GUIDELINES

Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis

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Abstract

Psoriasis is a common disease, which has a considerable impact on the healthcare system. Therefore, appropriate use of therapeutic resources is very important. Management of psoriasis in daily clinical practice is highly variable because many issues are still debated and not definitely addressed by the evidence-based medicine. Moreover, the different availability and reimbursability of drugs in each country justifies national guidelines. Expert consensus can provide helpful guidelines for optimizing patient care. A total of 20 dermatologists from different areas of Italy and with large experience in the treatment of psoriasis agreed to participate in the guidelines expert panel who aimed to reach consensus on the factors influencing psoriasis severity, the indications for systemic treatments, the parameters to be considered in the choice of treatment, and the factors to be considered in the choice of biological treatment. The recommendations for the use, screening and monitoring of systemic therapies were based on the 2015 S3 European Dermatology Forum/European Academy of Dermatology and Venereology psoriasis guidelines. Recommendations on the treatment of psoriasis in special patient populations were also agreed. The final document was discussed in a meeting moderated by a facilitator with participation of the entire group and adopting a nominal group technique to reach consensus. A statement was regarded as consented when agreement was achieved by at least 75% of the voting experts according to the Delphi procedure.

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Conflicts of interest

In the last three years, Prof. F. Ayala has served as a speaker, consultant, advisory board member for Abbvie, Janssen, Leo Pharma, Lilly, MSD, Novartis and Pfizer. A. Chiricozzi is a consultant and/or speaker for AbbVie and Novartis. A. Costanzo has a honorary from Lilly Abbvie, Janssen, Pfizer, Celgene, Novartis. P. Dapavo has conflict of interest with the following: Novartis, AbbVie, Pfizer, Celgene, Lilly. C. de Simone been reimbursed by Abbvie, Janssen-Cilag, Pfizer, Celgene, Leopharma for international conference attendance. G. Girolomoni has conflict of interest with the following: AbbVie, Abiogen, Allmirall, Amgen, Bayer, Biogen, Boehringer Ingelheim, Celgene, Eli-Lilly, Galderma, Hospira, Janssen, Leo Pharma, Merck, MSD, Mundipharma, Novartis, Otsuka,

Pfizer, Pierre Fabre, Regeneron, Sandoz, Sanofi, Sun Pharma. P. Gisondi has conflict of interest with the following: AbbVie, Abiogen, Bayer, Celgene, Eli-Lilly, Janssen, Leo Pharma, Merck, MSD, Novartis, Otsuka, Pfizer, Pierre Fabre. L. Naldi served as a consultant for the following companies Novartis, Janssen Cilag, Abbvie, Amgen, Pfitzer, Menarini. A. Parodi has conflict of interest with the following: Novartis, Amgen, Pfizer, Janssen-Cilag, Lilly, Galderma, Celgene, LEO Pharma, Almirall, UCB. L. Stingeni has conflict of interest with the following: AbbVie, Eli-Lilly, Novartis.

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Introduction

Psoriasis is a common disease that may have a considerable impact on the healthcare system.[1] Therefore, appropriate use of therapeutic resources is very important. Management of psoriasis in daily clinical practice is highly variable because many issues in psoriasis are still debated and not definitely addressed by the evidence-based medicine. Expert consensus can provide helpful guidelines for optimizing patient care. The primary goal of these guidelines was to assist healthcare professionals in the choice of the optimal systemic treatment for their patients with psoriasis. In particular, we aimed to reach a national consensus on the factors influencing psoriasis severity, the indications for systemic treatments, the parameters to be considered in the choice of treatment, and the factors to be considered in the choice of biological treatment and in the recommendations for the use, screening and monitoring of systemic therapies available including secukinumab and apremilast which were not addressed by the last version of the European guidelines.[2] Recommendations on the treatment of psoriasis in special patient populations were also agreed. The need for national guidelines arises from the different availability and reimbursability of drugs in each country. These consensus-based guidelines contain statements that were developed to assist clinicians in the care of patients with moderate-to-severe psoriasis. The statements are based on the best available evidence and their development followed a prespecified, standardized process. Nevertheless, guidelines do not replace the clinicians' knowledge and skills, as guidelines never encompass therapy specifications for all medical decision-making situations, and deviations from the recommendations may be justified or inevitable in specific situations.

Methods

A detailed description of the methodology that we used can be found in the methods report as supplementary file. Briefly, the 2015 version of the S3 European Dermatology Forum/European Academy of Dermatology and Venereology psoriasis guidelines[2] represented the base for developing the Italian guidelines. These guidelines were developed to assist clinicians in the care of patients with moderate-to-severe chronic plaque psoriasis. In particular, the objective of the guideline was reaching a national consensus on the factors influencing psoriasis severity, the indications for systemic treatments, the overall parameters to be considered in the treatment choice, complementary medicine, lifestyle interventions, and the factors to be considered in the choice of biological treatment and in the recommendations for the use, screening and monitoring of systemic therapies approved including acitretin, cyclosporine, methotrexate, apremilast, phototherapy, adalimumab, etanercept, infliximab, secukinumab and ustekinumab. Fumaric acid esters were not included because they are not currently licensed in Italy. Combination therapies (e.g. methotrexate associated with anti-TNF-α inhibitors) were not included. Treatments approved only for psoriatic arthritis, but not for chronic plaque psoriasis, were not considered as well. The consensus statements are based on the best available evidence and their development followed a standardized process. A systematic search of the literature was

Table 1 Factors influencing psoriasis severity

- Body surface area involvement
- Erythema, infiltration and scaling of skin lesions
- Localization of lesions in sensitive area (e.g. face, nails, genitalia, palmoplantar)
- Skin symptoms (e.g. pruritus, pain)
- Impact on quality of life
- No response to topical and/or systemic treatments
- Disease activity (i.e. continuous emergence of new lesions)
- Frequency and severity of relapses after treatment withdrawal
- Long disease history
- Comorbidities

Table 2 Treatment goals in moderate-to-severe psoriasis

- Treatment goals should be agreed with the patient based on informed discussion
- PASI75
- PASI90
- There is a need to define the minimum absolute PASI (i.e. <1 or 2)
- DLQI < 5

Table 3 Indications for systemic treatments

- PASI ≥ 10
- PASI < 10 but with involvement of sensitive area such as hands, palmoplantar, genital, scalp, face, and nails
- BSA ≥ 5% resistant to or in patients reluctant to topical therapy
- BSA < 5% with disseminated lesions
- Subjective perception of disease severity (e.g. DLQI ≥ 10)
- Active psoriatic arthritis
- Psoriasis associated with severe symptoms (e.g. itch, burning) that are not controlled by topical therapies

conducted from January 2014 to June 2016 to update the European guidelines using the Cochrane Library, MEDLINE and EMBASE databases. A total of 20 dermatologists from different areas of Italy and with large experience in the treatment of psoriasis agreed to participate in the guidelines expert panel. A draft of the guidelines including the results of the systematic literature review was initially circulated by emails to the expert panel. A Delphi technique was adopted to reach consensus on specific items.[3–7] The Delphi process consisted of one or two (if needed) rounds. Each statement was regarded as consented when agreement was achieved by at least 75% of the voting experts. The strength of recommendation was not expressed.

