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Review

Latin American Clinical Practice Guidelines on the Systemic Treatment of Psoriasis
SOLAPSO – Sociedad Latinoamericana de Psoriasis *(Latin American Psoriasis Society)*

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[Corrections added July 10, after first online publication. Patricia Levrero was incorrectly listed as Verónica P. Levrero]

Abstract

This Clinical Practice Guideline on the systemic treatment of Psoriasis includes the recommendations elaborated by a panel of experts from the Latin American Psoriasis Society SOLAPSO, who assessed the quality of the available evidence using the GRADE system and the PICO process to guide the literature search. To answer each question, the experts discussed the results of randomized controlled trials, observational studies and metanalysis evaluating the interventions identified (non-biologics, biologics and phototherapy) in different populations of patients with moderate to severe plaque-psoriasis, which was summarized in Tables ad-hoc. The main end-points considered to assess efficacy were PASI 50, 75, 90 and 100, PGA 0-1 and significant improvement of health-related quality of life. Specific adverse events, either severe or leading to treatment interruption, were also evaluated. The 31 recommendations included in this CPG follow the structure proposed by GRADE: direction (for or against) and strength (strong or weak). The goal of this CPG is to improve the management of patients with psoriasis by recommending interventions of proved benefit and providing a reference standard for the treating physician. Adhering to the contents of this CPG does not guarantee therapeutic success. The final decision on the specific treatment is the responsibility of the physician based on the individual circumstances and considering the values, the preferences and the opinions of the patient or caregivers.

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Introduction

Nora Kogan

Background

In 2009, SOLAPSO published the updated edition of their Treatment Guidelines on Psoriasis with a view to improving the knowledge on the disease and fostering its multi-disciplinary approach.[1] In 2015, SOLAPSO announced a new Clinical Practice Guidelines (CPG) to offer evidence-based recommendations for the management of psoriatic patients who would benefit from systemic treatment and convened a multi-disciplinary group of experts; the present Latin American Clinical Practice Guidelines on the Systemic Treatment of Psoriasis is the result of their work.

It is relevant to distinguish between CPGs and consensus guidelines. CPGs are based on a systematic, comprehensive, transparent and objective search and assessment of the available evidence, whereas consensus guidelines summarize the agreements reached by a group of experts which may not strictly be based on clinical evidence. The systematic classification of the evidence reduces biases and facilitates the interpretation of medical guidelines. CPGs have the potential of improving patient management by promoting clinically proved interventions, disregarding the noneffective. To achieve this goal, CPGs need to be referenced by physicians in their clinical practice, replacing subjective criteria and experience by objective data. This process of change is sometimes complex and for several reasons it is relatively frequent that doctors keep on their usual practices even despite they are not evidence-based.[2] The CPGs provides the treating physician with reference standards on practical aspects relevant for drug selection and patients monitoring.

Adhering to the guidelines does not guarantee treatment success. The final decision on the specific therapies must be taken by physicians and their patients, considering all circumstances of each case in particular.

SOLAPSO is proud to present the Latin American CPGs on the systemic treatment of psoriasis and hopes it will reach all health care professionals involved in the management of psoriasis and that it may contribute to increase the efficacy in controlling this disease, which still poses significant impairment in the patients' quality of life.

Goals

The CPG on the systemic treatment of Psoriasis aims at offering updated therapeutic information and become a reference frame to Latin American physicians, for their therapeutic decisions, with the main goal of improving patient care.

Treatment being the core of the CPGs, the authors have deliberatively excluded definitions, classifications, epidemiology, presentation and diagnosis of the disease, which can be found in the 2009 Guidelines.[1]

Methodology

Ariel Izcovich Ariel, Juan Martín Criniti

The CPGs have been prepared following the recommendations of the Methodology Manual for the Development of Clinical Practice Guidelines by the Under-Secretary of Public Health of the Government of Chile, using the GRADE system (Grading of Recommendations Assessment, Development and Evaluation) to assess the quality of the evidence, to produce evidence summaries and translate them into recommendations.[2]

The GRADE system clearly distinguishes between the quality of the evidence and the strength of the recommendation, and explicitly evaluates the relevance of the outcomes. Recommendations are produced through a transparent process incorporating patients values and preferences, acceptability, feasibility and resource considerations.[3,4]

The authors of these CPGs convened by SOLAPSO are experts from several countries in the region and a team of methodologists who searched and organized the evidence.

Questions were collected following the PICO structure to guide the literature search. Two CPGs on psoriasis developed under adequate standards of literature searches were identified and all citations in these CPGs found to be relevant to the purpose of our study were assessed.[5,6] A supplementary search of systematic reviews, randomized trials, and observational studies was performed in MEDLINE, Epistemonikos, Cochrane library, LILACS, and Google Scholar with temporal restriction (2012–2015). The search term in all cases was "Psoriasis."

Relevant information was extracted in *ad hoc* tables; evidence summaries were prepared for each comparison and each scenario following the GRADE Working Group suggested criteria.[7,8] To reach a consensus on each recommendation, the authors considered the balance between benefits and risks, the quality of the evidence, the values and preferences of the patients, as well as costs and other practical issues.

PICO Questions

Questions were selected by consensus of the authors and were based on the questions included in other CPGs on Psoriasis.[5] All questions were framed using PICO (Population, Intervention, Comparison, Outcome):

Populations

1 Moderate to severe plaque-type psoriasis adult patients
2 Moderate to severe plaque-type psoriasis pediatric patients
3 Moderate to severe plaque-type psoriasis adult patients over 65 years old
4 Moderate to severe plaque-type psoriasis in pregnant or breastfeeding patients
5 Patients with guttate psoriasis
6 Patients with erythrodermic psoriasis

7 Patients with generalized pustular psoriasis
8 Patients with palmoplantar pustular psoriasis
9 Patients with psoriasis of specific locations
10 Psoriasis (any type) and psoriatic arthritis patients
11 Psoriatic patients (any type) with specific comorbidities
12 Relapsing psoriatic patients (50% decrease from basal PASI)
13 Rebounding psoriatic patients (125–150% increase from basal PASI)

Interventions

1 Nonbiologics (listed alphabetically): Acitretin (ACT) – Cyclosporine (CsA) – Methotrexate (MTX)
2 Biologics (listed alphabetically): Adalimumab (ADA) – Etanercept (ETN) – Infliximab (IFX) – Secukinumab (SEC) – Ustekinumab (UST)
3 Phototherapies:
a Narrow band ultraviolet B phototherapy (NBUVB)
b Broad band ultraviolet B phototherapy (BBUVB)
c Psoralen and ultraviolet A phototherapy (PUVA)
4 The following interventions were also included for psoriatic arthritis patients: Certolizumab (CER) – Golimumab (GOL) – Apremilast (APM)

Outcomes

PASI 50: Proportion of patients with 50% or above reduction in the PASI index
PASI 75: Proportion of patients with 75% or above reduction in the PASI index
PASI 90: Proportion of patients with 90% or above reduction in the PASI index
PASI 100: Proportion of patients with 100% reduction in the PASI index
PGA 0–1: Proportion of patients reaching 0–1 in PGA score

Significant improvement in quality of life: Proportion of patients with a significant improvement in quality of life reported directly or measured by the Dermatology Life Quality Index (DLQI) (4–5 points improvement)

Severe adverse events (AE): Percentage of patients with severe AE

AE leading to treatment discontinuation: Proportion of patients with AE that lead to treatment discontinuation

Specific AE: Proportion of patients with specific AE considered relevant

Specific outcomes were considered for different patient subpopulations (e.g. NAPSI for ungueal involvement or ACR 50, 70, and 90 for psoriatic arthritis patients).

Summarizing the evidence

Based on the questions and comparisons identified, *ad hoc* tables were prepared summarizing the data from studies in the two reference CPGs and those studies found in the systematic reviews. These tables have been referenced throughout the CPG as Tables in the Technical Document (TD) which can be accessed in the online Supplementary Information article.

One table was prepared for each comparison in every clinical scenario. When possible, metanalysis were performed to assess the results of all trials evaluating the same comparison and measuring the same outcome, using Review Manager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 Maentel-Haenzel statistical method and random analysis model were used for dichotomic outcomes.

Inverse variance and random analysis model were used for continuous outcomes. Summary of findings (SoF) tables were prepared using the Guideline Development Tool (www.guidelinedevelopment.org). All the SoF tables are presented in the technical document (TD).

Rating the quality of evidence

The quality of the evidence was rated using the GRADE system as summarized in Table 1. For further information on GRADE please refer to http://www.gradeworkinggroup.org/

Assessing resources and costs

Resources and costs were considered informally. No economic evaluations were performed for these CPGs.

Patients values and preferences

In all recommendations, the authors considered the values and preferences of patients for each scenario and comparison based on their clinical experience.

Strong recommendations could only be made in those scenarios and comparisons where significant variability in the values and preferences of patients was assumed as unlikely.

Producing and formulating recommendations

The panel discussed the SoF tables and analyzed the information considering other aspects as already mentioned (values and preferences of the patients, costs, resources and implementation issues, among others).

Judgments by the panel regarding each of those aspects were recorded in evidence to decision frameworks as recommended by GRADE.

Each recommendation was reached by consensus of the authors and written following the GRADE system structure direction (for or against) and strength (strong or weak). The direction and strength of recommendations were expressed as: "The SOLAPSO CPGs Panel recommends . . ." (strong, for); ". . . suggests. . ." (weak, for); ". . . does not recommend" (strong, against); ". . . does not suggest" (weak, against) (Table 2). In cases where consensus could not be reached, the direction and strength of the recommendation were decided by voting.

