

ORIGINAL ARTICLE

Saudi practical guidelines on biologic treatment of psoriasis

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Abstract

The current treatment of psoriasis patients with biologic agents in the Kingdom of Saudi Arabia (KSA) is mainly based on clinical experience. Although there are published international guidelines for treatment with biologics, such as the European S3 guidelines (a joint project of the European Dermatology Forum, the European Academy of Dermatology and Venereology, and the International Psoriasis Council), many nations have found it beneficial to develop country-based guidelines that incorporate specific regional aspects of therapy (legal and practical). With the expanded role of biologic agents in the treatment of psoriasis in Saudi Arabia, a need for local Saudi guidelines has become evident. Here we present a practical approach to the evidence-based clinical administration of biologics for professionals who treat patients with psoriasis.

Keywords

Adalimumab, etanercept, infliximab, psoriatic arthritis, ustekinumab

History

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Introduction

The current treatment of psoriasis patients with biologic agents in the Kingdom of Saudi Arabia (KSA) is mainly based on clinical experience. Although there are published international guidelines for treatment with biologics, such as the European S3 guidelines (a joint project of the European Dermatology Forum, the European Academy of Dermatology and Venereology, and the International Psoriasis Council), many nations have found it beneficial to develop country-based guidelines that incorporate specific regional aspects of therapy (legal and practical) (1). With the expanded role of biologic agents in the treatment of psoriasis in Saudi Arabia, a need for local Saudi guidelines has become evident. Here we present a practical approach to the evidence-based clinical administration of biologics for professionals who treat patients with psoriasis.

The major intention of this guideline is to ensure that biologics are properly used by experienced dermatologists in systemic treatment of psoriasis and that the use of these agents incorporates the newest data on efficacy and safety. All biologics approved and available in the KSA are expected to offer superior clinical improvement in treatment of psoriasis and significantly improve quality of life compared with conventional agents. However, the use of biologic agents also requires careful screening of eligible patients and continuous monitoring during treatment in order to

achieve a favorable benefit/risk ratio. Updates to this guideline will be provided as needed to incorporate new data or agents.

There are several areas of knowledge required for the optimal treatment of psoriasis with biologic agents. Since the treatment of psoriasis requires long-term management, it is important to ensure adequate facilities and personnel (e.g. for infusion). Dermatologists who prescribe biologics need to be aware of the potential for clinical effectiveness of these drugs, but they also require in-depth knowledge of potential adverse events. In some cases, the recognition and treatment of adverse events associated with biologic agents may require interdisciplinary cooperation. Collaboration with the general physician or other healthcare professionals in treating these patients is mandatory for the success of therapy.

Eligibility criteria for biologic treatment

When selecting patients for biologic treatment, international eligibility criteria should be taken into account with particular consideration for patients who have failed, could not tolerate, or are contraindicated for topical therapy and at least one systemic treatment, preferably methotrexate (MTX). In general, the ‘‘Rule of 10 s’’ [$>10\%$ body surface area (BSA) involvement, a Psoriasis Area and Severity Index (PASI) score of 10 or higher, or a Dermatology Life Quality Index (DLQI) score of 10 or higher] is currently widely accepted as appropriate criteria for initiating biologic therapy (2). In European guidelines (including German and British national guidelines), biologics are considered a second-line treatment for psoriasis, mainly due to the approval policies of national or European drug agencies (3–6). According to US guidelines, biologics may be used as a first-line treatment in patients with moderate to severe psoriasis who are candidates for

systemic treatment. Recently, an international consensus conference showed an unmet need and proposed that patients with mild psoriasis (as determined by the physician global assessment [PGA]) may also be considered as candidates for systemic treatment in specific circumstances, including involvement of large areas of the scalp that do not respond adequately to topical treatment, involvement of visible areas such as the hands and face, and the presence of treatment-resistant areas (Figure 1) (7).

In patients with active psoriatic arthritis (PsA), biologics may be indicated even in patients with mild skin involvement if the rheumatologist confirms the presence and severity of arthritis.

