Consensus on the use of cyclosporine in dermatological practice. Italian Consensus Conference

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CONSENSUS PAPER

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Consensus on the use of cyclosporine in dermatological practice

G. ALTOMARE [1], F. AYALA [2], F. BARDAZZI [3], G. BELLIA [4], S. CHIMENTI [5], D. COLOMBO [4]
M. L. FLORI [6], G. GIROLOMONI [7], G. MICALI [8], A. PARODI [9], K. PERIS [10], G. A. VENA [11]

Cyclosporine A (CsA) efficacy and safety have been proven in various dermatoses both in adults and in children even as long-term treatment. Over the last 25 years, Italian dermatologists have gathered relevant experience about CsA treatment for psoriasis and atopic dermatitis. This paper has been developed by an Italian Consensus Conference and it is aimed at providing recommendations based on real-world clinical experience in adult patients, consistent with efficacy and safety data arising from the scientific literature. The paper is mainly focused on the analysis of the optimal therapeutic schemes for psoriasis and atopic dermatitis, in terms of doses and treatment duration, according to individual characteristics and to the severity of the disease. Moreover, it overviews ideal management, taking into account pharmacological interactions, influence of comorbidities, and the most common adverse events related to CsA treatment.

KEY WORDS: Cyclosporine - Skin diseases - Psoriasis - Dermatitis, atopic.

[1]IRCCS Galeazzi, University of Milan, Milan, Italy
[2]Department of Clinical Medicine and Surgery
Dermatology Clinic
University of Naples Federico II, Naples, Italy
[3]Dermatology Unit, Department of Specialist
Diagnostic and Experimental Medicine
S. Orsola-Malpighi Hospital
University of Bologna, Bologna, Italy
[4]Novartis Farma, Italy, Origgio, Varese, Italy
[5]Department of Dermatology
University of Rome "Tor Vergata", Rome, Italy
[6]Dermatology Unit
Department of Clinical Medicine and Immunology
University of Siena, Siena, Italy
[7]Section of Dermatology, Department of Medicine
University of Verona, Verona
[8]Dermatology Clinic, University of Catania
A.O.U. Policlinico Vittorio Emanuele, Catania, Italy
[9]Section of Dermatology
IRCCS University Hospital San Martino-IST
Genoa, Italy
[10]Department of Dermatology
University of L'Aquila, L'Aquila, Italy
[11]Private Practitioner, Bari and Barletta, Italy

Cyclosporine (cyclosporine A, CsA), was first isolated from the soil fungus *Tolypocladium inflatum* in 1970.[1] Its antifungal activity was demonstrated to be poor, whereas a potent immunosuppressive effect was found in 1976.[1] For this reason, two years later, CsA was successfully used in preventing kidney transplant rejection [2] and, in 1979, it was proven effective in the treatment of rheumatoid arthritis and psoriasis.[3] The original orally administered formulation of CsA (Sandimmun, Novartis) was approved in 1983 by the Food and Drug Administration (FDA) for the prevention of transplant rejection.

Corresponding author: Giampiero Girolomoni, Clinica Dermatologica, Università di Verona, Piazzale A. Stefani 1, 37126 Verona.
E-mail: giampiero.girolomoni@univr.it

Despite the increased availability of new therapeutic options, CsA is still one of the most widely used and effective systemic drugs for the treatment of psoriasis and atopic dermatitis, worldwide.[4-6] In Italy, it has been found to be the most frequently used systemic antipsoriatic therapy.[7]

It is noteworthy that the Italian experience in CsA is broad, and often long lasting, for most of its therapeutic indications, starting from transplant with 25-year experience. Moreover, several indications for CsA have originated from clinical trials conducted in Italy.

Upon these grounds, an Italian Consensus Conference was held to provide recommendations based on real-world clinical experience.

Pharmacokinetics

CsA is a cyclic endecapeptide,[8] able to act directly on cells of the immune system, primarily on T cells, because of its inhibitory effects on calcineurine. It targets the major T cell-driven pathways of immune-mediated response and inflammation. These effects explain its efficacy both in prevention of transplant rejections and in immune-mediated dermatoses.[9]

CsA absorption occurs within 30 minutes and the peak serum concentration (Cmax) is observed 2-4 hours after the administration.[10-15]

Due to its lipophilicity, CsA is widely distributed throughout the body. In plasma, it is mostly bound to lipoproteins (≥90%) and easily transferred between different lipoproteins, and to or from albumin as well.[5] It has a first-pass effect of 27% in the liver.[15]

CsA metabolism is highly dependent on cytochrome P450 isoenzymes 3A4 (CYP3A4) and 3A5 (CYP3A5) in the liver and small intestine, and dependent on the efflux p-glycoprotein pump (PGP) encoded by the multidrug resistance-1 gene (MDR1) in the gastrointestinal tract and liver.[5] The metabolites of CsA are mainly excreted in the bile; another 6% is eliminated in the urine, of which 0.1% remains unchanged.[12]

A higher CsA serum concentration reflects higher clinical efficacy and is obtained if the drug is administered before food intake.[5,16]

CsA dosage is established on a weight-per-weight basis (mg/kg/day, see below for further details).

Drug interactions

By virtue of its almost complete hepatic metabolism by cytochrome P450 IIIA, the plasmatic levels of CsA are increased or decreased by drugs that inhibit or stimulate cytochrome P450 activity, respectively (Tables I-III).[5] The consequent change in CsA bioavailability results in adverse effects that are potentially exerted on target-organ toxicity.[17]

Among patients with dermatoses, the use of some systemic antibiotics as well as of NSAIDS could be critical due to pharmacological interactions, leading

TABLE I.—*Drugs and foods that inhibit the cytochrome P450 system, leading to a higher concentration of cyclosporine.*[5]

– Allopurinol
– Amiodarone
– Antifungals (fluconazole, itraconazole, ketoconazole and voriconazole)
– Bromocriptine
– Calcium channel blockers (diltiazem, nicardipine, verapamil and mibefradil)
– Ciprofloxacin
– Danazol
– Doxycycline
– Furosemide
– Gentamicin and tobramycin
– Grapefruit juice
– Macrolide antibiotics (erythromycin, clarithromycin and josamycin)
– Methylprednisolone
– Metoclopramide
– Oral contraceptives and androgen steroids
– Protease inhibitors
– Ranitidine and cimetidine
– Statins (especially atorvastatin and simvastatin)
– Thiazide diuretics
– Ticarcillin
– Warfarin

TABLE II.—*Drugs that stimulate the cytochrome P450 system, leading to a lower cyclosporine level.*[5]

– Anticonvulsants (carbamazepine, phenobarbitone, phenytoin and valproate)
– Isoniazid
– Metamizole
– Nafcillin
– Octreotide
– Orlistat
– Probucol
– Rifabutin
– Rifampicin
– Selective serotonin reuptake inhibitors (sertraline)
– St John's Wort (*Hypericum perforatum*)
– Sulfinpyrazone
– Terbenafine

TABLE III.—*Drugs that may impair renal function during cyclosporine treatment.*[5]

