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REVIEW

Oral voclosporin: novel calcineurin inhibitor for treatment of noninfectious uveitis

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Abstract: Voclosporin, a novel immunomodulatory drug inhibiting the calcineurin enzyme, was developed to prevent organ graft rejection and to treat autoimmune diseases. The chemical structure of voclosporin is similar to that of cyclosporine A, with a difference in one amino acid, leading to superior calcineurin inhibition and less variability in plasma concentration. Compared with placebo, voclosporin may significantly reduce inflammation and prevent recurrences of inflammation in patients with noninfectious uveitis. Future studies have to show if these advantages are accompanied by greater clinical efficacy and fewer side effects compared with the classic calcineurin inhibitors.

Keywords: uveitis, immunosuppression, voclosporin

Introduction

Noninfectious uveitis is often chronic and relapsing, and typically affects people aged 20–60 years, ie, the working population. Nevertheless, children and older people can also be affected, albeit less frequently, and may have different underlying diseases.[1–3] Visual impairment occurs in many patients with uveitis, but blindness is a relatively rare complication in recent decades due to more potent drugs and more aggressive treatment strategies. Worldwide, uveitis is one of the five most important reasons for visual loss and accounts for 10% of cases of blindness due to secondary complications, eg, macular edema.[1,4,5]

Patients with uveitis reported markedly reduced general and vision-related quality of life compared with normal subjects.[6] The vision-related quality of life in patients with noninfectious uveitis is even worse compared with patients with infectious uveitis, and this is attributed to the often chronic relapsing course of the noninfectious disease.[7] Furthermore, general quality of life in patients with uveitis on chronic systemic immunosuppressive treatment has been shown to be reduced, being related to visual acuity and disease duration.[8] Therefore, treatment of uveitis with immunomodulatory agents has to be not only effective but also well tolerated by patients in terms of safety and quality of life.

Noninfectious uveitis may be limited to the eye itself (idiopathic uveitis) or be associated with a systemic autoimmune disease. The pathogenesis of noninfectious uveitis is thought to be due to a disruption of ocular immunotolerance. The blood retinal barrier and blood aqueous barrier are anatomical barriers that protect the eye from otherwise harmful immune reactions. Furthermore, the aqueous fluid and vitreous contain immunosuppressive cytokines (eg, transforming growth factor beta, vasoactive

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intestinal polpeptide, alpha-melanocyte-stimulating hormone, and calcitonin-releasing protein) regulating the activity of leukocytes.[9,10] If ocular immune privilege is broken, the uvea and adjacent tissue are infiltrated and damaged by inflammatory cells. Bacterial and viral antigens may trigger immune reactions, as well as the body's own antigens, mediated by trauma or inflammation.[11,12] Uveitis is an autoimmune disease primarily mediated by CD4-positive T helper cells.[13] These T cells produce a number of proinflammatory cytokines, such as interferon gamma and several types of interleukins. These cytokines spread inflammation to further immune cells.

