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TNF-alpha inhibitors and ustekinumab for the treatment of psoriasis: therapeutic utility in the era of IL-17 and IL-23 inhibitors

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Abstract

Psoriasis is a chronic inflammatory condition for which eleven FDA-approved biologic therapies are approved. Over the past decade, studies have documented the higher efficacy of IL-17 and IL-23 inhibitors for the treatment of psoriasis compared to the TNF-alpha inhibitors and ustekinumab, an IL-12/23 inhibitor. Despite this, there remains an important role for the use of TNF-alpha inhibitors and ustekinumab in the treatment of psoriasis. Here, we review how considerations of infection and malignancy risk, patient demographics, treatment resistance, and co-morbidities may make certain TNF-alpha inhibitors or ustekinumab an excellent choice for therapy in particular patient subgroups.

Keywords

TNF-alpha inhibitors; ustekinumab; adalimumab; etanercept; infliximab; certolizumab pegol; safety profile; comorbidities

INTRODUCTION

The selection of biologic agents for the treatment of psoriasis can be challenging due to the existence of eleven FDA-approved biologic therapies: four TNF-α inhibitors: etanercept, adalimumab, infliximab, and certolizumab pegol; one IL-12/23 inhibitor: ustekinumab; three IL-17 inhibitors: secukinumab, ixekizumab, and brodalumab; and three IL-23 inhibitors: guselkumab, tildrakizumab, and risankizumab. The newer IL-17 and IL-23 inhibitors have higher efficacy in psoriasis than the TNF-α inhibitors and ustekinumab, as evidenced by head-to-head trials[1–4] and network meta-analyses[5,6]. In one network meta-analysis, the probability of achieving complete clearance was assessed, ranking the following biologic

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agents from highest to lowest: 61.1% with risankizumab, 54.5% for brodalumab, 54.2% for guselkumab, 46.1% for ixekizumab, 40.9% for secukinumab, 28.9% for ustekinumab, 26.4% for adalimumab, and 16.8% for etanercept[6].

This poses the question: What is the therapeutic utility of older biologic agents in the treatment of psoriasis, specifically TNF-α inhibitors and ustekinumab? These older agents have a number of advantageous features: a longer record of safety data, real world evaluation in special patient populations, real world evaluation of use in combination therapy, and a greater number of medical indications besides psoriasis. Here, we review the specific niches where TNF-α inhibitors and ustekinumab may have utility compared to other biologic therapies.

Patients with Human Immunodeficiency Virus (HIV)

The treatment of psoriasis in patients with weakened immune systems can be challenging, including those infected with human immunodeficiency virus (HIV). For HIV-positive patients with mild-to-moderate psoriasis, the current first-line recommended treatment is topical therapy, and oral retinoids as second-line treatment[7]. For moderate-to-severe disease, the first-line treatment includes ensuring use of highly active antiretroviral therapy (HAART), and treatment with phototherapy or systemic therapies. Patients with recalcitrant psoriatic disease have shown success with the use of cyclosporine, methotrexate, hydroxyurea, ustekinumab, and TNF-α inhibitors[8]. When patients show poor response to methotrexate and cyclosporine, biologic agents were shown to be much more effective[8].

TNF-α inhibitors, particularly etanercept, have been safely used to treat psoriasis in the setting of HIV infection. In HIV-positive patients, there is an overexpression of TNF-α during all phases of the infection, which increases viral replication in infected cells and modulated CD4-lymphocyte apoptosis[9,10]. Increase in TNF-α ultimately leads to an increase in viral load that promotes disease progression[11–15]. In psoriatic disease, the inflammatory response is also mediated by TNF-α and other cytokines that are responsible for stimulating angiogenesis and proliferation of keratinocytes that contribute to the psoriatic plaque development[16]. There are many case reports that demonstrate the safety profile and potential beneficial effect of TNF-α inhibitor use in HIV-positive patients[17]: 31 cases of etanercept, 11 cases of adalimumab, and 5 cases of infliximab. One patient treated with etanercept showed marked improvement of cutaneous and articular involvement of psoriasis, and the CD4 count and viral load remained stable during the course of the treatment.[18] In two cases, the patients had concomitant HCV, which also remained stable during therapy[19,20], and only one case reported an adverse event, which involved recurrent polymicrobial infections, despite stable CD4 and viral counts[21]. There was a report of a successful treatment of psoriasis with adalimumab in a HIV-positive patient[22]. A recent multicenter, retrospective study evaluated the safety of adalimumab in patients with HIV[23]. A total of three patients positive for HIV, who were initiated on HAART before adalimumab treatment, had a baseline mean PASI score of 21.67. One patient showed 60% improvement in PASI at Week 12, one patient achieved PASI 75 at Week 24, and one patient achieved PASI 100 at Week 96. Their mean CD4 cell count remained stable and the HIV-RNA was undetectable during the treatment. Treatment with infliximab and HAART also showed marked improvement

