Role of Cyclosporine (CsA) in Immuno-dermatological Conditions

Abstract
Cyclosporine (CsA) is a calcineurin inhibitor that acts selectively on T cells. It has been used in dermatology since 1997 for its US Food and Drug Administration indication of psoriasis and off-label for various other inflammatory skin conditions, including atopic dermatitis, alopecia areata, urticaria, lichen planus and many others in pediatric, adults as well as in pregnant women. However, clinicians’ preferences for management differ, which may have a bearing on the treatment selection. Hence, the purpose of this review is to outline the role of CsA in various skin conditions through consensus statement from six national experts in the field of dermatology.

Keywords: Alopecia areata, Cyclosporine (CsA), lichen planus, psoriasis, vitiligo

Introduction
Cyclosporine (CsA), an immunsuppressive and anti-inflammatory agent that is derived from the fungus Tolypocladium inflatum, is a neutral, lipophilic, cyclic undecapeptide.[1] It is available as gelatin capsules, an oral solution, an intravenous formulation.[2] CsA acts by interfering with the early events involved in T-cell activation, specifically by preventing transcription of the interleukin (IL) 2 gene after antigen exposure. In the absence of IL 2, the primary T-lymphocyte growth factor, antigen-stimulated T cells do not undergo mitogenesis. Therefore, treatment with CsA prevents the generation of an antigen-specific population of T cells capable of coordinating an immune response.[3] CsA has been in clinical use for the past more than three decades.[2] In more recent years, it has been recognized as beneficial in the treatment of various dermatological conditions including psoriasis, atopic dermatitis, and others with inflammatory and immunological components.

Psoriasis is a genetically determined chronic immune-mediated inflammatory disease mediated by T-helper 1 (Th1)/Th17 T cells and dendritic cells with subsequent release of inflammatory cytokines including IL 17, IL-23, and tumor necrosis factor-α.[4] These soluble mediators are responsible for keratinocyte hyper proliferation, increased vascularity, and the inflammatory infiltrate that is present in psoriatic plaques.[5] These cytokines have also been implicated in a number of psoriasis comorbidities, including metabolic syndrome, cardiovascular diseases, and arthritis.[6] Psoriasis predominantly affects the skin, nails, and joints and typically presents with well-demarcated erythematous plaques with silvery scales, commonly involving the scalp, elbows, knees, and presacral region. Any area of skin may be involved, including the palms and soles, as well as the genital regions in up to 60% of patients.[7] The severity of psoriasis is generally defined by the total body surface area (BSA) involved, and BSAs of <3%, 3% to 10%, and >10% are considered as mild, moderate, and severe disease, respectively.[8] The Psoriasis Area and Severity Index (PASI) is a more specific means of quantifying the extent and severity of psoriasis ultimately producing a score from 0 (no disease) to 72 (maximal disease severity).[9]

Therapeutic management of psoriasis and the role of cyclosporine
Therapeutic management of psoriasis usually requires a patient-tailored approach in which combination and sequential therapies are often considered over time in order to augment response, to optimize

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the safety profile, and/or to meet specific clinical needs. There is a wide armamentarium of therapeutic tools available for the treatment of psoriasis which includes topical medications, and systemic non-biological and biological drugs. It is estimated that moderate-to-severe psoriasis accounts for about 25% of psoriasis patients, most of whom are likely to require systemic drugs or phototherapy.\[10\] When psoriasis requires systemic therapy, CsA is one of the effective and rapidly acting drugs. Since the time of the first observations documenting the clinical activity of CsA in psoriasis, more than 30 years ago, a considerable amount of clinical data has been accumulated in favor of the efficacy and safety of the drug in many immune-mediated skin disorders and especially psoriasis and atopic dermatitis.\[11\] In light of the current knowledge and after several years of experience gathered in clinical practice, CsA is often used in moderate-to-severe forms of psoriasis by several dermatologists.\[12\] Local preferences for management differ, which may have a bearing on the treatment selection. Hence, there is a clear need for a national consensus statement that outlines the role of CsA in various skin conditions such as psoriasis, atopic dermatitis, vitiligo, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), urticaria, lichen planus, and alopecia areata.

**Methods**

The Delphi method was selected for developing this consensus statement, as it is particularly well suited for addressing healthcare-related issues where the outcome represents the collective judgment of the panel of experts on topics under discussion. The Delphi method includes three basic characteristics: (1) repeated individual questioning of the experts; (2) the avoidance of direct confrontation among the experts (e.g., anonymity); and (3) interspersed controlled opinion and feedback. Available data on a given topic are reviewed extensively, presented, and discussed among the panelists. More importantly, by employing only anonymous voting by the panelists, the Delphi method settles controversy by eliminating the effects of either reputation or “personality.” This Delphi exercise began with the identification of six experts in the field of dermatology based on their vast clinical experience, their publication record, and participation at international and national meetings. The individual panelist was asked to provide their responses in the first round on a preliminary set of 68 questions in the survey. For round one, the panel set a target goal of achieving a minimum of 80% concordance/agreement rate for responses on individual questions as prerequisite criteria for the question to be retained for the second round of in-depth panel discussions. For round two, an online live meeting between panelists was set to discuss the responses to questions that did not meet the 80% concordance rate. During the meeting, evidence-based data for each question was presented to the panelist. This was followed by an in-depth discussion between panelists regarding their views about the presented data and their clinical experience in managing patients with various immuno-dermatological conditions. Using an anonymous response system, the panelists were asked to mark their responses for each question, and real-time tabulation along with viewing of their responses occurred.

Preliminary recommendations were made using the best available evidence extracted from published literature. The strengths of recommendations were graded as follows: grade A: category 1 evidence; grade B: category 2 evidence or extrapolation from category 1 evidence; grade C: category 3 evidence or extrapolation from category 1 or category 2 evidence; grade D: category 4 evidence or extrapolation from category 2 or category 3 evidence. Where definitive scientific evidence was lacking, “expert opinion” and consensus (e.g., the community standard) were used for suggested recommendations for key practical issues.