Corticosteroids are usually the first-line treatment in autoimmune uveitis. Application (topical, periorbital, intravitreal injection, oral formulations) and dosing depend on the anatomical type of uveitis according to the Standardization of Uveitis Nomenclature classification and severity of inflammation.[14] If inflammation is restricted to the anterior eye chamber, corticosteroid eyedrops are initiated. Systemic corticosteroids are administered for inflammation of the posterior eye segment including the vitreous. If inflammation is severe, the initial dosage is usually 1 mg/kg body weight, decreasing by 10 mg weekly. Low-dose corticosteroids at a dosage around 0.1 mg/kg body weight are often given as maintenance therapy to prevent further flares. Second-line immunosuppressive therapy is administered if inflammation requires high corticosteroid dosages over the long term or if low-dose treatment is accompanied by adverse effects. Antimetabolites (azathioprine, methotrexate) and T cell inhibitors (cyclosporine, mycophenolic acid) are the most commonly used corticosteroid-sparing drugs in noninfectious uveitis. Azathioprine is a prodrug that is metabolized into 6-mercaptopurine, which acts as a purine synthesis inhibitor, inhibiting DNA synthesis and consequently proliferation of cells. Azathioprine is usually administered at a dosage of 2 mg/kg daily. Azathioprine is moderately effective as a single corticosteroid-sparing immunosuppressive agent in terms of controlling inflammation and having corticosteroid-sparing benefits, but requires several months to achieve treatment goals.[15] Methotrexate inhibits tetrahydrofolate synthesis by inhibiting the enzyme dihydrofolate reductase. Folic acid is important for the synthesis of DNA, RNA, and proteins. Methotrexate reduces B and T cell proliferation, and is commonly used at a dosage of 15–25 mg weekly in adult patients with uveitis. Methotrexate is also effective for intraocular lymphoma when given directly into the eye.[16] Cyclosporine A binds to cyclophilin, thereby inhibiting calcineurin. Calcineurin dephosphorylates the nuclear factor of activated T cells, which is responsible for the transcription of interleukin-2. Cyclosporine A thus leads to reduced functioning of T cells. Cyclosporine A at a dosage of 151–250 mg/day is modestly effective for controlling intraocular inflammation.[17] Mycophenolic acid inhibits inosine monophosphate dehydrogenase, which is important for purine synthesis. Mycophenolic acid reduces proliferation of B and T lymphocytes. At the preferred dosage of 720 mg twice daily, mycophenolic acid is effective and well tolerated.[18] A similar drug, mycophenolate mofetil, has proven to be effective in managing ocular inflammation in approximately half of patients treated.[19]

Nowadays, biologic agents, such as tumor necrosis factor alpha inhibitors (adalimumab, infliximab) have demonstrated good efficacy in otherwise treatment-refractory uveitis.[20] However, high treatment costs and the lack of randomized controlled trials limit their use to selected cases.

Chemical and pharmacologic data

Voclosporin (Lux Biosciences Inc, Jersey City, NJ) was developed by Isotechnika Pharma Inc, Edmonton, AB, Canada, for the treatment of autoimmune diseases and prevention of allograft rejection. The molecular structure is very similar to that of cyclosporine A, with the exception of a functional group in an amino acid.[21] The molecular structure is already shown elsewhere.[22–24] Voclosporin is a calcineurin inhibitor leading to inhibition of activation of T cells and a decrease of proinflammatory cytokine (interleukin-2, interleukin-4, interferon gamma) production. Voclosporin consists of two isomers, ie, a trans and a cis isomer. These two isomers differ in the orientation of one modified functional group. While early clinical and nonclinical studies were performed using a virtually equal mixture of both isomers, ie, ISA247, nowadays the clinical studies use the more potent trans isomer, ie, LX211.[25,26] The blood concentrations of voclosporin may be quantified by mass spectrometry.[27] ISA-247/LX-211 demonstrated good absorption after oral administration in rabbits, cats, and dogs. The half-life is 6.0–8.8 hours and systemic exposure is dose-related.[32] Time to peak concentration is 1.5–2.0 hours after oral administration. ISA-247/LX-211 undergoes extensive first-pass metabolism, involving the cytochrome P450 enzyme. Fecal excretion is the primary route of elimination.[24]

ISA247 leads to comparable or even higher inhibition of lymphocyte proliferation, T cell activation, and cytokine production than that achieved by cyclosporine A in nonhuman primates. Allografts in monkeys treated with ISA247 survive longer than those treated with cyclosporine A.[28,29] This superior immunosuppressive potency of ISA247 compared

Table 1 Safety data from clinical trials of voclosporin for plaque psoriasis

Bissonnette et al[33]	Most frequently reported adverse events: nausea, headache, abnormal chemistry changes
	0.5 mg/kg/day group showed a similar percentage of side effects compared with placebo, and no change in mean serum creatinine levels
	1.5 mg/kg/day group showed a significant increase in mean creatinine levels
	Neither group had a significant increase in infection rate, mean blood pressure, serum lipid parameters, or significant electrocardiogram parameter alterations
Papp et al[34]	Most frequently reported adverse events: headache, nasopharyngitis, and upper respiratory tract infections
	All three groups (0.4, 0.6, 0.8 mg/kg/day) showed no significant changes in renal function, blood pressure, or mean lipid concentrations at 12 or 24 weeks

with cyclosporine A is also observed in vitro.[30] Voclosporin (LX211) has achieved effective suppression of experimental uveitis in rats, and furthermore inhibition of human T cell proliferation and function in vitro.[31]

