Am J Clin Dermatol (2014) 15:37–43
DOI 10.1007/s40257-013-0053-5

REVIEW ARTICLE

# Safety and Tolerability of Tumor Necrosis Factor-α Inhibitors in Psoriasis: A Narrative Review

**Ashley L. Semble · Scott A. Davis · Steven R. Feldman**

Published online: 27 November 2013


**Abstract** Tumor necrosis factor (TNF)-α inhibitors are an alternative to oral systemic therapies for psoriasis. Data regarding the safety of TNF-α inhibitors from randomized clinical trials may not fully reflect the effects on the clinic patient population receiving the therapy, but other sources of information are available. We performed a literature review to assess the safety and tolerability of the treatment of moderate-to-severe plaque psoriasis with TNF-α inhibitors. A literature search was conducted using PubMed for articles dating from January 2000 to October 2013. Randomized controlled, cohort, open-label, and observational studies were included, as well as case reports and letters to the editor. Articles found on PubMed describing the safety of anti-TNF-α therapy in psoriasis patients were included, while studies highlighting interleukin (IL)-12 and IL-23 inhibitors were excluded, as were non-English articles. In total, 58 articles were included in the review. TNF-α inhibitors exhibit both efficacy and tolerability in patients with moderate-to-severe plaque psoriasis. Adverse effects associated with these medications are not common and can be minimized with routine clinical monitoring and patient education. While the risk of severe adverse events is low, the lack of very large, long-term, randomized safety trials limits the ability to fully define the safety of these agents. TNF-α inhibitors have a good efficacy/safety ratio for use in patients with moderate-to-severe psoriasis. Serious adverse effects are not common, and common injection-site reactions are usually manageable. The benefits of TNF-α inhibitors outweigh the risks for moderate-to-severe psoriasis; however, there are potential adverse effects and the patient populations at highest risk include the elderly and those with a history of malignancy.

A. L. Semble · S. A. Davis (✉) · S. R. Feldman
Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1071, USA
e-mail: scdavis@wakehealth.edu

S. R. Feldman
Center for Dermatology Research, Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC, USA

S. R. Feldman
Center for Dermatology Research, Department of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

## 1 Introduction

Several treatment options exist for moderate-to-severe plaque psoriasis patients; however, many of them—including methotrexate, cyclosporine (ciclosporin), psoralen plus ultraviolet A (PUVA) therapy, and retinoids (acitretin)—can be inconvenient, costly, and risky. Methotrexate and cyclosporine require diligent monitoring by the physician in order to avoid life-threatening adverse effects, including serious cumulative toxicity leading to end-organ damage [1]. Their toxic thresholds limit prolonged use, and these drugs often require careful dosing adjustments. Clinicians employ techniques such as combination, rotation, sequential, and intermittent approaches to best serve the patient during long-term treatment and avoid serious adverse events (SAEs) [2]. Physicians often opt out of prescribing powerful systemic treatments altogether in favor of using only topical treatment, an approach that leaves patients without adequate symptom relief [3, 4].

Tumor necrosis factor (TNF)-α is a pro-inflammatory cytokine with multiple roles in the stimulation and regulation of the immune system. It increases adhesion of lymphocytes and neutrophils to the vascular endothelium,

and serves as a key messenger in the induction of psoriasis [5]. Three TNF-α inhibitors are currently approved for the treatment of plaque psoriasis: etanercept, infliximab, and adalimumab. While all three work to block TNF-α, infliximab and adalimumab are monoclonal antibodies and etanercept is a fusion protein that acts on TNF-α receptors. Etanercept functions as a soluble receptor for TNF-α and has higher affinity than the endogenous receptor. It acts to neutralize the pro-inflammatory effects of TNF-α, preventing binding of both TNF-α and TNF-β to their membrane receptors [6].