**Results**

**Use of cyclosporine in moderate to severe psoriasis**

**Optimum dose and duration of CsA treatment in moderate to severe psoriasis**

**Clinical evidence**

In clinical practice, dose-finding studies and consensus guidelines have identified that patients with severe disease who require rapid improvement can be started at a dose of up to 5 mg/kg/d and subsequently tapered.\[13–15\] However, exceeding the dose of 5 mg/kg/d does not yield any additional benefit in terms of efficacy in psoriasis, whereas it notably increases the risk of side effects.\[16\] In a large systematic review, cyclosporine in doses of 2.5 and 5 mg/kg/d produced PASI 75 rates between 28% to 85% and 50% to 97% respectively.\[17\] Short-term treatment (4–8 weeks) with CsA may be useful to obtain rapid control of particularly severe forms of disease such as generalized pustular psoriasis and psoriatic erythroderma attributed to its rapid onset of action.\[18\] In moderate-to-severe plaque psoriasis, CsA is generally used for induction of remission with intermittent short courses generally lasting up to 24 weeks, usually followed by maintenance therapy with another systemic and/or topical therapy.\[12\]

**Panel recommendations**

The panel was divided on the optimum dose and duration of CsA for moderate to severe psoriasis treatment. The panel felt that the choice of the initial dose is not only dependent on the personal experience of the dermatologist, but also on the severity of the condition, taking into account the strong influence of the dose on both the clinical response and adverse effects. The majority of the panelists were of the opinion to start with daily doses of
3–3.5 mg/kg/d and gradually step up or step down the dose based upon the response to treatment. Two panelists preferred to start at full dosages until the achievement of remission and then gradually taper the dose, adjusting it only in case of adverse reactions (step-down regimen). Five of the six panelists agreed that a dose of 3–5 mg/kg/d for the required duration of time could achieve a PASI >90 in moderate to severe psoriasis patients. The panel were of the opinion that duration of CsA treatment in clinical practice range from <3 weeks to 12–16 weeks based on the severity of the condition, prescribed dose, speed of desired clinical response, tolerability, and affordability.

The impact of discontinuation of CsA on psoriasis treatment outcomes

Clinical evidence

Once clinical remission is obtained, it should be decided whether the treatment has to be suddenly stopped or gradually tapered up to a maintenance minimum effective dose. Gradual tapering avoids early relapses, although the abrupt suspension of CsA was not reported to be associated with the rebound phenomenon.19 In a recent study, after drug withdrawal in PASI 75 responders, the average length of time before restarting systemic therapy was found to be 182 days, ranging from 120.1 days for patients with PASI scores of 13 or more to 287.5 days for patients with PASI scores of <13.20 The PISCES study also compared the effects of abrupt against gradual discontinuation of CsA. A total of 45% and 31% of subjects had not relapsed four and six months after stopping treatment, respectively. The median time to relapse was 109 days in the patients who abruptly stopped CsA and 113 days for patients who were tapered off. These results corroborated general clinical observation showing better preservation of remission by drug tapering rather than abrupt discontinuation.19

Panel recommendations

Five of the six panelists agreed that based on the severity of psoriasis, if the condition relapsed, restarting the treatment with the same dose to bring the condition under control. Lastly, for patients who are non-adherent to treatment, the panel recommended counseling sessions to address concerns and fears.

Ideal class of drug to switch over after achieving adequate response with CsA and giving methotrexate (MTX) and CsA concomitantly

Clinical evidence

Sequential or rotational therapies is a viable option that can improve outcomes for many patients. In the past, the rationale for switching treatments was often related to safety concerns and involved rotating between conventional systemic agents with different target-organ toxicities to reduce cumulative exposure. Long-term methotrexate therapy (i.e., >10 years) with appropriate laboratory monitoring under an expert can be effective for many patients with moderate-to-severe psoriasis; however, studies have shown that only an estimated 50–60% of patients who were given oral methotrexate at a doses of 15–20 mg/week achieved marked improvement, and approximately 30% adverse events.21 An observational, longitudinal analysis found that biologic-naïve psoriasis patients switched from a conventional systemic agent to a biologic agent experienced significant improvements in PASI and in health-related quality of life (QoL).22

Mohanan et al.23 reported that methotrexate and CsA combination therapy can be used with adequate monitoring in the treatment of moderate-severe psoriasis particularly in the treatment of refractory cases. However, more research is required on the long-term safety and remission periods on this combination. A study by Aydin et al.,24 observed that combination of CsA with methotrexate induces rapid control of disease activity in the acute and severe psoriasis. The combination works faster than either agent alone. It was also reported that patients with severe psoriasis had clinically significant improvement after the initiation of combination therapy.

Panel recommendations

All the members of the panel agreed that systemic agents are the ideal choice of drug to switch over after adequate response with CsA. The reason stated was relapses and rebounds were frequently noted if CsA is stopped abruptly. None of the panelists were in agreement with giving biologics as first option in poor resource settings. They reported that with topical agents alone, the risk of rebound is higher. However, they preferred methotrexate as their first choice and apremilast as their second choice. They also considered acitretin and emollients along with weekend potent topical steroids for recalcitrant lesions for a few weeks. Panelists mentioned that they would also consider new generation biologics when affordable in settings of severe disease. According to the panel, moisturizers are also effective, and sometimes for localized lesions, a combination of calcipotriol and corticosteroids or only short-term topical corticosteroids may be used along with moisturizers. Five of the six physicians in the panel agreed that methotrexate and CsA can be given concomitantly with appropriate clinical and laboratory monitoring.

Desired clinical benefit with a lower dose of CsA and CsA as rescue therapy in patients with erythrodermic psoriasis and pustular psoriasis

Clinical evidence

In a study by Yoichi Shintani et al.,25 (2011) where patients (N = 40) were given either 100 mg CsA emulsion once daily (group A) or 50 mg twice daily (group B), the number of patients with PASI-50 at week 6 was significantly higher in group A than in group B. At 12 weeks, PASI-50
was achieved by 82% in group A and 84% in group B. PASI-75 and -90 were achieved in both groups, but there was no significant statistical difference. In a study by Giannotti et al.,[26] 33 patients with severe erythrodermic psoriasis were given with 5 mg/kg/day, maximum initial dose of CsA. After six months, it was seen that the rapid and progressive improvement in the degree of skin involvement, pruritus, and the severity of the characteristics of the psoriatic lesions (erythema and desquamation) proved to be significant versus baseline with CsA treatment in patients.

