

GUIDELINES

French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults

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Abstract

These guidelines were developed by the psoriasis research group of the French Society of Dermatology with the aim of providing updated decision-making algorithms for the systemic treatment of adult patients with moderate-to-severe psoriasis. Our algorithms were generated after rigorous evaluation of existing guidelines on the treatment of psoriasis and of publications concerning new systemic treatments, not yet incorporated into existing guidelines. A total of nine existing guidelines and 53 publications related to new systemic treatments were found to meet our criteria for use in the generation of the algorithms. We have proposed two new algorithms to assess therapeutic responses, both of which incorporate emerging criteria for evaluating treatment goals. Updated therapeutic strategy algorithms, incorporating both established and new systemic therapies, were also generated for the treatment of plaque psoriasis and psoriatic arthritis, together with recommendations for the treatment of particular forms of psoriasis and treatment of patients with comorbidities.

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Conflicts of interest

FA, AV, MT and BG declare no conflicts of interest regarding the publication of these recommendations. During the past 3 years, MV has received research funding from Amgen, Boehringer, Novartis and Léo, and has participated as a board member for Lilly, Novartis and Léo. MV has also received payment from Abbvie, Janssen, Lilly, MSD, Pfizer and Medac for participation at conferences, and has been invited to attend conferences by Abbvie, Janssen, Lilly, Novartis and Pfizer.

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Introduction to the guidelines: goals and methodology

The aim of these guidelines on the management of psoriasis in clinical practice was to propose updated decision-making algorithms to practitioners involved in the treatment of patients with moderate-to-severe psoriasis. The new algorithms were developed to take into account new scientific data and the emergence of highly effective new drugs for the treatment of psoriasis. Our recommendations concern adult patients with moderate-to-

severe psoriasis warranting systemic therapy. Patients with psoriasis are primarily managed by dermatologists, but rheumatologists, general practitioners, nurses, and pharmacists are also involved in their treatment. These guidelines are targeted towards all health professionals involved in the management of patients with psoriasis.

The initial working group was made up of three dermatologists (FA, AV, MT), without any conflict of interest with the pharmaceutical industry. Relevant papers were selected using two different methods, depending on the therapeutic agent studied. The systematic approach to assessing and adapting existing

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guidelines (ADAPTE) method¹ was used for therapeutic agents already incorporated into existing guidelines, such as cyclosporin, methotrexate, acitretin, phototherapy, tumour necrosis factor (TNF) inhibitors, and ustekinumab. Published guidelines concerning the treatment of psoriasis were evaluated using the Appraisal of Guidelines, REsearch and Evaluation II (AGREE II) scale.² Guidelines published between January 2012 and July 2017, for which the total AGREE score was above or equal to 90 after two independent evaluations, were considered for the elaboration of the present guidelines. To identify relevant papers about apremilast, secukinumab and ixekizumab, we performed a literature search through MEDLINE database between January 2014 and October 2017 using terms from the Medical Subject Heading (MeSH): « apremilast », « secukinumab », « ixekizumab » and « psoriasis ». The articles were all selected through Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method.³ We focused on large and/or prospective cohorts and/or controlled randomized studies, limited to English papers. Recommendations were elaborated according to the French national authority for health (Haute Autorité de Santé, HAS) guidelines for clinical practice recommendations.⁴ A total of nine existing guidelines^{5–14} and 53 publications relating to new drugs were found to meet the criteria for use in the generation of our current guidelines. Details of the keywords used in the literature search and a flowchart of our analysis of selected guidelines and publications are available as supplementary material (Appendix S1 and S2).

The first version of the manuscript was reviewed by nine dermatologists, all of whom were experts in the field of psoriasis management. If a consensus was not achieved for a recommendation, a vote was performed, and participants were asked to agree or disagree with the recommendation. The initial working group then produced a document detailing the conclusions generated by this process, indicating whether a consensus had been reached or whether there was no consensus for each recommendation. This final document was then reviewed by public and private practice practitioners involved in psoriasis treatment. These reviewers were mainly dermatologists or practitioners involved in the management of associated comorbidities, e.g. gastroenterologists, rheumatologists and endocrinologists. Thirty-four practitioners were initially solicited, out of whom 30 reviewed the guidelines. Two patients suffering from psoriasis also reviewed the document.

When should a systemic treatment be initiated?

Our guidelines recommend that systemic therapy, including phototherapy, should be proposed to patients with any form of psoriasis meeting one of the following criteria:

- the disease is considered to be moderate-to-severe, defined as psoriasis covering over 10% of the body surface area (BSA), or resulting in a psoriasis area severity index (PASI) score >10 and/or a dermatology life quality index (DLQI) score >10;
- the disease has a significant impact on physical and social well-being, or on psychological well-being resulting in disease-related clinically relevant depression or anxiety;
- the disease is localized but cannot be controlled with topical therapy and is associated with significant functional impairment and/or high levels of distress, e.g. severe nail disease or involvement at high-impact sites (such as the palms and soles, genitals, scalp, face and flexures).

Therapeutic objectives

Treatment goals in both the current and previously published guidelines were established with the aim of avoiding suboptimal or unnecessary treatment. Several factors should be taken into account when establishing treatment goals for systemic therapy in patients with moderate-to-severe psoriasis, including the disease severity, measured as either an absolute value or by comparison with baseline values; the coexistence of psoriatic arthritis (PsA) or any other comorbidities; the impact of the disease on the physical, psychological and social well-being of the patient; the risk–benefit ratio of continuous systemic treatment, and the patient's point of view and level of satisfaction.

A European consensus meeting of expert physicians and use of a collaborative Delphi procedure led to the generation of a decision algorithm for plaque psoriasis in 2011.¹⁵ In this algorithm, a treatment response in plaque psoriasis was considered as adequate if it resulted either in a 75% reduction in the PASI (PASI 75) from baseline, or in a 50% reduction in the PASI (PASI 50) and a DLQI score of less or equal to five. Primary treatment failure was defined as not achieving a PASI 50 response.

All experts except one agreed to reject the 2011 algorithm. There is currently no consensus about treatment goals in plaque psoriasis, mainly resulting from a lack of correlative data concerning available criteria and patient satisfaction, e.g. the physical and psychological impacts of the disease need to be evaluated. Ongoing investigations of patient-reported outcomes and their correlation with absolute residual PASI scores, such as a visual analogue scale for pruritus or pain, will need to be integrated into the algorithm in the near future. Shared decision-making with patients, incorporating the safety aspects of drug interventions emerging from patient surveys, should also be incorporated.

The highly beneficial therapeutic response observed with some newly available biological agents for psoriasis treatment has led some authors to consider that certain criteria (i.e. PASI 50 and PASI 75) are outdated.^{16,17}

New criteria have emerged such as those listed below.

- Absolute PASI ≤ 3 : this parameter is easier to calculate than the PASI 75 response, is independent of