of psoriasis and stable CD4 and viral counts, though one adverse event of facial abscess responsive to antibiotics was reported[8].

Similarly, ustekinumab has demonstrated good safety profile and therapeutic outcomes in HIV-positive patients on HAART. There are 16 case reports that show successful treatment of psoriasis in patients with HIV infections with ustekinumab without subsequent complication.[17] In one case, a patient with HIV, HBV, and psoriasis was maintained on ustekinumab for four years without worsening of his cutaneous or HIV-associated conditions.[24]

Currently, there are only a small number of reports of use of an IL-17 inhibitor[25–27] or IL-23 inhibitor[28] in treating HIV-positive patients with psoriasis.

In conclusion, data suggest TNF-α inhibitors (particularly etanercept) and ustekinumab are safe and effective treatment options for psoriasis patients with HIV infection (Table 1). The risk benefit ratio should be carefully weighed for each patient along with monitoring of CD4 count and viral load and guidance from infectious disease specialists. Data on the use of IL-17 and IL-23 inhibitors in HIV-associated psoriasis is sparse, and more studies are needed to assess the safety of these other therapies in this population.

Patients with Hepatitis C virus (HCV)

TNF-α inhibitors are not recommended in HBV-positive patients, as there have been several reports of HBV reactivation in patients who received TNF-α inhibitors[29–29]. However, the use of TNF-α inhibitors in HCV is acceptable. The overexpression TNF-α in response to HCV in the body can lead to increase in serum levels of transaminases and liver fibrosis, and there are several studies that show how TNF-α can cause liver injury and refractoriness to interferon therapy[33–39]. Thus, reduction of TNF-α in patients with HCV can be beneficial.

In a randomized controlled clinical trial, Zein et al showed that using etanercept as an adjuvant to interferon alfa-2b and ribavirin was safe and effective in the treatment of HCV infection[40]. For 24 weeks, 50 HCV patients were randomly assigned to receive interferon and ribavirin with either etanercept or placebo. At the end of the trial, 12/19 (63%) patients who received etanercept showed complete eradication of the virus compared to 8/25 (32%) placebo patients (P=0.04). Furthermore, treatment with etanercept showed lower rate of adverse events, specifically cardiovascular, cutaneous, gastrointestinal, and neurologic, when compared to the placebo group. Later, a retrospective review showed that 61 HCV-positive patients who received TNF-α inhibitors had minimal change in their liver function and HCV viral load over the course of treatment[41]. There are other reports that evaluate the use of etanercept in patients with psoriasis and concomitant HCV infection, which also demonstrate a favorable safety profile[42–51].

The safety profile of other TNF-α inhibitors and ustekinumab in patients with HCV is still under investigation. In a cohort of 20 psoriatic patients with concomitant chronic HCV infection, treatment with adalimumab showed log rise of viral load in three patients with the median treatment period of 40 months[52]. However, since the viral load increase was not associated with destruction of hepatocytes, they did not meet the criteria for HCV

reactivation. One case report demonstrated how treatment with certolizumab pegol for 2.5 years resulted in PASI score of 0 with no adverse event[53]. Treatment with ustekinumab in one patient also resulted in HCV reactivation and hepatocellular cancer[54], but there is also a report of a successful treatment without any impact on liver function or viral load[55].