– Acyclovir
– Aminoglycosides (gentamycin and tobramycin)
– Amphotericin B
– Cimetidine and ranitidine
– Ciprofloxacin
– Clotrimazole and ketoconazole
– Colchicine
– Fibrates
– Melphalan
– Methotrexate
– Nonsteroidal antiinflammatory drugs
– Trimethoprim with sulfamethoxazole
– Vancomycin

to higher CsA concentration and, consequently, toxicity.[5]

CsA may reduce the clearance of some HMG-CoA reductase inhibitors. Thus, statins should be used with caution because of the risk of rhabdomyolysis.[5]

It is important to underline that heavy alcohol intake increases CsA levels.[18]

Grapefruit juice avoidance must be recommended during CsA treatment, since it inhibits the metabolism of CsA by suppressing cytochrome P450 enzyme activity.[5, 18]

Systemic CsA in dermatoses

CsA has been proven an effective therapeutic option for several dermatoses.[4-6] Its systemic use is authorized in Italy for psoriasis and atopic dermatitis.[19]

Psoriasis

Among the available systemic treatments for psoriasis, CsA has a particularly favorable profile, due to the rapid clinical response (4 weeks for the relief of symptoms, 10-16 weeks for a PASI 75 response) even in patients unresponsive to other therapies.[4, 20-22]

CsA has been proven effective in all variants of psoriasis (Table IV), where different schemes in terms of doses and treatment duration have been used.[4, 6, 20]

The clinical benefit of CsA therapy is related not only to the clinical response, but also to the effects on psychological distress, which are a common experience in patients with psoriasis (see below).[29, 30] Many studies indicate a clear dose-dependent response, with higher doses producing higher rates of remission.[6, 31-35]

To identify patients who may benefit from systemic treatments including CsA, the "rule of tens" has been proposed: a body surface area affected >10% or a Psoriasis Area Severity Index (PASI) >10 or a Dermatology Life Quality Index (DLQI) >10.[36]

Dose-finding studies and current consensus guidelines have identified 2.5 mg/kg/day CsA as ideal starting dose, to be gradually increased up to 5 mg/kg/day by 0.5-1 mg/kg/day at 2-4 weeks intervals.[4, 21-32] Tachyphylaxis did not occur if regimens with progressive increases were prescribed.[31] In patients who are unresponsive, or who respond inadequately after 3 months (PASI 50 not achieved), CsA withdrawal is recommended.[4] Drug reduction should be performed stepwise (0.5-1.0 mg/kg/day at 2 weeks intervals).[4]

Based on long-term clinical experience, six therapeutic strategies are currently used to treat moderate-to-severe psoriasis with systemic CsA (I=induction; M=maintenance; definition and treatment regimens are illustrated in Table V): 1) intermittent short-term therapy (I); 2) rescue therapy (I); 3) long-term continuous therapy (I+M); 4) combination therapy (I+M); 5) rotational therapy (I+M); and 6) week-end therapy (M).[4, 6, 37, 38]

TABLE IV.—*CsA in psoriasis variants.*

Plaque psoriasis	Lebwohl M *et al.* J Am Acad Dermatol 1998;39:464-75.[23]
Erythrodermic psoriasis	Fradin MS *et al.* Br J Dermatol 1990;122(Suppl 36):21-5.[24]
Palmoplantar pustular psoriasis	Erkko P *et al.* Br J Dermatol 1998;139:997-1004.[25]
Generalized pustular psoriasis	Ozawa A *et al.* J Dermatol 1999;26:141-9.[26] Farber EM. Cutis 1993;51:29-32.[27]
Nail psoriasis	Witkamp L *et al.* J Eur Acad Derm Vener 1996;7:49-58.[28]

TABLE V.—*Systemic cyclosporine treatment schedules.*

Intermittent short-term therapy	– Short course (12-16 weeks) until significant improvement is achieved, after which treatment is withdrawn – If relapse occurs, treatment is reinstituted at the previously effective dose
Rescue therapy	– Used in severe flares of disease until an alternative maintenance treatment is instituted
Long-term continuous therapy	– Clinical improvement maintained with the lowest effective dose
Combination therapy	– Cyclosporin can be combined with topical therapies, such as corticosteroids, anthralin, or vitamin D3 analogues, and other systemic treatments, such as methotrexate, fumaric acid esters and mycophenolate mofetil
Rotational therapy	– Treatment with cyclosporine can be rotated with other systemic agents (see text)
Week-end therapy	– Maintain remission (5mg/kg/day) for 2 consecutive days a week for 24 weeks

Moreover, CsA due to its fast therapeutic action, represents an appropriate "bridging" therapy, which is useful if associated with a new long term biological treatment which needs a certain time lapse to be effective.[4,21]

Intermittent short-term therapy

The most common systemic CsA regimen is represented by a short course (12-16 weeks) administration, followed by the withdrawal when a significant improvement (PASI 75) or remission (PASI≥90) is achieved. In case of relapse, a short-term course may be repeated at the previously effective dose.[4, 21, 23, 39-43]

In patients with severe psoriasis, a 1-year remission is obtained in 80% of cases with 2 courses of therapy, the remission after the first course lasting 4 months in 45% of cases.[41, 42] A slight advantage in terms of remission duration was observed with dose tapering.[41, 42]

Rescue therapy

The rapid onset of effect with short-term CsA is useful to control severe flares, particularly in severe psoriasis variants.[4] A starting dose of 5 mg/kg/day is recommended, followed by a gradual dose decreasing after remission.[13,14,17]

Long-term therapy

Long-term continuous therapy with CsA is a less common approach for severe psoriasis and is prescribed to obtain a significant clinical improvement with the lowest effective dose rather than a complete control.[15, 44-47] Its duration is limited to 2 years in Europe [9, 20, 21] with the possibility of a further prolongation in selected cases, and to 1 year in the United States.[48] The typical maintenance dose is 3-3.5 mg/kg/day.[49]

Combination therapy

The effects of systemic CsA associated with various topical treatments, as corticosteroids,[50-52] anthralin,[53] vitamin D3 analogues,[54] or systemic treatments, as methotrexate,[55] fumaric acid esters,[56] acitretin,[57] or mycophenolate mofetil [58] have been evaluated only in small case series and single case-reports.[4] The main advantage of combination therapy is the possibility to minimize toxicity due to the dose reduction,[4] even if the possibility of adverse effects arising from pharmacological interactions has to be taken into account.[6]

A recent Italian study reported a clinical response (therapeutic success or complete clinical remission) in 80% of patients with moderate-severe plaque psoriasis who received CsA plus systemic methotrexate or retinoids, or plus topical treatment and/or phototherapy.[59]

Rotational therapy

CsA treatment of psoriasis is not associated with tachyphylaxis,[4, 20, 51, 60, 61] allowing rotational therapy, whose rational is similar to that of combination therapy, characterized by the sequential use of the above mentioned systemic agents.[20, 61, 62]

An Italian study has proven, in patients with severe psoriasis, the superiority of the sequential therapy with CsA (3 mg/kg/day for 4 weeks) and narrow-band UVB phototherapy compared to narrow-band UVB phototherapy alone.[63]

