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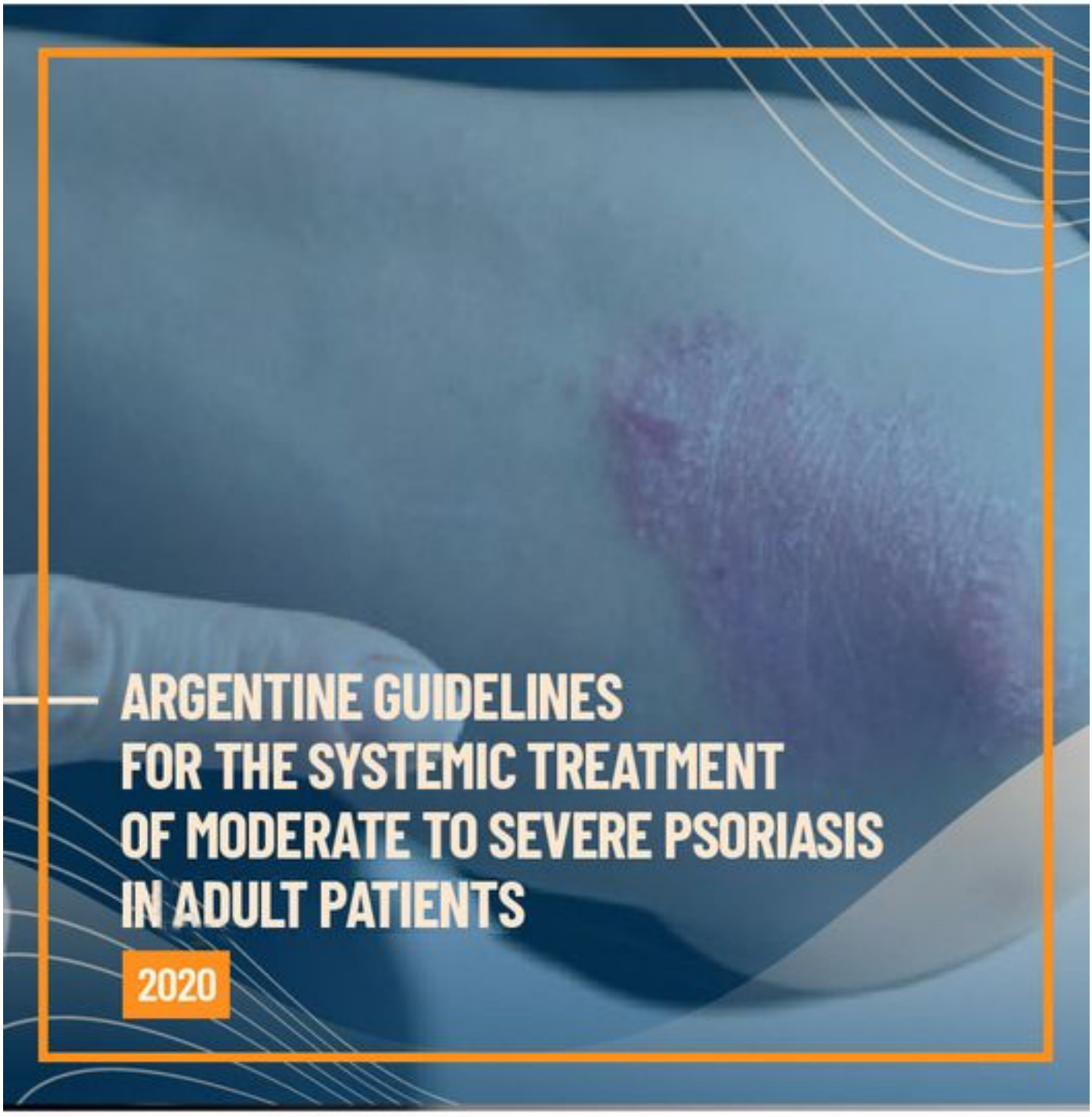

ARGENTINE GUIDELINES FOR THE SYSTEMIC TREATMENT OF MODERATE TO SEVERE PSORIASIS IN ADULT PATIENTS

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ARGENTINE GUIDELINES FOR THE SYSTEMIC TREATMENT OF MODERATE TO SEVERE PSORIASIS IN ADULT PATIENTS

SOARPSO (Sociedad Argentina de Psoriasis, [*Argentine Society of Psoriasis*])

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Introduction and methodological aspects

Objectives of the guideline

The aim of this guideline for the systemic treatment of adult patients with psoriasis is to provide recommendations based on the best available evidence.

