chinese medication which has immunodepressive and anti-inflammatory effects but with only limited efficacy. Oral administration of acitretin (20 mg/day) had been considered as an anti-psoriatic therapy for him, but it also produced an adverse reaction (hepatotoxicity), which made him discontinue acitretin therapy. When this patient first presented at our outpatient department, his lesions covered about 35% of the body surface, and the PASI score was 19 (**Figure 3**). The results of his blood and urine routine tests, biochemical test and other laboratory data were normal. We treated this patient with infliximab (5 mg/kg). Two weeks after the first infliximab infusion, the lesions did not regress. Cutaneous examination revealed that scaly plaques on the trunk and thighs became thinner, but unfortunately the scaly erythematous plaques were confluent and the range of lesions was broader. At that time, the lesions covered about 52% of the body surface, and the PASI score was 23.2 (**Figure 3**). The treatment with infliximab was maintained and we also combined it with TGP. At the follow-up visit after the second infliximab therapy, his cutaneous symptoms gradually ameliorated, and laboratory data were all normal.

Discussion

Treatment options are limited for the management of psoriasis patients with liver disorder history. Liver function is the major concern when selecting the optimal treatment in those patients. Systemic drugs such as MTX, acitretin and even biological agents are reported to cause liver test abnormalities[13–15]. In our clinical study, patients were treated with combination therapy of infliximab and TGP. No liver test abnormalities were seen during the combination therapy. What is more, in Case 1, the elevated hepatic enzyme returned to normal after the combination therapy with TGP. This phenomenon may be attributed to the anti-inflammatory and disease-modifying function of TGP. A clinical trial demonstrates that TGP can significantly reduce the incidence and severity of liver damage caused by MTX and leflunomide in treating active rheumatoid arthritis (RA) patients[10]. Moreover, several animal experiments reflect that TGP plays a role on liver histopathology. Wang *et al*. showed that TGP could retard the progression of hepatic fibrosis in rats by the inhibition of collagen synthesis and by decreasing oxidative stress[16]. Qin *et al*. also found that TGP protects hepatocytes from carbon tetrachloride (CCl_4)-induced oxidative stress by inhibiting the expression of proinflammatory mediators[17]. Considering that all patients in our study did not have severe adverse effects, infliximab combined with TGF is thought to be a promising combination therapy for patients with liver disorder history.

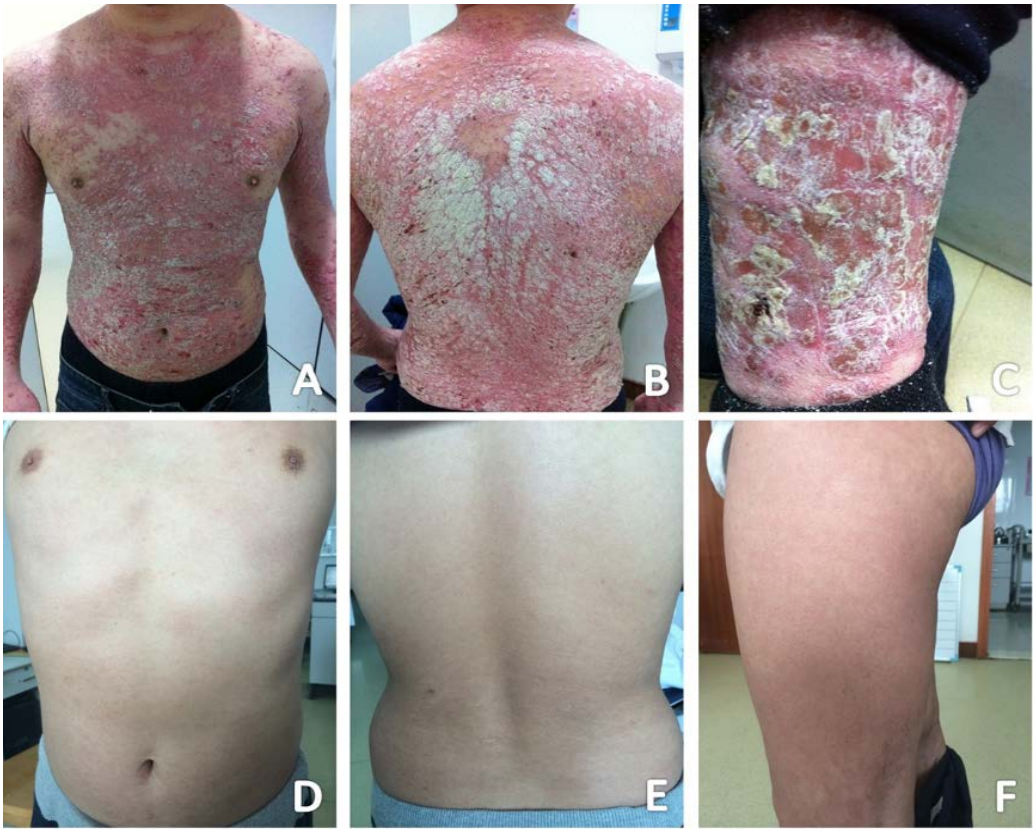

Figure 2. Generalized plaques with active border, red papules and effusion lesions of plaque psoriasis images before (**A**, **B** and **C**) and after (**D**, **E** and **F**) treatment with infliximab

