Clinical applications of PPI-TT guidelines on transitioning therapies in the treatment of moderate to severe psoriasis: an expert opinion of central Italy dermatologists

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Summary

Background. Optimization of treatment management in patients affected by moderate to severe psoriasis is important to achieve long-term control of the disease. The PPI-TT provided practical suggestions on management of systemic treatments for psoriasis. However, these guidelines do not take into account differences in regulations and clinical practice among European states.

Objective. Evaluate how PPI-TT guidelines can be applied to clinical practice in central Italy identifying criticisms and ways to improve them.

Methods. Experts from central Italy were invited to present clinical cases on treatment optimization and transitioning before PPI-TT guidelines were published. At a first board meeting PPI-TT guidelines were presented and clinical cases evaluated and discussed identifying discrepancies and criticisms. In a second meeting new cases were presented and discrepancies with PPI-TT were discussed.

Results. There was a high level of agreement between clinical practice and PPI-TT guidelines, discrepancies were found in: 1) management of combination therapies, and 2) in the optimization of biologic therapies.

Conclusion. The experts agreed on the importance of PPI-TT guidelines as a practical guide for the management of moderate-to-severe psoriasis patients but also suggest that these can be improved to adapt them to local clinical behavior and regulations.

KEY WORDS: psoriasis; biologic therapies; PPI-TT guidelines; transitioning therapies.

Introduction

The “Progressive Psoriasis Initiative Transitioning Therapies program” (PPI-TT), was established to provide a practical guideline, evidence based and agreed by experts, on the optimization and therapy in the management of moderate to severe psoriasis. Thirty-three countries were involved in this project, that was carried out between May 2011 and June 2012. A directing committee composed by nine dermatologists from Europe and Canada supervised the project. Participating dermatologists were invited to suggest clinically relevant questions related to three main topics: the optimization of systemic therapies, transitioning from conventional systemic therapies to biologics and transitioning from one to another biologic. Principal topics were: optimization of systemic conventional therapies (Methotrexate and Cyclosporine); modalities to interrupt a conventional systemic therapy; transition from conventional therapy to biologic; combination of conventional therapy with biologic therapy; optimization of biologic therapy and transition from one to another biologic drug. A detailed description of the methodology and results was recently published by Mrowietz et al. (1).

The PPI-TT project was carried out through a modified Delphi procedure and consisted in different phases. A similar method was employed to develop other consensus-based guidelines (2, 3). The results consisted in the definition of 16 questions related to the different topics,
followed by one or more answers useful for patients’ management (Table 1). Each answer had a higher or lower level of evidence according to the Oxford Centre for Evidence-Based Medicine Classification (4).

Table 1 - Guidelines for therapy optimization and transitioning of the PPI-TT initiative.

**RECOMMENDATIONS ON OPTIMIZING CONVENTIONAL SYSTEMIC THERAPIES: CYCLOSPORINE**

Q1A What is the maximum period for which conventional systemic therapies should be given to patients responding to treatment?

Treatment with cyclosporine is generally used intermittently for inducing a clinical response with one or several courses over 3-6 months.

When necessary, cyclosporine may be given to patients responding to treatment continuously for up to 2 years. In exceptional cases, where no other treatment options are available, treatment with cyclosporine can be extended for longer than 2 years with adequate monitoring. However, changes in the risk-benefit profile for cyclosporine can already occur from an early stage of treatment and this should be borne in mind when considering treatment options.

The long-term use of cyclosporine should be considered with caution because of the significant risk of renal toxicity, the development of arterial hypertension and the increased risk of skin cancer especially in patients with extensive previous phototherapy (e.g. >200 PUVA treatments). Long-term cyclosporine use should be considered with particular caution in patients with a history of cancer or who are immunosuppressed.

Regular monitoring should be performed according to the existing guidelines; skin examination to check for skin cancer is also recommended.

Q1B Following treatment with conventional systemic therapy, during what time period should we expect to see a clinical response? At what time points should we monitor patients for treatment response, for example, with PASI 75?

In clinical trials with cyclosporine starting dosages of 2.5-3 mg/kg/day, clinically meaningful responses (50% reduction in the mean PASI) have been observed after 4-6 weeks. (Level of evidence 2)

Higher starting dosages (5 mg/kg/day) lead to a more rapid onset of response (50% reduction in mean PASI within a mean time of 3-4 weeks) (Level of evidence 2) although this may be associated with greater toxicity than starting at a lower dosage.