Treatment goals

Before starting biologic therapy, it is preferable to define treatment goals for each patient. Assessment tools such as PASI, 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 2). The PASI is frequently used for assessing treatment goals; biologic agents are often able to result in marked reductions in initial clinical symptoms as measured by PASI. PASI 50 (a 50% improvement in baseline clinical symptoms) is considered the minimal threshold for response, PASI 75 is an optimal response, and PASI 90 is the maximal therapeutic response. The PGA is also an appropriate tool for evaluating psoriasis response. PGA 0 and 1 (clear or almost clear) is considered optimal, PGA 2 (mild) is considered acceptable, and PGA scores greater than 2 (moderate or severe) are considered a non-acceptable disease condition under systemic treatment with anti-psoriatic drugs, especially with biologics. Improvement of quality of life (QoL) should be accompanied by clinical improvement. The DLQI is an established tool for this purpose. DLQI scores below 5 are considered to represent a good QoL (4,7).

Biologic treatment has raised the bar for therapeutic success, and both patient and physician expectations are very important in

setting treatment goals. The tendency is to aim for PASI 90 and PGA 0 or 1 with considerable improvement of QoL. Timelines to reach this expectation vary among different biologics and individuals (e.g. 12–14 weeks for infliximab, adalimumab, and ustekinumab and 24 months for etanercept) (7,8). If the patient has PsA, the effects on swollen and tender joints must be included in the treatment goals in order to avoid irreversible joint damage. Interdisciplinary approaches in active PsA with radiographic control would be helpful in preventing irreversible joint deformities (9).

Screening, precautions and monitoring of biologics

All patients should be carefully examined before the initiation of biologic therapy. An appropriate examination includes consideration of general condition, concomitant diseases, existing co-medications, and a detailed family and personal medical history. Special attention should be paid to contra-indications for biologic therapy shown in Table 1 (2–6).

Screening for TB

According to Saudi guidelines for the testing and treatment of latent tuberculosis (TB), screening for an active or latent TB infection (LTBI) is mandatory before starting treatment with any biological treatment (10). Reactivation of TB has been associated with biologic therapy, and patients undergoing anti-tumor necrosis factor (TNF) therapy are at higher risk for developing TB than patients receiving conventional systemic anti-psoriatic treatment (11). In addition to several case reports of TB reactivation in patients on anti-TNF therapy (12), registry data from patients with rheumatoid arthritis and post-marketing reports to the FDA have identified numerous cases of TB reactivation associated with all anti-psoriatic biologics, including ustekinumab. Importantly, there is an increased incidence of extra pulmonary or disseminated cases of TB due to reactivation of LTBI in patients treated with TNF-inhibitors.



Figure 1. Criteria for reclassification of mild psoriatic disease to moderate-to-severe according to the European consensus recommendation (7).

Table 1. Contra-indications for biologic therapy.

- New York Heart Association class III or higher congestive heart failure except for ustekinumab.
- History of demyelinating disease (e.g. multiple sclerosis) except for ustekinumab.
- Serious hematologic disease (e.g. aplastic anemia).
- Current malignant tumor (in case of prior malignant disease, careful interdisciplinary analysis of the risk/benefit ratio should be done).
- Immune-compromised by congenital or acquired immunodeficiency syndrome.
- Pregnancy.

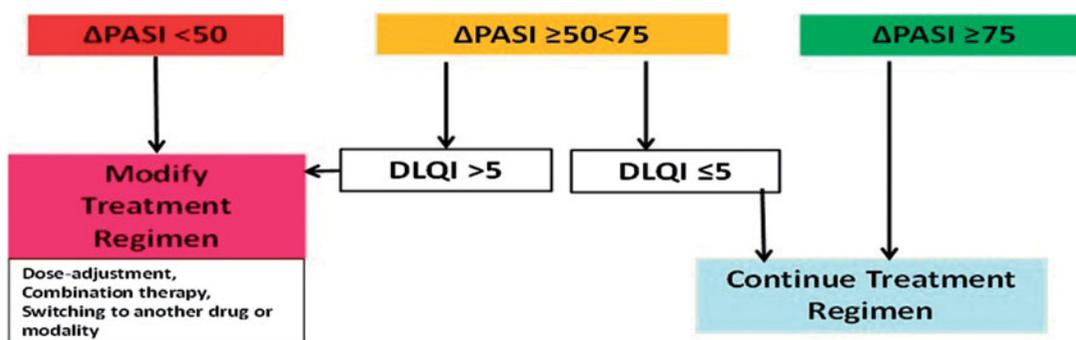


Figure 2. Use of treatment goals to guide therapy. Adapted from Mrowietz et al. (7).