For practical reasons, the CPGs have been organized in Chapters, each of which was assigned to one or more authors

Table 1 GRADE's approach to rating quality of evidence

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate effect across those considerations*
		↓ Lower if	↑ Higher if *	
Randomized trials	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias ** would reduce a demonstrated effect or * would suggest a spurious effect if no effect was observed*	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕
Observational trials	Low confidence			Low ⊕⊕
				Very low ⊕

Table 2 GRADE System: direction and strength of recommendations

	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that each patient should be aided so as to arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

who summarized the evidence and provided additional comments to the recommendations.

Declaration of interests

All authors filled in the declaration of interests form of WHO.

Chapter 1. Plaque-Type Psoriasis

Nora Kogan, Nélida Raimondo, Minerva Gómez Flores, Fernando Valenzuela

In adult patients with moderate to severe plaque-type psoriasis, which interventions should be considered?

To define which interventions should be considered, we assessed the results of the studies meeting the inclusion criteria: each intervention should be compared to placebo and measure the outcomes previously defined: PASI 50, PASI 75, PASI 90, PASI 100, PGA 0–1, QoL and AE. Following is a summary of the results assessed for each drug.

Nonbiologics (in alphabetical order)

Acitretin (TD Table 3.1.1)

ACT is a retinoid introduced in 1094 and widely used in the treatment of psoriasis, although it is not available in some Latin American countries.

Two RCT including 194 patients[9,10] informed that ACT would probably significantly improve the possibility of achieving PASI 75

(moderate quality evidence, MQE). In one of these trials, 47–69% of the patients reached PASI 75 at week 12, with better results with 35 mg/kg/day doses[9] Two trials[11,12] reported high probability of minor AE such as peeling, pruritus, alopecia, rhinitis, spasms, and erythema which significantly increased at higher doses (50 vs. 25 mg/kg/day) (high quality evidence, HQE). Other AE remained at similar levels with both doses (cheilitis, dry mouth, xerophthalmia).

Cyclosporine (TD Tables 3.1.3.1–3.1.3.2)

CsA is an immunosuppressive drug widely used in the treatment of psoriasis since the 1990s, currently presented in capsules. Nine randomized controlled trials (RCT) were found to meet the criteria of these CPGs to assess the efficacy and safety of CsA vs. placebo.[13–17] The results showed that CsA may be associated with a higher probability to reach PGA or PASI 75 and increased risk of AE (low quality evidence, LQE).

In most of these trials a relevant clinical response was seen after 4–8 weeks of treatment. Ellis *et al.*[13] evaluated CsA 3, 5 and 7.5 mg/kg/day vs. placebo in 85 patients controlled for 16 weeks and observed PGA 0–1 at week 8 in 65% of the patients in the CsA 5 mg/kg/day group and 36% in the patients receiving 3 mg/kg/day, with a statistically significant superiority of treatment vs. placebo.

The relapse rate in 189 patients previously treated with CsA was reported in the PREVENT study.[18]

CsA was discontinued for 8 days previous to the patients being randomized to oral CsA 5 mg/kg/day or placebo for two consecutive days/week, for a total period of 24 weeks. A total of 162 patients were randomized to CsA and 81 to placebo. At 24 weeks, 66.9% of the CsA-treated patients with moderate-severe psoriasis showed clinical success rates as defined for this study (no relapse or PASI 75) and 46.3% with placebo. This trial had a high withdrawal rate (22.2% of randomized patients), which was not related to side effects and may have led to an overestimation of efficacy.

Another RCT and an observational study (OS) also showed high withdrawal rates which might be related to AE (13.9–17%).[15,16]

The results of a prospective long-term cohort OS which investigated the incidence of malignancies in 1,252 severe psoriasis patients treated with CsA and followed up for 5 years show a possible increase in the incidence of malignancies in the long term (compared to the general population, the standardized incidence rate was 1.8) (LQE).[16] Furthermore, the results of 16 RCT (HQE) show a relation between renal impairment and CsA. Over 50% of the patients treated for ≥2 years might have ≥30% impairment in the creatinine value, 12.5% incidence of glomerulosclerosis at 3 years and 26% at 10 years.[17] CsA is probably related to higher risk of renal impairment when used for long periods.[13,17]

Methotrexate (TD Tables 3.1.7.1–3.1.7.2)

MTX was discovered by mid of the 20th century and has been widely used for the treatment of psoriasis since FDA approval in 1971.

Three studies met the criteria of these CPGs to assess the efficacy and the safety of MTX in the management of adult patients with moderate to severe psoriasis.[19–21]

For the efficacy evaluation, several studies have shown that MTX is probably related to increased probability of reaching PASI 75 and PGA 0–1 (MQE).

In the CHAMPION study,[21] MTX was compared to placebo in 163 patients, of which 110 received MTX 7.5 mg oral with dose increased as needed and as tolerated to 25 mg weekly for 16 weeks. After 16 weeks, 35.5% of MTX-treated patients achieved PASI 75 vs. 18.9% in the control group.

In one RCT comparing MTX vs. placebo, the mean PASI change from baseline showed an improvement of 73.9% with MTX and 32.0% in the placebo group at month 6.[19]

No significant AE were identified in the results assessed,[21] although a meta-analysis of 32 RCT including 13,177 patients[22] who received MTX for different rheumatological conditions informed an increase in the risk of hepatic AE (HQE). This meta-analysis included studies carried out from 1990 to 2014 and was aimed at assessing the relative risk and severity of the hepatic damage in patients treated with MTX. The results of these 32 studies showed that MTX was related to higher total risk of hepatic AE but not higher risk of hepatic failure, cirrhosis or mortality were found.

Biologics (in alphabetical order)

Adalimumab (TD Table 3.1.2)

ADA is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody containing only human peptide sequences and used since 2007 in the treatment of psoriasis. It is administered subcutaneously.

Seven RCT comparing ADA vs. placebo met the criteria of these CPGs and were included for efficacy and safety assessment.[20,21,23–27] Three of these studies – which included about 1,500 patients– informed a significant increase in the probability of achieving PGA 0, PASI 75, PASI 90, and PASI 100 both at induction and at maintenance (MQE).[21,25,26] In a multicentric, randomized, double-blind, placebo-controlled study, 147 patients received ADA (40 mg every other week or 40 mg/week) or placebo. At week 12, 53% of patients on ADA every other week, 80% of patients on ADA weekly, and 4% of the control group achieved PASI 75.[26]

In another 52-week, multicenter study of 1,212 patients randomized to receive ADA (40 mg) or placebo every other week for the first 15 weeks, 71% of the ADA group of patients reached PASI 75 at week 16, vs. 7% of the placebo-treated patients.[25]

In terms of quality of life, a possible clinically relevant improvement with ADA measured by DLQI was shown (LQE). One RCT assessed the impact of ADA on health-related quality of life in 84 adult patients with moderate to severe psoriasis treated with ADA 80 mg every other week and in 87 patients who received ADA 40 mg, one weekly injection throughout

16 weeks. The absolute reduction in the DLQI score in the ADA-treated patients was 3.3 and 5.7 points higher than the score of the placebo group, for both treatment groups, respectively.[20]

Nineteen RCT including a total of 6,672 patients informed a marginal increase in the risk of severe AE (MQE). The local reactions at the injection site (erythema, itching, pain, swelling, and bleeding) were the most frequent AE and they were observed in 20% of the ADA-treated patients vs. 14% of the untreated groups.[27] ADA was related with a possible increase in the risk of AE that lead to discontinue treatment, in the assessment of results of 22 RCT with 7,622 patients (LQE).

The main infections reported in these studies among patients treated with ADA were upper respiratory infections, bronchitis, urinary tract infections, and some more severe such as pneumonia, septic arthritis, prosthetic or postsurgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis.[5] The results of the PSOLAR registry,[28] evaluating the risk of severe infections in 12,095 psoriasis patients treated with biologicals or systemic drugs informed a possible significant increased risk in patients treated with ADA, although the global incidence (1.45 each 100 patients per year) might be related to the fact that ADA is more frequently used compared with other alternatives (LQE) (see 13.1).

Etanercept (TD Table 3.1.4)

ETN is a soluble TNF inhibitor, administered subcutaneously, used for the treatment of patients with moderate to severe psoriasis since 2004 and which plays an important role in the management of other inflammatory diseases such as rheumatoid arthritis.

The results of the 10 studies assessed[29–39] and showed the efficacy of ETN in the probability of achieving PASI 50, 75, 90, 100 and improving quality of life (HQE).

In a study with adult patients with plaque psoriasis, 112 patients were randomly assigned to treatment groups and received placebo or ETN 25 mg, subcutaneously twice a week for 24 weeks. After 12 weeks of treatment, 17 (30%) of the 57 ETN-treated patients and 1 (2%) of the 55 in the placebo group had achieved PASI 75, and after 24 weeks this score was found in 32 (56%) and 3 (5%), respectively.[29]

A 24-week, double-blind study compared ETN at a low dose (25 mg once weekly), a medium dose (25 mg twice weekly), or a high dose (50 mg twice weekly), vs. placebo. At week 12, PASI 75 was achieved in 4% of the patients in the placebo group, as compared with 14% of those in the low-dose ETN group, 34% percent in the medium-dose–ETN group, and 49 percent in the high-dose–ETN group. At week 24, the scores with ETN were 25, 44, and 59%, respectively.[35] Similar results were found by Papp *et al.*,[32] in a multicenter 24-week study in the U.S.A., Canada, and Western Europe, reporting 49 and 34% of patients reaching PASI 75 at week 12 in the ETN 50 mg and 25 mg twice weekly treatment groups, with better results at week 24, 54, and 45% PASI 75 in each group of patients, respectively.