The clinical response to cyclosporine in a patient population with dosages of 2.5–5 mg/kg/day can be expected to reach a maximum within 5-12 weeks. (Level of evidence 2)

PASI, Psoriasis Area Severity Index; PUVA, psoralen plus ultraviolet A; clinically meaningful response, a 50% reduction in the mean PASI in a population of patients.

**RECOMMENDATIONS ON OPTIMIZING CONVENTIONAL SYSTEMIC THERAPIES: METHOTREXATE**

Q2A What is the maximum period for which conventional systemic therapies should be given to patients responding to treatment?

Methotrexate may be given to patients for as long as it remains effective and well-tolerated.

Screening and monitoring of patients according to the existing guidelines is required.

In most cases, the risk of liver toxicity with methotrexate therapy is low; however, the impact of additional risk factors such as baseline liver disease (including HBV or HCV), alcohol intake, obesity and type 2 diabetes and the use of concomitant medications should be taken into account. The risk of liver toxicity may increase with cumulative doses of methotrexate.

There is no clear evidence for or against increased risk of malignancies or serious infections with methotrexate therapy in patients with psoriasis.

Q2B Following treatment with conventional systemic therapy, during what time period should we expect to see a clinical response? At what time points should we monitor patients for treatment response, for example, with PASI 75?

In clinical trials with oral methotrexate (5-7.5 mg weekly starting dose, escalating), clinically meaningful responses (50% reduction in the mean PASI) have been observed after 7-13 weeks. A reduction of the mean PASI by 75% has been observed within 14 weeks. (Level of evidence 2)

(to be continued) →
(Continued from Table 1)

| Higher oral starting doses (15-22.5 mg weekly) lead to more rapid onset of response (50% reduction in the mean PASI within a mean time of 3-4 weeks and 75% reduction in the mean PASI within 7 weeks). (Level of evidence 2) The clinical response to oral methotrexate in a patient population can be expected to reach a maximum within 12-20 weeks. (Level of evidence 2) Q3 If a patient does not respond to methotrexate within 16-24 weeks, should we increase the dose? What is the maximum dose we should use before considering treatment failure? Oral methotrexate therapy can be initiated at dosages between 5 and 15 mg/week with early monitoring (before the second dose). If a low starting dose is selected, rapid dosage escalation to 15 mg/week by week 3 can be considered. If at week 8 the response is insufficient, an increase in the dosage to 20 mg/week can be considered. For patients who are non-responders to 20 mg oral methotrexate treatment at 16-24 weeks the effect of further increasing the dose remains unclear. There is evidence for oral methotrexate only: increased efficacy and tolerability may be achievable by subcutaneous administration. Q4 What is the optimal safety monitoring (clinical, laboratory) of patients receiving methotrexate? How often? Current guidelines provide monitoring recommendations for screening, initiation and maintenance with methotrexate therapy. For methotrexate-naive patients, it is particularly important to assess for early signs of toxicity before administering the second dose of methotrexate. In addition to guideline recommendations, monitoring for liver toxicity may include measurement of PIIINP every 3-6 months in the same laboratory and assessment of the liver using transient elastography, if these tests are available. Liver biopsy is not routinely indicated but may be considered in specific clinical circumstances following discussion with a hepatologist. HBV, hepatitis B virus; HCV, hepatitis C virus; PASI, Psoriasis Area Severity Index; PASI 75, a 75% reduction in PASI; PIIINP, procollagen III N-terminal peptide; clinically meaningful response, a 50% reduction in the mean PASI in a population of patients. RECOMMENDATIONS ON STOPPING CONVENTIONAL THERAPY Q5 Can conventional systemic therapy be stopped in cases of sustained response/clearance using monotherapy? If so, how many months of sustained clearance should we see before stopping therapy? In which patient groups can we stop conventional systemic therapies (e.g. all patients, only those with previous slow relapses following discontinuation)? Continuous therapy is required to achieve long-term disease control. Therefore, stopping therapy is not generally recommended. However, if agreed with the patient, and after achieving a clinical response of clear or almost clear with good QoL for a prolonged period of time, for example, a minimum of 1 year, stopping conventional systemic therapy can be considered with careful follow-up. Consideration of stopping therapy in patients with well-controlled psoriasis should be based on: Patient preference Presence of individual risk factors with an impact on the long-term benefit-risk profile Prior course of disease including pattern of flares/rebound Presence of comorbidity Presence of PsA Disease phenotype, severity and impact on QoL Availability of treatment options in case of disease recurrence Type of treatment Recurrence of the disease can be expected within 2-6 months in many patients discontinuing therapy. There is little evidence to suggest the subgroups of patients in which therapy can be interrupted or stopped. Q6 In patients who have stopped conventional systemic therapy, what criteria should we use to determine when therapy should be reintroduced (e.g. loss of PASI 75, loss of PASI 50 (relapse), loss of DLQI<5 response, loss of PGA < 2, loss of PGA < 3)? (to be continued) →
There are no standard criteria for treatment reintroduction. Shared decision making between physician and patient is important. Patient management should take into account that after having experienced disease control for some time, patients may become less tolerant of disease recurrence. Recurrence of limited disease may be controlled with topical therapy or phototherapy. As a practical guide, consider reintroducing systemic therapy if there is a PGA >2 and/or PASI >5 and/or DLQI >5 or if there is rapid disease recurrence.

