Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics

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Psoriasis is a chronic, inflammatory multisystem disease that affects up to 3.2% of the US population. This guideline addresses important clinical questions that arise in psoriasis management and care, providing recommendations based on the available evidence. The treatment of psoriasis with biologic agents will be reviewed, emphasizing treatment recommendations and the role of the dermatologist in monitoring and educating patients regarding benefits as well as associated risks. (J Am Acad Dermatol 2019;80:1029-72.)

Key words: biologic agents; clinical guidelines for psoriasis; dermatology; guidelines; monoclonal antibodies; psoriasis; skin disease.

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American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The American Academy of Dermatology conflict of interest policy summary may be viewed at www.aad.org. The conflicts of interest of the individual working group members are listed in the text of this guideline.

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Dermatology (AAD) policy, a minimum 51% of work group (WG) members did not have any relevant conflicts of interest.

Participation in 1 or more of the activities listed here constitute a relevant conflict:

- Service as a member of a speaker bureau, consultant, or advisory board, for pharmaceutical companies on psoriasis disease state or psoriasis drugs that are in development or US Food and Drug Administration (FDA)-approved.
- Sponsored research funding or investigator-initiated studies (with partial or full funding from pharmaceutical companies) on psoriasis disease state or psoriasis drugs that are in development or FDA-approved.

If a potential conflict was noted, the WG member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas in which complete consensus was not achieved, are shown transparently in the guideline.

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Abbreviations used:

AAD:	American Academy of Dermatology
BSA:	body surface area
FDA:	Food and Drug Administration
HAART:	highly active antiretroviral therapy
IBD:	inflammatory bowel disease
IL:	interleukin
m-PPPASI:	Modified Palmoplantar Psoriasis Area Severity Index
NAPSI:	Nail Psoriasis Severity Index
NB-UVB:	narrowband ultraviolet B
NPF:	National Psoriasis Foundation
PASI:	Psoriasis Area Severity Index
PASI 75:	75% improvement in the Psoriasis Area Severity Index
PASI 90:	90% improvement in the Psoriasis Area Severity Index
PASI 100:	100% improvement in the Psoriasis Area Severity Index
PPPASI:	Palmoplantar Psoriasis Area Severity Index
PsA:	psoriatic arthritis
PSSI:	Psoriasis Scalp Severity Index
QOL:	quality of life
RCT:	randomized controlled trial
SCC:	squamous cell carcinoma
WG:	work group

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Vidhya Hariharan, PhD, has no conflicts of interest to disclose.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, nor should they be deemed either inclusive of all proper methods of care or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient and the known variability and biologic behavior of the disease. Furthermore, the treatment dosages used in clinical trials may not be effective in certain cases, and some patients may require shorter intervals between doses and/or higher treatment doses of a particular biologic agent. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies will likely require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline will cover the use of biologic agents in the treatment of psoriasis in adults; psoriasis in the pediatric population will be covered in the "Guidelines of care for the management and treatment of pediatric psoriasis" guideline. This guideline will not cover the treatment of psoriatic arthritis (PsA) in detail, its management is reviewed in detail by the American College of Rheumatology and

Table I. Clinical questions

What are the efficacy, effectiveness, effect of switching, and adverse effects of the following biologic drugs used as monotherapy or in combination with other psoriasis therapies to treat moderate-to-severe psoriasis in adults?

- Etanercept (FDA approval on April 30, 2004)
- Infliximab (FDA approval on September 27, 2006)
- Adalimumab (FDA approval on January 22, 2008)
- Certolizumab (FDA approval on May 27, 2018)
- Ustekinumab (FDA approval on September 25, 2009)
- Secukinumab (FDA approval on January 21, 2015)
- Ixekizumab (FDA approval on March 22, 2016)
- Brodalumab (FDA approval on February 15, 2017)
- Guselkumab (FDA approval on July 13, 2017)
- Tildrakizumab (FDA approval on March 21, 2018)
- Risankizumab (FDA approval pending)

FDA, US Food and Drug Administration.

National Psoriasis Foundation treatment guidelines.[6,7]

METHOD

A multidisciplinary WG of psoriasis experts consisting of dermatologists (including private practitioners), a rheumatologist, a cardiologist, and representatives from a patient advocacy organization was convened to update and expand on the previously published 2008 AAD psoriasis guideline.[1] The WG determined the scope of the guideline and identified important clinical questions with regard to biologic treatment of psoriasis (Table I). WG members completed a disclosure of interests that was periodically updated and reviewed for potential relevant conflicts of interests throughout the guideline development process.

An evidence-based model was used, and evidence was obtained by using a search of the PubMed and MEDLINE databases from January 1, 2008, to December 31, 2017, for clinical questions addressed in the previous version of this guideline published in 2008-2011, and for all newly identified clinical questions. Searches were limited to publications in the English language. Medical Subject Heading (MeSH) terms used in various combinations in the literature search included *psoriasis* (*vulgaris*, *plaque*, *guttate*, *erythrodermic*, *pustular*, *palmoplantar*, *inverse*, *nail*), *biologic therapy* (*adalimumab*, *etanercept*, *infliximab*, *secukinumab*, ustekinumab, *brodalumab*, *tildrakizumab*, *guselkumab*, risankizumab, *tofacitinib*), *biosimilar*, *cessation*, *interruption*, *failure* (*primary, secondary*), *combination therapy*, *anti−TNF-α inhibitors, interleukin inhibitors*, *therapy switch/alternate*, and *superior*.

After removal of duplicate data, 354 articles were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and utilized by the WG in developing recommendations. The Academy's prior published guidelines on psoriasis were evaluated, as were other current published guidelines on psoriasis.

The available evidence was evaluated by using a unified system called the Strength of Recommendation Taxonomy, which was developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*). Evidence was graded by using a 3-point scale based on the quality of methodology (eg, randomized controlled trial [RCT], case-control study, prospective or retrospective cohort study, case series) and the overall focus of the study (ie, diagnosis; treatment, prevention, and/or screening; or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life [QOL]).
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of best available evidence, as summarized in the tables in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In those situations in which documented evidence-based data are not available, we have utilized expert opinion to generate our clinical recommendations or opted not to issue a recommendation.

This guideline has been developed in accordance with the American Academy of Dermatology/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (May 2014),[2] which includes the opportunity for review and comment by the entire AAD membership and final

Table II. Strength of recommendations on the TNF-α inhibitor etanercept

Recommendation No.	Recommendation	Strength of recommendation
1.1	Etanercept is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
1.2	The recommended starting dose of etanercept is 50 mg taken as a self-administered subcutaneous injection twice weekly for 12 consecutive wk	A
1.3	The recommended maintenance dose of etanercept after the initial 12 wk is 50 mg once weekly. Etanercept administered at a dose of 50 mg twice weekly is more efficacious than a dose of 50 mg once weekly and may be required for better disease control in some patients	A
1.4	Etanercept is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	A
1.5	Etanercept is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
1.6	Etanercept can be recommended as a monotherapy treatment option for use in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe plaque psoriasis	B
1.7	Etanercept is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with significant psoriatic arthritis	A
1.8	Combination of etanercept and topicals, such as high-potency corticosteroids with or without a vitamin D analogue, is recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis	A
1.9	Etanercept may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
1.10	Combination of etanercept and methotrexate is recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
1.11	Etanercept may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
1.12	Etanercept may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults when clinically indicated	C
1.13	Etanercept may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

TNF-α, Tumor necrosis factor-α.

review and comment by the AAD Board of Directors. Additionally, this guideline has been developed in collaboration with the National Psoriasis Foundation, and as part of the review process, the National Psoriasis Foundation medical board members provided their feedback. This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

DEFINITION OF PSORIASIS

Psoriasis vulgaris is a chronic inflammatory skin disease that classically presents with well-demarcated, red plaques with silvery scale, commonly involving the scalp, elbows, knees, and presacral region, though any area of the skin may be involved, including the palms, soles, nails, and genitalia. Although the severity of psoriasis is defined in part by the total body surface area (BSA) involved, with involvement of less than 3% of BSA considered mild, involvement of 3% to 10% of BSA considered moderate, and involvement of greater than 10% considered severe disease, psoriasis can be severe irrespective of BSA when it has serious emotional consequences or when it occurs in select locations, including but not restricted to, the hands, feet, scalp, face, or genital area, or when it causes intractable pruritus. The Psoriasis Area Severity Index (PASI) is a more specific means of quantifying the extent and severity of psoriasis, as it takes into account not only BSA but also the intensity of redness, scaling, and plaque thickness, ultimately producing a score from

Table III. Level of evidence on the TNF-α inhibitor etanercept

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	1.1-1.3	I-III	10,11,14-20,22-34,51,56,61,72-75
Dosing range			
• Start with 50 mg twice per wk for 12 wk			
• Maintenance dose: 50 mg/wk; 50 mg twice per wk may be required in some patients			
Type of psoriasis			
• Scalp	1.4	I	39
• Nail	1.5	I-III	35-38,40
• Pustular, erythrodermic, inverse	1.6	II-III	41-43,45,47,48,76
Monotherapy for psoriasis with psoriatic arthritis	1.7	I	77,78
Combination therapy			
• Topical	1.8	I-II	50-54,79
• Acitretin	1.9	I-II	55,56,59
• Methotrexate	1.10	I-II	60-62
• Apremilast	1.11	II	63
• Cyclosporine	1.12	II	64
• Narrowband ultraviolet B phototherapy	1.13	II	67,68,80

TNF-α, Tumor necrosis factor-α.

0 (no disease) to 72 (maximal disease severity). The PASI is used for monitoring response to treatments in clinical trials and as a research tool to judge the severity of psoriasis. It is rarely utilized by dermatologists in clinical practice to guide management.

Psoriasis is an inflammatory, immune-mediated condition involving cutaneous T cells, dendritic cells, and keratinocytes, with subsequent release of a variety of cytokines and other soluble mediators. These chemical signals are responsible for keratinocyte hyperproliferation manifesting as characteristic scaly plaques, and they also contribute to the augmented inflammation underlying a number of systemic disease associations, including metabolic syndrome, cardiovascular disease, and PsA. To inhibit the inflammation underpinning this condition, a number of topical and systemic medications have been created with varying success. The term *biologic agents* refers to engineered monoclonal antibodies and fusion proteins that exert their therapeutic actions by blocking specific cytokines or cytokine receptors critical to psoriatic inflammation.

INTRODUCTION

Psoriasis is a common inflammatory disease of adults and children, affecting approximately 3.2% of the population.[3] Affected patients are frequently undiagnosed, undertreated, or even untreated.[4] Although skin involvement is often the most prominent and solely recognized manifestation of this disease, recognition of the condition as a chronic, multisystem inflammatory disorder is imperative to optimize management. Psoriasis follows a relapsing course and can negatively affect QOL. Psoriasis is associated with inflammatory arthritis, known as PsA, which has a prevalence ranging from 25% to 30% in psoriatic patients.[5] PsA will not be reviewed in detail in this guideline, as its management is reviewed in detail by the American College of Rheumatology and National Psoriasis Foundation treatment guidelines[6,7] and the previously published guideline by the American Academy of Dermatology.[8]

The majority of patients with mild-to-moderate psoriasis are capable of adequately controlling disease solely with topical medications or phototherapy. However, topical therapies used alone or combined with phototherapy may be insufficient for patients with moderate-to-severe disease. Biologic agents, as monotherapy or combined with other topical or systemic medications, have a high benefit-to-risk ratio, and because of that, they are a welcome addition to the armamentarium of psoriasis management.

This section will review the use of biologic agents in the treatment of adult psoriasis.

Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness is defined as its performance under real-world conditions.[9]

Table IV. Strength of recommendations on the TNF-α inhibitor infliximab

Recommendation No.	Recommendation	Strength of recommendation
2.1	Infliximab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
2.2	The recommended starting dose of infliximab is an infusion of 5 mg/kg administered at wk 0, wk 2, and wk 6, and thereafter it is administered every 8 wks	A
2.3	Infliximab is recommended to be administered at a more frequent interval (less than every 8 weeks and as frequently as every 4 weeks during the maintenance phase) and/or at a higher dose up to 10 mg/kg for better disease control in some adult patients	B
2.4	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque-type palmoplantar psoriasis)	B
2.5	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
2.6	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
2.7	Infliximab may be recommended as a monotherapy treatment option in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe plaque psoriasis	C
2.8	Infliximab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with significant psoriatic arthritis. Infliximab also inhibits radiographically detected damage of joints in patients with psoriatic arthritis	A
2.9	Combination of infliximab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
2.10	Infliximab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
2.11	Infliximab may be combined with methotrexate to possibly augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
2.12	Infliximab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults when clinically indicated	C

TNF-α, Tumor necrosis factor-α.