Three studies including 1,003 patients[30,31,33] evaluated the effect of ETN on quality of life, showing possible significant improvement. Krueger et al[30] in a multinational, randomized, phase III trial, evaluated 583 patients (193 received placebo, 196 ETN 50 mg per week, and 194 ETN 50 mg twice a week during the initial 12-week, double-blind period. Thereafter, all patients received ETN 50 mg per week). At week 12, in 72–77% of the patients receiving ETN improvement in DLQI was clinically meaningful (≥5-point improvement or 0 score).

Regarding the safety profile of the drug, the results of 28 RCT including 6,174 patients show that ETN is a safe drug. Some studies relate ETN with a probable marginal increase in the risk of AE (MQE) and TB reactivation (HQE).

Infliximab (TD Table 3.1.6)

IFX is a monoclonal antibody that works against TNF-α. It is administered intravenously and has been in use to treat psoriasis since 2005.

Ten RCT were included in the present CPGs in which IFX safety and efficacy was assessed.[40–49]

The efficacy assessment showed that IFX increases the probability of reaching PASI 75, 90, 100 and improving quality of life both at induction as well as at maintenance therapies (M/HQE).

To show the role of anti-TNFα in the pathogenesis of psoriasis, a double-blind RCT assessed the clinical benefit and safety of IFX against anti-TNFα in 33 patients with moderate to severe plaque psoriasis who were randomly assigned to intravenous placebo, IFX 5 mg/kg, or IFX 10 mg/kg at weeks 0, 2, and 6. Patients were assessed at week 10 for PGA; 3 patients had dropped out; 9/11 (82%) patients in the IFX 5 mg/kg group were responders (good, excellent, or clear rating on PGA), compared with 2/11 (18%) in the placebo group and 10/11 (91%) patients in the IFX 10 mg/kg group.[42]

Gottlieb *et al.* evaluated 249 patients with severe plaque psoriasis in a multicenter, double-blind, placebo-controlled trial, randomly assigned to receive IFX 3 or 5 mg/kg intravenous infusions or placebo given at weeks 0, 2, and 6. At week 10, 72% of patients treated with IFX 3 mg/kg and 88% of patients treated with IFX 5 mg/kg achieved PASI 75 compared with 6% of patients treated with placebo. PASI 90 was observed in 58% of the patients in the IFX 5 mg/kg group, 46% in those receiving 3 mg/kg and 2% for placebo. To assess the duration of the response, patients were followed up for 20 weeks after the last induction infusion; at week 20, 33% of the patients receiving IFX 5 mg/kg were still at PASI 75.[45]

In the EXPRESS phase III, multicenter, double-blind trial, 301/378 patients with moderate to severe plaque psoriasis received IFX 5 mg/kg infusions or placebo at weeks 0, 2, and 6, then every 8 weeks to week 46. At week 10, the proportion of

patients achieving PASI 75 from baseline was 80% in the treatment group, while 57% achieved PASI 90 vs. 3% and 1% for placebo, respectively. At week 50, 170/281 (61%) evaluable patients achieved PASI 75. Based on a predefined analysis on PASI 75 responders at week 10, the response to IFX was sustained, with most PASI 75 responders at week 10 maintaining this response through week 24 (203/229 patients; 89%) and week 50 (153/225; 68%).[41] As part of the EXPRESS study, Reich *et al.*[47] used DLQI and other self-evaluation parameters to assess the impact of long-term IFX maintenance therapy on health-related quality of life in patients with psoriasis. At week 10, IFX-treated patients had significantly greater improvement in DLQI scores than placebo-treated patients, persisting at week 24 with patients achieving PASI 100 reporting the greatest benefit (HQE).

The safety profile of IFX in psoriasis appears to be similar to what has been observed with this drug in other indications. The most frequent AE are injection site reactions, infections and TB reactivation.[5] In the studies considered in these CPGs to assess AE IFX was related with a probable increase of severe AE (MQE). In the EXPRESS study, three cases (1%) of non-melanoma skin tumors were reported in the IFX treatment group and the drug was also related to probable treatment interruption due to AE (MQE).[41]

Secukinumab (TD Table 3.1.8)

SEC is a recombinant, high-affinity, fully human immunoglobulin G1κ monoclonal antibody that selectively binds and neutralizes interleukin-17A. The drug was approved by the FDA in 2015 for the treatment of patients with moderate to severe psoriasis; it is administered subcutaneously with pre-filled syringes or self-injection devices (Sensoready™ pen).

Six RCT met the criteria to be included in these CPGs to assess the efficacy and safety of SEC.[50–55] In terms of efficacy, all outcomes assessed showed a significant increase in the probability of achieving PASI 50, 75, 90, 100 and improving quality of life with SEC (M/HQE). Langley *et al.*[55] combined the results of two phase 3, double-blind, 52-week RCT, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis, 738 patients) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis, 1,306 patients). Patients were randomly assigned to subcutaneous SEC at a dose of 300 mg or 150 mg (administered once weekly for 5 weeks, then every 4 weeks), or to placebo. The FIXTURE study also included one group treated with ETN at a dose of 50 mg administered twice weekly for 12 weeks, then once weekly.

At week 12, the proportion of patients who met the criterion for PASI 75 was higher with each SEC dose than with placebo or ETN: in the ERASURE study, the rates were 81.6% with 300 mg of SEC, 71.6% with 150 mg of SEC, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of SEC, 67.0% with 150 mg of SEC, 44.0% with ETN, and 4.9% with placebo. Similar results in PASI 75 at 12 weeks have been reported by other authors.[51,53]

The assessment of response over time in the ERASURE study showed that 80.5% of the patients in the SEC 300 mg treatment group maintained PASI 75 at week 52 and 72.4% of those in SEC 150 mg. In the FIXTURE study, these rates were 84.3 and 82.2%, respectively.

The quality of life results assessment showed higher probability of significant improvement with SEC (HQE).[55,56] The proportion of patients with a DLQI score of 0 or 1, indicating no impairment of health-related quality of life, was significantly higher at week 12 in each SEC-dose group than in the placebo group and showed similar absolute improvement variations in both groups (10.1 with SEC 150 mg and 11.4 with SEC 300).

The safety results of 5 RCT with 1,716 patients showed a probable marginal increase of severe AE and possible no higher risk of major cardiovascular events with SEC (M/LQE).

Nasopharyngitis, headache, upper respiratory tract infection, and diarrhea were among the most frequent AE. The incidence of reactions at the injection site was low. Some infections, particularly *Candida* sp. were observed at the induction treatment period.[51–53,55] Grade 3 neutropenia occurred in 9 patients receiving SEC (1.0%) and one patient receiving ETN (0.3%) developed grade 4 neutropenia.[55]

Ustekinumab (TD Table 3.1.9)

UST is a human monoclonal antibody directed against IL-12 and IL-23, and has been used for the treatment of psoriasis since 2008.

The results of 5 RCT with 2,596 patients were considered for the efficacy assessment and showed a higher probability of achieving PASI 75, 90, and 100 with UST both at induction and at maintenance, and that the drug is also probably related to a significant increase in the quality of life of these patients (HQE).[57–61]

Two long-term phase III, double-blind, placebo-controlled studies: PHOENIX 1 (Leonardi *et al.*, 766 patients, 76 weeks)[58] and PHOENIX 2 (Papp *et al.*, 1,230 patients, 52 weeks)[59] evaluated UST in two dose regimens: 45 mg and 90 mg at weeks 0 and 4 and then every 12 weeks. The primary endpoint was the proportion of patients achieving PASI 75 at week 12: 67.1–66.7% with UST 45 mg in PHOENIX 1 and 2, respectively, and 66.4–77.5% with UST 90 mg in PHOENIX 2. In PHOENIX 1, at week 40, patients were randomly assigned to maintenance UST or withdrawal. PASI 75 response was better maintained to at least 1 year in those receiving maintenance UST than in those withdrawn from treatment.

For the quality of life assessment, the results of 5 RCT with 1,836 patients were considered. All of these studies measured DLQI at induction and showed a probable improvement in quality of life; absolute score decrease in treated patients was 8.24 points higher (7.24–9.24) than in the control groups (MQE).[57–61]

Regarding safety, 5 RCT with 2,595 patients[57–61] showed probable absence of increased risk of severe AE and AE that lead to treatment discontinuation (MQE), and marginal increase in the risk of severe AE in the long term (LQE). Papp *et al.*[62] evaluated the safety of UST with data pooled from four studies of UST for psoriasis. Analyses included 3,117 patients who received one or more doses of UST (45, 90 mg), of which 1,482 were treated ≥4 years (838 patients ≥5 years). At year 5, event rates for overall AE were comparable between the two dose groups, and no dose-related or cumulative toxicity was observed with increasing duration of UST exposure for up to 5 years.

Recommendation # 1

In adult patients with moderate to severe plaque-type psoriasis, the SOLAPSO CPGs panel recommends the following therapeutic interventions as valid alternatives: ACT, ADA, CsA, ETN, IFX, MTX, PUVA, SEC, UST, NBUVB (interventions are listed alphabetically).

Comments:
Although ACT is not available in all Latin American countries, the panel valued the information assessed,[9–12] the cost and the experience with the use of this drug.
The experts agreed to include CsA as an alternative despite the quality of evidence about efficacy was low,[6] based on their personal experience with this drug, regarded as a possible choice at 3 or 5 mg/kg per day doses.
About phototherapy, the panel decided to exclude BBUVB from this scenario, based on the fact that the intervention is not indicated for psoriasis and since no qualifying evidence was found compared to placebo. The same criteria were used with excimer laser, although the panel acknowledged the use of the latter to treat local lesions.