In a retrospective systemic review including 97 HCV-seropositive patients who received biologic therapy for the treatment of psoriasis, 3/97 (3.09%) patients experienced viral reactivation in their follow-up visit (mean 15.31 years).[56] These three patients did not receive any antiviral prophylaxis or experienced hepatitis. The analysis also indicated that 3–10% of patients with HCV infection often show spontaneous fluctuations in HCV viral load, suggesting that biologic therapies pose minimal or no additive risk of HCV reactivation without antiviral prophylaxis.[57]

Similarly, there are case studies that report that TNF-α inhibitors have caused liver damage.[58–60] Drug-induced liver injury is an uncommon complication of TNF-α inhibitors, but there is good prognosis after drug discontinuation.[60] Therefore, it is recommended to closely monitor liver function tests prior to and during therapy.

3 patients with HCV were reported to be treated with secukinumab, an IL-17 inhibitor, and there was no significant elevation in liver enzymes or virus reactivation in these patients.[56] There is currently no available data on the use of IL-23 inhibitor in patients with HCV.

TNF-α inhibitors and ustekinumab have also been found to be both safe and effective in HCV-positive patients with other chronic inflammatory diseases, such as IBD[61–63], rheumatic arthritis[64–72], ankylosing spondylitis[73,74], juvenile idiopathic arthritis (JIA)[75].

In conclusion, the use of TNF-α inhibitors and ustekinumab may be safely used in patients with HCV. HCV viral load should be carefully monitored and a hepatologist should be included in the patient's medical care team for expert clinical management.

Transplant patients

There is a limited amount of data regarding the safety of TNF-α inhibitors and ustekinumab use in patients with psoriasis and solid-organ transplants since organ transplantation is often an exclusion criterion for many clinical trials. However, there are several case reports of liver[76–78], pancreas[79], and kidney[80] transplant patients with moderate-to-severe psoriasis treated with etanercept. In all cases, etanercept was well tolerated and demonstrated good safety profile with only one adverse event reported of recurrent cholangitis[78].

A systematic review evaluated the safety of TNF-α inhibitors used in liver transplant patients for IBD[81]. This meta-analysis of eight studies found there is no significant difference in the occurrence of serious infections between liver transplant recipients who were treated with and without TNF-α inhibitors. This study found that 53 liver transplant patients treated TNF-α inhibitors had an infection rate of 0.168 and 23 patients who were not treated with TNF-α inhibitors had a rate of 0.149 (P=0.886). There is one case of a liver transplant recipient treated with ustekinumab to manage CD with no reported adverse event after 12 months of follow-up[82]. Currently, there is no report of a transplant patient receiving ustekinumab for the treatment of psoriasis.

Reports of psoriasis transplant patients using IL-17 or IL-23 inhibitors are needed. However, IL-17 expression has been described in association with allograft rejection. A study recently demonstrated increased expression of IL-17 in tubular cells in patients with renal transplant patients experiencing acute antibody mediated rejection (ABMR).[83]

In summary, there is some evidence that suggests that the use of TNF-α inhibitors in treating psoriasis and IBD may be a safe and effective option after receiving organ transplantation. The use of these drugs should be based on careful selection of patients who need to be closely monitored for potential infections.

Malignancies

The risk of new onset or recurrent malignancies in patients receiving biologic therapy for psoriasis is an area of ongoing research. Several prospective studies have evaluated the incidence of malignancy in psoriasis patients receiving biologic therapy. In these studies, reported malignancies included nonmelanoma skin cancer (NMSC), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), melanoma, prostate cancer, colorectal cancer, breast cancer, and lymphoma. The biologic therapies studied included adalimumab, etanercept, infliximab, and ustekinumab. Adalimumab, etanercept, infliximab, and ustekinumab were not associated with increased risk of any cancer excluding NMSC [84–89]. Among these agents, a study with etanercept had the longest follow up period of 7 years (SIR 0.78 [CI: 0.59–1.00])[87].

Prospective studies evaluating the risk of NMSC in psoriasis patients on adalimumab[85,86] showed increased rates of NMSC, with SIR values of 1.76 (CI: 1.26–2.39), and 1.15 (CI: 1.04–2.11), respectively. A study evaluating 280 patients on any TNF-inhibitors also showed an increased risk of NMSC with a HR of 6.0 (CI: 1.6–22.4)[90]. However, the long-term study on etanercept which followed patients for 7 years did not show an increased risk of NMSC (SIR 0.54 [CI: .42-.69])[87]. Two studies showed no increased risk of BCC with etanercept use (SIR 0.52 [CI: 0.23–1.03] and SIR 0.55 [CI: 0.37–0.80], respectively)[88,91]. An increased incidence of SCC was seen with patients using adalimumab (SIR 3.84 [CI: 1.54–7.92])[86], but results for etanercept were mixed, one study showed increased risk (SIR 1.78 [CI: 1.11–2.69])[88], while another did not (SIR 1.08 [CI: 0.29–2.76])[91].