TNF-α INHIBITORS

Etanercept (FDA approval on April 30, 2004)

Etanercept is a recombinant human tumor necrosis factor-α (TNF-α) receptor protein fused with the Fc portion of IgG1 that binds to soluble and membrane-bound TNF-α and to tumor necrosis factor-β.[10,11] Etanercept is currently approved for treatment of moderate-to-severe adult and pediatric (in patients aged ≥4 years) plaque psoriasis, PsA, rheumatoid arthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. The approved dosing of etanercept in psoriasis is 50 mg given subcutaneously twice weekly for the first 12 weeks followed by 50 mg once weekly thereafter.[12] Multiple publications evaluating etanercept versus placebo, methotrexate, or other biologics have established the efficacy of this drug in patients with moderate-to-severe psoriasis.[13-33] A pooled analysis based on 1 phase II and 2 phase III RCTs showed that at week 12, a greater proportion of patients receiving etanercept, 50 mg twice weekly (49%), or etanercept, 50 mg weekly (33%), achieved a 75% improvement on the PASI (PASI 75) compared with those receiving placebo (3% [$P < .05$]).[11] At week 24, 44% of those receiving 25 mg twice weekly and 59% of those receiving 50 mg twice weekly achieved PASI 75 (Table II).[33]

Further reinforcing the efficacy of etanercept, in the RCT reSURFACE 2, etanercept was compared with tildrakizumab and placebo for the treatment of moderate-to-severe psoriasis. After 12 weeks, the percentages of patients who achieved PASI 75 were 66% in the group receiving tildrakizumab in a dose of 200 mg, 61% in those in the group receiving 100 mg

of tildrakizumab, and 48% in the group receiving etanercept, compared with 6% in the placebo group. Additionally, the rates of achieving a 90% improvement on the PASI (PASI 90) were 37% in the group receiving 200 mg of tildrakizumab, 39% in the group receiving 100 mg of tildrakizumab, and 21% in the group treated with etanercept, compared with 1% in the placebo group.[34]

With regard to difficult-to-treat areas, several clinical studies have provided evidence of the efficacy of etanercept in scalp and nail psoriasis.[35-38] An RCT with 124 patients with psoriasis and scalp involvement found that at week 12, there was a mean improvement in Psoriasis Scalp Severity Involvement (PSSI) score of 86.8% in the etanercept group compared with a 20.4% improvement in the placebo group ($P < .0001$).[39] A retrospective study of nail psoriasis found that at 12 weeks, there was a 41.7% improvement in Nail Psoriasis Severity Index (NAPSI) score in patients treated with etanercept.[40] The efficacy of etanercept in treating other forms of psoriasis such as pustular, erythrodermic, and palmoplantar has been reported in some RCTs,[41] although the vast majority of data have been obtained from case series and reports.[42-49]

Biologic medications as monotherapy may not always induce complete clearing in patients. When clinically required, etanercept may be combined with topical agents such as steroids and vitamin D analogues.[50-54]

As with other biologic agents, etanercept may be combined with systemic agents, such as acitretin, to increase efficacy.[55,56] The addition of acitretin might allow the reduction of etanercept dosing and also inhibit the development of cutaneous squamous cell carcinoma (SCC) in susceptible patients based on its efficacy for prevention of cutaneous SCC in other high-risk groups (ie, patients with xeroderma pigmentosum, transplant recipients who are taking immunosuppressive medication, and patients who have received large numbers of psoralen and ultraviolet A treatments).[57-59]

Etanercept may also be combined with methotrexate. This combination is well established in the treatment of both rheumatoid arthritis and PsA. Likewise, there are substantial and convincing data documenting the safety and efficacy of this combination for patients with psoriasis.[60-62] There are limited data from a retrospective case series indicating that apremilast could be combined with etanercept to improve efficacy.[63] However, the long-term safety and efficacy of this combination is unknown. Case series have shown that etanercept may be combined with cyclosporine to improve efficacy in the short term.[64,65] Likewise, the combination of etanercept with ultraviolet phototherapy increases efficacy,[66,67] although the long-term safety of this combination is not well studied. A 12-week, single-arm, open-label study evaluated the combination of etanercept, 50 mg twice weekly, and narrowband UV B (NB-UVB), 3 times weekly, in 86 patients. At week 12, 26.0% achieved a 100% improvement in PASI score (PASI 100), 58.1% achieved PASI 90, and 84.9% of patients achieved PASI 75.[68]

Although antietanercept antibodies have been detected in a small percentage of patients, a relationship between antietanercept antibodies and loss of efficacy has not been conclusively demonstrated (see the section Primary and Secondary Treatment Failure[12,69-71] (Table III*).

Infliximab (FDA approval on September 27, 2006)

Infliximab is a chimeric monoclonal antibody comprising a mouse variable region and human IgG1-α constant region. Infliximab binds to both the soluble and transmembrane TNF-α molecules, neutralizing the effects of TNF-α.[81] Infliximab is approved in adults for the treatment of psoriasis, PsA, rheumatoid arthritis, and ankylosing spondylitis. Additionally, it is FDA-approved for the treatment of Crohn's disease and ulcerative colitis in both adults and children. Infliximab is administered intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6 and thereafter every 8 weeks for psoriasis and PsA (Table IV).[82]

Multiple RCTs evaluating infliximab versus placebo, methotrexate, or other biologics have established the efficacy of this drug in patients with moderate-to-severe psoriasis.[13,81,83-88] In the pivotal infliximab phase III study in moderate-to-severe psoriasis, the rates of achievement of PASI 75 at week 10 were 75.5% and 70.3%, whereas PASI 90 was achieved by 45.2% and 37.1% in the groups receiving infliximab, 5 mg/kg and 3 mg/kg, respectively (vs a 1.9% rate of achievement of PASI 75 and 0.5% rate of achievement of PASI 90 with placebo [$P < .001$]).[84]

Infliximab is efficacious in the treatment of plaque-type palmoplantar and nail psoriasis.[35,38,89-91] An RCT treated 24 patients with palmoplantar plaque psoriasis with infliximab, 5 mg/kg at the standard dose interval, or placebo. At week 14, 33.3% and 66.7% of patients treated with infliximab achieved a 75% improvement in modified palmoplantar psoriasis area and severity index (m-PPPASI) and 50% improvement in m-PPPASI, respectively,

*[10,11,14-20,22-43,45,47,48,50-56,59-64,67-80]

Table V. Level of evidence on the TNF-α inhibitor infliximab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	2.1-2.3	I-III	51,81,83-88,112
Dosing range			
• 5 mg/kg at wk 0, wk 2, and wk 6, then every 8 wk			
• Frequent dosing (at least every 8 wk during maintenance phase) up to 10 mg/kg			
Type of psoriasis			
• Palmoplantar	2.4	I-II	89,92
• Nail	2.5	I-II	35,38,90,91,93
• Scalp	2.6	II	94
• Pustular, erythrodermic, or Inverse	2.7	II	42,43,96
Monotherapy for psoriasis with psoriatic arthritis	2.8	I-II	113-119
Combination therapy			
• Topical	2.9	II	50,51
• Acitretin	2.10	II-III	101,102
• Methotrexate	2.11	I-II	60,103
• Apremilast	2.12	II	63

TNF-α, Tumor necrosis factor-α.

compared with 8.3% for both a 75% improvement in m-PPPASI (P = .317) and a 50% improvement in m-PPPASI (P = .009) in the placebo group.[92] Additionally, in a phase III RCT assessing nail psoriasis, 373 patients with psoriasis were randomized 4:1 to receive infliximab or placebo. At weeks 10, 24, and 50, of the patients with baseline nail psoriasis, 6.9%, 26.2%, and 44.7% in the infliximab-treated group, respectively, had nail disease clearance versus 5.1% in the placebo group at week 24 ($P < .001$).[93] Infliximab is also efficacious in the treatment of scalp psoriasis. A retrospective cohort study found that after 4 weeks of treatment with infliximab, patients showed a 74% mean decrease in PSSI.[94] There are multiple case series and reports of rapid response to infliximab when it is used to treat other variants of psoriasis such as erythrodermic, generalized pustular, and palmoplantar pustular psoriasis.[42,43,95-100]

Infliximab may be combined with topical steroids and a vitamin D analogue to augment efficacy. However, rigorous evidence supporting this combination is lacking and the perception of safety is derived from informal observation and experience.[13,50] Infliximab can be used in combination with other systemic agents. Acitretin is considered negligibly immunosuppressive and therefore may be added to infliximab to increase efficacy.[101,102] The use of acitretin may also reduce the development of cutaneous SCC in susceptible patients on the basis of its efficacy for prevention of cutaneous SCC in other high-risk groups.[57-59] There are substantial and convincing data evaluating the safety and efficacy of the combination of methotrexate and infliximab in patients with psoriasis, especially those participating in studies on PsA, in which as many as 50% of the enrolled subjects were also receiving methotrexate.[60,103] Additionally, methotrexate reduces the immunogenicity of infliximab (see the comment on immunogenicity later). Because of the substantial risk of antibodies to infliximab, a significant number of patients will lose clinical response. Therefore, the addition of methotrexate to infliximab should be considered strongly for all patients. There are limited data from a retrospective case series indicating that apremilast may be combined with infliximab.[63] The long-term safety of this combination is unknown. Data are also too limited to advise combination of infliximab with other currently available biologic therapies. Although efficacy may be augmented by such a combination, the risk of significant adverse events is unknown.

Infliximab may be combined with NB-UVB phototherapy; however, no direct, well-designed study supports either the short- or long-term efficacy or safety of this combination. This recommendation is primarily extrapolated from studies of other TNFα-inhibitors used in combination with NB-UVB phototherapy.

It is relevant to consider that abnormally long intervals between infliximab infusions (>8 weeks) can increase the risk of infusion reactions and loss of efficacy owing to antibodies to infliximab.[104-106]

Infliximab has demonstrated the occurrence of efficacy-limiting immunogenicity (ie, a relationship between anti-infliximab antibodies, lowered serum

Table VI. Strength of recommendations on the TNF-α inhibitor adalimumab

Recommendation No.	Recommendation	Strength of recommendation
3.1	Adalimumab is recommended as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis	A
3.2	The recommended starting dose of adalimumab is 80 mg taken as 2 self-administered subcutaneous 40-mg injections of the initial dose, followed by a 40-mg self-administered subcutaneous injection 1 wk later, followed by 40 mg self-administered every 2 wk thereafter	A
3.3	A maintenance dose of adalimumab 40 mg/wk is recommended for better disease control in some patients	A
3.4	Adalimumab is recommended as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (palmoplantar psoriasis)	A
3.5	Adalimumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
3.6	Adalimumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
3.7	Adalimumab can be recommended as a monotherapy treatment option in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe psoriasis	B
3.8	Adalimumab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with psoriatic arthritis	A
3.9	Combination of adalimumab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
3.10	Adalimumab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.11	Adalimumab may be combined with methotrexate to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
3.12	Adalimumab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.13	Adalimumab may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.14	Adalimumab may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

TNF-α, Tumor necrosis factor-α.

levels of the drug, and loss of efficacy (see the section Primary and Treatment Secondary Failure).[71,82,107-109] Additionally, immunogenicity is correlated with infusion reactions to infliximab, which range from mild, moderate, or severe to serious (<1% of infusions).[109-111] A retrospective study showed that the use of acetaminophen, hydroxyzine, ranitidine, and methylprednisolone right before administration of infliximab, can reduce the number of infusion reactions and could prolong drug survival (Table V).[†]

Adalimumab (FDA approval on January 22, 2008)