Anti-TNF-α therapy can be used alone or in conjunction with other systemic treatments, such as methotrexate or phototherapy. Combination therapy is used in order to increase tolerability, or augment an inadequate response to monotherapy [7, 8]. While TNF-α inhibitors can be used in combination with disease-modifying antirheumatic drugs (DMARDs), etc., the goal of this review is to comprehensively review the safety and tolerability of these drugs when used as monotherapy.

**Table 1** Overview of reported important adverse effects of adalimumab

| |
|---|
| Common adverse events |
| URTI |
| Injection-site reactions |
| Headache |
| Uncommon adverse events |
| Infection (excluding URTI) |
| Reactivation of latent tuberculosis |
| Progression of recently acquired tuberculosis |
| Vasculitis |
| Drug-induced lupus |
| CNS demyelinating disorders |
| Increased risk of malignancy |
| Aggravation of congestive heart failure |

*CNS* central nervous system, *URTI* upper respiratory tract infection

**Table 2** Overview of reported important adverse effects of etanercept

| |
|---|
| Common adverse events |
| URTI |
| Injection-site reactions |
| Pruritus |
| Uncommon adverse events |
| Infection (excluding URTI) |
| Reactivation of latent tuberculosis |
| Progression of recently acquired tuberculosis |
| Vasculitis |
| Drug-induced lupus |
| CNS demyelinating disorders |
| Increased risk of malignancy |
| Aggravation of congestive heart failure |
| Aplastic anemia |

*CNS* central nervous system, *URTI* upper respiratory tract infection

**Table 3** Overview of reported important adverse effects of infliximab

| |
|---|
| Common adverse events |
| URTI |
| Acute infusion reaction (fever, nausea, chills) |
| Headache |
| Pruritus |
| Urticaria |
| Elevated transaminases |
| Uncommon adverse events |
| Infection (excluding URTI) |
| Reactivation of latent tuberculosis |
| Progression of recently acquired tuberculosis |
| Vasculitis |
| Drug-induced lupus |
| CNS demyelinating disorders |
| Increased risk of malignancy |
| Aggravation of congestive heart failure |
| Pancytopenia |

*CNS* central nervous system, *URTI* upper respiratory tract infection

## 2 Methods

We searched PubMed database for articles ranging from January 2000 to October 2013 using the following keywords: 'anti-TNF therapy,' 'TNF inhibitor,' 'TNF antagonist,' and 'psoriasis.' Randomized controlled trials (RCTs), cohort, observational, and open-label studies emphasizing safety and tolerability in psoriasis patients were reviewed, as well as case reports and letters to the editor. The main sources of data referenced by these articles were also included in the review. A meta-analysis was not conducted. The search generated 146 articles and 58 of these were reviewed for this paper.

Stated according to PICOS (participants, interventions, comparators, outcomes, and study design), the study objectives and questions addressed were as follows:

- *Participants*: all humans of any age with psoriasis;
- *Interventions*: treatment with any currently US FDA-approved TNF-α inhibitor;
- *Comparators*: other systemic treatments for psoriasis;
- *Outcomes*: reported adverse events from published literature;
- *Study design*: RCTs, cohort, observational, and open-label studies, case reports and letters to the editor.

## 3 Results/Discussion

### 3.1 Anti-Tumor Necrosis Factor (TNF)-α Therapy: Adverse Effects

Common (≥2 %) adverse effects of TNF-α inhibitors in moderate-to-severe plaque psoriasis patients include (1) injection-site reactions; (2) headaches; (3) upper respiratory tract infections (URTIs); (4) cellulitis; (5) urticaria; (6) elevated liver enzymes; and (7) pruritus (Tables 1, 2, 3).

Injection-site reactions have been observed with each of the three FDA-approved TNF-α inhibitors, though more cases occur for patients using etanercept than infliximab or adalimumab [9]. Infliximab has been reported least likely of the TNF-α inhibitors to cause injection-site reactions [10]. Headaches have been reported in adalimumab and infliximab patients, and it is not uncommon for patients receiving anti-TNF-α therapy to experience URTIs. TNF-α antagonists cause an increased susceptibility to URTIs in psoriasis patients [11]. This has been the most frequently reported SAE across adalimumab clinical trials for more than 10 years [12].