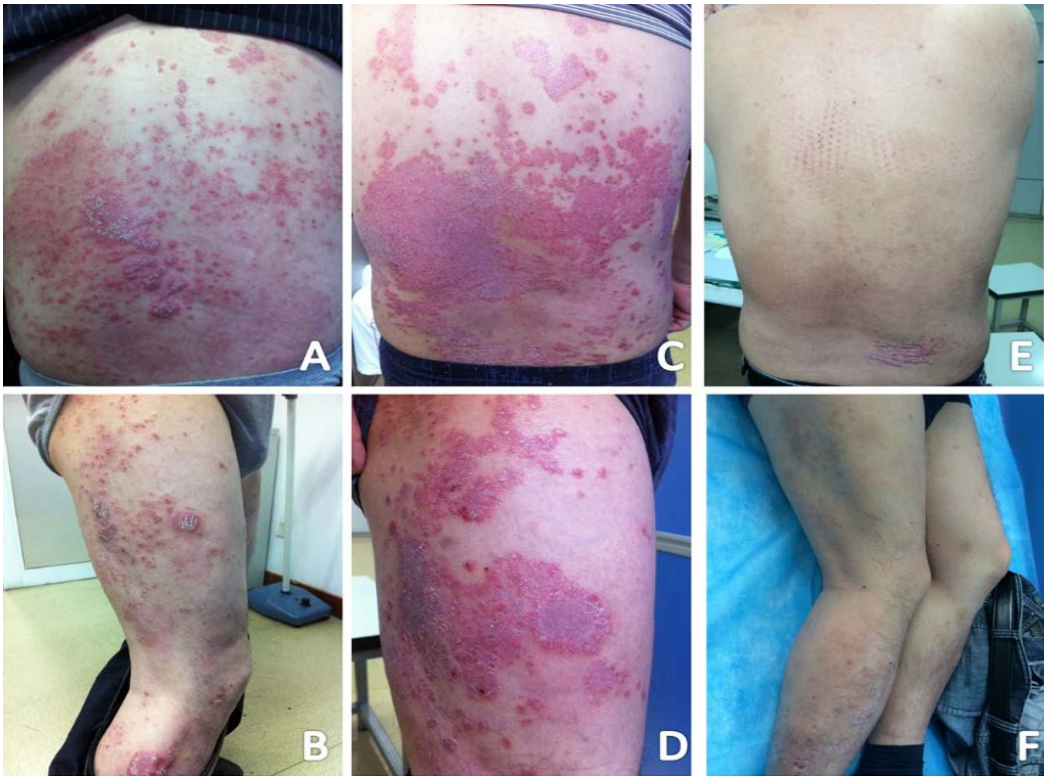

Figure 3. Erythematous plaques on the scalp, trunk and extremities, with scales covering the plaques before treatment (**A** and **B**). Two weeks after the first infusion of infliximab, the scaly erythematous plaques were confluent and the range of lesions was broader (**C** and **D**). Most scaly plaques were relieved after the second treatment of infliximab (**E** and **F**).

Compared with infliximab monotherapy, combination therapy of infliximab and TGP provides higher clinical remission rates. Previous studies have proved the safety and efficacy of infliximab monotherapy in treating psoriasis[18,19]. Three randomized clinical studies from Western countries showed that the PASI 75 response at week 14 were 75.5% (EXPRESS2), 87.9% (SPIRIT) and 72.4% (RESTORE1)[20–22]. Another double-blind trial published in Lancet reported that 80% of patients treated with infliximab achieved PASI 75 and 57% achieved PSAI 90[23]. As for the week 2 response, the PASI 50 rates ranged from 35.4% to 40%[21–23]. In our study, 61.5% (8/13) had at least 50% improvement in PASI score at week 2. Moreover, 81.9% (9/11) achieved a PASI 75 response at week 6. The mean time to achieve PASI 75 improvement was 4.2 weeks and the mean time to achieve PASI 90 improvement was 9.6 weeks. These results above suggested that our patients had higher clinical remission rates than those reported previously, which reflected that the combination therapy of infliximab and TGP might be more effective in treating psoriasis patients by comparing with the monotherapy of infliximab.

In Case 2 discussed above, we found that the patient developed an erythematous rash after the first infusion of infliximab. To our surprise, anti-TNF medications may also induce psoriasiform skin lesions[24]. Grinblat and Scheinberg reviewed the literature of this phenomenon between 2005 and 2007, and reported that more than 25 cases of all 50 cases were associated with the application of infliximab[25]. Several mechanisms such as infections and cytokine imbalance may be associated with the phenomenon. Interferon (IFN)-α produced by dermal plasmacytoid dendritic cells has been identified as a key element in psoriatic skin lesion formation. As TNF-α regulates IFN-α production and the inhibition of TNF-α has been shown to induce the overexpression of IFN-α–regulated genes, therefore it is proposed that TNF-α inhibition might induce locally sustained IFN-α production in patients developing psoriasis while undergoing anti-TNF therapy[26]. In another research, anti-TNF drug-induced psoriasiform skin lesions are attributed to the infiltrates of interleukin (IL)-17A/IL-22-expressing Th17 cells and IFN-expressing Th1 cells, and the severity of skin disease were positively correlated with the number of IL-17A-expressing T cells[27]. At the same time, TGP can inhibit the maturation and function of dendritic cells (DCS) by selectively blocking the activation of TLR4/5 activation *in vivo*, which in turn reduces T cell proliferation and leads to impaired Th1 and Th17 differentiation[28,29]. This might help to explain why the infliximab-induced exacerbation in Case 2 got resolved after combination with TGP.

One limitation of our study is the small sample size. Furthermore, because of the retrospective study, the treatment duration was varied among our patients, which might probably induce potential bias.

Conclusion

We present the experience of combination therapy of infliximab and TGP in psoriasis patients with liver disorder history. Considering that all patients in our study achieved remarkable improvements and did not have liver test abnormalities, infliximab combined with TGP is thought to be a promising combination therapy, especially for patients with liver disorder history. Further randomized controlled studies in large populations are needed in the future for a better understanding of the combination treatment.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of their article.

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