Systemic Management of Psoriasis Patients in Indian Scenario: An Expert Consensus

Abstract

Background: Psoriasis is a common inflammatory disease with significant comorbidities, and regardless of its extent, it affects the patients' quality of life. The various modalities of treating psoriasis comprise topical or systemic medications, phototherapy, and an array of biologic agents. There is a lack of Indian recommendations on the management of psoriasis with these different modalities and challenges faced by the clinicians in day-to-day practice. **Aim:** To develop India-specific consensus for systemic management of patients with moderate-to-severe psoriasis. **Method and Results:** A panel of dermatology experts, based on the evidence and international recommendations, coupled with their own clinical experience, developed recommendations for systemic management of patients with moderate-to-severe psoriasis. **Conclusion:** These recommendations are meant to provide guidance in terms of choice of systemic therapies, dosing, effectiveness, and safety. It also addresses clinical challenges that may be experienced during psoriasis management.

Keywords: *Biologics, conventional, Indian consensus, psoriasis, systemic*

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Introduction

Psoriasis is a common inflammatory disease affecting approximately 2–3% of the world population.[1] In India, the prevalence of psoriasis in adults varies from 0.44 to 2.8%. It is twice more common in males compared to females, and most of the patients are in their third or fourth decade at the time of presentation.[2]

The exact understanding of the etiopathogenesis of this remains unclear. The current consensus is that psoriasis is a predominantly T-cell-mediated disorder, genetically determined, and influenced by environmental factors.[3]

Beyond the physical dimensions of the disease, psoriasis has an extensive emotional and psychosocial effect on the patients,[4] which makes appropriate management mandatory.[5] However, with the added complexities of frequent relapses, nonresponse to conventional treatment, and involvement of difficult-to-treat areas such as palms, soles, and nails, it becomes difficult.[6] The wider range of available treatment options results in a paradox of plenty.[7]

The various modalities of treating psoriasis comprise phototherapy, topical or systemic medications, and an array of biologic agents.[3]

Topical therapies (such as corticosteroids, vitamin D analogs) and phototherapy are common first-line treatments. These therapies have limitations due to the lack of long-term efficacy and safety data. Further compliance can be an issue with certain modalities like phototherapy (only 11% of the patients receive the recommended regimen of at least three sessions weekly).[8] In India, access to phototherapy is a major limiting factor due to the financial burden and time constraints for traveling.

Systemic treatments such as methotrexate (MTX), cyclosporine, acitretin, and small molecules, like apremilast, are widely used in routine clinical practice worldwide.[9,10] Despite their availability and cost-effectiveness, only 0.5–22.6% of the patients are prescribed oral systemic therapies.[9] The main reasons reported in this survey for physicians not initiating or maintaining treatment were related to concerns about the long-term safety or tolerability and efficacy of the currently available oral systemic

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therapies. One of the reasons for the under-prescription could be the lack of specific guidelines or recommendations addressing such real-life clinical practice challenges.[11]

Biologics, though useful, are not widely accepted among Indian patients considering their high costs[3] and lack of long-term safety data in the Indian patients for most drugs.[6] Their usage also requires careful screening of eligible patients and continuous monitoring during treatment.[12,13] Counselling a patient, before the initiation of a biologic, is an integral part of management.

The recently published (2019) American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) recommendations highlight the key considerations regarding biologics usage. However, there is a need for country-specific recommendations.[14] Challenges like tuberculosis infection/potential reactivation, therapy cessation, suboptimal dosing due to affordability are specific to India.[8] There is also a lack of Indian recommendations among dermatologists on how and when to transit from one treatment to another in routine clinical practice.[15] Furthermore, there are some challenges with biologics as well. There are some patients who do not respond to certain biologics (primary inefficacy), whereas others who respond initially lose response over time (secondary inefficacy), and the patients who respond but do not reach the desired magnitude of response (partial response).[16]

To address this existing caveat in clinical practice, a group of Indian dermatologists created an India-specific consensus for systemic management of patients with moderate-to-severe psoriasis.