Cellulitis has been reported in psoriasis patients treated with adalimumab, and some cases have been reported of infliximab causing urticaria and elevated liver enzymes. Pruritus has been associated with those patients using etanercept and infliximab [13]. Overall, infliximab has the most diverse list of reported adverse effects. While the list of common adverse effects for infliximab is longer than those for etanercept and adalimumab, all TNF-α inhibitors are associated with potential adverse effects in psoriasis patients; clinicians must weigh the costs versus the benefits in all patients who might benefit from anti-TNF-α therapy.

All FDA-approved TNF-α inhibitors have reported a limited number of more severe adverse effects, though the risks reported vary. During the initial year of treatment, the likelihood of success with anti-TNF-α therapy in psoriasis is several orders of magnitude greater than the likelihood of serious toxicity [14]. Anti-TNF-α therapy has been associated with a number of relatively rare adverse effects (<2 % of patients treated) in psoriasis patients, including severe infections, opportunistic infections, reactivation of latent tuberculosis (TB) or progression of recently acquired TB, new onset or exacerbation of central nervous system (CNS) demyelinating disorders, possible increased risk of malignancy (specifically lymphoma), drug-induced lupus, exacerbation of congestive heart failure (CHF), and vasculitis [15]. The risk of a psoriasis patient developing lymphoma as a result of TNF-α therapy is roughly equivalent to that patient's overall lifetime risk of developing lymphoma without TNF-α therapy (2.3 %) [16].

While extremely rare, severe liver toxicity, lethal liver failure, and drug-induced lupus have been reported [17–19]. Biologic-induced CNS demyelinating disease is also rare, occurring in 0.1–1.7 % of psoriasis patients receiving anti-TNF-α therapy.

TNF-α inhibitors are associated with an increased risk of reactivation of latent infections, particularly TB. Among patients with autoimmune diseases, the initiation of anti-TNF-α therapy, as compared with non-biologic treatments, was not associated with an increased risk in hospitalizations for serious infections; however, TB is an exception [20]. The risk of a psoriasis patient developing TB after initiation of TNF-α inhibitors increased 57-fold (from a 0.3 % overall lifetime risk for psoriasis patients to 17.1 %); therefore, adequate TB surveillance should be conducted in patients receiving anti-TNF-α therapy [16]. Adequate prophylaxis can successfully minimize the risk of reactivation in patients with latent TB [21].

Rare, new-onset or "worsening" psoriasis on TNF-α inhibitors has been described. Case reports describe a pustular psoriasiform eruption of the palms and soles that most often occurs during the process of initiating the medication. Evidence does not yet exist regarding who specifically is susceptible to this adverse effect, and dosing changes have not been associated with such an eruption. The underlying pathophysiological mechanism to this adverse event remains elusive. A recent report suggests chronic TNF-α inhibition may cause proliferation of plasmacytoid dendritic cells and their unregulated proliferation of interferon-α, predisposing to a psoriasiform eruption [22]. Despite this theory, switching TNF-α inhibitors or increasing the dose of the anti-TNF-α agent may remedy the eruption; therefore, the mechanism by which these drugs work to cause new-onset psoriasis is still unclear [23]. New-onset psoriasis as a result of TNF-α inhibition may respond to topical corticosteroid therapy [24].

A few rare (<2 %) adverse events have been associated with specific TNF-α inhibitors. For example, cases of etanercept-induced aplastic anemia have been reported. Only infliximab has been associated with pancytopenia and occasional severe infusion reactions, including anaphylaxis [25].