The Saudi guidelines for testing and treatment of LTBI incorporate 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 guidance on targeted tuberculin testing in patients at risk of LTBI and treatment regimens for patients who develop TB. These guidelines recommend tuberculin skin tests (TST) with a purified protein derivative (PPD) for TB screening. The administration of TST requires proper technique by trained professionals, and reading of the test is performed between 48 and 72 hours after administration (the transverse diameter of the induration, but not erythema, is crucial in assessment of TST). The definition of a positive tuberculin reaction is dependent on the size of the TST and the risk status of the subjects: ≥ 5 mm is considered positive in high-risk individuals (those planning to initiate biologic or immunosuppressive therapy), whereas ≥ 10 mm is considered positive in moderate-risk individuals. For people at low risk for TB and with high risk of exposure to non-tuberculous mycobacteria (NTM; for whom tuberculin testing is not generally indicated), ≥ 15 mm of induration is considered positive.

Recently, interferon gamma release assays (IGRA – Quantiferon) have been introduced and incorporated into TB screening (11). These tests offer more specific and accurate interpretations for populations in which a large proportion of the population has been vaccinated with BCG, as IGRAs have a higher specificity for *Mycobacterium tuberculosis* than do PPD-based tests.

If patients with LTBI have normal chest radiographs and no symptoms or physical findings consistent with TB, treatment of LTBI is indicated. In patients with latent TB, treatment with isoniazid (INH) for at least 4 weeks prior to the start of biologic treatment and, optimally, for a total duration of 9 months is mandatory to minimize the risk of reactivation. Rifampin for 4 to 6 months is an acceptable alternative. However, rifampin therapy should be the exception and reserved for those individuals who cannot tolerate INH or for those exposed to cases with resistance to INH (10).

Treatment with biologics should be deferred in patients with active TB. If TB is suspected, chest X rays and sputum AFB stain and culture must be repeated immediately to exclude reactivation or rule out new infection. Since extra-pulmonary TB is more frequent in patients treated with biologic agents, chest radiographs alone may not be sufficient to exclude TB.

Annual PPD or IGRA-Quantiferon tests could be an effective method to monitor and discover asymptomatic new infection in high risk groups if the original results were negative (10).

Screening for hepatitis B and C

To exclude hepatitis B virus (HBV) infection, it is not sufficient to only measure antibodies to hepatitis B surface antigen (anti-HBs); antibodies to hepatitis B core antigen (anti-HBc) should be measured as well (13,14). Risk of developing severe hepatitis due to reactivation of HBV infection or to “cured” past HBV during treatment with biologic agents cannot be excluded. Case reports in psoriatic patients treated with TNF-alpha inhibitors (etanercept and adalimumab) showed that in exceptional cases (no detectable virus or a very-low viral load as determined by polymerase chain reaction [PCR] methods), treatment with etanercept and adalimumab could be considered in patients with HBV infection (15). Close monitoring of patients should include not only liver enzymes but also viral load/PCR measurements. Interdisciplinary management with a gastroenterologist is mandatory to assure

treatment success and avoid serious adverse events. If suggested by a gastroenterologist, antiviral treatment should be initiated before starting a biological therapy.

There is no clear consensus regarding management of patients with hepatitis C virus (HCV). If biologic treatment must be administered, sufficient follow-up should be performed. However, the risk of developing severe hepatitis is not as critical for patients with HCV as for those with HBV. If the HCV-infected patient has already been successfully treated with an antiviral therapy, the risk seems to be even lower (16). There are several published reports of successful treatment of HCV-infected psoriatic patients with adalimumab and etanercept (15).

Laboratory assessments

We suggest usage of slightly modified laboratory assessments as recommended by van Lümig et al. (17) before starting treatment with biologic agents (Table 2):

Recently published German guidelines state that routine analysis should be performed every month during the induction phase of biologic therapy and then every 3–6 months, or according to the actual symptoms and individual situation of patients (4). These recommendations are also suitable for daily practice in KSA.

Vaccinations

Routine vaccinations (tetanus, diphtheria, pertussis and inactivated influenza) should be performed at baseline. However, vaccinations performed during treatment with biologics, also offer sufficient protection. Influenza vaccination is recommended annually in patients receiving biologic therapy (18).