DLQI, Dermatology Life Quality Index; PASI 50, a 50% reduction on the Psoriasis Area Severity Index; PASI 75, a 75% reduction in PASI; PGA, Physician’s Global Assessment; PsA, psoriatic arthritis; QoL, quality of life.

RECOMMENDATIONS FOR TRANSITIONING FROM CONVENTIONAL SYSTEMIC THERAPY TO BIOLOGICAL THERAPY

Q7 In cases of non-response to conventional systemic therapies, should transitioning to a biological agent be done sequentially without a washout period, sequentially with a washout period, or should treatments be overlapped? What is the appropriate dosing schedule in each of these scenarios?

General
Recommendations for transitioning therapies will differ depending on the reason for transitioning. When transitioning from conventional systemic therapy to another drug for safety reasons, a treatment-free interval may be necessary until the safety parameter has normalized or stabilized.
When transitioning due to lack of efficacy, transitioning directly or with an overlap period can be considered.
When transitioning from conventional systemic treatments to biological treatments, approved induction dosages should be used.

Acitretin to a biological agent
Treatment transitioning from acitretin to TNF antagonists can be performed without a washout period or with an overlap. (Level of evidence 3)
Treatment transitioning from acitretin to ustekinumab can be performed without a washout period or with an overlap. (Level of evidence 5)
However, women of child-bearing age should continue with contraception for 2 years as recommended for the use of acitretin.

Cyclosporine to a biological agent
Treatment transitioning from cyclosporine to TNF antagonists can be performed without a washout period. (Level of evidence 4)
Treatment transitioning from cyclosporine to ustekinumab may be performed without a washout period. (Level of evidence 5)
A short overlap period (e.g. 2-8 weeks) of cyclosporine with TNF antagonists or ustekinumab can be considered in order to reduce the risk of rebound in partial responders but the overlap period should be minimized and the dose of cyclosporine tapered down as soon as possible. (Level of evidence 5)

Methotrexate to a biological agent
Treatment transitioning from methotrexate to TNF antagonists can be performed without a washout period. (Level of evidence 2)
Treatment transitioning from methotrexate to ustekinumab can be performed without a washout period. (Level of evidence 5)
Methotrexate can be overlapped or used concurrently with TNF antagonists (level of evidence 2) or ustekinumab (level of evidence 5).

TNF, tumour necrosis factor; partial responder (or intermediate responder), defined in the European treatment goals as achievement of an intermediate response of change in PASI >50 but <75 (as compared with disease severity at the time of treatment initiation), where DLQI >5 has not been achieved or where DLQI<5 has been achieved.

RECOMMENDATIONS ON COMBINING CONVENTIONAL SYSTEMIC THERAPY WITH BIOLOGICAL THERAPY

Q8 Is it efficacious to combine biological therapy with conventional systemic therapy? Is it safe to combine biological therapy with conventional systemic therapy?
There is no approved indication for any combination of a biological with conventional systemic therapies in psoriasis.

A conventional systemic therapy can be added to biological monotherapy with the intention to improve efficacy, optimize the risk-benefit profile, reduce the risk of immunogenicity (with methotrexate) and enhance long-term disease management.