While a number of adverse effects have been reported in psoriasis patients treated with TNF-α inhibitors, patients receiving even high-dose regimens of TNF-α therapy have not shown more frequent adverse effects than those patients receiving standard dosages. Etanercept and adalimumab dose escalation results in greater efficacy. However, dose escalation and reduction are considered off-label regimens for biologics; therefore, the safety data are relatively limited [26]. Increasing adalimumab dosage has similar safety, though patients on high-dose therapy saw results faster than those patients receiving lower doses [27]. High-dose regimens of etanercept (50 mg subcutaneous injection twice weekly for 12 weeks) are highly effective

and tolerable in psoriatic arthritis patients [28]. A longer study with a larger population group would be needed to further define TNF-α inhibitor safety at higher doses.

### 3.2 Adverse Effects: More Considerations

Psoriasis patients receiving anti-TNF-α therapy may have an increased risk for non-melanoma skin cancers (NMSCs) as compared with the general population; however, psoriasis patients are more likely to have used PUVA—a known cause of NMSC—than the general population [29]. An increased risk of melanoma has also been observed; however, most of these patients were previously exposed to cyclosporine, PUVA, retinoids, and other immunosuppressants that have been associated with an increased risk of all skin malignancies [13]. The incidence of melanoma is also increasing worldwide in the general population, regardless of medication [30]. There is also evidence that the chronic inflammation inherent to the conditions treated with anti-TNF-α therapy is itself associated with an increased potential for malignancy [31]. Therefore, the increased risk of NMSC and melanoma in psoriasis patients receiving adalimumab therapy could be the result of a psoriatic mechanism, not the anti-TNF-α therapy.

Few psoriasis patients who have received anti-TNF-α therapy have reported serious CHF events. A recent paper concluded that epidemiologic data are currently insufficient to reach definitive conclusions regarding the safety of TNF inhibitors on cardiovascular outcomes in psoriasis patients [32]. In one study, of the few psoriasis patients given adalimumab who had serious CHF events, three had two or more risk factors for CHF, including hypertension, hyperlipidemia, diabetes mellitus, myocardial ischemia, and obesity [13]. Therefore, psoriasis patients with preexisting heart or cardiovascular conditions should be carefully monitored while on anti-TNF therapy, though it cannot be concluded with certainty that anti-TNF-α therapy increases the risk of CHF.

Overall, age, disease activity, co-morbidities, and baseline corticosteroid use should be considered when evaluating SAEs in anti-TNF-α therapy. These other factors could contribute to an adverse event that might otherwise be solely attributed to TNF-α antagonists.

### 3.3 "Switching" Safety

Many patients begin TNF-α inhibitors when other treatment options have failed, or as a result of harmful adverse effects associated with other systemic treatments. One study switched 124 plaque psoriasis patients previously treated with traditional or biologic treatments to etanercept and charted their progress [6]. Patients were previously on such medications as cyclosporine ($n = 104$), PUVA therapy (49), retinoids (33), methotrexate (32), and biologics other than etanercept (27). Subjects were initially evaluated using the mean Psoriasis Area and Severity Index (PASI). After etanercept use, a substantial improvement in PASI score was observed. The mean (± standard deviation) PASI score decreased from 15.8 ± 6.7 (week 0) to 5.1 ± 4.3 (week 12), and to 3.0 ± 3.6 (week 24).

Short-term safety/tolerability was also assessed. Those with plaque-type psoriasis treated with etanercept experienced the following: injection-site reactions ($n = 11$), asthenia (9), cystitis (6), headache (5), herpes labialis (3), pharyngitis (2), and otitis (1). In total, 37 of 124 plaque psoriasis patients in this trial experienced an adverse event after switching to etanercept. None of these adverse events required therapy interruption, and all were resolved with specific medication [6].

