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Cyclosporine

Siklosporin

Nahide Onsun

Bezmialem Vakıf University Faculty of Medicine, Department of Dermatology and Venereology, İstanbul, Turkey

Abstract

Cyclosporine is an immunosuppressive agent used in the treatment of psoriasis. It shows its action through calcineurin inhibition and T-lymphocytes. With its rapid effect, it can be used as an induction therapy in plaque, pustular and erythrodermic psoriasis. Its most common side effects are elevated serum creatinin values and arterial hypertension. In long-term treatment not to exceed 2 years, it may be used under nephrology control.
Keywords: Cyclosporine, psoriasis, treatment

Öz

Siklosporin psoriasis tedavisinde kullanılan ve etkisini kalsinörin inhibisyonu ile T-lenfositleri üzerinden gösteren immünosüpresif bir ajandır. Süratli etki ile plak, püstüler ve eritrodermik psoriasiste indüksiyon tedavisi olarak kullanılabilir. En iyi bilinen yan etkileri serum kreatinin düzeylerinde yükselme ve arteriyel hipertansiyondur. Uzun süreli tedavide 2 yılı geçmemek üzere nefroloji kontrolü ile kullanılabilir.
Anahtar Kelimeler: Siklosporin, psoriasis, tedavi

General information and mechanism of action

Cyclosporine is a calcineurin inhibitor in the form of 11-amino acid cyclic polypeptide.

As an immunosuppressing agent, it inhibits the transcription of interleukin-2 and other cytokines formed by "T-helper" lymphocytes.

Since it can also inhibit T-cell mediated B-cell responses, it suppresses both cellular and humoral immunity. It is metabolised by the cytochrome p450 system.

Its half-life is 6-24 hours (may vary from person to person).

Since it is a lipophilic molecule, its microemulsion forms are better absorbed, increasing bioavailability[1].

Indications and dosage

It can be used as an induction therapy in plaque, pustular and erythrodermic psoriasis where rapid effect and cleansing is desired.

A long-term therapy not to exceed 2 years may be administered to selected patients under nephrology control.

It can be started with an initial dose of 2.5 mg/kg and continued for 4 weeks; at the end of this period, the dose may be increased up to a maximum of 5 mg/kg if necessary.

A long-term therapy may involve intermittent therapies, each lasting 8-16 weeks.

The dose in such intermittent therapies will be reduced by 0.5 mg/kg in 14-day intervals.

Address for Correspondence/Yazışma Adresi: Nahide Onsun MD, Bezmialem Vakıf University Faculty of Medicine, Department of Dermatology and Venereology, İstanbul, Turkey
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ORCID: orcid.org/0000-0001-6259-0219

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Maintenance dose in long-term continuous treatment: After 12 weeks, the dose will be decreased by 50 mg in 4-week intervals; if there is recurrence, 50 mg will be added[2,3].

Treatment and rules

An objective severity assessment with PASI, BSA and PGA should be carried out before the treatment. An assessment of the quality of life index will be made. Current arthritis, comorbidities, infections and malignancies will be evaluated. Drugs being used will be questioned especially in terms of interactions. Blood pressure will be measured at two different times. Necessary laboratory tests will be performed (Table 1).

Objective severity and quality of life index will be evaluated during the treatment. Clinical examinations will be repeated. The skin and mucosae will be examined for gingival hyperplasia, hypertrichosis and skin cancers. Tremor and dysesthesia will be questioned in neurological terms. An evaluation of joint involvement will be done. Drugs being taken will be checked. A gynaecological examination will be performed if needed. Laboratory values will be checked at regular intervals (Table 1). If the serum creatinin value is high or cyclosporine is being taken for more than a year, the creatinin clearance should be checked.

Table 1. Laboratory tests before and during treatment

Tests	Weeks in which testing will be ordered					
	Pre-treatment	2	4	8	12	16
Whole blood count	x	x	x	x	x	x
Liver enzymes[+]	x	x	x	x	x	x
Electrolytes[++]	x	x	x	x	x	x
Serum creatinin	x	x	x	x	x	x
Urine test	x		x			x
Uric acid	x		x	x	x	x
Pregnancy test	x					
Cholesterol, triglyceride	x					
Magnesium[+++]	x		x		x	
HBA/HBV	x					
HIV	x					

[+]: ALT, AST, billuribin, [++]: Sodium, potassium, [+++]: If there is cramping. Other tests may be required depending on the individual characteristics of the patient

Post-treatment

If patients have received phototherapy before or after the discontinuation of the treatment, they must be screened in regular intervals for skin cancers.