Week-end therapy and pulse therapy

An additional therapeutic maintenance schedule was proposed and evaluated by PREWENT (Psoriasis Relapse Evaluation with Week-End Neoral® Treatment) study, a 24-week, double-blind placebo-controlled trial, carried out in 22 Italian hospitals or university Dermatology units. CsA microemulsion was used in patients with chronic plaque psoriasis who had achieved clinical remission after continuous CsA therapy, and then randomized to receive oral CsA 5 mg/kg/day or placebo for two consecutive days/week for 24 weeks. Time to first relapse (adopting PASI as diagnostic criterion) was significantly longer with CsA and PASI was significantly lower at weeks 4-16 in CsA recipients. The incidence of adverse events was similar in both groups.[37]

Similar results have been reported by another Italian study, in which patients with severe chronic plaque psoriasis were assigned to a continuous schedule or 4-day therapy per week, administered for 6 months. PASI score and severity of itching were efficiently controlled in both groups. Moreover, the safety profile was shown more favourable in the group with intermittent 4 days per week administration.[64]

Consensus Conference Statements

— There is consensus on the **indications** reported by literature for the treatment of psoriasis variants, in particular for the doses and the duration of therapy

— However, in clinical practice, indications to start CsA treatment are less strict. It may be used in the following cases with PASI<10:

- resistance to topical drugs (experience suggests that resistance may occur even with PASI≥5);
- certain clinical characteristics, *e.g.* the site of the disease (palmoplantar psoriasis, genital psoriasis);
- characteristics of the patients, including sex, age, personal or social relationship and employment. In fact, the impact of psoriasis on a patient's quality of life (QoL) may be disproportionate to the clinical severity, due to his/her self-perception and his/her expectations about the treatment. Due to the young average age of psoriatic patients, the consequences of the psychological and emotional stress are particular relevant in terms of their impact on social and sexual life leading to low self-esteem, high anxiety, and sexual dysfunction

— In limited extent psoriasis, *e.g.* nail psoriasis where PASI and NAPSI (NAil Psoriasis Severity Index) may result quite low: CsA may be considered even if it is not the first-line treatment. The indication has to be established on the basis of the patient's characteristics (e.g. personal relationship and employment). In clinical experience,[65,66] CsA has proven effective when the ungueal variant was associated to generalized involvement

— A weight-per-weight **dose**, based on the ideal body weight is recommended. Adopting as a reference the actual body weight, overweight or obese patients may be exposed to high doses, even double that those of normal weight patients, with an increased risk of toxicity (see below for further details). In order to obtain a better compliance with the therapy, a fixed dose (200 mg/day) may be used in such patients

— To establish the optimal dose, the clinical severity has to be taken into account: for PASI higher than 20 and especially in cases with a relevant inflammatory component, an induction dose of 5 mg/kg may be appropriate; a dose of 2.5 mg/kg/day, although reported in clinical trials, has to be considered suboptimal in severe psoriasis

— Based on our experience, a satisfactory control of itching is generally obtained in few weeks, generally earlier than the control of skin lesions

— The clinical response has to be assessed after the first month, when both the profiles of efficacy and safety (see the section *Management of patients*) should be assessed. The treatment has to be carried out for at least 3 months, evaluating side effects

— After clinical remission is achieved, multiple possibilities can be evaluated about which the Consensus doesn't express a unanimous recommendation, rather the advice to make a choice according the individual patient's characteristics, clinical history, and needs:

- tapering after 3 months of treatment *or*
- tapering once PASI 0 has been reached *or*
- once PASI 0 has been reached, maintenance therapy for 1 month/for at least 1 month due to the high risk of relapse

— When a **relapse** occurs:

- during the tapering, then the full dose regimen is recommended followed by continuous therapy for 6 months
- immediately after/close to the treatment completion (unlikely possibility), the rotational therapy may be an option (see below)
- few months after the treatment completion, the treatment can be repeated, according to the disease extension and the severity of the relapse

— CsA high doses (5 mg/kg/day) may be used also to control severe flares

— The recommended dose for induction is ≥3 mg/kg/day

— The recommended dose for long-term therapy is 3 mg/kg/day

— The aim of **long-term therapy** is to achieve more prolonged clearance and improve the balance between effectiveness and safety. Our large experience of a good safety profile supports a prolonged duration of treatment at the minimal effective doses in selected cases

— Lifestyle modifications, including an appropriate diet, have a role in achieving a good control of the disease, as indicated by a recent Italian study where weight loss has been able to improve the response to low-dose CsA in obese patients with moderate-severe chronic plaque psoriasis [67]

— Clinical experience suggests the use of **combination regimens** in selected cases ("difficult cases" in terms of poor responsiveness or clinical complexity). Combination therapy provides the opportunity to facilitate decreases in the dose of each single drug and reduction of potential adverse effects

— In Italian clinical practice, the association of CsA with:

- fumaric acid esters is not registered in Italy
- acitretin or methotrexate is uncommon
- narrow band UVB is not infrequent
- topical corticosteroids or vitamin D/vitamin D analogues is very common

— The rational basis of **rotational therapy** is reducing the exposure to a single agent in a chronic (incurable) disease, improving both efficacy and safety profile

— Clinical experience suggests CsA use in cases of inadequate/incomplete responsiveness (not cured patients who need a continuous therapy). Notably, individual clinical history has to be taken into account

— Italian clinical research was relevant in the development of **week-end therapy**, a schedule related to CsA effectiveness in a "real-life" clinical setting. Week-end therapy is able to provide a longer maintenance of the remission and/or to reduce relapses in patients with moderate psoriasis. The PREWENT Study schedule consists in the administration of systemic CsA 2 days/week, **but a schedule of 3 days/week provides a better clinical response**. The choice should be based on the characteristics of the patient or of the disease [37]

— It is noteworthy that the administration of 5 mg/kg/day for 3 doses per week is equivalent to the administration of 3 mg/kg/day for 5 doses per week. However, it is largely safer in terms of potential nephrotoxicity, since the more prolonged discontinuation decreases vasoconstriction, a well described functional adverse effect

Atopic dermatitis

Atopic dermatitis is one of the most common chronic relapsing childhood dermatoses which affects up to 30% of children in most cases before the age of 5 years, but persists into adulthood in more cases than reported by the literature (up to 3%). Moreover, its onset may be observed in adult age, even in elderly patients. Overall, clinical experience suggests that atopic dermatitis is by far more frequent than expected according to diagnostic criteria.[68, 69]

In the diagnosis of atopic dermatitis several criteria have been established,[68-71] but there is no laboratory biomarker.

Current management of atopic dermatitis has not curative targets, while it is focused on symptoms relief.

CsA is the only immunosuppressant agent approved in Europe for the short-term treatment of severe atopic dermatitis that cannot be controlled with topical therapy.[4] It has not been formally approved by FDA for this indication, but it has been recommended by American Academy of Dermatology (AAD).[68, 72] There is no statement indicating the recommended dose in atopic dermatitis, although the therapeutic dosage used in psoriasis is conventionally administered.

