Biologics for Psoriasis and Psoriatic Arthritis

(Adalimumab, Etanercept, Golimumab, Infliximab, Ustekinumab)

National PBM Criteria for Use – Monograph with Literature Review

June 2013

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

EXECUTIVE SUMMARY

The purposes of this updated review of antipsoriatic biologic agents are to compare their pharmacologic properties and evaluate studies that address certain key clinical questions that are pertinent to the development of criteria for use of biologic agents for chronic plaque psoriasis (CPP) and psoriatic arthritis (PsA) in the Veterans Health Administration. No studies involving a U.S. Veteran population were found. The answers to the key questions can be summarized as follows:

CPP Q1: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

In short-term trials, ustekinumab was shown to be moderately more efficacious and had a lower incidence of injection site reactions than etanercept (1 high-quality head-to-head RCT). Indirect comparisons suggest that infliximab may be the most efficacious; however, there is no definite evidence to support that there is a difference among adalimumab, etanercept, and infliximab in terms of efficacy. Weak evidence suggests that adalimumab may be associated with a higher risk of paradoxical psoriasis, and that adalimumab and infliximab may be associated with a higher rate of tuberculosis than etanercept.

CPP Q2: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

Adalimumab was shown to be superior to methotrexate, with a large relative effect size and faster onset, and was associated with fewer cases of hepatotoxicity and had a lower risk of withdrawals due to adverse events (1 high-quality RCT). Indirect comparisons suggested that adalimumab and infliximab but not etanercept were better in efficacy than nonbiologics (methotrexate, cyclosporine) for CPP. A comparative effectiveness study provided early, unconfirmed evidence that, although biologic agents may be more effective than nonbiologic treatments, the gain in benefit is relatively small and may not be clinically important.

CPP Q3: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

There is no good evidence of the relative efficacy and safety of biologics in nonbiologic treatment failures. There is only a poor-quality, noncomparative study that showed that adalimumab may have potential benefit in treatment failures.

CPP Q4: In patients with chronic plaque psoriasis, is there a difference between antipsoriatic biologic or nonbiologic monotherapy and combination biologic-nonbiologic therapy?

There is weak evidence that combination etanercept-methotrexate or etanercept-acitretin therapy may be more efficacious than etanercept monotherapy.

CPP Q5: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

No VA-relevant pharmacoeconomic studies were found. Published studies suggest that a number of patient and clinical factors could affect the relative cost-effectiveness probabilities of individual nonbiologic and biologic therapies, including the extent to which treatments reduce hospitalizations and patient weight (for weight-based treatments such as cyclosporine, infliximab and ustekinumab).

PsA Q1: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

The findings from indirect comparisons in systematic reviews / meta-analyses have been inconsistent. One of the reviews showed that adalimumab, etanercept and infliximab were similar in efficacy; another showed infliximab to be most effective overall (for joint and skin outcomes), etanercept better than adalimumab for joint outcomes, and adalimumab to be better than etanercept for skin outcomes; and a third review concluded that the evidence was not strong enough to confirm that there is a clinically important difference between golimumab and other biologics (adalimumab, etanercept, and infliximab). Safety findings also showed some variability in systematic reviews of short-term studies and overall showed no definite evidence that there were substantial differences among adalimumab, etanercept, golimumab and infliximab. Long-term efficacy and safety of the biologics have not been adequately evaluated. At this time, the evidence is insufficient to draw definite conclusions about the relative safety and efficacy of TNFIs in PsA.

PsA Q2: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents and nonbiologic topical or systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

Indirect evidence suggest that TNFIs are better than methotrexate because, unlike nonbiologic systemic agents, they have been shown to be disease-modifying (i.e., reduce synovitis and prevent progression of joint erosion) and may be better tolerated.

One good-quality study evaluating methotrexate in PsA confirmed the lack of efficacy of this drug in reducing PsA synovitis. There is no evidence showing that methotrexate or other nonbiologic systemic therapies prevent progression of joint erosion.

PsA Q3. In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

One study suggested that TNFIs may have differential benefits depending on the outcome measure in nonresponders to nonbiologic systemic agents.

PsA Q4: In patients with psoriatic arthritis, is there a difference between biologic monotherapy and combination biologic-nonbiologic therapy in terms of efficacy, effectiveness, safety, or tolerability?

Recent evidence suggests that methotrexate is not efficacious and is not a DMARD in PsA (3 RCTs).

There is insufficient evidence to determine the efficacy and safety of biologic-nonbiologic combination therapy relative to biologic monotherapy.

PsA Q5: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

No VA-relevant pharmacoeconomic studies were found.

Conclusions

The biologic agents work by mechanisms different from those of conventional systemic agents and may be effective alternatives or add-on therapies to patients who have unsatisfactory responses to the older drugs. They

have been shown in premarketing and postmarketing studies over the past 5 to 10 years to be relatively well tolerated. There is, however, a safety trade-off in using TNFIs. Whereas they lack the major, relatively predictable treatment-limiting organ toxicities associated with methotrexate (cirrhosis, pulmonary fibrosis), cyclosporine (renal impairment, hypertension), and acitretin (teratogenicity, mucocutaneous toxicity, hyperlipidemia), TNFIs are associated with relatively unpredictable major harms including serious infections (e.g., sepsis, tuberculosis, and viral infections), autoimmune dysfunction (e.g., lupus, demyelinating disorders), and malignancies (e.g., lymphoma). TNFIs have also been associated with paradoxically inducing psoriasis and psoriasiform lesions.

For chronic plaque psoriasis without psoriatic arthritis, most evidence-based clinical practice guidelines recommend biologics as second-line therapies after trials of conventional systemic agents. However, the current available evidence supporting the efficacy and safety of biologics in the treatment of chronic plaque psoriasis is based mainly on patients who have received but not necessarily failed prior nonbiologic systemic agents. Biologic-naïve and nonbiologic nonresponders comprise smaller study subpopulations. As to whether one biologic agent is better than the others, the available evidence suggests that ustekinumab is moderately more efficacious than etanercept. For other biologic pairs, indirect comparisons suggest that infliximab and perhaps adalimumab may be better than etanercept but overall there are no definite clinically relevant differences in short-term efficacy or effectiveness. In addition, the available evidence suggests that the biologic agents, particularly infliximab and adalimumab, are overall more efficacious and effective than nonbiologic systemic agents, particularly methotrexate and cyclosporine. However, there is early, unconfirmed data suggesting that in real-world practice, the incremental gain in effectiveness of biologic agents over methotrexate is small and may not be clinically meaningful in terms of the impact on patient quality of life. The limited comparative short-term safety data that is available suggests that adalimumab may be better tolerated and less hepatotoxic than methotrexate. Further studies are needed to confirm early studies that suggest combination biologic-nonbiologic therapy may have advantages over biologic monotherapy. Long-term comparative safety data and cost-effectiveness studies that account for long-term toxicities and cost-driver outcomes such as hospitalizations are needed to supplement the existing efficacy and effectiveness studies in chronic plaque psoriasis. Given the lack of VA-relevant cost-effectiveness studies and lack of studies comparing treatment approaches, such as step-up (nonbiologics then biologics) versus step-down (biologics then nonbiologics) therapy, at this time there is insufficient evidence to support a recommendation to use antipsoriatic biologics as first-line therapy and insufficient clinical evidence to support mandating the use of nonbiologic systemic agents before biologics.

For psoriatic arthritis, the evidence is unclear about whether any biologic is better than the others. Biologics seem to be more efficacious than nonbiologic systemic agents, particularly methotrexate, based on indirect comparisons. There is convincing evidence that biologics are efficacious in reducing synovitis, whereas methotrexate is inefficacious for synovitis and produces probably clinically unimportant symptomatic improvement in psoriatic arthritis. Biologic agents approved for psoriatic arthritis have been shown to be disease-modifying; this is a clinically important advantage of the biologics over nonbiologic systemic agents. There is a lack of evidence that any of the nonbiologic treatment alternatives prevent progression of joint damage. In addition, indirect comparisons suggest that, relative to systemic nonbiologics as a class, biologics as a class may be better tolerated. For these reasons, adalimumab, etanercept, golimumab and infliximab have evidence to support their use as first-line treatment alternatives to conventional agents, particularly leflunomide (the nonbiologic agent with some evidence of efficacy) in patients with psoriatic arthritis. By extension, biologics would also be first-line treatment alternatives in patients with co-diagnoses of chronic plaque psoriasis and psoriatic arthritis. There is insufficient evidence to determine the efficacy and safety of biologic-methotrexate combination therapy relative to biologic monotherapy; however, there is weak evidence suggesting that combination therapy may be more effective than biologic monotherapy.

In general, the biologics with lowest acquisition costs and longer safety records and experience should be tried first using the lowest recommended effective dose. Among the TNFIs, adalimumab, etanercept, and infliximab have longer safety records and experience, and therefore may be preferable over golimumab (approved for PsA only) or ustekinumab, which is more efficacious than etanercept but lacks long-term experience and safety data.

However, each biologic agent has certain pharmaceutical advantages and disadvantages, so treatment that is less cost-effective may be more appropriate in some cases to individualize therapy.

Future research should evaluate treatment approaches (i.e., step-up, nonbiologic first then biologic, versus step-down, biologic first then nonbiologic). Longitudinal comparative effectiveness and safety studies in real-world practice settings and VA-relevant, comparative cost-effectiveness analyses are urgently needed to help determine optimal treatment sequence and approach in chronic plaque psoriasis and psoriatic arthritis in a U.S. Veteran population.

Background

A number of advances have occurred in antipsoriatic biologic therapy since the original (2004–2005) review by the VA Pharmacy Benefits Management Services (PBM). Adalimumab and ustekinumab were approved by the FDA for the treatment of chronic plaque psoriasis (CPP). Infliximab and golimumab gained FDA approval for management of psoriatic arthritis (PsA). Efalizumab was withdrawn from the U.S. market in 2009 because of several reports associating it with progressive multifocal leukoencephalopathy. Alefacept was discontinued by the manufacturer (Astellas) in November 2011. The use of biologics in combination with nonbiologic systemic therapy has become a new treatment option because only a small proportion of patients achieve complete clearance of plaques on biologic therapy alone.[1] More long-term data on safety, efficacy (in clinical trials), and effectiveness (during real-world experience) has become available.

Agents undergoing investigational studies include certolizumab pegol (Cimzia™ by UCB, Inc.) and briakinumab (investigational IL-12/23 inhibitor, ABT-874 by Abbott). Based on preliminary results of a Phase II trial reported as an abstract, certolizumab pegol shows beneficial effects in the short-term treatment of moderate to severe CPP.[2] Briakinumab has also been reported to show efficacy for CPP in four unpublished Phase III pivotal trials. According to the manufacturer's press release, briakinumab was more efficacious than either etanercept or methotrexate.[3] However, on January 17th, 2011, Abbott withdrew the new drug application for briakinumab in the U.S. and Europe because regulatory authorities provided feedback that indicated the need for more data and the potential for additional studies.

The purposes of this updated review of antipsoriatic biologic agents are to compare their pharmacologic properties and evaluate studies that address certain key clinical questions that are pertinent to the development of criteria for use of biologic agents in the Veterans Health Administration. The key questions are as follows: In U.S. veteran patients with chronic plaque psoriasis, is there a difference among (1) antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability; (2) antipsoriatic biologic agents and nonbiologic systemic agents in terms of efficacy, effectiveness, safety, or tolerability; (3) antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies); (4) antipsoriatic biologic agents only and combination biologic-nonbiologic therapies; (5) antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness. These are denoted CPP Q1–5. The same key questions were addressed for PsA and denoted PsA Q1–5.

REVIEW OF PRODUCT CHARACTERISTICS

FDA-approved Indications

Five immunosuppressive agents are approved for either CPP or PsA. Adalimumab, etanercept, and infliximab have been approved for both CPP and PsA; ustekinumab is approved for CPP; and golimumab is approved for PsA (Table 1). Refer to the prescribing information for these agents for a complete list of approved indications.

Table 1 Mechanisms and FDA-approved Psoriasis and Psoriatic Arthritis Indications

Agent	Mechanism	Moderate to Severe Plaque Psoriasis Indication (Year): Additional FDA Guidance ☑ = Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy	Psoriatic Arthritis Indication (Year): Additional FDA Guidance ⊙ = Reducing signs and symptoms of active psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function
Adalimumab (Humira® by Abbott)	Fully human anti–TNF-α mAb (Inhibits binding to p55 and p75 tmTNFRs; does not bind or inactivate TNF-β)	☑ *(2008):* When other systemic therapies are medically less appropriate. Should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.	⊙ *(2005):* For adults. Can be used alone or in combination with DMARDs.
Etanercept (Enbrel® by Immunex; mktd by Amgen and Pfizer)	Dimeric p75 sTNFR fusion protein; inhibits binding of TNF-α and TNF-β to tmTNFRs	☑ *(2004)*	⊙ *(1998):* Can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
Golimumab (Simponi® by Centocor Ortho Biotech)	Anti–TNF-α mAb (Binds to sTNFRs and tmTNFRs. Does not bind to TNF-β.)	—	Treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate *(2009)*
Infliximab (Remicade® by Centocor Ortho Biotech)	Chimeric anti–TNF-α mAb	Treatment of adult patients with chronic severe (i.e., extensive and / or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate *(2006):*	⊙ *(2006)*
Ustekinumab (Stelara® by Centocor Ortho Biotech)	Anti–IL-12/23 mAb	☑ *(2009)*	—

mAb, Monoclonal antibody; p55 and p75 TNFRs, a.k.a. TNFR1 and TNFR2, respectively; REMS (Risk Evaluation and Mitigation Strategies); sTNFRs, Soluble TNF receptors; tmTNFRs, Transmembrane TNF receptors; TNF, Tumor necrosis factor; TNF-β, a.k.a. lymphotoxin alpha (LT-α); TNFI, TNF Inhibitor

☑ Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy

⊙ Reducing signs and symptoms of active psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function

Dermatologic Off-label Uses for Which There is Insufficient Evidence

The following lists are not all-inclusive.

Antipsoriatic Biologics in General

- **Psoriasis types other than chronic, stable/nonflaring, moderate to severe plaque psoriasis.** These agents have been demonstrated to be efficacious in the treatment of chronic, stable/nonflaring, moderate to severe plaque psoriasis. There is insufficient evidence to support the efficacy and safety of biologics in the treatment of other types of psoriasis (e.g., guttate, erythrodermic, or pustular), mild psoriasis, and psoriasis in flare, and they should not be routinely used for these conditions. Biologic agents may be considered on a case-by-case basis for non-plaque psoriasis in patients who have had inadequate responses to traditional approaches. The Medical Board for the National Psoriasis Foundation (MBNPF) has recommended infliximab as a first-line treatment alternative and adalimumab and etanercept as second-line treatment alternatives for adult generalized pustular psoriasis.[4] For generalized pustular psoriasis in pregnancy, the MBNPF has recommended infliximab as a first-line treatment alternative. Biologics (adalimumab, alefacept, etanercept, and infliximb) are recommended as second-line systemic therapy for localized pustular psoriasis or palmoplantar pustular psoriasis. All of these recommendations are based on nonexperiemental descriptive studies (Level III evidence).
- **Oral Mucosal Disease.** Behcet's disease, recurrent apthous stomatitis, benign mucous membrane pemphigoid and lichen planus[5]
- Behcet's disease, non-infectious ocular inflammation, pyoderma gangrenosum and hidradenitis suppurativa[6]
- **SAPHO Syndrome.** [7]
- **20 inflammatory disorders.**[8]
- Lymphoedema associated with psoriatic arthritis (, adalimumab, etanercept, infliximab); see refs in Tong, 2009 #7006[9]
- Hidradenitis suppurativa, atopic dermatitis, pyoderma gangrenosum, and various blistering diseases (review of dermatologic off-label uses)[10]
- Use in hepatitis C–positive patients[11]
- Use in HIV-positive patients[12-14]
- Psoriatic ocular inflammatory disease[15]
- Cardiovascular disease associated with CPP (theoretical)[16]

Adalimumab

- Nail psoriasis. [17]
- Lymphedema associated with psoriatic arthritis[9]
- Erythrodermic psoriasis (case report)[18]

Etanercept

- Von Zumbusch pustular psoriasis in a patient with human immunodeficiency virus[19]
- Pustular psoriasis[20-22]
- Erythrodermic psoriasis (N = 10)[23]
- Pyoderma vegetans[24]

- Various inflammatory dermatologic disorders[25]

Infliximab

- Atopic dermatitis [primary reference of [26]][27]
- Hidradenitis suppurativa, etanercept failure[28]
- Keratoconjunctivitis sicca, severe refractory[29]
- Nail psoriasis: post hoc analysis of randomized placebo-controlled trial (N = 378)[30]; case reports[31-35]
- Pityriasis rubra pilaris [primary reference of [26]]
- Pustular psoriasis, palmoplantar or generalized: infliximab effective[36-39] or ineffective[40]
- Pyoderma gangrenosum[41,42]
- Ocular inflammatory disease, psoriatic [15]
- Sarcoidosis, cutaneous[primary reference of [26]]
- Intraarticular injections for PsA[43]

Off-label Uses for Which There Is At Least Fair-quality Evidence of Harm or Inefficacy

Infliximab in moderate to severe chronic heart failure, acute alcoholic hepatitis, and primary Sjogren's syndrome. There is evidence from double-blind randomized controlled trials that infliximab therapy results in lack of efficacy and harm when used for moderate to severe chronic heart failure[44] or acute alcoholic hepatitis,[45] and it is not efficacious for primary Sjogren's syndrome.[46]

Etanercept in treatment of heart failure. Two clinical trials showed that etanercept lacks efficacy in the treatment of heart failure, and the results of one of these trials suggested higher mortality in etanercept-treated patients relative to the placebo group.[47] In postmarketing safety surveillance, there have been reports of new and worsening heart failure in patients with and without risk factors.