Adalimumab is a human anti—TNF-α monoclonal antibody. It binds to soluble and membrane-bound TNF-α, inhibiting its interaction with TNF receptors.[120] Adalimumab is currently approved for 10 indications (ie, psoriasis in adults, PsA, juvenile idiopathic arthritis, ankylosing spondylitis, adult rheumatoid arthritis, adult and pediatric Crohn's disease, ulcerative colitis, hidradenitis suppurativa, and uveitis). Adalimumab dosing for psoriasis is 80 mg given subcutaneously initially, followed by 40 mg subcutaneously given the next week and at 2-week intervals thereafter.[121] Multiple RCTs evaluating adalimumab versus placebo, methotrexate, or other biologics have established the efficacy of this drug in patients with moderate-to-severe psoriasis (Table VI)[51,120,122-126]

The phase III RCT REVEAL assessed the efficacy of adalimumab for the treatment of moderate-to-severe plaque psoriasis, reporting that at week 16, PASI 75 was achieved by 71% and 7% of patients with psoriasis treated with adalimumab versus with placebo and PASI 90 was achieved by 45% and 2% of

†35,38,42,43,50,51,60,63,81,83-94,101-103,110,112-119

those treated with adalimumab versus with placebo, respectively. At week 40, the rates of achievement of PASI 75 and PASI 90 among patients treated with adalimumab were 67% and 40%, respectively.[122,124]

Two phase III RCTs (VOYAGE 1 and VOYAGE 2) compared guselkumab with adalimumab or placebo for the treatment of moderate-to-severe plaque psoriasis.[127,128] In VOYAGE 1 and 2, at week 16, more patients receiving guselkumab achieved PASI 75 than did patients receiving adalimumab or placebo (in VOYAGE 1, 91.2% of those receiving guselkumab vs 73.1% of those receiving antidrug antibodies vs 5.3% of those receiving placebo, and in VOYAGE 2, 86.3% of those receiving guselkumab vs 68.5% of those receiving antidrug antibodies vs 8.1% of those receiving placebo).[127,128] Additionally, in VOYAGE 2, at week 16, the rates of achievement of PASI 90 were 70.0% versus 46.8% versus 2.4% for guselkumab, adalimumab, and placebo, respectively.[128]

Adalimumab is effective in the treatment of hand and foot (palmoplantar) psoriasis.[129,130] The Randomized Controlled Evaluation of Adalimumab in Treatment of Chronic Plaque Psoriasis of the Hands and Feet (REACH) studied 72 patients (49 receiving adalimumab and 23 receiving placebo) with plaque-type psoriasis with palmoplantar involvement. At week 16, 30.6% of the adalimumab-treated patients achieved a hand and foot Physician Global Assessment score of clear or almost clear compared with 4.3% of the placebo-treated patients ($P = .014$).[130] Several clinical studies have shown that adalimumab is effective for nail and scalp psoriasis.[‡] Additionally, in several case series adalimumab has been used successfully to treat erythrodermic and generalized pustular psoriasis.[42,43,95]

Adalimumab can be combined with topical steroids and a topical vitamin D analogue to increase response.[13,50,133,134] Adalimumab can also be combined with multiple systemic agents to increase efficacy when necessary. Most of these recommendations are based on systematic reviews and case reports owing to the lack of clinical trials allowing the combination of therapies, except in PsA, in which case more than 50% of patients are maintained by administration of prior systemic agents (eg, methotrexate). Although many of these systemic agents have immunosuppressive effects, acitretin is considered to have a negligible effect on the immune system and therefore, in palmoplantar psoriasis, is frequently added to adalimumab to increase efficacy without increasing immunosuppression.[101,102,135,136]

Data have been collected regarding the safety and efficacy of adalimumab combined with methotrexate in patients with psoriasis. A retrospective study compared 203 patients with plaque psoriasis who were receiving either acitretin, cyclosporine, infliximab, or combination therapies (adalimumab, etanercept, or infliximab plus methotrexate) versus 168 patients who were receiving methotrexate monotherapy. Patients taking acitretin, infliximab, adalimumab and methotrexate, etanercept and methotrexate, and infliximab and methotrexate were more likely to have clear or almost clear skin compared with patients undergoing methotrexate monotherapy.[60] Additionally, methotrexate can have the potential to reduce the immunogenicity of adalimumab (see section on immunogenicity). Combining adalimumab with apremilast has also been reported in a case series and a case report; the long-term efficacy and safety of this regimen are unknown.[63,137] Adalimumab may also be combined with cyclosporine to increase treatment efficacy in the short term according to limited data from case reports and series.[138-141] The combination of adalimumab with NB-UVB may accelerate and improve the clearance of psoriatic lesions.[142] In a 24-week, open-label study, adult patients with moderate-to-severe psoriasis received adalimumab, 40 mg every other week, and NB-UVB phototherapy 3 times a week for 12 weeks. At week 12, 19 patients (95%) achieved PASI 75, 15 patients (75%) achieved PASI 90, and 11 patients (55%) achieved PASI 100.[143] It is important to consider that the long-term safety of this combination, particularly relating to the risk of skin cancer development, has not been well studied.[144] Nevertheless, no new safety signals were observed during the first 7 years of the ESPIRIT trial, a prospective registry evaluating the long-term safety and effectiveness of adalimumab for adult patients with chronic plaque psoriasis.[145-148] Furthermore, there are no new safety data from the upcoming 9-year analysis from the ESPIRIT registry (publication pending).

Adalimumab has demonstrated that efficacy-limiting immunogenicity—a relationship between antiadalimumab antibodies that lowers serum levels of the drug and leads to loss of efficacy—occurs (see the section Primary and Treatment Secondary Failure) (Table VII).[§]

Certolizumab (FDA approval on May 27, 2018)

Certolizumab is a humanized antigen-binding fragment of a monoclonal antibody (50 kDa) that

‡35,38,90,130-132

§35,38,42,43,50,51,60,63,90,101,102,120-134,138-143,149-159

Table VII. Level of evidence on the TNF-α inhibitor adalimumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	3.1-3.3	I-II	51,120-128,151-154
Dosing range			
• 80 mg during wk 1, followed by 40 mg at wk 2, then 40 mg every 2 wk thereafter			
• Maintenance dose: 40 mg/wk			
Type of psoriasis			
• Palmoplantar	3.4	I	129,130
• Nail	3.5	I-II	35,38,90,130-132
• Scalp	3.6	II	132
• Erythrodermic or Pustular	3.7	II	42,43
Monotherapy for psoriasis with psoriatic arthritis	3.8	I-II	155-159
Combination therapy			
• Topical	3.9	I-III	50,51,133,134
• Acitretin	3.10	II-III	101,102
• Methotrexate	3.11	I	60
• Apremilast	3.12	II	63
• Cyclosporine	3.13	II-III	138-141
• Narrowband ultraviolet phototherapy	3.14	II	142,143

TNF-α, Tumor necrosis factor-α.

has been conjugated with a 40-kDa polyethylene glycol moiety. It binds to TNF-α, blocking its interaction with TNF receptors. The absence of the Fc region prevents complement fixation and antibody-mediated cytotoxicity. Additionally, it obviates interaction with the neonatal Fc gamma receptor, therefore minimizing its transfer across the placenta. The polyethylene glycol moiety increases the half-life of certolizumab to a value similar to that of a whole antibody product.[160,161] Certolizumab is FDA-approved for the treatment of plaque psoriasis, PsA, Crohn's disease, ankylosing spondylitis, and rheumatoid arthritis. The approved dosing for moderate-to-severe psoriasis is 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week. Another dosing option may be considered for people who weigh 90 kg (198 pounds) or less: 400 mg (given as 2 injections of 200 mg each) initially and at week 2 and week 4, followed by a dose of 200 mg every other week.

The phase III trials for the treatment of moderate-to-severe psoriasis are now completed. Several clinical studies have found certolizumab to be an efficacious treatment for plaque psoriasis.[82,162,163] A phase II RCT treated 176 patients with moderate-to-severe psoriasis with placebo or certolizumab (200 or 400 mg) every other week until week 10. At week 12, 75% and 83% of patients receiving certolizumab in a dose of 200 or 400 mg every other week, respectively, achieved PASI 75 in contrast with 7% of patients in the placebo group ($P < .001$ for both treatment arms vs placebo).[82]

Certolizumab is likely to have class characteristics similar to those of other TNF-α inhibitors regarding treatment combination, efficacy in difficult-to-treat areas, and possibly, immunogenicity. Nevertheless, there is no evidence available on these topics, and these statements are based on extrapolation of data from other TNF-α inhibitors.

General comments and special circumstances

Time frame to assess response to treatment with TNF-α inhibitors

- Definitive response (positive or negative) to treatment with most TNF-α inhibitors is best ascertained after 12 to 16 weeks of continuous therapy, except for infliximab, for which the best time is after 8 to 10 weeks.[10,20,82,84,123,126] Consider dose escalation, an increase in frequency, or the addition of other modalities (such as topical corticosteroids or vitamin D analogues, methotrexate, acitretin, apremilast, or NB-UVB) in partially responding patients.[¶] Particularly in infliximab, consider an increase in

¶52,55,60,61,63,68,102,134,143

dosing frequency before an increase in dose in terms of mg/kg (Table VIII).[‖]

Patient weight and response to treatment with TNF-α inhibitors

- Compared with lower-weight patients, overweight or obese patients are less likely to respond to TNF-α inhibitors.[151] Therefore, overweight and obese patients frequently require a shorter dose interval or higher doses to achieve a satisfactory response. However, this effect is abrogated with infliximab, for which weight-based dosing is used.[151] TNF-α-inhibitors may display better responses with doses higher than the FDA-approved dose.[21,120,152] In contrast, on the basis of phase II studies and expert opinion, some patients might tolerate and respond to dosing at lower than the FDA-approved dose.

TNF-α inhibitors and risk of malignancy

- TNF inhibitors used as monotherapy in patients with moderate-to-severe psoriasis are not associated with a risk of solid tumor or lymphoreticular malignancy.[198,199] However, the addition of other immunosuppressant agents may alter the safety profile of TNF inhibitors.[198]
- Patients with a history of solid tumor malignancy who have failed other therapies such as ultraviolet phototherapy, methotrexate, and/or acitretin (if not contraindicated or impractical) may in certain circumstances receive TNF-α inhibitors without expectation of an increased risk of tumor recurrence.[200,201]

HIV and hepatitis B and C infections

- Use caution in patients with pre-existing immunosuppression-related conditions. Patients with HIV may receive TNF-α inhibitors if they are also receiving highly active antiretroviral therapy (HAART) that has effectively normalized their $CD4^+$ T-cell counts and they show no detectable viral load, provided that they have no recent history of opportunistic infection. Consultation with the patient's infectious disease provider is advised before initiating therapy with TNF-α inhibitors in this setting (expert opinion). Note that severe psoriasis can be a manifestation of poorly controlled or poorly managed HIV infection and that the use of HAART is likely to be an effective treatment of psoriasis in such individuals.[169-172]
- Patients with a history of or currently active hepatitis C may receive a TNF-α inhibitor for the treatment of psoriasis.[165-167] Concomitant management with an appropriate health care provider is warranted.
- Patients with a history of or currently active hepatitis B may receive a TNF-α inhibitor for the treatment of psoriasis. However, the patient should first be evaluated by an appropriate health care professional and may require concomitant treatment with an approved antiviral medication directed against hepatitis B. A hepatitis B core antibody test in this setting is recommended.[168] Patients with a history of hepatitis B (confirmed resolved infection) do not need to follow up with a specialist, but ongoing monitoring with HB surface antigen, anti-HB core antibody, and liver function tests should be considered along with other ongoing monitoring tests owing to the potential risk of reactivation.[167,168]

TNF-α inhibitors and IBD

- Patients with a history of concomitant inflammatory bowel disease (IBD) might benefit from TNF-α inhibitor therapy. In fact, adalimumab, infliximab, and certolizumab are approved for the treatment of IBD.[199,202,203]

TNF-α biosimilars. TNF-α biosimilars approved by the FDA should be considered similar to the reference branded version of the drug and therefore interchangeable. An interchangeable product means that the FDA has concluded that it may be substituted for the reference product without consulting the prescriber. The aforementioned guidelines/recommendation should apply similarly to biosimilar versions of TNF-α inhibitors.[108,184-197]

IL-12/IL-23 INHIBITORS

Ustekinumab (FDA approval on September 25, 2009)

