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The role of TNF inhibitors in psoriasis therapy: new implications for associated comorbidities

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Abstract

Over the past several years, tumor necrosis factor (TNF) antagonists have become first-line agents in the treatment of moderate-to-severe psoriasis. These medications are highly effective in treating both psoriasis and psoriatic arthritis and may also reduce the risk of cardiovascular events in patients with chronic inflammatory disorders. In this article we review the use of anti-TNF therapy in psoriasis and its implications in regards to the co-morbid conditions associated with psoriasis.

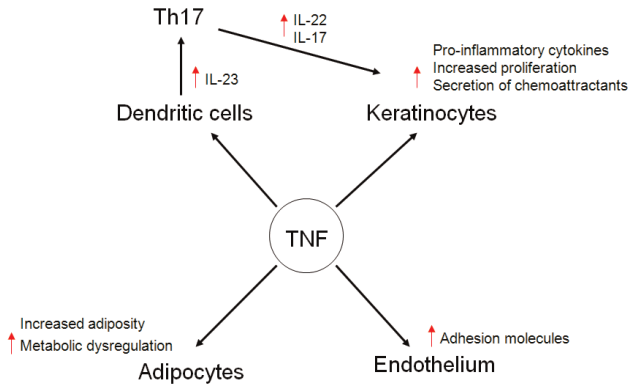
Introduction and context

Psoriasis is a common, chronic inflammatory disease of the skin affecting 1–3% of the general population and characterized by complex alterations in epidermal growth and differentiation with multiple biochemical, immunological, and vascular abnormalities [1]. Although the exact etiology of psoriasis remains unclear, current evidence indicates that it is T-cell driven. Individuals with active skin disease have elevated levels of tumor necrosis factor alpha (TNFα) in both blood and lesional skin [2]. TNFα, which is secreted by both T cells and antigen-presenting cells within lesional skin, has emerged as a key mediator in the disease process. Specifically, TNFα is a pro-inflammatory cytokine that amplifies inflammation through several distinct pathways: facilitating entry of inflammatory cells into lesional skin through induction of adhesion molecules on vascular endothelial cells; stimulating keratinocyte production of other pro-inflammatory mediators [3]; and finally activating dermal macrophages and dendritic cells (Figure 1). Recently, the efficacy of TNFα inhibitors in treating psoriasis has been attributed to their inhibition of Th17 T-cells [2], a newly identified population of T cells now thought to be central to psoriasis pathogenesis.

Currently, three TNFα antagonists are available for use in psoriasis: infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®). While all three block TNFα *in vivo*, they differ significantly in structure and exact mechanism of action. Infliximab is a chimeric human/murine monoclonal antibody that can bind both soluble and membrane-bound TNFα and effectively neutralize its activity [4]. Adalimumab, a fully human antibody [5], functions in the same way as infliximab, binding both soluble and membrane bound TNFα. In contrast, etanercept is a receptor fusion protein and is composed of two human TNFα receptors fused to the Fc portion of a human antibody. Etanercept binds free TNFα and weakly inhibits TNFα trimers *in vivo* [4]. Of these three antagonists, etanercept is the least effective [6]. Infliximab, due to its non-human (chimeric) structure, carries higher risk of inducing neutralizing antibodies, particularly in patients on intermittent therapy, and this can lead to decreased efficacy and lack of response to treatment [7]. Consequently, some dermatologists recommend concomitantly treating patients with methotrexate [8–13], although no clear guidelines exist.

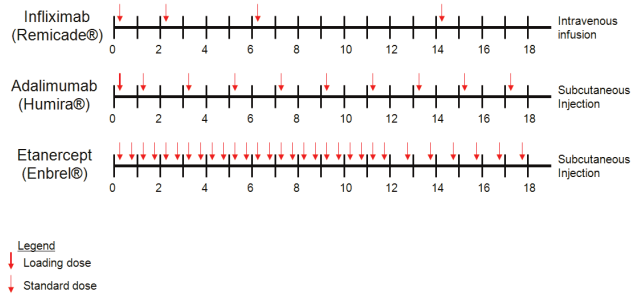
As mentioned above, there is a slight difference in the way that these agents work. Additionally, the dosing regimens for these three agents differ significantly

Figure 1. The biological effects of TNFα [27]



IL, interleukin; TNF, tumor necrosis factor.

Figure 2. Dosing regimens for the three TNF antagonists



Infliximab (5 mg/kg) is given through intravenous infusion at weeks 0, 2, and 6 and every 8 weeks thereafter as a maintenance. Adalimumab is initially given as a single 80 mg subcutaneous injection at week 0, 40 mg at week 1 and then every other week as a maintenance. Etanercept is given subcutaneously, usually in a 50 mg dose twice weekly for 12 weeks and then weekly as a maintenance. TNF, tumor necrosis factor.

(Figure 2 and Table 1). TNF antagonists cause immunosuppression and are contraindicated in patients with chronic leg ulcers, persistent or recurrent chest infections, indwelling catheters, demyelinating diseases, congestive cardiac failure (New York Heart Association classes III and IV) and malignancy (except adequately treated non-melanoma skin cancer) [14]. Latent tuberculosis can also reactivate during treatment, although this has been shown to be lower for etanercept [12] compared to the other two agents. Therefore, patients with untreated or latent tuberculosis should receive a full 9-month course of isoniazid before initiating treatment with TNF antagonists [12]. Furthermore, screening with the tuberculin skin test is recommended in all individuals prior to treatment [12], and patients receiving treatment are encouraged to undergo yearly tuberculosis screenings for the duration of the regimen [12].