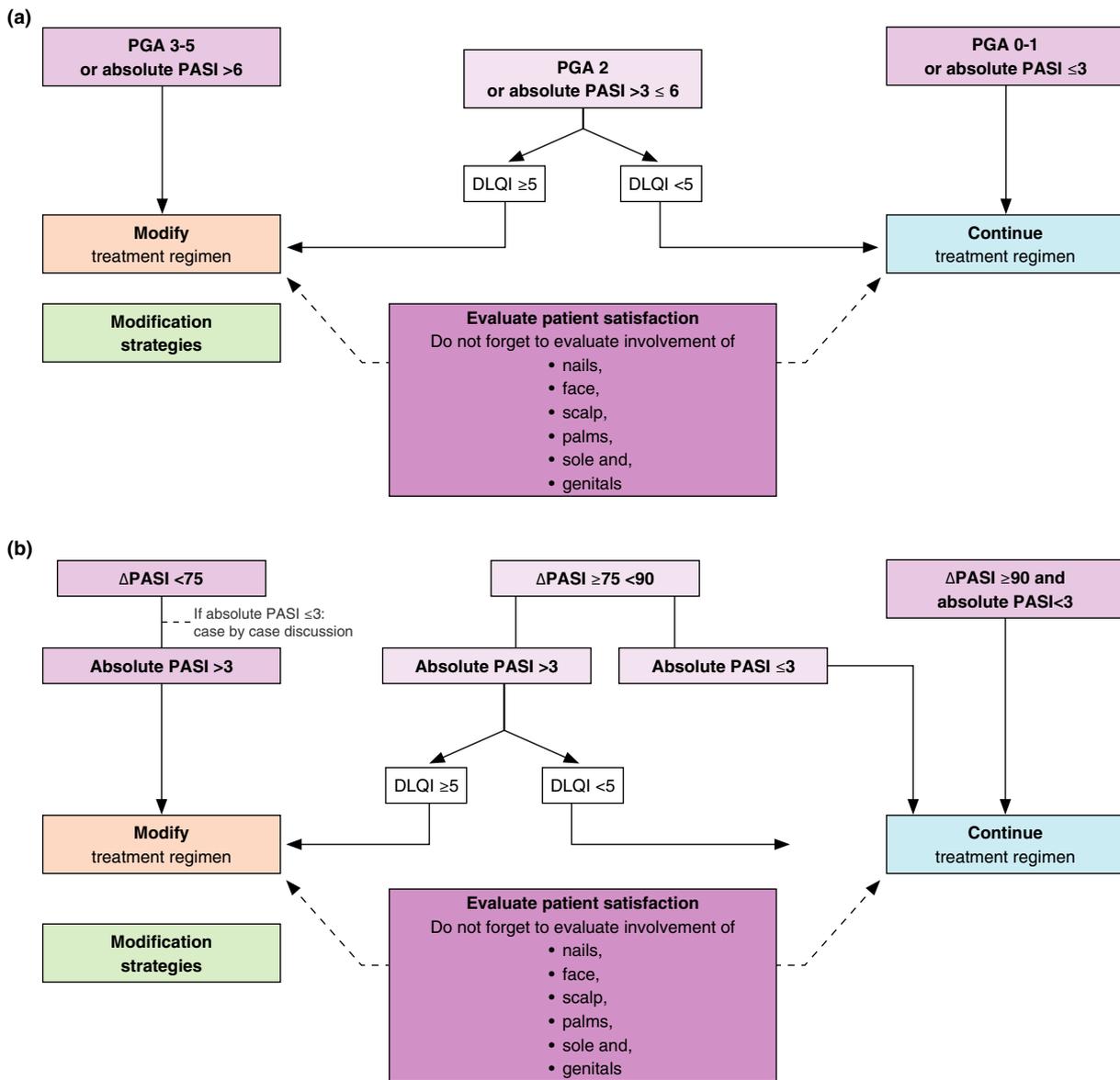


Figure 1 Treatment goals in plaque psoriasis. (a, b) Updated decision algorithms considered as acceptable by the current working group. DLQI, dermatology life quality index; PASI, psoriasis area severity index; PGA, physician global assessment.

variations in baseline severity and better reflects the clear or almost clear status (or a physician global assessment (PGA) score of 0–1) of the patient (Expert opinion).

- DLQI 0 or 1: have been proposed as scores indicating the absence of an impact of psoriasis on quality of life (Expert opinion).
- PASI 90 and PASI 100 responses: these criteria have emerged as a result of the high efficacy of some of the most recent biological agents. However, several authors question

their clinical relevance compared to other criteria, such as PASI 75 (Expert opinion).

In the absence of strong evidence from the literature and given the lack of consensus for a unique algorithm within our working group and among the interviewed experts, we have generated two updated decision algorithms for treatment goals in plaque psoriasis (Fig. 1a,b; Expert opinion). Out of a total of five proposals stemming from our study, only these two algorithms were considered as acceptable by the study participants. Both algorithms use

the new criteria for evaluating therapeutic response. There is no difference in therapeutic strategy between the two algorithms and it therefore remains a matter of choice as to which algorithm is used by healthcare professionals on a daily basis.

When should the treatment response be evaluated?

We found that there was no consensus regarding the optimal timing for efficacy assessments in the existing guidelines and publications that we reviewed. As a result of the specificity of each therapeutic agent, details of our recommendations for the timing of efficacy assessments are listed in the description for each molecule provided in Table 1(a–k). In contrast, our study revealed that there is a consensus about the need to assess treatment efficacy and safety at regular intervals (ideally twice a year) during maintenance therapy. We recommend that the assessment frequency is managed jointly by the general practitioner and the dermatologist, and is primarily driven by the safety monitoring recommendations (Expert opinion).

Systemic treatments for plaque psoriasis in patients without comorbidities

Our algorithm for the therapeutic strategy in patients suffering from plaque psoriasis without comorbidities is presented in Fig. 2. Treatments were classified by taking into account the following parameters: efficacy, safety, real-time follow-up data, drug survival and global price evaluation.

We recommend that if the patient meets one of the criteria for initiating a systemic treatment, then methotrexate should be proposed as the preferred therapeutic option (Expert opinion). Exceptions to this recommendation include:

- patients for which there is a contraindication to the use of methotrexate (Expert opinion);
- patients that are pregnant, breastfeeding, or plan to have child in the near future (men and women); we recommend that cyclosporin is used instead of methotrexate for treatment of these patients (Grade A);
- patients for whom there is a need for short-term disease control; we recommend that cyclosporin is used instead of methotrexate for treatment of these patients (Grade B).

Narrowband UVB phototherapy (NBUVB) can also be prescribed as a first-line treatment (Grade A). Home-based NBUVB is not currently available for use in France; however, where it is available we recommend that it is offered to compliant and adherent patients who are unable to follow a clinic-based phototherapy schedule (Grade B). For patients with large thick plaques, we recommend the use of psoralen UVA phototherapy (PUVA) or re-PUVA therapy rather than NBUVB, except in young female patients (Grade C). The addition of acitretin to PUVA therapy is an option in case of failure to respond to PUVA alone (Grade A).

As a result of its lower efficacy compared to other available treatments, acitretin should not be recommended as a monotherapy in the systemic treatment strategy for plaque psoriasis. However, we concluded that it may be beneficial to propose acitretin as a treatment option for some patients with methotrexate and cyclosporin contraindications (Expert opinion).

Biologic agents are not labelled in France as first line therapies, but as a treatment options for adults with moderate-to-severe psoriasis who have not responded to at least two standard systemic therapies, or if the patient is intolerant or has a contraindication to these treatments. Thus, biologic agents could not be proposed as first line therapies in the present algorithm.

We recommend that biological agents and apremilast are prescribed only after the contraindication of, intolerance to or failure of two systemic treatments, such as methotrexate, cyclosporin, or phototherapy. No consensus was reached as to whether or not acitretin should be included with methotrexate, cyclosporin and phototherapy in the list of the two failed or contraindicated systemic treatments.

Given the low efficacy of apremilast compared to biological agents and the risk of some potentially severe adverse events associated with apremilast therapy, we recommend that therapeutic strategies using biological agents are explored prior to initiating systemic treatment with apremilast (Expert opinion). Further studies are required to establish a place for apremilast in the therapeutic armamentarium.

Taking into consideration the short-term and long-term efficacies, the long-term safety and tolerability assessments, the administration regimens and the drug survival rates of the available biological agents, we suggest that adalimumab or ustekinumab should be the preferred first-line biological agents (Expert opinion). If treatment goals are not achieved, switching between these agents (i.e. from ustekinumab to adalimumab or another TNF inhibitor, or vice versa) or initiation of IL-17 inhibitor therapy should be considered (Expert opinion).

It should be noted that the initiation of a biosimilar should be based on existing national guidelines, such as those published in France on the status of biosimilar medicines.¹⁸

Details on systemic treatments for psoriasis

A short description of the systemic treatments for psoriasis is provided in Table 1(a–k). The clinical and paraclinical assessments associated with each treatment are described in Tables 2(a,b) and 3, respectively.

Treatment options for patients with comorbidities or those with special circumstances

Our recommendations for patients with comorbidities or special circumstances, such as patients with an alcohol addiction or breastfeeding mothers, were generated after an exhaustive literature review of these topics. A summary of the recommendations

Table 1 Summary of the systemic treatment options for psoriasis†

(a) Phototherapy (NBUVB, home-based NBUVB, PUVA, bath PUVA)	
Dosing scheme (for more detailed information: Appendix S3)	Refer to protocol regimens of the French society of photodermatology (2016). The initial dose and increase modalities depend on the Fitzpatrick skin type and tolerance scale. <ul style="list-style-type: none"> NBUVB (outpatient or at home when available): 3 sessions/week (Grade A), 20–30 sessions (Grade A). PUVA: use oral psoralen (8-methoxypsoralen) at 0.6 mg/kg followed 2–3 h later by exposure to UVA irradiation: 2–3 sessions per week, for 20–30 sessions (Grade A). A lack of improvement after 20 sessions is considered as a failure (Grade D). Bath PUVA: prepare the bath by diluting a 0.75% solution of psoralen in 80–100 L of water to obtain a concentration of 2.6 mg of psoralen per litre (Grade C). The bath should last 15 min and be followed by irradiation immediately after drying. The recommended doses of UVA are lower than those used for oral PUVA. Number of cumulative sessions of phototherapy during a lifetime should not exceed 200 (Grade C).
Efficacy (Monotherapy)	Onset of clinical effect: after 1 or 2 weeks. Efficacy assessment: after 20 sessions. <ul style="list-style-type: none"> NBUVB: PASI 75 = 62–70%. Home-based NBUVB: no difference in efficacy compared to classical NBUVB. PUVA: PASI 75 = 73–80%. Bath PUVA: PASI 75 = 47%.
Optional combination therapy	<ul style="list-style-type: none"> Acitretine (10–20 mg daily, to start 10–14 days before phototherapy): Grade A for PUVA, Grade B for NBUVB, Grade B for bath PUVA. Grade B for MTX, ADA and ETA with NBUVB. Grade C for USTK with NBUVB.
Adverse events	Erythema, itching, blistering, xerosis, hyperpigmentation, photoageing. The risk of skin malignancies is significantly increased with PUVA, limited data are available for NBUVB. For oral PUVA, nausea, abdominal pain may also occur.
Main contraindications	Absolute contraindications: increased sensitivity to light, concomitant phototoxic medication. Gene defects with increased photosensitivity or risk of skin cancer. History of melanoma. For PUVA: use of CSA, pregnancy or breastfeeding. Important relative contraindications: dysplastic nevi syndrome or multiple nonmelanoma skin cancers, patients under immunosuppressive medication, prior therapy with arsenic or ionizing radiation. For PUVA: severe liver or renal impairment, children, use of psoralen for cosmetic purposes. For home-based NBUVB: lack of compliance/adherence.
Precautions	See Tables 2(a,b) and 3 on clinical and biological pre-treatment procedures and surveillance.
Vaccination	No specific recommendation. Follow French immunization schedule. Live vaccines are permitted during treatment.
Surgery	Phototherapy can be maintained in patients undergoing surgery if the patient's condition allows it.
Cost in France (2017)	For 3 treatments/week: €250 monthly for NBUVB, €255 monthly for PUVA.
(b) Methotrexate (MTX)	
Dosing scheme	Starting dose <ul style="list-style-type: none"> In general, 7.5–15 mg/week by oral or s.c. delivery (Grade B). One RCT suggests a starting dose of 17.5 mg/week s.c. administration with dose escalation to 22.5 mg/week after 8 weeks if the patient has not achieved PASI 50 (Grade A). No low test dose is mandatory (Grade C). No weight-based adaptation. The s.c. administration might reduce gastrointestinal AEs reported in patients treated orally (Grade C) but has not demonstrated superiority compared to the oral route. Maintenance dosage <ul style="list-style-type: none"> 5–25 mg/week depending on efficacy and tolerability (Grade B). Use the lowest therapeutic dose. Folate supplementation: 5 mg/week of folic acid taken 24 h after administration of MTX (Grade B). Interrupting treatment after a given cumulative dose is not recommended if MTX is well-tolerated and the follow up required is completed (Expert opinion).
Half-life	2–7 h.
Efficacy (Monotherapy)	Onset of clinical effect: 4–8 weeks. Efficacy assessment: W12–16. <ul style="list-style-type: none"> Short-term efficacy (W16): PASI 75: 45% (W12–16)/PASI 90: 18%/DLQI: 9-point reduction. ACR20 (W12): 41%. Long-term efficacy (W52): PASI 75: 73%. Median drug survival: 30.1%, and 15.1% after 3 and 5 years.
Optional combination therapy	<ul style="list-style-type: none"> Grade A with ETA, Grade B with NBUVB, Grade B with INFLI, Grade C with ADA.
Main adverse events	Fatigue, nausea, vomiting, moderate hair loss, transaminase increase, bone marrow suppression, gastrointestinal and mucosal ulcerations, infections, liver fibrosis, interstitial pneumonia.