For the TNF antagonists, combination with methotrexate (5-15 mg/week) is safe (Level of evidence 4) and increases the long-term efficacy of the treatment regimen. (Level of evidence 3)

Due to the lack of evidence and the potentially increased toxicity, for example, an increased skin cancer risk, the combination of TNF antagonists or ustekinumab with cyclosporine should be used with caution. (Level of evidence 5)

The combination of etanercept 25 mg/week with acitretin showed similar efficacy as 2x25 mg/week etanercept monotherapy. (Level of evidence 2) The combination of acitretin with lower doses of etanercept 25 mg/week has a safety profile comparable to the monotherapy. (Level of evidence 3)

The combination of adalimumab with acitretin may be considered. (Level of evidence 4)

A treatment combination of methotrexate with ustekinumab may be used, but there is limited data on safety and efficacy (Level of evidence 5).

Data for the combination of acitretin with infliximab or ustekinumab are not currently available but an increased clinical response might also be expected. (Level of evidence 5)

Q9 What is the optimal safety monitoring (clinical, laboratory) of patients receiving combination therapy with a conventional systemic agent and a biological therapy? How often?

The optimal safety monitoring for combination therapy has not been determined.

All parameters recommended to be monitored for each drug as monotherapy should be assessed.

As a practical guide, the monitoring interval should be defined by the drug with the most stringent monitoring criteria. If synergistic toxicity is suspected, monitoring intervals may need to be reduced and additional parameters may need to be added.

Q10 If there is no response or insufficient response when combining a conventional systemic therapy with a biological agent, should we increase the dose of the conventional systemic therapy? Increase the dose of the biological? Reduce time intervals of the biological? Change to another biological?

The combination of a biological with a conventional systemic therapy is an option in the treatment of psoriasis; however, there is no clinical trial evidence on which to provide answers to these questions.

Conventional systemic therapy with methotrexate or acitretin can be added to a biological monotherapy with the intention to improve efficacy, optimize the risk-benefit profile, reduce the risk of immunogenicity (with methotrexate) and enhance long-term disease management. The conventional systemic therapy should be added beginning with the lowest recommended dosage, for example, 5-10 mg/week for methotrexate. The combined use of cyclosporine and a biological raises safety concerns.

If adequate response is still not achieved:
- Optimize the current therapy (e.g. increase the dosage of the conventional systemic therapy; increase the dose or decrease the treatment interval of the biological)
- Consider switching to another biological drug

RECOMMENDATION ON ADJUSTING BIOLOGICAL THERAPY

Q11 In a patient who is responding to a biological agent, can the dosing interval be increased or the dosage reduced?

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

Decreasing the dosage of biological therapy below the recommended range may be considered in patients on combination therapy, that is, methotrexate + TNF antagonists. (Level of evidence 5)

In clinical practice, dosing intervals have been increased with adalimumab and etanercept while maintaining clinical response. (Level of evidence 5 for adalimumab; Level of evidence 2 for etanercept)

With infliximab monotherapy, dosing intervals should not be increased over the intervals generally recommended. (Level of evidence 2)
The dosage of infliximab may be reduced from 5 mg/kg bodyweight to a minimum of 3 mg/kg bodyweight particularly if combined with methotrexate. (Level of evidence 5)
With ustekinumab, increasing the injection intervals beyond 12 weeks does not appear meaningful, but theoretically, the dose for a responding patient may be reduced from 90 to 45 mg. (Level of evidence 5)

Q12A Can biological therapy be stopped or interrupted in cases of sustained response/clearance? If so, how many months of sustained clearance should we see before stopping therapy?

Stopping biological therapy is not generally recommended. In patients with moderate-to-severe psoriasis, significant therapeutic breaks are difficult to achieve without risk of recurrence or an impact on efficacy following re-initiation of therapy - biological therapy should generally be administered using a continuous uninterrupted treatment regimen.
However, if agreed with the patient, and after achieving a clinical response of clear or almost clear with good QoL for a prolonged period of time, for example, a minimum of 1 year, stopping biological therapy can be considered with careful follow-up.
There is little evidence to suggest the subgroups of patients in which therapy can be interrupted or stopped. However, subgroups in which this might be considered include patients with:
- Patient preference
- Patients with a history of disease-free intervals or previously stable plaque-type psoriasis
- Absence of significant comorbidities
- Absence of PsA
- Low impact of disease on QoL
- No worsening of disease after previous dose reductions and treatment withdrawals

However, because biological therapies are typically considered for patients with more severe disease, and come after failed conventional systemic therapy, patients on biologicals are less likely to fulfill these criteria. Furthermore, fewer treatment options are available for these patients during treatment re-introduction following treatment failure.
Another consideration is that the risk of antibody formation against biological therapies increases with intermittent therapy. This is particularly important for the use of infliximab monotherapy where a higher risk of infusion reactions has been observed with intermittent therapy.

