وزارة الصحة
Ministry of Health

SAUDI PRACTICAL GUIDELINES ON BIOLOGIC TREATMENT OF CHRONIC PLAQUE PSORIASIS (2020)

وزارة الصحة
Ministry of Health

Table of Contents

ABSTRACT

Psoriasis is a common chronic and complex inflammatory skin disease that affects over 125 million people worldwide. Management of psoriasis in daily clinical practice is highly variable as there are many issues that are still debated and not definitely addressed by evidence-based medicine. Biologic therapy is now a well-established strategy for managing moderate-to-severe plaque psoriasis. There is a clear need for national guidelines due to the extended role and high availability of literature on these agents. As a result of an initiative of the Ministry of Health, a multidisciplinary expert panel of dermatologists and pharmacists with practical experience in the clinical management of psoriasis were invited to be part of a work group to update the previous practical guidelines on biologic treatment of psoriasis published in the Journal of Dermatological Treatment, 2014 [1]. The overall aim of these guidelines is to deliver evidence-based recommendations on the use, screening, and monitoring of biologic therapy in patients with moderate-to-severe plaque psoriasis. These guidelines also address the use of biologic therapy in special patient populations. The recommendations were developed after rigorous evaluation of existing International guidelines as well as the latest emerging evidence.

DISCLAIMER

Clinical practice guidelines are evidence-based decision-making tools for managing health conditions. They are based on the best information available at the time of writing, and are to be updated regularly. The present guidelines are not meant to serve as strict treatment guidelines. They are also not intended to replace clinical judgement of practicing physicians but are only tools to help manage patients who require biologic treatment for psoriasis. Decisions concerning treatment must always be taken on a case-by-case basis and the prescribing physicians need to personalize care and tailor the treatment regimen to patients' personal circumstances and medical history.

Physicians should also consult the approved product monographs within their institution's formulary for each drug for dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harms. Institution formulary restrictions may also need to be considered when selecting treatment options. Prescribing physicians should refer to their institution's formularies during the decision-making process for choosing specific agents within a recommended specific class.

UPDATE OF THE GUIDELINES

Updates of the present guidelines will be provided as needed to incorporate new data or agents.

ABBREVIATIONS USED

AFB	Acid- Fast Bacilli	MS	Multiple Sclerosis
ATIL	Anti TNF- α Induced Lupus	MTX	Methotrexate
BSA	Body Surface Area	NMSC	Nonmelanoma Skin Cancer
CHF	Congestive Heart Failure	NYHA	New York Health Association
COPD	Chronic Obstructive Pulmonary Disease	PASI	Psoriasis Area and Severity Index
DLQI	Dermatology Life Quality Index	PGA	Physician global assessment
EMA	European Medicines Agency	PSA	Psoriatic Arthritis
FDA	U.S. Food and Drug Authority	PSO	Psoriasis
HBV	Hepatitis B Virus	QoL	Quality of Life
HCV	Hepatitis C Virus	SFDA	Saudi Food and Drug Authority
IBD	Inflammatory Bowel Disease	SLE	Systemic lupus erythematosus
IL	Interleukin	SubQ	Subcutaneous
INH	Isoniazid	TB	Tuberculosis
IV	Intravenous	TNF	Tumor Necrosis Factor

LTBI	Latent Tuberculosis Infection	UVA	Ultraviolet A
MACE	Major Adverse Cardiovascular Event	WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Psoriasis is a common, chronic, inflammatory skin disease. The worldwide prevalence is about 2%, but differs according to countries [2]. It displays a lesser prevalence in Asian and some African populations, and high up to 11% in Caucasian and Scandinavian populations [3-7]. At present, psoriasis is recognized as a genetically determined, inflammatory T-cell mediated systemic disease. It affects skin, nails, scalp and joints with a number of comorbidities which include cardiovascular diseases, metabolic syndrome, inflammatory bowel disease, uveitis and psychological changes. Psoriasis has an unpredictable course. It can arise at any age, and is most common in the age group of 20-30 and 50–69 [6, 8, 9]. In 80 % of cases psoriasis is mild or moderate and adequately treated with topical corticosteroids, vitamin D-analogues, and phototherapy. 20% of patients suffer from severe psoriasis, requiring systemic drugs such as acitretin, methotrexate and biologic therapies [10]. Biologic therapies refer to complex engineered molecules including monoclonal antibodies and receptor fusion proteins. Biologics are different from the conventional systemic therapies in that they target specific inflammatory pathways. They are administered subcutaneously, or intravenously on different schedules. Biologics presently target two pathways crucial in the development and chronicity of the psoriatic plaque: the IL-23/Th17 axis and TNF-α-signaling [4].

1.2. Purpose

Management of psoriasis in daily clinical practice is highly variable as there are many issues that are still debated and not definitely addressed by evidence-based medicine. Biologic therapy is now a well-established strategy for managing

moderate-to-severe plaque psoriasis. There is a clear need for national guidelines due to the extended role and high availability of literature on these agents. As a result of an initiative of the Ministry of Health of the Kingdom of Saudi Arabia, an expert board of dermatologists and pharmacists with recognized practical experience in the clinical management of psoriasis were called to be part of a work group to update the earlier practical guidelines for biologic treatment of psoriasis published in the Journal of Dermatological Treatment in 2014 [1].

1.3. Aim and Scope

The overall aim of these guidelines is to deliver evidence-based recommendations on the use, screening, and monitoring of biologic therapy in patients with moderate-to-severe plaque psoriasis. These guidelines also aim to propose updated decision-making algorithms for practitioners involved in the treatment of these patients and consideration is given to special patient population.

2. METHODS

The first version of the Saudi practical guidelines on biologic treatment of psoriasis published in the Journal of Dermatological Treatment in 2014 represented the base for developing the current guidelines [1]. The multidisciplinary work group was made up of eight dermatologists and five pharmacists. Published guidelines concerning the treatment of psoriasis were evaluated using the Appraisal of Guidelines, Research and Evaluation II (AGREE II) scale [11]. A total of 6 guidelines were found to meet the criteria for use in the generation of the current guidelines: The European S3 Guidelines 2017 [12], British Association of Dermatologists Guidelines for Biologic Therapy for Psoriasis 2017 [13], American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) guidelines 2019 (biologics and comorbidities) [14, 15], UK National Institute for Health and Care Excellence (NICE) Guidelines, 2019 [16], and the French guidelines on the use of

systemic treatments for moderate-to-severe psoriasis in adults, 2019 [17]. Other articles with updated emerging evidence were also identified and evaluated.

Formal consensus methodology was adopted to reach consensus on specific items (Delphi process or consensus meetings with nominal group technique) [18]. The consensus statements are based on the best available evidence and their development followed a standardized process. The Delphi process consisted of one or two (if needed) rounds. A statement was regarded as consented when agreement was achieved by at least 75% of the voting experts. The strength of recommendation was not expressed.

3. PRESCRIBERS OF BIOLOGIC THERAPY

Biologic therapies should be prescribed by dermatologists with extensive clinical experience in the treatment of psoriasis with systemic agents, considering that the use of these therapies requires appropriate patient selection and follow up.

4. ELIGIBILITY CRITERIA FOR BIOLOGIC TREATMENT

Biologic drugs are generally indicated in moderate-to-severe psoriasis with a particular consideration for patients who have failed, could not tolerate, or cannot use at least one systemic treatment, preferably methotrexate (MTX) [13].