Table 1 Continued

(b) Methotrexate (MTX)	
Main contraindications	Severe infections, serious kidney and liver dysfunction, bone marrow suppression, men and women currently trying to conceive children , pregnancy, breastfeeding, pulmonary fibrosis or poor lung function, alcohol abuse, active peptic ulcer.
Precautions	See Tables 2(a,b) and 3 on clinical and biological pre-treatment procedures and surveillance. Inform the patient on how to take the drug (only once a week). If liver ultrasound is abnormal at baseline: check PIIP or Fibroscan®. Fibroscan® should be performed at baseline in obese patients if long-term treatment is planned. Adequate contraception for men and women is mandatory. After the end of treatment, contraception is recommended for 3 months in men and only 1 day in women (contraception should be continued until the end of treatment and conception is possible as soon as contraception is stopped).
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination. Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> No systematic interruption of MTX required prior to minor surgery (Grade B). Discuss interruption of MTX (30 h) prior to major surgery in patients with a history of healing disorders or wound infections (Grade C).
Cost in France (2017)	For 20 mg/week: between €84/year (oral form) and €1 080/year (s.c. form).
(c) Cyclosporin (CSA)	
Dosing scheme	<p>Starting dose</p> <ul style="list-style-type: none"> 2.5 mg/kg/day by oral delivery, divided in half and taken morning and evening (Grade A). In the absence of comorbidity, start with 5 mg/kg for faster action (Grade B). If there is no adequate response to the starting dose at W4–W8, or when rapid disease control is necessary, increase the dose to a maximum of 5 mg/kg (Grade B). Use the ideal weight for obese patients (Grade B). <p>Maintenance dosage</p> <ul style="list-style-type: none"> Intermittent therapy (2–4 months of treatment) or continuous therapy with minimal effective dose, depending on the clinical situation (Grade B). Slow tapering of CSA offers a slight delay in psoriasis relapse (Grade B). Consider other treatment options when disease relapses rapidly (Expert opinion). Avoid using CSA continuously for more than 2 years unless disease is severe and other treatment options cannot be used, and collaborate with a nephrologist (Grade C).
Half-life	7 h.
Efficacy (Monotherapy)	Onset of clinical effect: 4 weeks. Efficacy assessment: W8. <ul style="list-style-type: none"> Short-term efficacy: PASI 75: 60–88.6% at W8–W12/PASI 90: 29% at W12/DLQI: 9.3-point reduction at W12. Median drug survival 23.3% at 1 year.
Optional combination therapy	Given the lack of robust data on CSA therapy in combination, we recommend not to use CSA with any other systemic treatment, including phototherapy.
Adverse events	Renal impairment, arterial hypertension nausea, diarrhoea, liver dysfunction, gingival hyperplasia, paraesthesia, muscle pain, headache tremors, hypertrichosis, increased blood lipids.
Main contraindications	Impaired renal function, uncontrolled arterial hypertension, severe infectious disease, history of malignancy (possible exceptions: cured basal cell carcinoma, history of <i>in situ</i> squamous carcinoma) or current malignancy, concomitant PUVA therapy.
Precautions	See Tables 2(a,b) and 3 on clinical and biological pre-treatment procedures and surveillance. Be aware that CSA increases the risk of non-melanoma skin cancers in patients already treated with phototherapy.
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> No systematic interruption of CSA required prior to minor surgery (Grade B). Discuss interruption of CSA (35 h) prior to major surgery in patients with a medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	For a dose of 3 mg/kg/day in a 70 kg patient: €3 144/year.
(d) Acitretin	
Dosing scheme	<p>Starting dose</p> <ul style="list-style-type: none"> Use incremental dosing starting from 10 mg/day to achieve a target dose of 0.3–0.5 mg/kg daily (Grade B). <p>Maintenance dose</p> <ul style="list-style-type: none"> To be adapted to the clinical response and tolerance, usually between 0.5 and 0.8 mg/kg daily, with a maximum dose of 50 mg daily (Grade C). The degree of lip dryness may help to determine the maximum tolerated dose (Expert opinion).

Table 1 Continued

(d) Acitretin	
	<ul style="list-style-type: none"> • Long-term therapy must be discussed on a case-by-case basis according to clinical and biological tolerance. • Treatment must be initiated by a dermatologist.
Half-life	2–5 days.
Efficacy (Monotherapy)	Onset of clinical effect: 4–8 weeks. Efficacy assessment: after 3 or 4 months at the optimum dose; discontinue the treatment if response is inadequate (Expert opinion). Response rate is difficult to assess because of the low quality of published trials. PASI 75: 30% at W12–24 with a dose of 0.4 mg/kg. Drug survival at first year: 42.3%.
Optional combination therapy	Level A with PUVA therapy, Level B with NBUVB, Level B with ETA, Level C with INFLI.
Adverse events	Teratogenicity, hypervitaminosis A (cheilitis, xerosis), conjunctivitis (contact lenses may become unbearable), hair loss, photosensitivity, hyperlipidaemia, muscle, joint and bone pain, idiopathic intracranial hypertension, decreased colour vision and impaired night vision.
Main contraindications	Severe renal or hepatic impairment. Women of child-bearing age: pregnancy, breastfeeding, desire to have children or insufficient guarantee of effective contraceptive measures up to 3 years after discontinuation of therapy. Alcohol abuse. Blood donation.
Precautions	See Tables 2(a,b) and 3 on clinical and biological pre-treatment procedures and surveillance. Start treatment on the second or third day of the menstrual cycle, after satisfactory contraception for at least 1 month prior to treatment. Double contraception is recommended. Emphasize the need for reliable contraception in women of child-bearing age for up to 3 years after therapy. Check pregnancy test before starting treatment, then every month during treatment, and then every month for 2 months after treatment discontinuation. There is no need for contraception in men.
Vaccination	No specific recommendations. Follow the French immunization schedule. Live vaccines are permitted during treatment.
Surgery	Acitretin can be safely continued in patients undergoing surgery.
Cost in France (2017)	For 25 mg/day: €600/year.
(e) Infliximab (INFLI)	
Dosing scheme	Intravenous administration (day care hospital unit). <ul style="list-style-type: none"> • 5 mg/kg given at W0, W2, W6, every 8 weeks thereafter (continuous treatment is recommended, Grade A). • Possibility of increasing dosage or reducing administration intervals (Grade C). If loss of efficacy to standard-dose maintenance therapy occurs: INFLI 5 mg/kg every 6 weeks (Expert opinion).
Half-life	10 days
Efficacy (Monotherapy)	Efficacy assessment: W14 (after 4 doses). Induction efficacy (W10): <ul style="list-style-type: none"> • PASI 75: 81%/PASI 90: 55% • DLQI: 8.4-point reduction (median) • ACR 20: 77%. Stop INFLI in patients who have not responded adequately at W14. Long-term efficacy (W50): <ul style="list-style-type: none"> • PASI 75: 61%/PASI 90: 45%. Median drug survival: 65% 1st year/35% 3rd year.
Optional combination therapy	Level B with MTX 7.5–15 mg/week. Level C with acitretin.
Main adverse events	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, anaphylactic and anaphylactic-like reactions, serum sickness or serum sickness-like reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.
Main contraindications	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infections, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.
Precautions	See Tables 2(a,b) and 3 for clinical and biological pre-treatment procedures and surveillance.
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> • No systematic interruption of INFLI is required prior to minor surgery (Grade C). • Discuss interruption of INFLI prior to major surgery (3–5 half-lives = 4–7 weeks) in patients with a medical history of healing disorders or wound infections (Grade C). Surgery may be placed between two infusions (Expert opinion).