Side effects

The most common side effects are elevated serum creatinin values and arterial hypertension.

There may be an increase in serum triglyceride and cholesterol[4].

Side effects are usually associated with the dose; therefore, the lowest effective dose and shortest possible treatment time are recommended.

Contraindications

Cyclosporine is contraindicated in:
Kidney failure,
Uncontrollable arterial hypertension,
Malignancies,
Immunodeficiency,
Uncontrollable infections,
Having received PUVA therapy too long,
Cutaneous T-cell lymphoma, and
Cyclosporine-sensitive patients.

Drug Iinteractions

Erythromycin: Cyclosporine may increase its toxicity.

Grapefruit juice inhibits the metabolism of cyclosporine.

Alcohol may increase cyclosporine levels.

Aminoglycosides, ciprofloxacin, clotrimazole and fibrates increase its nephrotoxicity risk.

Non-steroid anti-inflammatory drugs: Increase the toxic effects of cyclosporine on kidney functions.

If used with **potassium sparing diuretics**, risk of hyperkalaemia develops.

May restrict metabolism of drugs such as **methotrexate, prednisolone, digoxin, repaglinide and simvastatin**, causing their plasma levels to increase.

Cyclosporine is generally not recommended to be used in combination with other agents used for the treatment of psoriasis. Suggestions for combination with cyclosporine are summarized in Table 2 below.

Table 2. Suggestions for combination

Acitretin	Not recommended	Strong agreement[*]	Cytochrome p450 inactivation competition with cyclosporine
Adalimumab	Not recommended	Agreement[**]	Increased immunosuppression
Etanercept	Not recommended	Agreement[**]	Increased immunosuppression
Infliximab	Not recommended	Agreement[**]	Increased immunosuppression
Ustekinumab	Not recommended	Agreement[**]	Increased immunosuppression + increased toxic effect (in a few cases)
Methotrexate	Not recommended	Poor Agreement[***]	Increased immunosuppression
Fumaric acid	-	Agreement[**]	No evidence-based data

[*]Agreement level >90%, [**]Agreement level 75-89%, [***]Agreement level 50-74%

Use in pregnancy

Cyclosporine is not a major teratogen agent and seems to be a safe alternative to be used during pregnancy in patients with resistant psoriasis[5]. Its pregnancy category is C.

Results of psoriasis patients registered in the Neoral Pregnancy Registry (NPR)[6]
Number of patients: 11
Abortion for treatment purposes: 0
Spontaneous abortions: 0
Ectopic pregnancy: 1
Stillbirth: 0
Live birth: 10
Mean gestetion time (weeks): 40±0.8
Number of premature births: 0
Mean birthweight: 3.51±518
Low birthweight: 0

Paediatric use

There is less information and data on the efficacy and safety of cyclosporine in children and adolescents than in adults. The dose recommended for children is 2-3.5 mg/kg/day, which can be given in divided doses[7]. The dose may be lowered after obtaining clinical response[8]. According to the consensus in Germany, cyclosporine should be used in children who experience severe attacks and who do not respond to other options. Cyclosporine has also been found effective in childhood generalized pustular psoriasis[9].

During the pandemic

Due to its antiviral effect on RNA viruses including the beta coronavirus family, cyclosporine has been shown as a first option in the treatment of COVID-19 pneumonia by some researchers[10].
Psoriasis patients in Italy who continued to take cyclosporine during the pandemic and who contracted COVID-19 were reported to have recovered without needing to be hospitalized[11].

EVIDENCE-BASED TREATMENT SUGGESTIONS

- It is an effective agent in moderate to severe psoriasis cases.
- It can be used in doses between 2.5 and 5 mg/kg/day.
- Its most common side effect is renal toxicity and hypertension.
- It should not be used in older patients with obesity, hypertension or renal failure.
- It should not be used in combination with ACE inhibitors and thiazide group of diuretics.
- It must never be used together with phototherapy and should be avoided during summer months.
- It should be used for situations that require rapid effect.
- Patients should be monitored carefully for infections and malignancy.
- Intermittent treatment is safer than continuous use.
- Continuous use should not exceed two years.

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