In general, any of the following criteria is currently widely accepted as appropriate criteria for initiating biologic therapy:

- Moderate-to-severe disease, which is defined as [1]:
    - ≥ 10% body surface area (BSA) involvement
    - ≥ 10 Psoriasis Area and Severity Index (PASI)
    - ≥ 10 Dermatology Life Quality Index (DLQI)
- Limited disease but with significant functional impairment and/or high levels of distress after failure of topical therapy. These special circumstances include [1]:

- Involvement of large areas of the scalp
- Involvement of visible areas such as the hands and face,
- Involvement of intertriginous areas and genitalia
- Involvement of palms and/or soles
- The presence of treatment resistant areas

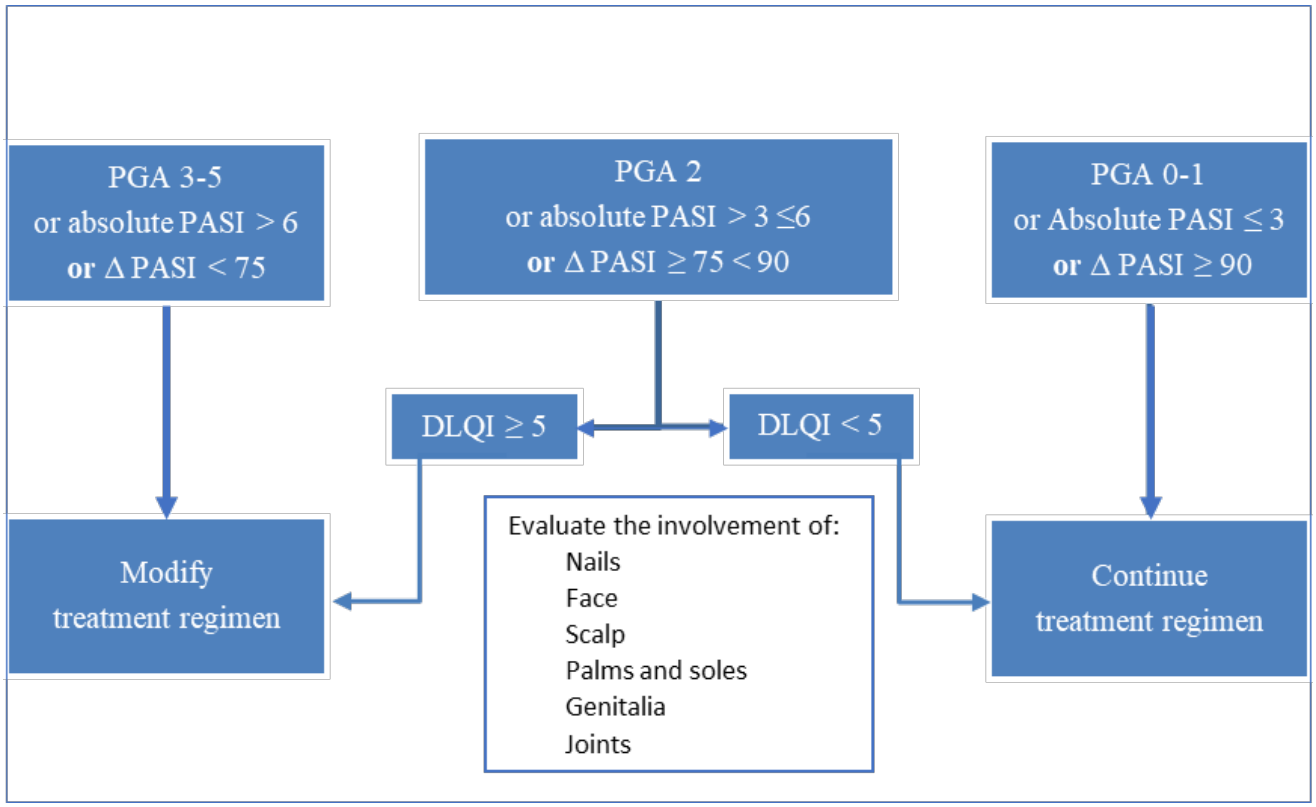
- Presence of psoriatic arthritis

5. TREATMENT GOALS

Before starting biologic therapy, it is preferable to define treatment goals for each patient. Assessment tools such as PASI, physician global assessment (PGA), BSA, and DLQI are recommended for use in daily practice in order to establish and monitor the achievement of treatment goals and guide therapy (Figure 1). The newly available biologic therapies for psoriasis are highly effective; and thus, we recommend that one of the following criteria should be achieved for the treatment goal of psoriasis[17, 19].

1. Absolute PASI ≤ 3.
2. PASI 90 response.
3. PGA score (0-1).
4. DLQI (<5)

Figure 1: Use of treatment goals to guide therapy



Treatment goals are generally evaluated between weeks 12 and 16.

6. SCREENING, PRECAUTIONS, AND MONITORING OF BIOLOGICS

6.1. Screening for TB

Pulmonary Tuberculosis (TB) is common in Saudi Arabia [20] as most cases are due to reactivation of latent TB (LTBI). LTBI is defined by WHO as: a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without clinical evidence of active TB[21].

The Saudi guidelines for testing and treatment of LTBI include statements by the Saudi Thoracic Society (STS), the Saudi Society of Medical Microbiology and Infectious Disease (SSMMID), the Saudi Association of Public Health (SAPH), and

the Society of Family and Community Medicine, thereby providing national recommendations for targeted tuberculin testing and treatment regimens for patients with LTBI [20]. These guidelines recommend Tuberculin Skin Test (TST) with purified protein derivative (PPD) for the screening. TST should be done and assessed by trained professionals. The induration is measured and should be recorded in millimeters. The interpretation of TST is dependent on the size of induration and the risk status of the subjects [20].

The interferon gamma release assays (IGRA-QuantiFERON-TB Gold test), have been incorporated into TB screening [1]. The IGRA is highly specific and sensitive in detecting LTBI, and it is not affected by prior BCG vaccination [20, 22]. Either TST or IGRA can be used for LTBI testing before initiating a biologic therapy [1, 14]. Baseline chest radiograph is recommended for all patients [13]. It is also needed for any patient with newly identified positive test [14, 20] .

During treatment with biologic therapy, annual screening is recommended, including medical history [22]. Either TST or IGRA -QuantiFERON test can be utilized [1]. Suspicion of TB infection should be maintained even after discontinuation of the biologic therapy for six months [22].

6.2. Screening for Hepatitis B and C

The patients who are eligible to receive immunosuppressive drugs, including biologics, must be screened for the following markers: antibody to hepatitis B core antigen (IgM/IgG), antibody to hepatitis B surface antigen (anti-HBsAg), HBsAg, and antibody to HCV (anti-HCV). In case HBV or HCV infection is diagnosed, a close collaboration with a hepatologist is required before and during an immunosuppressive therapy.

6.3. Laboratory Assessments

Table 1: Laboratory assessments prior to initiation of a biologic treatment [1, 13, 23-35]

No.	Parameter	Baseline	Follow-up*	Annual screening
1	CBC with differential	✓	6 months	✓
2	RFT	✓	6 months	✓
3	LFT	✓	6 months	✓
4	HBV/HCV	✓	-	✓
5	HIV	✓	-	✓
6	Pregnancy Test	✓	-	-
7	TST or IGRA	✓	-	✓
8	Chest X-ray	✓	-	-

CBC, complete blood count; RFT, Renal function tests; LFT, Liver function tests, HBV, hepatitis B virus; HCV, hepatitis C virus; TST, tuberculin skin test; IGRA, interferon gamma release assay

**or if clinically indicated*

Table 2: Assessment for possible associations (if clinically indicated) [1, 13, 23-35]

Parameter
- Lipid Profile - Uric Acid - HbA1c/FBS - Autoantibodies (anti-nuclear antibodies, anti-nuclear double strand DNA antibodies)

HbA1c, Glycated hemoglobin; FBS, Fasting Blood Sugar

6.4. Vaccinations

Patients should be up to date in vaccination and all recommended vaccines should be given before starting biologic therapy [1, 13].

Live vaccines (BCG, measles, mumps, rubella, yellow fever, oral polio, oral typhoid, varicella zoster, and nasal influenza vaccine) can cause disseminated or fatal infections in immunocompromised individuals; therefore are contraindicated in patients on biologic therapy and in infants (up to 6 months of age) whose mothers have received biologic therapy beyond 16 weeks gestation [13].

Despite the data regarding lack of placental transfer of certolizumab, there is no published data concerning the live vaccination in the newborns of mothers treated with this biologic therapy during pregnancy [36]. If a live vaccine is needed while on biologic therapy, discontinuation of the biologic agents is recommended. Some experts advise for 2 to 3 half-lives before and after vaccine administration, while others advise 4 weeks (or longer depending on the biologic's half-life) before and until 1 to 2 weeks after vaccination [14].

Inactivated vaccines are safe to be given while on biologic therapy [13]. Yearly influenza (inactivated) and pneumococcal vaccines are recommended, hepatitis A and B vaccine are recommended if not immunized [37].

In regards to Hajj season, patients who are planning to perform Hajj should be up to date on all routine vaccines, in accordance with MOH vaccine requirements and recommendations [38].

6.5. Infections

Patients on biologic therapy are more susceptible to infections. However, severe infections are very rare. In case of severe infection, temporary interruption of the biologic treatment should be considered. Biologic therapy may be subsequently reintroduced after sufficient anti-infective treatment [1].

7. BIOLOGIC AGENTS AVAILABLE FOR PSORIASIS IN SAUDI ARABIA

Table 3 below lists all biologic therapies that are currently registered and approved by SFDA for the treatment of moderate-to-severe plaque psoriasis.