Methodology

An advisory board meeting was organized with a steering committee of the top 10 dermatologists across India. The consensus was obtained on therapeutic approaches and current treatment challenges with respect to the following topics based on the current evidence, guidelines, and their clinical experience [Figure. 1]:

- **Conventional systemic agents**: The systemic agents discussed were the ones most commonly used in India, viz. methotrexate (MTX), cyclosporine (CsA), acitretin, and apremilast.
- **Biologics**: The biologics discussed were the ones currently available in India, viz. etanercept, infliximab, adalimumab (biosimilar), and secukinumab.
- **Clinical challenges with biologics:** The recommendations were focused primarily on the loss of efficacy and transition among the biologics.

Expert consensus recommendation

Therapeutic approaches and current treatment challenges with conventional systemic therapies

Conventional systemic therapy continues to find use in the majority of psoriasis patients in India because of the ease of administration, low cost, and vast experience of their use.[3]

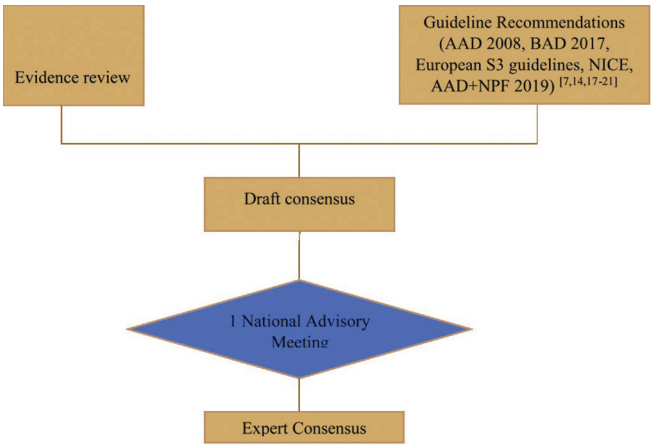

Figure 1: Methodology of the Expert Consensus Recommendation

The final Indian expert consensus recommendations for the appropriate and safe use of conventional drugs are enumerated in Table 1 with some additional points highlighted here.

Expert consensus recommendations for MTX

Since its approval in 1972 by the US Food and Drug Administration (FDA), MTX remains a gold standard for the management of psoriasis.[8,21,31]

Recommendations to monitor for hepatotoxicity were individualized to the current Indian practices. It was highlighted that the onset of efficacy is delayed (may take up to 16 weeks to achieve Δ PASI 75) so in the patients who need early onset of action, another drug should be chosen. There was a difference of opinion regarding the relapse and remission with MTX. Post-drug discontinuation, some doctors have experienced relapse immediately, whereas some have not.

Expert consensus recommendations for CsA

CsA is a calcineurin inhibitor indicated for the short-course treatment of moderate-to-severe psoriasis. It offers a rapid and significant resolution of the disease, sustained remission, and a positive impact on the quality of life (QoL), making it an ideal choice in a crisis.[32]

However, the treatment effect is short-lived and exacerbation occurs soon after the treatment discontinuation. Methotrexate and acitretin are recommended as sequential treatments after the initial flare is controlled by CsA with an overlap of 1 month to avoid relapse due to discontinuation of CsA. As per the international recommendations, combining cyclosporine with phototherapy is contraindicated. However, the Indian experts recommended the concomitant use of psoralen (P) and ultraviolet (UVA) (PUVA) as well as narrow-band ultraviolet B (NBUVB) with cyclosporine in Indian

Table 1: Expert consensus recommendations for conventional agents[7,8,10,15,17-30]