There was no increased incidence of melanoma, prostate cancer, colorectal cancer, breast cancer, and lymphoma with ustekinumab use in 3117 patients followed for 5 years[89]. Also, there was no increased incidence of lymphoma associated with etanercept or adalimumab use[85,87]. The psoriasis longitudinal assessment and registry (PSOLAR) is an ongoing observational study assessing adverse events, including malignancies (excluding NMSC), in patients on ustekinumab and other psoriasis treatments[92]. The study included a total of 12,090 patients with 48,870 person years of data. The 5 most frequently occurring malignancies were breast cancer, prostate cancer, lung cancer, melanoma, and lymphoma. Malignancy risk was evaluated in methotrexate, TNF-α inhibitor, and ustekinumab use. Exposures to these medications was further broken down by time period (>0 to <3 months, ≥3 to < 12 months, and ≥12 months). Their analysis showed that TNF-α inhibitor use of ≥12 months was associated with an increased risk of malignancy (OR = 1.54 [CI: 1.10–2.15]).

Methotrexate, ustekinumab, and TNF-α inhibitor use of shorter time intervals were not associated with increased risk of malignancy.

Malignancy risk has been studied in other patients on biologic therapy, including patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). In a meta-analysis analyzing the risk of malignancy in patients with RA enrolled in randomized controlled trials on biologic therapy, no statistically significant increased risk of developing malignancy was observed[93]. In patients with IBD, TNF-inhibitor therapy has been associated with a slight increase in risk of lymphoma in patients on TNF-inhibitor monotherapy, thiopurine monotherapy, and combination therapy[94]. The UNITI studies of ustekinumab use in patients with Crohn's disease reported prostate, colorectal and breast cancer in patients, but rates were not different from expected rates of the general US population[95,96]. In IBD patients, TNF-α inhibitor therapy has been linked with a risk of melanoma (OR 1.88 [CI: 1.08–3.29])[97], but this association was not replicated in a Quebec Claims Database Study[98].

Overall, ustekinumab has an excellent safety profile with regard to all malignancy types in psoriasis patients. Registry study data suggest use of TNF-inhibitors may increase the risk for NMSC, though etanercept showed no increased risk for NMSC in several studies. TNF-α inhibitors were generally found not to increase risk of non-NMSC malignancies in psoriasis patients, with the exception of the PSOLAR registry.

The VOYAGE 1 and 2 reported safety data for the use of guselkumab in patients with psoriasis treated through 100 weeks.[99] Through 52 weeks and 100 weeks, out of 1,221 patients treated with guselkumab, three and eight patients developed a malignancy other than NMSC, respectively. The reSURFACE 1 and 2 trials found that 19 patients treated with tildrakizumab developed malignancies (excluding NMSC).[100] The IMMerge trial comparing risankizumab to secukinumab over 52 weeks provided safety assessments of both biologics.[5] Of the 164 patients treated with risankizumab and 163 patients treated with secukinumab, zero non-NMSC malignancies were found for patients treated with either biologic. Recently, a case series and systemic literature review was conducted on IL-17 inhibitor use in patients with plaque psoriasis and a history of malignancy.[101] In their review, they identified a total of 10 patients, seven of whom were treated with secukinumab, one treated with ixekizumab, and two treated with both sequentially.[102–106]

Pediatrics

In recent years, biologic use in the pediatric population has shown to be safe and effective for the treatment of several inflammatory diseases, most notably plaque psoriasis. To date, etanercept, adalimumab, ustekinumab, ixekizumab, and secukinumab are FDA approved for the treatment of psoriasis in the pediatric population. The body of safety evidence for etanercept, adalimumab, and ustekinumab is large, given their previous safety data in juvenile idiopathic arthritis (etanercept and adalimumab)[107,108] and pediatric inflammatory bowel disease (ustekinumab and adalimumab)[107,109,110]. Etanercept is indicated in plaque psoriasis patients over the age of four, adalimumab is FDA indicated for the treatment of plaque psoriasis in adolescents over the age of 12, while ustekinumab is indicated for plaque psoriasis patients over the age of 6[107,108,111]. All three agents have proven safe in the pediatric population up to at least a year.