Results

All 20 members of the expert panel responded to 100% of the items in one or two (if needed) Delphi rounds. Consistent agreement was achieved for all 103 items, as reported in supplementary material. Factors influencing psoriasis severity are reported in Table 1; treatment goals are reported in Table 2; indications for systemic treatments are reported in Table 3; recommendations for screening and monitoring of small-molecule drugs including conventional as well as phototherapy and biologics for the treatments of chronic plaque psoriasis are reported in Tables 4 and 5; overall parameters to be considered in the choice of treatment of psoriasis are reported in Table 6; and factors to be considered in the choice of biological treatments are reported in Table 7.

The concept of psoriasis severity

The concept of severity relates to many different aspects of psoriasis including the extent of disease, location of lesions, degree of inflammation, responsiveness to treatment and impact on quality of life. No internationally validated categories of severity are recognized. Most of the definitions of disease severity and treatment success have been developed for use in clinical trials, while they are rarely used in daily clinical practice. The severity of chronic plaque psoriasis is generally assessed according to several tools including the PASI, the body surface area (BSA) and the Physician Global Assessment (PGA).[8] The multifaceted nature of the psoriasis burden drives the need for a specific focus on health-related quality of life (HRQoL) and patient-reported outcome (PRO) measures.[9] Patient's quality of life is commonly assessed by questionnaires including the Dermatology Life Quality Index (DLQI) and the Short Form (SF-36) Health Survey. According to the European S3 Guidelines on the systemic treatment of psoriasis vulgaris, moderate-to-severe disease is defined as a PASI score >10.[10] In line with this definition, the 'Rule of Tens' defines a patient's disease as severe if any one of the following criteria is met including PASI ≥ 10 or DLQI ≥ 10 or BSA ≥ 10%.[11] The European Medicines Agency (EMA) adopts a more stringent definition of psoriasis severity classes.[12] Finally, a recent European consensus agreed in using a more flexible categorization which takes into account also the patient perspective.[13] In particular, patients presenting with disease manifestations not adequately controlled by topical therapy and with significant impairment in the quality of life may require systemic treatments. These manifestations include the involvement of visible areas (i.e. face, scalps and hands), genitals, palms and/or soles, nails, or the presence of intense pruritus. Consequently, in daily practice, a systemic therapy could be indicated even if PASI or BSA is lower than 10. Consensus statements involving also patients' association have indicated PASI or BSA higher than 5 as the threshold for prescribing systemic treatments.[14,15] We reached consensus in identifying the most important factors influencing psoriasis severity that are listed in Table 1.

Treatments goals

Treatment goals have been agreed to help dermatologists in deciding when and how to progress along treatment algorithms, ultimately improving patient care. Treatment goals are based on a selected list of outcome measures that take into account not only the severity of skin symptoms but also the impact of disease on the quality of life. Change in severity is indicated in terms of percentage PASI change from baseline score. PASI75 response is a dynamic parameter that indicates the percentage of patients who have achieved at least a 75% improvement in their baseline PASI score during treatment. A PASI75 response is now widely accepted as a clinically meaningful improvement, and it also serves as the central evidence-based efficacy parameter in European guidelines.[2,10,13] However, the ultimate goal of therapy is the complete or almost complete clearing and an improvement of 90% or greater (PASI90 response) is currently considered as the most relevant treatment outcome, especially in patients with severe disease.[16,17] We discussed the opportunity of achieving a minimal absolute PASI value (i.e. minimal disease activity) as a better benchmark. A residual PASI of 1–2 may be considered; however, the supporting evidence is scarce. Not achieving a PASI50 is considered a treatment failure.[13] In between PASI50 and PASI75 but reaching a DLQI equal or below 5 is considered a partial treatment success. The time point to assess treatment goals is at the end of induction therapy (i.e. weeks 12–16). During maintenance treatment, an assessment of treatment goals

Table 4 Small-molecule drugs, including conventional and phototherapy for the treatments of chronic plaque psoriasis[20–29]

	Other label indications	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
Acitretin									
Chronic plaque psoriasis	Lichen planus; palmoplantar keratoderma; Darier's disease; Ichthyosis	Oral; 0.3–0.8 mg/kg daily with a maximum dose of 1 mg/kg daily	Depends on improvement and tolerance in the individual patient	PASI75 in 20–40% of patients at week 16. PASI90 in 5–10% at week 16	Vitamin A toxicity (xerosis, cheilitis, conjunctival inflammation, hair loss). Photosensitivity and hyperlipidaemia	Pregnancy or breastfeeding, severe renal or hepatic dysfunction	Statins, tetracyclines, methotrexate, antifungal imidazoles, phenytoin, vitamin A	Full blood count, liver enzymes, creatinine, lipids, pregnancy test	Full blood count, liver enzymes, creatinine, lipids, pregnancy test
Cyclosporine									
Chronic plaque psoriasis	Atopic dermatitis; uveitis; rheumatoid arthritis; nephrotic syndrome; transplant rejection	Oral; 2.5–5 mg/kg daily	It is generally used as a short-term therapy for 3–6 months. Courses can be repeated at intervals. Maximum cumulative duration of therapy is 2 years	PASI75 in 50–80% of patients; PASI90 in 30–40% of patients, after 8–12 weeks (3–5 mg/kg daily)	Renal failure, hypertension, hypertrichosis, gingival hyperplasia, malaise, paraesthesia, hypomagnesaemia; increased risk of lymphoproliferative disease in transplant patients. Increased risk of squamous cell carcinoma in patients with psoriasis after prolonged photochemotherapy	Impaired renal function; uncontrolled hypertension; severe dyslipidaemia; uncontrolled infections; malignant disease (current or previous, in particular haematologic diseases or cutaneous malignancies, with the exception of basal cell carcinoma)	Live vaccines, statins, aminoglycoside antibiotics, macrolide antibiotics except for azithromycin; antifungal imidazoles, hydantoin	Creatinine, uric acid, liver enzymes, potassium, urinalysis, full blood count, lipids, pregnancy test	Creatinine, uric acid, liver enzymes, potassium, urinalysis, full blood count, lipids, pregnancy test
Methotrexate									
Chronic plaque psoriasis	Psoriatic arthritis; rheumatoid arthritis; juvenile arthritis; Crohn's disease	Oral, s.c. or i.m. once weekly. Initial dose 7.5–15 mg weekly; maintenance dose 7.5–20 mg weekly. Folic or folinic acid limits side-effects. At least once 24 h after methotrexate	May be given for as long as it remains effective and well tolerated	PASI75 in 36–41% of patients at 16 weeks. PASI90 in 14–19% of patients at week 16	Nausea, malaise, hair loss, elevated liver enzymes, oral ulcers, bone marrow depression, renal and liver toxicity	Severe infections, severe liver or kidney disorders, bone marrow dysfunction, pregnancy or breastfeeding, impaired lung function or pulmonary fibrosis, alcohol abuse, immunodeficiency, acute peptic ulcer. Fatherhood or motherhood desire	Live vaccines, sulphonamides, ketoprofen, acitretin, tetracyclines	Blood count, liver enzymes, serum creatinine, pregnancy test, HBV/HCV	Blood count, liver enzymes, serum creatinine, pregnancy test. Liver elastography in selected patients