Table 1 Continued

(e) Infliximab (INFLI)	
Cost in France (2017)	Around €12 220 for the first year for Remicade® (5 mg/kg W0–W2–W6, then every 8 weeks for an 80 kg patient), not including the day hospital cost. Biosimilars are available (Inflectra®, Remsina®, Flixabi®).
(f) Adalimumab (ADA)	
Dosing scheme	s.c. administration. <ul style="list-style-type: none"> • Loading dose of 80 mg at W0, 40 mg W1, then 40 mg every other week. • If inadequate response at W16: possibility of transient increase in the dosing frequency to 40 mg every week (Grade B). The dose should subsequently be reduced again if an adequate response is achieved. If an adequate response is not achieved 4 months after increasing the dosing frequency, ADA should be stopped (Expert opinion). • No weight—dose adjustment for obese patients.
Half-life	2 weeks
Efficacy (Monotherapy)	Efficacy assessment: W16. Short-term efficacy (W16): <ul style="list-style-type: none"> • PASI 75: 71%/PASI 90: 45% • DLQI: 7-point reduction (median) • ACR 20: 52%. Stop ADA in patients who have not responded adequately at W16. Long-term efficacy (W48): <ul style="list-style-type: none"> • PASI 75: 63%/PASI 90: 48%. Mean drug survival: 79% 1st year/59% 3rd year.
Optional combination therapy	Level C with MTX 7.5–15 mg/week. Level B with NBUVB.
Main adverse events	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.
Main contraindications	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infection, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.
Precautions	See Tables 2(a,b) and 3 for clinical and biological pre-treatment procedures and surveillance.
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> • No systematic interruption of ADA required prior to minor surgery (Grade C). • Discuss interruption of ADA prior to major surgery (3–5 half-lives = 6–10 weeks) in patients with a past medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	Around €11 400 for the first year for Humira® (80 mg loading dose and 40 mg every other week, starting W1). No biosimilar available in France in 2017.
(g) Etanercept (ETA)	
Dosing scheme	s.c. administration. <ul style="list-style-type: none"> • 50 mg BIW for up to 12 weeks, followed by 50 mg QW is a more effective strategy than 50 mg QW from the beginning of treatment (Grade A). • Possibility of intermittent therapy (grade C). • No weight—dose adjustment for obese patients.
Half-life	70 h (3 days).
Efficacy (Monotherapy)	Efficacy assessment: W12. Induction efficacy (W12): <ul style="list-style-type: none"> • PASI 75: 38% (50 mg QW*)/52% (50 mg BIW) • PASI 90: 15% (50 mg QW*)/25% (50 mg BIW) • DLQI: 6-point reduction (median) • ACR 20: 59%. Stop ETA in patients who have not responded adequately at W12. Long-term efficacy (W96): <ul style="list-style-type: none"> • PASI 75: 51%. Median drug survival: 70% 1st year/40% 3rd year. *25 mg BIW
Optional combination therapy	Level A with MTX 7.5–15 mg/week. Level B with NBUVB and acitretin.
Main adverse events	Injection-site reactions, headache and muscle/bone pain, viral, bacterial or fungal infections (including tuberculosis), weight gain, allergic reactions, autoimmune processes, worsening of congestive heart failure, neurological disorders, nonmelanoma skin cancers.

Table 1 Continued

(g) Etanercept (ETA)	
Main contraindications	Cardiac insufficiency (NYHA grade III or IV), active tuberculosis or other serious infection, active malignancy, pregnancy, breastfeeding, demyelinating disease, hypersensitivity.
Precautions	See Tables 2(a,b) and 3 for clinical and biological pre-treatment procedures and surveillance. The needle cover on the prefilled syringe contains dry natural rubber and should not be handled by patients allergic to latex.
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> No systematic interruption of ETA required prior to minor surgery (Grade C). Discuss interruption of ETA prior to major surgery (3–5 half-lives = 9–15 days) in patients with a past medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	Around €12 670 for the first year for Enbrel® (50 mg BIW up to W12, followed by 50 mg QW). Biosimilar available (around €11 140 for the first year for Benepali®).
(h) Ustekinumab (USTK)	
Dosing scheme	s.c. administration. <ul style="list-style-type: none"> 45 mg at Week 0, Week 4 and then every 12 weeks. Adjusted for patients >100 kg: same scheme, but with a 90 mg dose. Suggested dose-escalation strategy (off-license): USTK 90 mg every 12 weeks (<100 kg) or USTK 90 mg every 8 weeks (>100 kg) (Grade C).
Half-life	3 weeks
Efficacy (Monotherapy)	<p>Efficacy assessment: W28.</p> <p>Induction efficacy (W28):</p> <ul style="list-style-type: none"> PASI 75: 70 (45 mg)–79% (90 mg)/PASI 90: 45 (45 mg)–48% (90 mg). DLQI: 8-point reduction (median). ACR 20: 42–49%. <p>Stop USTK in patients who have not responded adequately at W28.</p> <p>Long-term efficacy (W156):</p> <ul style="list-style-type: none"> PASI 75: 81 (45 mg)–83% (90 mg)/PASI 90: 43 (45 mg)–58% (90 mg). Median drug survival: 89% 1st year/75% 3rd year.
Optional combination therapy	Level C with NBUVB.
Main adverse events	Injection-site erythema, fatigue and muscle/bone pain, diarrhoea, viral, bacterial or fungal infections (no reactivation or new onset of tuberculosis), allergic reactions, exfoliative dermatitis, MACE.
Main contraindications	Active tuberculosis or other serious infection, pregnancy, breastfeeding, active malignancy, hypersensitivity.
Precautions	See Tables 2(a,b) and 3 for clinical and biological pre-treatment procedures and surveillance. In patients with increased cardiovascular risk, initiate the treatment in collaboration with a cardiologist and control risk factors. The needle cover on the prefilled syringe contains dry natural rubber and should not be handled by patients allergic to latex.
Vaccination	Follow the French immunization schedule Primary vaccination and/or boosters for HBV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	<ul style="list-style-type: none"> No systematic interruption of USTK required prior to minor surgery (Grade C) Discuss interruption of USTK prior to major surgery (3–5 half-lives = 9–15 weeks) in patients with a past medical history of healing disorders or wound infections (Grade C).
Cost in France (2017)	Around €14 920 for the first year for Stelara® (45 or 90 mg W0, W4, then every 12 weeks) No biosimilar available in France in 2017.
(i) Secukinumab (SEC)	
Dosing scheme	s.c. administration <ul style="list-style-type: none"> 300 mg, delivered in two injections of 150 mg each. 300 mg at W0, 1, 2, 3, 4 and then 300 mg every 4 weeks. No weight–dose adjustment.
Half-life	27 days
Efficacy (Monotherapy)	<p>Efficacy assessment: W16.</p> <p>Short-term efficacy (W12): PASI 75: 76–87%/PASI 90: 55–60%/DLQI 0/1: 55.8%/ACR 20: 58.2% (week 24) Stop SEC in patients who have not responded adequately at W16.</p> <p>Long-term efficacy (W104): PASI 75: 88.2%/PASI 90: 58%.</p> <p>Mean drug survival: unknown at this time. Intermittent dosing: not validated.</p>