*Table 3: Biologic agents and biosimilars available for treatment of psoriasis in Saudi Arabia**

Generic	Brand	Pharmacology classification	Strengths & formulations	FDA Approval	SFDA Registration [39]	Approved indication
Adalimumab [24]	Humira	Anti-tumor necrosis factor	40 mg/0.8 mL – SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis
Certolizumab pegol [25]	Cimzia	Anti-tumor necrosis factor	200 mg/mL – SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis
Etanercept [32]	Enbrel	Anti-tumor necrosis factor	50 mg/mL – SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis
Guselkumab [29]	Tremfya	Anti-IL-23/IL-39 antibodies	100 mg/mL – SQ Injection	✓	✓	Plaque psoriasis
Infliximab [23]	Remicade	Anti-tumor necrosis factor	100 mg/vial – Intravenous Infusion	✓	✓	Plaque psoriasis, Psoriatic arthritis
Infliximab [40]	Remsima (Biosimilar)	Anti-tumor necrosis factor	100 mg/vial – Intravenous Infusion.	✓	✓	Plaque psoriasis, Psoriatic arthritis
Ixekizumab [28]	Taltz	Anti-IL-17 antibodies	80 mg/mL – SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis
Risankizumab [31]	Skyrizi	Anti-IL-23/IL-39 antibodies	75 mg/0.83 mL – SQ Injection	✓	✓	Plaque psoriasis
Secukinumab [27]	Cosentyx	Anti-IL-17 antibodies	150 mg/mL – SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis
Ustekinumab [26]	Stelara	Anti IL-12/IL-23 antibody	45 mg/0.5 mL or 90 mg/mL SQ Injection	✓	✓	Plaque psoriasis, Psoriatic arthritis

*Listed in alphabetical order

\

Table 4 below presents details on evaluation of efficacy of all biologic therapies that are currently registered and approved by SFDA for the treatment of moderate-to-severe plaque psoriasis. Additionally, dosing scheme, type of anti-body, and half-life of these biologic therapies is also presented.

Table 4: Dosing schemes, type of antibody, efficacy, and half-life of biologic agents and biosimilars available for treatment of psoriasis in Saudi Arabia

Generic	Brand	Dose		Type of Anti-body	Efficacy		Half-life
		Loading dose	Maintenance Dose		Induction efficacy	Long-term efficacy	
Adalimumab [41, 42]	Humira	80 mg SubQ at weeks 0, then 40 mg SubQ at week 1	40 mg SubQ every other week	Fully Human	PASI 90 (W16): 45%	PASI 90 (W160): 50%	14 days
Certolizumab pegol [43]	Cimzia	400 mg SubQ at weeks 0, 2, and 4	200 or 400 mg SubQ every other week	Humanized	PASI 90 (W16 – 200mg): 35.8% PASI 90 (W16 – 400mg): 43.6%	PASI 75 (W48 – 200mg): 81% PASI 75 (W48 – 400mg) =83%	14 days
Etanercept [44, 45]	Enbrel	50 mg SubQ twice weekly for 12 Weeks	50 mg SubQ once weekly	Protein fusion receptor	PASI 90 (W12 – 50mg BIW): 21%	PASI 90 (W72): 27%	3.5 days
Guselkumab [46, 47]	Tremfya	100 mg SubQ at weeks 0, Week 4	100 mg SubQ every 8 weeks	Fully Human	PASI 90 (W16): 73.3% (Voyage 1) PASI 90 (W16): 70% (Voyage 2)	PASI 90 (W48): 76.3% (Voyage 1) PASI 90 (W24): 75.2% (Voyage 2)	18 days
Infliximab [48-51]	Remicade	5 mg/kg IV over at least 2 hours at weeks 0, 2, and 6	5 mg/kg IV over at least 2 hours every 8 weeks*	Chimeric monoclonal antibody to TNF	PASI 90 (W10): 57%	PASI 90 (W50): 45%	10-15 days
Ixekizumab [52]	Taltz	160 mg SubQ at week 0, followed by 80 mg SubQ every 2 weeks for 3 months	80 mg SubQ every 4 weeks	Humanized	PASI 90 (W12 – every 4 wks.): 59.7% (UNCOVER-2) PASI 90 (W12 – every 4 wks.): 65.3% (UNCOVER-3)	Not Available	13 days
Risankizumab [53]	Skyrizi	150 mg SubQ at Week 0, Week 4.	150 mg SubQ every 12 weeks	Humanized	PASI 90 (W16): 75.3% (UltIMMA-1) PASI 90 (W16): 74.8% (UltIMMA-2)	PASI 90 (W52): 81.9% (UltIMMA-1) PASI 90 (W52): 80.6% (UltIMMA-2)	28 days
Secukinumab [54]	Cosentyx	300 mg SubQ at weeks 0, 1, 2, 3, and 4	300 mg SubQ every 4 weeks	Fully Human	PASI 90 (W12 – 300mg): 59.2% (ERASURE) PASI 90 (W12 – 300mg): 54.2% (FIXTURE)	Not Available	27 days
Ustekinumab [55]	Stelara	100 kg or less; 45 mg SubQ initially and 4 weeks later Greater than 100 kg: 90 mg SubQ initially and 4 weeks later	100 kg or less: 45 mg every 12 wks. Greater than 100 kg: 90 mg every 12 wks	Fully Human	PASI 90 (W16): 57.6%	PASI 90 (W52 – 45mg): 45.9% PASI 90 (W52 – 90mg): 55%	21 days

*Time interval can be modified and dose per kg can be increased according to patient's responses

\

• BIW, twice weekly; O\W, once weekly; IV, Intravenous; SubQ, Subcutaneous

Note: efficacy is reported based on pivotal studies

Table 5: Adverse Event Incidence of biologic agents for treatment of psoriasis

	Induction Period (After 12 weeks to 16 weeks) [56]											Long-term (After 52 weeks) [57-59]										
Drug Name	SAE	D/C due to AE	Death	Candida	Headache	IBD	MACE	Malignancies	Ex-NMSC	SIE	NMSC	SAE	D/C due to AE	Death	Candida	Headache	IBD	MACE	Malignancies	Ex-NMSC	SIE	NMSC
Adalimumab	2.0	2.0	0.0	NA	6.0	NA	NR	NA	0.2	1.0	0.5	23	0.87	0.2	NR	NR	NR		0.5	NR	2.0	1.9
Certolizumab	NR	NR	0.0	NR	6.0	NR	0.2	NR	0.2	0.14	NR	11.5	5.08	0	NR	NR	NR	0.43	0.43	0	1.5	0.43
Etanercept	2.0	2.0	0.0	NR	7	NR	0.2	NA	0.5	0.5	0.3	9.0	0.32	0.5	NR	NR	NR	1.0	NR	NR	1.6	1.3
Guselkumab	2.1	1.5	0.1	NR	4.6	NR	0.2	0.3	0.1	0.2	NA	8.5	2.8	NR	NR	NA	R	1.0	1.0	NA	1.0	NA
Infliximab	3.0	7.0	0.0	NA	13	NA	NR	0.06	1.0	6.0	NR	7.9	1.38	0.6	NR	NR	NR	NR	NR	NR	2.4	0.3
Ixekizumab	2.1	2.0	0.0	1.0	4.4	0.3	0.2	0.3	0.2	0.4	0.1	5.4	3.0	0.2	2.4	5.7	0.4	0.4	0.5	0.3	NA	NA
Risankizumab	2.5	0.9	0.2	NR	NR	NA	0.1	0.6	0.2	0.7	NR	5.8	1.0	0.3	R	NR	R	0.3	0.7	0.2	1.2	NR
Secukinumab	2.7	1.8	0.05	0.6	5.3	0.1	0.4	0.4	NA	0.4	NA	9.1	3.3	0.1	2.9	8.0	0.4	0.8	0.9	0.4	1.6	NR
Ustekinumab	1.0	1.0	0.1	NA	7	NA	0.2	NA	0.2	0.6	0.4	7.1	2.8	0.3	NR	NR	NR	0.0	0.2	0.2	1.2	0.5