Ustekinumab is a human monoclonal antibody that binds with high specificity and affinity to the P40 subunit of both interleukin 12 (IL-12) and IL-23, thereby suppressing IL-12— and IL-23—mediated inflammation associated with psoriasis.[204] Ustekinumab is FDA-approved for the treatment of moderate-to-severe plaque psoriasis in adults and patients aged 12 to 17, PsA, and Crohn's disease.[205] The initial dose of ustekinumab for adult patients weighing 100 kg or less is 45 mg administered subcutaneously initially and 4 weeks thereafter, followed by 45 mg administered subcutaneously every 12 weeks. For patients weighing more than 100 kg, the dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every

‖30,31,51,60,63,73,75,78,102,108,113-119,153-159,164-197

Table VIII. Supplemental information for TNF-α inhibitors

Baseline monitoring

General screening

- CBC with differential
- Complete metabolic profile
- Referral for a chest radiograph for a positive TB test
- Referral to an infectious disease specialist should be considered on a case-by-case basis

TB test

- Pretreatment test for latent TB (PPD, T-Spot, or Quantiferon Gold)[164]

Hepatitis

- Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests)[165-168]

HIV test

- Pretreatment test for HIV is considered at the treating practitioner's discretion and depends on patient-specific risk factors[169-172]

Ongoing monitoring

Parameters

- Specific assessment for infections (eg, tuberculosis, histoplasmosis), especially in those using TNF-α inhibitors plus methotrexate[173]
- Screening for skin cancer, especially in those taking TNF-α-inhibitors and in high-risk patients (with a history of cutaneous malignancy or UV phototherapy)[174,175]
- Yearly testing for latent TB (PPD, T-Spot, or Quantiferon Gold) should be done in patients at high risk (eg, patients who are in contact with individuals with active TB because of travel, work, or a family relationship, and patients with selected underlying medical conditions). For patients who are not at high risk, screening should be done at the discretion of the dermatologist. This screening is particularly important for patients who are taking TNF- α inhibitors. Further, the result of the Quantiferon Gold test can remain positive after treatment of latent TB. Caution should be exercised when using the Quantiferon Gold test[176,177]
  - An annual chest radiograph may be considered at the discretion of the treating dermatologist (expert opinion [complete WG consensus was not achieved])
- CBC with differential and CMP are not supported by evidence and are to be assessed at the discretion of each physicians' criteria except in cases involving patients treated with infliximab, for whom it is recommended that liver function tests be repeated every 3 mo after initiation, and if the result is normal, every 6-12 mo thereafter

Frequency

- A follow-up visit may be scheduled from quarterly to twice yearly depending on time of treatment, response, and tolerability of medication

Adverse effects

- Multiple sclerosis (rare)
- Hepatotoxicity, especially with infliximab
- Drug-induced reversible lupus erythematosus without renal or CNS complications
- Exacerbation or new onset of CHF
- Cytopenia

Injection site reactions

- Mild: pruritic reaction[178,179]
- Moderate-to-severe: macular erythema to erythematous annular plaques[198,199]

Infusion reactions

Acute

- Occur during or within 24 h of infusion
- Mitigated and/or prevented by pretreatment with acetaminophen and diphenhydramine
- Infusion reaction severity categorized as mild, moderate, or severe
- Mild and moderate infusion reactions
  - Usually consist of nausea, fever, erythema, and itching
  - Resolve spontaneously after reduction of the infusion rate or temporary pause of the infusion
- Severe infusion reactions
  - Occur immediately after the infusion has been started
  - Are characterized by hypotension, chest tightness, respiratory distress, dyspnea, bronchospasm, laryngeal edema, urticaria, or rash
  - Require immediate discontinuation of the infusion

Continued

Table VIII. Cont'd

Delayed
- Begin 1-14 d after infusion
- Usually consist of myalgia, arthralgia, headache, fever, rash, and fatigue
- Missing an infusion increases the chances of an infusion reaction. The next infusion should be done more slowly and with appropriate pretreatment (ie, with antihistamines)

Contraindications

Relative
- Untreated hepatitis B infection
- History of lymphoreticular malignancy
- Active infection (including TB) or sepsis. Initiation of therapy in a patient with active infection should be done in consultation with an infectious disease specialist
- For TNF-α inhibitor therapy, significant New York class III or IV CHF or pre-existing multiple sclerosis[180]

Absolute
- History of allergic reaction to therapeutic agent or vehicle

Temporary discontinuation and reinitiation of therapy
- Uncomplicated infections requiring systemic antibiotics do not necessarily require discontinuation of therapy and should be determined by the treating physician
- Treatment can be restarted after full resolution of the symptoms and/or signs of infection and the completion of any antibiotic course
- The necessity of repeating the loading doses upon restarting administration of the medication depends on disease severity, as well as on the number of doses missed
- Consider repeating loading doses upon restarting administration of the medication if the patient is flaring and/or if more than 3-4 half-lives have passed since the previous dose[73,75,153,154]

Miscellaneous

Pregnancy and lactation
- TNF-α inhibitors are safe in pregnancy and during lactation
- TNF-α inhibitors are safe in men attempting conception with their partners
- Because of drug delivery to the fetus, neonates and infants should be considered immunosuppressed for at least 1-3 mo (depending on the TNF inhibitor) postpartum in mothers who have been on TNF-inhibitors[181]
  - There is a greater theoretical risk with use during the third trimester of pregnancy owing to transplacental transfer of TNF-α inhibitors
- *Exception*: certolizumab pegol has shown minimal to no placental transfer

PsA
- All TNF-α inhibitors have long-established efficacy and FDA approval for PsA
  - Improve the signs and symptoms of the disease
  - Improve functional status and quality of life
  - Inhibit progression of radiographically detected damage of joints
- Among the biologics TNF-α inhibitors should be considered as a preferred treatment option for patients with concomitant PsA[30,31,77,78,113-119,155-159,182,183]

Biosimilars
- TNF-α biosimilars approved by the FDA should be considered similar to the reference branded version of the drug. The aforementioned guidelines/recommendations should apply similarly to biosimilar versions of TNF-α inhibitors[108,184-197]

Supplemental information is expert consensus and not part of evidence-based recommendations.
Ab, Antibody; *Ag*, antigen; *CBC*, complete blood count; *CHF*, congestive heart failure; *CNS*, central nervous system; *CMP*, complete metabolic panel; *FDA*, US Food and Drug Administration; *HB*, hepatitis B; *PPD*, purified protein derivative; *PsA*, psoriatic arthritis; *TB*, tuberculosis; *TNF-α*, tumor necrosis factor-α; *UV*, ultraviolet.

12 weeks.[205] For patients aged 12 to 17 weighing less than 60 kg the dose is 0.75 mg/kg. For adolescents weighing 60 to 100 kg the dose is 45 mg, and for those weighing more than 100 kg the dose is 90 mg. The dosing frequency is the same as in adults (Table IX).

Multiple RCTs evaluating ustekinumab versus placebo or other biologics have established the efficacy of this drug in patients with moderate-to-severe psoriasis.[204,206-216] The PASI 75 rate at week 12 in an RCT (PHOENIX 1) was 67.1% in patients receiving ustekinumab in a dose of 45 mg, 66.4% in patients receiving ustekinumab in a dose of 90 mg, and 3.1% in the placebo group.[207] The PASI 75 rate at week 12 in the subsequent RCT (PHOENIX 2) was 66.7% in patients receiving ustekinumab in a dose of 45 mg, 75.7% in patients receiving ustekinumab in a dose of 90 mg, and 3.7% in the placebo group.[208]

Table IX. Strength of recommendations on the IL-12/IL-23 antagonist ustekinumab

Recommendation No.	Recommendation	Strength of recommendation
4.1	Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
4.2	The recommended starting doses of ustekinumab are as follows: (a) For patients weighing ≤100 kg, 45 mg administered subcutaneously initially and 4 wk later, followed by 45 mg administered subcutaneously every 12 wk (b) For patients weighing >100 kg, 90 mg administered subcutaneously initially and 4 wk later, followed by 90 mg administered subcutaneously every 12 wk	A
4.3	The recommended alternate dosage for ustekinumab is administered at higher doses (90 mg instead of 45 mg in patients weighing ≥100 kg) or at a greater frequency of injection (eg, every 8 wk in its maintenance phase) for those with an inadequate response to standard dosing	A
4.4	Ustekinumab can be used as monotherapy for adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque type palmoplantar psoriasis)	B
4.5	Ustekinumab can be recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
4.6	Ustekinumab can be used as monotherapy for use in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	C
4.7	Ustekinumab can be used as monotherapy for use in adult patients with other subtypes (palmoplantar, pustular, or erythrodermic) of moderate-to-severe plaque psoriasis. There is limited evidence for its use in inverse and guttate psoriasis	C
4.8	Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with plaque psoriasis of any severity when associated with psoriatic arthritis	A
4.9	Combination of ustekinumab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.10	Ustekinumab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis	B
4.11	Ustekinumab may be combined with methotrexate to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
4.12	Ustekinumab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.13	Ustekinumab may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.14	Ustekinumab may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

IL-12/IL-23, Interleukin 12/interleukin 23.

Additionally, CLEAR, which was an RCT comparing secukinumab, 300 mg, with ustekinumab at the label dose, found that at week 16, 79% of secukinumab-treated patients achieved PASI 90 compared with 57.6% in the ustekinumab-treated group.[214,215,217] A phase III RCT, IXORA-S, compared the efficacy of ixekizumab and ustekinumab at the label doses. At week 12, PASI 90 was achieved by 72.8% of patients in the ixekizumab-treated group and 42.2% of patients in the ustekinumab-treated group, respectively.[216]

With regard to difficult-to-treat areas, several studies and case series have shown that ustekinumab is efficacious in the treatment of hand and foot (either palmoplantar plaque or pustular),[218-223] nail,[35,90,224-226] and scalp psoriasis.[227,228] An open-label trial recruited 20 patients with moderate-to-severe psoriasis of the palms and soles, 50% of whom had pustules at baseline. After 16 weeks of treatment with ustekinumab, 35% of the subjects achieved clearance; 60% of them improved by 2 or more points on the Palm-Sole Physician's Global Assessment Scale. Of those receiving the 90-mg dose (based on weight), 67% achieved clearance compared with 9% receiving 45 mg (P = .02).[229] An open-label uncontrolled study with 27 patients with moderate-to-severe disease with nail involvement found that the median rates of improvement in NAPSI were 42.5% at week 16, 86.3% at week 28, and 100.0% at week 40.[230] The publications on successful treatment of scalp psoriasis with ustekinumab are primarily case reports. There are multiple

Table X. Level of evidence on the IL-22/IL-23 inhibitor ustekinumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	4.1-4.3	I, III	204-216,241,243
Dosage range • 45 mg if patient weighs ≤100 kg, 90 mg if patient is >100 kg. At wk 1 and wk 4, then every 12 wk • 90 mg for patients ≤100 kg, or maintenance therapy every 8 wk for patients with inadequate response			
Types of psoriasis			
• Palmoplantar	4.4	II-III	218,220,222,229
• Nail	4.5	I-II	90,224-226,230,244
• Scalp	4.6	III	227
• Palmoplantar, pustular, or erythrodermic	4.7	II-III	42,43,223,245
Monotherapy for psoriasis with psoriatic arthritis	4.8	I	246-250
Combination therapy			
• Topical	4.9	II	51
• Acitretin	4.10	II-III	101,102,238
• Methotrexate	4.11	I-II	238,239
• Apremilast	4.12	II	63
• Cyclosporine	4.13	III	238
• Narrowband ultraviolet B phototherapy	4.14	I	240

IL-12/23, Interleukin 12/interleukin 23.

reports of ustekinumab being used to successfully treat other variants of psoriasis, such as erythrodermic,[43] annular, and generalized pustular psoriasis.[42,231-233] Nearly all of the reports involved case series. The efficacy of ustekinumab for the treatment of guttate (postinfectious) and inverse psoriasis is unknown.