Even though there are no reports of adverse consequences, the use of live vaccines (e.g. measles, yellow fever, poliomyelitis live vaccine, TBC-BCG) must be avoided during treatment with a biologic since the possibility of infection with the vaccination agent cannot be ruled out (18).

Infections

Attention should be paid to any suspected infection with bacteria, fungi, protozoa, or viruses and appropriate examinations should be performed. The treating physician must be vigilant to avoid any complication, especially if pyrexia, cough, and dyspnea occur. 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 (4–6).

Table 2. Laboratory assessments prior to initiation of a biologic treatment (modified van Lümig et al. (17)).

Chemistry	Hematology	Additional
Creatinine	Hemoglobin	Antinuclear antibodies
C-reactive protein (CRP)	Hematocrit	Hepatitis B/C serology
Direct bilirubin	White blood cell count	Serum pregnancy test
Total bilirubin	White blood cell differentiation	HIV
Alkaline phosphatase (ALP)	Platelet count	
Alanine transaminase (ALT)		
γ -Glutamyl transferase (GGT)		
Cholesterol		
Triglycerides		
Urinalysis		

Table 3. Biologic agents available for the treatment of psoriasis in Saudi Arabia.

	Etanercept	Adalimumab	Infliximab	Ustekinumab
Action mechanism	Fully human soluble TNF receptor	Human monoclonal antibody to TNF	Chimeric monoclonal antibody to TNF	Human monoclonal antibody to IL 12/23
Property	Fusion protein receptor with Fc region of 100% human IgG1	100% human recombinant IgG1 monoclonal antibody	Chimeric recombinant IgG1 monoclonal antibody (15% mouse 75% human)	100% human recombinant IgG1 monoclonal antibody
Half-life	<3 days	14 days	8–9.5 days	3 weeks
Status of approval in Saudi Arabia	Psoriasis and PsA	Psoriasis and PsA	Psoriasis and PsA	Psoriasis
Frequency	Weekly	Every 2 weeks	Every 8 weeks	Every 12 weeks
Delivery me	S.C.	S.C.	I.V.	S.C.

Biologic agents available for psoriasis in Saudi Arabia

Table 3 lists biologic agents currently available in KSA for the treatment of psoriasis (19–22). These agents are described in more detail in the following sections.

Adalimumab

Adalimumab has shown excellent effectiveness in patients with psoriasis; 71–80% of patients with moderate to severe psoriasis who are treated with adalimumab (initial dose of 80 mg given subcutaneously, followed by 40 mg every other week) achieve at least a 75% improvement in PASI (PASI 75) after 12–16 weeks (23–27).

During the induction phase, adalimumab is one of the most highly effective medications for the treatment of psoriasis vulgaris. Adalimumab is also suitable for long-term therapy (28).

In patients with concomitant psoriatic arthritis, administration of a TNF- α antagonist is especially useful.

Given the vast numbers of patients who have been treated with adalimumab (including diseases other than psoriasis), the risk of adverse effects is readily evaluated (29). However, as for all TNF inhibitors, the risk of serious infection requires careful assessment of the indications for therapy, as well as education and monitoring of treated patients.

Preferred combination: MTX (low dosage <10 mg/week)

Etanercept

In patients treated with etanercept at the preferred dosage regimen for therapy initiation in psoriasis (2 \times 50 mg given subcutaneously every week for 12 weeks), about 50% of patients achieve PASI 75 (30–33). With lower doses (2 \times 25 mg or 1 \times 50 mg given subcutaneously once a week), about 35–38% achieve a PASI 75 after 12 weeks. The maximum efficacy of etanercept is not reached during the 12-week induction phase. Etanercept is suitable for long-term use. Based on the data from available studies, an increase in effectiveness in long-term therapy of psoriasis vulgaris may be expected in some patients (34,35).

Preferred combination: MTX (10–15 mg/week) or acitretin may have synergistic effects

Infliximab

After 10 weeks of infliximab therapy (5 mg/kg of body weight every 8 weeks after loading doses in weeks 0, 4, and 6), 75–80% of patients with moderate to severe psoriasis achieve PASI 75 (36,37). Infliximab is also suitable for long-term therapy. Based on data from available studies, the efficacy of long-term therapy may diminish in some psoriasis patients after 24 weeks of treatment (38). There are also indications that infliximab may be

suitable for the treatment of severe, rare forms of psoriasis (4). Several safety aspects must be taken into consideration for the use of infliximab, the most common of which are infusion reactions and the risk of serious infection. These safety issues require a careful assessment of the indications for infliximab use and thorough education and monitoring of the patient. Given the vast number of patients who have been treated with infliximab (for other diseases as well), the risk of adverse effects is readily assessed. For the physician, the effort involved in treatment is increased by the need for infusion management. Therapy should be given continuously every eight weeks in order to prevent more frequent infusion reactions that can occur with episodic administration.