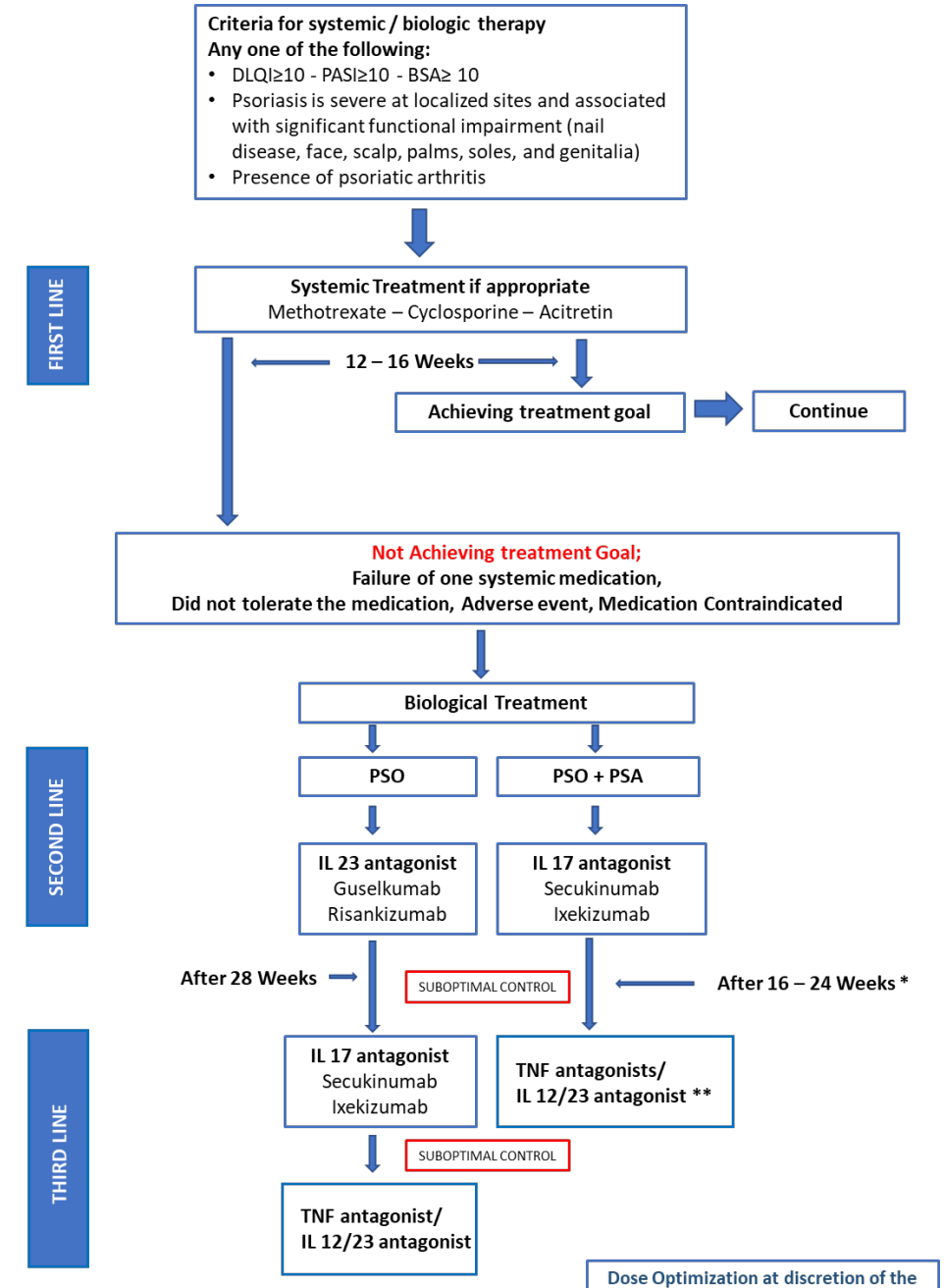
AE: Adverse Event; Ex-NMSC: Malignancy Excluded NMSC; NR: Not Reported; NA: Not Available; NMSC: Nonmelanoma Skin Cancer; MACE: Major Adverse Cardiac Event; SAE: Serious Adverse Event; SIE: Serious Infection; R: Rare

\

8. TREATMENT ALGORITHM

8.1. Biologic Therapy

Overview of evaluating treatment options for chronic psoriasis vulgaris (the order does not indicate priority)



*16 weeks for skin and 24 weeks for joint disease
** IL 12/23 antagonist used for patients with peripheral arthritis only

8.2. Apremilast

In a select group of patients apremilast may be considered. Apremilast is an oral phosphodiesterase inhibitor, approved for Pso & PsA, has a PASI 75 response of 33.1% at 16 weeks [60]. Sub analysis of pivotal studies data showed some response in palmoplantar, scalp and nail psoriasis [61, 62]. There is no restriction to using it in patients with malignancies [63]. Additionally, institution formulary restrictions may need to be considered when selecting apremilast (i.e. in MOH, apremilast is non formulary).

9. RECOMMENDATIONS FOR THE TREATMENT OF PSORIASIS WITH BIOLOGIC THERAPIES

In current routine clinical practice, near complete skin clearance with the least side effects should be the treatment goal for patients with moderate-to-severe psoriasis. In addition to defining treatment goals, and in order to improve psoriasis outcomes, it is important to implement strategies to promptly alter treatment regimens if goals are not met within about 12 – 16 weeks. When the clinical response of treatment with the chosen biologic therapy is unsatisfactory (suboptimal outcomes, primary or secondary treatment failure, or drug-related side effects), the possible courses of action that may be followed to improve the results are: a) doze optimization, b) combination strategies with non-biologic treatment, c) switching to another biologic therapy.

9.1. Transitioning

To improve patient outcomes, switching psoriasis treatment is a common, accepted practice that is used (e.g., when patients are experiencing suboptimal efficacy and/or intolerability with a given therapy). [64]. There are no evidence-based studies on the duration of the interval between discontinuation of the previous medication and

initiation of a biologic therapy. 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 of 3 or 4 half-lives of the previous therapy before the transition [14].

9.1.1. *Transitioning from conventional systemic therapy to biologic therapy*

General considerations [65]

Recommendations for transitioning from conventional systemic therapy to biologic therapy will differ depending on the reason for transition. For example:

- When transitioning due to safety reasons (development of medication-related side effects), a treatment-free interval may be necessary until the safety parameter has normalized or stabilized.
- When transitioning due to lack of efficacy, which could be primary or secondary inefficacy, or due to suboptimal response; transitioning directly or with an overlap period can be considered.
- Additionally, if a patient develops psoriatic arthritis, transitioning to a therapy that is efficacious in both psoriasis and psoriatic arthritis is required.

Irrespective of the reason for transitioning, approved induction dosages should be used for the new drug.

Cyclosporine to biologic therapy [65]

Transitioning from cyclosporine to TNF antagonists and ustekinumab can be performed without a washout period. A short overlap period (e.g. 2–8 weeks) of cyclosporine with TNF antagonists or ustekinumab can be considered in order to reduce the risk of rebound in partial responders but the overlap period should be minimized and the dose of cyclosporine tapered down as soon as possible.

MTX to biologic therapy [65]

Transitioning from MTX to TNF antagonists and ustekinumab can be performed without a washout period. MTX can be overlapped or used concurrently with TNF antagonists or ustekinumab.

9.1.2. Transitioning from one biologic therapy to another

General considerations before transitioning [65]

In the case of suboptimal response to a biologic therapy (etanercept, infliximab, adalimumab and ustekinumab), dose optimization or combination strategies with non-biologic treatment is preferred before transitioning to another biologic therapy [65]. This decision should be made with consideration to patient situation/preference and the cost inflation by dose optimization. Recommendations for dose optimization include:

- For *adalimumab*, an increase of dosage from 40 mg every other week to 40 mg/week [65].
- For *etanercept*, an increase of dosage from 50 mg/week to 50 mg twice weekly [65].
- For *ustekinumab*, with partial responders, an increase of dosage from 45 to 90 mg with 12-week dosing intervals. If this is unsuccessful, the interval can be shortened to 8 weeks [65].
- For *infliximab*, a reduction of the dosing intervals from every 8 weeks to every 6 weeks with 5 mg/kg can be considered in secondary non-responders, defined as the loss of at least 50% of the initial improvement. In special cases an increase of the dosage > 5 mg/kg can be considered [65]. The dose can be increased in some circumstances up to 10 mg/kg/dose and the interval can be shortened to 4 weeks [66].
- For *secukinumab,* dose optimization includes shortening the interval to every 2 weeks [67].

- For *ixekizumab*, a single report of administrating it every 2 weeks instead of 4 weeks [68]
- For IL-23 inhibitors, no data yet

General considerations after decision to transition has been made [65]

Recommendations for transitioning from one biologic therapy to another will differ depending on the reason for transition. For example:

- When transitioning due to lack of efficacy, no washout period is necessary; transition to the new biologic therapy at the time of the next scheduled dose of the original therapy, using the standard induction dose, followed by the maintenance dose.
- When transitioning due to safety reasons (development of medication-related side effects), a treatment-free interval may be necessary until the safety issue has resolved.