The data of a systematic review clearly demonstrated the efficacy of CsA in atopic dermatitis. Body surface area, erythema, sleep loss and corticosteroid use were reduced in the CsA group.[73]

A 47% improvement in itching has been described within 2 weeks in patients treated with high dose of CsA.[74]

Short-term therapy

According to the European guidelines, an initial dose of 5 mg/kg/day for 2 weeks has to be gradually tapered to a dose of 1.5 mg/kg/day over 3 months, based on the individual clinical response.[9,75-78]

A meta-analysis by Schmitt [47] demonstrated the effectiveness of short-term continuous CsA treatment (50% reduction in severity after 6-8 weeks of therapy). Patients treated with an initial dose of 4-5 mg/kg/day showed a more rapid response at 2 weeks (40% decrease in severity) in comparison to patients treated with a lower initial dose of 2.5-3 mg/kg/day (22% decrease in severity). Nevertheless, after a 6-8 week follow-up, no difference was observed between the two doses in terms of responses.

According to results of a recent double-blind randomized, multicentre trial, CsA is superior to prednisolone in inducing a stable remission of severe eczema.[79]

Long-term therapy

On the basis of the above mentioned results, the lowest effective dose is recommended if a maintenance therapy is needed.[6, 78]

Two randomized controlled studies reported the effect of CsA long-term therapy to control severe atopic dermatitis.[80, 81] In a pediatric population (2-16 years), intermittent short-term therapy (5 mg/kg/day) for 12 weeks was compared to a continuous 1-year course (5 mg/kg/day), the latter being associated to better outcomes in terms of short-term and sustained clinical response and patients' QoL.[80]

The second study,[81] which was performed in patients with severe atopic dermatitis, compared two long-term CsA regimens: an initial dose of 5 mg/kg/day tapered to 3 mg/kg/day as tolerated *vs* 3 mg/kg/day increased to 5 mg/kg/day as needed, both maintained the optimal dose for the following 10 months.

After 1 year, patients in the treatment group who started with 5 mg/kg/day showed slightly better results in terms of disease control (59.8% *vs.* 51.7%), and similar adverse events.

Considering relapse and worsening after CsA, data reported is highly variable, in terms of rates and time of occurrence.[4] However, there is no evidence of a rebound phenomenon on this drug withdrawal.[47]

Consensus Conference Statements (recommendations for adult patients with atopic dermatitis)

— When treating atopic dermatitis, a crucial point is the relevant **impact of the disease** on QoL. QoL scores should be used in conjunction with objective measures of severity as an assessment tool. Because of the rapid onset of action and marked efficacy, CsA is particularly useful in the treatment of atopic dermatitis

— Atopic dermatitis is often associated to severe itching, whose significant improvement is generally obtained in 1-2 weeks with CsA

— In the management of atopic dermatitis skin care, cleansing and bathing, lifestyle, diet restriction with avoidance strategies are important factors. Patients have to be informed and instructed in order to actively and effectively collaborate

— With **short-term therapy**, a high initial dose (4-5 mg/kg/day) is recommended to obtain a more rapid and sustained improvement

— With **long-term therapy**, the minimum effective dose of CsA to achieve substantial improvement in disease severity is appropriate

— The duration of treatment able to obtain a satisfactory clinical response (4-6 months) is longer than that indicated in clinical guidelines (2-3 months)

Impact of CsA on QoL

Dermatoses cause as much disability as that of other major medical conditions. For instance, disability from psoriasis is comparable to that from arthritis, hypertension and diabetes;[82] while QoL from atopic dermatitis is impaired to a similar extent as is seen in other common childhood diseases, such as asthma and diabetes.[83]

The impact on patient's QoL of dermatoses such as psoriasis and atopic dermatitis is relevant [82-85] and has been shown able to affect the adherence to medication.[84] Consequently, QoL assessment tools have been specifically developed for dermatologic conditions (*e.g.* the Dermatology Life Quality Index, DLQI, the Psoriasis Disability Index, PDI, the Eczema Disability Index, EDI, and the Psoriasis Index of Quality of Life, PSORIQoL). In addition, the updated "rule of tens" used to select patients with severe psoriasis who could benefit from systemic treatment includes QoL parameters.[9]

The impact of a dermatological condition on QoL doesn't show a clear relationship with the clinical severity of the disease, as assessed with PASI and depends more on patient's self-reported morbidity.[85, 86]

In patients with dermatoses, CsA has been shown able to improve QoL. Considering psoriasis, data of a 1-year substudy from PISCES (Psoriasis Intermittent Short Course of Efficacy of Sandimmun Neoral) has demonstrated an improvement in QoL ($P<0.001$) and a reduction in itching and disease extent/severity ($P<0.001$ for both).[87] Similar results have been observed for atopic dermatitis both in adults [74, 88] and in children.[80]

Considering the common experience of psychological distress in patients with psoriasis, generally with a higher burden in female patients, the PSYCHAE study, a large observational study performed in 39 Italian dermatology centers on more than 1500 patients, has shown that, differently to methotrexate and topical corticosteroids treatment, CsA treatment is able to control the risk of psychological distress assesses using the General Health Questionnaire (GHQ) and the Brief Symptoms Inventory (BSI).[29, 30] It is interesting to note that only 16% of physicians in the PSYCHAE trial declared that they considered a patient's psychological status when choosing a systemic therapy for psoriasis.[30]

Management of patients treated with systemic CsA

CsA is the most commonly used drug by Italian dermatologists for the treatment of moderate-severe psoriasis and atopic dermatitis unresponsive to conventional therapy.[7] However, due to its narrow therapeutic window, clinicians have to take into account the multiple pharmacological interactions, and the relevant influence of comorbidities on therapeutic strategy.[89]

Clinical evaluation

Before starting CsA treatment, a careful clinical evaluation has to be carried out (history, examination, baseline laboratory examinations).[5, 61]

Among comorbidities, previous or concurrent malignancies, hypertension, renal impairment, current infections, or a history of previous PUVA phototherapy have to be investigated.[5, 61] Skin surface should be inspected in order to identify the presence of cancerous or actinic lesions. In case of active herpes simplex infection or viral warts the treatment should be postponed after healing.[5, 61]

Hepatitis profiles including anti-HAV, HBsAg, anti-HBs, anti-HBc, anti-HCV and also anti-HIV should be checked in patients treated with CsA.[61]

The adherence to dental hygiene has to be recommended and checked at 6-months periodic examinations.[5, 6]

Laboratory tests have to be performed both at baseline and during the treatment. They include serum creatinine, potassium, magnesium, bilirubin, liver enzymes, uric acid, fasting lipids, urea nitrogen, blood cell count, and urine analysis.[21, 61] According to the international guidelines, the tests have to be repeated during CsA treatment at definite intervals (every 2 weeks during the first 2 months of treatment).[6, 20-22]

The physical examination should include blood pressure measurement, at least in two separate occasions basally, and continuous monthly monitoring during the treatment.[5]

Due to a variety of pharmacological interactions (Tables II-IV), it is crucial to investigate the use of any systemic drug (over-the-counter drugs included) before initiating a treatment with CsA, and to reiterate the investigation at each visit, eventually mentioning the specific class of medication.