Long term safety data for etanercept treatment of pediatric plaque psoriasis patients aged 4–17 is also available for up to 264 weeks[112]. An open label extension study demonstrated that while 89% of patients reported an adverse event through week 264, the most commonly reported events were upper respiratory tract infection, nasopharyngitis, and headaches. No malignancies or opportunistic infections were noted.

A recent long-term extension study of adalimumab in pediatric patients aged 4–18 demonstrated low rates of serious or severe adverse events, allergic reactions and injections-site reactions after 52 weeks[113]. Overall, there were 407.4 adverse events per 100 patient years with the most common adverse events being headaches and nasopharyngitis. No serious infections or malignancies were reported in this study.

Similar safety findings were noted in two studies evaluating ustekinumab in pediatric patients ages 6–12 and 12–17 in CADMUS Jr and CADMUS, respectively114,[115]. The original phase III CADMUS study demonstrated that ustekinumab was safe and effective through week 60[115]. The most common adverse events reported through week 60 were nasopharyngitis, upper respiratory tract infections, and pharyngitis. Furthermore, ustekinumab was also found to have a good safety profile in the phase III open label CADMUS Jr study when used in pediatric psoriasis patients aged 6–12114. Through week 56, adverse events were reported in 77% of patients, again with the most commonly reported being nasopharyngitis, upper respiratory tract infections, and pharyngitis. No malignancies, opportunistic infections, anaphylactic reactions, or tuberculosis cases were reported in either the CADMUS or CADMUS Jr study.

Overall, etanercept, adalimumab, ustekinumab and have demonstrated a good safety profile in the treatment of plaque psoriasis in the pediatric population for durations of one year (ustekinumab and adalimumab) to five years (etanercept). Studies demonstrate that these biologic agents are well tolerated and present as a valuable option for the treatment of psoriasis in the pediatric population

Pregnancy

Pregnant women with moderate to severe psoriasis pose a unique challenge for treatment given the high teratogenicity of many classic systemic options, such as methotrexate, acitretin, and cyclosporin[116,117]. While comprehensive, randomized clinical trials in this at-risk group are lacking given ethical concerns, several studies of anti-TNF alpha agents and ustekinumab suggest they are a reasonable and safe treatment option during pregnancy. Data specific to anti-TNF agents and ustekinumab exposure in pregnant patients with psoriasis is limited, but studies have explored these agents during pregnancy in other inflammatory disease states. Currently, no concrete evidence demonstrates that exposure of anti-TNF alpha agents or ustekinumab in pregnancy increases the risk of congenital malformations or fetal death[118,119].

Fetal exposure to these agents during pregnancy is dependent on the agents' molecule structures. Adalimumab, infliximab, and to a lesser extent etanercept, are actively transported across the placenta by the Fc receptor beginning at week 22 during pregnancy, much later than the period of organogenesis[120]. Notably, the certolizumab pegol molecule

completely lacks an Fc-region, therefore limiting the active placental transport of this drug during pregnancy entirely[120]. A case series of 14 pregnant women with chronic inflammatory diseases treated with certolizumab pegol during pregnancy demonstrated no congenital malformations and either undetectable (13) or minimal (1) neonate concentrations of the drug[121]. While not limited to only psoriatic patients, an analysis of prospective data on 528 pregnancies with certolizumab pegol maternal exposure during pregnancy demonstrated no teratogenic effect or increased risk of fetal death compared to the general population[122].

Ustekinumab, similar to anti-TNF alpha agents, is also transported across the placenta via the Fc region at the 22nd week of pregnancy. Data is limited on the impact ustekinumab has on pregnancy and the infant. Compiled pregnancy outcomes in women exposed to ustekinumab in the four psoriasis clinical trials resulted in 26 known pregnancy outcomes with no congenital anomalies or increased incidence of spontaneous abortion noted. Additionally, there was no association between longer ustekinumab exposure and adverse pregnancy outcomes[123].