Disease severity, comorbidities and individual preferences of the affected patients are considered important parameters in the selection of strategies for the treatment of psoriasis.[1-3]

For this purpose, a literature search was conducted in the following databases: MEDLINE (PubMed), Epistemonikos, Cochrane Library, Scielo and Google Scholar. The publication deadline was 31 May, 2020. Publications in Spanish, English and Portuguese were searched using the keywords "psoriasis", "*psoriase*", "*tratamiento*", "treatment" and "*tratamento*". The following where organized hierarchically:

- clinical practice guidelines based on evidence
- systematic reviews with and without quantitative component (meta-analysis)
- randomized and controlled trials (RCT)
- observational studies
- real-world registries
- evaluations of biosimilar drugs

The literature collected included five evidence-based clinical practice guidelines.[3-7] These and the other articles identified in the search were assessed using the current GRADE recommendations.[8] The corresponding evidence tables were developed and the results were submitted to a committee of dermatologists with expertise in psoriasis treatment, who were responsible for the development of this guideline. The selected questions for the development of the recommendations were based on the PICO (population, intervention, comparison, outcome) system proposed by the GRADE system. Based on the analysis of the evidence and the discussion among the authors, a total of 15 recommendations were developed and are presented with their rationale herein.

The direction and strength of the recommendations were expressed as suggested by the GRADE system and its adaptations (Table 1).[9]

Table 1. Formulation of the recommendations [8-10]
Strong recommendation ("**is recommended**..."): based on solid evidence regarding the net benefit of an intervention over its potential undesirable consequences. Most informed patients would choose the recommended option. Weak recommendation ("**is suggested**..."): the evidence of the net benefit of the intervention is of lower quality or the patients' choice will vary according their values and preferences. The desirable consequences of the intervention probably outweigh the possible undesirable effects. Good clinical practice point: recommended practice based on expert panel opinion.

Components of PICO questions

[P]opulation

a. Adult patients with moderate to severe plaque psoriasis

b. Elderly patients (≥ 65 years old) with moderate to severe plaque psoriasis

c. Pregnant or breastfeeding women with moderate to severe plaque psoriasis

d. Patients with erythrodermic psoriasis

e. Patients with generalized pustular psoriasis

f. Patients with palmoplantar pustular psoriasis

g. Patients with psoriasis in specific localizations

[I]ntervention

1. Nonbiologic systemic therapies (in alphabetical order: acitretin [ACI], cyclosporine [CsA], methotrexate [MTX]

2. Biologics (in alphabetical order: adalimumab [ADA], certolizumab pegol [CZP], etanercept [ETA], guselkumab [GUS], infliximab [IFX], ixekizumab [IXE], secukinumab [SEC], risankizumab [RIS], ustekinumab [UST])
3. Biosimilars
4. Selective immunosuppressants: apremilast (APR)
5. Phototherapies: narrowband ultraviolet B therapy, broadband ultraviolet B therapy, psoralen + ultraviolet A (PUVA)

[O]utcomes

- PASI75: Proportion of patients with ≥ 75% reduction in the PASI index
- PASI90: Proportion of patients with ≥ 90% reduction in the PASI index
- PASI100: Proportion of patients with 100% reduction in the PASI index
- Reduction of the affected body surface area (BSA)
- Absolute PASI ≤ 3
- Proportion of patients achieving a PGA score of 0-1
- Significant improvement in quality of life
    - Proportion of patients achieving a DLQI score of 0-1
    - Improvement of baseline DLQI by 4-5 points
- Safety outcomes
    - Proportion of patients with serious adverse events
    - Proportion of patients with treatment discontinuation due to adverse events
    - Percentage of patients with adverse events of special interest
- NAPSI (nail psoriasis)

PICO questions

1. In adult patients with moderate to severe plaque psoriasis, which should the first-choice treatment be?
2. Which is the best treatment regimen for elderly patients (≥ 65 years old) with moderate to severe plaque psoriasis?

3. Which is the best treatment regimen for pregnant or breastfeeding women with moderate to severe plaque psoriasis?
4. In patients with erythrodermic psoriasis, which should the first-choice treatment be?
5. In patients with generalized pustular psoriasis, which should the first-choice treatment be?
6. In patients with scalp psoriasis, which should the first-choice treatment be?
7. In patients with palmoplantar psoriasis, which should the first-choice treatment be?
8. In patients with nail psoriasis, which should the first-choice treatment be?
9. In patients with inverse psoriasis, which should the first-choice treatment be?

Target audience

The content of this guideline is intended for all healthcare professionals involved in the treatment of adult patients with psoriasis who require systemic treatment.

Treatment goals

Several factors should be taken into account when defining therapeutic goals for patients with moderate to severe psoriasis, including disease severity, absolute (or compared to baseline) values on validated and recognized scales, the presence of comorbidities, the impact of the disease on the physical, psychological and social well- being of the patient, and patient preferences, among others.[5] The new treatment goals in the systemic treatment of psoriasis are summarized in Table 2.