Etanercept in Wegener's granulomatosis. A study evaluating the addition of etanercept to standard therapy, including cyclophosphamide, for treatment of Wegener's granulomatosis showed that, relative to standard therapy alone, combined therapy was associated with a higher incidence of non-cutaneous solid malignancies and was not associated with improved clinical outcomes.[47]

Etanercept in Crohn's disease[48]

Etanercept in sarcoidosis[49]

Contraindications

Table 2 Contraindications

Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
None	Sepsis	None	Hypersensitivity to any murine proteins or other product components	None
			Administration of doses > 5 mg/kg to patients with moderate to severe (NYHA class III or IV) congestive heart failure	

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52]; Stelara (ustekinumab) package insert[53]

Warnings and Precautions

The following warnings and precautions summarize recommendations in the product information by action categories. Note that a particular adverse event may fall under different action categories; for instance, heart failure recommendations appear under 'Use with Caution' and 'Monitor Closely' depending on the agent. VA PBM criteria for use recommendations may differ from those shown in Table 3 to enhance patient safety. ***Refer to complete prescribing information for detailed descriptions of warnings and precautions for each agent.***

Table 3 Warnings and Precautions

Action Category	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Prior to initiating therapy					
Perform tuberculin skin test (or QuantiFERON®-TB gold blood test) and/or chest X-ray and treat patient if positive for latent tuberculin infection	☑	☑	☑	☑	☑
Consider anti-TB therapy in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed	☑	☑	☑	☑	☑
Consider anti-TB therapy in patients with a negative test for latent TB but having risk factors for TB infection. Consult with expert.	☑	☑	☑	☑	
Evaluate patients at risk for hepatitis B virus infection for prior evidence of HBV infection	☑	☑	☑	☑	
Administer all age-appropriate immunizations to patient		☑		☑	☑
Do not initiate therapy if the patient has contraindications (Table 2) or…					
Has active infection (including tuberculosis)	☑	☑	☑	☑	☑
Has received BCG vaccination within the past year					☑
Has Wegener's granulomatosis and is receiving immunosuppressives		☑			
Is being treated with anakinra	☑	☑	☑	☑	—
Is being treated with abatacept	☑	☑	☑	☑	—
Is being given live vaccine(s) with biologic therapy	☑	☑	☑	☑	☑
Use caution / weigh risks and benefits of therapy when considering agent if the patient…					
Has chronic or recurrent infection	☑	☑	☑	☑	☑
Has been exposed to tuberculosis	☑		☑	☑	
Has resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis	☑	☑	☑	☑	
Has a history of opportunistic infection			☑		
Has condition that may predispose to infections	☑	☑	☑	☑	
Has a household contact who is administered a live vaccine (potential risk for transmission)					☑
Is elderly (increased risk of infections or malignancies)	☑	☑	☑	☑	
Is a carrier of hepatitis B virus	☑	☑	☑	☑	
If patient has been treated for hepatitis B reactivation, and resumption of TNFI therapy is being considered	☑	☑	☑	☑	
Is at high risk for malignancy, has a history of malignancy, or develops a malignancy			☑††	☑	
Has central or peripheral nervous system demyelinating disorder	☑	☑	☑	☑	
Has seizure disorder				☑	
Has heart failure	☑	☑	☑		
Has [mild, NYHA Class I / II] heart failure; consider other treatment options first				☑	
Has ongoing or history of significant hematologic abnormalities or cytopenias		☑	☑	☑	
Is receiving or has received allergy immunotherapy, particularly for anaphylaxis§					☑§

Action Category	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Has moderate to severe alcoholic hepatitis		☑‡‡			
Has moderate to severe chronic obstructive pulmonary disease (COPD) (because of increased risk of cancer)				☑	
Consider the following therapy or tests:					
Empiric antifungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness	☑	☑	☑	☑	
Appropriate diagnostic testing, e.g., tissue culture, stool culture, as dictated by clinical circumstances; theoretically, patients with pharmacologic blockade of IL-12/23 may have increased risk for vulnerability to disseminated infections from mycobacteria, salmonella, and BCG vaccination					☑
Monitor patient closely…					
If patient develops new infection	☑	☑	☑	☑	
For signs and symptoms of infection during or after a treatment course	☑	☑	☑	☑	☑
For development of signs and symptoms of TB during or after treatment, including in patients who tested negative for latent TB infection prior to initiating therapy or who have previously or recently traveled to countries with a high prevalence of TB, or who have had a close contact with a person with active TB	☑	☑	☑	☑	☑
During and for several months after therapy if patient is a hepatitis B virus carrier	☑	☑	☑	☑	
If patient has heart failure		☑	☑	☑	
For nonmelanoma skin cancer, particularly if patient is at increased risk (e.g., prior phototherapy); consider periodic skin examinations		☑		☑	
Consider discontinuing therapy if the patient…					
Develops hematologic cytopenias or pancytopenia	☑	☑		☑	
Develops new or worsening psoriasis	☑		☑		
Develops reactivation of hepatitis B virus		☑			
Develops central or peripheral nervous system demyelinating disorders			☑		
Discontinue therapy if the patient…					
Develops a serious infection or sepsis	☑	☑	☑	☑	
Develops malignancy		☑			
Develops new or worsening symptoms of heart failure			☑	☑	
Develops a lupus-like syndrome	☑	☑		☑	
Has reactivation of hepatitis B	☑		☑		
Develops autoimmune hepatitis		☑			
Develops significant clinical signs of liver injury				☑	
Has an anaphylactic or other serious hypersensitivity reaction	☑	☑		☑	☑
Has significant exposure to varicella virus (discontinue temporarily); consider prophylactic treatment with Varicella Zoster Immune Globulin		☑			
Develops significant hematologic abnormality		☑			
Develops significant central nervous system adverse reaction				☑	
Develops reversible posterior leukoencephalopathy syndrome (RPLS)					☑

Sources: Amevive (alefacept) package insert[54]; Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

§ Ustekinumab may decrease the protective effect of allergy immunotherapy and increase the risk of an allergic reaction to a dose of allergen immunotherapy. This is a theoretical risk; ustekinumab has not been evaluated in patients who have had allergy immunotherapy.

Φ Recommended for pediatric patients

†† Other than successfully treated nonmelanoma skin cancer

‡‡ Etanercept increased 6-month mortality rates in a placebo-controlled study evaluating it for moderate to severe alcoholic hepatitis (N = 48).[47]

Special Populations

Pregnancy and Lactation

All of the antipsoriatic biologic agents are pregnancy Category B (Table 4), and this is a potential advantage of the biologics over nonbiologics agents such as acitretin (Category X), cyclosporine (Category C), methotrexate (Category X), and methoxsalen (Category C). A case report of birth defects has been reported with etanercept by the VATER Association.[55] Use in pregnant women only if clearly needed.

Table 4 Use of Biologics in Pregnancy and Nursing Mothers

Agent	Category	Pregnancy Registry	Passage of Drug into Breast Milk	Absorption of Drug from Ingested Breast Milk	Comments
Adalimumab	B	1-877-311-8972	Unknown	Unknown	
Etanercept	B	1-877-311-8972	Unknown	Unknown	
Golimumab	B	—	Unknown	Unknown	Avoid giving live vaccines to infants for 6 months†
Infliximab	B	—	Unknown	Unknown	Avoid giving live vaccines to infants for 6 months†
Ustekinumab	B	—	Probable	Unknown	

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

VATER Association: Constellation of certain congenital abnormalies including Vertebral defects, Anal atresia, Tracheoesophageal fistula with esophageal atresia, Renal and Radial bone anomalies (also VACTER when Cardiac defects are present)

† Do not give live vaccines to infants exposed to golimumab or infliximab in utero for 6 months following the mother's last injection during pregnancy.

It is not known whether the adalimumab, etanercept, golimumab, and infliximab are excreted in human milk. Consider options to either discontinue nursing or discontinue use of these biologic agents.

Because ustekinumab is excreted in the milk of lactating monkeys that were given ustekinumab and because IgG is excreted in human milk, ustekinumab is expected to be excreted in human milk. Whether it is systemically absorbed after oral administration is not known.

Elderly

The use of biologic agents in elderly patients (65 years or older) is limited. Except for adalimumab, no apparent differences in safety or efficacy have been observed between older and younger patients; however, the number of elderly patients may have been insufficient to detect true differences. For adalimumab, higher frequencies of serious infections and malignancies were seen among patients 65 years and older relative to younger patients in rheumatoid arthritis clinical trials. Prescribing information for etanercept, golimumab, infliximab advise to use caution when using biologic agents in elderly patients because of their increased risks for infections.

Table 5 Observed Differences Between Elderly (≥ 65 years) and Younger Patients in Clinical Trials

Agent	Overall	Efficacy	Safety	Comments
Adalimumab	No differences	No diff	Increased serious infections and malignancies	
Etanercept	No differences	—	—	Insufficient data
Golimumab	—	—	No differences in SAEs, serious infections, and adverse events	
Infliximab	—	—	CPP: Increased serious adverse events and serious infections	PsA: Insufficient data
Ustekinumab	No differences	—	—	

Renal or Hepatic Impairment

No formal studies have been performed on the effects of renal or hepatic impairment on the pharmacokinetics of golimumab.

Diabetics

Etanercept has been associated with hypoglycemia in patients on antidiabetic medications. Reduction in antidiabetic medication may be needed.

Table 6 Adverse Events and Postmarketing Safety Experience

Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Most Serious Adverse Events (or Serious Adverse Events†)				
TB, opportunistic, and other serious infections; hepatitis B reactivation Malignancies Anaphylaxis or serious allergic reactions Neurologic reactions / Demyelinating disease Heart failure Hematologic cytopenias Immune reactions including lupus-like syndrome New or worsening psoriasis, including pustular psoriasis	Infections Neurologic events Congestive heart failure Hematologic events	Serious infections Malignancies	Infections Allergic reaction Edema Pancytopenia Hypotension Constipation Intestinal obstruction Dizziness Bradycardia Hepatitis Dehydration Thrombocytopenia Lymphoma Anemia Hemolytic anemia Cellulitis Sepsis Serum sickness Lower respiratory tract infection (including pneumonia) Pleurisy Pulmonary edema Increased sweating Thrombophlebitis Leukopenia Lymphadenopathy	Infections Malignancies Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Most Common Adverse Events				
Injection site reactions Upper respiratory infections (including sinus infections) Headache Rash Nausea	Infections Injection site reactions	Upper respiratory tract infections Nasopharyngitis	Respiratory infections (e.g., sinus infections, sore throat) Infusion-related reactions Headache Abdominal pain	Nasopharyngitis Upper respiratory tract infections Headache Fatigue
Postmarketing Adverse Events				
Thrombocytopenia Anaphylaxis, angioneurotic edema Interstitial lung disease, including pulmonary fibrosis	Pancytopenia, anemia, leukopenia, neutropenia, thrombocytopenia,	Lymphomas and other malignancies, including acute and chronic	Hepatosplenic T-cell lymphoma (HSTCL)†† Lymphomas and	Serious allergic reactions (including angioedema, dyspnea, and

Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar) Systemic vasculitis	lymphadenopathy, aplastic anemia Congestive heart failure Angioedema, chest pain Autoimmune hepatitis, elevated transaminases Macrophage activation syndrome, systemic vasculitis Lupus-like syndrome Nonmelanoma skin cancers, lymphoma and other malignancies Convulsions, multiple sclerosis, demyelination, optic neuritis, transverse myelitis, paresthesias Uveitis Interstitial lung disease Cutaneous lupus erythematosis, cutaneous vasculitis (including leukocytoclastic vasculitis), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, subcutaneous nodule, new or worsening psoriasis (all subtypes including pustular and palmoplantar) Opportunistic infections, including atypical mycobacterial infection, herpes zoster, aspergillosis, and *Pneumocystis*	leukemia (observed with TNFIs)	other malignancies, including acute and chronic leukemia (observed with TNFIs) Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis; some cases of autoimmune hepatitis	hypotension) Hypersensitivity reactions (including rash and urticaria)

Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
	jiroveci pneumonia, protozoal infections			

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

† Product information for infliximab listed serious adverse events and not "Most serious adverse events"

†† All cases of hepatosplenic T-cell lymphoma were reported in patients with Crohn's disease or ulcerative colitis, mainly adolescent or young adult males, who had received concurrent treatment with azathioprine or 6-mercaptopurine.

New or Worsening Psoriasis (Paradoxical Psoriasis) and Other Dermatologic Reactions

TNFIs have been associated with paradoxically inducing new or worsening psoriatic lesions or psoriasiform exanthema in a subset of patients who may or may not have psoriatic conditions that are typically treated with TNFIs (e.g., rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, psoriatic arthritis).[56-62] The adverse effect seems to be common, occurring in about 1.5% to 5% of patients on TNFIs.[63] All of the older TNFIs that have been previously reviewed for this complication (infliximab, etanercept, adalimumab) have been associated with paradoxical psoriasis.[56,57,59,60,62-67] No apparent risk factors have been identified and the condition can occur at any time during TNFI therapy.[56,68] The morphology is often atypical, such as palmoplantar pustulosis and guttate psoriasis.[58] The etiopathogenesis is unclear but appears to be due to TNFI-induced, secondary autoimmune dysfunction, possibly in predisposed patients with genetic polymorphisms.[57] One proposed mechanism is that an imbalance in cytokine production due to TNF inhibition may lead to upregulation of plasmacytoid dendritic cells that overproduce unopposed TNF-α, ultimately resulting in altered T-helper-1 lymphocyte trafficking.[56,59,67] One author suggested that the psoriasiform lesions may instead be chlamydia-associated keratoderma blenorrhagicum.[69]

Switching to another TNFI usually does not cause relapse of the condition, suggesting that the mechanism may differ among agents. New psoriatic lesions have resolved with discontinuation of TNFI therapy, but may also resolve despite continued therapy or substituted TNFI therapy. Based on a literature review, Collamer, et al. recommended aggressive treatment of the worsened or new psoriatic lesions using traditional antipsoriatic therapies; discontinuation of TNFI therapy if the lesions are severe or intolerable or if the patient prefers to stop TNFI therapy; and consider switching to an alternate TNFI if traditional treatments are unsuccessful.[56] Topical corticosteroids, switching to another TNFI, and discontinuation of TNFI with addition of systemic therapy have varying success in resolving the paradoxical psoriasis.[58]

Other dermatologic reactions have been reported, including lichenoid eruptions,[70] cutaneous viral, bacterial, and fungal infections and uncommon dermatologic diseases such as interstitial granulomatous dermatitis, dermatitis herpetiformis, leucocytoclastic vasculitis and alopecia.[61,71]

Risk Evaluation and Mitigation Strategies for Biologics

All of the biologics for treatment of psoriasis or psoriatic arthritis have a Risk Evaluation and Mitigation Strategies (REMS) program or an element of REMS.

Table 7 Biologic Risk Evaluation and Mitigation Strategies

Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
TNFI REMS*	TNFI REMS*	Medication Guide	TNFI REMS*	IL-12/23 REMS†
Medication Guide	Medication Guide		Medication Guide	Medication Guide
Communication Plan	Communication Plan		Communication Plan	Communication Plan

* TNFI REMS: For histoplasmosis and other invasive fungal infections and other serious risks associated with TNFI use.

† IL-12/23 REMS: For risks of serious infections and malignancy, and reversible posterior leukoencephalopathy syndrome. Psoriasis Longitudinal Assessment and Registry (PSOLAR) voluntary disease-specific patient registry.

Biologic Drug Interactions

Drug interaction studies have been done with adalimumab; none have been performed with etanercept, infliximab, and ustekinumab.

Table 8 Drug Interactions

	Possible Effect and Recommendation				
Concomitant Agent	**Adalimumab**	**Etanercept**	**Golimumab**	**Infliximab**	**Ustekinumab**
Abatacept	—	Increased serious adverse events including infections; concurrent use not recommended	Increased serious infections and did not add benefits; concurrent use not recommended	—	—
Anakinra	Increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to individual agents alone	Increased infection rate. Avoid concurrent use	Increased serious infections and neutropenia; no added benefits; concurrent use not recommended	—	—
Cyclophosphamide	—	Concurrent use not recommended	—	—	—
CYP450 Substrates with Narrow Therapeutic Index	—	—	Possible changes in effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline)††	—	Possible changes in effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline)††
Methotrexate	Reduced clearance of adalimumab; however, no dosage adjustment necessary	May be given during etanercept therapy for PsA; no guidance for PsV.	Increased golimumab levels by 36% in patients with PsA. Decreased incidence of anti-golimumab antibodies. No influence on efficacy or safety of golimumab.	May decrease incidence of anti-infliximab antibody production and increase infliximab concentrations. May be used concomitantly with infliximab in PsA.	—
Rituximab	—	—	Increased serious infections in RA patients treated with rituximab who received subsequent treatment with a TNFI; no specific recommendations	—	—
Sulfasalazine	—	Mild decrease in mean neutrophil counts; clinical significance unknown	No effect on apparent clearance of golimumab	—	—
Phototherapy and other immunosuppressants	—	Glucocorticoids may be given with etanercept concomitantly.	—	Co-administration with immunosuppressants appears to reduce the frequencies of antibodies to infliximab and infusion reactions.	Safety of concurrent use not evaluated

Concomitant Agent	Possible Effect and Recommendation				
	Adalimumab	**Etanercept**	**Golimumab**	**Infliximab**	**Ustekinumab**
Vaccines, Acellular / Non-live	—	Not studied; effective immune response with pneumococcal polysaccharide vaccine; non-live vaccines may be given concurrently	Adequate immune response to pneumococcal vaccination; non-live vaccines may be given concurrently	Not studied. Possible decreased immune response. No specific recommendations.	May not elicit an adequate immune response.
Vaccines, Live and Live-attenuated	Avoid concurrent use	Possible disseminated infection; effective B-cell immune responses to pneumococcal polysaccharide but lower antibody titers. Avoid concurrent use.	Avoid concurrent use	Not studied; possible disseminated infection and lack of immune response. Avoid concurrent use.	Avoid concurrent use Avoid BCG vaccines during treatment, for 1 year prior to, and for 1 year after stopping treatment

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

PsA, Psoriatic arthritis; PsV, Psoriasis vulgaris (plaque psoriasis)

†† TNFI and IL-12/23 mAb therapy may lead to normalization of suppressed formation of CYP450 enzymes that is caused by increased levels of cytokines during chronic inflammation. However, a role for IL-12 or IL-23 in the regulation of CYP450 enzymes has not been reported.