In adult patients with moderate to severe plaque-type psoriasis, which should be the first-choice treatment?

To assess whether biological vs. nonbiological drugs should be indicated in adult patients with moderate to severe plaque-type psoriasis, the results of comparative studies among drugs of both categories were analyzed, also taking into account the results of each intervention vs. placebo. Several studies met the criteria of these CPGs and compared ETN vs. ACT, ADA vs. MTX, and IFX vs. MTX.

ACT vs. ETN (TD Table 3.1.11)

The results of two RCT including 102 patients were assessed to compare the efficacy and safety of ACT vs. ETN[12,63] suggesting that ETN could be superior than ACT in achieving PASI 75 at induction (LQE). There is uncertainty about the possibility of differences in the long term between both drugs (VLQE). No AE were reported in these studies.

ADA vs. MTX (TD Table 3.1.14)

One RCT[21] with 218 patients showed better results with ADA in the outcomes PASI 75, 90, and PGA 0–1 (HQE).

In this study, after 16 weeks, 79.6% of ADA-treated patients achieved PASI 75, compared with 35.5% for MTX. Statistically significantly more ADA-treated patients (16.7%) than MTX-treated patients (7.3%) achieved complete clearance of disease. MTX might be related to an increased risk of severe AE leading to study discontinuation (LQE).

IFX vs. MTX (TD Table 3.1.17)

The results of one RCT including 868 MTX-naïve patients (RESTORE 1)[40] showed that IFX is probably superior to achieve PASI 50, 75, 90 both at induction and at maintenance, and is also superior to improve quality of life (LQE).

Patients were randomized 3:1 to receive IFX 5 mg/kg at weeks 0, 2, 6, 14, and 22 or MTX 15 mg weekly with a dose increase to 20 mg weekly at week 6 for patients with PASI < 25 or switch at week 16 for patients with PASI < 50. The efficacy endpoints were PASI 75 and PGA 0–1 at weeks 16 and 26. PASI 75 was achieved by a significantly greater proportion of IFX-treated patients (78%) than MTX-treated patients (42%). Key secondary endpoints also were achieved by a greater proportion of IFX-treated patients. Similar responses were observed at week 26 in patients who switched from MTX to IFX at week 16.

The safety assessment showed that IFX could be associated with a higher risk of severe AE leading to treatment discontinuation (LQE). The overall incidence of AE was comparable among the groups, with a mild increase of serious and severe AE in IFX-treated patients.

Recommendation # 2

In adult patients with moderate to severe plaque-type psoriasis, the SOLAPSO CPGs panel suggests to start therapy with a nonbiological drug rather than with a biological drug.

Recommendation # 3

In adult patients with moderate to severe plaque-type psoriasis who will start therapy with a nonbiological drug, the SOLAPSO CPGs panel suggests MTX above all other available choices.

Recommendation # 4

In adult patients with moderate to severe plaque-type psoriasis who value short-term effectiveness, the SOLAPSO CPGs panel suggests biological drugs as first-choice therapy.

Comments:
The panel acknowledged that biological drugs could be more effective than nonbiologicals for the treatment of patients with moderate to severe plaque-type psoriasis, but they weighed the availability of long term safety information, the costs and the accessibility of nonbiologicals.
Since no difference was found in risk-benefit, the panel weighed experience, cost and availability to recommend MTX.
In patients with prior failure, adverse events or absolute contraindication of MTX, all other available therapeutic options should be considered. The panel decided not to formulate a statement recommendation for this scenario.
The panel agreed that specialists should be in charge of prescribing and using biologics, considering that the use of these drugs demand an adequate patient selection and follow-up, due to the potential adverse events and costs.

In adult patients with moderate to severe plaque-type psoriasis who are started on biologics (either as first or second line therapy), which should be the first-choice treatment?

The results of studies comparing biologics were assessed and completed considering also the results of each drug vs. placebo. Studies comparing ETN vs. IFX, ETN vs. SEC, ETN vs. UST, and SEC vs. UST were included.

ETN vs. IFX (TD Table 3.1.12)

The results of one RCT with 48 patients were assessed[64] suggest that IFX could be superior in achieving PASI 75, both at induction and as maintenance (LQE).

Due to the lack of direct comparative studies assessing the risk of AE, these CPGs considered the information of a multiple comparisons meta-analysis, where no significant differences were found in the risk of severe AE for both drugs (LQE).[27]

ETN vs. SEC (TD Table 3.1.18)

In the FIXTURE Study, with 973 patients, SEC showed better results than ETN in PASI 75, 90, 100 outcomes and in the evaluation of quality of life both at induction and maintenance (M/HQE).[55]

The proportion of patients who achieved PASI 75 at week 12 was higher with each SEC dose (150/300 mg) than with ETN, the rates were 77.1% with 300 mg of SEC, 67.0% with 150 mg of SEC, and 44.0% with ETN. The proportion of patients with PGA 0–1 at week 12 was higher with each SEC dose than with ETN: 62.5% with 300 mg of SEC, 51.1% with 150 mg of SEC, 27.2% with ETN. In the evaluation of the response over time, the rates according to PASI 75, PASI 90, PASI 100, and PGA 0–1 were higher with SEC than with ETN through week 52: 72.5% ETN, 82.2% SEC 150 mg, and 84.3% SEC 300 mg.

Possibly no significant differences in the risk of severe AE or MACE were found between these two interventions (LQE).[54,55]

ETN vs. UST (TD Tables 3.1.20.1 y 3.1.20.2)

The results of one RCT with 903 patients showed that UST is probably superior to achieve PASI 75, 90, 100 at the induction phase (MQE).[65]

In this study, Griffiths *et al.* compared UST and ETN randomly assigning patients to one of three treatment groups; UST at a dose of 45 or 90 mg at weeks 0 and 4 or ETN at a dose of 50 mg twice weekly for 12 weeks. At week 12, a total of 67.5% of patients who received 45 mg of UST and 73.8% of patients who received 90 mg of UST had at least 75% improvement in the PASI score, as compared with 56.8% of those who received ETN. The proportion of patients who reached PGA 0–1 at week 12 was also significantly higher in each UST group: 65.1% with UST 45 mg, 70.6% in UST 90 mg vs. 49.0% of patients who received high-dose ETN.

The safety of UST and ETN appeared to be generally similar, with probably no significant differences between both drugs regarding severe AE and those leading to treatment discontinuation (MQE).

SEC vs. UST (TD Table 3.1.19)

The results of one RCT with 676 patients showed that SEC was superior to UST as assessed by the PASI 75, 90, and 100 responses. Better results were also obtained with SEC at induction in the health-related quality of life evaluations (HQE).[66]

In this 52-week, double-blind study 676 subjects were randomized to receive SEC 300 mg subcutaneous injection or UST per label. Primary end point PASI 90 was achieved in 79.0% of patients treated with SEC in comparison with 57.6% of those receiving UST. The 100% improvement from baseline PASI score at week 16 was also significantly greater with SEC (44.3%) than UST (28.4%). Percentage of subjects with the DQLI score 0/1 at week 16 was significantly higher with SEC (71.9%) than UST (57.4%). The safety profiles of both drugs were comparable, there

are probably no differences between them in the risk of severe AE and those leading to treatment discontinuation (MQE).

Recommendation # 5

In patients with moderate to severe plaque-type psoriasis who are started on biologics, the SOLAPSO CPGs panel suggests anti TNF (ADA, ETN, INF) or anti-IL-12/23 (UST) as first-choice treatment.

Recommendation # 6

In patients with moderate to severe plaque-type psoriasis who are started on biologics and show preference for short-term efficacy, the SOLAPSO CPGs panel suggests SEC as first-choice treatment.

Comments:
In the efficacy assessment, the panel considered SEC to be superior than all other biologics. However, in their recommendations the panel prioritized the safety profile assessment weighing the long-term data available for all biologics, excepting SEC. They also agreed that further comparative studies are necessary to choose UST before anti-TNF (e.g. UST vs. ADA).
On assessing the comparative studies available, the panel acknowledged that some aspects -such as ETN safety shown in long-term studies or the intravenous administration of IFX- have as much weigh as superior efficacy, as found for SEC and UST.
Due to the particular profile of each biologic, regardless of efficacy, initial treatment with anti-TNF might be necessary.

In adult patients with moderate to severe plaque-type psoriasis with prior exposure and failure of biological therapies: which should be the treatment of choice?

(TD Tables 3.15.1 y 3.15.2)
The CPGs assessed the results of a study designed to evaluate the potential cost effectiveness of sequential biologic therapies in patients with psoriasis who have been exposed to previous biologic therapy.[67]

The PASI response rates from subgroup analyses of three randomized placebo-controlled trials evaluating IFX (121 patients) and UST (2 studies, 691 patients) showed a considerably higher probability that patients previously treated with a biological agent might reach PASI 75 if shifted to IFX and PASI 50, 75 and 100 if shifted to UST (HQE).

Recommendation # 7

In adult patients with moderate to severe plaque-type psoriasis with prior exposure and failure of a biological therapy, the SOLAPSO CPGs panel suggests that a different biological agent should be indicated other than shifting to a nonbiological drug or indicating a new course of therapy with the previously failing drug.

Comments:
The panel valued the evidence on the efficacy of biologics as second line treatment in patients previously exposed to these agents, and considered that there is insufficient data to decide which biological agent should be indicated in the event of a prior failure.

Which is the best treatment scheme for adult patients with moderate to severe plaque-type psoriasis over 65 years of age?