There is little to no data for pregnancy outcomes in psoriasis patients treated with IL-23 inhibitors. A post hoc analysis from tildrakizumab clinical trials demonstrated that out of 14 pregnancies, no increased rates of congenital anomalies or spontaneous abortions were reported.[124] The rate of spontaneous abortion was similar to the general population (2 cases, 14%), but it is important to note that patients discontinued treatment as soon as pregnancy was detected. Additionally, an analysis of pregnancy outcomes of guselkumab clinical trials demonstrated out of 12 known pregnancy outcomes, seven resulted in live births, two in spontaneous abortions, two in elective abortions, and one unspecified abortion.[125] There is no reported data on pregnancy outcomes of risankizumab clinical trials.

Furthermore, pregnancy outcomes associated with IL-17 inhibitor use is also limited. A global safety database of pregnancy outcomes in psoriasis, psoriatic arthritis or ankylosing spondylitis patients treated with secukinumab identified no safety signals for congenital malformations or spontaneous abortions.[126] At this time there is a lack of studies regarding the safety of brodalumab and ixekizumab during pregnancy.

Overall, certolizumab pegol may be the safest treatment option for plaque psoriasis during pregnancy. Use of other TNF-α inhibitors and ustekinumab during pregnancy have not been associated with congenital abnormalities to date. Additionally, while data is very limited IL-23 and IL-17 inhibitors have not demonstrated an increased risk of spontaneous abortion or congenital malformations.

Patients on combination psoriasis therapies

While biologics have greatly improved outcomes in psoriasis management, combination therapy is sometimes necessary to treat partial responders or non-responders. Patients who utilize combination treatments often have more severe disease. Retrospective analysis of the PSONET registry, identified 9,922 biologic treatment cycles with 982 (9.9%) of them involving combination treatment[127]. Out of the patients receiving combination therapy,

72.9% involved concomitant methotrexate use, 25.3% involved UVB therapy, acitretin or cyclosporin and 1.8% involved PUVA, fumaric acids or a second biologic.

Several studies have also explored the use of biologics with concomitant therapies. A prospective study of four patients treated with UVB phototherapy noted that patients demonstrated an accelerated therapeutic response to adalimumab[128]. Similar findings were found in an intraindividual randomized controlled study combining ustekinumab and UVB, where clearance of psoriatic lesions was accelerated on irradiated skin[129]. Again, this was also found to be true for patients treated with a combination of UVB and etanercept as demonstrated in a randomized controlled trial. The study showed that PASI 90 was achieved at week 16 in 42.9% of patients vs. 3.4% of patients on etanercept monotherapy ($p=0.018$)[130].

Etanercept has also been studied in combination with methotrexate, cyclosporin, and acitretin in prospective studies. Etanercept in combination with methotrexate achieved a superior PGA 0/1 than etanercept with a methotrexate taper (66.7% vs 37% [p=.025])[131]. Etanercept and low dose cyclosporine was found to be another safe and effective option in patients with refractory psoriasis[132]. Of note, etanercept combination therapy with acitretin was found to be more effective than acitretin alone, but was similar in efficacy to etanercept monotherapy[133].

The combination of etanercept and methotrexate has also been studied as combination therapy in the treatment of patients with psoriatic arthritis. Combination therapy showed greater efficacy than methotrexate monotherapy, but similar efficacy to etanercept monotherapy[134]. The FDA label of ustekinumab and etanercept list methotrexate as a possible combination therapy for patients with psoriatic arthritis. For adalimumab, the FDA label states that adalimumab can be used alone or in combination with non-biologic DMARDs for psoriatic arthritis.

Further studies comparing the effectiveness of combinations including IL-17 and IL-23 inhibitors to combinations including TNF-α and IL-12/23 inhibitors are needed.

Patients with comorbid diseases

Psoriasis is associated with many comorbidities including cardiovascular disease, psoriatic arthritis, uveitis, inflammatory bowel disease, metabolic syndrome, and psychological illnesses.

Cardiovascular comorbidity in patients with psoriatic disease has become a major focus in psoriasis research because of its association with high mortality.[135] Elevated levels of CRP and ESR have been positively correlated with disease severity as measured by PASI and development of atherosclerotic lesions[136,137]. CRP inhibits expression of nitric oxide synthase and prostacyclin synthase, which play an important role in preventing atherosclerosis. It also binds to low-density lipoprotein cholesterol, which stimulates its uptake by macrophages and upregulating expression of adhesion molecules on endothelial cells[138]. Studies have found that TNF-α inhibitors lower the levels of ESR and CRP in

rheumatoid arthritis[139,140] and Crohn's disease[141,142]. Ustekinumab has also been shown to decrease CRP and ESR levels in Crohn's disease.