Biologics and Concomitant Systemic Therapies

Expert opinion considers concomitant use of phototherapy with biologic agents to be relatively safe.

Table 9 Concomitant Medications

	Adalimumab	**Etanercept**	**Golimumab**	**Infliximab**	**Ustekinumab**
Co-medications Permitted in Clinical Trials					
Plaque Psoriasis	Noncorticosteroid shampoos; bland emollients; low- to mid-potency corticosteroids applied to palms, soles, face, and groin	Methotrexate ≤ 25 mg/wk Glucocorticoids Salicylates Nonsteroidal anti-inflammatory drugs Analgesics Vaccinations except live vaccines	—	Nonmedicinal emollients Nonprescription tar or salicylic shampoos	None reported
Psoriatic Arthritis	Methotrexate ≤ 30 mg/wk	Methotrexate ≤25 mg/wk Corticosteroids equivalent to ≤10 mg/d of prednisone. Topical therapies on scalp, axillae, and groin only.	Methotrexate Corticosteroids, oral equivalent to ≤ 10 mg of prednisone NSAIDs	1 of the following DMARDs: Methotrexate ≤15 mg/wk with folic acid, leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, or azathioprine. Corticosteroids (equivalent to ≤10 mg/d prednisone) NSAIDs One injection of intraarticular corticosteroids Standard topical treatments	—
Co-medications Not Permitted in Clinical Trials					
Plaque	Topical	Live vaccines	—	Systemic therapy	Systemic, photo-, or

	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Psoriasis	antipsoriatics; phototherapy; nonbiologic systemic therapies; biologic therapies			(UVB, PUVA, cyclosporine, methotrexate, or acitretin) Topical therapy	biologic therapy Topical therapy Immunosuppressants Vaccines
Psoriatic Arthritis	Cyclosporine, tacrolimus, DMARDs other than MTX ≤ 30 mg/wk, oral retinoids; topical antipsoriatics other than medicated shampoos or low-potency topical steroids; MTX at dosages > 30 mg/wk; prednisone-equivalent of >10 mg/d; TNFI	Other DMARDs Phototherapy Oral retinoids Topical vitamin A or D analogs Anthralin	Sulfasalazine Hydrochloroquine Cytotoxics Other biologics	PUVA Intramuscular or intravenous corticosteroids Cyclosporine Tacrolimus Monoclonal antibody or fusion protein	—
Co-medications Sanctioned in Product Information					
Plaque Psoriasis	—	—	N/A	—	—
Psoriatic Arthritis	Methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs	Methotrexate (in nonresponders to methotrexate alone)	Methotrexate	Methotrexate	N/A

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

Dosage and Administration

FDA-approved dosing regimens and storage requirements are summarized in Table 10.

Table 10 Dosage Regimens for Adults, Self-administration, Storage and Stability

	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Dosage in Plaque Psoriasis	80 mg s.c. then 40 mg every other week starting one week after initial dose	50 mg s.c. twice weekly for 3 months, then 50 mg once weekly Starting doses of 25 or 50 mg once weekly have also been shown to be efficacious	—	5 mg/kg i.v. at 0, 2, and 6 wk then every 8 wk	Patients 100 kg or less: 45 mg s.c. at 0 and 4 wk, then 45 mg every 12 wk Patients over 100 kg: 90 mg at 0 and 4 wk, then 90 mg every 12 wk. †
Dosage in Psoriatic Arthritis	40 mg s.c. every other week	50 mg s.c. once weekly (with or without methotrexate)	50 mg s.c. once a month	5 mg/kg i.v. (at 0, 2, and 6 wk) then every 8 wk	—
Pre-filled Syringe Available for Patient Self-Injection	Yes	Yes	Yes	No	No
Storage and Stability	Must be refrigerated at 2–8°C (36–46°F) and protected from light; keep in original carton. DO	Same as for adalimumab Use within 14 d after reconstitution.	Same as for adalimumab	Same as for adalimumab. No preservatives; do not store unused portions of	Same as for adalimumab. Store upright. No preservatives; discard

	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
	NOT FREEZE. Do not shake.			reconstituted solution for later use.	any unused portion.

Sources: Enbrel (etanercept) package insert[47]; Humira (adalimumab) package insert[50]; Remicade (infliximab) package insert[51]; Simponi (golimumab) package insert[52];Stelara (ustekinumab) package insert[53]

† Ustekinumab 45 mg was also efficacious in patients over 100 kg; however, 90 mg had better efficacy.

Off-label dosage regimens (dose escalation and reduction, and interrupted treatment) have been reviewed.[72] Safety and efficacy data on off-label dosing is limited. In general, dose escalation resulted in improved response rates but the gain in response was disproportionately less than the increase in dose (e.g., for etanercept, a 100% increase in dose from 25 mg to 50 mg twice weekly continuously resulted in an absolute response gain of 15%). Withdrawal then reinstitution of therapy generally results in a lower response rate than that initially observed.

Summary of Product Characteristics

The advantages and disadvantages of the antipsoriatic biologic agents are summarized in Table 11.

Table 11 Relative Characteristics of Biologic Agents for Psoriasis and Psoriatic Arthritis

	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Advantages	Self-injectable (s.c.) Less frequent dosing (every other week) than etanercept, and infliximab Familiarity with drug; > 5 years of safety experience Psoriasis Starter Package available to aid dosing May be used in combination with methotrexate or other DMARDs for psoriatic arthritis Relatively early onset	Self-injectable (s.c.) Familiarity with drug; > 5 years of safety experience May be used in combination with methotrexate for psoriatic arthritis Shorter duration / potentially faster resolution of AEs relative to TNF mAbs	Self-injectable (s.c.) Less frequent dosing than adalimumab, etanercept, and infliximab for psoriatic arthritis May be used in combination with methotrexate for psoriatic arthritis	Appears to be highly effective with early onset (2 wk)[73] May induce remissions of 6–8 mo (n = 30)[74] Familiarity with drug; > 5 years of safety experience	Least frequent and fewer injections (every 3 mo, s.c.) Lower incidence of injection site reactions than etanercept Lack of cytopenias (vs. TNFIs) Lacks increased risks and contraindications of congestive heart failure and demyelinating disease seen with TNFIs Lacks increased risk of hepatotoxicity (mainly seen with infliximab) Lacks lupus-like syndrome (vs. TNFIs) Unique mechanism of action; alternative in TNFI failures
Disadvantages	Congestive heart failure Demyelinating disease Lupus-like syndrome Autoantibodies Latex derivative in needle cap (potential allergic reactions)	Slower onset relative to TNF mAbs (although early onset (2 wk) possible[75]) Congestive heart failure Demyelinating disease Lupus-like syndrome Autoantibodies Latex derivative in needle cap (potential allergic reactions)	Limited safety experience Congestive heart failure Demyelinating disease Lupus-like syndrome Autoantibodies Latex derivative in needle cap (potential allergic reactions) Lacks FDA-approved indication for plaque psoriasis	Inconvenient; requires clinic visits every 2 to 4 wk for i.v. infusions Infusion reactions† Congestive heart failure Demyelinating disease Lupus-like syndrome Neutralizing antibodies lead to dose escalation	Requires administration by health care professional‡ Adverse effects might last longer due to drug's long duration Limited safety experience beyond 1 year Lacks data on adequacy of immune response with concomitant non-live vaccinations Latex derivative in needle cap (potential allergic reactions) Lacks FDA approval for psoriatic arthritis

† Mild infusion reactions preventable with acetaminophen 325 mg, nonsedating antihistamine, or both.[74]

‡ Ustekinumab should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician

Clinical Practice Guidelines in CPP and PsA

Comparison of Guideline Recommendations

See Table 12.

In moderate to severe CPP, biologics are generally recommended as second-line therapies following trials of nonbiologic systemic therapies.

In PsA, biologics are recommended as first- or second-line therapies. Nonbiologic agents may be ineffective or lack evidence of efficacy in certain subgroups of patients.

Table 12 Clinical Practice Guidelines on the Use of Biologics in Psoriasis and Psoriatic Arthritis

Reference	Role of Biologic Therapy (Strength of Recommendation or Level of Evidence as Reported in Guideline)	Strength of Recommendation – Level of Evidence by Agent				
		ADA	ALF	ETA	INF	UST
Plaque Psoriasis						
Consensus guidelines for the management of plaque psoriasis. 2012. U.S. North American Psoriasis Guidelines: National Psoriasis Foundation Update of Canadian Guidelines for the Management of Plaque Psoriasis. Also see Supporting Data.[76]	In aiming to achieve complete control of moderate to severe plaque psoriasis, the physician should consider each of the [alternative] regimens and choose ones that are safe for and acceptable to the individual patient.[‡] *No clinical reason supports reserving the biologics for second-line use.*	**D**	**D**	**D**	**D**	**D**
Diagnosis and management of psoriasis and psoriatic arthritis in adults. A national clinical guideline. 2010. Scottish Intercollegiate Guidelines Network - National Government Agency[77]	Patients with severe psoriasis who fail to respond to, have a contraindication to, or are intolerant of phototherapy and systemic therapies including CSA and MTX should be offered biologic therapy unless they have contraindications or are at increased risk of hazards from these therapies **(A)**	**A**		**A**	**A**	**A**
British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. 2005 Sep (revised 2009 Aug). British Association of Dermatologists - Medical Specialty Society.[78]	(a) *Severe disease* or exceptional circumstances (for example, disease affecting high-impact sites with associated significant functional or psychological morbidity such as acral psoriasis) **(D-3)** **AND** (b) *Fulfill at least one of the following clinical categories* **(D-3 and formal consensus)** (i) Phototherapy and alternative standard systemic therapy are contraindicated or cannot be used due to the development of, or risk of developing, clinically important treatment related toxicity. (ii) Intolerance to standard systemic therapy (iii) Unresponsive to standard systemic therapy[b] (iv) Significant, coexistent, unrelated comorbidity which precludes use of systemic agents such as CSA or MTX (v) Severe, unstable, life-threatening disease UST is recommended when TNFIs have failed or are contraindicated because UST has less exposure / safety data	**A-1++**		**A-1++**	**A-1++**	**A-1+**
AAD 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.[79]	TNFI +/– MTX for moderate–severe CPP +/– PsA	**A-I**	**A-I**	**A-I**	**A-I**	
Psoriatic Arthritis						
European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Gossec L,	In patients with active disease (particularly those with many swollen joints—usually ≥ 5, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extraarticular manifestation), treatment with DMARDs such as	NR	NR	NR	NR	NR

Reference	Role of Biologic Therapy (Strength of Recommendation or Level of Evidence as Reported in Guideline)	Strength of Recommendation – Level of Evidence by Agent				
		ADA	ALF	ETA	INF	UST
Smolen JS, et al. EULAR (2012)[80] A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the **EULAR** recommendations for the management of psoriatic arthritis. Ash (2012)[81]	MTX, sulfasalazine (SSZ), leflunomide, should be considered at an early stage. (**1B, 4** – for 'at early stage'; **B**) In patients with active psoriatic arthritis and clinically relevant psoriasis, a DMARD that also improves psoriasis, such as MTX, should be preferred. (**1B**; **A**) In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as MTX, therapy with a TNFI should be commenced. (**1B**; **B**) In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local steroid injections, TNFIs may be considered. (**2B**; **B**) TNFI therapy might exceptionally be considered for a very active patient naïve of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extraarticular manifestations, especially extensive skin involvement). (**4**; **D**) In patients who fail to respond adequately to one TNFI, switching to another TNFI agent should be considered. (**2B**; **B**)					
Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. 2006 Jul (revised 2010 Aug). National Institute for Health and Clinical Excellence (NICE) - National Government Agency[82]	ETA, INF and ADA are recommended for the treatment of adults with active and progressive PsA when the following criteria are met. • The person has peripheral arthritis with three or more tender joints and three or more swollen joints, *and* • The PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination. Treatment as described above should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. ETA, ADA or INF treatment should be discontinued in people whose PsA has not shown an adequate response using the PsARC at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria (one of which has to be joint tenderness or swelling score), with no worsening in any of the four criteria. People whose disease has a PASI-75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response	NA		NA	NA	
Diagnosis and management of psoriasis and psoriatic arthritis in adults. A national clinical guideline. 2010 Oct. Scottish Intercollegiate Guidelines Network - National Government Agency[77]	ADA, ETA, and INF are recommended for treatment of active PsA in patients who have failed to respond to, are intolerant of, or have had contraindications to at least two DMARDs: Leflunomide is recommended for the treatment of active peripheral PsA **(A).** Sulfasalazine may be considered as an alternative in the treatment of peripheral PsA **(C).** MTX may be considered in the treatment of PsA **(C).**	**A**		**A**	**A**	
British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009[78]	(i) Patients with active PsA or skin disease that fulfills defined BSR or BAD guideline criteria, respectively (ii) Patients with severe skin psoriasis and PsA who have failed or cannot use MTX may need to be considered for biologic treatment given the potential benefit of such treatment on both components of psoriatic disease.	**A-1++**		**A-1++**	**A-1++**	**A-1+**
Ritchlin, et al. (2009) Treatment recommendations for psoriatic	**Moderate–Severe Peripheral Arthritis:** Patients who (1) fail to respond to at least one DMARD (adequate trial is defined	**A**		**A**	**A**	

Reference	Role of Biologic Therapy (Strength of Recommendation or Level of Evidence as Reported in Guideline)	Strength of Recommendation – Level of Evidence by Agent				
		ADA	ALF	ETA	INF	UST
arthritis[83]	as ≥ 3 months, of which ≥2 months is at standard target dose unless intolerance or toxicity limits the dose) or (2) have a poor prognosis (even without DMARD failure). DMARDs have the potential to reduce or prevent joint damage and preserve joint integrity and function; however, none have been shown to do this in PsA. No evidence supporting DMARDs ahead of TNFIs, and the effect size for TNFIs is much larger than that for traditional DMARDs. ETA, INF and ADA are equally effective for the treatment of peripheral arthritis and for the inhibition of radiographic progression.					
	Moderate–Severe Skin Disease: TNFIs (ETA, ADA, and INF) are considered first-line therapies, along with phototherapy, methotrexate, fumaric acids (available in Germany) and CSA. ETA may be less effective in pts with high BMIs.	**A**		**A**	**A**	
	Nail Disease, Any Severity: INF and ALF.		**C**		**C**	
	Moderate–Severe Spinal Disease: INF, ETA and ADA. These agents likely to have similar treatment responses in PsA based on data for AS. Oral DMARDs are considered ineffective.	**A**		**A**	**A**	
	Severe Enthesitis: INF and ETA (evidence of efficacy shown in spondyloarthropathies).			**A**	**A**	
	Dactylitis, Any Severity: Some evidence available for INF. Treatment is largely empirical. NSAIDs **(D)** usually used initially. Injectable CS **(D)** are often used. DMARDs **(D)** used in resistant cases nearly always in the context of co-existing active disease.				**A**	
Guidelines of care for the management of **psoriasis** and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and **guidelines** of care for treatment with an emphasis on the biologics. [84]	Biologics often combined with DMARDs, particularly MTX. Combination therapy is considered by many to be the standard of care but lacks good-quality evidence.	**A-I**	NFS	**A-I**	**A-I**	

Table includes evidence-based clinical practice guidelines published since 2007. No guidelines had recommendations or evidence for golimumab.

† Patients with nondeforming psoriatic arthritis without any radiographic changes, loss of range of motion, or interference with tasks of daily living should not automatically be treated with tumor necrosis factor inhibitors.

‡ For the purposes of these guidelines, patients are considered to have moderate to severe psoriasis if they cannot achieve, or would not be expected to achieve, adequate control using topical agents, with adequacy defined by the patient's own perception of the disease and its burdens. Alternative regimens were: adalimumab, etanercept (50 mg twice weekly then stepped down to 50 mg weekly); etanercept (50 mg twice weekly); infliximab; PUVA or narrowband UVB (twice weekly); narrowband UVB (thrice weekly); RePUVA (thrice weekly) plus oral acitretin (daily); narrowband UVB (thrice weekly) plus alefacept (weekly); broadband UVB (twice weekly) plus topical calcipotriol (daily); broadband ReUVB with daily oral acitretin; narrowband ReUVB (four times weekly) plus topical tazarotene (daily); UVB plus crude coal tar (Goeckerman and related procedures); ustekinumab.

A At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; *or a* body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results. 1++ studies were high quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias. 1+ studies were well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1++ = High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+ = Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or e*xtrapolated evidence from studies rate as 2++.
2+ = Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2++ = high quality systematic reviews of case control or cohort studies or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.