Notably, evidence suggests that CsA is able to inhibit *in vitro* HCV replication. Some data confirm this property *in vivo*, in patients who underwent liver transplantation or with chronic active hepatitis.[90, 91] The Italian experience on patients with concomitant rheumatologic disorders and HCV infection indicates that CsA is effective and safe, and may contribute to better outcomes.[92, 93] Moreover, the short-term therapeutic association of CsA and anti-TNF shows a satisfactory safety profile (Table VI).[91-93]

Consensus Conference Statements

— CsA is endowed with a relevant manageability, with the possibility to dose changes (tapering or increasing according to either clinical response or adverse effect onset)

— There is a general consensus with the guidelines about baseline assessment and monitoring, with some differences, already discussed

— In contrast to guidelines recommendations, the screening for malignancies is exclusively based on clinical history

— The screening of infectious diseases is

TABLE VI.—*Laboratory examinations during cyclosporine treatment.*

Diagnostics	Period in weeks				
	Pretreatment	Week 4	Week 8	Week 12	Week 24
Full blood count (erythoracytes, leukocytes, platelets)	X	X	X	X	X
Liver function tests (transaminases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin)	X	X	X	X	X
Electrolytes (sodium, potassium)	X	X	X	X	X
Serum creatinine	X	X	X	X	X
Urine analysis and sediment	X	X	X	X	X
Uric acid	X	X	X	X	X
Cholesterol, triglycerides	X			X	
Magnesium	X			X	

Further specific test may be required according to clinical signs, risks and exposure

based on the patient's individual history. The measurement of blood infective markers is not mandatory, unless a high clinical suspicion is present

— The first time point for laboratory test **is scheduled at the first month**, later than what stated by guidelines (2 weeks)

Contraindications

CsA is contraindicated in uncontrolled hypertension, renal disease, serious infections, and in patients with a previous history of malignancy (excluding basal cell carcinoma).[5, 20-23, 78]

Moreover, the drug should be avoided in patients previously treated with a high cumulative dose of psoralen and ultraviolet A light phototherapy (PUVA), due to the risk of carcinogenicity.[5, 46]

Skin infections superimposed to atopic eczema do not represent an absolute contraindication, but an adequate antibiotic therapy is needed before CsA.[78]

A careful evaluation of the benefit/harm balance is requested in patients with epilepsy, severe hepatic dysfunction, immunodeficiency disorders, diabetes, obesity, premalignant conditions. Elderly patients (≥65 years), patients with a history of drug or alcohol abuse, poor compliant patients are at higher risk to develop adverse events.

For CsA use in pregnancy and lactation, see below.

Consensus Conference Statements

— There is consensus on the following absolute contraindications:
- poorly controlled hypertension,
- severe infections,
- malignancies (ongoing disease or previous history; particular caution with haematological malignancies and dermatological malignancies, with the exception of basal cell carcinomas)

— There is consensus on the following relative contraindications:
- liver impairment,
- concomitant administration of drugs able to pharmacologically interact with CsA (see above),
- concomitant PUVA (also previous PUVA treatment at dose >1000 J/cm^2,
- pregnancy and lactation (for more details, see below),
- antihypertensive treatment with a combination regimen of two or more agents

Management of adverse effects

The concern about adverse effects of CsA has limited its use also in dermatology, although the doses used to treat skin diseases are largely beneath those

considered at risk. To reduce the risk of side effects whose dose-dependency is definitely proven,[5, 18, 20, 21] recommendations of current guidelines in terms of dosage and monitoring have to be strictly followed.[20-23]

The risk of gingival hyperplasia is generally controlled by an adequate hygiene or antiseptic therapy. More severe cases may be cured by a CsA dose reduction or azithromycin administration for 3-5 days.[20]

Major concerns are related to renal impairment, hypertension, and hyperlipidemia, which are the most relevant even if not the most common adverse effects associated to CsA treatment. They may represent the reason why dermatologists show a certain resistance to embrace CsA use in their clinical practices.[5]

Consensus Conference Statements

— Patients must be adequately informed about the possibility of adverse effects and instructed on their management, thus reducing their anxiety or distress and, indirectly, their negative perception

— Side effects are dose-dependent in terms of incidence and severity, related to the duration of the therapy and reversible on discontinuation

— In clinical practice, mild neurological/neuromuscular side effects are reported (probably underreported and/or underdiagnosed): peripheral paraesthesias, limbs burning sensation. They do not usually result in treatment discontinuation, since they tend to improve or disappear in the first week(s) of treatment. However, if they are severe and/or persistent, treatment discontinuation is suggested

— Fatigue and gastrointestinal side effects (nausea, diarrhoea, discomfort, pain) are rather common, particularly in female patients. Gastrointestinal effects may be controlled with administration after the meals

— Oral hygiene is likely to reduce the risk of gingival hyperplasia, actually becoming an uncommon adverse event. It has to be treated with azithromycin, 500 mg/day for 3-5 days

— Hypertrichosis is underreported by patients, with the exception of female and pediatric patients, and is reversible

— Serious adverse effects are reported with limited frequency, but need careful and appropriate management

Renal impairment

Renal dysfunction associated to CsA therapy may be functional or structural. Its occurrence and characteristics are largely dose-dependent, damage being more frequent and more likely to become structural with prolonged therapy (over 2 years) or doses (higher than 5 mg/kg/day which is considered the highest recommended dermatological dose, i.e. up to 8-8.5 mg/kg/day which were used in the past in transplant recipients).[5, 94-96]

Kidney impairment, based on either vascular or tubular alterations, may lead to a decrease in renal glomerular filtration rate (GFR) and in renal blood flow (as reflected by a decreased creatinine clearance) leading to hypomagnesaemia, decreased bicarbonate concentration, hyperuricemia, and hyperkalemia.[97]

At lower doses, as those administered with intermittent short-term therapy, nephrotoxicity causes functional changes and is reversible on drug withdrawal.[5, 95, 96]

Long-term and/or high dose CsA therapy is a risk factor for tubular interstitial fibrosis [95, 96, 98] which is mediated by an in increase in Transforming Growth Factor-beta (TGF-β) [99] and is facilitated by older age, concurrent hypertension or obesity.

Recommendations about prevention, monitoring and management of renal nephrotoxicity following the S3-European guidelines [20] and an international statement consensus [34] are reported in Figure 1. The best predictive factor of nephrotoxicity is the percentage of serum creatinine increase over baseline values.[96, 100]

Factors likely to increase the risk of nephrotoxicity (*e.g.*, advanced age, diabetes, nephrotoxic drugs, obesity) should also be evaluated, and medication charts should be carefully reviewed for potential drug interactions.