The Medical Board of the National Psoriasis Foundation has recommended CsA as the first-line therapy for pustular psoriasis and it has shown efficacy in these patients at doses of 2.5 to 5 mg/kg/d.[27] A study by Umezawa et al.[28] pointed out that nearly 60% of efficacy was obtained with the treatment of CsA at a dose of 3.0–5.0 mg/kg/d in two divided daily doses.

Panel recommendations

The panel was divided in their responses when they were asked if a lower dose of CsA will give the desired clinical benefit/result. The difference in opinion was attributed to the fact that a low dose of CsA as monotherapy may not work in psoriasis if the disease is severe and unstable psoriasis. Although clinical benefit with lower doses was observed on some occasions by one physician in the panel. All the physicians were in 100% concordance that CsA can be used as rescue therapy in patients with erythrodermic psoriasis and pustular psoriasis.

Role of weekend CsA in chronic plaque psoriasis in terms of efficacy and safety

Clinical evidence

A 32-week prospective observational study with 21 patients of plaque psoriasis (PASI>12), treated with weekend (CsA at a dose of 5 mg/kg/d for 2 consecutive days/week) and continuous therapy (2 to 3 mg/kg/d ) for 20 weeks achieved PASI 75 in 80% and 75% respectively. The effectiveness of weekend CsA therapy might be explained by its rapid effect on inflammatory and endothelial cells, as evidenced by decreased skin T lymphocytes within 3 days.[29]

Panel recommendations

The whole panel had a positive opinion on the role of weekend CsA and weekly MTX together in chronic plaque psoriasis in terms of efficacy and safety and everyone agreed with the statement.

Role of CsA in Atopic Dermatitis (AD)

Optimum dose, duration, and age group of children for the treatment of AD by CsA

Clinical evidence

Optimum dose

As per the evidence studies, the starting dose of 2.5 mg/kg/d of CsA yielded positive results in children with AD. In non-responding patients, the dose can be increased in a stepwise manner to a maximum level of 5 mg/kg/d. The two main different CsA dosage regimens have proven equally efficacious, low dose (2–3 mg/kg/d) and high dose (5 mg/kg/d), the latter seeming to achieve a faster response.[10]

Optimum duration

A median duration of treatment of AD with CsA is 4.6 months. It is reported that CsA is effective in controlling severe AD in children over a one-year period and is well tolerated.[31]

Optimum age

In one of the prospective studies, children aged 2–16 years with severe AD refractory to topical steroid therapy, were randomly assigned to receive CsA intermittent short course or continuous long-term therapy. Both the groups showed significantly better results in clinical scores and QoL assessments. However, in the continuous arm, improvement was seen beyond eight weeks but fluctuated in the short course arm, reflecting the dose-tapering regimen.[32]

Panel recommendations

The panel was in 100% concordance with the recommended dose of 2.5–5 mg/kg/d of CsA for pediatric AD. The majority (>80%) of the panel were of the opinion that 8–12 weeks is the optimum duration of CsA in AD. Panelists felt that the duration of treatment depends on the age and severity of AD but a longer duration was preferred as no better alternative second-line treatment is available for AD. Only one panelist suggested two to four weeks and another suggested four to eight weeks of the duration of treatment of CsA; 67% of the panelists agreed that CsA can be given to patients of above two years of age whereas 33% were of opinion that it can also be given to below two years of patients. The preferred age is three years and above because of the vaccination schedule, but if necessary, then it should be given along with giving due consideration to the vaccination schedule. One doctor suggested that CsA is very safe in children, almost 10 times safer as compared to adults as renal medulla and number of active nephrons are much bigger up to 18 years of age, and after 20 years, there is a senility of the nephrons.

Use of CsA as weekend therapy in extensive AD (well-controlled dermatitis) but intractable pruritus

Clinical evidence

A 20-week study was conducted in patients with severe AD with a Scoring Atopic Dermatitis (SCORAD) score of >40 with 5 mg/kg/d dose of CsA on saturday and sunday,
allowing a longer duration of CsA treatment and decreasing the risk of relapse.\textsuperscript{[33]} Thus, this case series suggested that a CsA weekend regimen could be a new therapeutic option in patients with severe AD who have failed topical treatments and have the need to stop continuous treatment with CsA.\textsuperscript{[33]}

Panel recommendation

The panel agreed that in extensive AD but intractable pruritus, oral CsA can be used as a weekend therapy. However, one panelist suggested low dose should be administered daily/or alternative days or twice per week instead of the weekend.

The role and most common adverse effects of CsA in pediatric AD management

Clinical evidence

CsA is an immunosuppressant drug that acts directly on cells of the immune system by inhibiting T-cell function. It binds to cyclophilin and forms a complex that inhibits the activity of the enzyme calcineurin phosphatase which further leads to the transcription of several cytokine genes, particularly IL-2. Hence, CsA has been found to be safely used, effective, and well-tolerated in children with severe AD. However, studies to assess the long-term effectiveness and safety of CsA in AD are lacking.\textsuperscript{[34]}

The most common side effects encountered with CsA use are nausea, abdominal pain, nephrotoxicity, and hypertension. Even with close monitoring, patients will often experience adverse effects on renal function, with reversible nephrotoxicity developing in 19% to 24% during short-term treatment. If treatment is continued for more than two years, the risk of fibrosis and irreversible kidney damage increases substantially. In one study, 71% of patients treated with cyclosporine for an average of 4.5 years were found to have a serum creatinine level of 30% above baseline. The serum creatinine levels in most of these patients did not return to normal after the cyclosporine dose was decreased. Similar results were seen in the larger systematic reviews where patients were treated for longer than two years. Hypertension is most likely to develop in elderly patients taking cyclosporine but is typically reversible after the medication is discontinued.\textsuperscript{[35]}

Panel recommendation

All panelists were in agreement that “reduction in T-lymphocyte cytokine production, inhibition of T cells, improves clinical measures of disease, and decreases symptom scores” was the role of CsA in AD. In terms of the most common adverse events, the panel was divided in their responses. The majority of them were of the opinion that nausea, abdominal pain, and hypertrichosis are the most common adverse effects. However, some panelists chose nephrotoxicity and gum hypertrophy as the most common adverse events in pediatric AD.