Combination therapy with infliximab and MTX may help prevent the formation of antibodies.

Ustekinumab

After 12 weeks of ustekinumab treatment (45 mg subcutaneously in weeks 0 and 4 and then every 12 weeks), 67% of patients had at least a 75% improvement in PASI score (39–41).

During the induction phase, ustekinumab is highly effective against psoriasis vulgaris. In some patients, the maximum effectiveness of the drug is not reached until week 24 of treatment. Ustekinumab is suitable for long-term therapy. At present, there are data from a few thousand patients. Based on these data, there is no indication of an increased risk of infection (42). For an assessment of long-term safety, larger patient samples are needed. The risk of major adverse cardiac events (MACE) could be of particular relevance. Since the publication of unexpected data with a similar compound, briakinumab, an IL12/IL23 antibody that was withdrawn from development due to an increased risk of MACE in the first 3 months of treatment compared with placebo, there is an unanswered question if an increased risk of MACE could be a class effect for antibodies that target IL12/IL23 (43,44). Recently published studies, however, show no statistically significant effect of ustekinumab on MACE risk, but this could be due to the fact that these clinical studies did not have enough statistical power to detect this particular side effect. Other authors postulate that the increased risk for cardiovascular side effects may be dose-dependent; the higher dosage group (90 mg) in ustekinumab trials had a higher prevalence of MACE compared with placebo and the 45 mg treatment group (43). In addition, patients with more than two comorbidities seem to be at higher risk of MACE (45). It seems, however, that any increased risks may be limited to the induction treatment period (first 3–4 months), as they are not observed in long-term studies. Increased vigilance and post-marketing surveillance for cardiovascular events is recommended when anti-IL12/IL23 biologic agents are used.

Recommendations for the treatment of psoriasis with biologic agents

There are no established criteria for selecting specific biologic agents for psoriasis treatment. In the European psoriasis guidelines, therapeutic recommendations for induction therapy are based on the proportion of patients achieving a PASI 75 improvement after a period of 12–16 weeks of treatment (5).

Choice of agent based on type of psoriasis

The British Association of Dermatologists (BAD) guidelines for psoriasis suggest that for patients with chronic plaque psoriasis, etanercept and adalimumab may be considered as first choice. For patients requiring rapid disease control, adalimumab or infliximab may be considered as first choice. Due to lack of patient-years exposure, ustekinumab should be reserved for use as a second-line biologic agent when TNF therapy has failed or cannot be used.

Although there are no controlled trials, in life-threatening conditions such as erythrodermic psoriasis or generalized pustular form of psoriasis, biologics may be considered the treatment of choice. Biologics with a rapid onset of action like infliximab or adalimumab may be preferred in these circumstances. Table 4 shows therapeutic recommendations by disease site and phenotype based on Saudi dermatologist expert consensus.

Transitioning from systemic agents

When transitioning from conventional systemic therapy to biologic therapy for safety reasons, such as an adverse event, a treatment-free interval is not mandatory but may be necessary until the safety parameter has normalized or stabilized. When transitioning due to lack of efficacy, transitioning directly or with an overlap period can be considered (46).

Management of inadequate response

If a targeted response (PASI > 75) is still not achieved after an appropriate period of therapy with a biologic agent, the clinician should:

Optimize the current therapy (e.g. increase the dosage of the conventional systemic therapy; increase the dose or decrease the treatment interval of the biologics).

Consider switching to another biological drug.

Combination strategies with conventional treatments can be considered.

Table 4. Therapeutic recommendations based on disease site or phenotype according to expert consensus and literature review (23–42).