Table 2. New treatment goals for psoriasis
Absolute PASI ≤ 3 PGA 0-1 (0: no psoriasis lesions; 1: almost no lesions or almost clear) DLQI 0-1 PASI90 AND PASI100
DLQI: *Dermatology Life Quality Index*; PASI: *Psoriasis Area and Severity Index*; PGA: *Physician Global Assessment*

Calculating an absolute PASI ≤ 3 is easier than estimating a PASI75 response. It is also independent of variations in baseline disease severity and is closer to the concept of PGA 0-1.[5] The inclusion of a DLQI of 0-1 in the endpoints is based on the fact that this score indicates the absence of an impact of psoriasis on quality of life.[5] The PASI90 and PASI100 responses are endpoints that emerged as a result of the high efficacy of recent biological therapies.[5]

Treatment goals should be established prior to initiation of therapy and then reassessed periodically, taking into account the time required for the maximum effect of each drug. If the desired outcome is not achieved, treatment strategy should be modified.[5]

Conflicts of interest

Dr. Bourren is a speaker for Janssen and Abbvie laboratories; she has served on advisory boards for Janssen and Abbvie laboratories; she has received support for participation at conferences and webinars on behalf of Janssen, Abbvie and Novartis laboratories; she is currently involved in a research protocol for Lilly laboratory. Dr. Dei Cas has received professional fees from Abbvie, Janssen, Novartis and Lilly laboratories. Dr. Echeverría is a speaker and advisor for Abbvie, Amgen, Eli Lilly, Investi, Janssen, Novartis, Pfizer and Sanofi Genzyme laboratories. Dr. Kogan is the principal investigator at Abbvie, Boehringer-Ingelheim, Eli Lilly, Janssen, Novartis, Pfizer and Sanofi laboratories; she is also lecturer for Abbvie, Eli Lilly, Janssen, Novartis, Pfizer and Raffo laboratories. Dr. Maskin has participated in advisory boards and lectures sponsored by Abbvie, Janssen, Eli Lilly, L'Oreal, Novartis and Sanofi laboratories. Dr. Ortega has received payment from Abbvie and Novartis laboratories.

The remaining authors declare no conflicts of interest.

Recommendations

#1. For adult patients with moderate to severe plaque psoriasis, the following treatment (in alphabetical order) is **recommended**: acitretin (ACI), adalimumab (ADA), apremilast (APR), certolizumab pegol (CZP), cyclosporin A (CsA), guselkumab (GUS), ixekizumab [IXE], methotrexate (MTX), phototherapy (PHO), risankizumab (RIS), secukinumab (SEC), ustekinumab (UST). The factors influencing this selection include drug accessibility, availability, the experience and the safety profile.

Strength of the recommendation: strong, in favor

Statement of good practice: The eventual use of a biological therapy is warranted in those patients who were unresponsive to non-biological treatment, if the latter is contraindicated, or if it is required due to the severity of the disease.

In order to make this recommendation, the results of the clinical studies where each of the above-mentioned treatments were compared against placebo were assessed, considering the outcomes of the PICO questions with special focus on the endpoints listed in table 2. The rationale detailed herein is described based on the same drug alphabetical order as they were mentioned in the Recommendations text.

Non biological systemic therapies

ACI (ATC[11] code D052202) is an oral (P.O.) retinoid. In 2 RCT (n = 194) moderate-quality evidence showed that this drug may be associated with a higher probability of achieving a PASI75 response in this population.[12,13] In one of those studies, the improvement reached statistical significant levels with the dosage range from 50 to 75 mg.[13] However, the safety profile is also related to the administered dose; based on a retrospective analysis of the pooled data from 2 clinical trials,[14] the incidence of some adverse events such as shedding, pruritus, alopecia, and spasms increased

as higher doses were indicated. The teratogenic effect of ACI is also a variable to be considered; this drug is contraindicated during pregnancy.

CsA (ATC code L04AD01), in doses from 3 to 5 mg/kg/day, is an immunosuppressor used for the treatment of psoriasis, and available for P.O. administration. There is low-quality evidence from RCT and from observational studies suggesting that CsA is associated with the achievement of some goals such as PGA0-1 and PASI75 during induction therapy (8-10 weeks) and maintenance therapy (24 weeks) in patients with psoriasis. As regards the safety profile, a prospective cohort followed by up to 5 years yielded low-quality evidence that showed a potential increase in the incidence of malignancies in the treated patients. Furthermore, an analysis of the data from 16 RCTs reported that CsA has been associated with a creatinine increase of ≥ 30% in more than half of the patients that were followed for at least 2 years, as well as an incidence of glomerular sclerosis of up to 26% at 10 years. This high-quality evidence indicates that CsA is associated with a higher risk of renal impairment for long periods of time.[15-21] According to the experts, it is an effective alternative in the clinical practice when it is indicated for up to 6 months, including the monitoring of the known adverse events.