Due to the substantial cost and risks associated with TNF-inhibitor therapy, several guidelines have been published for their use in psoriasis [5,12]. It is recommended that these agents only be used in patients with extensive skin disease or in patients with limited

Table 1. Clinical guidelines for TNF inhibitor use [5]

	Infliximab	Adalimumab	Etanercept
Administration	Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Dosing schedule			
Induction	Weeks 0, 2, 6 = 5 mg/kg	Week 0 = 80 mg Week 1 = 40 mg	Months 0–2 = 50 mg twice weekly
Maintenance	Every 8 weeks = 5 mg/kg	Every 2 weeks = 40 mg	Every week = 50 mg
Efficacy			
Short-term	10 weeks: 80% of patients = PASI-75	12 weeks: 80% of patients = PASI-75	12 weeks: 49% of patients = PASI-75
Long-term	50 weeks: 61% of patients = PASI-75	60 weeks: 68% of patients = PASI-75	59% of patients = PASI-75
Baseline monitoring			
Required	PPD	PPD	PPD
Recommended	LFT, CBC, hepatitis panel	LFT, CBC, hepatitis panel	LFT, CBC, hepatitis panel
Ongoing monitoring			
Recommended	Yearly PPD Periodic history and physical Periodic LFT, CBC	Yearly PPD Periodic history and physical Periodic LFT, CBC	Yearly PPD Periodic history and physical Periodic LFT, CBC
Pregnancy class	B	B	B
Toxicities			
Common	Serum sickness Infusion reaction	Injection site reaction/pain Flu-like symptoms	Injection site reaction/pruritis Flu-like symptoms
Rare	Serious infection (TB) Lymphoma New onset CHF, lupus, MS, cytopenia Cancer	Serious infection (TB) Lymphoma New onset CHF, lupus, MS, cytopenia Cancer	Serious infection (TB) Lymphoma New onset CHF, lupus, MS, cytopenia Cancer

CBC, complete blood count; CHF, congestive heart failure; LFT, liver function test; MS, multiple sclerosis; PASI, Psoriasis Area and Severity Index; PPD, purified protein derivative test; TB, tuberculosis; TNF, tumor necrosis factor.

skin disease unresponsive to topical and/or targeted phototherapy. There are limited data regarding the use of these medications in children except for etanercept [5,13].

Recent advances

Over the past several years it has become apparent that psoriasis is associated with several co-morbidities, including lymphoma [14], myocardial infarction [15], and metabolic diseases such as obesity, diabetes, and hypertension [16]. The risk of these co-morbid conditions appears to be higher in individuals with more severe disease [14,15] and, not surprisingly, psoriasis has been associated with increased mortality [17]. While the majority of affected individuals are successfully managed with topical therapies, 20–30% of cases have severe extensive disease necessitating systemic treatment [7].

It remains unclear whether treatment with systemic agents can decrease the risk of co-morbid conditions associated with psoriasis. This is still a largely unexplored area of research in psoriasis, but several recently published studies have begun to provide some insights into this problem. Psoriasis has a complex relationship with metabolic diseases such as obesity [16]. Adipose tissue, including adipocytes and resident macrophages, may serve as a significant source of TNFα in obese individuals [16,18,19]. This source of circulating TNFα can create a pro-inflammatory state elsewhere in the body and can further amplify pre-existing inflammatory processes. Moreover, elevated levels of TNFα have also been suggested to disrupt normal adipocyte function, ultimately leading to increased total body adiposity and further metabolic dysregulation [19]. It is not surprising, therefore, that a correlation between body mass and psoriasis has been identified and obese patients seem to have decreased responses to systemic treatments [20]. Interestingly, TNF antagonists may also contribute to obesity [21–23]. Due to the association between obesity and higher levels of circulating TNFα [24], the efficacy of fixed dose anti-TNF agents (etanercept and adalimumab) has been questioned in obese individuals [25].

Few studies exist on whether TNF antagonists have any effect on glucose control. In a recent study of 12 psoriasis patients with two or more risk factors for type 2 diabetes mellitus, treatment with etanercept was shown to slightly lower fasting insulin levels [26]. However, no difference was seen in insulin secretion and insulin sensitivity while on treatment [26].

As more evidence emerges correlating elevated C-reactive protein levels directly with increased risk of cardiovascular disease, suppressing chronic inflammation has become a top priority in the treatment of psoriasis. Since TNFα is a recognized mediator of systemic inflammation, it has been hypothesized that TNF antagonists may have cardioprotective properties [25]. Although insufficient data exist to reach any definitive conclusions in this regard, one recent study demonstrated that etanercept significantly reduced C-reactive protein levels in obese patients with moderate-to-severe plaque psoriasis, indicating that adequately treated patients may have decreased risk for future cardiovascular events [18]. However, it is not clear whether this 'protective' effect lasts once treatment is discontinued.

Implications for clinical practice

Anti-TNFα antagonists continue to be one of the most effective medications in treating psoriasis, significantly decreasing the overall burden of the disease. Furthermore, with recent data suggesting that these drugs may decrease cardiovascular risk in patients with chronic inflammatory diseases, TNF antagonists may play a larger role in psoriasis treatment in the future. However, given the potential risks of infection and malignancy, the use of these agents should be carefully evaluated.

Abbreviations

TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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