Psoriasis (localization or type)	Adalimumab	Etanercept	Infliximab	Ustekinumab
Nail	**	*	***	**
Scalp	***	***	***	**
Palmoplantar	*	*	*	*
Genital/intertriginous	**	*	**	**
Pustular (localized)	**	–	**	*
Pustular (generalized)	***	–	***	–
Face	***	***	***	***
Erythrodermic	***	–	***	*
Gutatte	–	–	–	–
Juvenile (children)	**	***	–	–

Levels of recommendation range from –, not recommended; *, suggested; **, recommended; ***, strongly recommended.

Strategies for primary and secondary non-responders include: For adalimumab, an increase of the dosage from 40 mg every other week to 40 mg per week.

For etanercept, an increase of the dosage from 50 mg per week to 2 × 50 mg per week.

For ustekinumab, with primary partial responders, the dose can be increased from 45 to 90 mg with 12-week dosing intervals. If this is unsuccessful, the dose can be further increased to 90 mg at 8-week intervals.

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.

Combination therapy with non-biologic systemic agents

Conventional systemic therapy with MTX or acitretin can be added to biologic monotherapy with the intention to improve efficacy, optimize the risk-benefit profile, reduce the risk of immunogenicity (with MTX), and enhance long-term disease management. The conventional systemic therapy should be added beginning with the lowest recommended dosage (e.g. 5–10 mg/week for MTX). The combined use of cyclosporine A and a biologic raises safety concerns and therefore is not commonly used in daily practice.

Transitioning between biologic agents

In cases where all efforts to keep the patient on the same biologic treatment have failed, a switch to another biologic is possible (46). Recent investigation showed that a switch between TNF inhibitors (e.g. from infliximab or etanercept to adalimumab) is possible, and patients still respond to the second biologic (47). However, the probability of response may decrease with frequent switches. Switching abruptly from one biologic to another should be avoided. Individual treatment optimization may require adding topical treatment or systemic treatment to a biologic. Combination therapy with biologics (TNF inhibitors) and MTX (5–15 mg/week) is widely used and generally preferred.

There are recently published recommendations regarding the transition from one biologic to another (46). The opinion of our group is that it is not practical to wait for 5 half-lives before initiating treatment with another biologic agent. We suggest the following for switching times between biologic agents:

Etanercept to another biologic: 2–3 days.

Adalimumab to another biologic: 2 weeks.

Infliximab to another biologic: 4 weeks.

Ustekinumab to another biologic: 8–12 weeks.

Data from a consensus meeting support our recommendations (46).

Maintenance biologic therapy

During successful maintenance with biologic monotherapy, a dosage reduction can be considered to limit drug exposure. However, long-term efficacy and safety data have only been generated for the approved dosage and there is a theoretical risk of decreased efficacy when using reduced dosages. In addition, there is some evidence to suggest that a lower dosage of a biologic drug may increase the risk of anti-drug antibody formation (48).

Decreasing the dosage of biologic therapy below the recommended range may be considered in patients on combination therapy (i.e. MTX plus TNF antagonists). With ustekinumab, increasing the injection intervals beyond 12 weeks does not appear to be a useful means of reducing drug exposure, but

theoretically the dose for a responding patient may be reduced from 90 mg to 45 mg.

Continuous biologic therapy, generally, results in greater improvements in efficacy over time compared with intermittent therapy. Stopping biologic therapy is not generally recommended. In patients with moderate-to-severe psoriasis, significant therapeutic breaks are difficult to achieve without risk of recurrence or an impact on efficacy following re-initiation of therapy (48). Another consideration is that the risk of antibody formation against biologic therapies 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. Biologic therapy should generally be administered using a continuous uninterrupted treatment regimen. However, after achieving a clinical response of clear or almost clear with good QoL for a prolonged period of time (e.g. a minimum of two years), the termination of biologic therapy can be considered with careful follow-up and the patient's approval (46,49).

If therapy has been withdrawn and restarted, an induction dosing schedule should be used for reintroduction of the biologic agent, with the possible exception of infliximab (because of the increased risk of infusion reactions).

Psoriatic arthritis

TNF inhibitors as well as ustekinumab are approved for the treatment of PsA. Ustekinumab, however, is less effective than TNF inhibitors (50). The dermatologist should consider ultrasound imaging to obtain an accurate assessment of suspicious joint findings.

Interdisciplinary individual treatment optimization with a rheumatologist is needed in patients with active arthritis to assure proper control of joint symptoms (9).

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Declaration of interest

The authors report no conflict of interest.

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