(TD Tables 3.3.1–3.3.3)
Seven studies met the criteria of these CPGs to evaluate the efficacy and safety of the interventions in treating adult patients over 65 years of age with moderate to severe plaque-type psoriasis[68–74] and to compare differences in treatment results between adult patients younger or older than 65 years of age.

The results assessed, including three observational studies with ADA[69,70,73] and one RCT[72] showed possibly no differences in efficacy for ETN and ADA in adult patients younger or older than 65 years of age, and that ETN, ADA, and IFX could be related with a higher risk of AE in older adults (LQE).

Recommendation # 8

In adult patients older than 65 years of age with moderate to severe plaque-type psoriasis, the SOLAPSO CPGs panel suggests the same therapeutic options used for younger adults.

Comments:
In the light of the limited evidence available for this group of patients, the panel considered that the treatment options assessed are probably similarly effective in adult patients younger or older

than 65 years of age, although a marginal increase of AE could occur among the latter. Special attention should be given by the treating physician to comorbidities in patients older than 65 years of age, particularly those counter-indicating some drugs as CsA in nephrosclerosis (see 13.2).

Which is the best treatment scheme in pregnant or breast-feeding women with moderate to severe plaque-type psoriasis ?

(TD Tables 3.4.1. y 3.4.2)

Treatment of pregnant or breast-feeding women with moderate to severe plaque-type psoriasis will probably demand special considerations, particularly regarding treatment safety for both the patient and the fetus or the newborn.

No trials were identified to provide specific information to answer this question. Three cohort trials were therefore identified to assess the incidence of AE in pregnant women[75–77] and case reports were analyzed to determine drug levels in the babies of breast-feeding women with psoriasis under therapy.[78–80]

Recommendation # 9

In pregnant or breast-feeding women with moderate to severe plaque-type psoriasis, the SOLAPSO CPGs panel suggests phototherapy or CsA as treatments of choice.

Comments:

The panel strongly weighed the uncertainty regarding safety of biologics in pregnant or breast-feeding women and their fetus or newborns.

Treating pregnant or breast-feeding patients with these drugs might be considered when short term effectiveness is a priority (e.g. severe disease and patients who do not respond to CsA).

In addition, the panel emphasized the counter-indication of BCG immunization in newborns of women who have been treated with anti-TNF, particularly IFX, and the counter-indication of CsA, MTX, and ACT in breast-feeding women.

Chapter 2: Children

Carla Castro

Treatment of children with moderate to severe plaque-psoriasis

(TD Tables 3.2.1, 3.2.2 y 3.2.3)

Although most cases of psoriasis in children are mild and may be managed with topical treatment, a small percentage presents moderate to severe disease and require systemic treatment.

All interventions were considered, with a view to assessing any special case that might imply that a different therapeutic approach should be indicated in children with moderate to severe psoriasis, as compared to treating adult patients. The trials identified which met the criteria for this CPGs compared ETN vs. placebo, MTX vs. placebo and UST vs. placebo[81–85]: Two placebo-controlled RCT, one with ETN (211 patients),[81] another with UST (110 patients)[85] and two observational studies evaluating MTX in children.[83,84]

Both drugs are probably comparable to achieve the outcomes PASI 75, 90, and 100 and also to improve health related quality of life at induction (MQE).

The trial assessing long-term efficacy of this drug in children with moderate to severe plaque-psoriasis aged 4–17[81] related ETN to a probable significantly higher probability of reaching PASI 75, 90 and PGA 0–1 at 12 weeks, and also probably higher probability of improved health related quality of life, as measured by DLQI scale (MQE).

In a 48-week double-blind trial by Paller *et al.,*[82] 211 children with psoriasis aged 4–17 were initially randomly assigned to ETN 0.8 mg/kg/day (maximum dose 50 mg) or placebo 1 daily subcutaneous injection, followed by ETN for 24 weeks. At week 12, 57% of patients receiving ETN achieved PASI 75, as compared with 11% of those receiving placebo; a significantly higher proportion of the patients in the ETN group had PASI 50 (75% vs. 23%), PASI 90 (27% vs. 7%), and PGA 0–1 was 53% vs. 13%.

In the long-term follow-up study[81] responses at week 96 were similar to those observed in the double-blind trial: PASI 50, 89%; PASI 75, 61%; PASI 90, 30% and PGA 0–1 in 47% of patients. AE were reported in 80.1% of cases: upper tract respiratory infections 24.9%, nasopharyngitis 17.1%, streptococcal pharyngitis 12.7%, acne 11.6%, sinusitis 10.5%; there were two withdrawals related to AE.

The two OS assessing MTX vs. placebo[83,84] in 37 patients found good treatment response at induction and maintenance phases and reported AE: increased transaminases 24%; gastrointestinal symptoms 40%, oral ulcers 3%, night cough and leg pain 3% (VLQE).

In the phase III CADMUS study, Landells *et al.*[85] evaluated UST in 110 patients aged 12–17 years who had moderate to severe plaque-type psoriasis. High-quality evidence showed increased probability of achieving all the percent improvement end-points assessed.

Patients were randomly assigned to UST standard dosing or half-standard dosing at weeks 0 and 4 and every 12 weeks or placebo at weeks 0 and 4 and at week 12 were shifted to either branch with UST. At week 12, 67.6 and 69.4% of patients receiving UST (standard of half-standard, respectively) achieved PGA 0–1 vs. 5.4% for placebo. Significantly greater proportions receiving UST achieved PASI 75 (78.4, 80.6, 10.8%) or PASI 90 (54.1, 61.1, 5.4%) (UST standard dosing, half-standard dosing or placebo, respectively).

AE with ETN, MTX, and ADA in children may be comparable to the findings in adult patients (L/MQE), with probably more AE at medium term (5.5% AE and 3.6% AE leading to treatment discontinuation). The most frequently reported AE were infections: nasopharyngitis (34.5%), upper respiratory tract infections (12.7%), and pharyngitis (8.2%) (MQE).

Recommendation # 10

In children with moderate to severe plaque-type psoriasis the SOLAPSO CPGs panel recommends the following therapeutic alternatives: ACT, ADA (patients ≥4 years old), CsA, ETN (patients ≥8 years old), MTX and UST (patients ≥12 years old) and phototherapy (*drugs listed alphabetically*)

Comments:
The panel weighed the safety profile showed by ACT, MTX, and phototherapy in clinical experience.
Some case reports and small case series showed that ACT may be moderately effective in children with moderate to severe plaque psoriasis and that, overall, the use of acitretin was well tolerated, with minimal adverse effects (Di Lernia, Napolitano).[86,87] *ADA was approved by the European Commission in April 2015 for the treatment of children with severe plaque psoriasis. The results of two trials evaluating ADA vs. MTX were also considered.*[88,89] *Based on these results and their personal experience, the panel agreed to recommend ADA in children with moderate to severe plaque-type psoriasis.*
The panel acknowledged that age (besides history and comorbidities) is a relevant factor at the time of indicating a biological agent, and emphasized that special consideration should be given to reduce the burden of the treatment in children whenever possible.

In children with moderate to severe plaque-psoriasis, which should be the first-choice treatment?

(TD Tables 3.2.1-3.2.3; 3.1.1-3.1.9)
To assess which of the recommended drugs should be indicated as first choice in pediatric patients with moderate to severe plaque-type psoriasis these CPGs included the results of two trials comparing drugs of each category and the analysis was completed considering also the results of each agent vs. placebo. No specific comparative studies were found for this subgroup to enlarge the assessment.

Recommendation # 11

In children with moderate to severe plaque-type psoriasis the SOLAPSO CPGs panel suggests treatment with a non-biological agent, considering MTX as first treatment choice.

Comments:
In the absence of evidence supporting that the efficacy and safety of the available therapeutic alternatives might be different in children and adults, the panel agreed to make the same recommendations (see 1.1).

When biologicals are indicated in children with moderate to severe plaque-type psoriasis (either as first line or after a prior failure), which should be the first-choice?

No studies comparing biological agents in children were identified. In the absence of specific evidence to answer this question, the panel decided to refer to the evidence assessed for the same question in adult patients.

Recommendation # 12

In children with moderate to severe plaque-type psoriasis who are started on biologicals either as first-line treatment or after a prior therapeutic failure, the SOLAPSO CPGs panel suggests any of the agents approved for use in pediatric patients (ADA, ETN).

Comments:
The panel acknowledges that age (besides history and comorbidities) is a relevant factor at the time of indicating a biological agent.
The panel emphasizes that special consideration should be given to reduce the burden of the treatment in children whenever possible.
In patients who strongly value short term effectiveness or treatment burden (less number of injections) it might be preferable to start therapy with Anti IL 12-23 or Anti IL 17.

In children with moderate to severe plaque-psoriasis with prior exposure and failure of biological therapies: which should be the treatment of choice?

Trials comparing different biological agents in the treatment of children with psoriasis were not identified. In the absence of specific evidence to answer this question, the panel decided to use indirect information from the same scenario in adult patients.

Recommendation # 13

In children with moderate to severe plaque-type psoriasis with prior exposure and failure of a biological therapy, the SOLAPSO CPGs panel suggests a different biological agent other than either shifting to a nonbiological or indicating a new course of therapy with the previously failing drug.

Chapter 3: Clinical Presentations

Juan Carlos Diez de Medina, Manuel Franco, Jorge Alex Abarca Duran, María Cecilia Brions

Patients with erythrodermic psoriasis

(TD Tables 3.6.1–3.6.8)

The results of meta-analysis evaluating the efficacy of biologics in psoriasis subtypes showed that these drugs appear to be effective in treating erythrodermic psoriasis (VLQE).[90]

Data from a meta-analysis by Sighn *et al.*[27] showed probably no differences among IFX, ADA, and ETN in the risk of serious AE or those leading to treatment discontinuation. The long-term safety results from Papp *et al.*[62] were also considered to assess UST safety profile for this localization (MQE).