Table 1 Continued

(i) Secukinumab (SEC)	
Optional combination therapy	No data for skin psoriasis. Can be used in combination with DMARDs in PsA (Grade C).
Adverse events	Infections (upper respiratory tract, candida), diarrhoea, neutropenia, inflammatory bowel disease onset and flare.
Main contraindications	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.
Precautions	Avoid if possible in patients with a history of inflammatory bowel disease (Grade C). Close monitoring of patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (possible class effect – Expert opinion). In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk – Expert opinion).
Vaccination	Follow the French immunization schedule Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	No data available about surgery. We recommend interrupting SEC 4 weeks before performing scheduled surgery. Resume medication after healing (American College of Rheumatology and American Association of Hip and Knee Surgeons recommendations).
Cost in France (2017)	Cosentyx® <ul style="list-style-type: none"> • First year: €19.375 • then €14 857/year. No biosimilar available in 2017.
(j) Ixekizumab (IXE)	
Dosing scheme	s.c. administration. <ul style="list-style-type: none"> • Loading dose of 160 mg, 80 mg every other week until week 12, then 80 mg every 4 weeks. • No weight–dose adjustment.
Half-life	13 days
Efficacy (Monotherapy)	Efficacy assessment: W16. In case of partial response at week 16, improved response can be observed until week 20. Induction efficacy (W16): <ul style="list-style-type: none"> • PASI 75: 84% (81–88%)/PASI 90: 69% (65–72%) (Grade A) • DLQI 0/1: 59.9%/ACR 20: 57.9%. Stop IXE in patients who have not responded adequately at W16. Long-term efficacy (W60): <ul style="list-style-type: none"> • PASI 75: 74%/PASI 90: 57% (Grade B). Mean drug survival: NA. Intermittent dosing: treatment can be stopped in patients who achieve PGA 0/1 at week 12 and then reintroduced in case of relapse (80 mg every 4 weeks) (Grade C).
Optional Combination therapy	No
Adverse events	Infections (upper respiratory tract, candida), injection site reactions, neutropenia, inflammatory bowel disease onset and flare.
Main contraindications	Hypersensitivity, active infection, pregnancy, breastfeeding, active malignancy.
Precautions	Avoid if possible in patients with a history of inflammatory bowel disease (Grade C). Close monitoring of patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (possible class effect – Expert opinion). In patients with increased cardiovascular risk, initiate in collaboration with a cardiologist and control risk factors (no long-term safety assessment in patients at high cardiovascular risk – Expert opinion).
Vaccination	Follow the French immunization schedule. Primary vaccination and/or boosters for HBV and HAV/annual influenza/pneumococcal vaccination (especially the elderly). Live-attenuated vaccines are contraindicated during treatment.
Surgery	No data available about surgery. We recommend interrupting IXE 4 weeks before performing scheduled surgery. Resume medication after healing (American College of Rheumatology and American Association of Hip and Knee Surgeons recommendations).
Cost in France (2017)	Taltz® <ul style="list-style-type: none"> • First year: €18 532, • then €13 421/year No biosimilar available in 2017.
(k) Apremilast (APR)	
Dosing scheme	Oral administration. <ul style="list-style-type: none"> • One-week titration for first-time users. Treatment is started with a dose of 10 mg on day 1 and increased daily by 10 mg over 1 week up to the recommended dose of 30 mg twice a day. • No dose adjustment required, except for severe renal impairment (clearance <30 mL/min): maximal dose: 30 mg once a day.

Table 1 Continued

(k) Apremilast (APR)	
Half-life	6–9 h
Efficacy (Monotherapy)	Efficacy assessment (W16): PASI 75: 29–33%; PASI 90: 9–10%; ACR 20:32–41%. Discontinue treatment in non-responders at W16. Long-term efficacy (W52): PASI 75: 42% (Grade C). Median time to loss of PASI 50/PASI 75 response upon drug discontinuation: 12.4 weeks/5.1 weeks. Mean drug survival: unknown. Intermittent dosing: not validated.
Optional combination therapy	No data for skin psoriasis. Can be used in combination with DMARDs in PsA (Grade C).
Adverse events	Diarrhoea (at onset, long-term persistence possible), nausea, asthenia, insomnia, upper respiratory tract infections, headaches, depression, weight loss.
Main contraindications	Hypersensitivity, pregnancy.
Precautions	Avoid in patients with psychiatric disorders and/or a history of suicide attempts and/or severe depression (Expert opinion).
Vaccination	No specific recommendation was given in the SmPC. Follow the French immunisation schedule. No data available about live-attenuated vaccines.
Surgery	No data available about surgery.
Cost in France (2017)	First year (including titration) = €7061, then €7368/year

†Molecules are categorized into three groups: classical systemic therapies, biologic agents and apremilast. The order of presentation of molecules within each group was chosen randomly.

ACR, American College of Rheumatology; ADA, adalimumab; APR, apremilast; BIW, twice weekly; CHF, chronic heart failure; CSA, cyclosporin; DLQI, dermatology life quality index; DMARDs, disease-modifying anti-rheumatic drugs; ETA, etanercept; HAV, hepatitis A virus; HBV, hepatitis B virus; INFLI, infliximab; IXE, ixekizumab; MACE, major adverse cardiovascular event; MTX, methotrexate; NBUVB, narrowband UVB phototherapy; NYHA, New York heart association; PASI, psoriasis area severity index; PIIIP, procollagen III peptide; PsA, psoriatic arthritis; PUVA, psoralen UVB phototherapy; QW, once weekly; RCT, randomised controlled trial; s.c., subcutaneous; SEC, secukinumab; SmPC, summary of product characteristics; TNFi, tumour necrosis factor inhibitors; USTK, ustekinumab; W, weight.

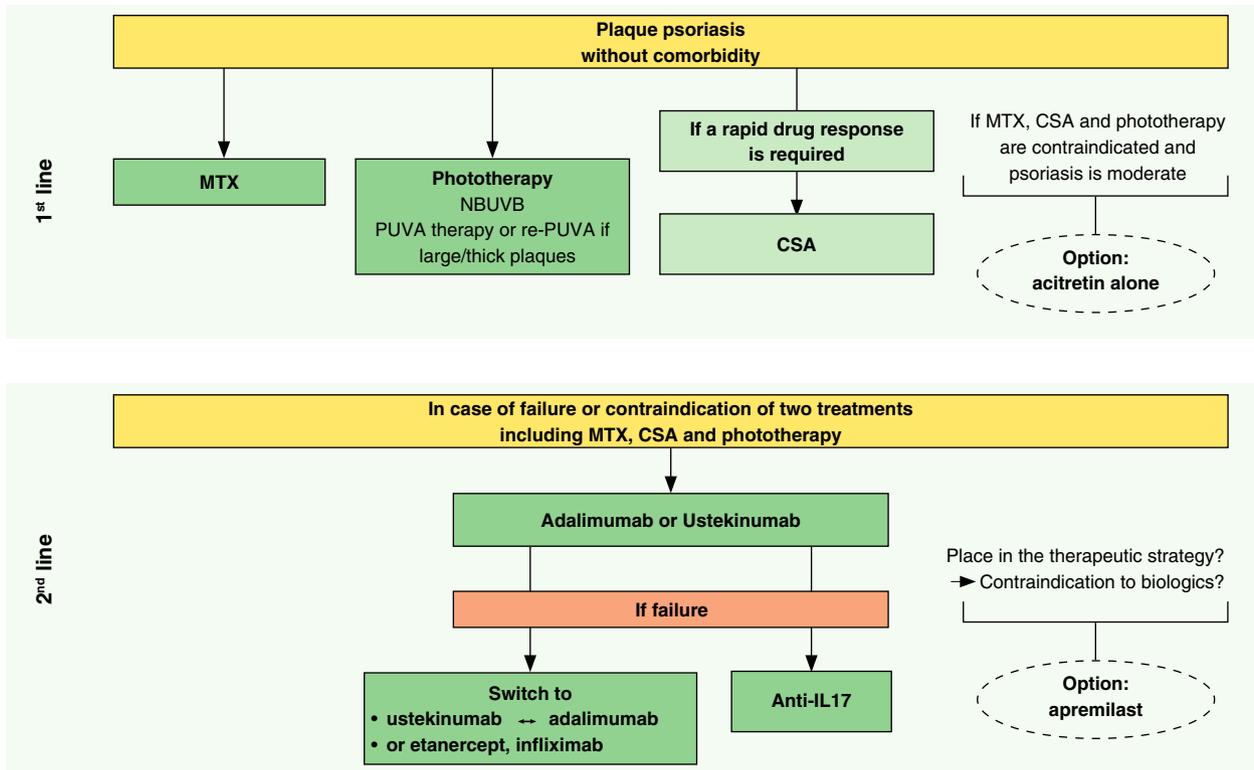


Figure 2 Treatment algorithm for patients suffering from plaque psoriasis without comorbidities. CSA, cyclosporin; MTX, methotrexate; NBUVB, Narrowband UVB; PUVA, psoralen UVA; re-PUVA, retinoid psoralen UVA.

Table 2 Summary of the clinical assessments associated with first-line (a) and second-line (b) systemic treatments for psoriasis. Adverse events are listed in order of frequency

Management	(a) First-line systemic treatments	MTX	CSA	Acitretin
Information to the patient	<p>Phototherapy</p> <ul style="list-style-type: none"> Long-term risk of skin cancer, synergistic effects of additional UV exposure during leisure time or self-treatment. Make sure that the patient wears goggles and protection for chronic sun-exposed areas (face, neck) and genital regions during the session. 	<ul style="list-style-type: none"> Adequate contraception for men and women. After the end of treatment, continued contraception is recommended for 3 months in men and for only 1 day in women (contraception should be continued until the end of treatment and conception is possible as soon as contraception is stopped). Inform the patient on how to take the drug (QW) and about early symptoms of AE. 	<p>CSA</p> <ul style="list-style-type: none"> CSA is permitted during pregnancy but may increase the probability of pregnancy-related complications. Reliable contraception is advised (note that the efficacy of progestin-containing contraceptives can be reduced). Avoidance of excessive sun exposure. Follow national cancer screening recommendations (breast, cervix, colon) 	<p>Acitretin</p> <ul style="list-style-type: none"> Teratogenic risk and necessity of long-term effective contraception (at least 3 years after discontinuation). Provide written information. Alcohol avoidance. Blood donation is forbidden during treatment and for up to 3 years after cessation of treatment. Start treatment on the second or third day of the menstrual cycle, after satisfactory contraception for at least 1 month prior to treatment.
Clinical examination before treatment	<ul style="list-style-type: none"> Preneoplastic skin lesions and malignant skin lesions. Dysplastic nevi. Concomitant medication (photo-toxic and immunosuppressive drugs). 	<ul style="list-style-type: none"> Past or active infection. Signs of liver cirrhosis and respiratory failure. Concomitant medication. Vaccination status. 	<ul style="list-style-type: none"> Medical history of arterial hypertension, malignancies, renal and liver diseases. Past or active infection. Malignancies. Blood pressure measurement on two separate occasions. Concomitant medication. Vaccination status. 	<ul style="list-style-type: none"> Concomitant medication. Signs of liver cirrhosis and metabolic syndrome.
Clinical examination during treatment	<ul style="list-style-type: none"> Control erythema before dosage and increase and record UV dose. Record the cumulative UV dose and the number of sessions. Lifelong screening of skin cancer is mandatory. 	<ul style="list-style-type: none"> AE: fatigue, nausea, vomiting, gastro-intestinal and mucosal ulcerations, signs of liver cirrhosis and respiratory failure, persistent cough. 	<p>Objective assessment of the disease (PAS/PGA/BSA/arthritis/DLQI) and evaluation of patient satisfaction</p> <ul style="list-style-type: none"> AE: signs of renal impairment, nausea, diarrhoea, hypertrichosis, gingival hyperplasia, paraesthesia. Blood pressure measurement. Skin cancer screening. Regular gynaecologic screening for papillomavirus infection. 	<ul style="list-style-type: none"> AE: hypervitaminosis A (cheilitis, xerosis), headache, conjunctivitis (contact lenses should be used with caution).