Ustekinumab had a higher drug survival rate than TNF-α inhibitors did.[234-237] Additionally, 1 study found that biologic-naive patients and concomitant treatment with methotrexate were positive predictors of longer drug survival.[234]

When clinically required, ustekinumab may be combined with topical corticosteroids and a vitamin D analogue to augment efficacy. However, rigorous prospective studies examining this combination are unavailable and the perception of safety is derived from informal observation and experience.[13]

Like TNF-α inhibitors, ustekinumab may be combined with other systemic agents to increase treatment efficacy.[135,238] Acitretin is considered negligibly immunosuppressive and may be added to ustekinumab.[101,102] On the basis of clinical experience with transplant patients,[57-59] the use of acitretin might also inhibit the development of cutaneous SCC in susceptible patients. There are substantial and convincing data evaluating the safety and efficacy of the combination of methotrexate and ustekinumab in patients with psoriasis, especially in those participating in studies on PsA.[238,239] Apremilast is a relatively new systemic agent, and there are limited data from a retrospective case series indicating that it may be combined with ustekinumab.[63] The long-term safety of this combination is unknown. There are also limited data from case reports and series indicating that ustekinumab may be combined with cyclosporine.[238] Ustekinumab has been combined with NB-UVB phototherapy with improved clinical response.[240] Nevertheless, the long-term safety of this combination is not well studied. There is not enough evidence to recommend a combination of ustekinumab with other currently available biologic therapies. Although efficacy may be augmented by such a combination, there is an unknown level of risk of significant adverse events.

Antibodies against ustekinumab are generated in certain patients.[204-208,241] Efficacy-limiting immunogenicity—a relationship between antiustekinumab antibodies, lowered serum levels of drug, and loss of efficacy—occurs (see the section Primary and Secondary Treatment Failure) (Table X).[#]

General comments and special circumstances

Time frame to assess response to treatment with IL-12/IL-23 inhibitors

- Definitive response (positive or negative) to treatment with ustekinumab is best ascertained after 12 weeks of continuous therapy. Consider dose

[#]42,43,51,63,90,101,102,204-216,218,220,222-227,230,238-250

escalation (eg, increasing dosing frequency to every 8 weeks or increasing the dose from 45 mg to 90 mg) or the addition of other modalities (such as topical corticosteroids or vitamin D analogues, methotrexate, acitretin, or ultraviolet light) in partially responding patients.[210,211,241,243]

Patient weight and response to treatment with IL-12/IL-23 inhibitors

- Like other biologic therapies, ustekinumab displays higher responses with higher doses.[241] Overweight or obese patients often need the higher dose (90 mg) of ustekinumab to achieve the response of lower-weight patients taking the 45 mg dose.[207,208,251] Additionally, serum concentrations of ustekinumab were also affected by weight, with lower serum concentrations found in heavier patients at each dose.[252] However, some patients might tolerate and respond to lower dosing (eg, longer intervals of time between doses).[243]

IL-12/IL-23 inhibitors and risk of malignancy

- There is no definitive evidence that ustekinumab used as monotherapy for moderate-to-severe psoriasis increases the risk of solid tumor or lymphoreticular malignancy.
- Patients with a history of solid tumor malignancy who have failed other therapies such as ultraviolet phototherapy, methotrexate, and/or acitretin, if not contraindicated or impractical, may in certain circumstances receive ustekinumab without expectation of an increased risk of tumor recurrence.[198]

HIV and hepatitis B and C infections

- Use caution with patients with pre-existing immunosuppression-related conditions. As long as patients with HIV have no recent history of opportunistic infection, they may receive ustekinumab if they are also receiving highly active antiretroviral therapy (HAART) that has effectively normalized their $CD4^+$ T-cell counts and if they show undetectable viral load. Consultation with the patient's infectious disease care provider is advised before initiating ustekinumab therapy (expert opinion). It also should be considered that severe psoriasis may be a manifestation of poorly controlled or poorly managed HIV infection and that the use of HAART is likely to be an effective treatment of psoriasis in such individuals.[169-171,201]
- In patients with a history of or currently active hepatitis C, ustekinumab might be considered for the treatment of psoriasis. Concomitant management with an appropriate health care provider is warranted.[167,253,254]
- In patients with currently active hepatitis B, ustekinumab might be considered for the treatment of psoriasis. However, the patient should first be evaluated by an appropriate health care professional and may require concomitant treatment with an approved antiviral medication directed against hepatitis B. A hepatitis B test core antibody test in this setting is recommended. Patients with a history of hepatitis B (confirmed resolved infection) do not need to follow-up with a specialist but require monitoring because of the risk of reactivation.[253,254]

IL-12/IL-23 inhibitors in the setting of multiple sclerosis and IBD

- Patients with a history of concomitant multiple sclerosis and/or IBD might benefit from ustekinumab therapy. Ustekinumab is FDA-approved for the treatment of Crohn's disease (Table XI).**

IL-17 INHIBITORS

Secukinumab (FDA approval on January 21, 2015)

Secukinumab is a human IgG1 monoclonal antibody that binds IL-17A. It is FDA-approved for the treatment of adult plaque psoriasis, PsA, and ankylosing spondylitis (Table XII).

The initial dose of secukinumab is 300 mg by self-administered subcutaneous injection at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks.[256] Multiple RCTs evaluating secukinumab versus placebo have established the efficacy of this drug in patients with moderate-to-severe psoriasis.†† In 2 phase III RCTs, ERASURE and FIXTURE, the percentage of patients who achieved PASI 75 at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo ($P < .001$). The percentages of patients achieving PASI 90 with secukinumab, 300 mg, versus with placebo in the ERASURE and FIXTURE studies were 59.2% versus 1.2% and 54.2% versus 1.5%, respectively.[29] Additionally, the percentage of patients achieving PASI 100 with secukinumab, 300 mg, versus with placebo in the ERASURE and FIXTURE

** [164,169-173,176,177,207,246-249,253-255]

†† [29,32,213,215,257-261]

Table XI. Supplemental information for IL-12/IL-23 inhibitors

Baseline monitoring
General screening
- CBC
- CMP
- Referral for chest radiography in cases with a positive TB test
- Referral to an infectious disease specialist should be considered on a case-by-case basis

TB test
- Pretreatment test for latent TB (PPD, Quantiferon Gold, T-Spot)[164]

Hepatitis
- Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests)[253,254]

HIV test
- Pretreatment test for HIV is considered at the treating practitioner's discretion and depends on patient-specific risk factors[169-172]

Ongoing monitoring
Parameters
- Periodic history and physical examination, including screening for nonmelanoma skin cancer
- Screening for adverse effects (see later)
- Yearly testing for latent TB (PPD, T-Spot, or Quantiferon Gold) should be done in patients at high risk (eg, patients in contact with individuals with active TB because of travel, work, or a family relationship, and patients with selected underlying medical conditions). For patients who are not at high risk, screening should be done at the discretion of the dermatologist. Further, the result of the Quantiferon Gold test can remain positive after treatment of latent TB. Caution should be exercised when using the Quantiferon Gold test[176,177]
  - An annual chest radiograph may be considered at the discretion of the treating dermatologist (expert opinion [complete WG consensus was not achieved])
- CBC with differential and CMP are not supported by evidence and are to be assessed at the discretion of each physician's criteria except in cases involving patients treated with infliximab, for whom it is recommended that liver function tests be repeated every 3 mo after initiation, and if the result is normal, every 6-12 mo thereafter

Frequency
- Follow-up visits can be scheduled from quarterly to twice yearly on the basis of time of treatment, response, and tolerability of medication

Infections
- Overall, IL-12/IL-23 inhibitors are well tolerated. Combination of IL-12/IL-23 inhibitors with methotrexate can increase the risk of infection[173]
- Serious opportunistic infections (eg, tuberculosis) are rarely observed in clinical trials or practice[164]

Adverse events
- Hypersensitivity reactions, including anaphylaxis and angioedema

Miscellaneous
Pregnancy and lactation
- The safety of IL-12/IL-23 inhibitors during pregnancy and lactation is uncertain
- Il-12/IL-23 inhibitors are acceptable for men attempting conception with their partner

Contraindications
Relative
- Untreated hepatitis B infection
- History of lymphoreticular malignancy
- Active infection (including TB) or sepsis. Initiation of therapy in patients with active infection should be done in consultation with an infectious disease specialist

Absolute
- History of allergic reaction to therapeutic agent or vehicle

Temporary discontinuation and reinitiation of therapy
- Presence of febrile illness, especially illness requiring treatment. Treatment can be restarted after full resolution of the symptoms/signs of infection and completion of any antibiotic course
- The necessity of repeating the loading doses depends on disease severity and the number of doses missed
- Consider repeating loading doses upon restarting administration of the medication if the patient is flaring and/or if more than 3-4 half-lives have passed since the previous dose[207]

PsA

Continued

Table XI. Cont'd

- Ustekinumab has established efficacy and FDA approval for the treatment of PsA; however, it does not have the label for prevention of joint destruction as TNF-α inhibitors do[246-249]
- Ustekinumab is considered less effective than TNF-α inhibitors for PsA, and patients who are switched to ustekinumab from a biologic therapy that is effective for PsA might develop worsening of their arthritis and other musculoskeletal manifestations

Supplemental information is expert consensus and not part of the evidence-based recommendations.
Ab, Antibody; *Ag*, antigen; *CBC*, complete blood count; *CMP*, complete metabolic panel; *FDA*, US Food and Drug Administration; *HB*, hepatitis B; IL-12/IL-23, interleukin 12/interleukin23; *PPD*, purified protein derivative; *PsA*, psoriatic arthritis; *TB*, tuberculosis; *TNF-α*, tumor necrosis factor-α; *UV*, ultraviolet.

Table XII. Strength of recommendations on the IL-17 antibody secukinumab

Recommendation No.	Recommendation	Strength of recommendation
5.1	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
5.2	The recommended starting dose of secukinumab is 300 mg by self-administered subcutaneous injection at wk 0, wk 1, wk 2, wk 3, and wk 4, followed by 300 mg every 4 wk	A
5.3	The recommended maintenance dose of secukinumab after the initial 12 wk is 300 mg every 4 wk	A
5.4	Secukinumab is recommended at a dose of 300 mg, which is more effective than 150 mg	A
5.5	Secukinumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the head and neck, including the scalp	B
5.6	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
5.7	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe palmoplantar plaque psoriasis	A
5.8	Secukinumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe palmoplantar pustulosis	B
5.9	Secukinumab can be used as monotherapy in adult patients with erythrodermic psoriasis	C
5.10	Secukinumab may be used as monotherapy for adult patients with plaque psoriasis when associated with psoriatic arthritis	A

IL-17, Interleukin 17.

studies was 24.1% versus 0% and 28.6% versus 0.8%, respectively. The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept.

Additionally, CLEAR, the RCT comparing secukinumab, 300 mg, with ustekinumab per the labeled dosing, found greater efficacy with secukinumab.[214,215,217] At week 16, 79% of the secukinumab-treated patients achieved PASI 90 compared with 57.6% in the ustekinumab-treated group. Regarding secukinumab dosing, in several RCTs, secukinumab showed greater efficacy at the 300-mg dose than at the 150-mg dose. The higher dose seems to be equally safe. Nevertheless, a dose of 150 mg may be acceptable for some patients.[29,213,215,258-261] The response to secukinumab was maintained in RCTs for up to 52 weeks with continued dosing of every 4 weeks.[257,260,261] An RCT assessing the efficacy of dosing secukinumab as needed after the initial course of 12 weeks found such dosing to be less effective than continued every 4 weeks dosing.[257]

Secukinumab is also effective in head, neck, nail, palmoplantar, erythrodermic, and generalized pustular psoriasis.[262-265] The higher (300-mg) dose may be more effective in the treatment of these types of psoriasis.

The RCT GESTURE was designed to assess the efficacy of secukinumab in palmoplantar psoriasis in patients with plaque psoriasis (palmoplantar pustular psoriasis was excluded). At week 16, both secukinumab doses were superior to placebo;

Table XIII. Level of evidence on the IL-17 antibody secukinumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	5.1-5.4	I-II	29,32,213-215,257-261,267
Dose range • 300 mg at wk 0, wk 1, wk 2, wk 3, and wk 4, then every 4 wk • Maintenance dose: 300 mg every 4 wk after initial 12 wk • Recommended effective dose: 300 mg vs 150 mg			
Type of psoriasis			
• Scalp	5.5	II	262
• Nails	5.6	I	213
• Palmoplantar psoriasis	5.7	I	266
• Palmoplantar pustulosis	5.8	N/A	Expert opinion
• Erythrodermic	5.9	III	264,265
Monotherapy for patients with psoriatic arthritis	5.10	I	261

IL-17, Interleukin 17.