To assess the efficacy of interventions to treat erythrodermic psoriasis in children, the results of a systematic review by Van Geel *et al.*[91] were considered. The studies evaluating the efficacy of ACT, CsA, ETN, and MTX reported complete remission with ACT, one failure with CsA, three patients reaching PASI 75 with ETN 0.8 mg/kg per week vs. no improvement with inferior doses; and 6/6 patients treated with MTX reaching PASI 75 at induction. No AE were reported in these series (VLQE). For the safety assessment the CPG considered the results of studies with adult patients for each intervention.

Recommendation # 14

In patients with erythrodermic psoriasis the SOLAPSO CPGs panel recommends the following therapeutic alternatives: ACT, ADA, CsA, ETN, IFX, and UST (*drugs listed alphabetically*).

Comments:

Erythrodermic psoriasis is infrequent, there are few studies on this presentation. No comparative studies between drugs or any other RCT could be identified. Therefore, the panel decided to consider all the drugs that showed beneficial effects in published studies in which patients with erythrodermic psoriasis were treated.

In patients with erythrodermic psoriasis, which should be the first-choice treatment?

No studies comparing the different therapeutic alternatives for the management of patients with erythrodermic psoriasis were found.

Recommendation # 15

In adult patients with erythrodermic psoriasis the SOLAPSO CPGs panel suggests treatment with CsA or IFX above all other alternatives. In children, CsA or ACT is suggested as first-choice therapy.

Comments:

In the absence of comparative studies the panel weighed the pharmacodynamic properties of CsA and IFX which appear as first choice therapy, based on their rapid action which is essential for these patients.

Patients with guttate psoriasis

(TD Tables 3.5.1–3.5.3)

The results of one RCT comparing penicillin or erythromycin for 14 days with a placebo or rifampin added during the last 5 days of treatment show no apparent benefit for the patients in improving their psoriasis (VLQE).[92] In assessing the effect of tonsillectomy in these patients, the authors reported total remission results in 9/10 patients and no AE (VLQE).[93,94]

Recommendation # 16

In patients with guttate psoriasis the SOLAPSO CPGs panel suggests treatment with NBUVB phototherapy as first choice, followed by MTX or RE. Searching and eventually treating the focus of infection is also suggested.

Comments:

The panel considered the results of small studies evaluating antibiotics and tonsillectomy plus other pathophysiologic grounds.

The NBUVB suggestion as first line option, as well as MTX or RE, were based on the clinical experience of the panel members, since evidence in this particular scenario is scarce.

Patients with generalized pustular psoriasis

(TD Tables 3.7.1–3.7.6 and .7.7–3.7.10)

The results of a meta-analysis evaluating biologic therapy in erythrodermic and pustular psoriasis were included to assess ADA, ETN, IFX, and UST[90] as well as the results of a 52-week OS evaluating the efficacy and safety of SEC in generalized pustular psoriasis.[95]

High rates of response were reported with ADA 6/6 (100%), ETN 9/10 (90%), IFX 28/30 (96%), and UST 7/7 (100%).[90] In the study by Imafu *et al*[95] at week 12, PASI 75 was reached in 83.3% of the patients; PASI 90 in 58.3% and PASI 100 in 16.6% (VLQE).

The AE assessment found serious AE reported in 10–12% of the patients in the meta-analysis comparing ADA, ETN, IFX and UST[90]; over the 52-week treatment period, SEC was well tolerated: nasopharyngitis, urticaria, diabetes mellitus, and arthralgia were the most frequently reported AE (VLQE).[95]

To assess the management of generalized pustular psoriasis in children, the results of 8 OS with ACT, CsA, IFX, and MTX vs. placebo were considered. Good treatment response was found for all interventions (VLQE).[96]

Recommendation # 17

In patients with generalized pustular psoriasis, the SOLAPSO CPGs panel suggests all the therapeutic alternatives indicated for erythrodermic psoriasis, plus SEC.

Comments:

The panel considered that there is no evidence to support that pustular psoriasis should be treated as a different entity compared to other presentations.

In patients with generalized pustular psoriasis, which should be the first-choice treatment?

Recommendation # 18

In adult patients with generalized pustular psoriasis, the SOLAPSO CPGs panel suggests treatment with CsA or IFX above all other alternatives and suggests CsA and ACT as first-choice in children.

Comments:

In the absence of reliable evidence, the panel weighed the pharmacodynamic properties of CsA and IFX which appear as first-choice drugs based on their rapid action. ACT should be considered, despite its delayed onset of action. SEC is also considered a therapeutic option in this scenario.

Exploring alternative differential diagnosis is recommended, to discard other auto inflammatory pustular diseases (DITRA) generally treated with anti-IL-1 drugs.

In adult patients showing patterns of generalized pustular psoriasis of subacute presentation ACT may be considered an alternative to the agents suggested.

Patients with palmoplantar pustular psoriasis

(TD Tables 3.8.1–3.8.5)

We assessed the results of a systematic review of RCTs including patients with chronic palmoplantar pustular psoriasis randomized to receive one or more interventions.[97]

The review included 23 trials and 724 people. The studies comparing CsA and UST vs. placebo, PUVA and retinoids, alone or in combination found a possible significant improvement with CsA persisting after 12 months in one RCT with 58 subjects (LQE). The use of systemic retinoids and PUVA appears as a valid alternative; however, a combination of both was better than the individual treatments, with a probable significant higher clearance (MQE).

The results of 5 OS with a total of 33 participants showed variable response rates with UST: some studies reported 100% and others 50% (LQE).[98–103]

Considering that phototherapy is one of the most frequent interventions for this localization, the results of studies evaluating NBUVB vs. PUVA were also assessed.[103] One RCT with 50 patients followed-up for 9 weeks suggests that PUVA may be more effective than UBV-BE, with percentages of improvement of 85.4% for PUVA and 61% for UBV-BE measured by severity index scores (LQE).

One patient at this study had a phototoxic reaction with PUVA; palmar hyperpigmentation was found in 52% of the patients. No serious AE were reported in all the other assessed studies.

Studies comparing CsA, ETN, and IFX vs. placebo in children with palmoplantar pustular psoriasis in the systematic review by Van Geel *et al*.[95] reported excellent response rates with ETN, good response rates with IFX and lack of response with CsA (VLQE).

Recommendation # 19

In patients with palmoplantar pustular psoriasis phototherapy, the SOLAPSO CPGs panel recommends PUVA, RE-PUVA, and NBUVB and suggests RE-PUVA as first-choice.

Comments:

In the absence of evidence on the efficacy of biologics in the management of patients with palmoplantar pustular psoriasis, except for the results of one report with UST in adult patients, considering that phototherapy is usually indicated to treat these patients and also considering the efficacy, administration and less AE observed in clinical practice with PUVA, the panel decided to suggest this

intervention as first-choice, followed by UVA or UVB, based on their clinical experience and availability.

Chapter 4: Special Localizations

Jaime Martínez, Gerardo Bran Quintana, Lilia Barahona, Evelyn Castro Vargas

Patients with scalp psoriasis

(TD Tables 3.9.1–3.9.5)

Studies comparing ADA, ETN and UST vs. placebo and one comparative study of ADA vs. IFX met the criteria of these CPGs to assess the efficacy of these drugs in the management of adult patients with scalp psoriasis.

An observational study with 663 patients showed that 68.2% of the patients treated with ADA reached PASI 75 at week 16, and there were also large improvements in their scalp symptoms as shown by a median decrease from baseline PSSI of 100% (77.2 ± 96.9%) (LQE).[104]

The results for ETN showed a possible higher probability of reaching PASI 50, 75, and 90 at induction (MQE).[105]

Two OS found a very rapid treatment response with UST, 4/4 patients showed complete remission at week 16 (VLQE).[106,107]

The results of a RCT comparing ADA vs. IFX in patients with scalp psoriasis were not conclusive uncertain to support better results with either intervention (VLQE).[108]

In patients with scalp psoriasis, which should be the first-choice treatment?

Recommendation # 20

In patients with severe scalp psoriasis, the SOLAPSO CPGs panel suggests treatment with phototherapy, MTX or ACT above all other alternatives.

Comments:

Scalp psoriasis is the most frequent presentation of the disease. Only severe forms require systemic treatment.

Although evidence is limited, the panel agreed to privilege topical therapy and indicate MTX or ACT when needed.[109]

The panel acknowledged that despite the available evidence, the use of biologics in this presentation is still infrequent.

Patients with palmoplantar psoriasis

(TD Tables 3.10.1–3.10.7)

Comparative studies of ADA, IFX, MTX, SEC, and UST vs. placebo were found to assess the results of these interventions in the management of patients with palmoplantar psoriasis, as well as one comparative study of MTX vs. ACT.