A difference is apparent between US and European guidelines with respect to the duration of continuous treatment to prevent chronic nephrotoxicity: a maximum of 1 year is recommended by the Ameri-

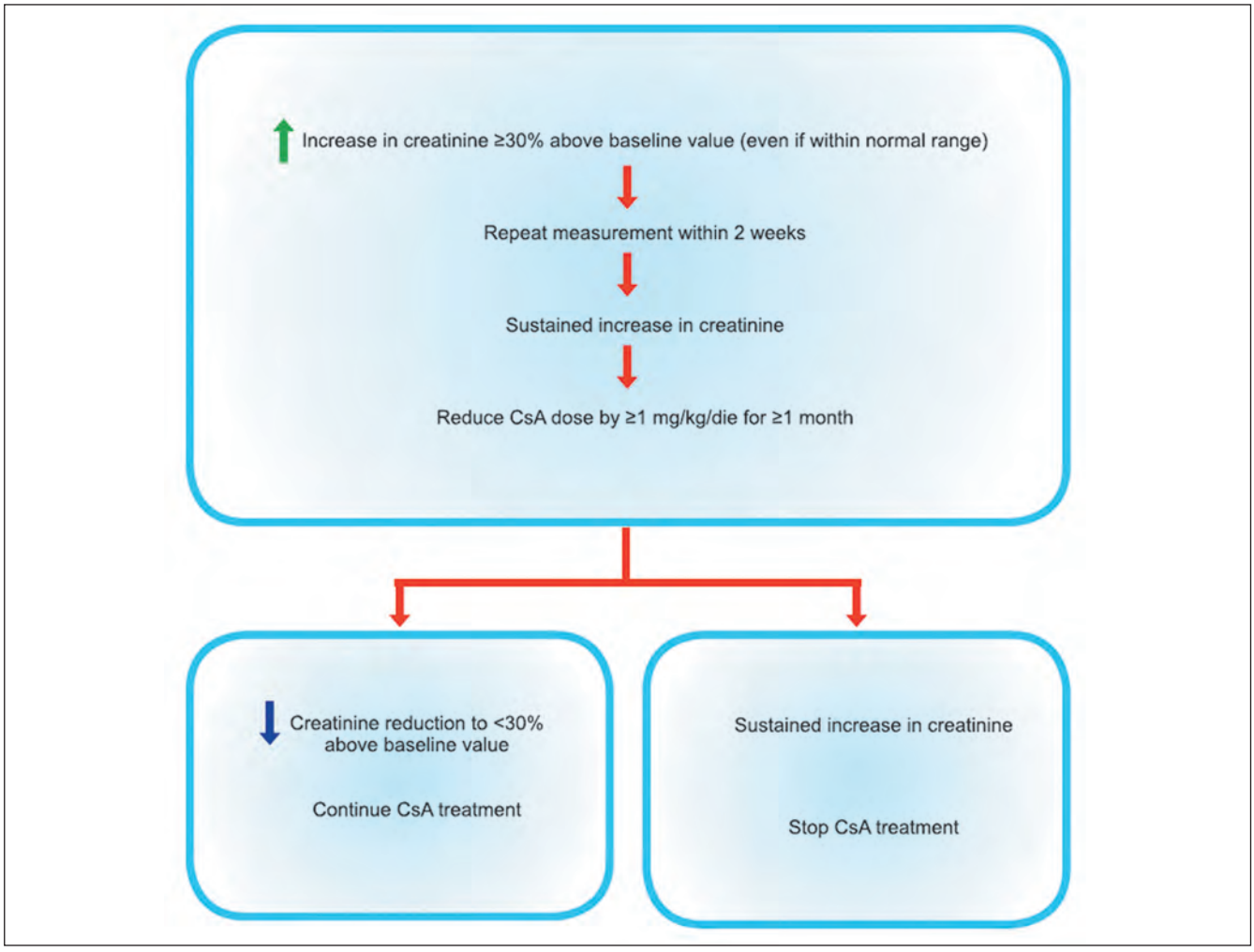

Figure 1.—Management of nephrotoxicity.[22]

can Academy of Dermatology, while the British Association of Dermatology and the European Association of Dermatology and Venereology recommend 2 years.[5, 18, 20-22, 96] These strict limitations are somewhat inconsistent with the long-term experience gathered with transplanted patients who have undergone lifelong treatment with CsA.

Consensus Conference Statements

— There is consensus on the flow chart proposed by the international guidelines (Figure 3).

— Serum creatinine and blood urea nitrogen are the laboratory tests of reference. Following this flow chart, *i.e.* decreasing the CsA dose by 25% if creatinine rises 30% over baseline and by 50% if the rise is ≥50%, the incidence of CsA nephrotoxicity is rather low and reversible. Estimated glomerular filtration rate (eGFR, to be estimated using Cockroft Gault) is not a routine laboratory measure and may be evaluated when serum creatinine is increased

— Among agents able to increase nephrotoxicity, aminoglycosides, amphotericin B, ciprofloxacin, vancomycin, lovastatin, cimetidine, acyclovir, and NSAIDs have to be mentioned

TABLE VII.—*Magnesium-rich foods.*[101]

Food	Mg (mg/hg)
Dried almonds	264
Dried beans	170
Dried nuts	160
Whole wheat flour	120
Spinach	60
Potatoes	38
Chicken breast	32

— The onset of hypomagnesaemia, which occurs earlier than that of hyperkalaemia, is a good even if poor predictor of renal impairment. Several conditions (*e.g.* administration of diuretics and aminoglycosides or alcohol consumption) are able to induce hypomagnesaemia, which favours nephrotoxicity. The daily recommended intake of magnesium is 400-420 mg. A list of magnesium rich foods is presented in Table VII

HYPERTENSION

The incidence of new-onset hypertension with CsA treatment ranges from 0% to 57%, being higher with a long-term treatment and lower with short-course therapies and reversible after dose reduction and/or withdrawal or with the use of antihypertensive drugs.[5, 20, 41, 61, 76] However, some studies show the lack of a clear relationship between CsA dose and frequency of hypertension occurrence,[5, 61, 100] thus suggesting a role for an individual variability in the sensitivity to CsA hypertensive effect.[5, 100] This hypothesis supports the use of antihypertensive drugs rather than a reduction of the dose to manage the onset of hypertension.[100]

The differences observed between patients with atopic dermatitis (lower incidence) and with psoriasis (higher incidence) may be explained by their younger age and the increased association of obesity, respectively.[5, 102, 103] A regular monitoring of blood pressure is crucial in patients with psoriasis, as they are known to be at increased risk of cardiovascular morbidity and mortality.[104]

A flow-chart reporting the recommendations from current guidelines about the management of hypertension