33.3% of subjects taking secukinumab, 300 mg, 22.1% of those taking secukinumab, 150 mg, and 1.5% taking placebo achieved a Palmoplantar Investigator's Global Assessment response of 0 or 1, respectively.[266]

Currently, there are no published reports of combination of secukinumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

Neutralizing antisecukinumab antibodies have been found rarely (in <0.4% of patients). Nevertheless, they were not associated with loss of efficacy (see the section Primary and Secondary Treatment Failure) (Table XIII).[‡‡]

Ixekizumab (FDA approval on March 22, 2016)

Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17A. It is FDA-approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and for PsA. The initial dose of ixekizumab is 160 mg by self-administered subcutaneous injection followed by 80 mg on weeks 2, 4, 6, 8, 10, and 12. The maintenance dose of ixekizumab after the initial 12 weeks is 80 mg every 4 weeks.[268] Nevertheless, some patients may require an 80-mg dose every 2 weeks to maintain response to treatment (Table XIV).[269,270]

Multiple RCTs evaluating ixekizumab versus placebo establish the efficacy of this drug in patients with moderate-to-severe psoriasis.[30,72,269-274] Data from a phase III RCT (UNCOVER-3) showed that after the 12-week induction phase, ixekizumab was superior to placebo and etanercept in the treatment of moderate-to-severe psoriasis. Patients were treated with ixekizumab, 80 mg every 4 weeks, etanercept, or placebo. At week 12, the percentages of patients who achieved PASI 75 were as follows: with ixekizumab every 4 weeks, 84.2%; with etanercept, 53.4%; and with placebo, 7.3 %. Additionally, the percentages of patients who achieved PASI 90 were as follows: with ixekizumab every 4 weeks, 65.3%; with etanercept, 25.7%; and with placebo, 3.1%. The percentages of patients who achieved PASI 100 were as follows: with ixekizumab every 4 weeks, 35%; with etanercept, 7.3%; and with placebo, 0%.[30]

A phase III RCT (IXORA-S) compared the efficacy of ixekizumab and ustekinumab at the label doses. At week 12, 72.8% versus 42.2% of patients achieved PASI 90 in the ixekizumab- and ustekinumab-treated groups, respectively.[216]

Ixekizumab was found to be efficacious in the treatment of other forms of psoriasis such as scalp, palmoplantar (nonpustular), nail, erythrodermic, inverse, and generalized pustular psoriasis.[27,271,272,275,276] An RCT assessed the efficacy of ixekizumab for scalp psoriasis. At week 20, patients with scalp psoriasis who received ixekizumab in doses of 25, 75, and 150 mg had an improvement from baseline PSSI of 75.3%; (P = .001), 83.7% (P = .001), and 82.2% (P < .001), respectively, compared with 18.8% in the group receiving placebo. By week 48, 78.0% of patients with scalp psoriasis had complete resolution of their lesions (PSSI, 0).[275]

‡‡29,32,213-215,256-267

Table XIV. Strength of recommendations on the IL-17 antagonist ixekizumab

Recommendation No.	Recommendation	Strength of recommendation
6.1	Ixekizumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
6.2	The recommended starting dose of ixekizumab is 160 mg by self-administered subcutaneous injection followed by 80 mg at wk 2, wk 4, wk 6, wk 8, wk 1, and wk 12	A
6.3	The recommended maintenance dose of ixekizumab after the initial 12 wk is 80 mg every 4 wk	A
6.4	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
6.5	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with erythrodermic psoriasis	B
6.6	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
6.7	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with generalized pustular psoriasis	B
6.8	Ixekizumab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis when associated with psoriatic arthritis	A

IL-17, Interleukin 17.

The same RCT assessed the response to ixekizumab in nail psoriasis.[271,275] At week 20, patients with nail psoriasis in the 75- and 150-mg groups had significant improvement from baseline NAPSI (improvements of 63.8% [$P = .003$] and 52.6% [$P = .009$], respectively, compared with −1.7% in the group receiving placebo). By week 48, 51.0% of patients with nail psoriasis showed complete resolution of their lesions (NAPSI, 0).

An RCT assessed the efficacy of ixekizumab in genital psoriasis; at 12 weeks, the ixekizumab-treated patients showed a significant (73%) improvement in the Static Physicians Global Assessment of genitalia psoriasis compared with 8% in the placebo group.[277]

Currently, there are no published reports of combination of ixekizumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

The presence of neutralizing anti-ixekizumab antibodies has been demonstrated. Neutralizing antibodies were associated with reduced drug concentrations and loss of efficacy (see the section Primary and Secondary Treatment Failure (Table XV).[30,72,216,268-279]

Brodalumab (FDA approval on February 15, 2017)

Brodalumab is a human monoclonal antibody that binds to IL-17 receptor A and blocks the biologic activities of IL-17A, IL-17F, IL-17A/F, and IL-17E (also known as IL-25).

It is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or lost response to other systemic therapies. The dose of brodalumab is 210 mg by self-administered subcutaneous injection on weeks 0, 1, and 2, followed by 210 mg every 2 weeks.[280] Multiple RCTs evaluating brodalumab versus placebo have established the efficacy of this drug in patients with moderate-to-severe psoriasis.[72,213,281-284] Two phase III studies (AMAGINE-2 and AMAGINE-3) showed that at week 12, PASI 75 was achieved by 86% and 67% of the patients receiving brodalumab at the 210-mg dose and by 85% and 69% of those receiving the 140-mg dose of brodalumab versus 8% and 6% of those receiving placebo, respectively ($P < .001$) (Table XVI).

The PASI 90 response rates at week 12 with 210 mg of brodalumab were higher than those with ustekinumab (70% versus 47% [AMAGINE-2] and 69% versus 48% [AMAGINE-3], respectively).

The PASI 100 response rates at week 12 with 210 mg of brodalumab were higher than with ustekinumab (44% versus 22% [AMAGINE-2] and 37% versus 19% [AMAGINE-3], respectively [$P < .001$]). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 and 27% in AMAGINE-3 ($P = .007$).

Brodalumab is effective in erythrodermic, nail, scalp, and generalized pustular psoriasis.[285]

There is also evidence from RCT showing that brodalumab is efficacious in the treatment of PsA.[281]

However, at the time of writing of this guideline, brodalumab has not been FDA-approved for the treatment of PsA.

Currently, there are no published reports of combination of brodalumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

The presence of antibrodalumab antibodies has been demonstrated. However, no neutralizing antibodies were detected (see the section Primary and Secondary Treatment Failure) (Table XVII).[72,213,280-285]

General Comments and special circumstances

Time frame to assess response to treatment with IL-17 inhibitors

- Definitive response (positive or negative) to treatment with IL-17 antagonists is best ascertained after 12 weeks of continuous therapy. Consider dose escalation in partially responding patients.[32,72,258,273,274,285] Consider the addition of other modalities (such as topical corticosteroids, methotrexate, or ultraviolet light) in partially responding patients. Although there are no published data supporting combination therapy for the IL-17 inhibitors, there is no reason to consider such combination unsafe.
- Given their similar mechanism of action, the efficacies of all IL-17 antagonists are comparable.[256,263,268]

IL-17 inhibitors and risk of malignancy

- There is no definitive evidence that IL-17 antagonists used as monotherapy for moderate-to-severe psoriasis increase the risk of solid tumor or lymphoreticular malignancy. Long-term safety studies are necessary to more fully evaluate the risk of malignancy related to IL-17 inhibitor use.

HIV and hepatitis B and C infections

- Use caution in patients with pre-existing immunosuppression-related conditions (expert opinion).
- Patients with a history of or currently active hepatitis C may receive an IL-17 inhibitor for the treatment of psoriasis.[167] Concomitant management with an appropriate health care provider is warranted.
- Patients with a currently active hepatitis B may receive an IL-17 inhibitor for the treatment of psoriasis. However, patients should first be evaluated by an appropriate health care professional and may require concomitant treatment with an approved antiviral medication directed against hepatitis B. A hepatitis B core antibody test in this setting is recommended.[167] Patients with a history of hepatitis B (confirmed resolved infection) do not need to follow-up with a specialist but require monitoring because of the risk of reactivation.

IL-17 inhibitors and infections

- Treatment with IL-17 inhibitors is associated with increased risk of infection, particularly by mucocutaneous *Candida* infection.[173]

IL-17 inhibitors in the context of IBD

- Patients with a personal history of or active IBD might experience reactivation or worsening of their disease.[286] Although the number of patients presenting with this adverse effect in clinical trials was relatively small, it is recommended that the use of IL-17 inhibitors be avoided in patients with a personal history of or active IBD.

IL-17 inhibitors in the context of depression and suicidal ideation

- Rare cases of suicidal ideation and completed suicides have occurred during brodalumab treatment, resulting in a boxed warning in the package labeling. Therefore, brodalumab can be prescribed by providers only through a restricted program under a risk evaluation and mitigation strategy called the SILIQ risk evaluation and mitigation strategy program (SILIQ is a brand name for brodalumab manufactured by Bausch Health, Laval, Canada). Brodalumab should not be considered as a treatment option in patients with suicidal ideation, recent suicidal behavior, or history of suicidal ideation.[263] A casual association between treatment with brodalumab and increased risk of suicidal ideation and behavior has not been established (Table XVIII).[§§]

IL-23 INHIBITORS

Guselkumab (FDA approval on July 13, 2017)

Guselkumab is a fully human IgG1 lambda monoclonal antibody that blocks the p19 subunit of IL-23.[291] Guselkumab is FDA-approved for moderate-to-severe plaque psoriasis in adults.[290] The recommended dose is 100 mg at week 0, week 4, and every 8 weeks thereafter.[290] Multiple RCTs evaluating guselkumab versus placebo plus an active comparator (adalimumab) have established the efficacy of this drug in adult patients with moderate-to-severe psoriasis up to 52 weeks.[292] A phase III RCT (VOYAGE 2) compared guselkumab with adalimumab or placebo for the treatment of moderate-to-severe psoriasis. At week 16, a higher percentage of patients receiving guselkumab achieved PASI 90 (70.0% vs 46.8% vs

§§29,164,169-173,176-179,206,256,261,263,268,278,279,286-290

2.4%) than did patients receiving adalimumab and placebo, respectively. Of nonresponders to adalimumab who switched to guselkumab, 66.1% achieved PASI 90 at week 48.[128] Guselkumab has also been shown to improve responses in patients inadequately responding to ustekinumab (Table XIX).[125,127,128,292]

Guselkumab is also effective in treating the scalp, nail, and plaque-type palmoplantar psoriasis.[127]

Currently, no evidence supports combination of guselkumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

The presence of antiguselkumab antibodies has been demonstrated. Neutralizing antibodies have also been found. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions (see the section Primary and Secondary Treatment Failure) (Table XX).[125,127,128,291-293]

Tildrakizumab (FDA approval on March 21, 2018)

Tildrakizumab is a humanized IgG1, monoclonal antibody designed to selectively block IL-23 by binding to the p19 subunit. Tildrakizumab is FDA-approved for the treatment of moderate-to-severe plaque psoriasis. The recommended dose is 100 mg given by in office physician-administered subcutaneous injection at week 0 and week 4 and every 12 weeks thereafter. In phase III clinical trials for the treatment of adult moderate-to-severe plaque psoriasis, tildrakizumab has been shown to be effective at 100 mg or 200 mg at week 0 and 4 and every 12 weeks thereafter.[34,294,295] In the phase III RCT reSURFACE 2 study, 1090 patients were randomly assigned (314 to tildrakizumab, 200 mg; 307 to tildrakizumab, 100 mg; 156 to placebo; and 313 to etanercept). At week 12, 66% in the tildrakizumab, 200-mg, group and 61% in the tildrakizumab, 100-mg, group achieved PASI 75, compared with 6% in the placebo group and 48% in the etanercept group.[34] The percentages of patients who achieved PASI 90 in reSUFACE 2 were 37% in the group treated with 200 mg of tildrakizumab, 39% in the group treated with 100 mg of tildrakizumab, and 21% in the group treated with etanercept compared with 1% in the placebo group (Table XXI).[34]

Currently, there is no evidence to support combination of tildrakizumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

Neutralizing antibodies against tildrakizumab have been reported. Their presence was associated with lower serum concentrations of tildrakizumab and reduced efficacy (Table XXII).[34,294-296]

Risankizumab (FDA approval pending as of December 2017)

Risankizumab is a humanized IgG1 monoclonal antibody that selectively inhibits IL-23 by binding to the p19 subunit. As of December 2017, risankizumab was not yet FDA-approved for the treatment of moderate-to-severe plaque psoriasis. Risankizumab has been shown to be effective in 2 phase II and III trials (Table XXIII).[297,298]

An RCT assigned 166 patients to receive risankizumab subcutaneously (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg [depending on body weight] at weeks 0, 4, and 16). At week 12, 77% of patients receiving risankizumab (the 90-mg and 180-mg groups pooled), as compared with 40% in the ustekinumab-treated group, achieved PASI 90 ($P < .001$); in contrast, 45% in the pooled groups treated with 90 mg and 180 mg of risankizumab, as compared with 18% in the ustekinumab-treated group, achieved PASI 100.[298]

Currently, there is no evidence to support combination of risankizumab with topical or systemic therapies, but there is no reason to consider such combination unsafe.