Retrospective studies suggest that TNF-α inhibitors and ustekinumab can reduce the incidence of cardiovascular disease in psoriatic patients. In a large retrospective cohort study, Wu et al. concluded that TNF-α inhibitors can significantly reduce the incidence of myocardial infarction (MI) compared to topical treatments, but did not show a statistically significant difference in MI incident rate when compared to oral agents or phototherapy[144]. However, later head-to-head comparative studies demonstrated that TNF-α inhibitors were superior to both methotrexate[145] and phototherapy[146] in lowering cardiovascular event risk in patients with psoriasis. A total of 403/9148 (4.4%) patients on TNF-α inhibitors experienced cardiovascular events, including MI, stroke or transient ischemic attack, and unstable angina, compared to 602/8581 (7.0%) patients on methotrexate ($P<0.0001$)[145]. Treatment with TNF-α inhibitors also resulted in lower hazard ratio of major CV events compared to treatment with methotrexate while taking potential confounding factors into consideration (HR = 0.55; $P<0.001$). Regression analysis of the 24-month follow-up period suggested that there is an 11% reduction in the risk of developing a major CV event with every 6 months of treatment with TNF-α inhibitors (HR = 0.89; $P=0.02$). Similar results were demonstrated in a head-to-head comparison study with over 20,000 subjects treated with either TNF-α inhibitors and phototherapy (0.9% vs. 1.4%; $P=0.46$)[146]. These results were replicated in a retrospective cohort study within a large health maintenance organization with more than 3 million members, in which the incidence of major cardiovascular events in TNF-α inhibitor users (HR=0.78) were significantly lower compared to both topical therapy (HR=1.00) and phototherapy users (HR=1.13)[147]. A recent phase 4, randomized crossover study (the VIP-U trial) also showed that ustekinumab can transiently decrease aortic vascular inflammation, with long-lasting effects in the reduction of inflammatory cytokines that play a role in cardiovascular diseases.[148]

A longitudinal prospective case-cohort study found that psoriasis treatment with TNF-α inhibitor results in successful clinical improvement of both severe skin lesions and vascular inflammation, measured by positron emission tomography/computed tomography (PET/CT)[149]. Compared to vascular inflammation at treatment-naïve baseline, there was a 6% reduction in psoriasis severity and aortic vascular inflammation after 1 year of treatment with TNF-α inhibitors ($P=0.04$). This reduction was comparable with vascular inflammation after low-dose statin therapy. Similar PET/CT study was conducted with ustekinumab, which was shown to reduce systemic and vascular inflammation seen in CVD and metabolic syndrome[150]. On the other hand, several retrospective studies were not able to find any significant difference in the overall MI risk with use of TNF-α or IL-12/23 inhibitors[151] compared to methotrexate or phototherapy[153,154].

Currently, there are only a few studies that report the relationship between IL-17 inhibitors and cardiovascular biomarkers[155–157] and none such published studies on inhibitors that only block IL-23.

TNF-α inhibitors and ustekinumab may also be useful in treatment of psoriasis patients with other medical indications for these therapies (Table 2). As psoriasis patients frequently

present with these co-morbidities, or develop these co-morbidities over time, the ability to treat two or more conditions with a single drug is invaluable. For example, a recent systematic review highlighted the utility of ustekinumab, certolizumab, adalimumab, and infliximab as effective options for the concomitant treatment of psoriasis and inflammatory bowel disease[158]. Due to the shared common inflammatory pathway, these agents were successful in treating both diseases, simultaneously.

Additionally, a small retrospective study explored the outcomes of eight patients with psoriasis and psoriatic ocular inflammatory disease treated with infliximab or adalimumab[159]. 3/8 patients had psoriatic scleritis, 3/8 had psoriatic panuveitis, and 2/8 with psoriatic anterior uveitis. Seven of the 8 patients achieved remission of their psoriatic ocular inflammatory disease.