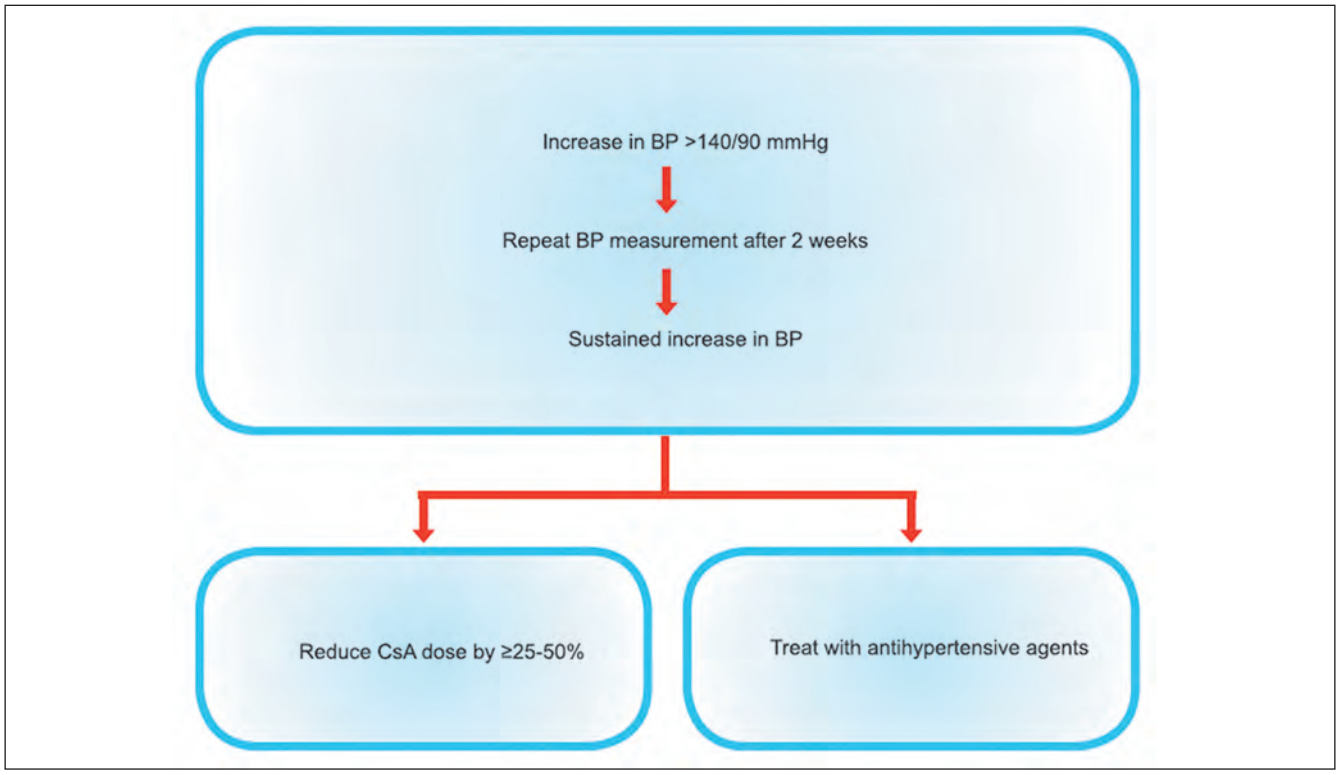

Figure 2.—Management of hypertension.[22, 61]

associated to CsA treatment is reported in Figure 2. The choice of the antihypertensive drug is of particular interest and somewhat controversial both in literature and in clinical practice. Calcium channel blockers are the first choice thanks to their vasodilating effect, conferring some protection against nephropathy, although nifedipine should be avoided because of an increased risk of gingival hyperplasia. The calcium channel blockers of the dihydropyridine class, *i.e.* isradipine and amlodipine represent a good choice, since they do not modify CsA levels and exert a vasodilating effect on the afferent arteriole, which confers protection against nephropathy.[104-106] Beta-blockers may also be used, taking into account the possibility of the disease worsening, while thiazide diuretics are contraindicated because of a potential increase in nephrotoxicity. Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics should be avoided as they may cause hyperkalemia and a decrease in GFR.[5, 22, 61]

The monitoring and control of hypertension, as well as of hyperlipidemia (see below) is crucial in patients with psoriasis because of their increased risk of cardiovascular morbidity and mortality.[103]

Consensus Conference Statements

— There is consensus on the flow chart proposed by the international guidelines,[20, 22] although a closer monitoring is considered more appropriate, particularly at the beginning of the treatment (daily monitoring during the first week or with blood pressure levels ≥140/90 mmHg)

— To manage hypertension, there is consensus on calcium channel blockers as the first choice (excluding nifedipine for the increased risk of gingival hyperplasia; preferring isradipine and amlodipine because they don't alter CsA levels). In clinical practice thiazide diuretics (even if contraindicated in renal impairment) are prescribed for short courses. Angiotensin-converting enzyme inhibitors (risk of hyperkalemia although associated to a protective vasodilating effect) and potassium-sparing diuretics (risk of hyperkalemia) are contraindicated

If blood pressure levels are under control with a previously defined antihypertensive schedule, there is controversy about the need of any therapeutical change. In particular, angiotensin-converting enzyme inhibitors are not absolutely contraindicated if already included in the schedule. Considering the broad range of positions on this clinical question, it is highly recommended to seek the advice of a specialist consultant for a decision on any individual case

Hyperlipidemia

Hyperlipidemia has to be carefully monitored and controlled with diet or medications (Figure 3).[20, 61] However, caution is needed with the co-administration of CsA and statins to detect myopathy (rhabdomyolysis) at an early stage. Cases of muscle toxicity have been reported with pravastatin, atorvastatin and lovastatin. Fluvastatin is the most studied and recommended lipid-lowering drug.[20, 61]

Consensus Conference Statements

— The absolute increase in lipid levels is moderate, generally higher in cholesterol levels than in triglycerides levels

— Dietary intervention is mandatory

— There is consensus about fluvastatin as first choice therapy, due to its peculiar mechanism of action, different to that of other statins.[107, 108] Moreover, pravastatin has a somewhat peculiar metabolism, being only partially catalyzed by cytochrome P-450 isoenzymes and, differently from other statins, competing less with CsA for uptake by hepatocytes [109]

Malignancy

An increased risk of malignancy after long-term CsA treatment has been described in patients who underwent organ transplantation.[111, 112] A large review, investigating the incidence of malignancy in patients treated with CsA for up to 5 years for severe psoriasis, showed that the incidence of extracutaneous malignancy was not higher than that reported in the general population.[112]

CsA enhances the induction of skin tumours by UVA exposure.[113]

Actually, the risk of cutaneous squamous cell carcinoma (SCC) increases with longer duration of therapy, only in patients with a previous history