There are no data available on antidrug antibodies and their impact on risankizumab efficacy (Table XXIV).[297,299]

General comments and special circumstances

Time frame to assess response to treatment with IL-23 inhibitors

- Definitive response (positive or negative) to treatment with IL-23 antagonists is best ascertained after 12 weeks of continuous therapy. Consider dose escalation in partially responding patients.[291,294,295,297] Consider the addition of other modalities (such as topical corticosteroids or vitamin D analogues, methotrexate, or ultraviolet B light) in partially responding patients. Although there are no published data supporting combination therapy for the IL-23 inhibitors, there is no reason to consider such combination therapy unsafe.

IL-23 inhibitors and risk of malignancy

- The effect of guselkumab on solid tumor or lymphoreticular malignancy, when used as monotherapy for moderate-to-severe psoriasis, is unknown. Large long-term follow-up studies are necessary to more fully define the risk of cancer associated with IL-23 inhibitors.

Table XV. Level of evidence on the IL-17 antagonist ixekizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adult Dosing range • 160 mg at wk 0, then 80 mg every 2 wk until wk 12 • Maintenance dose 80 mg every 4 wk after wk 12	6.1-6.3	I-II	30,72,216,269-274
Type of psoriasis			
• Scalp	6.4	I-II	271,272,275,276
• Erythrodermic	6.5	I-II	272,273
• Nail	6.6	I-II	27,271,272,275
• Pustular	6.7	I-II	272,273
Monotherapy for psoriasis with psoriatic arthritis	6.8	I	278,279

IL-17, Interleukin 17.

Table XVI. Strength of recommendations on the IL-17 antibody brodalumab

Recommendation No.	Recommendation	Strength of recommendation
7.1	Brodalumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
7.2	Brodalumab can be used as monotherapy in adult patients with generalized pustular psoriasis	B
7.3	The recommended dose of brodalumab is 210 mg by self-administered subcutaneous injection at wk 0, wk 1, and wk 2 followed by 210 mg every 2 wk	A

Table XVII. Level of evidence on the IL-17 antibody brodalumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults for plaque psoriasis, pustular psoriasis, and dosing range (210 mg at 0, 1, and 2 wk, and 210 mg every 2 wk thereafter)	7.1-7.3	I-II	72,213,281-285

Immunosuppressed patients and patients with HIV

- Use caution in patients with pre-existing immunosuppression-related conditions (expert opinion) (Table XXV).[¶¶]

ROLE OF THE DERMATOLOGIST

Even though the FDA-approved biologics are an overall safe treatment option for psoriasis, dermatologists should be aware of common adverse events and monitoring recommendations. Additionally, they should educate patients regarding the increased risk of infections, as well as regarding not discontinuing or modifying their treatment without first seeking the advice of their dermatologist. These steps may help ensure initial treatment success and its maintenance over time. Dermatologists and health care providers, in general, should encourage patients to remain up-to-date with age-appropriate vaccines and cancer screening. In addition, dermatologists must consider interacting with appropriate medical colleagues to maximize care for their patients with psoriasis.

¶¶164,169-173,176,177,207,256,278,281,288,290,291,299

Table XVIII. Supplemental information for IL-17 inhibitors

Baseline monitoring

General screening

- CBC
- CMP
- Referral for chest radiograph for positive TB test
- Referral to infectious disease specialist should be considered on a case-by-case basis

TB test

- Pretreatment test for latent TB (PPD or Quantiferon Gold)[164]

Hepatitis

- Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests)[288,289]

HIV test

- Pretreatment test for HIV should be considered at the treating practitioner's discretion and depends on patient-specific risk factors[169-172]

Medical history

- Evaluate for the history of IBD before starting administration of an IL-17 inhibitor[286]

Ongoing monitoring

Parameters

- Periodic history and physical examination, including screening for nonmelanoma skin cancer
- Specific assessment for infections
- Exacerbation/development of IBD
- Yearly testing for latent TB (PPD, T-Spot, or Quantiferon Gold) should be done in patients at high risk (eg, patients in contact with individuals with active TB because of travel, work, or a family relationship, and patients with selected medical conditions). For patients who are not at high risk, screening should be done at the discretion of the dermatologist. Further, the result of the Quantiferon Gold test can remain positive after treatment of latent TB. Caution should be exercised when using the Quantiferon Gold test[176,177]
  - An annual chest radiograph may be considered at the discretion of the treating dermatologist (expert opinion [complete WG consensus was not achieved])
- Periodic assessment of suicidal ideation is recommended for patients treated with brodalumab and might necessitate more frequent follow-up visits

Frequency

- Follow-up visits can be scheduled from quarterly to twice yearly on the basis of time of treatment, response, and tolerability of medication
- Periodic assessment for suicidal ideation is recommended for patients treated with brodalumab and might necessitate more frequent follow-up visits

Adverse effects

- Rare cases of increased liver transaminases have occurred with secukinumab[256,290]
- There is also a small risk of IBD with IL-17 inhibitor use, necessitating care when used in that patient population[286]
- Rare cases of neutropenia have been reported with IL-17 inhibitors. Cases of hepatotoxicity have been observed
- Cases of suicidal ideation and completed suicides have occurred during brodalumab treatment, resulting in a boxed warning in the package labeling. Therefore, brodalumab must be prescribed by providers through a restricted program under a REMS called the SILIQ REMS program (SILIQ is a brand name for brodalumab manufactured by Bausch Health, Laval, Canada)[263]
- Overall, IL-17 inhibitors are well tolerated. Treatment with IL-17 inhibitors is associated with increased risk of infection, particularly risk of mucocutaneous *Candida* infection. The combination of IL-17 inhibitors with methotrexate can increase the risk of infection[173]

Injection site reaction

- Injection site pain and injection site reaction (up to 20%) can occur with ixekizumab use
- Mild: pruritic reaction[178,179]
- Moderate-to-severe: macular erythema to erythematous annular plaques[178,179]

Contraindications

Relative

- Active history or currently active IBD
- Presence of suicidal ideation in patients on brodalumab
- Recent suicidal behavior or history of suicidal ideation in patients on brodalumab

Absolute

- History of allergic reaction to the therapeutic agents or vehicle

Continued

Table XVIII. Cont'd

- Brodalumab and secukinumab are contraindicated in patients with IBD

Temporary discontinuation and reinitiation of therapy

- Presence of febrile illness, especially illness requiring antibiotic treatment. Treatment can be restarted after full resolution of the symptoms/signs of infection and completion of any antibiotic course
- The necessity of repeating loading doses upon restarting administration of the medication depends on disease severity and the number of doses missed
- Consider repeating doses upon restarting administration of the medication if the patient is flaring and/or if more than 3-4 half-lives have passed since the previous dose (extrapolated from Krueger et al[206])

Miscellaneous

Pregnancy and lactation

- There are no studies on human pregnancy
- Animal studies with secukinumab have shown no harm to the developing fetus
- Animal studies with ixekizumab at higher doses than recommended have shown no harm to the developing fetus, but higher neonatal deaths were observed
- Animal studies with brodalumab at higher doses than recommended have shown no harm to the developing fetus
- All IL-17 inhibitors are likely acceptable for men attempting conception with their partner
- The presence of IL-17 inhibitors in excreted human milk has not been studied

Psoriatic arthritis

- Secukinumab and ixekizumab are also efficacious and FDA-approved for the treatment of psoriatic arthritis[29,261,268,278,279]

Supplemental information is expert consensus and not part of the evidence-based recommendations.
Ab, Antibody; *Ag*, antigen; *CBC*, complete blood count; *CMP*, complete metabolic panel; *FDA*, US Food and Drug Administration; *HB*, hepatitis B; IBD, inflammatory bowel disease; IL-17, interleukin 17; *PPD*, purified protein derivative; *PsA*, psoriatic arthritis; *REMS,* risk evaluation and mitigation strategy; *TB*, tuberculosis; *TNF-α*, tumor necrosis factor-α; *UV*, ultraviolet.

Table XIX. Strength of recommendations on the IL-23 inhibitor guselkumab

Recommendation No.	Recommendation	Strength of recommendation
8.1	Guselkumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
8.2	The recommended dose of guselkumab is 100 mg by self-administered subcutaneous injection at wk 0, wk 4, and every 8 wk thereafter	A
8.3	Guselkumab is recommended as a monotherapy treatment option in adult patients with scalp, nail, and plaque-type palmoplantar psoriasis	A

ROLE OF PATIENT PREFERENCES

- Efficacy and safety data should be discussed with patients to make a treatment decision regarding initiation of a biologic or when considering switching biologic treatments.
- In addition to disease severity, QOL assessment should be considered and discussed with patients before starting administration of or switching biologic agents.
- Other factors that can affect patient preference and should be discussed with patients, include dosing schedule, cost, and route of administration.
- Biologics with less frequent dosing schedule (ie, every 8-12 weeks) may be preferred by some patients over others with more frequent dosing.

PRIMARY AND SECONDARY TREATMENT FAILURE

Primary failure is defined as initial nonresponse to treatment. Primary failure to respond to a TNF-α-inhibitor does not preclude successful response to a different TNF-α inhibitor. Nevertheless, it may portend reduced efficacy with other TNF-α

Table XX. Level of evidence on the IL-23 inhibitor guselkumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	8.1	I	125,127,128,291-293
Dosing range • 100 mg in wk 0 and wk 4, then every 8 wk	8.2	I	125,127,128,291-293
Types of psoriasis • Scalp, nail, palmoplantar	8.3	I	127,128

Table XXI. Strength of recommendations on the IL-23 inhibitor tildrakizumab

Recommendation No.	Recommendation	Strength of recommendation
9.1	Tildrakizumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
9.2	The recommended dose is 100 mg given by in office physician-administered subcutaneous injection at wk 0 and wk 4 and every 12 wks thereafter	A

Table XXII. Level of evidence on the IL-23 inhibitor tildrakizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	9.1-9.2	I	34,294,295
Dosage range • 100 mg at wk 0 and wk 4, then every 12 wk			

inhibitors.[300] Regarding IL-12/IL-23 inhibitors, failure of another biologic therapy does not preclude successful response to ustekinumab.

All biologics approved for use with psoriasis may lose efficacy in a patient who initially responds favorably to this medication (secondary failure). One reason for loss of efficacy may be attributed to the presence of antidrug antibodies. The concomitant use of methotrexate with biologic agents in other immune-mediated diseases has been shown to increase biologic drug survival. Nevertheless, the reported use of methotrexate in combination with biologics for the treatment of psoriasis is limited, and there are no RCTs to make a recommendation for combination therapy at this time.[‖‖]

RESTARTING/RESUMING BIOLOGIC TREATMENT AFTER DISCONTINUATION

The necessity of repeating the loading doses upon restarting administration of the medication depends on the disease severity and how many doses were missed. Consider repeating the loading doses upon restarting administration of the medication if the patient is flaring and/or if more than 3 to 4 half-lives have passed since the previous dose (see Table VI for biologic agents' half-lives). Retreatment after discontinuation may result in a small percentage of patients not being able to recapture their previous robust level of response.[73,75,153,154,207]

SWITCHING BIOLOGIC TREATMENTS

If clinically needed, all other therapies for psoriasis, including other biologics, may be switched with a different biologic agent with the possibility of improved efficacy, safety, and/or tolerability.[152,239,293,300,308-323] It is important to stress that not all switches may result in improvement and that, at this time, there are insufficient data to make more specific recommendations.