Adalimumab /etanercept to another biologic therapy [65]

Administer the first treatment with the new biologic therapy at the time point of the next scheduled drug dosage (typically 2 -weeks for adalimumab and 1- week for etanercept).

Infliximab to another biologic therapy [65]

Administer the first treatment with the new biologic therapy as early as 2–4 weeks after the last infliximab dose. Transitioning from infliximab to IL-17 and IL-23 inhibitors can be done after 4-weeks.

9.2. Adjusting biologic therapy

9.2.1. Dose Reduction

- During successful maintenance with biologics as monotherapy, a dose reduction can be considered to limit drug exposure. However, long-term efficacy and safety data has only been generated for the approved doses. Moreover, there is a risk of decreasing efficacy. In addition, there is some evidence to support that a longer interval might increase the risk of anti-drug antibody formation [65].
- Decreasing the dose may be considered in patients on combination therapy [65].
- In clinical practice, dosing intervals have been increased with adalimumab and etanercept while maintaining clinical response [65].
- With infliximab monotherapy, intervals should not be increased over the recommended intervals. The dose of infliximab may be reduced from 5 mg/kg bodyweight to a minimum of 3 mg/kg bodyweight particularly if combined with methotrexate [65].
- With ustekinumab, the dose for a responding patient may be reduced from 90 to 45 mg. Moreover, few reports exist for prolongation of interval between injections [69].

9.2.2. Dose discontinuation/interruption

In cases of sustained response/clearance:

- Discontinuation of biologic therapy is not generally recommended due to risk of recurrence or failure to recapture the initial response [65].
- However, if agreed with the patient, and after achieving a clinical response of clear or almost clear with good QoL for a prolonged period of time (i.e. a minimum of 1 year), discontinuing biologic therapy can be considered with careful follow-up [65].
- There is little evidence to suggest which subgroups of patients can discontinue the biologic medication. These subgroups include [65]:
    - Patient preference

- Patients with a history of disease-free intervals or previously stable plaque-type psoriasis
- Absence of PsA
- Low impact of disease on QoL
- No worsening of disease after previous dose reductions and treatment withdrawals

- However, because biologic therapies are typically considered for patients with more severe disease, and as a second line after failing conventional systemic therapy; patients on biologics are less likely to fulfil these criteria. Furthermore, fewer treatment options are available in case of relapse after discontinuation.
- Another consideration is that the risk of antibody formation increases with intermittent therapy. This is particularly important for the use of infliximab monotherapy where a higher risk of infusion reactions has been observed with intermittent therapy [65].

Efficacy with biologic therapy following treatment discontinuation/interruption:

- In patients receiving biologic therapy, there is a high likelihood of disease recurrence within several months of discontinuation of treatment, although some patients may maintain disease control for a prolonged period of time [65]. Generally, maintaining PASI-90 response for a longer duration is documented with IL-17 as compared to anti-TNF inhibitors, as well as a higher percentage of patients will recapture PASI-90 after restarting IL-17 in comparison to anti-TNF [70].
- Continuous biologic therapy generally results in greater improvements in efficacy over time compared with intermittent therapy[65].
- In clinical trials with primary responder patients, up to 20% fail, to regain a PASI 75 response after the re-initiation of the same biologic monotherapy. This decrease in efficacy may be greater with intermittent use of the drug [65].

- Where therapy has been withdrawn and restarted, an induction dosing schedule should be used for re-introduction of the biologic therapy, with the possible exception of infliximab (because of the increased risk of infusion reactions) [65].

10. SPECIAL PATIENT POPULATIONS

Psoriasis is a systemic inflammatory disease that is associated with an increased risk of comorbidities, which can have significant impact on the decision to use one therapy over another. Choosing the right therapy in certain patient populations can also be challenging. Thus, it is important to tailor treatment regimens for psoriasis patients based on their individual special needs and characteristics.

This section of the guidelines covers choice of biologic therapy in pregnancy and lactation, as well as in pediatrics and adolescents. In addition, recommendation of the choice of treatment are presented for patients with the following comorbidities: metabolic syndrome (including obesity), malignancy, demyelinating disease (multiple sclerosis), cardiovascular disease, congestive heart failure, inflammatory bowel disease, and lupus erythematosus. This section also provides insights for choosing appropriate biologic therapy for treatment of moderate-to-severe psoriasis in the setting of chronic infections such as hepatitis and tuberculosis.

10.1. Pregnancy and Lactation

The treatment of psoriasis in pregnancy or in patients planning a pregnancy can be challenging. Likely due to the immunomodulatory changes of pregnancy, it is reported that 55% of psoriasis patients improve during pregnancy, while 23% experience worsening [71]. Patients who are pregnant or are lactating require special considerations to ensure treatment safety and efficacy. Generally, any medications in pregnancy should be avoided unless benefits outweigh risks. In women of childbearing potential or those who become pregnant, risks and benefits of

continuing versus stopping biologic therapy should be discussed [13]. It is preferred to discontinue all biologic agents before pregnancy or at 16 – 26 weeks of pregnancy [72]. In general, advise mothers who have received biologic therapy for psoriasis beyond 16 weeks' gestation that their infants should not receive any live vaccinations until they have reached 6 months of age (e.g. rotavirus and BCG) [13]

10.1.1. TNF-α inhibitors

TNF- α inhibitors can be used during lactation. They are safe in men attempting conception with their partners. There is a greater theoretical risk with use during the third trimester of pregnancy owing to transplacental transfer of TNF-α inhibitors [14]. Certolizumab pegol has shown minimal to no placental transfer, so it is labeled as the best choice for pregnant psoriatic patients [73]. Etanercept is considered an alternative to certolizumab if certolizumab is not available [73].

10.1.2. IL-12/IL-23 inhibitors

The safety of IL-12/IL-23 inhibitors during pregnancy and lactation is uncertain. They are acceptable for men attempting conception with their partners [14].

10.1.3. IL-17 inhibitors

There are no studies on human pregnancy. 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 [68].

10.1.4. IL-23 inhibitors

Safety during pregnancy for IL-23 inhibitors is unknown [14] . The presence of IL-23 inhibitors in secreted human milk has not been studied [14]. However, antibodies are effectively secreted during lactation [14], but generally have no significant impact [74].

10.1.5. Contraception

There are no known interactions between biologic therapies and contraceptive methods. Advise women of childbearing potential who are starting biologic therapy for psoriasis to use effective contraception and discuss conception plans with the treating physician [13].

The recommendations for the use of biologic therapy in pregnancy are summarized in Table 6 below.

Table 6: Summary of recommendations for biologic therapy options in pregnancy

	Certolizumab pegol	Etanercept	Adalimumab	Infliximab	IL-12/IL-23 inhibitors	IL-23 inhibitors	IL-17 inhibitors
Pregnancy	Most Preferred	Alternative to Certolizumab if not available	Higher placental transfer	Higher placental transfer	The safety is uncertain	The safety is unknown	The safety is uncertain

10.2. Pediatric and adolescents

The choice of treatment for pediatrics and adolescents should be made on an individual basis after discussion between the treating clinician and the patient, or their parents or guardian, about the advantages and disadvantages of the treatments available.

Among the multiple biologic therapies available for treatment of psoriasis in adults, only adalimumab, etanercept, and ustekinumab are approved for treating plaque psoriasis in children and young people [13] . Recommendations on choice of biologic therapy for pediatrics and adolescents are summarized in table 7 below.

Table 7: Summary of recommendations for choice of biologic therapy in pediatrics and adolescents

	FDA approved for moderate-to-severe pediatric plaque psoriasis	Doses in children (subcutaneous)
Adalimumab	≥ 4 years [16]	<u>10 kg to <15 kg:</u> 10 mg every other week <u>15 kg to <30 kg:</u> 20 mg every other week <u>≥30 kg:</u> 40 mg every other week
Etanercept	≥4 years [14]	0.8 mg/kg weekly, with a maximum of 50 mg per week
Ustekinumab	≥ 6 years [75]	<u><60 kg:</u> 0.75 mg/kg <u>≥60 kg:</u> as adult. The dosing frequency is the same as in adults at weeks 0 and 4, then every 12 weeks thereafter.

***Infliximab** is FDA-approved for the treatment of Crohn's disease and ulcerative colitis in children 6 years of age and older[14].