Parameters	Methotrexate	Cyclosporin	Acitretin	Apremilast
Dose and dosing frequency	7.5-25 mg per week, with folic acid 5 mg weekly[#] No routine recommendations for the test dose	3 to 5 mg/kg in three divided doses	Incremental dose and achieve a target dose of 25 mg daily Max. dose - 50 mg	30 mg BID Treatment is initiated with a 10 mg morning dose followed by dose escalation as per patients' tolerance
Duration of therapy	Continuous therapy is recommended in responders with regular monitoring	3-4 months in one treatment cycle Maximum 2 years with the adaptation of rotational therapy*	Maybe daily, alternate days or less, used long-term, often years	Maybe daily, alternate days or less, used long-term, often years
Screening protocol	Full blood count (FBC), Transaminases and albumin; Serum creatinine, blood urea nitrogen (BUN); Urine analysis, Pregnancy test, Hepatitis B antigen (HBs-Ag); Hepatitis C virus (HCV), Human immunodeficiency virus (HIV), Chest X-ray (CXR), Ultrasound whole abdomen	FBC, LFT, Serum (Sr). creatinine, Sr. electrolytes, Sr. Magnesium, Urine analysis, Lipid profile, Sr. uric acid; HBs-Ag, HCV screening, HIV Blood pressure at two different time points, Pregnancy test	FBC In women of childbearing age pregnancy must be excluded by negative pregnancy test within 2 weeks before therapy. Effective contraception must be practiced for at least 4 weeks before and during therapy with acitretin, and for 3 years after treatment with acitretin has ceased; LFT; RFT; Lipid profile; Blood sugar levels	Full blood count, LFT Serum creatinine/eGFR Pregnancy test (urine) Hepatitis B and C[†] Optional HIV
Monitoring protocol	Differential blood count, Sr. creatinine BUN; Liver function test after 1, 2, 4, 12 weeks, then every 3 months In case of 3 persistent elevations of LFTs, fibroscan (if possible) or withdrawal methotrexate	At weeks 2,4 then every 4 weeks for 3 months and then 3 monthly FBC, LFT Sr. electrolytes; Sr. creatinine; Urine analysis Sr. magnesium every 6 months; Lipids - every 3 months; Blood pressure - after 2, 4, 6, 8, 10, and 12 weeks, then every month	Liver enzymes every 2-4 weeks for the first 2 months of therapy and then every 3 months; If abnormal results are obtained, weekly checks should be instituted and acitretin dose adjusted accordingly; Should be discontinued if transaminases are elevated to 3 times their upper normal limit; Fasting serum cholesterol and triglycerides every 2-4 weeks for the first 2 months and then every 3 months; Blood sugar levels in diabetic patients; X-rays are indicated in patients with musculoskeletal abnormalities; RFTs every 4 to 8 weeks	Full blood count ALT, AST Serum creatinine/eGFR Weight
Efficacy	Psoriasis area and severity index (PASI) 75 response by week 16 with optimal dosing Quality of life: Dermatology life quality index (DLQI) <5 in 16 weeks	PASI: The onset of response by 4 weeks PASI 75 response by 8-12 weeks in 50%-70% Quality of life: DLQI <5 in 6-8 weeks	Slow onset of response approximately 3 to 6 months PASI: PASI 75 response in 34% to 52% of patients at 8 to 12 weeks	All or none phenomenon PASI: PASI 75 response in 41% with 30 mg bd dose at 16 weeks

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Table 1: Contd...

Parameters	Methotrexate	Cyclosporin	Acitretin	Apremilast
Concomitant medication Indicated	Topical treatment Occasional phototherapy* Biologics** Cyclosporine Apremilast	Topical treatment Methotrexate Acitretin A short course of steroids in GPP; Phototherapy (PUVA as well as NBUVB)	Topical treatment Phototherapy Etanercept Methotrexate	Acitretin Adalimumab Methotrexate Etanercept Secukinumab
Relapse and Remission	Relapse is seen on an average between 3 and 4 months after discontinuation of methotrexate Managed by either reintroducing methotrexate or giving cyclosporine/biologics	An overall exacerbation pattern on discontinuation. Relapses were seen soon after treatment discontinuation (1-3 months). Although Indian experts recommended a maximum of 2 years of therapy with an adaptation of rotational therapy with cyclosporine, international guidelines recommend a maximum of 1-year therapy with cyclosporine[18]	Relapse is seen on an average between 2 and 6 months after discontinuation of acitretin. Managed by either reintroducing acitretin or switch to other conventional systemic agents or biologics.	Relapse is seen between 5 and 12 weeks after discontinuation of apremilast. Managed by either reintroducing apremilast or switch to other conventional systemic agents or biologics.
Safety Concerns (Adverse Effects)	Very frequent: Nausea, malaise, hair loss Frequent: Elevated transaminases, bone marrow suppression, gastrointestinal ulcers, pneumonitis Occasional: Fever, chills, depression, infections Rare: Nephrotoxicity, liver fibrosis, and cirrhosis Very rare: Interstitial pneumonia, alveolitis	Renal failure High blood pressure Gingival hyperplasia Headache Hypertrichosis	Hyperlipidemia Hepatotoxicity Teratogenic Mucocutaneous lesions (Cheilitis, dry mouth, nose bleed) Skeletal AEs Hair loss Elevated liver enzymes Elevated cholesterol	Diarrhea, increased gastrocolic reflex Depression (In patients with predisposing factors) Weight loss (Withdraw apremilast if weight loss of more than 10% basal weight is seen after the initial period) Upper respiratory tract infection (URTI) Nausea Nasopharyngitis Headache Serious infections (rare)
Absolute Contra-indications	Severe infections Severe liver disease Renal failure Conception (men and women)/breastfeeding Alcohol abuse Bone marrow dysfunction/ hematological changes Immunodeficiency Acute peptic ulcer Significantly reduced lung function Hypersensitivity to methotrexate	Kidney dysfunction Uncontrolled arterial hypertension Uncontrolled infection Current or past malignancy (exception nonmelanoma skin cancer) Hypersensitivity to CsA	Pregnancy (contraception starting 1 month before treatment, and the patient must wait 3 years after cessation to become pregnant) Severe liver failure Severe kidney failure Allergy to drug components	Severe acute infection Hypersensitivity to the active substance (s) or to any of the excipients Pregnancy or breastfeeding Galactose intolerance Lactase deficiency or glucose-galactose Malabsorption