### 3.4 Randomized Controlled Trials and TNF-α Inhibitors

The efficacy and safety of TNF-α inhibitors has been studied extensively; however, these drugs are often tested in RCTs that purposely exclude the patients at greatest risk, including geriatric patients [33]. Some rheumatology studies revealed that many patients prescribed biologics would not be eligible for RCTs [34]. One study looked at all patients who were put on TNF-α inhibitors from 1 January 2005 to 1 November 2010 at 13 dermatology departments widely distributed across Spain. Of those patients who received the medications, 29.8 % would have been ineligible for RCTs for a variety of reasons, including treatment of psoriasis other than chronic plaque psoriasis (12.2 % of patients), age older than 70 years (7.4 %), chronic hepatic disease (5.9 %), and a history of hepatitis B infection (4.5 %). Patients ineligible for RCTs were more likely to experience SAEs. Previous cancer (excluding NMSC) and age older than 70 years show significant associations with the risk of SAEs. For every 40 patients treated that are not eligible for RCTs, one SAE would be observed in a mean follow-up of 2.1 years compared with eligible patients. A large percentage of psoriasis patients that are placed on TNF-α inhibitors are not representative of the data coming out of RCTs [35].

This study brings to light the issues surrounding the need for safety data that better represent patients receiving these medications; however, there is inherent risk in obtaining safety data in at-risk patients. Observational studies that follow these patients in a clinical setting would be helpful towards our greater understanding of the adverse effects of these medications; however, the findings of such studies are limited by the lack of a randomized control group for comparison.

Biologics prescribed to these patients may not be intrinsically more dangerous in patients ineligible for RCTs; the use of these drugs may simply add to a previously higher baseline risk in these patients. Regardless, dermatologists must be aware that the data coming out on anti-TNF-α therapy does not always reflect the patient populations seen in the clinic.

### 3.5 Who is at Greatest Risk?

Psoriasis is found across a broad population. Heritability plays a significant role in susceptibility. As yet, there is little information to define subsets of psoriasis patients at greatest risk of adverse effects from anti-TNF-α therapy. As use of these medications increase, additional research will be necessary in order to identify underlying risk factors for development of anti-TNF adverse effects. Anti-drug antibodies may be detected in patients who experience adverse effects while on anti-TNF-α therapy [36]. Studies like this show promise towards a better understanding of the etiology of anti-TNF adverse effects in the future.

There is only limited information on the adverse effects of anti-TNF-α therapy in children and adolescents with psoriasis. Excluding etanercept, no randomized clinical trials have been performed in patients with psoriasis during childhood and adolescence [36]. Biologics are currently not recommended for children with psoriasis unless the disease is refractory to non-biologic therapies. Current recommendations state that only children with severe, widespread, refractory pustular, plaque, or psoriatic arthritis should be considered for anti-TNF-α therapy. Of all the currently available biologics, etanercept has showed the fewest and least severe adverse effects in children and adolescents [44]. To the extent that safety data can be generalized across diseases, safety of anti-TNF-α therapy for inflammatory arthritis in children gives some reassurance for anti-TNF-α therapy use in children with psoriasis.

Over the past decade, TNF-α inhibitors have provided an alternative treatment for pregnant women with moderate-to-severe psoriasis [37, 38]. While acitretin and methotrexate must be avoided in women of child-bearing potential (particularly acitretin, which is listed as pregnancy category X), TNF-α inhibitors are listed as pregnancy category B, although pregnant women are typically excluded from controlled trials [39–41]. The risk to pregnant women may be minimal, particularly as compared with more dangerous options such as acitretin (pregnancy category X) and methotrexate, which is an abortifacient [42, 43]. With more safety research, TNF-α inhibitors may be deemed safe enough for pregnant women to use without harming mother or fetus. This would give clinicians an arguably safe alternative to more dangerous medications for women with moderate-to-severe psoriasis who wish to become pregnant.

There is limited safety knowledge regarding TNF-α inhibitors in pregnant women. TNF-α inhibitors are pregnancy category B, and have been on the market for more than 10 years in the USA without reports of SAEs [45]. One study showed that direct exposure to anti-TNF-α therapy during pregnancy did not lead to a higher incidence of birth defects; however, this study only followed patients with inflammatory bowel disease (IBD), not psoriasis [46]. Other studies have confirmed these data in patients with other inflammatory diseases [47, 48]. Overall, the risk of TNF-α antagonists has been described as relatively low and the benefits may outweigh the risks [49].

