Ciclosporin

Instructions for use [1,2]

Table 1: Instructions for use (Ciclosporin)

Pre-treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- History and clinical examination should focus on previous and concomitant diseases (e. g., arterial hypertension; severe infections; malignancies, including cutaneous malignancies; renal and liver diseases) and concomitant medication (see drug interactions)
- Measurement of the blood pressure on two separate occasions
- Laboratory parameters (see **Table 2**)
- Reliable contraception (caution: reduced efficacy of progesterone-containing contraceptives)
- Regular gynaecologic screening according to national guidelines
- Consultation on vaccination; susceptibility to infections (take infections seriously, seek medical attention promptly); drug interactions (inform other treating physicians about therapy); avoidance of excessive sun exposure; use of sunscreens

During treatment

During therapy with low dose ciclosporin (CsA; 2.5 to 3 mg/kg daily), follow-up intervals may be extended to two months or more. Shorter intervals may be needed in patients with risk factors, after dose increases, or those who must take concomitant medications that are likely to contribute to adverse drug reactions.. Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)

- HRQoL (such as DLQI/Skindex-29 or -17)
- Clinical examination should focus on status of skin and mucous membranes (hypertrichosis, gingival changes), signs of infections, gastrointestinal or neurological symptoms (tremor, dysaesthesia), musculoskeletal/joint pain

- Repeat recommendation for sun avoidance and sun protection
- Check of concomitant medication
- Measurement of blood pressure
- Laboratory parameters (see **Table 2**)
- Reliable contraception
- Regular gynaecologic screening according to national guidelines
- If creatinine is significantly elevated and/or patient on therapy for > one year, perform creatinine clearance (or creatinine-EDTA clearance where available).
- Determination of the CsA level is recommended in selected cases

Post-treatment

- After discontinuation of CsA, patients should be followed up for skin cancer, especially in case of extensive prior therapeutic or natural UV exposure.

[1] due to personal-financial conflict of interest 3 abstentions

Recommendations for lab controls [1-3]

Table 2: Recommended laboratory controls (Ciclosporin)

	Period in weeks				
Diagnostics	**Pre-treatment**	**4**	**8**	**12**	**16, thereafter every 4-8 weeks**
Full blood count*	x	x	x	x	x
Liver enzymes**	x	x	x	x	x
Sodium, potassium	x	x	x	x	x
Serum creatinine	x	x	x	x	x
Urine status	x	x			x
Uric acid	x	x	x	x	x
Pregnancy test (urine or blood)***	x				

Cholesterol, triglycerides	x****		x		x
Magnesium*****	x		x		x
HBV	x				
HIV	x				

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.

* Erythrocytes, leucocytes, platelets

** Transaminases (AST, ALT), AP, γGT, bilirubin

*** Pregnancy test is recommended as it is important to know if a patient is pregnant when starting a systemic treatment. Ciclosporin is the suggested conventional treatment option, for women who are wanting to conceive or who are pregnant.

**** Recommended two weeks before and on the day of treatment initiation (fasting)

***** Only with indication (muscle cramps)

The recommendations are based on clinical experience. No evidence is available.

Adverse drug reactions [4]

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The rate of adverse effects generally demonstrated a clear dose and duration dependency. In case of short-term treatment, the adverse effects are generally reversible after drug withdrawal. In case of long-term treatment (i. e. up to two years), kidney abnormalities may be irreversible.

Kidney abnormalities

The most frequent and clinically relevant reported adverse effects include increment of serum creatinine, urea nitrogen and uric acid due to a reduced glomerular filtration rate and consequently creatinine clearance. Arterial hypertension could be also reported because of vasoconstriction of renal arteries. In case of long term cyclosporin treatment the most clinically relevant adverse effect is the impairment of renal function. In particular, kidney abnormalities follow a pattern of increasing severity from elevation of serum creatinine, reduction of the glomerular filtration rate to structural damage such as interstitial fibrosis, tubular atrophy and glomerular sclerosis.

Malignancies

As with other immunosuppressive therapies, CsA carries an increased risk of developing lymphoproliferative disorders and other malignant tumours, especially of the skin. The incidence of malignancies appears to be dependent primarily on the degree and duration of immunosuppression and on other preceding or concomitant therapies, such as photochemotherapy or MTX. Patients must

be monitored carefully following long-term therapy with CsA. An increased risk of skin cancer, especially squamous cell carcinomas, has been observed in patients with psoriasis who have received long-term photochemotherapy (high cumulative doses of PUVA, > 1000 J/cm²). Moreover, nodal or cutaneous B- and T-cell lymphomas and HPV-associated carcinoma have been reported in psoriasis patients treated with CsA.