10.3. Metabolic Syndrome

The prevalence of metabolic syndrome increases with increased BSA affected by psoriasis [15] .

10.3.1. Obesity

The relationship between psoriasis and obesity is unclear. Increased levels of pro-inflammatory cytokines (e.g., TNF- α , IL-1b, and IL-6) and adiponectin are detected in the serum of obese patients [15].

When treating a patient with psoriasis, regardless of baseline weight, the effect of treatment on weight management is an important variable to consider [15]. Overweight and obese patients frequently require a shorter dose interval or higher doses to achieve a satisfactory response . Infliximab and ustekinumab are dosed based on weight [76].

10.4. Malignancy

A correlation between psoriasis and malignancy has been noted in several studies. There may be minimal increased incidence of certain malignancies in patients with psoriasis, particularly cutaneous T-cell lymphoma, head and neck cancers, and digestive tract malignancies [15]. Some studies suggest an increased risk for NMSC in patients who have received psoralen UVA phototherapy [77], or have used cyclosporine, or receiving TNF inhibitors [73, 78].

With regards to infliximab specifically, an exploratory clinical study evaluating its use in patients with moderate to severe COPD, has reported more malignancies in infliximab treated patients compared with control patients [79]. All patients in the study had a history of heavy smoking. Thus, caution should be exercised in considering treatment for patients with increased risk for malignancy due to heavy smoking [15, 73].

It is best to avoid all biologic therapy in patients with concurrent malignancy or a history of malignancy. It is also recommended to discuss the decision to initiate immunosuppressive therapies, in psoriasis patients with a current or recent diagnosis of cancer in the previous five years on individual basis and consulting the treating oncologists (taking into consideration type and staging of cancer, the risk of recurrence and the severity of psoriasis) to reach an informed decision, respecting the patient's preference.

10.5. Surgery

For the elective major surgery it is better to discontinue biologic therapy for about 4 to 5 half-lives before surgeries [37]. This is despite the use of biologic therapy does not appear to affect the rates of surgical complications, like infections [80-85]. Data is still limited whether biologic treatments should be stopped or continued in psoriatic patients who are undergoing major surgeries. A practical approach would be to discontinue the biologics only for mouth/ gastrointestinal surgery and to be continued for clean surgeries [37].

10.6. Hepatitis

It is generally accepted that biologics should not be initiated in patients with active hepatitis B infection [23, 24, 32]. Risk of developing severe hepatitis due to reactivation of HBV infection with biologic agents cannot be excluded, therefore management of psoriatic patients with a hepatologist should be considered in the cases of chronic carriers of HBV or those with positive serology and positive symptoms such as nausea, appetite loss, and pruritus [86]. The infliximab insert warns about HBV reactivation and recommends monitoring of HBV carriers during and several months after therapy [23].

There is no clear consensus regarding management of patients with HCV. However, the risk of developing severe hepatitis is not as critical for patients with HCV as for those with HBV [1]. If the HCV-infected patient has already been successfully treated with an antiviral therapy, the risk seems to be even lower [87]. There are several published reports of successful treatment of HCV-infected psoriatic patients with adalimumab and etanercept [1]

The safety profile of ustekinumab in patients with hepatitis is controversial [73]. IL-17 inhibitors appear to have a favorable safety profile, but the available data are limited [73]. Data are also limited on IL-23 inhibitor use in patients with hepatitis[73].

10.7. Tuberculosis (TB)

Patients who receive anti -TNF biologic therapy are at increased risk of LTBI reactivation [1, 20]; the risk may be greater with the monoclonal antibodies (infliximab and adalimumab) than etanercept. Also ustekinumab may facilitate reactivation of tuberculosis [13]. The atypical clinical presentation of infection with extrapulmonary and disseminated disease in patients treated with TNF antagonist's incidence is higher [1, 13]. There are no reported LTBI cases with IL-17 and IL-23 so far [73] .

If patients with LTBI have normal chest radiograph and no symptoms or signs of active TB, treatment of LTBI is indicated. Treatment with isoniazid (INH) for 9 months or rifampin for 4 months (only when INH regimen is not feasible and after consulting with a TB specialist due to high risk of rifampicin-resistance) [1, 20], aim to complete one month of treatment before starting the biologic therapy[1].

If active TB is suspected, treatment with biologics should deferred, and chest x-ray, sputum AFB stain and culture must be repeated to rule out any new infection or reactivation [1]. Referral to a TB expert is indicated in case of LTBI or active TB [78]

.

10.8. Demyelinating Diseases/Multiple Sclerosis (MS)

- Do not use TNF-α antagonists in patients with demyelinating diseases and review alternative interventions in patients who have an affected first-degree relative with demyelinating disease [76, 88].
- Stop treatment and seek specialist advice if neurological symptoms suggestive of demyelinating disease develop during TNF-α antagonist therapy [89] .
- IL 12/ 23 inhibitor may be used in patients with MS as it does not improve or worsen MS [76, 90].
- IL-17 inhibitors can be used with some benefit in MS symptoms [76, 91].
- Data are limited for the IL-23 inhibitors, but there are no reports of MS worsening with these drugs [76].

10.9. Cardiovascular Disease

- TNF-α inhibitors are preferred systemic agents for treatment of psoriasis in patients with coexisting cardiovascular risk factors [76, 92, 93].
- IL 12/ 23 inhibitor has some potential cardioprotective benefit, but more long-term data are needed [76, 94] .
- More data are needed for the use of IL-17 and IL-23 inhibitors [76].

10.10. Congestive Heart Failure (CHF):

- Avoid TNF-α antagonist therapy in people with severe cardiac failure [New York Health Association (NYHA) class III and IV] [76, 95, 96] .
- Discontinue TNF-α antagonist therapy in the event of new or worsening pre-existing heart failure and seek specialist advice [76, 95, 96] .
- IL 12/23, IL-17, and IL-23 inhibitors appear to be safe to use in CHF patients [97].

10.11. Inflammatory Bowel Disease (IBD)

- Patients with a history of concomitant IBD might benefit from TNF-α inhibitor therapy. In fact, adalimumab, infliximab, and certolizumab are approved by the US FDA for the treatment of IBD [98-101]. Etanercept is not as effective as other TNF-α inhibitors for Crohn's Disease [102] .
- IL 12/23 inhibitor is also approved for Crohn's disease but not ulcerative colitis [103] .
- IL-23 inhibitor use in Crohn's disease has promising results in preliminary studies, but more data is needed to draw definite conclusions [104] .
- Exercise caution and consult a gastroenterology specialist before using IL-17 inhibitors in patients with IBD, or those with first degree relatives with IBD [105-108].

10.12. Lupus Erythematosus

- There is concern for development of de novo lupus or flare-up of lupus during treatment with TNF- α blockers, also known as anti TNF- α induced lupus (ATIL) [109, 110].
- IL 12/23 inhibitor is the safest treatment option for concomitant lupus and psoriasis as it reportedly improves SLE symptoms, specifically oral ulcerations, anemia or thrombocytopenia, and lupus arthritis [111, 112] .
- There is not enough data regarding the use of IL-17 and IL-23 inhibitors in patients with SLE, but no new cases of lupus induction or flare have been reported yet [76]

.

CONCLUSION

These guidelines represent a summary of the scientific evidence currently available on the efficacy of the biologic treatments indicated for psoriasis on the Saudi market at the time of publication and the selection criteria for the use of these drugs. Additionally, expert opinion has been utilized to generate clinical recommendations for situations in which documented evidence-based data was not available. The choice of biologic therapy should always be based on knowledge of the published response rates in clinical trials and take into account the disease course at the time of prescription and the characteristics of the patient.

FUNDING SOURCE

This guidelines project was funded by the Ministry of Health, Kingdom of Saudi Arabia.