D Evidence level 3 (non-analytic studies; e.g., case reports, case series) or 4 (expert opinion); *or e*xtrapolated evidence from studies rated as 2+

A-I A = Recommendation based on consistent and good quality patient-oriented evidence; I = good-quality, patient-oriented evidence

EULAR Categories of Evidence

1A From meta-analysis of randomised controlled trials

1B From at least one randomised controlled trial
2A From at least one controlled study without randomisation
2B From at least one type of quasi-experimental study
3 From descriptive studies, such as comparative studies, correlation studies, or case-control studies
4 From expert committee reports or opinions and/or clinical experience of respected authorities

EULAR Strength of Recommendations

A Category I evidence
B Category II evidence or extrapolated recommendations from category I evidence
C Category III evidence or extrapolated recommendation from category I or II evidence
D Category IV evidence or extrapolated recommendation from category II or III evidence

ADA, Adalimumab; ALF, Alefacept; AS, Ankylosing spondylitis; BAD, British Association of Dermatologists; BSR, British Society for Rheumatology; CPP, Chronic plaque psoriasis; CS, Corticosteroids; CSA, Cyclosporin-A; DMARD, Disease Modifying Antirheumatic Drug; ETA, Etanercept; GOL, Golimumab; INF, Infliximab; MTX, Methotrexate; NA, Not applicable; NBUVB, Narrowband ultraviolet B; NFS, Need further studies; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; PUVA, Psoralen and ultraviolet A; UST, Ustekinumab; UV, Ultraviolet

COMPARATIVE STUDIES IN CHRONIC PLAQUE PSORIASIS

The literature search found no trials that stated U.S. Veterans were part of the study population. Therefore, key questions were amended and this section summarizes the otherwise relevant studies.

Efficacy Measures in CPP

Psoriasis Area and Severity Index (PASI). The PASI grades the average redness, thickness, and scaliness of the lesions (each on a scale from 0 [None] to 4 [Severe]), weighted by the area of involvement.

Physician Global Assessment (PGA). The standard is referred to as the *static* form. The physician rates the global assessment at a point in time on a scale of increasing severity from 0 (Clear) to 6.

Dermatology Life Quality Index (DLQI). Quality of life measure. DLQI overall scores range from 0 to 30, with higher scores indicating a more impaired functional status. The MCID for the DLQI in patients with PsA has not been established, but in psoriasis it has been estimated to be a five-point improvement

Disease Severity. One definition of severe psoriasis is a PASI of ≥ 10 plus a DLQI > 10.[85] In a 2005 review of the PASI instrument alone,[86] severe psoriasis was defined as a PASI > 12 and moderate psoriasis as a PASI of 7 to 12.

Response. In clinical trials, responders are typically defined as those who achieve at least 75% improvement (reduction) in PASI scores (PASI-75). However, in practice, a combination of lesion severity, clinician's global assessment, and patient's report of quality of life changes provide a more comprehensive assessment of response.

CPP Q1 In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

Efficacy in CPP: Head-to-Head Trials

ACCEPT Trial.[87] In the first head-to-head trial to directly compare biologic agents, ustekinumab was shown to be superior in efficacy and similar in safety to etanercept in patients with moderate to severe chronic plaque psoriasis for a period of 12 weeks. The NNTs for the PASI-75 responder rate were 9.4 and 5.9 for ustekinumab 45 mg and 90 mg, respectively, reflecting a moderate benefit relative to etanercept. Additional details of this trial are available in the National PBM Ustekinumab Monograph available at www.pbm.va.gov.

Efficacy in CPP: Indirect Comparisons Based on Systematic Reviews / Meta-analyses of Placebo-controlled Trials

See Appendix, Table 21.

The results of meta-analyses showed the following indirect comparisons:

- In one fair-quality systematic review, infliximab and adalimumab were better than etanercept and alefacept in achieving PASI-75.[88]
- In another fair-quality systematic review, infliximab was better than adalimumab, which in turn was better than etanercept in achieving PASI-75.[89]
- In a low-quality systematic review / meta-analysis of 3 placebo-controlled trials that evaluated PASI-75 responder rates at 24 weeks, adalimumab, etanercept and infliximab were similar in efficacy, with NNTBs (95% CI) of 1.6 (1.6 to 1.7), 2.1 (1.8 to 2.5) and 1.4 (1.3 to 1.5), respectively.[90]
- Alefacept is the least effective relative to infliximab, adalimumab, and etanercept (fair quality).[88]
- The rank order from best to worst in terms of improving DLQI-measured HRQoL was infliximab, etanercept, then alefacept (two systematic reviews of poor[91] and fair[92] quality).

Effectiveness in CPP: Long-term Comparative Studies

No long-term comparative studies were found. The literature search found four noncomparative, open-label, long-term studies of etanercept,[93-96] one of adalimumab (the REVEAL study, published twice to report 3-year efficacy and safety of continuous therapy[97] and interrupted therapy with retreatment[98]), and one of infliximab in combination with nonbiologic systemic agents.[99]

Safety: Evidence Reviews from Clinical Practice Guidelines

According to the Scottish Intercollegiate Guidelines Network clinical practice guideline on the management of psoriasis and psoriatic arthritis, there do not appear to be any significant differences in safety between agents in terms of incidence of adverse effects although the adverse effect profiles differ.[77] Therapy should be individualized based on factors such as comorbidity, presence of psoriatic arthritis, and adverse effects. The most common adverse effects for the biologic agents evaluated were as follows:

- Adalimumab—upper respiratory tract infection, nasopharyngitis, and injection site reactions.
- Infliximab—infusion reactions and antibody formation; unclear whether the incidences are higher than with placebo.
- Etanercept—injection site reactions.

Safety: Head-to-Head Trials

Injection Site Reactions with Etanercept. The only head-to-head study that has provided comparative safety data between biologic agents was a 12-week Phase III trial that compared ustekinumab and etanercept in patients with moderate to severe CPP.[87] The main difference in safety was a higher incidence of injection site reactions with etanercept (14%) than with ustekinumab (0.7%).

Safety in CPP and Across Disease Conditions: Indirect Comparisons from Systematic Reviews / Meta-analyses of Placebo-controlled Trials

In a meta-analysis that specifically evaluated the risk of major adverse cardiovascular events (MACEs) with anti-IL-12/23 agents (ustekinumab and briakinumab) relative to TNFIs, neither class of biologics showed a statistically significant difference from placebo in the rate of MACEs in patients with CPP; however, one could not exclude the possibility of a Type II error.[100]

In a low-quality systematic review, the risks of lymphoma, TB and demyelinating disease with TNFIs were estimated from rheumatoid arthritis studies.[90] For lymphoma, the NNT varied widely, even between harm (increased risk) and benefit (decreased risk), partly depending on the study design (Table 13). For TB, the results

of the different studies consistently showed an increased risk of harm, although the NNT estimates varied widely at least partly because of variability among studies in country and the underlying prevalence of TB as well as in TB screening practices. For demyelinating disease, there was also wide variability in NNTs, with studies showing increased risk of harm except for one postmarketing study of infliximab. It is unclear whether any of these estimates of risk and NNTs can be applied to patients with psoriasis.

Table 13 Systematic Review of Major Harms with TNFIs in Patients with Rheumatoid Arthritis

Study Design	ADA	ETA	INF
Lymphoma			
Controlled and open-label clinical trials	NNTH 2100	NNTH 5900	NNTH 15,000
Postmarketing surveillance	NNTB 3000	NNTB 2300	NNTB 1800
Cohort studies	—	NNTH 1400	NNTH 1900
Tuberculosis			
North American controlled and open-label clinical trials	NNTH 1300	—	—
North American postmarketing surveillance	NNTH 7200	NNTH 160,000	NNTH 4200
North American cohort studies			NNTH 2100
European controlled and open-label clinical trials	NNTH 78 NNTH 330	—	—
European postmarketing surveillance	—	NNTH 19,000	NNTH 1400
European cohort studies	—	NNTH 2200	NNTH 71 NNTH 900
Demyelinating Disease			
Controlled and open-label clinical trials	NNTH 1400	NNTH 1200	NNTH 3500
Postmarketing surveillance	NNTH 50,000	NNTH 360,000	NNTB 40,000

Source: Dharamsi (2009)[90]

Safety in CPP: Controlled Observational Studies

Potentially Higher Risk of Paradoxical Psoriasis with Adalimumab. In a British Society for Rheumatology Biologics Register (BSRBR) study involving patients with severe rheumatoid arthritis, 25 incident cases of psoriasis occurred in 9826 TNFI-treated patients (5265 etanercept, 3569 infliximab, 3907 adalimumab) and none in 2880 DMARD-treated patients.[101] The crude incidence rates were 1.04 (95% CI 0.67 to 1.54) per 1000 person years for TNFI-treated patients and 0 (upper 97.5% CI 0.71) per 1000 person years in the comparison group. The difference did not reach the level of statistical significance. For the TNFIs, the crude rates (95% CI) per 1000 person years were 0.59 (0.22 to 1.28) for etanercept, 0.88 (0.32 to 1.93) for infliximab and 1.84 (0.98 to 3.15) for adalimumab. The adjusted incidence rate ratios were higher with adalimumab than etanercept (4.6, 95% CI 1.7 to 12.1) and infliximab (3.5, 95% CI 1.3 to 9.3). According to the authors, the results suggested that the risk of paradoxical psoriasis is higher with TNFIs than DMARDs and that adalimumab therapy was associated with a higher risk than the other two biologic agents. It is unclear whether these findings can be applied to patients with CPP.

Potentially Higher Risk of Tuberculosis with Adalimumab and Infliximab. A 3-year prospective incidence study with case-control analysis used the French Research Axed on Tolerance of bIOtherapies (RATIO) Registry to compare the risk of TB with TNFI monoclonal antibodies (mABs; adalimumab, infliximab) and soluble TNF receptors (sTNFRs; etanercept).[102] Of 69 validated cases of TB, in which no appropriate anti-TB drug prophylaxis had been given, one patient had psoriasis, 40 rheumatoid arthritis, 18 spondylarthritides, 9 inflammatory colitis and one Behcet's disease. These patients were treated with adalimumab (n = 28), infliximab (n = 36) or etanercept (n = 5). Two TNFI-treated control patients without TB were randomly matched to each of the cases. The sex- and age-adjusted incidence of TB in TNFI-treated patients relative to the general French population was 116.7 per

100,000 patient-years. The standardized incidence ratio (95% CI) was 12.2 (9.7 to 15.5) overall, 29.3 (20.3 to 42.4) with adalimumab, 18.6 (13.4 to 25.8) for infliximab and 1.8 (0.7 to 4.3) for etanercept. In the case-control analysis, adalimumab and infliximab exposures were independent risk factors for TB, with odds ratios (95% CI) of 17.1 (3.6 to 80.6) and 13.3 (2.6 to 69.0), respectively, relative to etanercept. Age, first year of TNFI therapy, and being born in an endemic area were also risk factors. The authors concluded that the risk of TB was higher for patients treated with TNFI mAb agents than for those treated with sTNFR therapy, and early TNFI therapy and lack of chemoprophylaxis increased the risk of TB reactivation. It is unclear whether and to what extent these results apply to patients with CPP. A research grant from INSERM (Réseau de recherche clinique 2003 and 2006) and an unrestricted grant from Abbott, Schering Plough and Wyeth supported RATIO; however, the pharmaceutical companies had no role in the planning and conduct of the study.

CPP: Long-term Safety Studies

No long-term, prospective, comparative safety studies comparing biologic agents were found.

A notable published report was a 10-year experiential study for adalimumab across different indications. The results showed that rates of serious adverse events remained relatively stable over time, and malignancy and standardized mortality rates in adalimumab-treated patients were not greater than those for the general population.[103]

Indirect Comparisons of Biologics in Terms of Adverse Event Profiles Across Indications: Cochrane Meta-analysis

A Cochrane network meta-analysis evaluated 160 RCTs and 46 open-label extension studies (OLEs) to compare biologics in terms of adverse event profiles across any disease condition except human immunodeficiency disease (HIV / AIDS).[104] There were 14 RCTs, 8 OLEs for psoriasis and 7 RCTs and 7 OLEs for psoriatic arthritis. Most of the studies involved rheumatoid arthritis or cancer. The number of RCTs / OLEs for the biologic agents FDA-approved for psoriasis or psoriatic arthritis was 22 / 10 for adalimumab, 39 / 10 for etanercept, 8 / 1 for golimumab, and 40 / 18 for infliximab. In addition, for certolizumab (investigational for psoriasis), the corresponding numbers were 6 / 1. Indirect pairwise treatment comparisons and stratified meta-analyses showed the following results:

- Certolizumab was associated with a higher odds of serious adverse events (OR 1.63, 95% Credible Interval [CrI] 1.01–2.62; $p < 0.05$) relative to adalimumab.
- Certolizumab was associated with significantly ($p < 0.05$) higher odds of serious infections relative to adalimumab (3.90, 1.03–17.17), etanercept (3.68; 1.01–16.3) and golimumab (OR for golimumab versus certolizumab 0.23, 95% CrI 0.04–0.97).
- No statistically significant differences were seen in other indirect pairwise treatment comparisons for serious adverse events and serious infections and for other outcome measures (withdrawals due to adverse events and total adverse events).
- Psoriasis but not psoriatic arthritis was one of the risk factors for increased total adverse event rates.

Thus, weak evidence suggests that there seems to be no important differences among the biologic agents approved for psoriasis or psoriatic arthritis in terms of serious adverse events, serious infections, withdrawals due to adverse events, and total adverse events, when these agents are evaluated across disease states.

CPP Q2 In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

Efficacy in CPP: Active-controlled Trials (Biologics Versus Nonbiologics)

One manufacturer-sponsored, good-quality, active-controlled trial (CHAMPION) that compared adalimumab, methotrexate and placebo (N = 271) was found by the literature search.[105] In terms of the percentage of patients achieving PASI-75 after 16 weeks (the primary efficacy measure), adalimumab (79.6%,) was superior to methotrexate (35.5%; p<0.001 versus adalimumab) and placebo (18.9%; p<0.001). The calculated NNT was 2.3 (1.8–3.2). The difference in PASI-75 responder rates between adalimumab and methotrexate reached statistical significance at week 2 (4.6% versus 0%, respectively). In terms of the mean percentage PASI improvement at week 4, adalimumab (56.5%) was better than methotrexate (22.0%; p<0.001) and placebo (15.4%; p<0.001). Adalimumab was also superior to methotrexate in the other efficacy measures including PGA of 'clear' or 'minimal' at all time points. The overall incidence of adverse events was similar among treatment groups. Rates of discontinuations due to adverse events were numerically lower on adalimumab (0.9%, 1/107) than methotrexate (5.5%, 6/110) and placebo (1.9%, 1/53). Increases in liver enzymes were also less common on adalimumab (1.9%) than methotrexate (9.1%) and placebo (7.5%). The results suggested that adalimumab had a large antipsoriatic effect size and a faster onset relative to methotrexate as titrated in the study. A limitation of this study was that the study duration may have been too short or the upward dose titration rate too slow to observe the full effect of methotrexate by week 16. Whereas adalimumab efficacy seemed to plateau by week 16, methotrexate efficacy continued to increase although at a slower rate at the later time points. Had the study continued for an additional 4–8 weeks, the authors speculated on the basis of the response curves that methotrexate efficacy might have improved marginally.

For additional details, see Appendix, Table 20.

Efficacy in CPP: Indirect Comparisons from Systematic Reviews / Meta-analyses

The results of a fair-quality meta-analysis of 2 active-controlled RCTs[105,106] and 20 placebo-controlled RCTs (N = 9917) involving biologics or systemic nonbiologics showed the following indirect comparisons[88]:

- The rank order for agents based on the point estimates for probability (95% CI) of PASI-75 response at 10–16 weeks was (from highest to lowest): infliximab (81%, 75%–86%), adalimumab (71% (63%–79%), etanercept 50 mg twice weekly (50%, 43%–58%), methotrexate (42%, 27%–54%), cyclosporine 33% (17%–49%) and alefacept (15%, 9%–21%).
- The NNT (95% CI) for PASI-75 was 1 (1.2–1.4) for infliximab, 1 (1.3–1.7) for adalimumab, 2 (1.9–2.6) for etanercept (50 mg twice weekly), 3 (2.0–4.4) for methotrexate, 4 (2.3–8.3) for cyclosporine, and 11 (6.1–20.1) for alefacept.
- Infliximab (5 mg/kg i.v. at weeks 0, 2, and 6 then every 8 weeks) and adalimumab (40 mg every other week) are each more efficacious than methotrexate (15–22.5 mg weekly) and cyclosporine (3 mg/kg/d).
- Etanercept (50 mg twice weekly) is not different in efficacy from either methotrexate or cyclosporine (3 mg/kg/d).

In another fair-quality meta-analysis, infliximab (77%; 95% CI 72%–81%) and adalimumab (64%; 61%–68%), but neither etanercept 50 mg twice weekly (44%, 40%–48%) nor etanercept 25 mg twice weekly (30%; 25%–35%), were significantly better than cyclosporine (33%; 13%–52%).[89]

Effectiveness in CPP: Comparative Effectiveness Study of Biologics and Nonbiologics

A notable comparative effectiveness study evaluated the real-world effectiveness of methotrexate, phototherapy and biologic therapies for treatment of CPP using a nonrandomized, cross-sectional, single-visit design. Ten centers participating in the Dermatology Clinical Effectiveness Research Network in the U.S. provided data on 713 eligible patients who were receiving monotherapy with one of the treatments of interest. Relative response rates (i.e., relative risks) were derived from modified Poisson modeling. The study population was 85% white, 51% male, with a mean age of 48.6 years, body mass index of 28.8, and median duration of psoriasis of 19 years. Patients had a median of two co-morbidities, and psoriatic arthritis had been diagnosed in 23% of patients. The practice setting of the dermatologist was academic in 57% and private in 53% of patients. Of note, greater than recommended doses were used in 12% of adalimumab-treated patients, and doses of 50 mg twice weekly (recommended for use only in the first 3 months of CPP therapy) were used in 36% of etanercept patients. The median (IQR) duration of treatment without interruption was 1.8 (1.0–4.0) months for narrow-band ultraviolet-B (NBUVB), 4.0 (2.0–6.0) months for ustekinumab, 10.5 (4.0–24.0) months for methotrexate; 11.0 (3.0–16.8) months for adalimumab; and 12.0 (6.0–36.0) months for etanercept. The findings are summarized in Table 14.