Use of CsA in children

Clinical evidence

Findings from a clinical trial by Harper et al., (2017)\textsuperscript{[32]} concluded that not only CsA is effective in controlling severe AD in children over a one-year period but is also well tolerated. Furthermore, QoL also had improved significantly by week 12 in both short course and continuous arms and the improvement remained significant at month 12 for the continuous arm only. Another retrospective study by Hernández-Martín A et al., (2017)\textsuperscript{[31]} also stated that CsA therapy can provide sustained remission in some patients, thus confirming its efficacy and tolerance with mandatory strict monitoring.

Panel recommendation

All panelists agreed to use CsA in children. However, their responses in terms of its use were divided. Some of the panel members preferred to use CsA for long-term therapy while some preferred it for short-term therapy.

Ways to monitor the use of CsA in children

Clinical evidence

The monitoring guidelines suggested that before CsA treatment is initiated, basic clinical and laboratory screening tests should be performed. Some investigators have advocated determining the pretreatment glomerular filtration rate in addition to the serum levels of creatinine because the former is better for detecting latent renal disease.\textsuperscript{[36,37]}

Panel recommendations

The panel was divided in terms of how to monitor the use of CsA in children. About 45% of the panelists were in concordance to use the visual analog scale for symptoms to monitor the use of CsA. Some of the panelists felt that sign scores are a good option for monitoring CsA use. Other response options like the QoL questionnaires, physician’s global assessment (PGA), and creatinine level were preferred by only one member of the panel.

Role of CsA in Urticaria

Use of CsA in urticaria and commonly prescribed dose in these patients

Clinical evidence

In a study by Tsutomu Ohtsuka, the response of oral cyclosporine therapy in 15 patients with chronic idiopathic urticaria (CIU) was studied and found that all of the patients responded to it. Oral cyclosporine therapy was judged as effective when all the edematous erythema was completely resolved and no pruritus was found. So, it was concluded that CsA can be used in urticaria but only when antihistamines fail and prolonged steroid treatment is required.\textsuperscript{[38]} The efficacy of CsA is dose-dependent, and
moderate doses of CsA appear to be more effective than lower doses. Galindo Bonilla et al.,[39] suggested that the most effective CsA regimen in the treatment of CSU is 3 mg/kg/d for 6 weeks, followed by 2 mg/kg/d for 3 weeks and 1 mg/kg/d for 1 week and subsequent discontinuation. On the other hand, the results of a meta-analysis by Kulthanan et al.,[40] showed that low-dose CsA (from 2 to <4 mg/kg/d) for 12 weeks significantly improves clinical severity in 70% of patients with CSU.

Panel recommendations
The entire panel responded that they prescribe CsA to their urticarial patients. Concordance (83%) was achieved in terms of CsA prescribing dose of 2.5–5 mg/kg/d.

Average duration of treatment with CsA and its indication for the use in urticaria

Clinical evidence
A study by Godse et al.,[41] reported that patients with severe disease ranging from six weeks to five years, unresponsive to antihistamines and showing a positive autologous serum skin test (ASST) are advised to take 3 mg/kg per day of CsA for 12 weeks along with cetirizine (10 mg). The average urticaria activity score was 5.4 and within two weeks of starting cyclosporine, the score came down to 1.6. Low-dose CsA is effective in treating CIU patients and can be given safely for three months. Kessel et al., (2010)[42] discussed that when patients do not respond to antihistamine therapy, even on off-label doses, CsA becomes a good therapeutic option in such instances for severe patients.

Panel recommendations
Concordance was achieved for the option of 8–12 weeks about the recommended treatment duration with CsA for Urticaria. The entire panel agreed that CsA should be used when antihistamines fail.

Role of CsA in Lichen Planus (LP)

Use, the recommended dose, and mean duration of treatment of CsA for treating LP

Clinical evidence
In several studies, topical CsA has been studied in the treatment of oral LP and has shown positive results.[43–48] Topical CsA therapy may be more effective in oral LP than in cutaneous LP because of the relatively higher absorption through mucous membranes and the same was demonstrated by several studies.[2] One of the clinical studies described two patients with severe cutaneous lichen planus, treated with orally administered CsA, 6 mg/kg per day, had a complete clearing and remained free of disease at 10 months.[2] The mean duration of CsA treatment in LP is 6–30 months.[2] In one case report, within two weeks of therapy, patients noted a marked reduction in pruritus, and new lesions ceased to appear. By three to four weeks, the lesions began to flatten. By eight weeks, both patients had complete remission.[47]

Panel recommendations
All panelists were in agreement that CsA can be used for the treatment of the LP. With respect to the dosage of CsA, 83% of the panelists recommended 2.5–5.0 mg/kg/d as the optimum dose in LP. Alternatively, the panel felt that a dose of 3–3.5 mg/kg/d should also be considered as an option. Panel responses were divided for the mean duration of CsA in treating LP. Variation in the responses was acknowledged as the panel felt that dosage and duration depends on the severity of the disease. Some panels preferred 8–12 weeks as the optimum duration while others were of the opinion that 12–16 weeks were the ideal mean duration of CsA in treating LP.

Role of CsA in oral LP

Clinical evidence
Studies have reported that CsA oral solution is the preference and its topical administration to the mucous membrane is effective in treating oral LP. This evidence is supported by a double-blind study, where eight patients had substantial improvement with topically administered cyclosporine in comparison with eight patients who received only its vehicle.[43] In another double-blind study, patients with oral LP resistant to conventional treatment received either cyclosporine or triamcinolone acetonide 0.1% in an aqueous solution. Symptomatic improvement was noted in 90% of the cyclosporine-treated group versus 60% of the latter group.[48] Furthermore, “Swish and Spit” 5 mL of medication three times daily is preferred over “Swallow after Swish”.[2]

Panel recommendations
More than half (60%) of the panel felt that CsA oral solution cannot be used in oral LP. As per their clinical experience, they highlighted that it is not practical in India because of its cost issues. The dose of 150 mg/d would have to be administered to the patients which would not make it cost-effective. One panelist felt that CsA oral solution is not efficacious while another pointed out its availability issues. Therefore, a consensus was arrived on not preferring CsA oral solution for oral LP. However, those who voted in favor of CsA recommended spit after swish over swallow after swish for the oral suspension.