Table 4 *Continued*

	Other label indications	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
Apremilast									
Moderate-to-severe plaque psoriasis in adult patients who failed to respond to, or who have contraindications to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA	Psoriatic arthritis	Oral; 30 mg twice daily, morning and evening without regard to meals. Initial 5-day titration period	Approved for continuous treatment regimen	PASI75 in 28.8–33.1% and PASI90 in 8.8–9.8% of patients at week 16	Transient nausea and diarrhoea. Upper respiratory tract infections. Uncommon suicidal ideation and behaviour.	Pregnancy or breastfeeding. Active infections	None	None	None
Phototherapy									
Moderate-to-severe plaque psoriasis in adult or adolescent (>12 years) patients	Many	Narrowband UVB (nb UVB) or PUVA. Individual dose depending on skin type	20–30 treatments for induction. Maintenance for few months	PASI75 in >75% of patients after 6 weeks (PUVA) and PASI 90 29–38% (UVB-nb)	Erythema, itching, blistering, increased risk of cutaneous malignancies. Nausea (PUVA)	Photodermatoses/ photosensitive diseases, cutaneous malignancies. Concomitant cyclosporine. Pregnancy or breastfeeding only for PUVA	Drugs causing phototoxicity or photoallergy	Antinuclear antibodies. Ocular examination (PUVA)	Liver enzymes (PUVA)

s.c., subcutaneous; i.m., intramuscular.

Table 5 Biological drugs for the treatment of chronic plaque psoriasis[24,25,30–35]

Indications	Other label indications	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
Adalimumab									
Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy Severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies	Psoriatic arthritis; rheumatoid arthritis; juvenile arthritis; spondyloarthritis; ankylosing spondylitis; Crohn's disease (including children >6 years); ulcerative colitis; suppurative hidradenitis	Loading dose at is 80 mg s.c., followed by 40 mg every other week, beginning 1 week after the induction dose. Patients with inadequate response beyond week 16 may benefit from an increase in dosing frequency to 40 mg every week	Adalimumab is approved for continuous treatment regimen	PASI75 in 71–80% and PASI90 in 45–52% of patients at week 16	Injection-site reaction; upper respiratory tract infections. Rare cases of drug-induced lupus erythematosus, demyelinating disease, opportunistic or serious infections including tuberculosis and malignancies including lymphoma	Pregnancy/ breastfeeding, active infections, active tuberculosis, active chronic hepatitis B, demyelinating disease, congestive heart failure (NYHA grade III or IV); cancer, excluding non-melanoma skin cancer, within 5 years	Live vaccines	Full blood count, liver enzymes, creatinine, lipids, pregnancy test (urine), HBV/HCV, HIV, TB screening	Liver enzymes, lipids. TB monitoring
Etanercept									
Adults and children >6 years with moderate-to-severe plaque psoriasis who failed to respond to, or who have a contraindications to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA	Psoriatic arthritis; rheumatoid arthritis; juvenile arthritis; spondyloarthritis; ankylosing spondylitis	2 × 50 mg weekly from week 0 to 12 (induction phase) and then 50 mg weekly thereafter (maintenance phase) by s.c. injection	It is the only biologic approved for either intermittent or continuous treatment regimen	PASI75 in 38–49% and PASI90 in 11–21% after 12 weeks (2 × 50 mg weekly)	Injection-site reactions; upper respiratory tract infections. Rare cases of drug-induced lupus erythematosus, demyelinating disease, serious infections including tuberculosis and malignancies	Pregnancy/ breastfeeding, active infections, active tuberculosis, active chronic hepatitis B, demyelinating disease, congestive heart failure (NYHA grade III or IV); cancer, excluding non-melanoma skin cancer, within 5 years	Live vaccines	Full blood count, liver enzymes, creatinine, lipids, pregnancy test (urine), HBV/HCV, HIV, TB screening	Liver enzymes, lipids. TB monitoring

Table 5 *Continued*

Indications	Other label indications	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
Infliximab									
Moderate-to-severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA	Psoriatic arthritis; rheumatoid arthritis; juvenile arthritis; ankylosing spondylitis; Crohn's disease and ulcerative colitis (including children >6 years)	5 mg/kg bodyweight at weeks 0, 2 and 6 (induction phase) and then every 8 weeks thereafter (maintenance phase)	It is approved for continuous treatment regimen	PASI75 in 80.4% and PASI90 in and 57.1% of patients at week 10	Infusion reaction, flushing, pruritus; upper respiratory tract infections. Rare cases of drug-induced lupus erythematosus, demyelinating disease, opportunistic or serious infections including tuberculosis and malignancies (lymphoma)	Pregnancy/ breastfeeding, active infections, active tuberculosis, active chronic hepatitis B, demyelinating disease, congestive heart failure (NYHA grade III or IV); cancer, excluding non-melanoma skin cancer, within 5 years	Live vaccines	Full blood count, liver enzymes, serum creatinine, lipids, pregnancy test (urine), HBV/HCV, HIV, TB screening	Liver enzymes, lipids. TB monitoring
Ustekinumab									
Moderate-to-severe plaque psoriasis in adults and children above the age of 12 years who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate or PUVA	Psoriatic arthritis	45 mg for patients with a bodyweight of ≤100 kg and 90 mg for those >100 kg at weeks 0 and 4 (induction), then every 12 weeks	It is approved for continuous treatment regimen	PASI75 and PASI90 in 67% and 42% of patients receiving 45 mg; 66–76% and 37–51% receiving 90 mg at week 12, respectively	Injection-site reactions; upper respiratory tract infections, nasopharyngitis, cellulitis, herpes zoster. Very rare exfoliative dermatitis	Pregnancy/ breastfeeding, active infections including active tuberculosis, active chronic hepatitis B and C, HIV; cancer, excluding non-melanoma skin cancer, within 5 years	Live vaccine	Full blood count, liver enzymes, creatinine, pregnancy test (urine), HBV/HCV, HIV, TB screening	TB monitoring