MTX (ATC code L01BA01) is a folic acid analogue used for the treatment of psoriasis. Based on the analysis of the pooled data available from RCTs, MTX therapy is characterized by a higher probability of achieving PASI75, PASI90 and PGA0-1 since the induction phase (low to moderate-quality evidence).[22,23] This therapy is accompanied by the indication of 5 mg of folic acid P.O. 48 hours after MTX administration. The recommended monitoring laboratory tests are performed within 7 to 14 days following the first dose, separated from the drug administration. The subsequent monitoring tests may be indicated on a monthly or quarterly basis, according to the opinion of the experts.

In terms of safety profile, a meta-analysis of 32 RCTs (n = 13177) in which MTX was indicated in patients with various indications (including psoriasis) reported a higher risk of increased liver transaminases, although no major risk of serious events was

reported (including cirrhosis, liver impairment and mortality).[24] Note that its safety profile does not seem to be different between oral and subcutaneous (SC) formulations, based on the available evidence.[25] MTX is considered as a category "X" drug in terms of its use during child-bearing age both for women and men. Additionally, the team of experts does not recommend the intramuscular administration of MTX.

Biological systemic therapies

ADA (ATC code L04AB04) is a human immunoglobulin G1 anti-tumor necrosis factor alpha (TNF-α) monoclonal antibody. It is administered subcutaneously. There is data from 7 RCTs that compared the efficacy and safety of ADA *versus* placebo.[26-32] These trials reported a significant increase in the probability of achieving PGA0-1, PASI75, PASI90 and PASI100 during the induction and maintenance therapy with ADA (high-quality evidence). Moreover, one of the RCTs showed a potential clinically relevant improvement in the absolute DLQI score with 40 and 80 mg doses administered fortnightly.[26]

A network meta-analysis with moderate-quality evidence reported a marginal increase in the risk of serious adverse events (data from 19 RCTs) or adverse events that led to treatment discontinuation (data from 22 RCTs).[32] The risk of severe infections did not significantly differ from the expected rate for placebo.[32]

CZP (ATC code L04AB05) is a monoclonal antibody formed by the Fab fragment of a humanized recombinant antibody anti-TNF-α expressed in *E. coli*. CZP molecule is conjugated with polyethylene glycol. There is high-quality evidence from 3 RCTs showing that SC administration of CZP is significantly superior to placebo in achieving the endpoints such as PASI75, PASI90 and PGA0-1 at doses of 200 or 400 mg SC every 2 weeks, not only during the induction therapy but also during the 48-week follow up (Studies CIMPACT and CIMPASI 1 and 2).[33-35] The safety profile is consistent with that of other drugs of the same therapeutic class, with a probable increase in the risk of serious adverse events or treatment discontinuation *versus* placebo (low to moderate-quality evidence), and with no new safety signals.[34,35]

GUS (ATC code L04AC16) is a fully human IgG1 monoclonal antibody that selectively binds to interleukin (IL) 23. According to the pooled data analysis from 5 RCTs (n = 1592), there is high-quality evidence showing statistically higher efficacy of GUS on PASI75, PASI90 and PASI100 endpoints versus placebo.[36-40] The meta-analysis of such information does not suggest that GUS is associated with an increased risk of serious adverse events or events that lead to treatment discontinuation.[41]

IXE (ATC code L04AC13) is a humanized IgG4 monoclonal antibody that targets IL 17A. Based on the results from 4 RCTs (n=1383), IXE therapy is associated with an improvement in PASI75, PASI90 (high-quality evidence for both parameters) and PASI100 (moderate-quality evidence).[42-43] Regarding its tolerability profile, a 5-year meta-analysis of safety outcomes (n=3736) reported serious adverse event, severe infection and major cardiovascular event rates consistent with placebo. The incidence of inflammatory bowel disease was 0.4% in patients treated with IXE *versus* cero cases in those who received placebo. This potential association requires further research.[44]

RIS (ATC code L04AC18) is a humanized IgG1 monoclonal antibody. Its mechanism of action consists in the selective binding to the p19 subunit of IL23 in order to inhibit the interaction with its receptor. RIS therapy is associated with a significant improvement in PASI75, PASI90 and PASI100 endpoints (high-quality evidence from at least 3 RCTs).[45-46] A meta-analysis assessing the tolerability of RIS therapy in patients with psoriasis (n=798) showed that the prevalence of severe adverse events was consistent with that reported for placebo, while the discontinuation rate due to adverse events reached 0.7% for RIS *versus* 3.9% for placebo.[43]