These agents present a unique opportunity to treat psoriasis and several of its associated comorbidities with only one medication, which may decrease the risk of side effects and increase patient adherence.

DISCUSSION

With many new developments in psoriasis treatment, clinicians may wonder what the therapeutic utility of some of the older biologic therapies is. These include TNF-α inhibitors and ustekinumab, which emerged over a decade ago.

Though not as efficacious as IL-17 and IL-23 inhibitors, TNF-α inhibitors and ustekinumab have a long track record of use, allowing evaluation of their safety in trials, registries, and real word studies. TNF-α inhibitors and ustekinumab are valuable in the treatment of special subpopulations of psoriatic patients where data for the newer IL17 and IL23 biologic therapies are still limited (Table 1). This includes in patients with chronic infectious diseases, such as HIV and HCV, as well as transplant patients, pediatric patients, and patients with malignancy. The lack of active transport across the placenta suggests certolizumab pegol is one of the most appropriate biologics to use during pregnancy. It is important to note that data from the PSOLAR studies and a comparative cohort study have indicated slight increased risk of infection in patients using TNF-α inhibitors.[160,161]

TNF-α inhibitors and ustekinumab have been well studied in combination with other therapies. Etanercept, ustekinumab, and adalimumab have all been shown to have enhanced efficacy for psoriasis in combination with phototherapy. These three therapies can also be used and in combination with DMARDs, such as methotrexate, and the FDA labels for these therapies indicates this therapeutic combination can be utilized for psoriatic arthritis.

Furthermore, TNF-α inhibitors and ustekinumab have shown promising results in their effect on cardiovascular comorbidities, with retrospective studies showing attenuation of cardiovascular events and prospective vascular imaging studies showing decrease in inflammatory burden. Comparison of these agents with the effects of IL-17 and IL-23 inhibitors on cardiovascular outcomes is needed using prospective, randomized trials.

Etanercept, adalimumab, infliximab, certolizumab, and ustekinumab and are FDA approved for the treatment of a large number of inflammatory conditions, and are thus extremely useful for the treatment of patients with multiple conditions (Table 2). Psoriasis can co-occur with psoriatic arthritis, inflammatory bowel disease, uveitis, and axial spondylitis. A simpler regimen utilizing one biologic agent to treat multiple diseases may lead to decreased side effects and improved patient compliance.

CONCLUSION

There are several FDA-approved biologic therapies for the treatment of psoriasis. In newer studies, IL-17 and IL-23 inhibitors show greater efficacy compared to TNF-α and IL-12/23 inhibitors. While IL-17 and IL-23 inhibitors can be beneficial in special subpopulations of psoriatic patients, there are more limited data on the safety of IL-17 and IL-23 inhibitors. TNF-α and IL-12/23 inhibitors have more robust safety data in patients with chronic infections (e.g., HIV, HCV), history of solid organ transplantation and malignancies, psoriasis comorbidities, and combination psoriatic therapies. TNF-α and IL-12/23 inhibitors also show efficacy and safety in pediatric patients and pregnancies. In summary, though new biologic therapies continue to emerge, TNF-α inhibitors and ustekinumab continue to serve as valuable options for the treatment of psoriasis in a large variety of scenarios.

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Table 1.

TNF-α inhibitors and ustekinumab recommendation in special subpopulations of psoriatic patients

PATIENT NICHE	THERAPIES TO CONSIDER
HIV-POSITIVE	Etanercept, adalimumab, ustekinumab
HCV-POSITIVE	Etanercept
SOLID-ORGAN TRANSPLANT	Etanercept
MALIGNANCIES	Etanercept, ustekinumab
PEDIATRICS	Etanercept, ustekinumab
PREGNANCY	Certolizumab pegol

Table 2.

FDA indications for TNF-α inhibitors and ustekinumab

Indication	Etanercept	Infliximab	Adalimumab	Certolizumab	Ustekinumab
PSORIASIS	X	X	X	X	X
PSORIATIC ARTHRITIS	X	X	X	X	X
RHEUMATOID ARTHRITIS	X	X	X	X	
ANKYLOSING SPONDYLITIS	X	X	X	X	
JUVENILE IDIOPATHIC ARTHRITIS	X		X		
INFLAMMATORY BOWEL DISEASE		X	X		X
HIDRADENITIS SUPPURATIVA			X		
UVEITIS			X		