Table 5 *Continued*

Indications	Other indications label	Dosage	Duration	Efficacy	Safety	Contraindications	Important drug interactions	Drug screening	Drug monitoring
Secukinumab									
Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy	Psoriatic arthritis; ankylosing spondylitis	300 (given as two s.c. injections of 150 mg) with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4	Secukinumab is approved for continuous treatment regimen	PASI75 and PASI90 response rate in 75.9–86.7% and 55–60.3% of patients at week 12, respectively	The most common adverse events include upper respiratory tract infections. Candida infections and mild-to-moderate neutropenia are rare but possible events	Active infection (e.g. active tuberculosis; viral hepatitis B and C). Caution should be exercised in patients with Crohn's disease. Cancer, excluding non-melanoma skin cancer, within 5 years	Live vaccines	Full blood count	Full blood count

s.c., subcutaneous; TB, tuberculosis.

should be made in intervals given by the safety monitoring recommendations (usually every 8–12 weeks). In the case that the goal is not met, there are several strategies that may increase efficacy such as increasing the dose, reducing the time interval between administrations or adding another drug (combination therapy). However, this may be an off-label drug use, because such variations are not backed up by the summary of product characteristics. Changing the drug is indicated when adjustments are ineffective or inappropriate.[18,19]

When is a systemic treatment indicated?

Treatments of psoriasis are numerous and they can be topical, systemic or phototherapy. A major issue with topical therapy is adherence, which may reduce dramatically in the long term, rendering treatments ineffective. Topical therapy alone is indicated in mild psoriasis. For patients with moderate-to-severe psoriasis, the topical agents remain useful when combined with systemic treatments. We reached consensus in identifying all the conditions requiring systemic treatment, as reported in Table 2. Systemic treatments for chronic plaque psoriasis approved in Italy at the moment of writing this manuscript include either phototherapy, narrowband ultraviolet [UV] B light (UVB-nb), or photochemotherapy (i.e. psoralen plus UVA light), and systemic agents such as cyclosporine, methotrexate, acitretin, apremilast, TNF-α blockers (etanercept, infliximab, adalimumab), ustekinumab, secukinumab, and etanercept and infliximab biosimilars. Fumaric acid esters are not available in Italy yet. The schematic recommendations for the use, screening and monitoring of systemic therapies are reported in Tables 3 and 4. Drug monitoring could be adapted according to the specific patient's characteristics including comorbidities. Most of the recommendations are in line with the recent S3 European guidelines.[2]

Parameters to be considered in the choice of the treatment

Treatment decisions are based on the characteristics of the disease (e.g. severity, location, psoriatic arthritis), patient-related features (e.g. age, previous treatment failures) and the characteristics of the treatments (e.g. efficacy and safety issues) as reported in Table 5. Some considerations can be addressed in the choice of the biological drug including those reported in Table 6. There are a few biomarkers capable of predicting treatment outcome. In particular, body mass index predicts poor response and long-term efficacy to conventional and biological treatments.[36,37] Specific TNFAIP3 single nucleotide polymorphisms have been associated with a higher response rate to etanercept and adalimumab.[38] Similarly, IL-17A and IL-17F single nucleotide polymorphisms predict a higher response to ustekinumab, infliximab or adalimumab.[39] Finally, a faster and higher response to ustekinumab has been reported in HLA-Cw6-positive patients.[40]

Table 6 Parameters to be considered in the choice of treatment of psoriasis

Disease-related factors	Patient-related factors	Treatment-related factors
Disease severity	Age and sex	Short- and long-term effectiveness
Active disease (e.g. onset of new lesions)	Treatment history	Safety
Skin areas involved	Impact on quality of life	Tolerability
Frequency of relapses	Likelihood of adherence	Flexibility
Pruritus or other symptoms	Patient expectations	Practicability
Psoriatic arthritis	Desire for remission	Impact on lifestyle
Cardiometabolic disorders	Fear of side-effects	Cost

Table 7 Factors to be considered in the choice of biological treatments

- Comorbidities which may contraindicate or raise a caution on the use of selected biologics, e.g. latent tuberculosis, severe heart failure, personal history or strong family history of demyelinating disease or alopecia areata for TNF-α blockers, and Crohn's disease for IL-17a inhibitors
- Presence of concomitant diseases which may benefit of the same treatment, e.g. psoriatic arthritis, Crohn's disease, ulcerative colitis, pyoderma gangrenosum, uveitis, Behcet's disease and hidradenitis suppurativa for anti-TNF-α monoclonal antibodies.
- Disease history, previous treatments, rapid relapse after treatment withdrawal, intermittent or continuous disease activity
- Disease severity, activity and stability
- Request for a flexible treatment (e.g. a treatment which can be more easily interrupted and restarted)
- Need for a rapid response

Long-term management

Psoriasis is a lifelong disease with a chronic relapsing course, and most patients require a long-term management. Long-term management is not well addressed in clinical trials, as these include selected patient populations followed in a special medical setting. Therefore, registry data become very important for the purpose of evaluating long-term therapies. The retention rate of conventional systemic treatments is limited mostly by poor tolerability and metabolic adverse events.[41] In contrast, the retention rate of biological agents is much longer as the safety profile is more favourable, with the main reason for discontinuation being secondary inefficacy.[42,43] Biological therapies are generally safer than conventional treatments. The only major concern emerging from registries or long-term studies is an increased risk of infections including upper respiratory infections, bacterial skin infections and herpes zoster with TNF-α inhibitors, particularly infliximab.[44] In contrast, ustekinumab appears to be associated with lower incidence of infections.[45] When patients lose an adequate response to biological drugs, the possible options include increasing the dose and/or shortening the dosing interval, combination therapy with a topical or another systemic treatment, or switching to a different drug.