SEC (ATC code L04AC10), an IgG1 human monoclonal antibody, targets IL-17A and prevents the interaction with its specific receptor. The indication of SEC administered SC in patients with moderate to severe plaque psoriasis has been

associated with significant benefits in key endpoints such as PASI75, PASI90, and PASI100 (high-quality evidence of at least 3 RCTs)[47-48] and PGA0-1 (moderate-quality evidence of at least 3 RCTs).[47-48] This intervention may be associated with a greater risk of treatment discontinuation due to adverse events *versus* placebo, and with a potential higher risk of major cardiovascular events (MACEs). However, a pooled analysis of data from 10 Phase 2 or Phase 3 studies (n=3993) showed an incidence of MACE over a 52-week follow-up period that was similar for SEC, ETA and placebo.[49]

UST (ATC code L04AC05) is an IgG1 human monoclonal antibody that binds to the P40 subunit of IL-12 and IL-23. There is moderate to high-quality evidence from 5 RCTs showing the efficacy of UST in adult patients with psoriasis in moderate to severe plaque in terms of PASI75, PASI90, PASI100 and PGA0–1 endpoints.[50-54] UST long-term safety was confirmed by a pooled analysis of data from 4 studies (n=3117).[55]

As for ETA (a construct protein comprising the p75 receptor of the TNF coupled to the Fc portion of an IgG1 human monoclonal antibody, ATC code L04AB01) and IFX (a chimeric IgG1 monoclonal antibody, ATC code L04AB02), the team of experts **suggests** the use of these drugs in adult patients with moderate to severe plaque psoriasis, based on the available evidence[56-64] and on factors such as accessibility, availability and experience.

Small molecules

APR (ATC code L04AA32) is a phosphodiesterase-4 inhibitor that reduces inflammatory response by modulating the expression of pro-inflammatory cytokines. There is moderate-quality evidence from at least 5 RCTs showing the efficacy of APR in the treatment of patients with moderate to severe psoriasis based on PASI90, as well as a probable improvement on DLQI score.[65-68] Regarding the safety profile, a recent update stated that adverse events are frequently reported but they are usually mild to moderate and do not tend to result in treatment discontinuation.[69]

Phototherapies

Phototherapies (PUVA, UVB and new devices) reduce skin inflammation, although they do not have an impact on systemic inflammation. There is low to very low methodological quality evidence reporting the efficacy of PHO with narrowband UV (1 RCT), with an associated prevalence of painful erythema of 8%.

#2. In adult patients with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with SEC is **recommended** as compared to ETA.

Strength of the recommendation: strong, in favor

Phase 3 studies ERASURE (*Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis*) and FIXTURE (*Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis*) compared the efficacy of SEC therapy *versus* the administration of ETA or placebo. In two analyses of the pooled data from both studies (moderate to high-quality evidence),[47,71] the proportion of patients with psoriasis that reached PASI75 at Week 12 was 77.1% for SEC 300 mg, 67% for SEC 150 mg and 44% for ETA ($p < 0.001$ for both doses of SEC). Significantly higher rates were also achieved for SEC in relation with PGA0-1. Furthermore, this clinical response was faster in participants receiving SEC (3-week or 3.9 week median for the doses of 300 and 150 mg, respectively) as compared with participants treated with ETA (median: 7 weeks).[47] Additionally, SEC administration was associated with a sustained response in most of the patients by Week 52.[47]

#3. In adult patients with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with SEC is **recommended** as compared to UST.

Strength of the recommendation: strong, in favor

There is high-quality methodological evidence from studies CLEAR[72] and CLARITY,[73-74] which reported that SEC administration was associated with statistically significant benefits as compared to UST based on PASI75, PASI90, PASI100 and DLQI0-1 endpoints. This data was confirmed in the long-term follow-up (52 weeks).[74] The safety profile of SEC was consistent with that described for

UST and with the data reported in the pivotal Phase 3 studies of SEC, both in the short term[72] and in the long term.[74]

#4. In adult patients with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with IXE is **recommended** as compared to UST.

Strength of the recommendation: strong, in favor

There is at least 1 RCT (study IXORA-S) that carried out a head-to-head comparison of the efficacy and safety of IXE (n=136) *versus* UST (n=166) over 52 weeks of treatment in adult patients with psoriasis.[75] This study reported that a significantly higher proportion of patients treated with IXE reached the objectives of PASI90, PGA 0 or PGA0–1, as compared to those who received UST. On the other hand, although the reactions in the administration site were more frequent with IXE, no statistically significant differences were reported between both treatment groups for treatment-related adverse events, serious adverse events and treatment discontinuation rates.[75]

#5. In adult patients with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with GUS or RIS is **recommended** as compared to UST.