Table 14 Physician- and Patient-reported Outcomes on Monotherapy as Measured at a Single Visit (N = 713)

Outcome	MTX N = 174 (24.4%)	ADA N = 152 (21.3%)	ETA N = 191 (26.8%)	UST N = 73 (10.2%)	NBUVB N = 123 (17.3%)	P-value
PGA, median (IQR) (0/Clear to 5/Severe)	1.7 (1.3–2.0)	1.3 (1.0–1.7)	1.7 (1.0–2.0)	1.7 (1.0–2.1)	1.7 (1.0–2.0)	<0.001
PASI, median (IQR) (≤ 2 = no or minimal disease)	3.8 (1.8–6.6)	2.5 (1.2–4.8)	2.9 (1.8–4.9)	4.0 (1.0–7.9)	3.5 (2.0–5.5)	0.02
BSA, %, median (IQR) (< 3% = mild disease)	3.0 (1.0–6.0)	2.0 (0.7–5.0)	2.0 (0.5–4.5)	3.0 (0.6–9.1)	3.3 (1.0–6.5)	0.01
DLQI, median (IQR) (2–5 = small effect on pt's life)†	3 (1–5)	2 (0–5)	2 (1–5)	3 (1–6)	3 (1–7)	0.15
Topical Rx Drug Use in Past Week, d	2 (0–7)	2 (0–6)	1 (0–4)	0 (0–4)	4 (1–7)	<0.001
PGA Responder Rate (PGA of clear or almost clear, scores ≤ 1), % of pts (95% CI)	23.8 (17.7–30.9)	47.7 (39.5–56.0)	34.2 (27.5–41.4)	36.1 (25.1–48.3)	27.6 (20.0–36.4)	<0.001
DLQI Responder Rate (No or small effect, scores ≤ 5), % of pts (95% CI)	78 (70–83)‡	78.0 (70.5–84.3)	75 (69–81)‡	72 (60–81)‡	68.3 (59.2–76.5)	0.32

ADA, Adalimumab; BSA, Body surface area; DLQI, Dermatology Life Quality Index; ETA, Etanercept; MTX, Methotrexate; NBUVB, Narrow-band ultraviolet-B; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; UST, Ustekinumab

† DLQI scores 0-1 = no effect; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect on patient's life

‡ Estimated from graph

There were relatively small but statistically significant treatment differences in terms of the primary effectiveness measure, Physician Global Assessment of clear or almost clear skin (scores ≤ 1), as well as the secondary measures, PASI scores of ≤ 2 (no or minimal disease), lesion body surface area of less than 3% (considered to be mild disease) and patient-reported frequency of topical prescription drug use in the previous week.

Adalimumab was associated with significantly higher PGA response (PGA of clear or almost clear) than methotrexate and NBUVB. However, in terms of DLQI response (defined as scores of ≤ 5, indicating no effect or small effect of the disease on quality of life), there was a relatively narrow range of responder rates (68.3% with NBUVB to 78.0% with adalimumab, with overlapping 95% CIs) and no significant treatment differences. Subgroup response predictors for PGA responders were female sex, normal or under normal weight, treatment in private practice, longer duration of current treatment, and lower likelihood of topical prescription use in the past week.

Relative response results are shown in Table 15.

Table 15 Relative PGA Response Results (N = 704)

Statistical Measure	MTX	ADA	ETA	UST	NBUVB
Adjusted Relative Risk (95% CI)†	1 (Ref)	2.15 (1.60–2.90)	1.45 (1.06–1.97)	1.57 (1.06–2.32)	1.35 (0.93–1.96)
Risk Difference (95% CI)	—	0.27 (0.14–0.45)	0.11 (0.01–0.23)	0.13 (0.01–0.31)	0.08 (–0.02–0.23)
NNT (95% CI)	—	4 (3–7)	10 (5–100)	8 (4–100)	12 (4–100)

NNT, Number needed to treat with the particular treatment to gain one additional PGA responder relative to methotrexate; values were rounded up, as per convention.

† Adjusted for sex, race, ethinicity, body mass index, skin type, frequency of topical use, practice setting of dermatologist, marital status, income and insurance.

Each of the three biologics had significantly greater adjusted relative response rates than methotrexate. NBUVB was not statistically significantly different from methotrexate in this regard. The 95% CIs for adjusted relative risks among the biologics overlapped, so one could not conclude that there are significant differences among biologics in responder rates.

There were a number of limitations to the study, including lack of randomization, lack of blinding of assessors, different assessment patterns with NBUVB therapy than other therapies, differences in duration of use between the newer agent ustekinumab and the other treatments, lack of longitudinal assessments, lack of safety assessments, potential insufficient sensitivity in DLQI to detect differences in real-world clinical practice, lack of assessment of combination therapies, and limitation to patients in only one dermatology practice network.

The authors concluded that, although there were differences among the monotherapies studied, the differences were small and may not be clinically relevant. The responder rates seemed to be lower in the real-world setting than in randomized clinical trials. Longitudinal comparative effectiveness studies are needed to confirm the findings of the study.

Safety in CPP: Short-term Studies of Biologics Versus Traditional DMARDs

In the 16-week CHAMPION trial that evaluated adalimumab with methotrexate, serious and overall adverse event incidences were similar among adalimumab, methotrexate and placebo groups.[105] However, 9.1% of the methotrexate group had increased liver enzyme concentrations as compared with 1.9% in the adalimumab and 7.5% in the placebo group. Withdrawals due to adverse events were more frequent in the methotrexate group (6/110, 5.4%) than in the adalimumab group (1/107, 0.9%) or placebo group (1/53, 1.9%). Of the 6 discontinuations due to adverse events in the methotrexate group, 4 involved the hepatic system (3 patients with abnormal liver enzyme or total bilirubin tests and 1 with hepatitis).

Safety in CPP: Long-term Studies of Biologics Versus Traditional DMARDs

Duration of therapy with DMARDs is limited because of the potential risk for cumulative organ toxicity. One proposed advantage of biologic agents over traditional DMARDs is an improved safety profile that may make continuous disease control possible. This proposed advantage has not been studied in long-term controlled trials.

CPP Q3 In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

Efficacy and Safety in CPP Nonresponder Subgroup / Difficult-to-Treat Patients

The major clinical trials that supported the approval of biologics for marketing in the U.S. involved patients who were candidates for systemic therapy or phototherapy and may or may not have received prior topical or systemic

therapies. The trial results do not reflect the efficacy of biologics in patients who previously failed systemic therapies.

There were no comparative studies. The literature search found eight low-quality reports relevant to the use of biologics in patients who had failed either nonbiologic,[107,108] biologic,[109-111] or either of these two types of treatments.[112-114] Most of these studies were small (N = 5–85) and retrospective[107,112] or prospective observational studies mainly 3–6 months in duration.[108-111,113]

PRIDE (Open-label Access PRogram to Evaluate the Safety and Effectiveness of Adalimumab When Added to InaDEquate Therapy for the Treatment of Psoriasis) was a multicenter, Phase IIIb observational study involving 203 patients at 26 Canadian sites.[114] Adalimumab therapy (80 mg at Week 0 then 40 mg every other weeks from Weeks 1 through 23) was added in patients who had failed to respond to or were intolerant of prior therapies, including biologics in 38.4% of patients. The primary efficacy measure showed that at Week 16 adalimumab add-on therapy achieved a PASI-75 responder rate of 70.9%. PASI-90 and PASI-100 were achieved in 49.3% and 24.1% of patients, respectively. PASI scores decreased from baseline to Week 16 by a mean of 79.5%. Responder rates and mean percentage PASI improvement were maintained through Week 24. Serious adverse events occurred in 9 patients, 4 of whom had serious adverse events considered possibly or probably related to adalimumab. This study lacked a control group and provided low-quality evidence to support the use of adalimumab in nonresponder or difficult-to-treat patient subgroups.

Given the paucity of data and low-quality study designs, the short- and long-term comparative efficacy and safety of biologics in patients who have failed prior systemic nonbiologic or biologic therapies is unclear.

CPP Q4 In patients with chronic plaque psoriasis, is there a difference between antipsoriatic biologic or nonbiologic monotherapy and combination biologic-nonbiologic therapy?

Whereas several biologics are labeled for use with or without methotrexate or other disease-modifying agents for PsA or rheumatoid arthritis (see Table 1), none of the biologics have FDA approval for use in combination with other systemic agents to treat CPP. The proposed advantages of using biologic-nonbiologic combination therapy over biologic monotherapy in CPP include improved cost-effectiveness by allowing reduction of the biologic dose when combined with nonbiologic therapy[115]; improving efficacy while reducing risk for dose-related toxicities[116]; prevention of relapses during transition to biologic therapy or treatment of relapse during biologic therapy[117]; avoidance of rapid deterioration of psoriasis after abrupt discontinuation of methotrexate[118]; and improved response to monotherapy in partial responders.[118,119] The addition of biologic therapy to nonbiologic therapy has also been reported to allow reduction of the dose or discontinuation of nonbiologic systemic therapy including phototherapy.[120]

The actual short- and long-term advantages of combination therapy over biologic monotherapy have not been adequately evaluated. The literature search found two low-quality randomized clinical trials comparing biologic monotherapy with biologic-nonbiologic combination therapy. In general, the results of each study favored combination therapy over monotherapy (Table 16).

Other studies involving combination therapy were case reports,[116,121,122] and noncomparative retrospective[99,118] or prospective[113,115,123-126] open-label observational studies.

In a retrospective case-note review of 118 patients treated with biologics in a U.K. tertiary care center, 30% required combination therapy with other systemic agents either at transition to biologic therapy or to treat relapse during biologic therapy.[117]

Table 16 Biologic-Nonbiologic Combination Therapy Versus Monotherapy: Randomized Controlled Trials in Patients with Moderate to Severe Chronic Plaque Psoriasis

Reference / Quality	Combination Therapy	Monotherapy	Design	N	PASI-75 Responders, % of Pts	PGA 'Clear' or 'Almost Clear,' % of Pts	AEs
Zachariae (2008)[127] Low	1) ETN (50 mg biw / 25 mg biw) + MTX	2) ETN (50 mg biw / 25 mg biw) + MTX Taper in first 4 wk	24-wk OL; inadequate response to MTX	59	1) 70*‡ 2) 35	1) 66.7% 2) 37%*	Similar. No cases of TB, CA, or OI.
Gisondi (2008)[119] Low	1) Low-dose ETN (25 mg qwk) + ACI (0.4 mg/kg/d)	2) High-dose ETN (25 mg biw) 3) ACI (0.4 mg/kg/d)	24-wk SB RCT	60	1) 44* 2) 45† 3) 30	—	No sig changes in AST, ALT, chol, TG. WDIEs: 0/0/4**

ACI, Acitretin; biw, Twice weekly; CA, Cancer; ETN, Etanercept; MTX, Methotrexate; NB-UVB, Narrowband ultraviolet-B; OI, Opportunistic infection; OL, Open-label; TB, Tuberculosis; TG, Triglycerides; tiw, Three times weekly; WDAE, Withdrawal due to adverse event(s); WDIE, Withdrawals due to inefficacy

* P ≤ 0.03 Combination therapy versus nonbiologic monotherapy

** P < 0.05

† P = 0.001 Etanercept versus acitretin

‡ P = 0.031 adjusted for gender

CPP Q5 In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

In a U.K. model-based pharmacoeconomic analysis, methotrexate and cyclosporine were shown to be less beneficial than biologics in terms of QALYs but were cost-saving (because of reduced hospitalizations) and therefore the most cost-effective, and were considered to be the first and second agents, respectively, in the authors' 'optimal treatment sequence' for moderate-to-severe CPP.[128] Of the biologics, adalimumab had higher QALYs and marginally lower aggregate treatment-related costs (i.e., for drug acquisition, monitoring, and administration) relative to etanercept and lower QALY but lower costs relative to infliximab. The authors reported that adalimumab had the highest probability of being cost-effective following failure or inadequate response to nonbiologic systemic treatments, as long as a decision-maker was willing to pay about £30,000 or more for an additional QALY. The results were sensitive mainly to assumptions about duration of hospitalization, but also a number of other assumptions including frequency of intermittent etanercept dosing,[129] psoriasis severity and patient weight (for weight-based treatments such as cyclosporine and infliximab). The model did not account for adverse events because of a lack of data on long-term safety. The authors noted that, although most cost-effective, methotrexate and cyclosporine are not recommended for extended use in most patients because of their high risk of toxicity with long-term use. The model also assumed that response at the end of the trial period (12–16 weeks) would be maintained beyond that time, which has not been validated. The study was funded by Abbott Laboratories (manufacturer of adalimumab) and co-authored by an Abbott employee; therefore, there is potential for bias. It is unclear whether and to what extent the results of this study could be applied to VA.

Another pharmacoeconomic study compared health care costs before and after starting biologic therapy.[130] The longitudinal cohort study evaluated adherence and health care costs of 186 alefacept-, efalizumab-, or etanercept-treated patients with CPP who were enrolled in North Carolina Medicaid. Patients were less than 65 years of age and had at least 6 months' worth of data either pre- or post-biologic treatment initiation. The most commonly prescribed systemic agents were methotrexate (14.3% of cases); PUVA (9.4%) and prednisone (8.2%). The results showed that prescription drug use costs were significantly higher during the post-biologics treatment period than during the pre-biologics period ($11,706 versus $3797), whereas other (nonprescription) health care costs were significantly lower ($6801 versus $12,764) and total health care costs were not significantly different between post- and pre-biologics treatment periods ($16,156 versus $14,662). Overall adherence to biologics (measured as the Medication Possession Ratio, MPR) was also better during the post-biologics period overall (OR

0.66) with no differences between biologic treatments. Measures of health care utilization showed significant decreases during the post-biologics period relative to the pre-biologic period; the mean number of outpatient visits decreased from 9.8 to 4.4; emergency department visits from 1.9 to 1; and hospitalizations from 0.9 to 0.4 ($p<0.001$ for each outcome measure). The results of this study probably have low external validity to a VA population because the study population (59% females, median age 41 years) and cost assumptions are not representative of the VA situation.

Other pharmacoeconomic studies that were found were outdated, poor quality, not pertinent to the key question or not relevant to VA.[128,131-139]

Summary of Comparative Studies in CPP

CPP Q1: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

In short-term trials, ustekinumab was shown to be moderately more efficacious and had a lower incidence of injection site reactions than etanercept (1 high-quality head-to-head RCT). Indirect comparisons suggest that infliximab may be the most efficacious; however, there is no definite evidence to support that there is a difference among adalimumab, etanercept, and infliximab in terms of efficacy. Weak evidence suggests that adalimumab may be associated with a higher risk of paradoxical psoriasis, and that adalimumab and infliximab may be associated with a higher rate of tuberculosis than etanercept.

CPP Q2: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

Adalimumab was shown to be superior to methotrexate, with a large relative effect size and faster onset, and was associated with fewer cases of hepatotoxicity and had a lower risk of withdrawals due to adverse events (1 high-quality RCT). Indirect comparisons suggested that adalimumab and infliximab but not etanercept were better in efficacy than nonbiologics (methotrexate, cyclosporine) for CPP. A comparative effectiveness study provided early, unconfirmed evidence that, although biologic agents may be more effective than nonbiologic treatments, the gain in benefit is relatively small and may not be clinically important.

CPP Q3: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

There is no good evidence of the relative efficacy and safety of biologics in nonbiologic treatment failures. There is only a poor-quality, noncomparative study that showed that adalimumab may have potential benefit in treatment failures.

CPP Q4: In patients with chronic plaque psoriasis, is there a difference between antipsoriatic biologic or nonbiologic monotherapy and combination biologic-nonbiologic therapy?

There is weak evidence that combination etanercept-methotrexate or etanercept-acitretin therapy may be more efficacious than etanercept monotherapy.

CPP Q5: In patients with chronic plaque psoriasis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

No VA-relevant pharmacoeconomic studies were found. Published studies suggest that a number of patient and clinical factors could affect the relative cost-effectiveness probabilities of individual nonbiologic and biologic therapies, including the extent to which treatments reduce hospitalizations and patient weight (for weight-based treatments such as cyclosporine, infliximab and ustekinumab).

COMPARATIVE STUDIES IN PSORIATIC ARTHRITIS

PsA Outcome Measures

Outcome measures used in PsA clinical trials have been largely borrowed from those developed for rheumatoid arthritis and not all measures have been validated for PsA.