Q12B Can efficacy with biological therapy be regained following therapeutic interruption and re-initiation using the same therapy? How long can the therapeutic interruption last without losing efficacy?

Continuous biological therapy generally results in greater improvements in efficacy over time compared with intermittent therapy.
In clinical trials with primary responding patients, up to 20% fail to regain a PASI 75 response after the first reintroduction of the same biological monotherapy. This decrease in efficacy may be greater with intermittent use of the drug.
In patients receiving biological therapy, there is a high likelihood of disease recurrence within several months of cessation of treatment although some patients may maintain disease control for a prolonged period of time.
Where therapy has been withdrawn and restarted, an induction dosing schedule should be used for re-introduction of the biological agent, with the possible exception of infliximab (because of the increased risk of infusion reactions).
PASI 75, a 75% reduction in Psoriasis Area Severity Index; PsA, psoriatic arthritis; QoL, quality of life; TNF, tumour necrosis factor.

RECOMMENDATIONS ON TRANSITIONING FROM ONE BIOLOGICAL THERAPY TO ANOTHER

Q13 In the case of inadequate response to a biological therapy (etanercept, infliximab, adalimumab and ustekinumab), should we increase the dose or reduce treatment intervals before switching? Which is preferable?

There is no established definition of inadequate clinical response. In published clinical trials with the biological agents a primary non-response was defined as not achieving PASI 50.
Strategies for primary and secondary non-responders, include:
- For adalimumab, an increase of the dosage from 40 mg every other week to 40 mg/week. (Level of evidence 3)

(to be continued)
For etanercept, an increase of the dosage from 50 mg/week to 2 x 50 mg/week. (Level of evidence 4)

For ustekinumab, with primary partial responders, the dose can be increased from 45 to 90 mg with 12 week dosing intervals. If this is unsuccessful, the dose can be further increased to 90 mg at 8 week intervals. (Level of evidence 2)

For infliximab, a reduction of the dosing intervals from every 8 weeks to every 6 weeks with 5 mg/kg can be considered in secondary non-responders, defined as the loss of at least 50% of the initial improvement. (Level of evidence 4). In special cases an increase of the dosage > 5 mg/kg can be considered (Level of evidence 5).

Alternatively, combination strategies with conventional treatments can be considered. (Level of evidence 5)

If at the end of the induction phase there is an inadequate clinical response (primary inadequate response), or in the case of secondary non-response to biological monotherapy, and if the aforementioned strategies have been considered, it is recommended to switch to another drug.

**Q14** When transitioning from one biological therapy to another, for whatever reason, should transitioning to a different biological agent be done:

- sequentially without a washout period?
- sequentially with a washout period? If so, how long should we wait before giving the new biological therapy? What factors should influence this decision (dosing interval, elimination half-life, potential for rebound, other)? What is the appropriate dosing schedule for the second biological? Should we use the maintenance dose or the loading dose?

**General**

In the situation where switching biologicals has been decided due to failure of efficacy, switching is advisable without a washout period at the time of the next scheduled dose, using the standard induction dose, followed by the maintenance dose.

If switching is necessary for reasons of safety, a treatment-free interval may be necessary until the safety parameter has normalized or stabilized.