Strength of the recommendation: strong, in favor

GUS additional benefits are recognized in patients with psoriasis who have not responded adequately and early to UST therapy. However, there is no data from long-term head-to-head comparisons between both therapies in individuals who have not received UST previously. The COMPASS analysis, which assessed the individual data of the participants in the studies VOYAGE-1 and 2 (GUS) and NAVIGATE (UST), estimated that GUS therapy was associated with a significantly

higher probability of achieving PASI75, PASI90 and PASI100 response, both by Week 16 and by Week 40 (high-quality evidence).[76]

Moreover, there is high-quality evidence derived from one Phase 2 RCT (n=166), in which a head-to-head comparison was performed between RIS (90 OR 180 mg) and UST administration. Based on the pooled analysis of the data for both doses, RIS was associated with a significantly higher proportion of patients who achieved PASI90 and PASI100 compared with UST therapy after 12 weeks of administration. This efficacy was maintained for up to 20 weeks after the last indicated dose of either drug.[77]

#6. In adult patients with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with GUS or RIS is **recommended** as compared to ADA.

Strength of the recommendation: strong, in favor

One Phase 2 RCT (study X-PLORE) gathered high-quality methodological evidence of the comparison between GUS and ADA for the treatment of adult patients with moderate to severe plaque psoriasis.[78] The study also included a placebo arm, but participants in this group were switched to receive GUS from Week 16. The proportion of patients who achieved PGA0-1 was significantly higher by Week 40 in each of the dosing groups of GUS when compared with the participants treated with ADA. Upon the end of the placebo phase, the proportion of overall adverse events, serious adverse events, and infections was similar for the control group and for both treatments; between Week 16 and Week 52, infections were reported in 30% and 37% of the patients who received GUS and ADA, respectively.[78]

Furthermore, the multicenter RCT IMMVent yielded high-quality evidence to compare the efficacy of RIS (n=301) relative to ADA (n=304) in adult patients with moderate to severe plaque psoriasis.[79] The PASI90 was achieved in 72% and 47% of the cases, while sPGA0-1 was achieved in 84% and 60% of the patients,

respectively; both differences achieved at Week 16 reached statistically significant levels. Between Week 16 and Week 44, the participants who had responded to ADA were randomized again either to continue with said treatment or to switch to RIS; PASI90 was achieved in 66% of the patients who started RIS compared with 21% of those who continued in the ADA group.[79] No new safety signals were observed in these patients.

Note: following the closure of the literature search for this guideline, the international multicenter study IMMerge was published, which reported that therapy with RIS was at least as good as SEC administration in achieving PASI90 at Week 16, while it was statistically superior in achieving such endpoint after 52 weeks of administration. Moreover, RIS was associated with a statistically higher probability of achieving PASI100 and sPGA0-1 after one-year follow up.[80]

#7. In adult patients with moderate to severe plaque psoriasis, the available evidence **does not suggest** differences in the efficacy and safety between the new drug and its biosimilar for ETA *vs*. GP2015, ADA *vs*. ABP501 and IFX *vs*. CT-P13.

Strength of the recommendation: weak, in favor

A biosimilar is a biological medicinal product that contains a version (copy) of the active ingredient of the originally-approved biologic. Biosimilars are manufactured according to regulatory authorities' specific requirements in terms of quality, safety and efficacy; moreover, their comparability with the reference product must be confirmed.[81] When this guideline was drafted, there were 3 approved biosimilars in Argentina for the treatment of patients with psoriasis.

GP2015 is a biosimilar product of ETA, assessed under the study EGALITY; in this RCT (n=480) high-quality methodological evidence was collected on the absence of statistically significant differences between both products to achieve PASI75 at

Week 12. Regarding safety, the incidence of serious adverse events or events that led to treatment discontinuation was consistent for both interventions. The crossover from one strategy to the other was not associated with increased anti-ETA antibodies or anti-biosimilar antibodies (moderate-quality evidence).[82]

ABP501 is a biosimilar drug of ADA, and its efficacy and safety were reported in a Phase 3 study in which 326 patients with moderate to severe plaque psoriasis completed the planned follow-up. Based on the collected data, no statistically significant differences were found between both treatment strategies by Week 16 in the improvement of absolute PASI and in PASI90 and PASI100 endpoints (high-quality evidence). The safety profile was comparable in both treatment groups, with no differences in the proportion of adverse events of interest. The crossover of the patients initially treated with ADA that switched to ABP501 was not associated with new safety signals or a higher incidence of immunogenicity (moderate-quality evidence).[83]

CT-P13, a biosmilar of IFX, was assessed in a Phase 4 randomized study NOR-SWITCH that included a total of 482 patients, from which 35 had been diagnosed with plaque psoriasis. In the subgroup of participants with this diagnosis, the efficacy of CT-P13 was as good as that of the innovator product IFX for a pre-defined margin of 15%. No differences were reported in the proportion of adverse events (including those considered serious or that led to treatment discontinuation) between both strategies.[84]

#8. In elderly patients with moderate to severe plaque psoriasis, the use of the same lines of treatment as younger adults is **suggested**, based on the available evidence and on the expert committee experience. Frequent comorbidities in this age group should be considered.