In one OS with 11 patients, 36% reached PGA 0–1 and 72% showed improvement in the health related quality of life measurements (VLQE).[110] A RCT comparing IFX vs. placebo included 24 patients; although the PASI 75 end-point at week 14 was not achieved, at that point PPASI 75 and PPPASI 50 were achieved in 33.3 and 66.7% of patients, respectively, as well as a 50.3% reduction in the affected area in palms and soles, compared to a 14.9% increase in the control group; and uncertainty about the long-term impact on PPPASI 100 (VLQE).[111]

A review of 44 OS comparing MTX vs. placebo showed that 75% of the patients receiving MTX reached PGA 0–1 (VLQE).[112]

The results from four RCT with 127 patients in all, evaluating SEC vs. placebo in patients with palmoplantar psoriasis show a significant increase in the probability of reaching PASI 75, PASI 90, and PASI 100 with this biologic (HQE).[51,53,113,114]

The efficacy of UST was assessed through the results of an OS with 20 patients: 35% reached PGA 0–1 in palms and soles and 60% achieved over 50% PGA improvement at week 16 (LQE).[98]

One RCT compared MTX vs. ACT in 111 patients with palmoplantar psoriasis, randomized to receive MTX 0.4 mg/kg weekly or ACT 0.5 mg/kg daily. Patients were evaluated by modified PPPASI (m-PPPASI) score for palm and sole involvement at baseline and subsequent intervals for 12 weeks. Marked improvement (m-PPPASI 75) was achieved in 12 (24-%) patients treated with MTX compared with 4 (8%) in the ACT group. There are possible no differences in the possibility of reaching PPPASI 50 (LQE).[115]

The safety assessment showed data comparable to the observations for each drug in different localizations.

Recommendation # 21

In patients with palmoplantar psoriasis, the SOLAPSO CPGs panel suggests to start treatment with ACT or MTX above all other alternatives.

Comments:

In the absence of reliable evidence, the panel based their suggestions on the clinical experience with the use of these drugs.

The comparison of MTX and ACT did not provide enough information to prioritize one over the other.

No data was found on the use of CsA for this localization.

Treatment with biologics should be considered after prior treatment failures, following the suggestions in the management of patients with plaque-type psoriasis.

Patients with nail psoriasis

(TD Tables 3.11.1–3.11.5)

To assess the efficacy of ADA, one RCT was considered comparing ADA vs. placebo to treat moderate to severe chronic plaque psoriasis involving the hands and/or feet.[116] The trial included 36 patients and the authors concluded that ADA is effective in these localizations, with efficacy largely maintained to 28 weeks (VLQE).

The efficacy of IFIX for the treatment of nail psoriasis was assessed through the results of a long-term phase III RCT (50 weeks) involving 305 patients randomized 4:1 to IFX (5 mg/kg) or placebo at weeks 0, 2, 6, and every 8 weeks through week 46, with placebo crossover to IFX at week 24.[117] Of the patients receiving IFX 6.9, 26.2, and 44.7% had nail disease clearance at weeks 10, 24, and 50, respectively, vs. 5.1% in the placebo group at week 24. IFX might increase the probability of reaching total improvement at induction (MQE) and maintenance (LQE).

To assess SEC in this localization, a phase 2 placebo-controlled regimen-finding study was considered. Subjects treated received any of 3 SEC 150-mg induction regimens either 1, 3, or 4 injections at different intervals. SEC showed a beneficial effect on psoriasis of the nails, as assessed by the composite fingernail score which improved with the 3 and 4 injections induction regimens and worsened with placebo (LQE).[113]

One RCT designed to evaluate and compare the efficacy and safety of MTX and CsA in psoriatic nail[118] with NAPSI as primary outcome included 34 patients controlled for 3 months. The mean percentages of reduction of the NAPSI score with MTX and CsA were 43.3 and 37.2%, respectively, showing moderate effectiveness on psoriatic nail and no significant differences between both agents (LQE).

Studies comparing different therapeutic choices in the treatment of nail psoriasis could not be identified.

Regarding safety, all the studies assessed were comparable with the findings for all other localizations.

Recommendation # 22

In patients with nail psoriasis, the SOLAPSO CPGs panel recommends the same systemic treatment alternatives indicated for adult patients with moderate to severe plaque-type psoriasis (*Recommendation # 1*)

Recommendation # 23

In patients with nail psoriasis, the SOLAPSO CPGs panel suggests MTX as first line therapy above all other alternatives.

Comments:

In the absence of high quality evidence on efficacy and long-term studies, the panel based their recommendation on clinical experience with MTX.

Patients with inverse psoriasis

(TD Table 3.13)

To assess if there are specific considerations that might lead to different therapeutic approaches of inverse psoriasis with respect to palmoplantar psoriasis, only one case report was identified, providing VLQE to support any intervention.[119]

Studies comparing different therapeutic choices in the treatment of inverse psoriasis could not be identified.

Recommendation # 24

In patients with inverse psoriasis, the SOLAPSO CPGs Panel recommends the systemic treatment alternatives indicated for adult patients with moderate to severe plaque-type psoriasis (*Recommendation # 1*) but does not recommend CsA and phototherapy.

Recommendation # 25

In patients with inverse psoriasis, the SOLAPSO CPGs panel suggests MTX or ACT as first line interventions above all other alternatives.

Comments:

Based on the limited available evidence, the panel considered that the therapeutic approach of palmoplantar psoriasis and nail psoriasis should be similar. CsA and phototherapy were not considered in this scenario.

Chapter 5: Arthritis

Simón Gusis, Nora Kogan

Patients with plaque-type psoriasis and predominant joint involvement

(TD Tables 3.12.1–3.12.9)

To define which interventions should be considered for this scenario, the CPG assessed the results of the studies meeting the inclusion criteria which compared each intervention vs. placebo and measured the outcomes previously defined: ACR20, ACR50, ACR70, PsARC, HAQ-DI, DAS28, and AE. Following is a summary of the results assessed for each drug.

Adalimumab (TD Table 3.12.1)

Two RCT with 413 patients in all[120,121] showed a possible increase in ACR20, 50 and 70 with ADA at induction (MQE). These results persisted up to week 24 in one of these studies, with 313 patients.[121] An OS with 298 patients showed sustained efficacy levels at 2 years follow-up, with 58.7% ACR 20, 42.7% ACR 50, and 29.8% ACR 70 (LQE).[122] Severe AE were also reported in this study with ADA (18.1%) as well as AE which lead to treatment discontinuation (6.7%).

Certolizumab (TD Table 3.12.2)

CER is an anti-TNF monoclonal antibody which has shown to be clinically effective for the treatment of rheumatoid arthritis and is also considered for psoriasis. One phase 3 trial in patients with psoriatic arthritis showed that CER could be effective to reach ACR 20, 50, and 70 (M/HQE).[123] The authors reported that ACR20 response at week 12 was significantly higher in the group of patients receiving CER 200 mg every 2 weeks and 400 mg every 4 weeks (58.0 and 51.9%, respectively vs. 24.3% in the control group). The study also showed a probable higher probability of improved quality of life as measured by HAQ-DI (−0.50 CER vs. −0.19 placebo) and PsARC at week 24 (MQE).

Etanercept (TD Table 3.12.3)

The results of the RCT assessed showed probable improvement with ETN at 12 and 24 weeks follow-up (MQE) and probable improvement in quality of life (LQE).[124–126]

Infliximab (TD Table 3.12.4)

The results of two RCT with 304 patients showed a possible increase in ACR 20, 50, and 70 at induction (LQE) and a probable improvement in quality of life (clinically meaningful improvement in HAQ; ~0.3 unit decrease) at week 14 (MQE).[127,128]

Methotrexate (TD Table 3.12.5)

The results of one RCT were assessed to evaluate MTX vs. placebo in PsA. This was a 6-month double-blind RCT comparing MTX (15 mg/week) with placebo in 221 patients with active PsA; the primary outcome was PsARC. The study provided LQE to support MTX as a disease-modifying drug in PsA.[129]

Secukinumab (TD Tables 3.12.6.1–3.12.6.3)

Two RCT evaluating the efficacy of SEC 75, 150, and 300 mg vs. placebo were included to assess the effectiveness of this biologicin the treatment of PsA. With a total of 1,000 patients and 24 weeks follow-up, the results of these studies showed the probable efficacy of SEC in improving ACR 20, 50, and 70 (M/HQE). Higher doses schemes showed even better results. In the safety profile assessment, a probable increase in AE was found for SEC after 52 weeks follow-up in PsA patients (LQE).[130,131]

Ustekinumab (TD Table 3.12.7)

Three RCT evaluating UST vs. placebo in patients with PsA, with over 1,000 patients controlled for 12 and 24 weeks, showed a probable improvement in ACR 20, 50, and 70 with UST (MQE) and improvements in PsA signs/symptoms in a diverse population of patients (HQE).[132–134]

Golimumab (TD Table 3.12.8)

GOL is a human anti-TNF monoclonal antibody, which has shown benefits in the management of patients with rheumatoid arthritis. Continued clinical efficacy and safety through 1 and 5 years was found for GOL in the RCT assessed comparing GOL 150 and 300 mg vs. placebo in 405 patients with PsA (146 patients at each branch receiving GOL and 113 patients in the control group) (LQE).[135,136]

Apremilast (TD Table 3.12.9)

APM is an oral phosphodiesterase 4 inhibitor (PDE4). The results of 5 RCT evaluating APM vs. placebo in over 1,400 patients showed improvement in ARC 20 at 16 and 24 weeks, as well as the probability of sustained clinical efficacy through 1 year of treatment (M/HQE). Improvement in quality of life as measured by HAQ-DI was also reported, although the clinical significance of these results is uncertain (HQE).[137–143]

Recommendation # 26

In patients with plaque-type psoriasis and predominant joint involvement, the SOLAPSO CPGs panel recommends the following agents as therapeutic alternatives: ADA, APM, CER, ETN, GOL, IFX, MTX, SEC, and UST *(drugs listed alphabetically)*.

Comments

Although APM is not available in Latin America, the panel considered the value of the results assessed and the experience with the use of this drug.

The panel notes that CER and GOL have not been approved for the treatment of skin psoriasis.