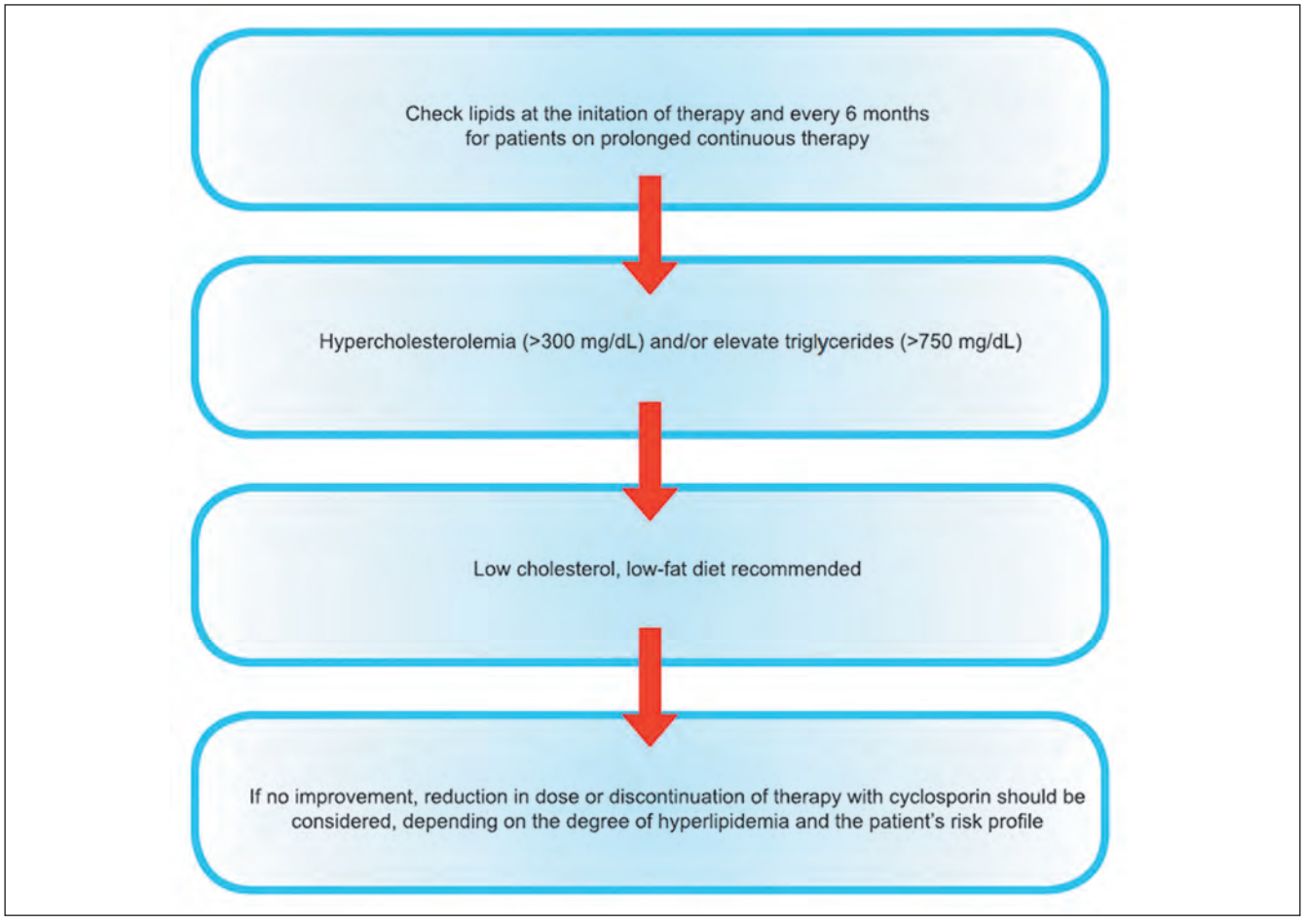

Figure 3.—Management of hyperlipidemia.[20, 61]

of PUVA or immunosuppressant agents.[112, 114-116] In fact, duration of exposure to CsA, psoralen and UVA, exposure to methotrexate, and to immunosuppressants has a significant impact on the incidence of non-melanoma skin cancers.[112]

As a consequences current guidelines suggest to avoid association of CsA and PUVA or immunosuppressants and/or to be cautious in case of an individual history of a high cumulative dose of PUVA or a previous history of SCC or melanoma.[20, 22, 23] Again, it has to be pointed out that this association is routinely prescribed in transplant recipients.

An increased risk of lymphoma has been shown in transplant recipients, while in patients with autoimmune dermatoses data are controversial and confined to isolated cases reports.[5] As far as solid tumours are concerned, comprehensive studies and single cases [117] failed to show an increase in their incidence in patients treated for psoriasis.[112, 115]

Infections

CsA administration may increase the general risk of bacterial, parasitic, viral, and fungal infections, as well as the risk of infection with opportunistic pathogens, but the actual incidence of infective complications when treating psoriasis is low.[5, 20, 117] Management of infection depends on appropriate and prompt antibiotic therapy (for the choice of drugs, see drug interactions). In case of herpes simplex infections, CsA therapy should be deferred until resolutions.[5, 20, 22]

Vaccinations given concomitantly with CsA may be less effective. Studies in patients with transplan-

tation taking CsA have shown inconsistent effectiveness of the influenza vaccine. Live vaccines are contraindicated and should be avoided.[20, 61]

Pregnancy and lactation

Because of the state of immunologic tolerance of pregnancy, several patients with autoimmune dermatoses report an improvement during gestation.

The need for contraception should be discussed with women of child-bearing age taking into account that CsA can reduce the efficacy of oral contraceptives.[20]

CsA has been classified in category C drug by the FDA Pregnancy Labeling Task Force [118] (studies on animals have shown an adverse effect on the foetus, and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). CsA passively crosses the placental blood barrier to achieve 10-50% of the maternal plasma concentration.[119] Its levels decrease with pregnancy due to the increased volume distribution and metabolism.[120] CsA is excreted in breast milk and its levels show a broad variability in terms of milk-to maternal serum concentration ratio, depending on the time of sampling and maternal dose.[121]

Most safety data on humans are derived from analyses of pregnancy outcomes in transplant recipients and suggest that there is no evidence of teratogenicity.[20, 61, 122, 123] A limited number of observations up to an age of approximately 7 years in children exposed to CsA in utero show preserved renal function and normal blood pressure levels.[10, 11]

Among the oral medications approved for psoriasis, CsA is considered the safest and it has been suggested as the best choice for pregnant women.[61] A certain number of cases of prematurity and/or developmental delay is reported in children born to mothers with solid-organ transplantations.[5] Pregnant women receiving immunosuppressive therapies after transplantation, including CsA or CsA containing regimens, are at risk of premature delivery (<37 weeks).[10, 11]

Breastfeeding is contraindicated in mothers taking CsA, mainly because of concerns about immunosuppression in the neonate.[20-22, 36, 124] There is evidence, even from small studies, of no adverse events associated to breastfeeding during CsA treatment.[121, 125, 126]

Consensus Conference Statements

— When starting CsA, a baseline pregnancy test is not mandatory

— CsA is contraindicated during pregnancy Drug discontinuation is recommended when planning an intended gestation or when an unplanned gestation is ascertained

— Clinical experience demonstrates a good safety profile for CsA:[5]

- cases of administration in neonatal or pediatric age without the evidence of adverse events
- approximately 700 pregnancies without negative adverse events in women who previously underwent organ transplantation [123, 127]
- there is no evidence of adverse events in pregnant women who did not discontinue CsA treatment during pregnancy
- there is no evidence of teratogenicity

— Since no teratogenicity has been proven, CsA is of choice when a systemic drug is needed

— Cases of premature delivery have been reported

— CsA safety profile is better than that of alternative agents (*e.g.* etretinate administration has to be avoided for 2 years prior the conception)

— At present there are no adequate and well controlled studies in pregnant women and, therefore, CsA should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus

Therapeutic abortion is not an absolute indication in case of exposure to CsA of a pregnant patient. The choice has to be made on the basis of an acceptable risk-to-benefit balance, providing the patient with the opportunity to make an informed decision and taking into account her individual needs and preferences

Pediatric use

Children are less susceptible to CsA toxicity because of a reduction in drug bioavailability and a lower predisposition to nephrotoxicity.[5] CsA has been used at high doses in pediatric transplant recipients and in children with atopic dermatitis or psoriasis with no serious adverse effects.[5, 40, 81, 128, 129] Theoretically, pedi-

atric patients better tolerate higher CsA doses, due to a different pharmakocinetics with clearance rates up to four times those of adults, this meaning lower blood concentrations for the same dose.[130-132]

Consensus Conference Statements

— CsA has been used starting from the first year of life and cases of high dose treatment in pediatric patients who underwent organ transplantation are described. However, caution is needed, when changes in standard schedules or guidelines are adopted

— CsA management in pediatric patients (usually to treat atopic dermatitis) needs specific considerations and caution, even if better tolerance is proven

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