Table 2 Continued

Management	(b) Second-line systemic treatments	USTK	SEC/IXE	APR
Information to the patient	INFLI/ADA/ETA	<ul style="list-style-type: none"> • Possible weight gain during treatment. • Increased risk of infection. • Need for contraception. • Follow national cancer screening recommendations (breast, cervix, colon). • Rare cases of hypoglycaemia during treatment in diabetic patients. 	<ul style="list-style-type: none"> • Increased risk of infection, notably fungal infections. • Need for contraception. • Follow national cancer screening recommendations (breast, cervix, colon). 	<ul style="list-style-type: none"> • Risk of diarrhoea and nausea after treatment initiation. • Increased risk of infection. • Risk of depression. • Need of contraception.
Clinical examination before treatment	Objective assessment of the disease (PASI/PGA/BSA/arthritis/DLQI)	<ul style="list-style-type: none"> • Known chronic heart failure or heart failure symptoms. • Adenopathy. • Active/latent/exposure to tuberculosis. • Active or chronic infection. • Cancer. • Live vaccine: recent? In the future? 	<ul style="list-style-type: none"> • Inflammatory bowel disease (per-sonal or familial history). • Candidiasis. • Cardiovascular risk factors. • Adenopathy. • Active/latent/exposure to tuberculosis. • Active or chronic infection. • Cancer. • Live vaccine: recent? In the future? • Psychiatric disorders. • Suicide attempts. 	<ul style="list-style-type: none"> • Chronic infection. • Adenopathy. • Psychiatric disorder. • Suicide attempts. • Cancer.
Clinical examination during treatment	Objective assessment of the disease (PASI/PGA/BSA/arthritis/DLQI) and evaluation of patient satisfaction	<ul style="list-style-type: none"> • Weight gain. • Injection-site reactions. • Infections. • Cancer (particularly nonmelanoma skin cancer). 	<ul style="list-style-type: none"> • Cardiovascular risk factors and events (MACE). • Injection-site reactions. • Infection (candidiasis). • Diarrhoea, weight loss. • Psychiatric disorders. • Suicide attempts. • Cancer. 	<ul style="list-style-type: none"> • Diarrhoea. • Weight loss. • Psychiatric disorder/depression. • Suicide attempts. • Infection. • Cancer.

Molecules are categorized into three groups: classical systemic therapies, biologic agents and apremilast. The molecules order within each group was chosen randomly. ADA, adalimumab; AE, adverse event; APR, apremilast; BSA, body surface area; CSA, cyclosporin; DLQI, dermatology life quality index; ETA, etanercept; INFLI, infliximab; IXE, ixekizumab; MACE, major adverse cardiovascular event; MTX, methotrexate; PASI, psoriasis area severity index; PGA, physician global assessment; QW, once weekly; SEC, secukinumab; USTK, ustekinumab.

Table 3 Summary of the paraclinical assessments associated with systemic treatments for psoriasis

	MTX	CSA	Acitretin	INFLI	ADA	ETA	USTK	SEC	IXE	APR
Blood count	X W1, W2, W4, then every 2–3 months	X W4		X	X	X	X	X	X	X
AST, ALT, GGT, bilirubin	X W2, W4, then every 2–3 months	X W4, W12	X W4, W8, then every 3 months	X Only for INFLI: before every infusion	X	X	X	X	X	X
Creatinine	X W4, then every 2– 3 months	X W2, W4, then every mo	X	X	X	X	X	X	X	X
Electrolytes, magnesium		X								
CRP				X	X	X	X	X	X	X
Fasting blood glucose (if elevated, up HbA1c dosage)		X Then every 3 months	X	X	X	X	X	X	X	
Albumin	X									
Plasma protein electrophoresis				X	X	X				
Cholesterol, triglycerides		X W4, W12	X W4, then every 3 months							
Pregnancy test	X	X	X Every month during treatment and 1 and 2 months following discontinuation. Avoid pregnancy for 3 years	X	X	X	X	X	X	X
HBV/HCV	X	X		X	X	X	X	X	X	X
HIV	X	X		X	X	X	X	X	X	X
TST or IGRA				X	X	X	X	X	X	
PIIP or Fibroscan®	Every 6–12 months for PIIP or 1– 2 years for Fibroscan®. Fibroscan® should be performed as a pretreatment in obese patients.									
Chest X-Ray	X			X	X	X	X	X	X	
Liver ultrasound	X									

X, pretreatment recommended.

ADA, adalimumab; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APR, apremilast; CRP, C-reactive protein; CSA, cyclosporin; ETA, etanercept; GGT, gamma-glutamyl transferase; HbA1c, Glycated haemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; IGRA, interferon gamma release assay; INFLI, infliximab; IXE, ixekizumab; MTX, methotrexate; PIIP, procollagen III peptide; SEC, secukinumab; TST, tuberculin skin test; USTK, ustekinumab; W, weeks; X, pretreatment recommended. Molecules are categorized into three groups: classical historical systemic therapies, biologic agents and apremilast. The molecules order within each group was chosen randomly.

to be considered in these patients is provided in Table 4. Details of the findings are available in the full version of the manuscript (Appendix S4).

Management of particular forms of psoriasis

The recommendations for management of particular forms of psoriasis are summarized in Table 5.

Table 4 Summary of the recommendations for systemic treatments in patients with comorbidities or with special circumstances

Comorbidities and special circumstances		
Global management	First-line systemic treatments Phototherapy, MTX, CSA, acitretin	Second-line systemic treatments TNFi (ETA, ADA or INFLI), USTK, anti-IL17 (IXE or SEC), APR
Active alcohol abuse Refer to an addictologist for withdrawal.	<ul style="list-style-type: none"> Prefer NBUVB (Grade C) rather than PUVA. Acitretin, MTX, and CSA should not be considered as first-line treatments (Grade B). 	<ul style="list-style-type: none"> Prefer TNFi (particularly INFLI for improving compliance) or USTK (Grade C). Consider anti-IL 17 or apremilast (Expert opinion) – population excluded from clinical trials.
Breastfeeding	<ul style="list-style-type: none"> Prefer NBUVB (Expert opinion) or CSA (Grade A). Consider MTX (Grade C) (wait 24 h after the administration of MTX to breastfeed a child). Avoid PUVA (insufficient data) (Expert opinion). Absolute contraindication: Acitretin (Grade A). 	<ul style="list-style-type: none"> Consider start or maintenance of TNFi if there is no alternative (Expert Opinion). Avoid USTK, anti-IL17 and APR (Expert opinion): not enough available data.
Cancer (cured) Close collaboration with oncologist and/or multidisciplinary cancer care team.	<ul style="list-style-type: none"> Prefer MTX or phototherapy (except in cases of skin cancer) or acitretin (Grade C). Avoid CSA (Grade A). 	<ul style="list-style-type: none"> Case-by-case decision (Grade C). The initiation of a biological agent has to be discussed with the oncologist and depends on the stage and prognosis of the tumour (Grade B). If no alternative, consider USTK or TNFi (prefer ETA or ADA) (Grade C). Not enough follow-up data for APR and anti-IL17.
Demyelinating disease Involve a neurologist.	<ul style="list-style-type: none"> Prefer MTX (Grade C). Consider phototherapy (Grade C). No data available for acitretin and CSA (be aware of the neurotoxic effects of CSA, Expert opinion). 	<ul style="list-style-type: none"> Prefer USTK (Grade C) – longer follow-up data compared to anti-IL17). Consider anti-IL17 (Grade C) – no negative effect of SEC on multiple sclerosis in phase II). Avoid TNFi (Grade C). No data available for APR.
Diabetes <ul style="list-style-type: none"> Involve a diabetologist in case of uncontrolled diabetes. If possible, delay treatment initiation in patients with a glycosylated haemoglobin >8%. 	<ul style="list-style-type: none"> Prefer phototherapy (Grade C). Consider acitretin (Grade C) except in patients with dyslipidaemia. Consider MTX in case of phototherapy and acitretin contraindications (Grade B). Apply caution because of the increased risk of infection and hepatic fibrosis. Avoid CSA (Grade B). 	<ul style="list-style-type: none"> Prefer biological agents with a short half-life or those with fewer associations with an increased infectious risk (Avoid INFLI) (Expert opinion). Refer to major cardiovascular risk section below. Not enough data but no negative feedback for anti-IL17 and APR.
Heart failure Involve a consultant cardiologist.	<ul style="list-style-type: none"> Prefer NBUVB (Grade C) or acitretin (Expert opinion) or MTX (Expert opinion). Avoid CSA because of the associated increase in blood pressure (Grade A). 	<ul style="list-style-type: none"> NYHA I or II CHF: consider TNFi (prefer ETA) or USTK (Grade C). NYHA III or IV CHF: prefer USTK (Expert opinion). Avoid TNFi in NYHA class III or IV CHF (deleterious) (Grade A). Not enough data but no negative feedback for anti-IL17 and APR.
Hepatitis B or C Involve a consultant hepatologist.	<ul style="list-style-type: none"> Prefer NBUVB (Grade C) rather than PUVA. Consider acitretin if liver enzymes are normal (Grade C). Consider CSA in patients with chronic HCV (Grade C). No sufficient data for CSA therapy in patients with HBV (active, inactive, occult or resolved). Consider MTX only in case of resolved HBV (Grade C). 	<ul style="list-style-type: none"> In case of active HBV infection (HBV DNA >2000 IU/mL), TNFi must be deferred until the infection is controlled with an adequate antiviral treatment (Grade C). Consider TNFi (prefer ETA, Grade C) before USTK (less data available, Grade C) in cases with inactive HBV (HBV DNA <2000 IU/mL, normal transaminases, HbsAg+), in association with antiviral prophylaxis and regular liver tests and close HBV DNA load monitoring. Consider TNFi in cases of occult (HBV DNA <200 IU/mL, HbsAg–, antiHBc+, anti-HBs–),