Role of CsA in alopecia areata

Use of CsA in treating alopecia areata and its types

Panel recommendations
The panel was divided with only 60% of them saying they would use CsA in the treatment of alopecia areata. The
difference of opinion was because of the higher recurrence rate in some patients and undesirable side effects like hypertrichosis due to the administration of higher doses. One physician stated that CsA has been stopped for alopecia areata in his practice. When the panel was asked for which type of alopecia areata does CsA offers better treatment outcomes, they had various opinions to deliver but concluded by saying that CsA is not recommended in androgenic alopecia but works well for alopecia areata and alopecia totalis.

**Recommended dose and mean duration of CsA used in treating alopecia areata**

**Clinical evidence**

Findings from a systematic review conducted by Husein-EIAhmed et al.,[49] suggested the following protocol to use CsA: In monotherapy, the optimal target dose of CsA is 5 mg/kg/d, whereas an association with corticosteroids, it is 3 mg/kg/d. If a patient’s tolerance or side effects preclude this optimal dose, then the highest tolerable dose has to be taken. The target dose should be maintained for not less than 6 months and preferentially for 12 months. Açkgöz et al., (2013)[50] reported that all patients who were receiving oral CsA for more than six months showed significant hair growth after the treatment. In the systematic search of Husein-EIAhmed et al.,[49] therapy durations ranged from 2 to 13 months. Interestingly, they observed that the hair regrowth is almost the same regardless of whether CsA is taken for six or more months or not. Studies by Lai et al and Gupta et al., suggested at least two to three months of CsA therapy to note any substantial hair regrowth or for inducing remission of alopecia areata.[51,52]

**Panel recommendations**

According to the panel, the recommended dose of CsA for alopecia areata was 2.5–5.0 mg/kg/d, which was agreed upon by almost 83% of the physicians in the panel. When asked about the optimum duration of CsA treatment, the panel was divided between 8–12 weeks, 12–16 weeks, and >16 weeks. The difference of opinions was due to variations in recurrence rates in alopecia areata patients.

**CsA in combination with oral prednisolone for the treatment of alopecia areata**

**Clinical evidence**

CsA can be used in combination with oral prednisolone for the treatment of alopecia areata. Kim et al., (2008)[53] conducted a study with a total of 46 patients with severe alopecia areata that were treated with a combination of CsA (200 mg twice daily, two 100 mg tablets) and methylprednisolone (24 mg twice daily for men, 20 mg twice daily for women, and 12 mg twice daily for children). He reported that 38/43 (88.4%) of patients showed significant hair regrowth and 5/43 (11.6%) were treatment failures. Similarly, Teshima et al.[54] treated six cases of refractory alopecia areata with oral CsA (2.5 mg/kg per day) and prednisolone (5 mg/d) which resulted in marked improvements in all patients, and there was no recurrence for more than six months after the cessation of treatment.

**Role of CsA in SJS and TEN**

**Role, dose, and duration**

**Clinical evidence**

Based on findings from studies, CsA can be used in the treatment of SJS and TEN. Improvements were seen in time to cessation of disease progression or new lesion formation (average time – 2.2 days), re-epithelialization (average time – 13 days), and duration of hospital stay (average time of stay – 11.7 days).[55] Low-dose CsA of 3 to 4 mg/kg/d is sufficient for the adequate treatment of SJS/TEN as reported by one study.[56] Another study recommended the dosage range of CsA to be 3 to 10 mg/kg/d, with the time of arrest of progression from 5 to 48 hours and a time of re-epithelialization of 7 to 28 days.[56] Furthermore, findings by Reese et al.,[57] reported that patients experienced a noticeable symptomatic improvement within 24 hours following initiation of CsA therapy. To conclude, symptom improvement starts within 24 hours following initiation of CsA therapy, and the average response time after CsA administration was 2.2 days (range 1.5–3 days).[55]

**Panel recommendations**

There was 100% concordance that CsA can be used in the treatment of SJS and TEN. Concerning the duration of CsA treatment, most panelists suggested 4–6 days, while some felt 2–4 days were required for CsA to act in SJS-TEN conditions. Equal responses were received from the panel for the recommended adequate dose in patients with SJS-TEN. Half of the panel felt 2.5–5.0 mg/kg/d is the optimum dose, while the other half felt that >5 mg/kg/d is the adequate dose in treating the condition.

**Measuring response to treatment with CsA in SJS/TEN**

**Clinical evidence**

The most widely used scales to measure the response of CsA in SJS/TEN are Score of Toxic Epidermal Necrolysis (SCORTEN) and Total Body Surface Area (TBSA). In one of the studies analyzing the accuracy of SCORTEN and ABCD-10 (age, bicarbonate, cancer, dialysis, 10% body surface area) in predicting mortality
in SJS-TENS, the predicted mortality for SCORTEN was 3.48 and 2.33 for ABCD-10. This study concluded that SCORTEN behaved as a reliable predictor of mortality in patients with TEN, outperforming the newer ABCD-10.[60]

Panel recommendations

The panel recommended the use of the SCORTEN scale to measure the response of CsA in SJS/TEN.

**Role of CsA in vitiligo**

**Use of CsA for vitiligo management**

Clinical evidence

A 12-week open-labeled, single-center study on 18 patients with progressive vitiligo using oral CsA at 3 mg/kg/d dose and no other additional therapy reported that CsA was well-tolerated with minor adverse effects observed in only a few patients. Improvement in vitiligo was assessed using Vitiligo Area Scoring Index (VASI).[60] In another study conducted by Mehta et al.,[61] it was reported that both oral dexamethasone mini pulse (OMP) and CsA were effective in inducing arrest of disease progression (ADP); however, CsA halted the disease progression earlier as compared to OMP and the mean (SD) time to achieve ADP was significantly lower in group 2 as compared to group 1 (10.92 [4.12] weeks vs. 13.90 [3.92]) weeks). None of the patient who had achieved ADP after initiation of treatment relapsed during the treatment period of four months and follow-up period of two months after stopping treatment. Although considered a rescue drug in dermatology, low-dose cyclosporine can be an effective therapeutic alternative in vitiligo patients.