Infections

As with other immunosuppressive therapies, CsA may increase the risk of various bacterial, parasitic, viral and fungal infections, as well as the risk of infections with opportunistic pathogens. Although CsA has some inhibitory effects on HCV replication, it should be considered with caution in patients with HCV, HBV as well as HPV infection. Infections deserve special attention as possible trigger factors for psoriasis relapse. Patients in whom an infection-triggered exacerbation of psoriasis is probable should first be treated with appropriate therapy for the infection, followed by a re-examination of the indication for CsA.

Others

Gingival hyperplasia and hypertrichosis are described in less than 15% of patients. Paresthesias, more commonly as burning sensations in the hands and/or feet, tremors and muscle cramps likely related to decreased serum Mg. CsA should be used with more caution in obese elderly persons because the risk of developing renal failure increases with age and obesity.

Special consideration during treatment [5]

Surgery

Consider discontinuing CsA for one week prior to elective surgery.

Measuring CsA blood levels

When treating patients with psoriasis, it is generally not necessary to measure CsA blood levels. An assay may be performed to obtain information about drug intake (in case of a discrepancy between [higher] doses and clinical response or discrepancy between [lower] doses and occurrence of ADR) or with the simultaneous intake of drugs that might influence CsA levels. In case drug levels are measured, C2 (post two hours) monitoring is the best predictor of exposure to CsA.

Measuring glomerular filtration rate

A periodic measurement of GFR is the most accurate method to assess renal tolerance under long-term or repeated treatments.

Duration of treatment

Most physicians consider CsA suitable as a short term induction therapy only. Due to its possible adverse drug reactions during long term use and in light of many other treatment options, long term treatment for psoriasis of more than two years is usually avoided.

Important contraindications [6]

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects. The absolute contraindications include the following:

- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease
- History of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma in situ)
- Current malignancy
- Simultaneous PUVA therapy or extensive previous UV exposure with high risk of cutaneous malignancy
- Severe hepatic diseases (e.g. liver failure)
- Breastfeeding

Drug interactions [7,8]

Please see SmPC and other sources for complete listing. There is the potential for multiple drug reactions, compared to other anti-psoriatic systemic agents. The guideline subcommittee decided to comment on the following aspects.

The availability of CsA depends primarily on the activity of two molecules – the hepatic enzyme cytochrome P450-3A4 (CYP3A4), which is involved in its metabolism, and the intestinal P-glycoprotein, an ATP-dependent transporter protein that transports various drugs, among them CsA, from the enterocytes back into the intestinal lumen. The activities of these molecules may both vary for genetic

reasons and be influenced by drugs and herbal substances. Above all, modulators and substrates of CYP3A4 are relevant for therapeutic practice.

Ciclosporin levels are increased by (CYP3A inhibition)

Calcium antagonists, amiodarone, macrolide antibiotics, aminoglycoside antibiotics, tetracyclines, quinolones, imidazoles antimycotics, oral contraceptives, androgenic steroids, danazol, allopurinol, bromocriptine, methylprednisolone (high doses), ranitidine, cimetidine, metoclopramide, propafenone, protease inhibitors (e. g., saquinavir), acetazolamide, amikacin, statins (above all atorvastin and simvastatin because of increased risk of myopathies), cholic acids and derivatives (ursodeoxycholic acids), grapefruit juice.

Ciclosporin levels are decreased by (CYP3A induction)

Carbamazepine, phenytoin, barbiturates, metamizole, rifampicin, octreotide, ticlopidine, nafcillin, probucol, troglitazone, intravenously administered sulfadimidine and trimethoprim, St John's wort.

Other interactions

- Aminoglycosides, amphotericin B, trimethoprim and sulfamethoxazole, vancomycin, ciprofloxacin, aciclovir, melphalan, NSAIDs possibly reinforce nephrotoxic effects.
- Increased risk of a gingival hyperplasia with the simultaneous intake of nifedipine.
- Increased immunosuppression risk with simultaneous treatment with other immunosuppressive agents.
- CsA may reduce the effect of progesterone-containing contraceptives.
- During CsA therapy, an increased plasma level of some drugs including digoxin, colchicine, corticosteroids, statins and NSAIDs could occur as a result of reduced clearance.

Overdose/measures in case of overdose

Determine CsA blood level, interrupt CsA, determine vital parameters, liver, renal values, electrolytes and if needed, introduce additional measures (including consultation with other specialists).

References

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