Although elderly individuals have been safely treated with anti-TNF-α therapy, this group is likely to experience several concomitant illnesses that may lead to increased SAEs. For example, age has a significant effect on the likelihood of developing an SAE such as lymphoma. One study reported an additional 122 cases of lymphoma per 100,000 per year among patients with psoriasis that were 65 years or older [50]. Elderly individuals are more likely to have a prior malignancy than younger individuals due to their advanced age, and clinicians should use caution when prescribing TNF-α antagonists in the geriatric population [40].

Another study found that patients older than 65 years treated with TNF-α inhibitors have a higher rate of infections and mortality than younger patients or patients of the same age that did not receive these drugs. However, this study only included patients with IBD [51]. In contrast, a study of psoriatic arthritis and psoriasis patients concluded that anti-TNF-α therapy in this age group is a safe option, and can even greatly improve elderly patients' quality of life [35].

The use of biologics in psoriasis patients who also have chronic infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV should be limited; however, TNF-α inhibitors, particularly etanercept, appear to be safe and well-tolerated in the setting of chronic HCV, without a negative effect on the underlying HCV infection [52, 53]. Chronic HBV may reactivate during therapy with TNF-α antagonists; however, this was found in a study involving Crohn's patients, not psoriasis patients [54]. The use of anti-TNF-α agents in a short series of HIV-infected patients was not associated with significant clinical adverse effects, nor a negative effect in CD4 counts and HIV viral load levels; however, definitive counseling or guidelines are currently unavailable [55]. Again, this finding was limited to a study that only included patients with rheumatic disease, not solely plaque psoriasis.

Intermittent use of biologic therapy has been associated with a rebound phenomenon once treatment is discontinued, despite a positive early response in these patients. Some patients also experienced a decreased degree of

response compared with the first treatment, particularly with infliximab [56]. Most patients respond well to re-initiation of TNF-α inhibitors after a holiday, particularly those patients receiving etanercept [57]. Due to concerns regarding intermittent biologic use, anti-TNF-α therapy seems more effective in a continuous than in an as-needed setting [58].

## 4 Conclusions

Overall, TNF-α inhibitors are considered safe for adults with moderate-to-severe psoriasis; while a number of uncommon (<2 %) adverse effects may occur, it is difficult to ascertain whether these are due to the drug or to the underlying disease. Thorough histories should be performed in order to screen for pre-existing conditions; many SAEs, such as NMSCs, melanoma, and cardiovascular events, arise from such conditions or previous treatments. Common adverse events observed in moderate-to-severe psoriasis patients taking these drugs do not usually require therapeutic interruption, and often resolve with specific medication, though adjunctive topical therapy alone may not be sufficient. Patient education concerning potential adverse effects is critical. Putting the risks in proper perspective may be difficult. While there are inherent limitations in our ability to precisely define how frequently severe adverse effects occur and whether those adverse effects are due to the drug or the underlying disease, we do know that the frequency of SAEs is low.

**Conflicts and Acknowledgments** The Center for Dermatology Research is supported by an unrestricted educational grant from Galderma Laboratories, L.P. Dr. Feldman is a consultant and speaker for Galderma, Stiefel/GlaxoSmithKline, Abbott Labs, Warner Chilcott, Janssen, Amgen, Photomedex, Genentech, BiogenIdec, and Bristol Myers Squibb. Dr. Feldman has received grants from Galderma, Astellas, Abbott Labs, Warner Chilcott, Janssen, Amgen, Photomedex, Genentech, BiogenIdec, Coria/Valeant, Pharmaderm, Ortho Pharmaceuticals, Aventis Pharmaceuticals, Roche Dermatology, 3M, Bristol Myers Squibb, Stiefel/GlaxoSmithKline, Novartis, Medicis, Leo, HanAll Pharmaceuticals, Celgene, Basilea, and Anacor, and has received stock options from Photomedex. Ms. Semble and Mr. Davis have no conflicts to disclose.