Panel recommendations

The panel was divided when asked if CsA can be used for vitiligo management in their clinical opinion, with only 67% using it in their practice. Out of the physicians who used it, 75% said that CsA can be used only in progressive vitiligo and the rest used CsA in stable vitiligo as well.

**Recommended dose and average duration of CsA for vitiligo**

Clinical evidence

In a study conducted by Taneja et al.,[60] CsA was given (3 mg/kg/d), in two divided dosages without additional therapy, it was reported that CsA was well tolerated with minimum adverse effects in the included patients of progressive vitiligo. When we looked for the literature for duration of treatment, a study by Mehta et al.,[61] reported that patients who were treated with CsA (3 mg/kg/d) for four months had early disease stabilization in active vitiligo.

Panel recommendations

Majority (67%) of the panel physicians recommended a CsA dose of 2.5–5 mg/kg/d. When asked about the recommended duration, the panel was divided equally on the duration between 4–8 weeks, 8–12 weeks, and 12–16 weeks.

Average number of days taken to see a response post-treatment with CsA and the use of CsA in smoothing out pigmentation in vitiligo treated surgically

Clinical evidence

In the study by Mehta et al.,[61] early onset of the arrest of disease progression was seen in 10.92 weeks which is approximately 77 days or 11 weeks in patients treated with CsA. A prospective study conducted by Mutalik et al.,[62] reported that patients with vitiligo when treated postoperatively with CsA showed encouraging results at six months’ follow-up. The vitiligo patches were re-pigmented completely leaving behind no tell-tale signs of vitiligo. The study suggested that postoperative addition of CsA in autologous non-cultured melanocyte-keratinocyte cell transplant (NCMKT) may contribute to enhanced and uniform pigmentation in difficult-to-treat areas, such as eyelids, lips, and areolae. CsA resulted in rapid and uniform re-pigmentation without leaving any perilesional halo in patients after NCMKT for localized, stable vitiligo (post-surgical vitiligo).

Panel recommendations

The panel was divided into three opinions when asked to indicate the average number of days post-CsA treatment when an active response is seen in patients with vitiligo. The average number of days they indicated was 90 days, 60-75 days, and 28 days. The majority (75%) of the physicians in the panel reported that CsA helps in smoothing out the pigmentation in post-surgical vitiligo.

**Role of CsA in the pediatric population**

Clinical evidence

It has been reported that CsA can be prescribed in the pediatric population for indications such as “childhood psoriasis, pediatric dermatoses, auto-immune hemolytic anemia (AIHA), and the relapsing nephrotic syndrome”. [63,64]

Panel recommendations

The whole panel was in concordance that CsA can be prescribed to the children population. The panel suggested the following indications where CsA can be given – “Atopic dermatitis, Lichen planus, Psoriasis, Urticaria, Alopecia areata, Vitiligo, and SJS and TEN”.

**Dose and mean duration of CsA in pediatric population**

Clinical evidence

The recommended CsA dose in the pediatric population ranged from 2 to 4 mg/kg/d.[65] Furthermore, according to Perrett et al., the duration of treatment ranged from 6 to 16 weeks.[66]
Panel recommendations

Five of the six panelists recommended a dose of 2.5–5.0 mg/kg/d in the pediatric population. For the mean duration, responses were divided. Most of them suggested 14–16 weeks as the optimum mean duration. Two panelists felt that 9–14 weeks should be the duration of CsA.

Monitoring the use of CsA in children

Clinical evidence

The monitoring guidelines suggested that before CsA treatment is initiated, basic clinical, and laboratory screening tests should be performed, including measurement of blood pressure, complete blood cell count (CBC) with differential count, determination of serum electrolytes and blood urea nitrogen (BUN), urinalysis, creatinine clearance, and measurement of serum levels of creatinine, magnesium, transaminases, and alkaline phosphatase.[36,37]

Panel recommendations

The panel was equally divided among “Sign scores” (37%) and “Visual analog scales for symptoms” (37%) for monitoring the use of CsA in children. One of the panelists preferred QoL questionnaires and another chose PGA to monitor the use of CsA in the pediatric population.

Adverse event management of CsA

Investigations to be done before initiating CsA treatment and the recommended frequency of the investigations during the course of the treatment with CsA

Clinical evidence

As per the clinical evidence and suggested guidelines, CsA has multiple drug interactions that need to be evaluated before starting the drug. Frequent monitoring of blood pressure, renal function, electrolytes, lipid profile, and liver function tests are required to ensure safety and tolerability of CsA for psoriasis treatment. Patients should be screened for hepatitis, tuberculosis status, and family history of renal disease.[15,67,68]

Panel recommendations

The entire panel suggested that liver function tests, serum creatinine, electrolytes, CBC, and lipid profile test are the investigations to be carried out before initiating treatment with CsA. Almost 17% suggested BUN, TB quantifier, hepatitis markers, serum magnesium, and serum uric acid. The panel was a bit divided on the frequency of these investigations. Almost 67% of them said fortnightly for the 1st month, thereafter monthly once till on treatment. While 33% said once in a month, till on treatment.

Managing a patient on CsA who has developed bacterial infection, fever with CsA

Clinical evidence

CsA may increase the risk of various bacterial, parasitic, viral, and fungal infections, as well as the risk of infections with opportunistic pathogens. Patients in whom an infection-triggered exacerbation of psoriasis has occurred should be first treated with appropriate therapy for infection, followed by a re-examination of the indications for CsA. In one of the clinical evidence, hyperkalemia and hypomagnesemia was observed in patients upon increasing the CsA dosage.[69,70]

Panel recommendations

The panel had different opinions in managing patients on CsA who have developed bacterial infection and fever. About 50% of them suggested that CsA should be stopped, 33% said that broad-spectrum antibiotics should be started and 17% said that patients should be referred to an infectious disease specialist.

Dose dependency and reversibility of side effects like gingival hyperplasia and hypertrichosis

Clinical evidence

As per the clinical studies, hypertrichosis is a cosmetically undesirable side-effect of CsA therapy, with the most noticeable change typically arising in female gender with dark hair. Gingival hyperplasia is more commonly seen at higher doses as used for transplant patients but has been reported in patients with psoriasis. However, the cessation of cyclosporine therapy resulted in a progressive resolution of the induced hypertrichosis.[15,71]

Panel recommendations

Almost everyone (83%) in the panel agreed that side effects like gingival hyperplasia and hypertrichosis are dose-dependent and the entire panel agreed that these side effects are reversible.