Measures of Change in PsA Disease Status

American College of Rheumatology (ACR) Response Criteria / ACR20. ACR20 requires a 20% reduction in the tender joint count (TJC), a 20% reduction in the swollen joint count (SJC), and a 20% reduction in three out of five additional measures: patient global self-assessment (PtGA), physician global assessment (PhGA), pain, disability and an acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). Distal interphalangeal (DIP) joints should be included for PsA trials.[140] Since the ACR response criteria assess absolute changes (i.e., from swollen to not swollen or from tender to not tender joints), analyses by oligoarthritis and polyarthritis subgroups would be desirable in clinical trials since patients with oligoarthritis may seem to respond less well than patients with polyarthritis. ACR20 has been shown to have discriminatory validity in PsA.[141] The ACR20 and other levels of ACR response may be interpreted as follows:

- ACR20: generally accepted to be the minimal clinically important difference (MCID); reflects 'some' response to an intervention.
- ACR50: reflects significant and important changes
- ACR70: reflects major changes; near remission

Psoriatic Arthritis Response Criteria (PsARC). These are an unvalidated composite index comprised of four measures: PtGA of articular disease (Likert scale, 1–5), PhGA of articular disease (Likert scale, 1–5), joint pain / tenderness score and joint swelling score. Treatment response has been defined as an improvement in at least two of the four measures, one of which has to be a joint score, with no worsening in any of these four measures.[141] For PtGA and PhGA, improvement has been defined as a decrease by one category and worsening as an increase by one category. For joint pain / tenderness score and joint swelling score, improvement has been defined as a decrease by 30%, and worsening as an increase by 30%.

European League Against Rheumatism (EULAR) Response Criteria. The EULAR defined a good response as a disease activity score (DAS) ≤ 2.4 or a DAS28 ≤ 3.2 ("low" disease activity) in combination with an improvement > 1.2 (twice the measurement error) in DAS or DAS28.[141] A nonresponse was defined as an improvement ≤ 0.6, and also as an improvement ≤ 1.2 with a DAS > 3.7 or DAS28 > 5.1 ("high" disease activity). Scores outside these parameters were defined as a moderate response.

Radiologic Assessments of Joint Damage / Disease Progression

These methods were developed for RA and none of them score additional radiographic changes that are specific to PsA, although radiologic tests are the only means of assessing disease progression in PsA. It is important for trials to stratify treatment groups by baseline radiographic findings.

Modified Steinbrocker Method. This method assigns a score for each joint. Validated for PsA.

Sharp Method / Total Sharp Score (TSS). This method grades all hand joints separately for erosions on a scale of 0–5 and joint space narrowing on a scale of 0–4 for a maximum possible score of 149. Biologic trials in PsA have used a modified TSS that includes the DIP and metatarsophalangeal joints of the feet and interphalangeal joint of the first toe.

Measures of Absolute PsA Disease Status

In practice, the goal of therapy for PsA is low disease activity. For this reason, measures of absolute disease status may be of more practical interest than measures of change in status. Like the measures of change in status, the following measures of absolute status were borrowed from measures for rheumatoid arthritis (RA) disease activity. Although they appear to have discriminatory value in biologic clinical trials for PsA,[141] it is unclear what a certain score means in PsA and whether it is necessary to include DIP joint counts.

Disease Activity Score (DAS). Calculated as

$$DAS = 0.53938\sqrt{(RAI)}+0.06465(SJC44)+0.330\ln(ESR)+0.0072(PtGA),$$

where RAI is the Ritchie Activity Index.

DAS of 28 joint counts (DAS28). A DAS28 score of ≤ 3.2 has been used to define "low" disease activity, and a DAS28 of > 5.1 has been used to define "high" disease activity. DAS28 is calculated as

$$DAS28 = 0.56\sqrt{(TJC28)}+0.28\sqrt{(SJC28)}+0.70\ln(ESR)+0.014(PtGA).$$

PsA Disability Measures

Health Assessment Questionnaire (HAQ). The full HAQ covers five generic patient-centered health dimensions: (1) disability; (2) pain and discomfort; (3) adverse treatment effects; (4) economics; and (5) death.

Short HAQ. This is the 2-page version of the HAQ that is commonly referred to in the literature as "the HAQ." The short HAQ contains the HAQ Disability Index (HAQ-DI), the HAQ visual analog (VAS) pain scale, and the VAS patient global health scale.

HAQ Disability Index (HAQ-DI). This index is composed of 20 questions that ask the patient to rate his/her ability to perform activities over the past week in eight categories of functional ability – dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The rating scale ranges from 0 (no disability) to 3 (completely disabled). The eight category scores are averaged into an overall HAQ-DI score on a noncontinuous scale with 25 possible values (i.e., 0, 0.125, 0.250, 0.375 … 3), where 0 = no disability and 3 = completely disabled. Scores of 0 to 1 are generally considered to represent mild to moderate difficulty, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability. The MCID for the overall HAQ-DI score in PsA has been shown to be about 0.35.[142] Negative changes (e.g., –0.35) represent improvements in disability scores.

PsA Q1 In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

PsA: Systematic Reviews / Meta-analyses

See Table 22 in Appendix.

In one good-quality meta-analysis,[143] indirect analyses (6 RCTs, N = 982) showed the following:

- Adalimumab, etanercept and infliximab had similar effects in terms of ARC20 and PsARC responder rates and serious adverse event (SAE) rates, and these measures showed relatively narrow 95% CIs.
- In terms of ARC50, ARC70, PASI 50, PASI 75, and PASI 90, the three agents were also similar, with the exception that etanercept was not significantly different from placebo in PASI 75 responder rates at 12 weeks; however, the 95% CIs were wide and the results at 24 weeks showed a statistically significant difference from placebo.
- The three agents were also similar in terms of WDAEs and upper respiratory tract infections.
- Withdrawals for any reason were significantly lower with etanercept than placebo (RR 0.24, 95% CI 0.12–0.49), whereas adalimumab and infliximab showed no significant differences from placebo, and the

95% CIs for the risk differences (RDs) showed no overlap between etanercept and either of the other two agents, suggesting that withdrawal rates may be lower with etanercept but this is based on inconclusive indirect comparisons.

- Adalimumab showed no significant difference from placebo in terms of the incidence of injection site reactions, whereas etanercept showed a significantly higher incidence (RR 4.27, 95% CI 2.25–8.13; RD 0.23, 95% CI 0.14–0.33); furthermore, the 95% CI for the RD did not overlap with that for adalimumab, suggesting a lower rate of injection site reactions with adalimumab than etanercept (inconclusive indirect comparison).

Indirect comparisons in an NICE health technology assessment systematic review / meta-analysis[140] showed the following:

- Relative to placebo, 12- or 24-week therapy with adalimumab, etanercept or infliximab was efficacious in reducing joint and skin symptoms and improving function, with short-term evidence to support their ability to delay progression of joint disease.
- Infliximab was numerically most effective overall across measures of joint symptoms and skin disease (ARC, PsARC and PASI) but 95% CIs overlapped.
- For joint disease (ARC, PsARC), etanercept had a numerically greater effect than adalimumab but 95% CIs overlapped.
- The opposite was found for skin disease, with a numerically greater effect observed with adalimumab than with etanercept but 95% CIs overlapped.
- Infliximab showed greater improvement than etanercept (based on nonoverlapping 95% CIs) in the change in the Health Assessment Questionnaire (HAQ) scores, which reflect levels of physical disability and pain (and are a component of ACR).
- Adalimumab, etanercept and infliximab showed rapid onset in efficacy in preventing radiologic disease progression in terms of the Total Sharp Score (TSS) up to 24 weeks; however, this is an insufficient duration of time to assess TSS.
- In follow-on observational studies, each agent seemed to maintain beneficial TSS effects with observation periods up to 2.8 years for adalimumab, up to 2 years for etanercept and up to 1 year for infliximab but effects over time are uncertain because studies were uncontrolled.
- In cost-effectiveness analyses, etanercept was best for PsA patients with concomitant mild to moderate skin disease, whereas all three TNFIs were similar in cost-effectiveness for patients with concomitant moderate to severe psoriasis. (Also see question 6 on comparative cost-effectiveness of systemic agents on page 39.)
- In safety evaluations, short-term PsA RCTs reported few events and therefore relative indirect comparisons could not be made (Appendix, Table 22).
- Longer term evaluations of serious adverse events (up to 5 years for adalimumab, 7 years for etanercept, and 6 years for infliximab in a total of 39 nonrandomized studies and 4 RCTs involving patients with conditions other than PsA), were done in studies that were heterogeneous and therefore could not provide estimates of relative risk of serious adverse events for each agent.
- In general, withdrawals due to adverse events were typically seen in less than 10% of patients across studies with etanercept having the highest estimate of 13.8% in one study, suggesting that the majority of non-PsA patients can tolerate what the authors described as medium-term biologic therapy.

In a systematic literature review to support the European League Against Rheumatism (EULAR) recommendations on the pharmacotherapy of psoriatic arthritis, adalimumab, etanercept, golimumab, and

infliximab showed similar efficacy in indirect comparisons for articular manifestations of PsA.[81] For skin manifestations, etanercept (50 mg weekly) had a lower risk ratio for PASI-75 response and may be less efficacious than the other TNFIs, although a higher dose of 100 mg weekly performed better.

In another meta-analysis of 4 placebo-controlled RCTs (N = 820), fixed effects mixed treatment comparisons using ACR20 as the outcome measure showed that the odds ratio (95% credible interval, CrI) of achieving ACR20 response at 3 months relative to placebo was 6.42 (4.06–10.38) for adalimumab, 10.28 (5.70–19.30) for etanercept, and 6.40 (3.29–12.68) for infliximab.[144] There were no statistically significant treatment differences among the three agents in indirect comparisons. Based on effects relative to placebo, the probability of being the best treatment for the ACR20 outcome was highest with etanercept (79%) followed by infliximab (13%) and adalimumab (8%).

An NICE single technology appraisal of golimumab for psoriatic arthritis[145] ultimately concluded that

- While the Phase III GO-REVEAL trial results showed that golimumab 50 mg significantly improved joint disease response and skin disease response at 14 weeks relative to placebo, and preliminary meta-analyses suggested that golimumab was somewhat less efficacious than etanercept in terms of HAQ results, the overall evidence, including additional radiologic data, was not strong enough to confirm there was a clinically important difference between golimumab and other biologics (adalimumab, etanercept and infliximab).
- Golimumab's long-term adverse event profile seemed to be similar to those of the other TNFIs.
- In cost-effectiveness analyses, etanercept dominated both adalimumab and golimumab, and ICERs for golimumab were £24,000 per QALY gained relative to adalimumab and £45,000 per QALY gained relative to infliximab; golimumab was associated with lower costs and fewer QALYs than infliximab.
- The 50-mg dose of golimumab should be an option (alongside etanercept, infliximab and adalimumab) for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met: (1) the person has peripheral arthritis with three or more tender joints and three or more swollen joints; **and** (2) the psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination, with the caveats that the least expensive agent be used as the initial therapy and that treatment be discontinued if the patient does not show an adequate response using PsARC criteria at 12 weeks.

In addition to the systematic reviews / meta-analyses described above, the Public Summary Document summarizing Australia's Pharmaceutical Benefits Advisory Committee (PBAC) review of golimumab[146] made the following major points based on indirect comparisons:

- There were no significant differences between golimumab and adalimumab or etanercept, and golimumab met the PBAC's non-inferiority criteria for both between-agent comparisons.
- There were no statistically significant indirect differences between golimumab and etanercept or adalimumab for PASI-75 and, although indirect comparisons in meta-regression analyses showed golimumab to be statistically superior to etanercept at 12 weeks, these results were unreliable because of methodological limitations and moderate heterogeneity among etanercept trials.
- Clinical trial adverse event profiles of adalimumab, etanercept and golimumab for up to 24 weeks seem to be similar.

A meta-analysis sponsored by Merck, Sharp and Dohme, the maker of golimumab, showed no statistically significant differences among adalimumab, etanercept, golimumab and infliximab in terms of PsARC, HAQ (PsARC responders), HAQ (PsARC nonresponders), and PASI response.[147] The findings were based on indirect comparisons using placebo-controlled trials involving patients who had failed previous DMARD therapy. In addition, estimates of effect sizes seemed to depend on the analytic approach.

PsA: Comparative Long-term Effectiveness and Safety of Biologics

Three comparative long-term studies were found. The British Society for Rheumatology Biologics Register (BSRBR, 2002–2006) was used to evaluate the persistence in use of first and second TNFI therapy, identify potential predictors of drug discontinuation, and determine reasons for withdrawals due to adverse events.[148] Persistence data was available from 566 patients with PsA (mean age 45.7 years; 53% female; mean disease duration 12.4 years), 316 of whom were treated with etanercept for a mean of 2.1 person-years, 162 with infliximab for a mean of 2.5 person-years, and 88 with adalimumab for a mean of 1.6 person-years. The results showed that infliximab tended to be associated with a shorter persistence on treatment relative to the other two TNFIs (Table 17).

Table 17 Survivor Function for PsA Patients Stopping Their First Course of Initial TNFI Therapy

Reasons for TNFI Discontinuation	Etanercept n = 316	Infliximab n = 162	Adalimumab n = 88
	Proportion, mean (95% CI)		
All Reasons			
Year 1	0.86 (0.81–0.89)	0.71 (0.63–0.77)	0.91 (0.82–0.95)
Year 2	0.79 (0.73–0.83)	0.52 (0.44–0.59)	0.70 (0.54–0.81)
Year 3	0.64 (0.55–0.73)	0.43 (0.35–0.51)	0.66 (0.49–0.79)
Inefficacy			
Year 1	0.94 (0.91 to 0.96)	0.87 (0.81 to 0.92)	0.93 (0.85 to 0.97)
Year 2	0.92 (0.88 to 0.94)	0.78 (0.69 to 0.84)	0.80 (0.64 to 0.89)
Year 3	0.86 (0.78 to 0.92)	0.79 (0.58 to 0.77)	0.75 (0.57 to 0.87)
Adverse Events			
Year 1	0.97 (0.94 to 0.98)	0.93 (0.87 to 0.96)	0.99 (0.92 to 0.99)
Year 2	0.95 (0.92 to 0.97)	0.86 (0.78 to 0.91)	0.92 (0.75 to 0.98)
Year 3	0.91 (0.84 to 0.95)	0.72 (0.72 to 0.89)	0.92 (0.75 to 0.98)

Factors associated with significantly higher drug discontinuation rates overall were female sex (HR 1.3; 95% CI 1.0–1.7); another baseline co-morbidity (HR 1.5; 1.1–2.0); and use of infliximab rather than etanercept (HR 2.8; 2.1–3.7). Adverse immune system disorders (including drug hypersensitivity and infusion reactions) leading to treatment withdrawal occurred in 7.4% of patients on infliximab, 1.1% of patients on adalimumab, and 0.6% of patients on etanercept. Other common adverse events that led to withdrawal of therapy for the three TNFIs were infections, gastrointestinal disorders (nausea, vomiting, diarrhea), and nervous system disorders, particularly headache. The use of infliximab rather than etanercept was also a predictor of discontinuation due to inefficacy (HR 3.8; 2.0–7.3 in multivariate analyses) and a predictor of discontinuation due to adverse events (HR 3.1; 1.4–6.2).

The authors of the BSRBR study noted that the results are inconclusive about the relative efficacy of the three TNFIs because several limitations of the data could have affected treatment discontinuation rates (e.g., infliximab was the first agent approved and patients may have wanted to switch therapy as newer agents became marketed).[148] Furthermore, other factors could have affected patient response to therapy (e.g., 73% of patients received infliximab before its market approval for PsA and 78% of patients received 3 mg/kg of infliximab, less than the eventual licensed dose for PsA of 5 mg/kg).

Another smaller study that used the South Swedish Arthritis Treatment Group register (SSATGR) had also shown worse treatment persistence with infliximab than etanercept.[149] Of 261 patients, 119 received etanercept, 114 infliximab, and 38 adalimumab; concomitant methotrexate therapy was given in 161 (62%) of the patients. Duration of TNFI therapy was not reported; however, data at 12 months was collected. The analyses for predictors of treatment discontinuation showed that etanercept-treated patients had about one-half the risk of

stopping therapy relative to infliximab-treated patients (p = 0.01). No significant difference was shown between infliximab and adalimumab (p = 0.12) or between adalimumab and etanercept (p = 0.96). The results of subgroup multivariate regression analysis on the reasons for treatment discontinuation showed that etanercept was associated with a significantly lower risk of withdrawals due to adverse events (HR 0.30, 95% CI 0.11–0.80, p = 0.02) relative to infliximab. No differences were seen in withdrawal due to treatment failure (HR 0.55, 95% CI 0.25–1.20). Safety data did not reveal obvious differences among the three agents. This study was subject to confounding by indication, variable access to the different TNFIs over time, and lower than recommended doses of infliximab—limitations similar to those of the BSRBR study.

At this time, the evidence from long-term studies is insufficient to draw definite conclusions about the relative safety and effectiveness of TNFIs in the treatment of patients with PsA.

