Cyclosporine

Dr. Rajiv Sukumaran DO MS FRCS, Dr. Jayasree Rajiv DO

Cyclosporine, cyclosporin or cyclosporine, is an immunosuppressant drug widely used in post-allogeneic organ transplant, to reduce the activity of the patient’s immune system and hence the risk of organ rejection. It has been studied in transplants of skin, heart, kidney, lung, pancreas, bone marrow and small intestine. Cyclosporine is a cyclic nonribosomal peptide of 11 amino acids (an undecapeptide) produced by the fungus Tolypocladium Inflatum Gams, initially isolated from a Norwegian soil sample.

Indications

The immuno-suppressive effect of Cyclosporin was discovered on January 31, 1972, by employees of Sandoz (now Novartis) in Basel, Switzerland, in a screening test on immune-suppression designed and implemented by Hartmann F. Stähelin. Cyclosporin was subsequently approved for use in 1983.

Apart from the use as a transplant medicine, Cyclosporin is also used in psoriasis and infrequently in rheumatoid arthritis and related diseases, although it is only used in severe cases. It has been investigated for use in many other autoimmune disorders. Cyclosporin has also been used to help treat patients with ulcerative colitis who do not respond to treatment with steroids. [2] This drug is also used as a treatment of posterior or intermediate uveitis with non-infective etiology.

Cyclosporine A has been investigated as a possible neuroprotective agent in conditions such as traumatic brain injury, and has been shown in animal experiments to reduce brain damage associated with injury. Cyclosporine A blocks the formation of the mitochondrial permeability transition pore, which has been found to cause much of the damage associated with head injury and neurodegenerative diseases.

Mode of action

Cyclosporine (cyclosporin A, CsA) has potent immunosuppressive properties, reflecting its ability to block the transcription of cytokine genes in activated T cells. It is well established that CsA through formation of a complex with cyclophilin inhibits the phosphatase activity of calcineurin, which regulates nuclear translocation and subsequent activation of NFAT transcription factors. In addition to the calcineurin/NFAT pathway, recent studies indicate that CsA also blocks the activation of JNK and p38 signaling pathways triggered by antigen recognition, making CsA a highly specific inhibitor of T cell activation. Here we discuss the action of CsA on JNK and p38 activation pathways. We also argue the potential of CsA and its natural counterparts as pharmacological probes. It has also an effect on mitochondria. Cyclosporine A prevents the mitochondrial PT pore from opening, thus inhibiting cytochrome c release, a potent apoptotic stimulation factor. However, this is not the primary mode of action for clinical use but rather an important effect for research on apoptosis.

Adverse effects and interactions

Treatment may be associated with a number of potentially serious adverse drug reactions (ADRs) and adverse drug interactions. Cyclosporine interacts with a wide variety of other drugs and other substances including grapefruit juice, although there have been
studies into the use of grapefruit juice to increase the blood level of cyclosporine.

Adverse drug reactions can include gum hyperplasia, convulsions, peptic ulcers, pancreatitis, fever, vomiting, diarrhea, confusion, breathing difficulties, numbness and tingling, pruritus, high blood pressure, potassium retention and possibly hyperkalemia, kidney and liver dysfunction (nephrotoxicity and hepatotoxicity), and obviously an increased vulnerability to opportunistic fungal and viral infections.

**Formulations**

Cyclosporine is available in 25 mg and 100 mg tablets. Atopica® formulation is available in 10, 25, 50 and 100 mg sizes. It is also available in an injectable form. There is an ophthalmic preparation that is available for specific treatment of the eye. The drug is marketed by Novartis under the brand names Sandimmune, the original formulation, and Neoral for the newer microemulsion formulation. Generic Cyclosporin preparations have been marketed under various trade names including Cicloral (Sandoz/Hexal) and Gengraf (Abbott). Since 2002 a topical emulsion of Cyclosporin for treating keratoconjunctivitis sicca has been marketed under the trade name Restasis. Annual sales of Cyclosporin are around $1 billion.

**Cyclosporin and Eye**

Dry-eye syndrome (keratoconjunctivitis sicca) is an extremely common and painful condition, affecting more than 1 million people in the U.S., especially older adults, post-menopausal women, and those with Sjogren's Syndrome, rheumatoid arthritis, lupus, Parkinson's and other chronic diseases. Characterized by insufficient tear production, the syndrome eventually may lead to vision loss.

Cyclosporin applied topically as 0.05% drops showed increased tear production and less need for artificial tears. Unlike artificial tears, which temporarily replenish eye moisture, it helps treat the cause of dry-eye syndrome: reduced tear production due to inflammation. Treatment of dry eye syndrome with topical cyclosporine significantly reduced the numbers of activated lymphocytes within the conjunctiva. Significant reductions were observed with respect to the percentages of CD4+ and CD23+ cells in the conjunctival impression cytology specimens and clinical and symptom scores following treatment with topical Cyclosporine A, while no change occurred in the

\[ \text{[R-[[R^*,R^*(E)]]-cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-\alpha-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]} \]
percentages of CD8+ and CD45RA+ cells. Topical cyclosporine A treatment is a very effective alternative in severe VKC cases. Clinical efficacy of topical cyclosporine A treatment in severe, resistant VKC cases can be (at least partly) related to reduction of the CD23+ and CD4+ cell populations on the conjunctival surface.

Exposure to cyclosporine A directly modified fibroblast behavior. Cyclosporin A reduced PIP and interleukin 1 (IL-1) production in a dose-dependent manner. Interleukin 6 and IL-8 were increased by 10 µg/mL of CsA, whereas transforming growth factor, PIIP, and total protein were unaffected. Cyclosporin A exposure induced apoptosis is time and dose-dependent.

Other uses in the eye

Intermediate and posterior noninfectious uveitis, stromal keratitis induced by herpes simplex virus (HSV) are treated with cyclosporine A eyedrops and acyclovir ointment.

Serpiginous choroiditis

Bilateral inflammatory serpiginous choroiditis have been treated with Cyclosporine-A. Its usefulness seems to be greater when the serpiginous choroiditis is in its acute stage; chronic stages, however, also seem to improve with treatment to a lesser degree. Its main indication is when there is involvement of the macular region of the second eye, when the first eye is already damaged. We consider Cyclosporine-A, in these situations, to be a first choice treatment.

Cyclosporin Implant to treat uveitis is under trial. Other uses are in Corneal grafts, Mooren’s Ulcer, non-healing ulcers etc.

References


6. Rosenthal RA, Schlech BA, Buck SL. Preservative efficacy of a new lubricant eye drop without traditional preservatives. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); April 30-May 4, 2006; Fort Lauderdale, FL.


8. Christensen MT, Meadows DL, Tudor MR, Stone RP. A report from clinical evaluations of a new liquid gel concept artificial tear. Poster presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); April 30-May 4, 2006; Fort Lauderdale, FL.