Modifying the treatment plan for hirsutism in pediatric patients taking CsA

Panel recommendations

When the panel was asked how they would modify the treatment plan for hirsutism in pediatric patients taking CsA, 50% of them said that they would taper down the dose by 1mg/kg/d and 17% were divided equally among continuing the same dose, and tapering down the dose by 50% of the initial dose.

Managing hypertension in patients on CsA treatment

Clinical evidence

All the clinical evidence that has been gathered reported that patients should regularly monitor their blood pressure to avoid chronic hypertension as well as kidney damage. If blood pressure does not normalize (140/90 mm Hg) after multiple-dose reductions, then the cyclosporine should be discontinued. Alternatively, elevated blood pressure can be adequately treated with antihypertensive medications due to their ability to relax vascular smooth muscles and they do not interact with cyclosporine metabolism.
β-blockers can also be used for blood pressure control. British Association of Dermatologists guidelines for the safe and effective prescribing of oral cyclosporine in dermatology 2018 quoted that the development of hypertension does not automatically necessitate cessation of cyclosporine therapy, as it is often possible to reduce the dose of cyclosporine, or treat the hypertension, to maintain satisfactory blood pressure. Treatment of hypertension preferably includes calcium antagonists such as nifedipine, isradipine, felodipine, or amlodipine which do not interact with ciclosporin metabolism and are also nephroprotective. Calcium antagonists have the disadvantage of inducing gingival hyperplasia, possibly adding to this effect of cyclosporine. Verapamil and diltiazem inhibit ciclosporin metabolism and are best avoided unless ciclosporin blood levels can be monitored. Angiotensin-converting-enzyme (ACE) inhibitors and thiazide diuretics are also used in the treatment of ciclosporine induced hypertension. It is best to avoid thiazide diuretics, because they enhance nephrotoxicity. Potassium-sparing diuretics should also not be used, because ciclosporine can induce hyperkalemia.

Panel recommendations

Half of the panel suggested that adding antihypertensive medication to the regimen would help in managing hypertension in patients on CsA treatment. 33% said that reducing the dose of CsA by 25% would help and 17% said that a physician’s consultation should be considered. One of the physicians in the panel stated that it depends on the age of the patient and the severity of hypertension.

Use of CsA and increase in the risk of developing malignancies

Clinical evidence

It was observed from the evidence that patients who were treated with CsA for more than two years have a chance of higher risk of developing malignancies like basal cell carcinoma, squamous cell carcinoma, melanoma, and others. Also, it has been observed that the incidence of tumors was seven times higher after the first use of CsA as compared to that in the previous five years. Additionally, findings from a systematic review by Arora et al., 2021 suggested not to recommend combination of cyclosporine and phototherapy due to greater chances of non-melanoma skin cancers.

Panel recommendations

The entire panel agreed when asked if the use of CsA can tend to increase the risk of development of malignancies. While indicating the kind of malignancies that patients generally develop while using CsA, a majority of 83% of the panelists said that it was non-melanoma skin cancer. 17% of the panel was divided equally between gastric cancer, melanoma, lung cancer, and lymphoma.

Changes in dosage if a patient on CsA has an increase in urea, creatinine upper limit of normal (ULN) <3 times and ULN >3 times or has a risk of renal failure and the next modality of treatment

Clinical evidence

The treatment protocol prescribes dose reduction or discontinuation of CsA treatment in case of serum creatinine increase >30% compared with baseline. This is supported by clinical studies that reported lowering daily dosage may prevent CsA-induced nephrotoxicity if a daily dose of ≤3 mg/kg is used. Furthermore, clinical and lab investigations is recommended to gauge patients’ response. Before starting therapy, women should be informed of the risks associated with cyclosporine during pregnancy.

Panel recommendations

Majority of the panel reported that reducing the dose of CsA by 25% is the recommended change in dosage if a patient on CsA has an increase in urea and creatinine (ULN >3 times).

The next modality of treatment according to the panelists was as follows: work with physician/nephrologist for dose adjustment, as it depends on the underlying condition; MMF/MTX can be given with an opinion from nephrologists.

CsA in patients who are having high hepatic enzymes (>3 times of ULN)

Clinical evidence

According to EuroGuiDerm Guideline by Nast et al., CsA is contraindicated in severe hepatic diseases (e.g., liver failure). In a retrospectively analyzed liver biochemical test results in 59 patients with endogenous uveitis who received CsA, all patients had normal liver tests before treatment and had at least six determinations during a 6–36 month course of therapy with CsA at a dose of 2–10 mg/kg/day. Thirty-four (58%) patients developed at least one abnormality of liver tests, and 19 (32%) had a prolonged pattern of abnormalities. The usual abnormalities consisted of a mild, transient increase in alkaline phosphatase levels occasionally accompanied by slight elevations in serum bilirubin and aminotransferase activities. Peak alkaline phosphatase levels ranged from 125 to 243 units/liter and persisted for 7 days to 48 months. Thus, biochemical evidence of mild cholestatic liver injury was common in patients receiving CsA. These abnormalities are usually self-limited and asymptomatic but may cause diagnostic difficulty if a preexisting liver disease is present. There are limited studies available on usage of cyclosporine in patients with raised hepatic enzymes.

Panel recommendations

Majority (67%) of the panelists were of the opinion that CsA cannot be given to patients who are having high hepatic...
enzymes (>3 times of ULN). These are the reasons for this contraindication-“Because of metabolic implications and drug interaction if a patient is on polypharmacy, CsA will aggravate hepatic enzyme levels further, and it can worsen hepatic failure”. Panel members also suggested that patients with liver disease require close monitoring as CsA is contraindicated in severe hepatic disease.