PsA Q2 Is there a difference among antipsoriatic biologic agents and nonbiologic topical or systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

PsA: Inefficacy of Methotrexate

A brief review of the evolving literature on the questionable efficacy of methotrexate in PsA is needed to provide some perspective on comparisons between biologics and nonbiologic agents. Expert consensus guidelines for the treatment of PsA recommend methotrexate as standard therapy for moderate to severe disease even in the face of weak supporting data.[83,84,150-152] According to U.K.'s National Institute of Health and Clinical Excellence (NICE) guidance, methotrexate is considered one of the DMARDs of choice for PsA that is unresponsive to NSAIDs despite a lack of well-designed trials.[153] Based on a small randomized trial (N = 21) that showed reduction in skin plaques and joint inflammation with intravenous methotrexate at high doses (now considered to be too toxic),[154] a Cochrane review concluded that parenteral methotrexate was one of only two DMARDs with demonstrated benefit in PsA.[155] Observational studies have shown that low-dose oral methotrexate was associated with clinical improvement of PsA.[156,157] Other observational studies have shown that an absence of methotrexate co-therapy with TNFIs was either a predictor[149,158] or not a predictor[159] of premature treatment discontinuation. Exploratory subgroup analyses that compared methotrexate users with methotrexate nonusers in TNFI trials had failed to show additional benefit with concomitant methotrexate therapy.[160]

There are other and more recent data suggesting that methotrexate may lack efficacy in PsA. Oral methotrexate in doses up to 15 mg/week has shown minimal or no benefit for PsA in two small placebo-controlled trials.[161,162]

The first large (N = 221), placebo-controlled randomized trial (Methotrexate in Psoriatic Arthritis, MIPA) in the U.K. showed improvements over time in both active and placebo groups but there was no statistically significant treatment difference in the primary and most secondary efficacy measures, confirming the lack of benefit of methotrexate (15–25 mg/week) for synovitis in active PsA.[163] The results did show borderline symptomatic benefit in terms of patient and clinician global scores and psoriasis skin scores at 6 months but none of the synovitis efficacy measures (i.e., PsARC, ARC20, disease activity score for 28 joints (DAS28), swollen and tender joint counts, erythrocyte sedimentation rate, C-reactive protein, pain, and HAQ) showed a beneficial effect. The PsARC responder odds ratio (OR) for all patients was 1.8. The authors noted that, in other trials, stronger effects were seen with leflunomide[a] (OR 3.4) and etanercept (OR >20). One of the key messages from this good-quality, landmark trial was "There is insufficient evidence to support the use of MTX as a standard treatment for PsA." The trial authors also questioned whether methotrexate should be classified as a disease-modifying antirheumatic drug (DMARD) given the absence of evidence from randomized trials that methotrexate improves synovitis or retards joint erosion. The authors also noted that five trials of sulfasalazine and one trial of auranofin also showed lack of benefit with these agents.

[a] Leflunomide is nonformulary in VA.

Thus, although practice guidelines and NICE recommendations suggest the use of TNFIs after failure on a nonbiologic systemic agent ("DMARD"), the body of evidence from controlled trials thus far does not support the standard use of methotrexate for PsA.

PsA: Indirect Comparison of Biologic and Nonbiologic Therapies

A fair-quality systematic review and meta-analysis evaluated the efficacy and toxicity of biologic agents and nonbiologic systemic DMARDs for PsA.[164] Eleven RCTs assessed DMARD monotherapy and one study, DMARD combination. Only one small RCT evaluated methotrexate. Five assessed TNF inhibitors and one alefacept. Withdrawal due to lack of efficacy (WDLE) was used as the outcome measure for efficacy, and withdrawal due to adverse events (WDAEs) was used as the measure for toxicity. The results showed that TNFIs (5 studies, 882 patients) had a lower risk ratio (versus placebo) for WDLEs (RR 0.25, 95% CI 0.13–0.48; p = 0.0001) than 'All DMARDs' (12 RCTs, 1081 patients; RR 0.39, 95% CI 0.27–0.57; p = 0.00001); however, the 95% CIs overlapped. The RR for toxicity with TNFIs was not statistically significant relative to placebo, whereas All DMARDs showed a significantly increased risk for toxicity (RR 2.32; 1.55–3.47; p = 0.0001). The NNT / NNH ratio was numerically lower with TNFIs (0.25) than with All DMARDs (0.86). Therefore, as a class, the TNFIs did not show indirect evidence that they differed in efficacy relative to systemic DMARDs, but may be better tolerated.

PsA Q3 In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

One relevant study was found. It was a prospective randomized study of 100 consecutive patients who had not responded to prior DMARD therapy and were attending a PsA clinic in Italy.[165] Patients were randomized to infliximab (5 mg/kg every 6–8 weeks, adjusting dosage as clinically indicated; N = 30), etanercept (25 mg twice weekly; N = 36) or adalimumab (40 mg every other week; N = 34) and followed up for one year. Combination methotrexate and TNFI was used in 51 of the patients (90% infliximab, 40% etanercept, 30% adalimumab). The results at one year varied by outcome measure, as summarized below:

- The three TNFIs were similar in ACR response rates (75% infliximab, 72% etanercept, 70% adalimumab)
- Adalimumab ($p<0.01$) and infliximab ($p<0.001$) were better than etanercept in PASI response.
- Etanercept was better than adalimumab and infliximab ($p < 0.018$ for both comparisons) in tender joint counts.
- No treatment differences were seen for swollen joint counts.
- Etanercept was better than adalimumab in decreasing HAQ ($p<0.002$).
- No patients reached remission, defined as absence of swollen and tender joints
- Minimal disease activity (MDA, defined as absence of swollen joints and no more than two tender joints associated with a HAQ score <0.5) was reached with TNFI as a group and specifically by 26 patients on etanercept and 16 on adalimumab.
- Adalimumab was associated with the lowest rate of adverse events (6%; $p<0.001$) relative to infliximab (23%) and etanercept (17%).
- There were no reported cases of tuberculosis or demyelinating disease.

The authors concluded that although all three agents were effective and safe, they showed some "therapeutic peculiarities" that should be considered when individualizing therapy.

PsA Q4 In patients with psoriatic arthritis, is there a difference between biologic monotherapy and combination biologic-nonbiologic therapy in terms of efficacy, effectiveness, safety, or tolerability?

PsA: Biologics Plus Methotrexate

Also refer to section called *PsA: Inefficacy of Methotrexate* (page 36).

In contrast to studies showing a lack of efficacy with methotrexate for PsA, the results of one low-quality study evaluating biologic-methotrexate combination therapy showed that combination therapy was better than monotherapy in ACR20 response rates but was associated with numerically higher incidences of serious adverse events and withdrawals due to adverse events (Table 18). There is insufficient evidence to determine the efficacy and safety of biologic-methotrexate combination therapy relative to biologic monotherapy.

Table 18 Biologic-Methotrexate Combination Therapy Versus Methotrexate Monotherapy: Randomized Controlled Trial in Patients with Psoriatic Arthritis

Reference Quality	Combination Therapy	Monotherapy	Design	N	ACR20, % of Pts	PASI-75, % of Pts	AEs
Baranauskaite (2012),[166] RESPOND Study Low	1) INF 5 mg/kg at wk 0, 2, 6, 14 + MTX 15 → 20 mg/wk	2) MTX 15 → 20 mg/wk	16-wk OL RCT; MTX-naïve pts not receiving DMARDs; no double dummy	115	1) 86.3* 2) 66.7	1) 97.1** 2) 54.3	SAEs 1) 4% (2/57) 2) 0% (0/54) WDAEs 1) 12% (7/57) 2) 3% (2/58) AEs 1) 46% (26/57) 2) 24% (13/54)

OLE, Open-label extension

* P < 0.02; ** P < 0.0001

PsA: Biologics Plus Nonbiologics Other than Methotrexate

Etanercept combined with cyclosporine was better than etanercept plus methotrexate in PASI-75 responder rates in an open-label pilot RCT.[167] However, the benefits were counterbalanced by a higher rate of hypertension in the cyclosporine combination group (Table 19).

Table 19 Direct Comparisons of Combination Therapies: Randomized Trial in Psoriatic Arthritis

Reference Quality	Combination Therapy	Comparator	Design	N	ACR20, % of Pts	PASI-75, % of Pts	AEs
Atzeni (2011)[167] Low	1) ETA 50 mg qwk + CSA 3 mg/kg/d	2) ETA 50 mg qwk + MTX 7.5–15 mg/wk	24-wk OL Pilot RCT; moderate–severe PsA; resistant to at least one DMARD	41	Not evaluated†	1) 53† 2) 32	SAEs: NSD except for HTN more frequent in ETA+CSA gp.

* P < 0.02; ** P < 0.0001; † P < 0.05

† Mean ↓ in DAS28 scores: 1) 1.70 ± 0.52; 2) 1.58 ± 0.82; (NSD). Remission (DAS28 ≤ 2.6): 2 vs. 1.

Another study showed that in patients who only partially responded (PASI < 50) to etanercept (50 mg twice weekly) after 12 weeks of therapy, the addition of calcipotriol cream to etanercept (25 mg twice weekly) resulted in an additional 37 (31%) of 120 patients achieving at least PASI-50 by week 24.[126]

PsA Q5 Is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

No VA-relevant studies were found. Brief findings from two systematic reviews / meta-analyses with cost-effectiveness evaluations were described under PsA Q1.

Summary of Comparative Studies in Psoriatic Arthritis

PsA Q1: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability?

The findings from indirect comparisons in systematic reviews / meta-analyses have been inconsistent. One of the reviews showed that adalimumab, etanercept and infliximab were similar in efficacy; another showed infliximab to be most effective overall (for joint and skin outcomes), etanercept better than adalimumab for joint outcomes, and adalimumab to be better than etanercept for skin outcomes; and a third review concluded that the evidence was not strong enough to confirm that there is a clinically important difference between golimumab and other biologics (adalimumab, etanercept, and infliximab). Safety findings also showed some variability in systematic reviews of short-term studies and overall showed no definite evidence that there were substantial differences among adalimumab, etanercept, golimumab and infliximab. Long-term efficacy and safety of the biologics have not been adequately evaluated. At this time, the evidence is insufficient to draw definite conclusions about the relative safety and efficacy of TNFIs in PsA.

PsA Q2: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents and nonbiologic topical or systemic agents in terms of efficacy, effectiveness, safety, or tolerability?

Indirect evidence suggest that TNFIs are better than methotrexate because, unlike nonbiologic systemic agents, they have been shown to be disease-modifying (i.e., reduce synovitis and prevent progression of joint erosion) and may be better tolerated.

One good-quality study evaluating methotrexate in PsA confirmed the lack of efficacy of this drug in reducing PsA synovitis. There is no evidence showing that methotrexate or other nonbiologic systemic therapies prevent progression of joint erosion.

PsA Q3. In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents in terms of efficacy, effectiveness, safety, or tolerability when used in nonbiologic systemic treatment failures (i.e., patients who have not responded adequately or did not tolerate nonbiologic systemic therapies)?

One study suggested that TNFIs may have differential benefits depending on the outcome measure in nonresponders to nonbiologic systemic agents.

PsA Q4: In patients with psoriatic arthritis, is there a difference between biologic monotherapy and combination biologic-nonbiologic therapy in terms of efficacy, effectiveness, safety, or tolerability?

Recent evidence suggests that methotrexate is not efficacious and is not a DMARD in PsA (3 RCTs).

There is insufficient evidence to determine the efficacy and safety of biologic-nonbiologic combination therapy relative to biologic monotherapy.

PsA Q5: In patients with psoriatic arthritis, is there a difference among antipsoriatic biologic agents and nonbiologic systemic agents in cost-effectiveness?

No VA-relevant pharmacoeconomic studies were found.

CONCLUSIONS

The biologic agents work by mechanisms different from those of conventional systemic agents and may be effective alternatives or add-on therapies to patients who have unsatisfactory responses to the older drugs. They have been shown in premarketing and postmarketing studies over the past 5 to 10 years to be relatively well tolerated. There is, however, a safety trade-off in using TNFIs. Whereas they lack the major, relatively predictable treatment-limiting organ toxicities associated with methotrexate (cirrhosis, pulmonary fibrosis), cyclosporine (renal impairment, hypertension), and acitretin (teratogenicity, mucocutaneous toxicity, hyperlipidemia), TNFIs are associated with relatively unpredictable major harms including serious infections (e.g., sepsis, tuberculosis, and viral infections), autoimmune dysfunction (e.g., lupus, demyelinating disorders), and malignancies (e.g., lymphoma). TNFIs have also been associated with paradoxically inducing psoriasis and psoriasiform lesions.

For chronic plaque psoriasis without psoriatic arthritis, most evidence-based clinical practice guidelines recommend biologics as second-line therapies after trials of conventional systemic agents. However, the current available evidence supporting the efficacy and safety of biologics in the treatment of chronic plaque psoriasis is based mainly on patients who have received but not necessarily failed prior nonbiologic systemic agents. Biologic-naïve and nonbiologic nonresponders comprise smaller study subpopulations. As to whether one biologic agent is better than the others, the available evidence suggests that ustekinumab is moderately more efficacious than etanercept. For other biologic pairs, indirect comparisons suggest that infliximab and perhaps adalimumab may be better than etanercept but overall there are no definite clinically relevant differences in short-term efficacy or effectiveness. In addition, the available evidence suggests that the biologic agents, particularly infliximab and adalimumab, are overall more efficacious and effective than nonbiologic systemic agents, particularly methotrexate and cyclosporine. However, there is early, unconfirmed data suggesting that in real-world practice, the incremental gain in effectiveness of biologic agents over methotrexate is small and may not be clinically meaningful in terms of the impact on patient quality of life. The limited comparative short-term safety data that is available suggests that adalimumab may be better tolerated and less hepatotoxic than methotrexate. Further studies are needed to confirm early studies that suggest combination biologic-nonbiologic therapy may have advantages over biologic monotherapy. Long-term comparative safety data and cost-effectiveness studies that account for long-term toxicities and cost-driver outcomes such as hospitalizations are needed to supplement the existing efficacy and effectiveness studies in chronic plaque psoriasis. Given the lack of VA-relevant cost-effectiveness studies and lack of studies comparing treatment approaches, such as step-up (nonbiologics then biologics) versus step-down (biologics then nonbiologics) therapy, at this time there is insufficient evidence to support a recommendation to use antipsoriatic biologics as first-line therapy and insufficient clinical evidence to support mandating the use of nonbiologic systemic agents before biologics.

For psoriatic arthritis, the evidence is unclear about whether any biologic is better than the others. Biologics seem to be more efficacious than nonbiologic systemic agents, particularly methotrexate, based on indirect comparisons. There is convincing evidence that biologics are efficacious in reducing synovitis, whereas methotrexate is inefficacious for synovitis and produces probably clinically unimportant symptomatic improvement in psoriatic arthritis. Biologic agents approved for psoriatic arthritis have been shown to be disease-modifying; this is a clinically important advantage of the biologics over nonbiologic systemic agents. There is a lack of evidence that any of the nonbiologic treatment alternatives prevent progression of joint damage. In addition, indirect comparisons suggest that, relative to systemic nonbiologics as a class, biologics as a class may be better tolerated. For these reasons, adalimumab, etanercept, golimumab and infliximab have evidence to support their use as first-line treatment alternatives to conventional agents, particularly leflunomide (the nonbiologic agent with some evidence of efficacy) in patients with psoriatic arthritis. By extension, biologics would also be first-line treatment alternatives in patients with co-diagnoses of chronic plaque psoriasis and

psoriatic arthritis. There is insufficient evidence to determine the efficacy and safety of biologic-methotrexate combination therapy relative to biologic monotherapy; however, there is weak evidence suggesting that combination therapy may be more effective than biologic monotherapy.

In general, the biologics with lowest acquisition costs and longer safety records and experience should be tried first using the lowest recommended effective dose. Among the TNFIs, adalimumab, etanercept, and infliximab have longer safety records and experience, and therefore may be preferable over golimumab (approved for PsA only) or ustekinumab, which is more efficacious than etanercept but lacks long-term experience and safety data. However, each biologic agent has certain pharmaceutical advantages and disadvantages, so treatment that is less cost-effective may be more appropriate in some cases to individualize therapy.

Future research should evaluate treatment approaches (i.e., step-up, nonbiologic first then biologic, versus step-down, biologic first then nonbiologic). Longitudinal comparative effectiveness and safety studies in real-world practice settings and VA-relevant, comparative cost-effectiveness analyses are urgently needed to help determine optimal treatment sequence and approach in chronic plaque psoriasis and psoriatic arthritis in a U.S. Veteran population.

APPENDIX

For the update of this review, studies comparing antipsoriatic biologic agents (adalimumab, etanercept, golimumab, infliximab, and ustekinumab) with each other or with nonbiologic systemic agents were identified using computerized searches of PubMed and the Cochrane Central Register of Controlled Trials from 2006 to December 2010. An updated literature search was done for publications from January 2011 to December 2012. Search terms favored sensitivity over specificity and consisted of the generic drug names (*adalimumab, etanercept, golimumab, infliximab,* and *ustekinumab)* paired with *psoriasis or psoriatic arthritis, English,* and *human.* Studies that involved adult and older patient populations were included. Reports were excluded if the majority of subjects were less than 18 years of age, or efalizumab or alefacept, which are no longer marketed in U.S., were the only comparator. Clinical practice guidelines or consensus recommendations issued by professional organizations or expert panels were included if they discussed the place in therapy of biologics relative to nonbiologics or individual biologics versus other biologics (i.e., they offered comparative drug recommendations).