Biosimilars

Patent's expiration of biologics, such as infliximab and etanercept, has stimulated several companies to produce biosimilars.[46] The EMA defines a biosimilar as a biological medicinal product, which is similar to a biological medicine that has already been authorized, the so-called reference medicinal product. The only advantage of biosimilars compared to originator molecules is the lower cost, which however may be very important for improving access to expensive biological agents. A biosimilar and its reference product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions. The EMA has established that the development of biosimilars must satisfy the so-called comparability exercise. The demonstration of biosimilarity is significantly different from generic drug approval, where only pharmacokinetic equivalence must be shown. Very extensive, non-clinical physiochemical and biological characterization is required to address structural, functional and immunogenicity concerns, prior to efficacy and safety trials. In this context, the distinction between biosimilars and 'biomimics' – versions of monoclonal antibodies or fusion proteins available in countries where regulation is less strict – is of great importance. Biomimics are also known as 'biocopies', 'intended copies' or 'non-regulated biologics'.[47] The key question for biosimilars is indeed not whether differences exist compared with the reference product, but whether differences are clinically relevant. Both the EMA and the Food and Drug Administration require randomized controlled trials to establish clinical equivalence; however, rare adverse events and long-term efficacy and safety issues will be assessed only through postmarketing surveillance. Extrapolation of analytical and clinical data permits the approval of a biosimilar for a therapeutic indication in which it has not been clinically evaluated, but for which the reference agent is approved.[48] Separate clinical trials for biosimilars in different therapeutic indications would be desirable, but they will raise the cost of biosimilars. Therefore, postapproval registry would become very important for evaluating the efficacy and safety of biosimilars. Recently, the Italian Society of

Dermatology (SIDeMaST) and the Italian Society of Hospital-based Dermatologists (ADOI) have established a Web-based registry with the aim of collecting data on the efficacy and safety of biosimilars in patients with psoriasis and psoriatic arthritis (www.psobiosimilars.it). A direct consequence of the biosimilarity is the interchangeability, which means the possibility to switch among similar molecules, and extrapolation, which means the use in all diseases for which the reference product is indicated.[49] Currently, there are limited data on switching to a biosimilar in terms of maintenance of response, immunogenicity or other safety issues, but data from registries can help answer these concerns. The decision of using either originator or biosimilar must be an exclusive decision of the prescribing physician. The interchangeability and substitution between molecules should be left to expert and informed clinicians. It is very important that nomenclature of biosimilars identifies exactly the molecule used. The international non-proprietary name plus the commercial name can better identify the molecule used, particularly for pharmacovigilance purpose. The point of view of patients' associations should also be carefully considered. Informing patients via therapeutic education programs is advisable, and this could be implemented with patient organization support. A consensus between clinicians, patients, payers and/or public health organizations is essential to carefully consider advantages and issues related to the use of biosimilars, from different point of views. However, as currently usual for the available biologics, the final clinical decisions should always be made on an individual basis, taking into account both the characteristics of the individual patient and the clinician's advice. At the moment of writing this manuscript, the biosimilars available in Italy include an infliximab biosimilar (CT-P13), which is commercialized by two companies (Remsima® by Mundipharma and Inflectra® by Hospira), and an etanercept biosimilar (Benepali® by Biogen).

Complementary medicine

A major reason of psoriasis undertreatment is the patient's fear of side-effects of drugs.[50] Therefore, many patients are looking for alternative treatments,[51] which may include thermal spring water balneotherapy, traditional Chinese medicine, herbal therapies, dietary supplements and climatotherapy. In Italy as well as in other European countries, patients with psoriasis commonly chose thermal spring balneotherapy because they perceived it as safe. Several studies have confirmed the anti-inflammatory properties of some thermal spring water *in vitro* models, and a limited number of clinical trials indicated moderate efficacy of balneotherapy alone or in association with UVB-nb phototherapy.[52,53] However, existing evidence is not sufficiently robust to draw firm conclusions.

Lifestyle interventions

Systematic reviews document the association between psoriasis severity and its response to treatment with smoking, overweight or obesity, and, less consistently, alcohol abuse.[54,55] In addition, a growing body of evidence associates psoriasis with depression and sleep disturbance.[56,57] In spite of these associations, limited data are available on the impact of lifestyle interventions on psoriasis outcome and prevention of disability.[58]

Clinical assessment In consideration of the above-mentioned associations, patients with moderate-to-severe psoriasis should have the following variables assessed at baseline and periodically afterwards, based on clinical judgement: blood pressure, body mass index, waist circumference, smoking status and average consumption of alcoholic beverage. In addition, it is advisable to monitor selected laboratory variables including serum lipids and fasting glucose. Finally, patients with psoriasis should be assessed regularly for anxiety, depression and sleep disturbance. These variables are incompletely captured by quality-of-life indexes.

Behavioural interventions Behavioural interventions are fully justified only when evidence supports their effectiveness. Changing behaviour is a complex task, and changes may not be stable over time. An important part in lifestyle interventions is played by patient-centred communication. Training on communicational procedures should be offered to dermatologists.[59]

Smoking cessation interventions Cigarette smoking is recognized as the single most important source of preventable mortality worldwide, and it plays a major role in cardiovascular morbidity and mortality. For cardiovascular conditions, the impact of quitting smoking in reducing risks is well documented. While smoking can affect psoriasis in a dose-dependent fashion, no data support the impact of smoking cessation on psoriasis improvement or response to treatment. In spite of these limitations, dermatologists should screen for tobacco use and offer advice on smoking cessation interventions to motivated patients with psoriatic disease.

Weight reduction interventions The impact of reducing weight in diabetes and cardiovascular disease is well documented. Some evidence exists from randomized trials that bodyweight reduction could ameliorate psoriasis and could increase response to systemic treatment.[60] Weight loss advice should be given by dermatologists to overweight or obese patients during the routine management of the disease. More structured interventions to change behaviour should be considered in high-risk patients with the help of a dietician. Bariatric surgery should not be discouraged in severely obese patients.

Interventions on psychiatric comorbidities Limited evidence from small randomized trials suggests the effectiveness of interdisciplinary care involving psychiatric support on the quality of life of patients with psoriasis.[61] Giving the bearing of psychiatric

comorbidities on quality of life and their impact on disease management, patients with psychological distress or symptoms of depression should be offered referral to a psychiatrist and psychological support.