Management of dyslipidemia in patients who are on CsA treatment

Clinical evidence
Irrespective of CsA effectiveness in its immunosuppression, its treatment is associated with elevated plasma cholesterol, triglyceride levels and an increased risk of cardiovascular disease. CsA-treated patients on the other hand show several-fold higher systemic exposure of all statins, both those that are metabolized by CYP3A4 and fluvastatin (metabolized by CYP2C9). Therefore, the mechanism for this interaction does not seem to be solely caused by inhibition of CYP3A4 metabolism, but it is probably also a result of inhibition of statin-transport in the liver, at least in part. There is no information on possible interaction effects of cyclosporine on the pharmacokinetics of lipid-lowering drugs other than statins, but it is not likely that any clinical relevant interference exists with Ezetimibe, fish oil, or bile acid sequestrants.[80] Here are some ways for treating the CsA-induced hyperlipidemia – “Diet, Statins, Fibrates and Ezetimibe, and PCSK9 Inhibitors.”[81]

Panel recommendations
Varied responses were received for this question. Most (40%) of the panel members suggested monitoring lipid profiles frequently. Some (20%) of the panelists mentioned adding statins while some (20%) suggested adding fenofibrates. One panelist recommended reducing the cyclosporine dosage. Another panelist advised to physician’s/endocrinologist’s help.

CsA drug interactions

Drug interactions of CsA with the drugs listed below

Clinical evidence
Methotrexate: According to a study by Aydin,[24] there were no drug interactions reported between CsA and MTX.

Apremilast: There is a higher risk of gastrointestinal side effects and hence the combination of apremilast with CsA is not advised.[82]

Macrolides: Possibly reinforce nephrotoxic effects

Azoles: Possibly reinforce nephrotoxic effects

Cyclosporine is metabolized primarily by the cytochrome P450 3A4 subtype (CYP3A4). Therefore, CsA use can increase or decrease the levels of other medications that are metabolized by CYP3A4, such as statins, calcium channel blockers, and warfarin.[78] In the case of concomitant cyclosporine and statin therapy (high dose), severe rhabdomyolysis was reported. Increased nephrotoxicity can be seen when other nephrotoxic medications, such as aminoglycosides and nonsteroidal anti-inflammatory medications, are used in conjunction with cyclosporine. Potassium-sparing diuretics can potentially elevate serum potassium with concomitant cyclosporine treatment, possibly leading to hyperkalemia.[13]

Panel Recommendations
Majority (84%) of the panelists voted that CsA has no drug interactions with “Methotrexate”. For the drug “Apremilast”, some (40%) of the panel members felt that it can have a drug interaction with CsA while some (60%) voted no drug interaction between these drugs. Similarly, for “Acitretin” panelists gave mixed responses. 60% voted that there will be drug interaction and 40% said there will be no interaction with CsA. Panelists were in 100% concordance that “Macrolides” and “Azoles” will have drug interactions with CsA.

CsA usage in pandemic and pregnancy

CsA in vaccinated patients

Clinical evidence
According to clinical evidence, the use of cyclosporine is associated with an impairment of the humoral response to vaccines as they reduce antibody production, lowering protective antibody titers, so, it is better to discontinue CsA during vaccination. Furthermore, no data are available on how long cyclosporine needs to be stopped for optimal responses to vaccination.[83,84]

Panel recommendations
All panelists are in 100% agreement that CsA can be used in patients who are vaccinated potentially weighing the risk vs benefit.

Administration of CsA during the gap of two subsequent vaccine shots

Clinical evidence
Extrapolating from this literature and based on currently available evidence, the coronavirus disease 2019 (COVID-19) TF recommends that patients who are to receive an mRNA-based COVID-19 vaccine can continue their biologic or oral therapies for psoriasis and/or PsA in most cases. No data were available at the time of analysis for cyclosporine (as used for psoriasis and other inflammatory diseases) on the efficacy of any approved vaccine.[85]

Panel recommendations
Panel was in concordance that CsA can be administered during the gap of two subsequent vaccine shots.
**Advice on CsA usage during vaccination**

**Clinical evidence**

The patients with the psoriatic disease who do not have contraindications to vaccination should receive an mRNA-based COVID-19 vaccine as soon as it becomes available to them. Additional vaccine platforms are undergoing testing.[85]

**Panel recommendations**

The panel was divided in terms of opinion on advice on CsA usage during vaccination. Most of them (50%) suggested stopping the use of CsA three days prior and post seven days to vaccination. Few panelists (33%) felt that CsA usage can be continued without any change. One panelist suggested stopping using CsA a week before and after the vaccination.

**Use of CsA during COVID infection**

**Clinical evidence**

According to guidance on the use of immunosuppressive agents, there is insufficient evidence to recommend discontinuation of systemic immunosuppressive agents at this time. Physicians should use their clinical judgments to stop or continue the usage of these drugs on the patients. Physicians should weigh the risk vs. benefits of the use of immunosuppressive agents on a case-by-case basis. For patients on systemic immunosuppressive agents who have tested positive for COVID-19 or exhibit signs/symptoms of COVID-19, it is recommended that physicians should discontinue or postpone the systemic immunosuppressive agents until the patient recovers from COVID-19.[86,87]

**Panel recommendations**

Majority (66%) of the panelists felt that CsA cannot be used during the COVID infection.

**Prescription of CsA in all trimesters of pregnancy**

**Clinical evidence**

As per the clinical evidence, in pregnant women who underwent transplantation and were administered CsA (1.4–14 mg/kg/d), an elevated rate of premature birth, low birth weight, an increase in preterm labor rate was observed. The most frequent complications in the mother being hypertension, anemia, urinary tract infections, and preeclampsia.[15,88–90]

**Panel recommendations**

Most (67%) of the panelists agreed that CsA can be prescribed in in second and third trimesters of pregnancy. Panelists were of the opinion that CsA crosses the placental blood barrier and is a category C drug in pregnancy; therefore, it should be withheld in the first trimester. The pregnancies in women treated with cyclosporine are considered high risk.[91] Pregnancy registries show no increase in the risk of teratogenicity, although there were trends towards low birth weight and prematurity.

**Prescribing CsA during the lactation period**

**Clinical evidence**

According to the American Academy of Pediatrics and the National Psoriasis Foundation (NPF), CsA should be avoided during lactation due to the possible risk of infant immunosuppression.[89] On the contrary, a clinical evidence found out that the exposure to CsA in infants was very low and hence breastfeeding could be considered, but with constant follow-up of infant levels.[92–94]

**Panel recommendations**

Five of the six panel members were of the opinion not to prescribe CsA during the lactation period.

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