Table 20 Active-controlled Randomized Trial of Biologics in Plaque Psoriasis

Outcome Measure at 16 Weeks	Adalimumab (A) 40 mg qow (B) 80 at wk 0 then 40 mg qow	Placebo	MTX (A) 15–22.5 mg/wk (B) 15 mg/wk (C) 7.5–25 mg/wk	ARR (95% CI), BIO vs. Active	NNT (95% CI), BIO vs. Active
Responders, PASI-75, % (n/N)	**(A) 79.6 (86/108)*†**	**18.9 (10/53)**	**(C) 35.5 (39/110)**	**44.1 (31.5–54.7)**	**2.3 (1.8–3.2)**
Achieved PGA of 'clear' or 'almost clear', % (n/N)	**(A) 73.1 (NR)*†**	**11.3 (NR)**	**(C) 30.0 (NR)**	**43.1**	**2.3**
SAEs, % (n/N)	**1.9 (2/107)**	**1.9 (1/53)**	**0.9 (1/110)**	**1.0**	
Serious Infections, % (n/N)	**0**	**0**	**0**	**0**	
WDAEs, % (n/N)	**0.9 (1/107)**	**1.9 (1/53)**	**5.5 (6/110)**	**–4.6**	
AEs, % (n/N)	**(A) 73.8 (79/107)**	**79.2 (42/53)**	**(C) 81.8 (90/110)**	**–8.0**	

Reference and Quality: Saurat, et al. (2008), CHAMPION trial[105,168], High

* p<0.001 vs. placebo; † **p<0.001 vs. methotrexate**

Table 21 Systematic Reviews and Meta-analyses of Placebo-controlled Trials of Biologics for Plaque Psoriasis

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
RR of achieving PASI-75 vs. PBO at ≤ 14 wk								
Reich (2008)[91]	ALF 3 (1289) ETA 4 (1446) INF 4 (1072)	10–12	—	(A) 10.68 (6.15–18.57) (B) 11.92 (8.17–17.39)		(A) 25.48 (14.04–46.23)		Heterogeneity among INF studies (p = 0.03)
Brimhall (2008),[169]	16 (7931)	10–14		A) 10.20 (5.87–17.72)* (B) 11.73 (8.04–17.11)* (C)10.43		(A) 17.4 (6.41–47.19)*; NNT 2 (1.24–1.38) (B) 16.52 (5.96–45.80)*; NNT = 2; 1.28–1.45)		
NNT for achieving PASI-75 vs. PBO at ≤ 14 wk								
Brimhall (2008),[169]	16 (7931)	10–14		A) 4 (2.96–4.10) (B) 3 (2.07–2.49) (C) 3 (2.41–3.72)		(A) 2 (1.24–1.38) (B) 2 (1.28–1.45)		
RR of achieving PASI-75 vs. PBO at 24 wk								
Reich (2008)[91], Poor	ALF 3 (1289) ETA 4 (1446) INF 4 (1072)	24 wk		NSD between ALE, ETA, INF		NSD between ALE, ETA, INF		
Probability of achieving PASI-75, %								
Canadian HTA[88]		??	71*	50		81%*		INF and ADA > ETA and systemics
Reich (2008)[91], Poor	ALF 3 (1289) ETA 4 (1446) INF 4 (1072)	24		(A) 51 (0.4–100) (B)56 (0–100)		(A) 79 (4–100)		Wide CIs suggest NSD
PASI-75 Absolute Risk Difference (RD) vs. PBO (95% CI), %								
Schmitt (2008)[89], Fair	Total 11 (3890) CSA 3 (182) ADA 1 (1212) ETA 4 (1447) INF 3 (1049)	CSA 8–10 ADA 16 ETA 12 INF 10	64 (61–68)	(A) 30 (25–35) (B) 44 (40–48)		(B) 77 (72–81)		Only the DB studies included in meta-analyses are included here, except those for EFA. RD (95% CI): PBO 4 (3–4) CSA (2.5–5 mg/kg) 33 (13–52)
Mean Difference Between Tx and PBO in ↓ from BL in DLQI HRQoL (95% CI)								
Reich (2008)[91], Poor	ALF 3 (NR) ETA 3 (NR) INF 2 (NR)	NR ALF 10–12 ETA, INF	—	(A) 5.66 (3.27–8.04) (B) 6.07 (3.99–8.16)		(A) 8.52 (4.95–12.08)		Differences in relative effects of BRMs are uncertain INF > ETA50 > ETA25 > ALF
Improvement (↓) in DLQI Descriptor Bands, BL→EP (band of 0–1 = 'no effect at all'; 2–5 = 'small effect'; 6–10 = 'moderate effect"; 11–20 = 'very large effect'; 21–								

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
30 = 'extremely large effect' on HRQoL)								
Katugampola (2007)[92], Poor	ALF 1 (507) ETA 1 (1965) INF NR	ALF 14 ETA 12 INF 10	—	(B) 12→4		(A) 13→3		PBO group data not reported; may include data from OL studies
Achieved DLQI of 0 ('no effect'), % of pts (scale 0–30, least–greatest impairment)								
Katugampola (2007)[92], Poor	ALF 1 (507) ETA 1 (1965) INF 2 (627)	ALF 12 ETA 12–24 INF 10–46	—	(B) 28		(B) 47		See footnotes for domains that improved† PBO group data not reported; may include data from OL studies
SAEs, RR (95% CI)								
Brimhall (2008),[169]	16 (7931)	24 ALE 12–24 ETA 10–30 INF		(C) 1.17 (0.59–2.33)		(C) 1.26 (0.56–2.84)		NSDs vs. PBO
AEs, RR (95% CI)								
Brimhall (2008),[169]	16 (7931)	24 ALE 12–24 ETA 10–30 INF		(C) 1.05 (0.96–1.16)		(C) 1.18 (1.07–1.29)*		ETA NSD
AEs, NNH (95% CI)								
Brimhall (2008),[169]	16 (7931)	24 ALE 12–24 ETA 10–30 INF		(C) 46 (–48–14)		(C) 9 (5.99–19.61)		
Ryan (2011)[100], Good	UST 5 (2591) ETA (vs. BRIA) 2 (420) INF 4 (1492) ETA 6 (2228) ADA 3 (1436)	12–20 UST 12 ETA (vs. BRIA) 10–24 INF 12–24 ETA 12–24 ADA	Range 0.00–0.04 (CIs inc 0)	ETA vs. BRIA Range 0.0–0.04 (CIs inc 0) ETA vs. PBO Range –0.04–0.00 (CIs inc 0)		Range –0.04–0.00 (CIs inc 0)	0.01 (–0.01–0.03)	Results for briakinumab not shown here. Study did not calculate overall risk difference for each TNFI.

BL, Baseline; EP, End point

† DLQI HRQoL domains that improved:Etanercept—Symptoms and feelings and daily activities; infliximab—All 6 domains

Table 22 Systematic Reviews / Meta-analyses of Placebo-controlled Trials of Biologic Agents in Psoriatic Arthritis

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
ACR20 Responder Rate, RR (95% CI) vs. PBO								
Saad (2008)[143], GOOD	6 (982), 2 RCTs per biologic	ADA 12 ETA 12 INF 14–16	3.42 (2.08–5.63)*	5.50 (2.15–14.04)*		5.71 (3.53–9.25)*		*P<0.004 NSD among TNFIs
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	3.65 (2.56–5.17)*	4.19 (2.74–6.42)*		5.47 (3.43–8.71)*		*P<0.00001 NSD among TNFIs
ACR50 Responder Rate, RR (95% CI) vs. PBO								
Saad (2008)[143], GOOD	6 (982), 2 RCTs per biologic	ADA 12 ETA 12 INF 14–16	8.71 (4.30–17.66)*	10.68 (4.40–25.89)		14.73 (5.11–42.43)*		*P<0.05
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	10.08 (4.74–21.44)*	10.84 (4.47–26.28)*				*P<0.00001

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
Saad (2008)[143], GOOD	ADA 1 (313) ETA 1 (205)	ADA **24** ETA **24**	6.33 (3.36–11.92)*	9.52 (3.52–25.75)*		—		*P<0.05
ACR70 Responder Rate, RR (95% CI) vs. PBO7								
Saad (2008)[143], GOOD	6 (982), 2 RCTs per biologic	ADA 12 ETA 12 INF 14–16	15.75 (4.44–55.82)*	14.75 (1.97–110.51)*		19.21 (3.77–97.87)*		*P<0.05
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	26.05 (5.18–130.88)*	16.28 (2.20–120.54)*				*P = 0.006
Saad (2008)[143], GOOD	1 (313) 1 (205)	ADA 24 ETA 24	18.77 (4.59–76.72)*	9.27 (1.20–71.83)*				*P<0.05
Probability of ACR20 Response, % (Credible Interval, %) [ACR20 is generally accepted to be the MCID for arthritis symptoms.]								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	0.56 (0.43–0.69)	0.61 (0.46–0.75)		0.68 (0.53–0.81)		PBO 0.14 (0.11–0.17)
PsARC Responder Rate, RR (95% CI)								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	2.24 (1.74–2.88)*	2.60 (1.96–3.45)*		3.44 (2.53–4.69)*		*P<0.0001
PsARC Response, mean (SD) [95% Credible interval]								
Yang (2012)[145], UTD	NR	ADA NR ETA NR GOL 14 INF NR	0.585 (0.070) [0.441–0.716]	0.712 (0.070) [0.562–0.832]	0.764 (0.065) [0.622–0.871]	0.793 (0.057) [0.001–0.799]		PBO 0.247 (0.036) [0.175–0.318] CrIs overlapped
Probability of PsARC Response, mean % (Credible Interval, 2.5%–97.5%)								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	59 (44–71)	71 (57–83)		79 (67–89)		PBO 25 (0.18–0.32)
Mean TSS annualized rate of progression, mean difference (Active–PBO)								
NICE Health Technology Assessment[140], GOOD	1 ADA (144/PBO 152)	ADA 24		–0.56 (–0.86 to –0.26)*				*P = 0.0006 ADA showed rapid onset
TSS change from baseline, mean difference (Active–PBO)								
NICE Health Technology Assessment[140], GOOD	1 ETA (101 / PBO 104)	ETA 24	–0.3*					*P<0.001 ETA showed rapid onset
TMVdHSS change from baseline, mean difference (Active–PBO)								
NICE Health Technology Assessment[140], GOOD	1 INF (NR)	INF 24				–1.52		"Significant" but p-value NR
HAQ, mean % change from baseline, WMD (95% CI).								
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	NR	–48.99 (38.53–59.44)*		–60.37 (–75.28 to –45.46)		*P<0.0001 P-value NR for INF
HAQ, mean change from baseline, WMD (95% CI). [MCID is –0.3.]								
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	–0.27 (–0.36 to –0.18)*	NR		NR		*P<0.0001
HAQ, change from baseline in responders, mean [95% Credible Intervals]								
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	–0.48 [–0.60 to –0.35]	–0.63 [–0.81 to –0.46]		–0.66 [–0.79 to –0.52]		PBO –0.24 [–0.34 to –0.15], below the MCID. In responders, mean changes in HAQ was lower with ADA but all CrIs overlapped.

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
Yang (2012) NICE Single Health Technology Assessment[145], UTD	NR	ADA NR ETA nr GOL 14 INF NR	–0.482 (0.065) [–0.604 to –0.349]	–0.635 (0.091) [–0.814 to –0.456]	–0.440 (0.085) [–0.609 to –0.276]	–0.659 (0.709) [–1.026 to –0.286]		PBO –0.266 (0.044) [–0.356 to –0.182] CrIs overlapped among TNFIs
HAQ, change from baseline in nonresponders, mean [95% Credible Intervals]								
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	–0.13 [–0.26 to –0.001]	–0.19 [–0.38 to 0.00]		–0.19 [–0.33 to –0.06]		PBO 0. In nonresponders, changes in HAQ were all below the MCID.
Yang (2012) NICE Single Health Technology Assessment[145], UTD	NR	ADA NR ETA NR GOL 14 INF NR	–-0.136 (0.068) [–0.268–0.002]	–0.195 (0.099) [–0.392–0.0002]	–0.031 (0.088) [–0.261–0.142]	–0.198 (0.073) [–0.338–0.056]		PBO 0 [0–0] CrIs included 0. Changes in HAQ were all below the MCID of –0.35.
PASI 75 Responder Rate, RR (95% CI) vs. PBO								
Saad (2008)[143], GOOD	4 (385) ADA 1 (138) ETA 1 (38) INF 2 (209)	ADA 12 ETA 12 INF 14	11.33 (3.65–35.17)*	11.00 (0.65–186.02)		27.03 (7.88–92.74)*		ETA NSD *P<0.05
Saad (2008)[143], GOOD	ADA 1 (138) ETA 1 (128)	ADA 24 ETA 24	41.00 (5.80–289.75)*	7.05 (1.68–29.65)*				*P<0.05
Probability of PASI 75 Response, mean (Credible Intervals, %)								
NICE Health Technology Assessment[140], GOOD	6 in 43 publications, 2 per biologic	ADA 12 ETA 12 INF 14	0.48 (0.28–0.69)	0.18 (0.08–0.31)		0.77 (0.59–0.90)		PBO 0.04 (0.03–0.06). **INF > ETA**
PASI Change from BL in pts with ≥3% BSA psoriasis at baseline, mean								
Yang (2012) NICE Single Health Technology Assessment[145], UTD	NR	ADA NR ETA NR GOL 14 INF NR	–5.18	–2.50	–4.49	–7.22		GOL ranked 3rd highest
SAEs, Risk Difference vs. PBO (95% CI)								
Saad (2008)[143], GOOD	6 (1029) ADA 2 (413) ETA 2 (265) INF (351)	ADA 12 ETA 12 INF 14	–0.01 (–0.05–0.02)	–0.01 (–0.05–0.04)		0.01 (–0.03–0.02)		
WDs, Risk Difference vs. PBO (95% CI)								
Saad (2008)[143], GOOD	5 (755) ADA 2 (413) ETA 2 (265) INF 1 (57)	ADA 12 ETA 12 INF 14	–0.02 (–0.07–0.02)	–0.19 (–0.29 to –0.09)*		0.02 (–0.06–0.10)		*P<0.05 ETA CIs don't overlap with others
WDAEs, Risk Difference vs. PBO (95% CI)								
Saad (2008)[143], GOOD	5 (1029) ADA 2 (413) ETA 1 (205) INF 2 (451)	ADA 12 ETA 12 INF 14	0.01 (–0.01–0.03)	0.00 (–0.02–0.02)		0.03 (–0.01–0.06)		
WDAEs								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INFRCTs – All GOOD	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	NR	NR		0		
Serious Infection, Range of differences (Active–PBO) across PsA RCTs, %								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INF RCTs – All GOOD	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	NR–0.3	NR		NR		Based on rates across heterogeneous studies; unreliable estimates of risks
Cancer, Range across PsA RCTs, %								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INF RCTs – All GOOD	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	NR	NR / 0		NR / –0.5		Based on rates across heterogeneous studies; unreliable estimates of risks
TB, Range across PsA RCTs, %								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INF RCTs – All GOOD	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	NR	NR		NR		Based on rates across heterogeneous studies; unreliable estimates of risks
Mortality, Range across PsA RCTs, %								

Outcome Measure / Reference, Quality	No. of RCTs (N)	Time Point (wk)	Adalimumab	Etanercept (A) 25 mg s.c. 2x/wk (B) 50 mg s.c. 2x/wk (C) Pooled doses (D) 25 mg s.c. qwk	Golimumab	Infliximab (A) 5 mg/kg at Wk 0, 2, 6, then q8wk (B) 5 mg/kg at Wk 0, 2, 6 (C) Various regimens	Ustekinumab	Comments
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INF NRS / RCTs	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	NR–0	NR		0		Based on rates across heterogeneous studies; unreliable estimates of risks
URTI, Risk Difference vs. PBO (95% CI)								
Saad (2008)[143], GOOD	6 (1029) ADA 2 (413) ETA 2 (265) INF 2 (351)	ADA 12 ETA 12 INF 14	0.00 (–0.07–0.07)	0.03 (–0.11–0.18)		–0.06 (–0.12–0.00)		
URTI, range of differences in rates across trials (Active–PBO), %								
NICE Health Technology Assessment[140], GOOD 2 ADA, 2 ETA, 2 INF	6 in 43 publications ADA 417 ETA 265 INF 304	ADA 12–24 ETA 12–24 INF 16–24	–2.2 to 5.5	–3 to 14		–7.9 to –4.0		Based on rates across heterogeneous studies; unreliable estimates of risks
Injection Site Reactions, Risk Difference vs. PBO (95% CI)								
Saad (2008)[143], GOOD	4 (678) ADA 2 (413) ETA 2 (265)	ADA 12 ETA 12	0.03 (–0.01–0.08)	0.23 (0.14–0.33)*				*P<0.05 Increased risk with ETA; CIs don't overlap

TMVdHSS, Total modified van der Heijde-Sharp score; TSS, Total Sharp Score; UTD, Unable to determine

Table 23 Indirect Comparisons of Biologics and Traditional Systemic Agents in Psoriatic Arthritis:Systematic Review of Placebo-controlled Trials

Outcome Measure	TNFIs	Sulfasalazine	Gold Salts	Leflunomide	All NBSAs	Comments
Withdrawals Due to Lack of Efficacy, RR (95% CI)	0.25 (0.13–0.48)*	0.45 (0.23–0.89)*	0.25 (0.11–0.54)*	0.44 (0.23–0.83)*	0.39 (0.27–0.57)*	TNFIs were ETA (2 RCTs), ADA (1), INF (2). One small 12-wk study evaluated low-dose MTX but outcome measures were CGA, Sx scores, PGA, ESR.
WDAEs, RR (95% CI)	2.20 (0.82–5.91)	1.76 (0.98–3.14)†	2.34 (1.10–4.97)*	3.86 (1.20–12.39)*	2.32 (1.55–3.47)*	NSD w/TNFIs.
NNT / NNH	0.25	0.93	0.79	0.45	0.86	

Reference and Quality: [164], FAIR. Average Jadad score of RCTs was 3 (72% of RCTs had Jadad score of 3). **No. of RCTs (N):** 5 TNFIs (882), 1 ALF (185), 12 NBSAs (1081), 18 Total (2148). **Time Point (wk) for TNFIs, ALF and NBSA, respectively: 12–50, 12 and 12–52.**

ADA, Adalimumab; CGA, Clinician Global Assessment; ESR, Erythrocyte sedimentation rate; ETA, Etanercept; MTX, Methotrexate; NBSAs, Nonbiologic systemic agents; NNH, Number-needed-to-treat for harm; NNT, Number-needed-to-treat (for benefit); PGA, Patient Global Assessment; TNFI, Tumor necrosis factor inhibitor

* P ≤ 0.03; † P = 0.06

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