**Adalimumab to another biological agent**

Administer the first treatment with etanercept after a treatment transitioning from adalimumab at the time point of the next scheduled drug dosage (typically 2 weeks). (Level of evidence 3)

Administer the first treatment with infliximab after a treatment transitioning from adalimumab at the time point of the next scheduled drug dosage (typically 2 weeks). (Level of evidence 5)

Administer the first treatment with ustekinumab after a treatment transitioning from adalimumab at the time point of the next scheduled drug dosage (typically 2 weeks). (Level of evidence 4)

**Etanercept to another biological agent**

Administer the first treatment with adalimumab after a treatment transitioning from etanercept at the time point of the next scheduled drug dosage (typically 1 week). (Level of evidence 3)

Administer the first treatment with infliximab after a treatment transitioning from etanercept at the time point of the next scheduled drug dosage (typically 1 week). (Level of evidence 4)

Administer the first treatment with ustekinumab after a treatment transitioning from etanercept at the time point of the next scheduled drug dosage (typically 1 week). (Level of evidence 2)

**Infliximab to another biological agent**

Initiation of the first treatment with adalimumab after a treatment transitioning from infliximab can be considered as early as 2-4 weeks after the last infliximab dose, particularly in cases of treatment failure. (Level of evidence 5)

Initiation of the first treatment with etanercept after a treatment transitioning from infliximab can be considered early as 2-4 weeks after the last infliximab dose, particularly in cases of treatment failure. (Level of evidence 4)

Initiation of the first treatment with ustekinumab after a treatment transitioning from infliximab can be considered as early as 2-4 weeks after the last infliximab dose, particularly in cases of treatment failure. (Level of evidence 4)

**Ustekinumab to another biological agent**

Initiation of the first treatment with adalimumab, etanercept or infliximab after a treatment transitioning from ustekinumab should be performed at 8-12 weeks but can be considered as early as 2-4 weeks after the initial biological dose in cases of treatment failure. (Level of evidence 5)

**Dosing schedule for the second biological**

The second biological should be used starting with the defined induction dosage and followed by the maintenance dosage.
The general objective of PPI-TT project was to provide a tool to guide dermatologists in the correct management of systemic therapies and in the transitioning from one to another therapy. Being an international project, however, answers provided by the consensus not always reflect the clinical practice in the different countries or regional prescribing and dosing limitations, such as those imposed by the regional health authorities in Italy.

Our project had the objective to adapt the Transitioning Therapies program to the clinical reality of center Italy with the idea to extend the results to other Italian areas.

In this manuscript we describe the results of this project consisting in the evaluation of PPI-TT guidelines use in central Italy through the analysis of real life cases by a group of experts in psoriasis management.

Methods

Nine dermatologists from 8 different hospital and university centers, all of them experts in the treatment of moderate to severe psoriasis were invited to present clinical cases on systemic therapy in psoriasis focusing on the transitioning modalities, before the results of the Psoriasis progressive Initiative Transitioning Therapies program (PPI-TT) were published. The experts presented 18 clinical cases in a “board” meeting. During the same meeting the results of the Transitioning Therapies program were explained and distributed, and the same clinical cases evaluated focusing on common points and differences with the guidelines. The experts were then invited to perform therapy optimization and transitioning on other patients, following the PPI-TT guidelines as close as possible.

At a second meeting, the same experts examined clinical cases presented by each center and agreed to publish this point-of-view paper on the use of PPI-TT guidelines in central Italy focusing on strengths and weak points.

Results

During the first experts meeting, critical points for the application of PPI-TT guidelines in Italy were discussed. Here are the results of this discussion.

Optimization of conventional therapy

Generally, the experts found that the PPI-TT statements on the optimization of conventional treatment (Questions 1 to 7) are very useful and mostly reflect their clinical practice. However, analysis of clinical cases raised these points:

• Some of the conventional systemic drugs toxicity evaluation modalities (Question 4) are not diffused in Italy (e.g. PIIINP and fibroscan monitoring for hepatic fibrosis evaluation during methotrexate treatment).
• Phototherapy (Narrow band UVB and PUVA), that is considered as a conventional systemic treatment is not taken into account in this section of the PPI-TT guidelines. The experts agreed that short UV therapy course can be useful into optimize both conventional systemic drugs and biologics. However, transitioning from NB-UVB or PUVA to cyclosporine should be carefully evaluated considering the risk of developing cutaneous Squamous Cells Carcinomas (SCC) (5, 6).

• The possibility to associate MTX with cyclosporine is not considered in PPI-TT guidelines, not even in the section dealing with transitioning from one to another drug, and there is no sufficient data on psoriasis in the literature. The experts agree that a short (4-8 weeks) combination therapy period can be performed when shifting from cyclosporine to methotrexate to avoid psoriasis rebound (7) However it should be pointed out that this combination may be potentially harmful due to the immunosuppression induced by the combined use of these two drugs.
• The experts agree that reaching DLQI >5 alone is not a sufficient parameter to influence the decision of restarting a systemic treatment. PASI and BSA should be considered as the main criteria for this decision.