In patients with plaque-type psoriasis and predominant joint involvement, which should be the first-choice treatment?

To answer this question, the results of trials meeting the inclusion criteria of these CPGs comparing ETN vs. ADA, ETN vs. IFX, and MTX vs. CsA were considered. The evaluation

was completed with the results of each intervention compared with placebo.

ETN vs. ADA vs. IFX (TD Tables 3.12.10 y 3.12.11)

One RCT compared the efficacy and safety of ETN vs. ADA vs. IFX in patients with PsA with inadequate response to a previous DMARD (INF 5 mg/Kg every 6–8 weeks, ETN 50 mg weekly, or ADA 40 mg every other week, or placebo). Efficacy was defined as the percentage of ACR20 responders and as clinical remission and/or minimal disease activity at 12 months treatment. Possible no relevant differences in ACR 20 were found among all the interventions evaluated. No differences were observed in HAQ and there is uncertainty about the impact of all three agents on this efficacy parameter (LQE).[144]

MTX vs. CsA (TD Table 3.12.12)

Two RCT comparing MTX vs. CsA in PsA found similar efficacy of both agents to improve PsA signs/symptoms as measured by DAS 28 (LQE).[145,146]

Recommendation # 27

In patients with plaque-type psoriasis and predominant joint involvement, the SOLAPSO CPGs panel suggests treatment with nonbiological drugs as first-choice.

Recommendation # 28

In patients with plaque-type psoriasis and predominant joint involvement who are started with a nonbiological, the SOLAPSO CPGs panel suggests MTX above all other alternatives.

Comments:

In the absence of comparative studies between biological and nonbiological agents, the panel weighed the experience with the use of nonbiologics, their wide availability, the information on long-term safety and their low cost. Suggesting MTX as first-choice is based on the experience with this drug compared with other nonbiologics (DMARDS), considering that the evidence currently available does not show the superiority of any agent. In treatment failures, all other alternatives should be considered.

Treatment with biological drugs as first-choice is suggested for those patients who prioritize short-term effectiveness and patients who have specific counter-indication for treatment with nonbiologics.

In patients with plaque-type psoriasis and predominant joint involvement who are started on biologics (either as first or second line therapy), which should be the first-choice treatment? *(TD Tables 3.12.10, 3.12.11)*

To answer this question, the results of a study comparing ETN vs. ADA vs. IFX were considered[144] and the assessment was completed by also considering the results of the studies evaluating each agent vs. placebo.

Recommendation # 29

In patients with moderate to severe plaque-type psoriasis and joint involvement who are started on therapy with a biological agent, the SOLAPSO CPGs panel suggests anti–TNF (ADA, ETN, INF), CER, GOL or anti-IL-12/23 above SEC or APM.

Comments:

The recommendation of one biologic over the others is based on the currently available information about long-term efficacy and safety.

Which biological to choose should be decided considering the cutaneous involvement, assuming that the effect on the skin is heterogeneous.

All agents may be used in patients without skin involvement; CER and GOL should only be considered in patients with minor skin involvement.

Chapter 6: Considerations about Routes of Administration, Co-morbidities, and Adverse Effects of Biologicals

Patricia Levrero, Orestes Blanco González

In patients with plaque-type psoriasis who discontinue an effective treatment, which should be the next choice? *(TD Table 3.14.1)*

The information of cohorts of patients who interrupted their treatments and the response rates after restart was considered as first end-point to assess this decision. All studies identified provided HQE for re-treatment with each intervention.

The results found by Gottlieb *et al.*[147] in two OS with 123 patients showed that 67% of patients reached PASI 75 at week 26 with IFX 10 mg/kg and 87.9% at week 10 with IFX 5 mg/kg.[45] One study using ADA reported effectiveness (76% of patients reaching PGA 0–1), similarly to one using UST (85.6% reaching PASI 75).[58,148]

Three OS were found to assess ETN in this scenario, their results are consistent to suggest that ETN is effective in re-treatment. Gordon *et al.* did not find differences in PASI with ETN as initial therapy or as re-treatment.[149] Moore *et al.,* reported PGA < 2 in 72% of responders at week 12 and 59% at week 24, and significantly better results at week 24 in continued treatment.[150] Griffiths *et al.*[151] found 90% response (PGA < 2) after treatment with ETN.

Recommendation # 30

In patients with moderate to severe plaque-type psoriasis who interrupt an effective therapy, the SOLAPSO CPGs panel recommends to resume the scheme, except in the case of patients who discontinue therapy with IFX, who should be shifted to a different drug.

Table 3 Risk factors for complications in the treatment of psoriasis

	Interpretation	Quality	Source
Psoriatic arthritis	Psoriatic arthritis could increase the risk of infections	LQE[a]	Prospective cohort studies (PSOLAR registry) and retrospective.[28,153–155]
Metabolic syndrome	No studies could be identified	–	–
Diabetes	Diabetic patients could be at a higher risk of infections	LQE[a]	Prospective cohort studies (PSOLAR registry).[153]
Previous severe infections	The risk of severe infection could be higher in patients with a history of previous severe infections.	LQE[a]	Prospective cohort studies (PSOLAR registry).[153]
Tuberculosis	The risk of TB reactivation could probably be higher in patients with a history of TB	LQE[b]	Randomized studies and prospective cohorts suggest that treatment with biologics increases the risk of reactivation.[27,151,156]
Cardiovascular disease	Patients with a history of cardiovascular disease are significantly at a higher risk of cardiovascular events	LQE[a]	Prospective cohort studies (PSOLAR registry).[153]
Liver disease	The risk of hepatic fibrosis is higher in patients with a history of liver disease when treated with MTX. Possible higher risk of severe adverse effects in patients treated for their psoriasis with or without biologics	VLQE[a,c]	Prospective cohort studies.[153,157]
Hepatitis B or C	Previous hepatitis B could lead to psoriasis reactivation with treatment. Hepatitis B or C could be associated with an increased risk of severe adverse effects	VLQE[a,c,d]	Series of cases, prospective cohort studies.[154,157,158]
Mental disorders or diseases	No studies were identified	–	–
Neurologic disease	No studies were identified	–	–
Chronic renal disease	The risk of severe adverse effects could be higher in patients with chronic renal disease	VLQE[a,c]	Prospective cohort studies.[159,160]
Respiratory disease	No studies were identified	–	–
Gastrointestinal diseases	No studies were identified	–	–
History of neoplasias	The risk of malignancy is significantly higher in patients with neoplasia	LQE[a]	Prospective cohort studies (PSOLAR registry).[28,153,160]
HIV	HIV infection would not increase the risk of severe adverse effects	VLQE[a,c]	Prospective cohort studies.[155]

[a]Correlation identified in observational studies.
[b]Despite the relation between latent TB and reactivation has been well shown, the increased risk with biologic treatment is uncertain (LQE) due to the limited number of events.
[c]The limited number of events results in wide CI which include the possibility of absence of harms.
[d]Inconsistency in the results.

Comments:
The panel considered that patients who discontinue an effective treatment course should restart therapy with the same drug, which has already proved to be effective and safe for the patient; this decision should also be regarded as a means for not to disregard valid therapeutic alternatives.
The recommendation about avoiding re-treatment with IFX was based on the probability of severe reactions to infusion.

Which is the best administration scheme for biologics in patients with moderate to severe plaque-type psoriasis? *(TD Table 3.18.1)*

Two RCT were considered, evaluating the efficacy and safety of continued vs. intermittent administration of IFX in over 500 patients with moderate to severe plaque-type psoriasis who were followed up through 52 weeks. The results show that there is a higher probability of reaching PASI 75, PASI 90, PGA 1–2 and improving quality of life with continuous treatment (MQE).[46,152]

Recommendation # 31

In patients with moderate to severe plaque-type psoriasis who are started with biologicals, the SOLAPSO CPGs panel suggests continuous above intermittent administration.

Comments:
The panel acknowledged that efficacy and improvement in quality of life in patients receiving biologicals in continuous administration outweigh costs and discomfort.
Also, the panel highly valued both the probability that continuous administration of biological agents might avoid immunogenicity and the potential impact of limiting future therapeutic decisions.

Co-morbidities (TD Tables 3.16.1 y 3.16.2)
OS were assessed to determine the impact of comorbidities on the risk of AE. The findings are summarized in Table 3.

Adverse effects of biologicals (TD Table 3.17)
Table 3.17 is cited throughout these CPGs in all comparisons with biologics. This Table summarizes the results of three OS on the long-term evaluation of AE with these agents (LQE).

The incidence of severe infections, cardiac events and malignancies was assessed based on the data of the Biobadaderm Registry, with 1,956 patients at 1 year[156,158] and the PSOLAR registry[28,153] with 12,095 participants, which suggest a possible increase in the risk of infections with IFX and ADA and a possible absence of increased risk of cancer or cardiac events. ADA and IFX could increase the incidence of severe infections as compared to the other therapeutic alternatives, with an incidence of 1.45 each 100 patients per year (LQE).

This finding is somehow inferior in the PsoBest Registry[161] with 2,699 patients at 1 year: 0.56 severe infections each 100 patients per year and no differences as compared with nonbiologicals (LQE).

About the use of these CPGs

These CPGs summarize the judgment of the group of experts convened by SOLAPSO and includes recommendations which have been agreed after a careful assessment of the evidence, in the expectation that they may become a useful reference standard in clinical practice.

Under no circumstances should these recommendations replace the criteria of the treating physician about a therapeutic decision based on each patient and circumstance, as well as on the values, the preferences and the opinions of the patient or caregivers.

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Supporting Information

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

Appendix S1. SOLAPSO Clinical Practice Guidelines - Technical Document.