Special patient populations

Systemic therapy of psoriasis in children Early-onset psoriasis, i.e. during infancy, childhood or adolescence, has a significant impact on the child's quality of life, and those young patients who cannot be managed with topical therapy should be considered for systemic treatment. Most current systemic treatments for childhood psoriasis are off-label, including methotrexate, cyclosporine, acitretin, infliximab, secukinumab and apremilast. In contrast, etanercept, adalimumab and ustekinumab have been approved for psoriasis vulgaris in children and adolescents.[62–64] Effectiveness and safety data of methotrexate, cyclosporine and acitretin in paediatric patients are derived mainly by case series.[65] In particular, methotrexate has been administered at doses between 0.2 and 0.4 mg/kg/week.[66] Few data exist about cyclosporine efficacy and safety in childhood and adolescence psoriasis. Recently, a retrospective analysis of a group of children and adolescents (n = 38, age < 17 years) with plaque psoriasis treated with cyclosporine at several Italian dermatology centres was conducted.[67] Median patient age was 12.3 years. Treatment duration ranged from 1 to 36 months. The median dose per day was 3.2 mg/kg (range 2–5 mg/kg). Fifteen patients (39.4%) achieved a complete clearance or a PASI75 response at week 16. Eight patients (21.05%) discontinued the treatment due to laboratory alterations or adverse events. Serious adverse events were not reported.[67] Existing studies concerning retinoids in the treatment of psoriasis in children include mainly case series. Even though most publications described few and tolerable adverse effects such as cheilitis and hair loss, more serious adverse effects have been reported, including significant bone changes.[68,69]

Systemic therapy of psoriasis in the elderly The continuous increase in the aged population and the chronic course of psoriasis make management of psoriasis in the elderly an important healthcare issue. People aged 65 years or over will account for a predicted 29.5% in Europe by 2060.[70] Any treatment approved for adults can be prescribed also in elderly patients. However, some considerations are needed. Elderly patients often suffer from multiple comorbidities, such as cardiovascular diseases, diabetes mellitus, hypertension, dyslipidaemia, liver disease, osteoporosis or chronic kidney disease. These conditions could contraindicate the use of certain treatments. Moreover, the multidrug regimens commonly used in the elderly expose the patient to the risk of potentially harmful drug interactions, particularly with cyclosporine or methotrexate. Another concern is linked to the deterioration in both innate and acquired immunity that occur in the elderly leading to a condition usually defined as 'immune-senescence'.[71] Immune-senescence may play a role in the greater risk of neoplasms and infectious diseases in elderly people and may impair the response to vaccination and defence against infection. In addition, there is scarcity of data in the literature regarding treatment of psoriasis in the elderly population.[72] Therefore, dermatologists tend to avoid systemic drugs in older patients for safety concerns and to prescribe only topical therapies, which can be inadequate. Acitretin could worsen the skin xerosis that is quite common in the elderly. Methotrexate should be used with caution as it may be eliminated more slowly in the elderly because of a reduced renal clearance.[72] Elderly patients may be more sensitive to cyclosporine adverse effects. The elderly population is generally excluded from randomized clinical trials. However, some studies have addressed the use of biologics in the elderly including adalimumab, ustekinumab and etanercept.[73–75] We agreed that for appropriately screened and monitored elderly patients who require a systemic treatment, all therapies can be safely used. Long-term prospective studies investigating the efficacy and safety profiles of systemic treatments in elderly patients with psoriasis are needed.

Pregnancy or patients wishing pregnancy in the near future

The treatment of psoriasis in pregnancy or in patients wishing pregnancy in the near future may be challenging. Psoriasis course during pregnancy may be highly variable. Likely due to hormonal effects, half of patients improve during pregnancy, while 23% experience worsening.[76] In a study on 162 pregnancies, psoriasis itself was associated with prematurity/low birthweight after correcting for confounding factors.[77] When planning pregnancy in the near future, the primary consideration is to minimize risk for the patient and the fetus. Mid-potency topical corticosteroids for limited periods are the preferred topical therapy. Long-term use of potent or very potent steroids during pregnancy may be associated with low birthweight.[78] Tazarotene is teratogen; therefore, it is contraindicated in pregnancy. Salicylic acid, coal tar and calcipotriol are best avoided. The calcineurin inhibitor tacrolimus may be used in sensitive areas such as face and skin folds where no other alternative exists, as systemic adsorption is very low.[79] UVB-nb phototherapy is considered safe and useful to treat pregnant patients. Phototherapy degrades folic acid, lowering its serum levels. Deficit of folic acid in prepregnancy and the first trimester could contribute to neural tube defects. Therefore, folic acid supplementation during phototherapy and monitoring its levels are strongly recommended.[80] Patients should also be informed that phototherapy may induce or worsen melasma. Psoralens are a known mutagen and PUVA therapy is markedly associated with low birthweight and possibly premature fetal abnormalities; therefore, it is contraindicated during pregnancy.

Acitretin is teratogen and it is pregnancy category X; i.e., it is contraindicated during pregnancy. Fertile female patients must be informed of the need to avoid conception for at least 2 years after withdrawal. Methotrexate is an abortifacient, teratogen and mutagen agent; therefore, it is pregnancy category X. Doses of 10 mg per week during the critical 6–8 weeks after conception are associated with the aminopterin syndrome.[81] Methotrexate should be withdrawn 3 months before conception in a planned pregnancy, but in unplanned pregnancy it must be withdrawn immediately and the patient referred for obstetric counselling. Male contraception is also recommended in patients receiving methotrexate for at least 3 months before conception. Cyclosporine is pregnancy category B, and it has been proved not to be teratogen with successful pregnancy outcomes in transplanted patients. However, its use in pregnancy could be associated with increased risks of hypertension, low birthweight, intrauterine growth retardation and premature delivery. Therefore, it is best avoided in pregnancy.

Biologics are pregnancy category B as they are not abortifacient, teratogen or embryotoxic. Data from meta-analyses and systematic reviews of cohort and observational studies on patients with inflammatory bowel diseases or inflammatory arthritis diseases suggest that use of anti-TNF-α therapy during pregnancy is not associated with an increased risk of unfavourable pregnancy outcomes.[82,83] These studies however are generally confounded by disease activity, concomitant medications (especially immunosuppressant therapies), comorbidities and other maternal characteristics. Physiologically, immunoglobulins G are actively transported to the fetus as part of the priming of the fetal immune protection from week 16 to the third trimester. Thus, infliximab and adalimumab are actively transported across the placenta. The immunosuppressive neonatal hazard of biologics may be avoided by stopping therapy with infliximab and adalimumab in the last trimester. Live vaccinations are not recommended within the first 6 months of life in the offspring of women who were on anti-TNF-α therapy during pregnancy. Due to a shorter half-life and less placental transfer, etanercept may be safer if biological therapy is required during pregnancy. Five reports of pregnancy during ustekinumab treatment have been reported, with one resulting in miscarriage.[84] No data exist regarding ustekinumab in breast milk; therefore, ustekinumab should be avoided during breastfeeding.