## Reference

1. Menter A, Griffiths CE. Current and future management of psoriasis. Lancet. 2007;370(9583):272–84.
2. Van de Kerkhof PC. Therapeutic strategies: rotational therapy and combinations. Clin Exp Dermatol. 2001;26(4):356–61.
3. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. J Am Acad Dermatol. 2007;57(6):957–62.
4. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. JAMA Dermatol 2013;149(10):1180–5.
5. Terajima S, Higaki M, Igarashi Y, Nogita T, Kawashima M. An important role of tumor necrosis factor-alpha in the induction of adhesion molecules in psoriasis. Arch Dermatol Res. 1998;290(5):246–52.
6. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol. 2009; 10(5):319–24.
7. Zanni GR. Psoriasis: issues far more serious than cosmetic. Consult Pharm. 2012;27(2):86.
8. Daly M, Alikhan A, Armstrong AW. Combination systemic therapies in psoriatic arthritis. J Dermatolog Treat. 2011;22(5): 276–84.
9. Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. J Dermatolog Treat. 2004;15(5): 280–94.
10. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23(Suppl 2):1–70.
11. Smith CH, Anstey AV, Barker JN, et al. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987–1019.
12. Leonardi C, Papp K, Strober B, et al. The long-term safety of adalimumab treatment in moderate to severe psoriasis: a comprehensive analysis of all adalimumab exposure in all clinical trials. Am J Clin Dermatol. 2011;12(5):321–37.
13. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013;72(4):517–24.
14. Langley RG, Strober BE, Gu Y, Rozzo SJ, Okun MM. Benefit-risk assessment of tumour necrosis factor antagonists in the treatment of psoriasis. Br J Dermatol. 2010;162(6):1349–58.
15. Stubgen JP. Tumor necrosis factor-alpha antagonists and neuropathy. Muscle Nerve. 2008;37(3):281–92.
16. Kaminska E, Patel I, Dabade TS, et al. Comparing the lifetime risks of TNF-alpha inhibitor use to common benchmarks of risk. J Dermatolog Treat. 2013;24(2):101–6.
17. Thiefin G, Morelet A, Heurgue A, Diebold MD, Eschard JP. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept. Joint Bone Spine. 2008;75(6):737–9.
18. Tobon GJ, Canas C, Jaller JJ, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. Clin Rheumatol. 2007; 26(4):578–81.
19. Sfikakis PP, Kollias G. Tumor necrosis factor biology in experimental and clinical arthritis. Curr Opin Rheumatol. 2003; 15(4):380–6.
20. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA. 2011; 306(21):2331–9.
21. Gomez-Reino JJ, Carmona L, Angel DM. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007;57(5):756–61.
22. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: a literature review and potential mechanisms of action. Arthritis Rheum. 2008;59(7):996–1001.
23. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or

psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9(1):1–14.
24. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum. 2005;52(8):2513–8.
25. Kleyn CE, Griffiths CE. Infliximab for the treatment of psoriasis. Expert Opin Biol Ther. 2006;6(8):797–805.
26. Brezinski EA, Armstrong AW. Off-label biologic regimens in psoriasis: a systematic review of efficacy and safety of dose escalation, reduction, and interrupted biologic therapy. PLoS One. 2012;7(4):e33486.
27. Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. J Dermatol. 2010;37(4):299–310.
28. De Felice C, Mazzotta A, Esposito M, Bianchi L, Chimenti S. High-dose initiation of etanercept in psoriatic arthritis and plaque psoriasis: efficacy, safety and impact on patients' quality of life. J Dermatolog Treat. 2006;17(6):355–8.
29. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J Natl Cancer Inst. 1998;90(17):1278–84.
30. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. J Invest Dermatol. 2009;129(7):1666–74.
31. Hochberg MC, Lebwohl MG, Plevy SE, Hobbs KF, Yocum DE. The benefit/risk profile of TNF-blocking agents: findings of a consensus panel. Semin Arthritis Rheum. 2005;34(6):819–36.
32. Armstrong AW, Brezinski EA, Follansbee MR, Armstrong EJ. Effects of biologic agents and other disease-modifying antirheumatic drugs on cardiovascular outcomes in psoriasis and psoriatic arthritis: a systematic review. Curr Pharm Des. Epub 2013 Apr 2.
33. Garcia-Doval I, Carretero G, Vanaclocha F, et al. Risk of serious adverse events associated with biologic and nonbiologic psoriasis systemic therapy: patients ineligible vs eligible for randomized controlled trials. Arch Dermatol. 2012;148(4):463–70.
34. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003;48(2):313–8.
35. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol. 2009;22(2):415–26.
36. Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. N Engl J Med. 2008;358(3):241–51.
37. Boker A, Kimball AB, Rolz-Cruz G. Biologicals in the treatment of psoriasis. Curr Opin Investig Drugs. 2007;8(11):939–46.
38. Fantuzzi F, Del GM, Gisondi P, Girolomoni G. Targeting tumor necrosis factor alpha in psoriasis and psoriatic arthritis. Expert Opin Ther Targets. 2008;12(9):1085–96.
39. Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Arch Intern Med. 2000;160(5):610–9.
40. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826–50.
41. Tauscher AE, Fleischer AB Jr, Phelps KC, Feldman SR. Psoriasis and pregnancy. J Cutan Med Surg. 2002;6(6):561–70.
42. Kozma C, Ramasethu J. Methotrexate and misoprostol teratogenicity: further expansion of the clinical manifestations. Am J Med Genet A. 2011;155A(7):1723–8.
43. Vermeire S, Carbonnel F, Coulie PG, et al. Management of inflammatory bowel disease in pregnancy. J Crohns Colitis. 2012;6(8):811–23.
44. Marji JS, Marcus R, Moennich J, kay-Wiggan J. Use of biologic agents in pediatric psoriasis. J Drugs Dermatol. 2010;9(8):975–86.
45. Arsenescu R, Arsenescu V, de Villiers WJ. TNF-alpha and the development of the neonatal immune system: implications for inhibitor use in pregnancy. Am J Gastroenterol. 2011;106(4):559–62.
46. Schnitzler F, Fidder H, Ferrante M, et al. Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. Inflamm Bowel Dis. 2011;17(9):1846–54.
47. Makol A, Wright K, Amin S. Rheumatoid arthritis and pregnancy: safety considerations in pharmacological management. Drugs. 2011;71(15):1973–87.
48. Viktil KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. Scand J Rheumatol. 2012;41(3):196–201.
49. Bogas M, Leandro MJ. Biologic therapy and pregnancy. A systematic literature review. Acta Reumatol Port. 2011;36(3):219–32.
50. Gelfand JM, Berlin J, Van VA, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. Arch Dermatol. 2003;139(11):1425–9.
51. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30–5.
52. Piccolo D, Di CA, Fargnoli MC, Paoloni M, Vecchiotti S, Peris K. Effective control of psoriasis by etanercept in a patient with HCV-related diseases. Eur J Dermatol. 2008;18(4):459–60.
53. Ferri C, Ferraccioli G, Ferrari D, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008;35(10):1944–9.
54. Ojiro K, Naganuma M, Ebinuma H, et al. Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. J Gastroenterol. 2008;43(5):397–401.
55. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008;67(5):710–2.
56. Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol. 2007;143(6):719–26.
57. Gordon KB, Gottlieb AB, Leonardi CL, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. J Dermatolog Treat. 2006;17(1):9–17.
58. Gelfand JM, Kimball AB, Mostow EN, et al. Patient-reported outcomes and health-care resource utilization in patients with psoriasis treated with etanercept: continuous versus interrupted treatment. Value Health. 2008;11(3):400–7.