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Table 1: Contd...

Parameters	Methotrexate	Cyclosporin	Acitretin	Apremilast
Relative Contra-indications	Ulcerative colitis History of hepatitis Active desire to have a child for women of childbearing age and men Gastritis Diabetes mellitus Previous malignancies Congestive heart failure	Liver dysfunction Pregnancy and lactation Concomitant use of substances that interact with CsA; Concomitant phototherapy or PUVA pretherapy with a cumulative dose>1,000 J/cm^2; Concomitant use of other immunosuppressants/ retinoids/long-term pretherapy with MTx; Uncontrolled chronic hepatitis B (positive HbsAg)	Mild hepatic impairment (adjust dose) Mild renal impairment (adjust dose) Alcohol consumption (liver toxicity, re-esterification to etretinate) Drug interactions (increases toxicity) Concomitant organ toxic medication (increases toxicity) Active infections (assess the possibility of acitretin toxicity exacerbating infection) Poorly controlled dyslipidemia Metabolic syndrome Uncooperative or noncompliant patient Pediatric or elderly patient (lower tolerance for toxicity?)	Acute and chronic infections Malignancies or lymphoproliferative disorders Severe impairment of renal function (eGFR <30 mL/min). Underweight Depression and suicidal ideation Comedication with cytochrome P450 3A4 (CYP3A4) enzyme inducer

[#]No consensus could be obtained whether to avoid folic acid on the day before and after MTX administration. However, it was agreed that concomitant use of folic acid and MTX does not reduce the efficacy of MTX. *MTX should be avoided on the day of phototherapy **Biologics such as TNFi (As per new AAD-NPF guidelines. IL-17i may be given)[14]

patients, especially in recalcitrant situations where the options are limited. This is because the risk of combining the drugs has not been documented in type IV or V skin. As a matter of precaution, this combination is better avoided.

The expert guidance on the use of CsA in children was similar to the available literature evidence.[33-37]

Acitretin: Guidance on the appropriate use in the management of psoriasis

Acitretin is a second-generation synthetic retinoid that was first synthesized 35 years ago and was first introduced 25 years ago in Spain. It holds a unique role in the management of psoriasis because of its different modes of action.[22]

The efficacy of acitretin is dose-dependent, and the response varies from patient to patient.