Although current evidence does not indicate an increased risk of congenital malformations or unfavourable pregnancy outcomes, alternative treatments should be considered for psoriasis throughout pregnancy with UVB-nb phototherapy as the preferred therapy. Biologics may be used only in high-need situations and when no alternative treatments are available.

Patients with concomitant hepatitis C or B infection

Hepatitis B and C are quite common in the Mediterranean area. In Italy, the prevalence of hepatitis C virus (HCV) infection varies from 2% to 8%, being more frequent in individuals over 65 years and in the southern regions.[85] The prevalence of hepatitis B virus infection (HBV) is lower compared to HCV but with a similar north–south increasing gradient. A recent national study found that 0.32% (100 of 31 190 blood donors) were positive for both HBsAg and anti-HBc antibodies (Ab) and 0.01% (two of 31 190) for HBsAg alone.[86] Screening patients for HBV and HCV infection is recommended before starting treatment with immunosuppressive agents including biologics, methotrexate and cyclosporine. Before initiating acitretin, serologic screening for HBV and HCV should be considered when viral hepatitis is suspected such as in case of elevated liver enzymes. Immunosuppressive treatments can lead to reactivation of HBV or, more rarely, HCV infections, sometimes leading to fulminant infections.[87] In patients with hepatitis infection, the benefits of using any immunosuppressive therapy must be weighed against the potential for viral reactivation or exacerbation of the infection. HBV reactivation is highly preventable through screening and administration of prophylactic antiviral therapy (e.g. lamivudine). When screening for HBV, the serologic markers to be determined include HBsAg, Ab anti-HB core and anti-HBs. When HBsAg and anti-HBc Ab are negative, HBV infection can be excluded. A patient who has had a previous infection may require HBV DNA levels testing and prophylaxis with antiviral drugs such as lamivudine before therapy is initiated. If a positive marker is found, or the patient is known to have had prior hepatitis infection, referral to an infectologist or hepatologist is recommended. Prior/current HBV infection is not necessarily an absolute contraindication to treatment, but it is important to carefully monitoring. How frequent this monitoring should be performed and which markers should be tested will be individualized to the patient. HCV infection is screened by anti-HCV Ab. If anti-HCV Ab is positive, PCR analysis for HCV RNA needs to be performed to rule out a chronic active HCV infection. Screening for hepatitis A is not necessary before starting biological therapy, as it is a self-limiting disease. Due to their low potential for systemic absorption, topical therapies for psoriasis can be considered safe in patients with hepatitis. UVB-nb is also a valuable option. In HCV-positive patients, cyclosporine, the TNF-α antagonists and ustekinumab may be used safely if close liver function and viral load monitoring is performed.[88–90] In HBsAg-positive patients, a course of antiviral therapy is recommended, starting 2–4 weeks before the biological therapy to 6–12 months after the end of therapy. In patients with occult HBV infection (i.e. HBsAg negative but anti-HBc Ab positive), monitoring of HBsAg and HBV DNA every 3 months is recommended.[91] Methotrexate is contraindicated in patients with hepatitis B or C as well as alcoholic liver disease. Acitretin may be used cautiously. No data are yet available for secukinumab and apremilast.

Patients with HIV infection

Psoriasis can be exacerbated by HIV infection, and it is generally more severe in HIV-infected individuals with worsening psoriasis correlating with higher HIV viral loads.[92] Collaboration with infectologist is important to optimize antiretroviral treatment strategy such as reducing HIV RNA load and enhancing $CD4^+$ cell counts.[93] As there are no randomized controlled trails in HIV-infected patients with psoriasis, recommendations are derived from case reports, existing guidelines or consensus statements. Topical therapy with or without phototherapy should be recommended as first-line treatment. Phototherapy (UVB-nb or PUVA) alone or combined with acitretin seems to be safe and effective. However, it should be considered that HIV-infected patients might undergo phototoxicity due to photosensitizing drugs such as trimethoprim or highly active antiretroviral therapy (HAART). The increased risk of skin cancers in these patients because of immunosuppression supports the cautious use of phototherapy as an induction and not as a maintenance treatment. Acitretin may be used as second-line treatment. Caution is advised when acitretin is used in combination with protease inhibitors, such as indinavir, that may result in an increased risk of retinoid-like adverse effects, such as mucocutaneous xerosis, cheilitis, paronychia and hyperlipidaemia.[94] Methotrexate and cyclosporine may be considered only in severe, refractory cases. Cyclosporine should be prescribed at lower dose (e.g. 2.5 mg/kg/day) monitoring its serum concentration because of the possible increased bioavailability when used in combination with protease inhibitors.[95] The use of methotrexate should also be cautious because of the risk of leukopenia or liver toxicity that may occur in patients receiving HAART. Reliable seropositive patients, who are adherent to medication regimens and frequent monitoring and have failed other treatment modalities, could be candidate to biologics. Due to less immunosuppressive impact and more cases reported, etanercept may be proposed before the others.[96] We agreed to consider biological therapy in patients with HIV only (i) in people with severe psoriasis and (ii) with a viral load persistently below the level of detection and (iii) where other therapeutic modalities being ineffective, and (iv) in collaboration with an infectologist. Several cases of HIV-positive patients treated with etanercept, adalimumab and ustekinumab have been reported.[97]