Transition from conventional systemic to biologic

The experts think that PPI-TT suggestions on the management of the therapy transition from systemic to biologic treatment (Questions 7 to 12) are very useful and mostly reflect current clinical practice.

However, the analysis of real life clinical cases raised some problems:

• The transitioning from cyclosporine to ustekinumab (Question 8b) could be also performed with a short overlap period (2-6 weeks) to avoid rebounds after cyclosporine discontinuation in partial responders. The PPI-TT guidelines do not consider the possibility to associate systemic steroids to biologics, particularly in those patients who suffer important disease flares after therapy discontinuation. The experts agree that 1-2 weeks of steroid therapy (prednisone 0.5-1 mg/kg/day) could enhance the clinical response to biologics and reduce immunogenicity of biologics (8, 9). The experts think that the optimal modality to associate methotrexate to biologics should be at the beginning of biologic therapy to reduce the immunogenic potential of biologic drugs (10).

Transitioning from one to another biologic

Expert discussion on the optimization of biologic therapy and transition from one biologic to another raised several considerations that should be taken into account to apply PPI-TT guidelines in Italy.

• The most important point is that in Italy it is not allowed to change dosing and frequency of biologic administration. These can be used only following the administration schedule approved for the indications which are present in the SPC. This makes impossible to adapt biologic therapies to patients’ clinical needs, e.g. by reducing administration fre-
Evaluation of PPI-TT guidelines in psoriasis treatment

- In two cases NB-UVB therapy was associated to biologic drug (adalimumab) was performed in two patients under ustekinumab treatment who developed arthralgia (lack of data on ustekinumab in psoriatic arthritis).
- Two patients were shifted from etanercept to adalimumab instead of increasing etanercept to 50 mg twice weekly because this dosage is off-label in Italy after the first 12-week induction period.

Transitioning from one to another biologic
- In two cases the washout period (etanercept to adalimumab) was 4 weeks instead of one week.
- Switch to anti-TNF instead of adding MTX was performed in two patients under ustekinumab treatment (1). However, differences in local laws and practice may influence the use of these guidelines at a regional level. For these reasons we developed a project aimed at evaluating how PPI-TT guidelines can be applied to dermatology centers in Italy. In this manuscript we report the results of an analysis of the PPI-TT guidelines performed by a group of experts from central Italy. Clinical cases of therapy optimization and therapy transitioning observed before the PPI-TT guidelines publication was analyzed. The experts found a very good level of correspondence between their clinical management and PPI-TT guidelines.

Discussion

Treatment optimization and management of therapy transition in moderate to severe psoriasis has a critical impact on the efficacy of long-term treatment in these patients (16). PPI-TT guidelines were implemented to serve as a practical guide for dermatologists dealing with these aspects of therapy management (1). However, differences in local laws and practice may influence the use of these guidelines at a regional level. For these reasons we developed a project aimed at evaluating how PPI-TT guidelines can be applied to dermatology centers in Italy. In this manuscript we report the results of an analysis of the PPI-TT guidelines performed by a group of experts from central Italy. Clinical cases of therapy optimization and therapy transitioning observed before the PPI-TT guidelines publication was analyzed. The experts found a very good level of correspondence between their clinical management and PPI-TT guidelines. However, they also identified some differences and points to be improved. In particular, association therapies with NB-UVB, PUVA and steroids are not deeply evaluated in the PPI-TT guidelines, and suggestions on how a second biologic drug should be chosen after failing a first one are lacking. In a second phase of the project, the experts tried to perform transitioning and treatment optimization according to the PPI-TT guidelines. Presentation of these clinical cases revealed only a few cases where clinical behavior differed from what suggested in PPI-TT guidelines. Most of these cases were related to therapeutic associations between biologics and NB-UVB, steroids and leflunomide. In other patients it was not possible to optimize biologic treatment by increasing or reducing the drug dosage because this is off-label in Italy.

In conclusion the experts agreed on the importance of PPI-TT guidelines as a practical guide for the management of moderate-to-severe psoriasis patients but also suggest that these can be improved to adapt them to local clinical behavior and regulations.

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