Strength of the recommendation: weak, in favor

Advanced age tends to be an exclusion criterion in most RCTs; on the other hand, pharmacokinetic and pharmacodynamic differences described with aging, as well as the higher prevalence of drug interactions, may be associated with an increased susceptibility to adverse reactions.[85] However, experts have suggested that the definition of elderly requires more restrictions, given the increasing number of patients over the age of 65 who have good health and are socially active and that, therefore, do not represent the population of fragile individuals.[85]

Most of the existing evidence on the treatment of psoriasis in patients over the age of 65 corresponds to subgroups of clinical trials,[86-87] narrative reviews[88-91] and to a systematic review carried out when most of the current therapies were not available[92] (low to very low quality evidence).

According to the available information and to the authors' experience, for this age group we suggest using the same treatments as for younger adults, considering the age-associated comorbidities.

#9. In pregnant women with moderate to severe plaque psoriasis, based on the existing evidence, the treatment with PHOTO (UVB), CER or CsA is **suggested**. The systemic treatment shall be indicated only if strictly necessary.

Strength of the recommendation: weak, in favor

The management of pregnant women with moderate to severe plaque psoriasis requires special consideration, given the importance of the treatment regarding maternal and fetal safety. No RCTs that include this group of patients have been conducted, and the existing evidence has been obtained from the reviews of cohort studies and case reports.[93-95]

Phototherapy with UVB, and CsA are considered as category B alternatives for the systemic treatment of psoriasis in pregnant women when it is strictly necessary.[5] CsA is a category "C" drug in this group of patients.

Recently, based on the moderate-quality evidence obtained from a postmarketing surveillance database, the exposure of 1138 pregnant women to CER has not been associated with teratogenic effects or with a higher risk of fetal death; therefore, this therapeutic strategy may be considered a safe strategy.

#10. In patients with psoriatic erythroderma, given the scarce available evidence and based on the experience and availability, the Expert Committee **suggests** the use of ACI, ADA, CsA, ETA, IFX, IXE, MET or SEC (in alphabetical order, not preference-based). For the selection of the drug, several factors shall be considered, including whether the erythroderma is acute or chronic.

Strength of the recommendation: weak, in favor

Erythroderma is an unusual form of psoriasis and there is little literature on this condition; no head-to-head studies have been published to date comparing the drugs used for the treatment of this condition. A recent systematic review of 23 retrospective uncontrolled studies gathered low-quality evidence on the benefits of various systemic agents and biological treatments, although it is not possible to establish a first line of therapy due to the lack of RCTs or head-to-head comparisons between available treatments.[97]

#11. For patients with generalized pustular psoriasis, given the scarce available evidence and based on the experience and availability, the Expert Committee **suggests** the use of ACI, CsA, or IXE (in alphabetical order, not preference-based).

While systemic corticosteroids are usually contraindicated in patients with psoriasis, they may be used in this group of patients under exceptional circumstances, for a short period of time, and together with other treatments.

Strength of the recommendation: weak, in favor

There is scarce and very low quality evidence on treatment strategies for patients with generalized pustular psoriasis, mainly obtained from two meta-analyses of observational studies.[98,99] Based on the current information, the Expert Committee's experience and treatment availability, therapy with ACI, CsA or IXE is suggested for this group of patients.[5]

#12. For patients with palmoplantar psoriasis, the Expert Committee **suggests**, in order of preference, using ACI, ACI + PHO, MTX, APR and biological therapies, with the possibility of combining systemic treatments or topical medications + systemic drugs.

Strength of the recommendation: weak, in favor

For this group of patients, the available information was obtained from 3 RCTs[100-102] and from a meta-analysis of 37 studies (n=1663).[103] The gathered evidence was thought to be of low to very low quality, with limitations as to the interpretation as a result of the design of the studies and the risk of bias. Based on the authors' experience and the published information,[5-7,103] the administration of ACI, ACI + PHO, MTX, APR or biological agents is suggested for these patients, in this order of preference.

#13. For patients with scalp psoriasis, the use of APR, MTX and biological therapies, in this order of preference and with the possibility of combination with topical treatments, is **recommended**.