Table 4 Continued

Global management	First-line systemic treatments Phototherapy, MTX, CSA, acitretin	Second-line systemic treatments TNFi (ETA, ADA or INFLI), USTK, anti-IL17 (IXE or SEC), APR
		<ul style="list-style-type: none"> • or resolved (anti-HBs+) HBV or in chronic HCV patients, in association with regular liver tests and close HBsAg/HCV RNA monitoring (Grade C). • No sufficient data available for anti-IL17 or APR.
HIV infection		
<ul style="list-style-type: none"> • Involve a relevant specialist. • Optimise effective antiretroviral treatment (Grade C). • Close monitoring of bacterial and mycobacterial infections. 	<ul style="list-style-type: none"> • Prefer NBUVB (Grade C) rather than PUVA. • Consider acitretin or MTX (Grade C). • Consider CSA only if NBUVB, acitretin or MTX are contraindicated (Grade C). 	<ul style="list-style-type: none"> • Consider ETA (before ADA, UST, INFLI) if no alternative and the viral load is persistently undetectable (Grade B). • Insufficient data available for anti-IL17 and APR.
Inflammatory bowel disease		
Close collaboration with a gastroenterologist.	<ul style="list-style-type: none"> • Prefer MTX (Grade A). • Consider CSA (Grade B) or NBUVB (Grade C). • No data available for acitretin. 	<ul style="list-style-type: none"> • Prefer ADA, INFLI or USTK (Grade A). • Avoid Anti-IL17 (Grade C). • No data available for APR.
Liver disease (cirrhosis, fibrosis)		
Involve a consultant hepatologist.	<ul style="list-style-type: none"> • Prefer NBUVB (Grade C) rather than PUVA. • Acitretin and CSA should not be considered as first-line treatments (Grade C). • Avoid MTX (Grade C). 	<ul style="list-style-type: none"> • Consider TNFi or USTK in patients with steatosis or compensated cirrhosis (Grade C). • No data are available for APR and anti-IL17.
Major cardiovascular risk		
Involve a consultant cardiologist.	<ul style="list-style-type: none"> • Prefer MTX (Grade B). • Consider phototherapy or acitretin (Expert opinion). • Avoid CSA because of increased blood pressure (Grade A). 	<ul style="list-style-type: none"> • Prefer TNFi (Grade A). • Consider USTK (Grade A) or anti-IL17 (Grade B) in case of TNFi failure and control of risk factors. • No data are available for APR but no negative feedback.
Obesity		
Dietary intervention: encourage weight loss (Grade B).	<ul style="list-style-type: none"> • Prefer phototherapy with prudent gradual increases of UV doses (Grade C) or MTX with close hepatic monitoring (Grade C). • Consider acitretin (Grade C). • Avoid CSA (Expert opinion) 	<ul style="list-style-type: none"> • Prefer USTK (Grade C- weight-based dosage and no association with weight gain). • In case of USTK failure, consider IXE (Grade C) before TNFi, SEC and APR (Expert opinion).
Pregnancy		
Close collaboration with an obstetrician-gynaecologist and paediatrician if CSA or TNFi are maintained during pregnancy.	<ul style="list-style-type: none"> • Prefer NBUVB (Grade B). • Consider CSA (Grade B). • Avoid PUVA (no sufficient data) (Expert opinion). • Absolute contraindication: acitretin, MTX, (Grade A). 	<ul style="list-style-type: none"> • Consider start or maintenance of ETA throughout if there is no alternative (Grade C). ADA or INFLI can be maintained until the 3rd trimester if there is no alternative (Expert opinion). • Avoid USTK and anti-IL17 and APR (Expert opinion): not enough available data.
Pregnancy (future planning)		
Interrupting treatment is mandatory for:	<ul style="list-style-type: none"> • acitretin: 3 years before conception (Grade A); • MTX: 24 h before for women and 3 months for men (Grade A); • PUVA (Expert opinion). • Continuation of CSA (Grade B) or NBUVB (Grade B) is allowed. 	<ul style="list-style-type: none"> • Consider maintenance of ETA if there is no alternative (Grade C). If there is no alternative, ADA or INFLI can be initiated or continued if necessary but must be discontinued at the end of the second trimester of pregnancy (Expert opinion). • Ideally interrupt TNF inhibitors before conception (according to SmPC): <ul style="list-style-type: none"> ○ ETA: 3 weeks before ○ ADA: 20 weeks before ○ INFLI: 24 weeks before • Interrupt the following treatments according to SmPC (5–7 half-lives before conception): <ul style="list-style-type: none"> ○ USTK: 15 weeks before

Table 4 Continued

Comorbidities and special circumstances		
Global management	First-line systemic treatments Phototherapy, MTX, CSA, acitretin	Second-line systemic treatments TNFi (ETA, ADA or INFLI), USTK, anti-IL17 (IXE or SEC), APR
		<ul style="list-style-type: none"> ○ IXE: 10 weeks before ○ SECU: 20 weeks before ○ APR: 1 day before
Psychiatric disorders (depression)		
Involve a consultant psychiatrist.	<ul style="list-style-type: none"> • Prefer phototherapy or CSA (Grade B). • Consider MTX (Expert opinion). • Insufficient data available for acitretin. 	<ul style="list-style-type: none"> • Prefer TNFi or USTK (Grade B). • Avoid APR (Grade B) and anti-IL17 (Expert opinion, possible class effect).
Renal impairment†		
Close collaboration with a nephrologist.	<ul style="list-style-type: none"> • Prefer NBUVB (Grade C) rather than PUVA. • Consider MTX or acitretin only in case of early and moderate renal impairment (GFR > 60 mL/min) (Grade C) • (In case of renal insufficiency stage 1 or 2: use MTX with standard dose. In case of stage 3: use a reduced dose of MTX. In case of stage 4 or 5: do not use MTX). • Contraindication: CSA (Grade A). 	<ul style="list-style-type: none"> • Prefer TNFi or USTK (Grade B). • Consider APR (dosage must be adapted in case of severe renal insufficiency) (Grade C) or consider anti-IL17 (Grade C).

†Five stages of renal insufficiency defined by the GFR (in mL/min/1.73 m²): GFR <90 (stage 1), GFR = 60–89 (stage 2), GFR = 30–59 (stage 3), GFR = 15–29 (stage 4), GFR <15 (stage 5).

ADA, adalimumab; APR, apremilast; CSA, cyclosporine; CHF, chronic heart failure; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INFLI, infliximab; IXE, ixekizumab; MTX, methotrexate; NBUVB, narrowband UVB phototherapy; NYHA, New York heart association; PUVA, psoralen UVB phototherapy; SEC, secukinumab; TNFi, tumour necrosis factor inhibitors; USTK, ustekinumab.