Caution is recommended on the concomitant use of methotrexate and acitretin, as sporadic severe hepatotoxic reports have been reported. Similarly, a combination of CsA and acitretin is not recommended as this may lead to CsA toxicity. Teratogenicity is a serious concern with acitretin, and adequate monitoring is required, especially in the higher-risk groups.[7,19,20,22,29,30,38]

Apremilast: Guidance on the appropriate use in the management of psoriasis

Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, approved by the US FDA in 2014, is the first oral drug to receive FDA approval for psoriasis since 1996.[39] Although its exact mechanism of action in psoriasis is unclear, it has shown efficacy in moderate-to-severe plaque psoriasis.[8] The Indian expert consensus was in line with the international literature and guidelines (European S3 Guidelines).[10,15,17] The experts agreed that it works well in mild to moderate psoriasis rather than severe psoriasis. It also improves psoriasis at difficult sites such as palmoplantar, nail, and scalp. They also recommended regular weight monitoring in the patients on apremilast. Depression is mentioned in the summary of product characteristics (SmPC) as a potential side effect, with apremilast, however, the experts were of the opinion that depression is more often reported in patients with predisposing factors. The drug does not seem to be a good choice for arthropathy.

Practical challenges with conventional systemics

Clinicians are always in a dilemma about the duration of therapy, due to concerns of toxicity with conventional systemics. The consensus was that the therapy should not be stopped, considering the chronic nature of the disease. Nonetheless, due to safety concerns, the duration of treatment needs to be individualized. The board agreed that the patients can be continued on treatment with strict monitoring protocols or can be considered for discontinuation or tailoring of therapy if sustained remission has been maintained for 6 months.

The criteria for the re-initiation of therapy as suggested by the experts:

- The Dermatology Life Quality Index (DLQI)>5
- Physician Global Assessment (PGA)>2
- The body surface area (BSA)>10
- Psoriasis Area and Severity Index (PASI)>5.

Therapeutic Approaches and Current Treatment Challenges with Biologics

Over the past few years, newer and even more effective biologic therapies with more targeted mechanisms of action have become available to the patients.[40]

Biologics targeting tumour necrosis factor (TNF-α) were developed first and are often referred to as the first-generation biologics: etanercept, infliximab, and adalimumab. They are indicated in patients with chronic moderate-to-severe psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.[41-43]

Second-generation biologics emerged from 2009 with antibodies targeting the IL-23/Th17-pathway: ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab.

Secukinumab is the only second-generation biologic available in India at present. It is indicated as the first-line systemic in moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[18,44]

Eligibility criteria for biologics in psoriasis

Indian dermatologists concurred that biologics are generally administered as per the international guideline recommendations and literature evidence (AAD 2008, AAD 2019, BAD 2017, European S3,) and protocol. [7,13,14,17,18,21] Additionally, in line with the international recommendations, biologics are the first-line therapy in patients with a limited disease where there is significant impairment of quality of life. In such scenarios, secukinumab is the preferred biologic, considering the safety and its approval as the first-line systemic indication in patients with moderate-to-severe psoriasis [Figure 2].[38]

Guidance on the appropriate use of biologics

The recommendations on biologics were limited to etanercept, adalimumab, infliximab, and secukinumab on the basis of their availability in the Indian market and aligned to the international recommendations [Table 2]. The screening and monitoring on the overall biologics were similar across both classes due to TB concerns in India, although the risk is less with the interleukin-17 inhibitor.

Considering that India is a self-pay market, India-specific changes/adaptations have been recommended with regards to the dose and duration of therapy.[13] Conversely, the final consensus stated that for optimal benefits, dosing should be as per the drug label.

The proposed ranking of biologics (available in India) in terms of efficacy was as follows:

1. Secukinumab
2. Adalimumab/Infliximab
3. Etanercept.

Clinical challenges with biologics

There is limited evidence on the practical challenges faced with biologics. There is inconsistent data on the criteria to determine the primary failure and secondary failure and the management of psoriasis in such scenarios. The experts agreed that the secondary failure should be when there is

- Loss of PASI 50 response
- DLQI score >5
- Absolute PASI >5
- BSA >10.

In case of secondary failure, one should follow the algorithm as shown in Figure 3 to rule out the other causes.[15,20,45,46] The expert recommendations on the above-mentioned issues were based on their clinical experience and literature review [Table 3].