Strength of the recommendation: strong, in favor

For this population of patients with psoriasis, there is a sub-analysis of the study BELIEVE, in which ADA administration was associated with a probability of achieving PASI75 in 77.8% of the 668 participants; the sub-analysis described that this therapy improved the scalp-related symptoms (low-quality evidence).[104]

On the other hand, an RCT comparing ETA therapy *vs*. placebo in patients with scalp psoriasis reported a significantly higher mean reduction in the Psoriasis Scalp Severity Index (PSSI) in the intervention group (moderate-quality evidence).[105]

There is also a comparative study that included 21 participants with scalp psoriasis, in which they were administered either ADA or IFX. There was a minor trend, but not statistically significant, toward achieving PASI75 among patients treated with ADA, thus, it was not possible to draw definite conclusions (very low quality evidence).[106]

Furthermore, APR treatment was compared against placebo in a combined analysis of the 1225 patients that participated in studies ESTEEM-1 and ESTEEM-2, which included 66.7% and 65.5% of moderate to severe scalp psoriasis cases, respectively. Both studies reported a significant improvement in ScPGA (Scalp Physician Global Assessment) score at Week 16, which was maintained during the 52-week follow-up (high-quality evidence).[107]

Based on recent literature evidence[5,7,104-108] and on the clinical experience, the Expert Committee recommends using APR, MTX or biological therapies for the systemic treatment of these patients.

#14. For patients with nail psoriasis, the use of ACI, APR, MTX and biologics, not in order of preference, **is suggested**.

Strength of the recommendation: weak, in favor

There are few clinical studies on the efficacy of the different interventions in patients with nail psoriasis. In an RCT that included 36 participants with psoriasis in said localization, ADA administration was associated with a 50% improvement in baseline NAPSI score *vs*. 8% in the control group (very low quality evidence).[109] Regarding IFX, its efficacy was assessed in a Phase 3 RCT, with a subsequent crossover, of 50 weeks, which enrolled 305 patients with nail psoriasis. A “total” improvement in nail compromise was observed, as well as a positive variation in NAPSI absolute score during induction and maintenance therapy (low-quality evidence).[110] SEC therapy in patients with nail psoriasis was assessed in a Phase 2 RCT that included 68 participants with psoriasis in said localization; the intervention group reported an improvement in NAPSI score of 19% ± 6.12%, compared with a reduction of 14.4%

± 11.92% in the control group (low-quality evidence).[111] Moreover, the efficacy of UST was reported in a sub-analysis of the study PHOENIX, which included 545 participants with nail compromise. As reported, the average NAPSI score improved from 4.5 to 2.4 points by Week 24 (UST 45 mg) and from 4.4 to 2.2 points (UST 90 mg).[112]

As regards APR, the pooled analysis of data from studies ESTEEM-1 and ESTEEM-2 showed the therapy was associated with an improvement in baseline NAPSI score of 43.6-60% for the intervention. At Week 16 of treatment, the administration was associated with a significantly higher probability of achieving NAPSI-50 and ScPGA responses. These results were generally maintained after one year of follow-up (moderate-quality evidence).[107]

ACI and MTX indication is supported by the international literature[5,7] and by the authors' experience.

All safety outcomes from the analyzed studies were comparable with those reported for psoriasis in other localizations.[7,107,109-112]

#15. For patients with inverse psoriasis, the use of MTX, biologics, or APR, not in order of preference, **is suggested**.

Strength of the recommendation: weak, in favor

No comparative RCTs on the efficacy were identified among the different therapeutic strategies for patients with inverse psoriasis. There is one meta-analysis of 14 studies, which reported a shortage of proper-quality studies to make therapeutic recommendations, especially for systemic treatments.[113]

Based on experience, the Expert Committee suggests the administration of MTX, biologics or APR for this group of patients.

Note

The recommendations provided in this guideline derive from a detailed evaluation of the evidence using the GRADE methodology by a team of experts, members of SOARPSO, representative of the whole country.

As in every clinical practice guideline, the recommendations serve as guidance for the management of patients and they should not replace the professional judgment of the treating physician on a case-by-case basis, which shall include the opinions and preferences of the patient.

List of abbreviations

ACI: acitretin

ADA: adalimumab

APR: apremilast

ATC: Anatomical, Therapeutic, Chemical (ATC) classification system

CsA: ciclosporin A

CZP: certolizumab pegol

DLQI: Dermatology Life Quality Index

ETA: etanercept

GRADE: *Grading of Recommendations, Assessment, Development and Evaluations*

GUS: guselkumab

IFX: infliximab

IL: interleukin

IXE: ixekizumab

MTX: methotrexate

PASI: Psoriasis Area and Severity Index

PGA: Physician Global Assessment

PHO: phototherapies

PSSI: Psoriasis Scalp Severity Index

RCT: randomized and controlled trial

RIS: risankizumab

SC: subcutaneous

SEC: secukinumab

TNF-α: tumoral necrosis factor-alpha

UST: ustekinumab

UVB: ultraviolet B

P.O.: per oral

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