Patients with latent tuberculosis infection

Latent tuberculosis infection (LTBI) is a dormant form of TB, without symptoms and not infectious.[98] In LTBI, mycobacterium tuberculosis is inactive, but it remains alive in the body and it could be reactivated. TB reactivation is frequently extrapulmonary and disseminated. In Italy the prevalence of latent TB in patients with moderate-to-severe psoriasis is 8.2%.[99] Screening for LTBI is mandatory in patients who are candidate to biologics because of increased risk of LTBI reactivation, particularly with TNF-α inhibitors. Although the risk of LTBI reactivation significantly differs among biologics, caution and vigilance are required for all biologics. The risk of LTBI reactivation is lower in those treated with etanercept than in those treated with infliximab or adalimumab. Rare cases of LTBI reactivation in patients treated with ustekinumab have been reported.[100] Screening for LTBI includes medical history, chest X-ray and tests to disclose active cellular immunity to TB antigens. Suggestive symptoms for TB include coughing, hemoptysis, fever, night sweats and weight loss. It is very important to ask patients whether they have had a history of TB, and if so, whether they were appropriately treated and whether they were from or had a prolonged visit (>3 months) in endemic areas.[101] Those who are particularly at risk of TB infection include HIV-positive patients, intravenous drug users, prisoners or homeless, mycobacterial laboratory employees and immunosuppressed patients. It is also important to know whether the patient has had a bacillus Calmette–Guérin (BCG) vaccination. A negative chest X-ray is not sufficient to rule out the presence of LTBI. If the chest X-ray has been performed more than 3 months ago, a new 2-projection chest X-ray is required. Tests for assessing active cellular immunity to TB antigens include the tuberculin skin test (TST) and the interferon-α release assay (IGRA). The positive predictive value for TB infection by the TST depends on the local prevalence of TB and on the concomitance of the mentioned risk factors (immigrants, intravenous drug users, prisoners, children <4 years, HIV-infected patients). False-negative TSTs include those related to the PPD (PPD expiration) and those related to the patient [HIV infection, recent infections and vaccinations, malignancy, metabolic diseases, immunosuppressive therapy or extreme ages (newborn, elderly)]. False-positive TSTs include those related to the administration of PPD (inexperience, high amount of antigen) and cross-reactions (BCG vaccination and most environmental non-tuberculosis mycobacteria). In general, a skin induration ≥5 mm will be considered as positive. In the case of doubtful reaction, patient may then be referred to the pulmonologist or the infectologist. The IGRA has a higher sensitivity and specificity compared to TST.[102] The most widely used IGRA in Italy is the QuantiFERON®-TB Gold test (QFT-G), based on the amount of IFN-γ that is released in response to the antigens. The IGRA is not affected by prior BCG vaccination; however, it does not distinguish between active TB and LTBI. In the case of immunosuppressed patients, IGRA test could be false negative due to impaired T-cell responses. For example, negative results of TST or IGRA of HIV-infected patients with a low CD4 count cannot rule out a TB infection. In comparison with the TST (reaction by the T-memory cells), the IGRA (reaction by the T-effector cells) is less sensitive for old infections, while sensitivity for recent infections is higher. Therefore, a negative IGRA does not rule out an old infection. A positive IGRA finding is sufficient for a diagnosis of LTBI. Divergent views exist on how the TST and the IGRA should be integrated for LTBI screening. The U.S. Centers for Disease

Control and Prevention guidelines state that the IGRA can replace the TST.[103] The British guideline of 2009 recommends a two-step strategy, confirmation of positive TST results using an IGRA.[104] The European guideline 2009 suggests the IGRA in patients whose TST result is uncertain.[10] We totally agreed to use in Italy the IGRA when possible, and the TST only when the IGRA is not available. Given that there is still a risk of active TB under biological therapy, even if LTBI was correctly treated, rescreening for LTBI during biological treatment is suggested every year. In case of LTBI, biological therapy could be initiated if concomitant prophylactic antitubercular antibiotics are prescribed. Generally, antibiotic prophylaxis with isoniazid 300 mg/day is initiated 3 weeks before starting biologics therapy and it is continued for 6 months overall.[105] TB prophylaxis could induce adverse drug reactions including liver toxicity and may be ineffective.[106]

Patients with a history of neoplasm

Patients with a history of neoplasm require extreme caution in the prescription of immunosuppressive drugs. It is not usually possible to consider a cancer as definitely cured, with no risk of recurrence as opposed to a dormant cancer which may have an increased risk of recurrence when immunosuppressed. Patients with neoplasm are excluded from randomized controlled clinical trials. Indeed, European guidelines recommended that biological therapy should be avoided in patients with a current or recent past history of malignancy (except for non-melanoma skin cancer) unless the malignancy has been diagnosed and treated more than 5 years previously and the likelihood of cure is high.[10] It should be also considered that patients with psoriasis may be at increased risk of cancer. In particular, psoriasis confers a higher risk of non-melanoma skin cancer particularly in those with previous exposure to PUVA and cyclosporine.[107] It has been also reported a small increase in lymphoma (particularly Hodgkin's lymphoma and cutaneous T-cell lymphoma) and some solid cancers in patients with psoriasis.[108] Treatment with TNF-α antagonists or ustekinumab does not appear to increase the risk of neoplasm, except for non-melanoma skin cancer.[109] For patients with recent malignancy (i.e. within 5 years) we recommend topical therapy, phototherapy and/or acitretin. In cases where these treatments are not sufficient, methotrexate could be considered. Cyclosporine is generally contraindicated, and phototherapy is not indicated in patients with cutaneous malignancy including melanoma. In the case of inadequate response to phototherapy, acitretin or methotrexate, we recommend to discuss the decision to initiate biologics or apremilast, case by case with cancer specialists and to reach an informed decision. The elements to be taken into account for the shared decision are the type and staging of cancer, the risk of recurrence and the burden of psoriasis in the individual patient. In some cancers with relatively good prognosis, where flares of psoriasis cannot be controlled by other therapies, cautious prescription of immunosuppressive therapies could be considered. Biologics are contraindicated during the treatment of an invasive cancer. Finally, all patients should be encouraged to participate in cancer screening programs appropriate for their age and gender and that regular, comprehensive dermatological assessment for skin cancer, including melanoma, is recommended before and at regular intervals during biological therapy.

Patients undergoing surgical procedures

It has been reported that continuing biological treatments in patients with psoriasis undergoing surgical procedures did not increase the risk of postoperative complications, while perioperative withdrawal of biological therapy could increase the risk of psoriasis flare.[110–112] In the case of major surgery, the risk of infection should be balanced with the risk of psoriasis flare depending upon the type of surgery, patient characteristics and after counselling with the surgeon. Major surgery is any invasive operative procedure in which a more extensive resection is performed; e.g., a body cavity is entered, organs are removed or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, meninges), the surgery is considered major. Infliximab, adalimumab and ustekinumab should be withheld at least 4, 2 and 6 weeks before major surgery, respectively. They can then be restarted as neither postoperative infection nor delayed wound healing is recognized.[113] Patients with psoriasis who need minor surgical treatments including dental treatments and skin surgery may continue the biological treatment.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The method report of the italian guidelines on psoriasis can be found as supplementary material online.