REFERENCES

1. Hamadah, I.R., et al., *Saudi practical guidelines on biologic treatment of psoriasis.* J Dermatolog Treat, 2015. **26**(3): p. 223-9.
2. Christophers, E., *Psoriasis--epidemiology and clinical spectrum.* Clin Exp Dermatol, 2001. **26**(4): p. 314-20.
3. Parisi, R., et al., *Global epidemiology of psoriasis: a systematic review of incidence and prevalence.* J Invest Dermatol, 2013. **133**(2): p. 377-85.
4. Rendon, A. and K. Schakel, *Psoriasis Pathogenesis and Treatment.* Int J Mol Sci, 2019. **20**(6).
5. Rachakonda, T.D., C.W. Schupp, and A.W. Armstrong, *Psoriasis prevalence among adults in the United States.* J Am Acad Dermatol, 2014. **70**(3): p. 512-6.
6. Langley, R.G., G.G. Krueger, and C.E. Griffiths, *Psoriasis: epidemiology, clinical features, and quality of life.* Ann Rheum Dis, 2005. **64 Suppl 2**: p. ii18-23; discussion ii24-5.
7. Kim, B.R., et al., *Risk of acute infections in patients with psoriasis: A nationwide population-based cohort study.* J Am Acad Dermatol, 2019.
8. Furue, M. and T. Kadono, *Psoriasis: Behind the scenes.* J Dermatol, 2016. **43**(1): p. 4-8.
9. Armstrong, A.W., *Psoriasis.* JAMA Dermatol, 2017. **153**(9): p. 956.
10. Navarini, A.A. and R.M. Trueb, *[Psoriasis].* Ther Umsch, 2010. **67**(4): p. 153-65.
11. Brouwers, M.C., et al., *AGREE II: advancing guideline development, reporting, and evaluation in health care.* Prev Med, 2010. **51**(5): p. 421-4.

12. Nast, A., et al., *European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC.* J Eur Acad Dermatol Venereol, 2017. **31**(12): p. 1951-1963.
13. Smith, C.H., et al., *British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017.* Br J Dermatol, 2017. **177**(3): p. 628-636.
14. Menter, A., et al., *Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics.* J Am Acad Dermatol, 2019. **80**(4): p. 1029-1072.
15. Elmets, C.A., et al., *Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities.* J Am Acad Dermatol, 2019. **80**(4): p. 1073-1113.
16. *NICE Pathway Systemic biological therapy for psoriasis 2019.*
17. Amatore, F., et al., *French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults.* J Eur Acad Dermatol Venereol, 2019. **33**(3): p. 464-483.
18. McMillan, S.S., M. King, and M.P. Tully, *How to use the nominal group and Delphi techniques.* Int J Clin Pharm, 2016. **38**(3): p. 655-62.
19. Mahil, S.K., et al., *Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR).* Br J Dermatol, 2019.
20. Al Jahdali, H.H., et al., *Saudi guidelines for testing and treatment of latent tuberculosis infection.* Ann Saudi Med, 2010. **30**(1): p. 38-49.
21. WHO. *WHO LTBI FAQs*. 2018 [cited 2020 26 JAN]; Available from: https://www.who.int/tb/publications/2018/ltbi_faqs.pdf?ua=1.
22. Nast, A., et al., *Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris--update 2015--EDF in cooperation with EADV and IPC.* J Eur Acad Dermatol Venereol, 2015. **29**(12): p. e1-22.
23. *Product Information: REMICADE(R) lyophilized concentrate for intravenous injection, infliximab lyophilized concentrate for intravenous injection. Janssen Biotech, Inc. (per FDA), Horsham, PA, 2011.*
24. *Product Information: HUMIRA(R) subcutaneous injection, adalimumab subcutaneous injection. AbbVie Inc. (per FDA), North Chicago, IL, 2015.*
25. *Product Information: CIMZIA(R) subcutaneous injection, Certolizumab pegol subcutaneous injection. UCB Inc (per manufacturer), Smyrna, GA, 2019.*
26. *Product Information: STELARA(R) subcutaneous injection, intravenous injection, ustekinumab subcutaneous injection, intravenous injection. Janssen Biotech Inc (per FDA), Horsham, PA, 2019.*
27. *Product Information: COSENTYX(R) subcutaneous injection, secukinumab subcutaneous injection. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2018.*
28. *Product Information: TALTZ(R) subcutaneous injection, ixekizumab subcutaneous injection. Eli Lilly and Company (per manufacturer), Indianapolis, IN, 2019.*
29. *Product Information: TREMFYA(R) subcutaneous injection, guselkumab subcutaneous injection. Janssen Biotech Inc (per FDA), Horsham, PA, 2019.*
30. *Product Information: ILUMYA(TM) subcutaneous injection, tildrakizumab-asmn subcutaneous injection. Merck & Co. Inc (per manufacturer), Whitehouse Station, NJ, 2018.*

31. *Product Information: SKYRIZI(TM) subcutaneous injection, risankizumab-rzaa subcutaneous injection. AbbVie Inc (per FDA), North Chicago, IL, 2019.*
32. *Product Information: Enbrel(R) subcutaneous injection solution, etanercept subcutaneous injection solution. Amgen Inc. (per FDA), Thousand Oaks, CA, 2015.*
33. *Series, Micromedex Healthcare. "Internet database. USA Thomson Reuters (Healthcare) Inc. http://www. micromedex. com/products/hcs/. Accessed 2019..*
34. *National Institute for Health and Care Excellence (NICE): Clinical guideline on psoriasis – Assessment and management (2012, updated 2017).*
35. Hsu, S., et al., *Consensus guidelines for the management of plaque psoriasis.* Arch Dermatol, 2012. **148**(1): p. 95-102.
36. Furer, V., et al., *2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases.* 2019.
37. Poelman, S.M., C.P. Keeling, and A.I. Metelitsa, *Practical Guidelines for Managing Patients With Psoriasis on Biologics: An Update.* J Cutan Med Surg, 2019. **23**(1_suppl): p. 3s-12s.
38. Al-Tawfiq, J.A. and Z.A. Memish, *The Hajj 2019 Vaccine Requirements and Possible New Challenges.* J Epidemiol Glob Health, 2019. **9**(3): p. 147-152.
39. *Pharmaceutical and herbal products list, Saudi food and drug authority. https://www.sfda.gov.sa/ar/drug/search/Pages/default.aspx.*
40. *Product Information: REMSIMA(R) lyophilized concentrate for intravenous injection, infliximab lyophilized concentrate for intravenous injection. Celltrion Healthcare Co. Ltd., May 26, 2016.*
41. Menter, A., et al., *Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial.* J Am Acad Dermatol, 2008. **58**(1): p. 106-15.
42. Gordon, K., et al., *Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL.* J Am Acad Dermatol, 2012. **66**(2): p. 241-51.
43. Gottlieb, A.B., et al., *Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2).* J Am Acad Dermatol, 2018. **79**(2): p. 302-314.e6.
44. Leonardi, C.L., et al., *Etanercept as monotherapy in patients with psoriasis.* N Engl J Med, 2003. **349**(21): p. 2014-22.
45. Leonardi, C., et al., *Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study.* J Drugs Dermatol, 2010. **9**(8): p. 928-37.
46. Blauvelt, A., et al., *Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial.* J Am Acad Dermatol, 2017. **76**(3): p. 405-417.
47. Reich, K., et al., *Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial.* J Am Acad Dermatol, 2017. **76**(3): p. 418-431.

48. Reich, K., et al., *Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.* Lancet, 2005. **366**(9494): p. 1367-74.
49. Gottlieb, A.B., et al., *Pharmacodynamic and pharmacokinetic response to anti-tumor necrosis factor-alpha monoclonal antibody (infliximab) treatment of moderate to severe psoriasis vulgaris.* J Am Acad Dermatol, 2003. **48**(1): p. 68-75.
50. Menter, A., et al., *A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis.* J Am Acad Dermatol, 2007. **56**(1): p. 31.e1-15.
51. Barker, J., et al., *Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1).* Br J Dermatol, 2011. **165**(5): p. 1109-17.
52. Griffiths, C.E., et al., *Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials.* Lancet, 2015. **386**(9993): p. 541-51.
53. Gordon, K.B., et al., *Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials.* Lancet, 2018. **392**(10148): p. 650-661.
54. Langley, R.G., et al., *Secukinumab in plaque psoriasis--results of two phase 3 trials.* N Engl J Med, 2014. **371**(4): p. 326-38.
55. Langley, R.G., et al., *Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up.* Br J Dermatol, 2015. **172**(5): p. 1371-83.
56. Loos, A.M., et al., *Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis.* J Am Acad Dermatol, 2018. **79**(1): p. 135-144.e7.
57. Mansouri, Y. and G. Goldenberg, *Biologic safety in psoriasis: review of long-term safety data.* J Clin Aesthet Dermatol, 2015. **8**(2): p. 30-42.
58. Loft, N.D., et al., *Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies.* J Eur Acad Dermatol Venereol, 2019.
59. Curtis, J.R., et al., *Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials.* RMD Open, 2019. **5**(1): p. e000942.
60. Papp, K., et al., *Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1).* J Am Acad Dermatol, 2015. **73**(1): p. 37-49.
61. Rich, P., et al., *Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2).* J Am Acad Dermatol, 2016. **74**(1): p. 134-42.
62. Bissonnette, R., et al., *Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in*

Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. J Am Acad Dermatol, 2016. **75**(1): p. 99-105.