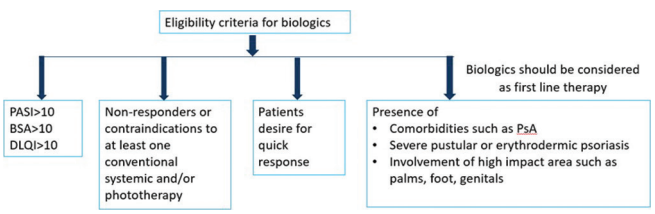

Figure 2: Expert consensus on eligibility criteria for biologics

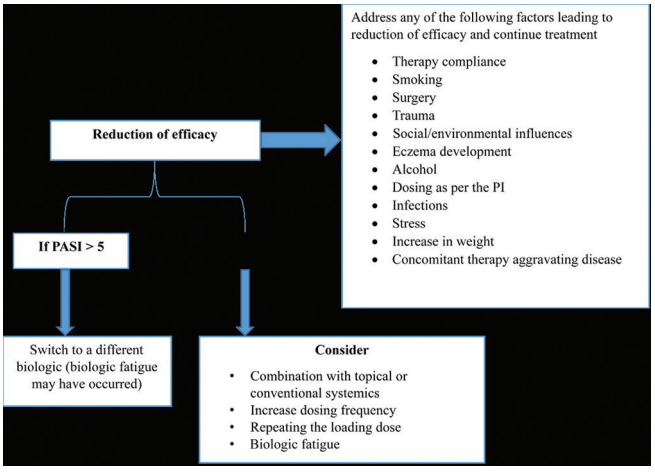

Figure 3: Expert Consensus Recommendations on Addressing Reduction of Efficacy

Table 2: Expert consensus recommendations for biologics

Parameters	Etanercept	Infliximab	Adalimumab	Secukinumab
Dose and dosing frequency	50 mg per week subcutaneously (s.c) for 12 weeks, followed by 25 mg once or twice a week. Minimum 12 weeks, till clearance of skin and/or affordability.	5 mg/kg at day 0, week 2, week 6, followed by every 8-12 weeks dosing. 6-8 weeks for clearance and can be maintained depending upon affordability.	80 mg: day 0, 40 mg at week 1, followed by 40 mg every 2 weeks s.c 6-8 weeks for clearance and can be maintained depending upon affordability.	300 mg sc at week 0, 1, 2,3, and 4 weeks followed by monthly dosing of 300 mg (150 mg after 6 months in case of economic constraints). 4-6 weeks for clearance and can be maintained depending upon affordability.
Efficacy	PASI 50 response by 8-12 weeks. PASI 90/100 response is not achieved Maximum efficacy reached is PASI 75 response.	PASI 50 response by 2 weeks. PASI 90/100 response 6 weeks but limited experience.	PASI 50 response by week 4. PASI 90/100 response by 12 weeks.	PASI 50 response by 2-4 weeks. PASI 90-100 response by 4-8 weeks.
Concomitant Medications indicated	Methotrexate/acitretin	Methotrexate low dose	Methotrexate low dose	Generally, not required
Remission	12 weeks	6 to 8 weeks	6 to 8 weeks	16-24 weeks
Maintained				
Safety	TB and other infections risk are greater with TNF inhibitors Infusion reactions are very common with infliximab			Secukinumab has a better safety profile compared to other biologics. *Candidiasis* is commonly seen with secukinumab in the initial stages of therapy

Table 3: Expert consensus recommendations for switching biologics

In case of efficacy failure - No washout period is needed, and new biologic can be initiated at the next dose.
Primary failure
Primary failure to TNF inhibitor, switch the drug class (switch to secukinumab).
In case of primary failure to secukinumab, switch to TNF inhibitors.
Secondary Failure
Switching can be done within the classes.
In case of safety concerns - Wait for four half-lives or till concerned safety parameter has normalized/stabilized

Conclusion

The management of psoriasis has evolved in the last decade with a newer class of biologics marking a watershed in the management of psoriasis. The PASI 90 response is now considered as treatment success instead of PASI 75. Due to the differences in the global health care markets as compared to India, the application of global guidelines to India has been challenging. Thus, there has been a requirement for India-specific recommendations based on the integration of evidence and clinical experience.

It was, therefore, the aim of this expert panel to address issues such as choice of therapy, dosing, effectiveness, and safety. for systemics, biologics. It also addressed the clinical challenges faced with these in the ongoing management of psoriasis with these drugs.

The experts contemplated on each of these points by reviewing the published scientific evidence, guideline recommendations, and combined it with their real-world clinical experience for a structured and individualized approach to the treatment.

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Conflicts of interest

There are no conflicts of interest.

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