Table 5 Summary of the management recommendations for particular forms of psoriasis

Management of particular forms of psoriasis		
	First-line systemic treatments: phototherapy, MTX, CSA, acitretin	Second-line systemic treatments: TNFi, USTK, anti-IL17, APR
Nonpustular palmoplantar psoriasis	<ul style="list-style-type: none"> • Idem plaque psoriasis. 	<ul style="list-style-type: none"> • Idem plaque psoriasis.
Pustular palmoplantar psoriasis	<ul style="list-style-type: none"> • Prefer CSA (Grade B). • Consider local PUVA therapy (Grade B) or acitretin (Grade B) or acitretin and local PUVA therapy in combination (Grade B). • Consider MTX (Grade C). 	<ul style="list-style-type: none"> • Prefer ETA or UTSK (Grade B): more available data for both molecules. • In case of failure, consider other TNFi or anti-IL17 (Grade B).
Generalized pustular psoriasis	<ul style="list-style-type: none"> • Prefer CSA (Grade C) or acitretin (Grade C). • Consider MTX (Grade C). • Phototherapy not recommended (Expert opinion). 	<ul style="list-style-type: none"> • Prefer INFLI (Grade B, rapidity of action). • Consider USTK (Grade B). • Consider anti-IL17 (Grade C). • No data available for APR.
Erythrodermic psoriasis	<ul style="list-style-type: none"> • Prefer CSA (Grade B). • Consider acitretin (Grade C) or MTX (Grade C). • Phototherapy not recommended (Expert opinion). 	<ul style="list-style-type: none"> • Consider TNFi (prefer INFLI for speed of action), or USTK or anti-IL17 (Grade D). • No available data for APR.
Nail psoriasis	<ul style="list-style-type: none"> • Prefer MTX (Grade B). • Consider CSA (Grade B) or acitretin (Grade C). 	<ul style="list-style-type: none"> • Prefer USTK or TNFi (prefer ADA or INFLI) or APR (Grade B). • In case of failure, consider switching from USTK to TNFi and vice versa (Grade B) or consider anti-IL17 (Grade C).
Scalp psoriasis	<ul style="list-style-type: none"> • Idem plaque psoriasis. 	<ul style="list-style-type: none"> • Idem plaque psoriasis.

APR, apremilast; CSA, cyclosporine; ETA, etanercept; INFLI, infliximab; MTX, methotrexate; PUVA, psoralen UVB phototherapy; TNFi, tumour necrosis factor inhibitors; USTK, ustekinumab.

Psoriatic arthritis

Treatment recommendations for PsA have been issued by the European League Against Rheumatism (EULAR).¹⁹ These

recommendations were based on rigorous guideline development procedures, including a systematic review of the literature and evidence-based guideline development methods, and were

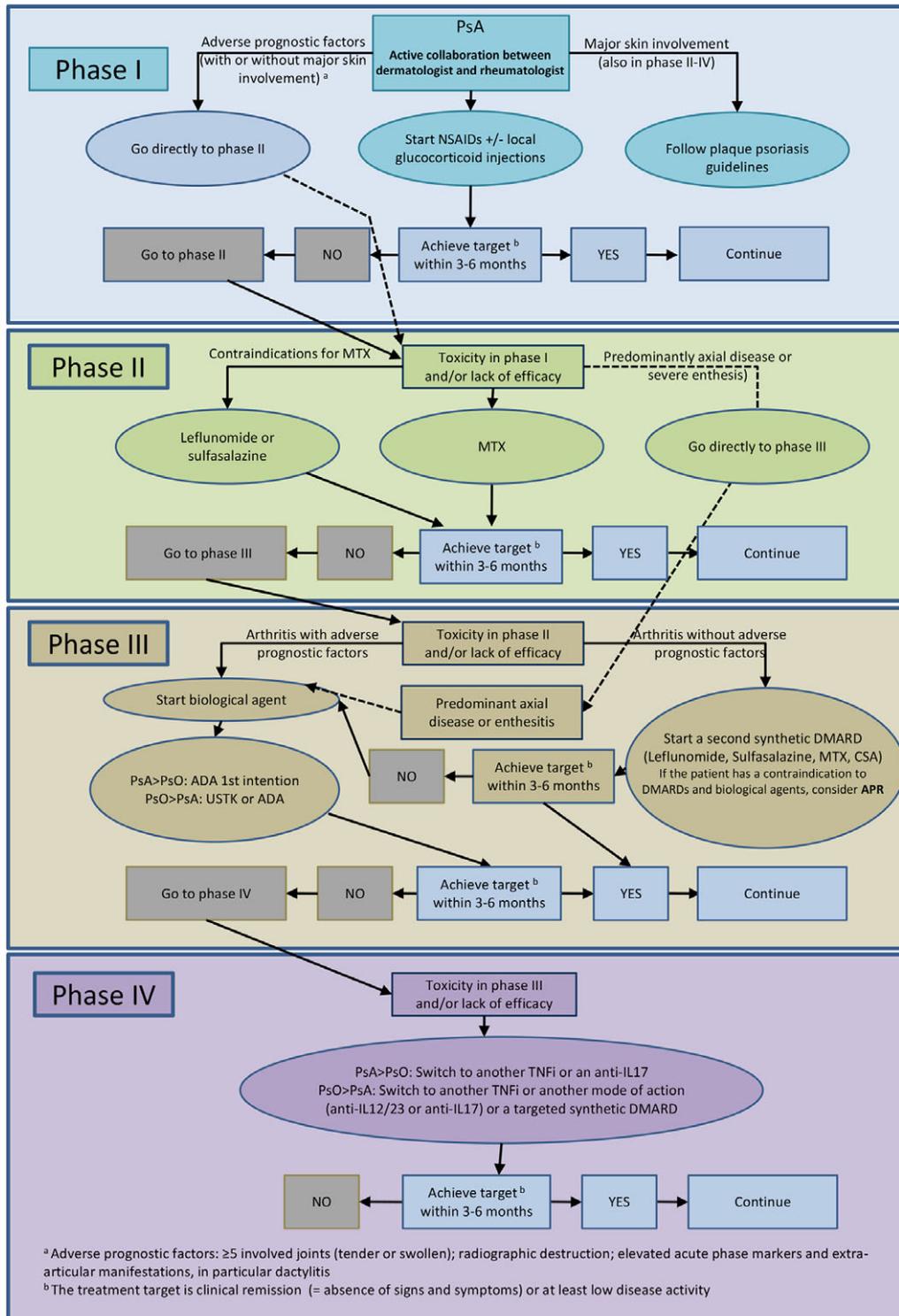


Figure 3 Psoriatic arthritis treatment algorithm – adapted from the EULAR, GRAPPA and UK NICE guidelines.^{6,9,19,20} APR, apremilast; ADA, adalimumab; CSA, cyclosporin; DMARD, disease-modifying anti-rheumatic drugs; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitors; USTK, ustekinumab.

updated in 2015 to include newly approved therapies such as IL-17 inhibitors, IL-12/23 inhibitors and anti-PDE4 agents.^{9,20} The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have also published PsA treatment recommendations.⁶ Gossec *et al.*²¹ compared the EULAR and GRAPPA recommendations and concluded that the recommendations of the EULAR were primarily rheumatological, whereas those of the GRAPPA were balanced between the rheumatological and dermatological aspects of psoriasis.

The British society of dermatology has also published guidelines regarding the treatment of psoriasis and PsA.¹⁴ Given the available data and the recent UK guidelines, we have modified the EULAR PsA algorithm to include apremilast and ixekizumab (Fig. 3). The main difference between our algorithm and that of the EULAR concerns phase III of the treatment strategy and the introduction of a biological agent. We propose categorizing patients according to two major clinical profiles. The first clinical profile would include psoriasis patients for whom skin involvement predominates over PsA. In such patients, we recommend that adalimumab or ustekinumab are used as first-line biological agents, similarly to patients with plaque psoriasis. The second clinical profile would include patients for whom PsA predominates over cutaneous involvement. In such patients, we recommend that a TNF inhibitor is used as a first-line biological agent. In case of failure, switching to a second TNF inhibitor or to another class of inhibitors (anti-IL17 or anti-IL12/23) should be considered. At present, secukinumab is the only anti-IL17 treatment approved for PsA but efficacy data are available for both ixekizumab and secukinumab. Anti-IL12/23 should be considered in case of peripheral PsA.

We recommend that apremilast, the therapeutic effect of which appears to be limited with no available data on its impact on peripheral bone structural damage, should only be used in PsA when there are contraindications to biotherapy, or in non-severe and non-active forms of the disease.

In the absence of published data and available tools for comparing the criteria for the degrees of severity of cutaneous and articular involvement, it appears that it is the patient who chooses which form of psoriasis (articular or cutaneous) affects them the most. In case of patient-reported predominant rheumatological involvement, the overall management of the patient should be ensured by the rheumatologist in collaboration with the dermatologist, and vice versa in case of predominant skin involvement.

Unmet needs in the French psoriasis guidelines

Several questions could not be addressed in the present recommendations as a result of a lack of evidence-based data. Notably, we were not able to provide satisfactory answers to the following questions.

- What is the exact place of apremilast in the therapeutic armamentarium?
- How long before and after surgery should apremilast be tapered?
- Should methotrexate be prescribed in association with biological agents?
- In patients treated with biological agents who experience complete clearing, is it possible to adjust or stop the treatment? What would be the best strategy; a gradual or immediate stop?

Further studies are necessary to provide clear answers to these questions.

Planned update of the French psoriasis guidelines

An update of the present guidelines will be necessary by 2020.

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Supporting information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:

Appendix S1. List of keywords used.

Appendix S2. Flowchart of analysis of selected guidelines and publications.

Appendix S3. Dosing scheme of phototherapy in psoriasis.

Appendix S4. Full version of the manuscript.