There are no evidence-based studies on duration of the interval between discontinuation of the

[‖‖]71,149,150,202,208,210,242,301-307

Table XXIII. Strength of recommendations on the IL-23 inhibitor risankizumab

Recommendation No.	Recommendation	Strength of recommendation
10.1	Risankizumab is not FDA-approved but can be used as monotherapy in adult patients with moderate-to-severe plaque psoriasis	B
10.2	The approved dose will likely be 150 mg given by self-administered subcutaneous injection at wk 0, wk 4, and then every 12 wk	A

Table XXIV. Level of evidence on the IL-23 inhibitor risankizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	10.1-10.2	I	297,299
Dose range • 150 mg at wk 0 and wk 4, then every 12 wk			

previous medication and initiation of a biologic. This may depend on the treatment that is being discontinued, disease severity, and response to prior treatment, as well as on expert opinion, and it should be assessed on a case-by-case basis. Therefore, whereas some experts will start administration of a new biologic as soon as it is available for the patient, others may wait for a period equal to as many as 3 or 4 half-lives of the previous therapy before the transition (see Table VI for biologic agents' half-lives).

BIOLOGICS AND SURGERY

- On the basis of expert opinion, all biologics can be continued through low-risk surgical procedures in patients with psoriasis and PsA. Low-risk surgical procedures are defined as surgical procedures without a break in sterile technique during which the respiratory, gastrointestinal, and genitourinary tracts are not entered. Moderate- and high-risk surgical procedures include surgical procedures during which the respiratory, gastrointestinal, or genitourinary tract is entered without the presence of contamination. These also include surgical procedures during which there is a major break in sterile technique, spillage from the gastrointestinal tract, or an active infection or devitalized tissue (Table XXVI).

Moderate- and high-risk surgical procedures require a case-by-case approach in collaboration with the surgeon(s)/medical team. Risk assessment should consider each patient's individual risk factors and comorbidities. If considered necessary, the biologic agent could be discontinued approximately 3 to 4 half-lives before and until 1 to 2 weeks after elective surgery if there are no postoperative complications (Table XXVII).[324]

BIOLOGICS AND VACCINES

Inactivated or "dead" vaccines may be given during treatment with all biologics. For administration of live vaccines, consultation with an infectious disease specialist is recommended. Although there is scarce evidence from case series suggesting that varicella zoster, MMR (measles, mumps, and rubella), and yellow fever vaccines could be administered while patients are also taking TNF-α inhibitors,[325] discontinuation of all biologic agents is recommended before administration of a live vaccine. Experts differ on the length of discontinuation before and after administration of live vaccinations. Although some experts advise discontinuation of biologics 2 to 3 half-lives before and after administration of live vaccines, others advice discontinuation of biologics 4 weeks before (or longer depending on the half-life of the biologic) and until 1 to 2 weeks after vaccination. These recommendations are based on experts' opinion (Table XXVIII).

PATIENT EDUCATION

The importance of education of patients with psoriasis cannot be overemphasized. Psoriasis is a complex, multisystem disease that affects the skin and joints, has numerous comorbidities, and affects not only health but also overall QOL. As such, educating the patient regarding the etiology, comorbidities, treatment options, and lifestyle factors associated with psoriasis optimizes shared decision making and the patient-provider relationship and enables whole person care. It also positively affects patient satisfaction and adherence to treatment. Education should be provided regardless of disease severity and can be provided via verbal discussion, pamphlets, and trusted Internet resources. Patients

Table XXV. Supplemental information for IL-23 inhibitors

Baseline monitoring

General screening

- CBC
- Complete metabolic profile
- Referral for chest radiograph for positive TB test
- Referral to infectious diseases specialist should be considered on a case-by-case basis

TB test

- Pretreatment test for latent TB (PPD or Quantiferon Gold) (extrapolated from Kamili and Menter[164])

Hepatitis

- Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests)[288,299]

HIV test

- Pretreatment test for HIV is considered at the treating practitioner's discretion and depends on patient-specific risk factors[169-172]

Ongoing monitoring

Parameters

- Periodic history and physical examination, including screening for nonmelanoma skin cancer
- Yearly testing for latent TB (PPD, T-Spot, or Quantiferon Gold) should be done in patients at high risk (eg, in patients in contact with individuals with active TB because of travel, work, or a family relationship, and in patients with the underlying medical condition). For patients who are not at high risk, screening should be done at the discretion of the dermatologist. Further, the result of the Quantiferon Gold test can remain positive after treatment of latent TB. Caution should be exercised when using the Quantiferon Gold test[176,177]
  - An annual chest radiograph may be considered at the discretion of the treating dermatologist (expert opinion [complete WG] consensus was not achieved)
- Screening for adverse effects (see later)
- Hepatitis B and C screening
- Evaluate for infections

Frequency

- Follow-up visits can be scheduled from quarterly to twice yearly on the basis of time of treatment, response, and tolerability of medication

Infections

- Phase III studies indicate that both guselkumab and tildrakizumab are well tolerated. Nevertheless, there is an increased risk of infection[278,281]
- Combination of IL-23 inhibitors with methotrexate can increase the risk of infection[173]

Adverse effects

- Rare cases of increased liver transaminase levels have occurred with use of IL-23 inhibitors[256,290]
- IL-23 inhibitors have demonstrated no unique adverse events of interest (extrapolated from Strober et al[299])

Contraindications

Absolute

- History of allergic reaction to the therapeutic agents or vehicle

Temporary discontinuation and reinitiation of therapy

- Presence of febrile illness, especially illness requiring antibiotic treatment. Treatment can be restarted after full resolution of the symptoms/signs of infection and the completion of any antibiotic course.
- The necessity of repeating loading doses upon restarting administration of the medication depends on disease severity and the number of doses missed
- Consider repeating doses upon restarting administration of the medication if the patient is flaring and/or if more than 3-4 half-lives have passed since the previous dose (extrapolated from Leonardi et al[207])

Miscellaneous

Pregnancy and lactation

- Safety during pregnancy for IL-23 inhibitors is unknown
- The presence of IL-23 inhibitors in secreted human milk has not been studied; however, antibodies are effectively secreted during lactation and caution is recommended.

Supplemental information is expert consensus and not part of evidence-based recommendations.

Ab, Antibody; *Ag*, antigen; *CBC*, complete blood count; *HB*, hepatitis B; *IBD*, inflammatory bowel disease; *IL-23*, interleukin 23; *PPD*, purified protein derivative; *TB*, tuberculosis.

Table XXVI. Perioperative risk stratification

Low-risk surgery	Moderate-risk surgery	High-risk surgery
Endoscopic procedures (GI, GU, or respiratory)	Urologic surgery	Emergency surgery
Dermatologic procedure	Thoracic or abdominal surgery	Complicated thoracic or abdominal or genitourinary operation
Breast biopsy/excision	Head and neck surgery	Surgical procedures on an infected area
Ophthalmologic procedure		
Orthopedic surgery/joint replacement		

GI, Gastrointestinal; *GU*, genitourinary.

Table XXVII. FDA-approved biologic agents for psoriasis and their doses

Biologic agent	Loading dose	Maintenance
Etanercept (Enbrel is a brand name for etanercept manufactured by Immunex Corp., Thousand Oaks, CA)	50-mg subcutaneous injection twice weekly for 12 wk	50-mg subcutaneous injection once per wk
Infliximab (Remicade is a brand name for infliximab manufactured by Janssen Biotech, Inc., Horsham, PA)	5-mg/kg IV infusion administered in wk 0, wk 2, and wk 6	5-mg/kg IV infusion administered every 8 wk*
Adalimumab (Humira is a brand name for adalimumab manufactured by AbbVie Inc., North Chicago, IL)	80-mg subcutaneous injection (2×40 mg at the initial dose), followed by a 40-mg subcutaneous injection 1 wk later	40-mg subcutaneous injection every 2 wk
Certolizumab (Cimzia is a brand name for certolizumab manufactured by UCB, Inc., Smyrna, GA)	(a) 400 mg (b) Alternative regime, for patients who weigh $<$90 kg: 400 mg initially and at wk 2 and wk 4	(a) 400 mg every other wk (b) 200 mg every other wk
Ustekinumab (Stelara is a brand name for ustekinumab manufactured by Janssen Biotech, Inc., Horsham, PA)	(a) For patients weighing $\leq$100 kg: 45 mg administered subcutaneously initially and 4 wk later (b) For patients weighing $>$100 kg: 90 mg administered subcutaneously initially and 4 wk later	(a) Patients $\leq$100 kg: 45 mg administered subcutaneously every 12 wk (b) Patients $>$100 kg: 90 mg administered subcutaneously every 12 wk
Secukinumab (Cosentyx is a brand name for secukinumab manufactured by Novartis Pharmaceuticals Corporation, East Hanover, NJ)	300-mg subcutaneous injection at wk 0, wk 1, wk 2, wk 3, and wk 4	300-mg subcutaneous injection every 4 wk
Ixekizumab (Taltz is a brand name for ixekizumab manufactured by Eli Lilly and Company, Indianapolis, IN)	160-mg subcutaneous injection followed by 80 mg on wk 2, wk 4, wk 6, wk 8, wk 10, and wk 12	80-mg subcutaneous injection every 4 wk
Brodalumab (Siliq is a brand name for brodalumab manufactured by Bausch Health, Laval, Canada)	210-mg subcutaneous injection on wk 0, wk 1, wk 2	210-mg subcutaneous injection every 2 wk
Guselkumab (Tremfya is a brand name for guselkumab manufactured by Janssen Biotech, Inc., Horsham, PA)	100-mg subcutaneous injection on wk 0 and wk 4 and every 8 wk thereafter	100-mg subcutaneous injection every 8 wk
Tildrakizumab (Ilumya is a brand name for tilfrakizumab manufactured by Sun Pharmaceutical Industries Inc., Cranbury, NJ)	100 mg administered subcutaneously initially and 4 wk later	100 mg administered subcutaneously every 12 wk

IV, Intravenous.
*Time interval can be modified and dose per kg can be increased according to the patient's response.

Table XXVIII. Half-lives of biologic agents

Biologic agent	Approximate half-life, d
Etanercept	3.5
Infliximab	10
Adalimumab	14
Certolizumab	14
Ustekinumab	21
Secukinumab	27
Ixekizumab	13
Brodalumab	11
Guselkumab	18
Tildrakizumab	23
Risankizumab	11

should be made aware of psoriasis support groups, such as the National Psoriasis Foundation (www.psoriasis.org) and the International Federation for Psoriasis (www.IPFA-pso.org). Patients should also be aware of the side effect profile of prescribed therapies and have input in the treatment plan. Although biologic agents have shown tremendous efficacy and safety in clinical trials, pharmacovigilance is fundamental, and dermatologists serve a key role in the potential prevention and detection of adverse events over time. Repetition of key concepts during follow-up visits reinforces patient knowledge over time.

PEDIATRIC CONSIDERATIONS

Children are affected by psoriasis and its comorbidities. There is limited evidence for the treatment of pediatric patients with biologic agents. Etanercept is the only biologic approved for plaque psoriasis in children aged 4 to 17, whereas ustekinumab is approved for plaque psoriasis in adolescents aged 12 to 17. Because the pediatric population has a unique physiology and social considerations relative to adults, the care of children with psoriasis will be reviewed in a document titled "Guidelines of Care for the Management of Psoriasis in Pediatric Patients," which is the pediatric section of these guidelines.

GAPS IN RESEARCH

Significant knowledge regarding psoriasis and advancement in psoriasis treatment have been gained over the past 30 years. Despite this, in review of the currently available highest level of evidence, the expert WG acknowledges that much has yet to be learned. The advent of new medications with unique mechanisms of action affords significant opportunities for better disease control with minimal toxicity. Nevertheless, there is still limited evidence regarding long term-adverse events, impacts on future comorbidities, pediatric treatment, pregnancy and lactation, and treatment combination for many of the newer biologic agents. There is also an important need to identify biomarkers that can potentially predict the appropriate biologic agent for individual patients.

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