63. *Product Information: OTEZLA(R) oral tablets, apremilast. Amgen Inc, Thousand Oaks, CA 2014-2020.*
64. Kerdel, F. and M. Zaiac, *An evolution in switching therapy for psoriasis patients who fail to meet treatment goals.* Dermatol Ther, 2015. **28**(6): p. 390-403.
65. Mrowietz, U., et al., *A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis.* J Eur Acad Dermatol Venereol, 2014. **28**(4): p. 438-53.
66. Torii, H., et al., *Efficacy and safety of dose escalation of infliximab therapy in Japanese patients with psoriasis: Results of the SPREAD study.* J Dermatol, 2017. **44**(5): p. 552-559.
67. Phung, M., et al., *Secukinumab dose optimization in adult psoriasis patients: A retrospective, multicenter case series.* JAAD Case Rep, 2018. **4**(4): p. 310-313.
68. Langley, R.G. and K. Papp, *Efficacy and safety of continuous every-2-week dosing of ixekizumab over 52 weeks in patients with moderate-to-severe plaque psoriasis in a randomized phase III trial (IXORA-P).* 2018. **178**(6): p. 1315-1323.
69. van Bezooijen, J.S., et al., *Prolongation of Biologic Dosing Intervals in Patients With Stable Psoriasis: A Feasibility Study.* Ther Drug Monit, 2017. **39**(4): p. 379-386.
70. Umezawa, Y., et al., *Long-term efficacy and safety results from an open-label phase III study (UNCOVER-J) in Japanese plaque psoriasis patients: impact of treatment withdrawal and retreatment of ixekizumab.* J Eur Acad Dermatol Venereol, 2019. **33**(3): p. 568-576.
71. Murase, J.E., et al., *Hormonal effect on psoriasis in pregnancy and post partum.* Arch Dermatol, 2005. **141**(5): p. 601-6.
72. Porter, C., et al., *Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): Consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer.* J Reprod Immunol, 2016. **116**: p. 7-12.
73. Kaushik, S.B. and M.G. Lebwohl, *Psoriasis: Which therapy for which patient: Focus on special populations and chronic infections.* J Am Acad Dermatol, 2019. **80**(1): p. 43-53.
74. Flint, J., et al., *BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids.* Rheumatology (Oxford), 2016. **55**(9): p. 1693-7.
75. *Product Information: STELARA(R) subcutaneous injection, intravenous injection, ustekinumab subcutaneous injection, intravenous injection. Janssen Biotech Inc (per EMA), 2020 https://www.ema.europa.eu/en/medicines/human/EPAR/stelara.*
76. Kaushik, S.B. and M.G. Lebwohl, *Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents.* J Am Acad Dermatol, 2019. **80**(1): p. 27-40.
77. Pouplard, C., et al., *Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies.* J Eur Acad Dermatol Venereol, 2013. **27 Suppl 3**: p. 36-46.
78. Nast, A., et al., *European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC.* J Eur Acad Dermatol Venereol, 2015. **29**(12): p. 2277-94.
79. Rennard, S.I., et al., *The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2007. **175**(9): p. 926-34.

80. Hernandez, C., J. Emer, and J.K. Robinson, *Perioperative management of medications for psoriasis and psoriatic arthritis: a review for the dermasurgeon.* Dermatol Surg, 2008. **34**(4): p. 446-59.
81. Bibbo, C. and J.W. Goldberg, *Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy.* Foot Ankle Int, 2004. **25**(5): p. 331-5.
82. Busti, A.J., et al., *Effects of perioperative antiinflammatory and immunomodulating therapy on surgical wound healing.* Pharmacotherapy, 2005. **25**(11): p. 1566-91.
83. Colombel, J.F., et al., *Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy.* Am J Gastroenterol, 2004. **99**(5): p. 878-83.
84. Pieringer, H., U. Stuby, and G. Biesenbach, *Patients with rheumatoid arthritis undergoing surgery: how should we deal with antirheumatic treatment?* Semin Arthritis Rheum, 2007. **36**(5): p. 278-86.
85. den Broeder, A.A., et al., *Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study.* J Rheumatol, 2007. **34**(4): p. 689-95.
86. McIntyre, N., *Clinical presentation of acute viral hepatitis.* Br Med Bull, 1990. **46**(2): p. 533-47.
87. Aslanidis, S., et al., *Inhibition of TNFalpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases.* Clin Rheumatol, 2007. **26**(2): p. 261-4.
88. Gomez-Gallego, M., J. Meca-Lallana, and A. Fernandez-Barreiro, *Multiple sclerosis onset during etanercept treatment.* Eur Neurol, 2008. **59**(1-2): p. 91-3.
89. Kemanetzoglou, E. and E. Andreadou, *CNS Demyelination with TNF-alpha Blockers.* Curr Neurol Neurosci Rep, 2017. **17**(4): p. 36.
90. Segal, B.M., et al., *Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study.* Lancet Neurol, 2008. **7**(9): p. 796-804.
91. Havrdova, E., et al., *Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study.* J Neurol, 2016. **263**(7): p. 1287-95.
92. Armstrong, E.J., C.T. Harskamp, and A.W. Armstrong, *Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies.* J Am Heart Assoc, 2013. **2**(2): p. e000062.
93. Gulliver, W.P., et al., *Psoriasis Patients Treated With Biologics and Methotrexate Have a Reduced Rate of Myocardial Infarction: A Collaborative Analysis Using International Cohorts.* J Cutan Med Surg, 2016. **20**(6): p. 550-554.
94. Papp, K., et al., *Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR).* J Drugs Dermatol, 2015. **14**(7): p. 706-14.
95. Menter, A., et al., *Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics.* J Am Acad Dermatol, 2008. **58**(5): p. 826-50.
96. Desai, S.B. and D.E. Furst, *Problems encountered during anti-tumour necrosis factor therapy.* Best Pract Res Clin Rheumatol, 2006. **20**(4): p. 757-90.

97. Bai, F., et al., *Short-Term Efficacy and Safety of IL-17, IL-12/23, and IL-23 Inhibitors Brodalumab, Secukinumab, Ixekizumab, Ustekinumab, Guselkumab, Tildrakizumab, and Risankizumab for the Treatment of Moderate to Severe Plaque Psoriasis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials.* J Immunol Res, 2019. **2019**: p. 2546161.
98. Hanauer, S.B., et al., *Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.* Lancet, 2002. **359**(9317): p. 1541-9.
99. Sands, B.E., et al., *Infliximab maintenance therapy for fistulizing Crohn's disease.* N Engl J Med, 2004. **350**(9): p. 876-85.
100. Hanauer, S.B., et al., *Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.* Gastroenterology, 2006. **130**(2): p. 323-33; quiz 591.
101. Sandborn, W.J., et al., *Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study.* Aliment Pharmacol Ther, 2014. **40**(8): p. 903-16.
102. Sandborn, W.J., et al., *Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial.* Gastroenterology, 2001. **121**(5): p. 1088-94.
103. Feagan, B.G., et al., *Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease.* N Engl J Med, 2016. **375**(20): p. 1946-1960.
104. Feagan, B.G., et al., *Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study.* Lancet, 2017. **389**(10080): p. 1699-1709.
105. Hueber, W., et al., *Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial.* Gut, 2012. **61**(12): p. 1693-700.
106. van de Kerkhof, P.C., et al., *Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis.* J Am Acad Dermatol, 2016. **75**(1): p. 83-98.e4.
107. Gordon, K.B., et al., *Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis.* N Engl J Med, 2016. **375**(4): p. 345-56.
108. Reich, K., et al., *Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials.* J Am Acad Dermatol, 2017. **76**(3): p. 441-448.e2.
109. Wetter, D.A. and M.D. Davis, *Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic.* Mayo Clin Proc, 2009. **84**(11): p. 979-84.
110. Williams, E.L., S. Gadola, and C.J. Edwards, *Anti-TNF-induced lupus.* Rheumatology (Oxford), 2009. **48**(7): p. 716-20.
111. Winchester, D., K.C. Duffin, and C. Hansen, *Response to ustekinumab in a patient with both severe psoriasis and hypertrophic cutaneous lupus.* Lupus, 2012. **21**(9): p. 1007-10.
112. Varada, S., et al., *Treatment of coexistent psoriasis and lupus erythematosus.* J Am Acad Dermatol, 2015. **72**(2): p. 253-60.