Clinical data

In a 12-week, randomized, double-blind, placebo-controlled Phase II study of 201 patients with plaque psoriasis, ISA247 appeared safe and effective for treating moderate to severe psoriasis. The most effective concentration was 1.5 mg/kg/day, but serum creatinine increased in this patient group.[33] The efficacy of ISA247 in psoriasis was confirmed by a Phase III study of 451 patients for 24 weeks. The highest administered dose (0.4 mg/kg twice a day) achieved the best results for psoriasis area and severity index.[34] Both psoriasis studies examined quality of life between placebo and verum groups and found the highest verum concentrations to improve disease-related quality of life.[35,36] Further studies are evaluating the effect of voclosporin in kidney and renal transplantation and the safety and tolerability of the ophthalmic solution in patients with keratoconjunctivitis sicca.

Published data on side effects in patients treated with voclosporin for uveitis are limited (see Table 1). The mode of action of voclosporin is similar to that of cyclosporine A, with probably similar side effects. Data on development of malignancy while on treatment with cyclosporine A for inflammatory ocular disease are also scarce. Lane et al did not observe an increased risk of malignancy in patients with severe ocular inflammatory eye disease treated with systemic immunosuppressive agents compared with patients treated with systemic corticosteroids.[37] Kempen et al followed on with data showing that calcineurin inhibitors would probably not increase cancer risk to a degree that outweighs the expected benefits of therapy for ocular inflammation.[38] Voclosporin demonstrated less nephrotoxicity compared with calcineurin in animal studies.[32]

Uveitis trials

Up until now, three clinical studies of voclosporin in the treatment of noninfectious uveitis have been performed. The LUMINATE (Lux Uveitis Multicenter Investigation of a New Approach to Treatment) clinical development program was initiated in 2007 by Lux Biosciences Inc to assess the safety and efficacy of voclosporin for the treatment, maintenance, and control of all forms of noninfectious uveitis. The aim of the LUMINATE program, which was recently presented by Anglade et al, was to ensure that voclosporin would become the first corticosteroid-sparing agent to be approved by the US Food and Drug Administration for noninfectious uveitis. Three randomized, double-blind, placebo-controlled, Phase II/III trials in patients with noninfectious, sight-threatening uveitis were performed. The first study included patients with active intermediate, anterior and intermediate, posterior, or panuveitis. The second study included patients with quiescent intermediate, anterior and intermediate, posterior, or panuveitis in patients requiring systemic immunosuppression. The third study included patients with active anterior uveitis requiring systemic immunosuppression. The final results of the three studies are not yet comprehensively published, but some data are available.[23,39,40] In patients with active intermediate, posterior, and panuveitis, voclosporin 0.4 mg/kg and 0.6 mg/kg twice daily reduced inflammation by about 50% compared with 29% in the placebo group at 16 and 24 weeks. Uveitis recurrences were reduced by 50% in the group with quiescent uveitis. In all three studies, 96%–98% of patients were able to reduce their oral prednisolone dosage to $\leq$5 mg daily. However, no significant effect for voclosporin was observed for anterior uveitis.

Nearly 20% of patients treated with 0.6 mg twice daily experienced deterioration of renal function. This was seen in only 8.2% of patients in the 0.4 mg/kg group. Hypertension was experienced by 7.5% of patients in the 0.4 mg/kg group and by 10.3% of patients in the 0.6 mg/kg group.[41]

The recently presented data are very promising, but the Food and Drug Administration has requested an additional clinical trial prior to final approval of voclosporin for the

treatment of noninfectious uveitis. Therefore, Lux Biosciences Inc is currently planning a Phase III study to assess the efficacy and safety of voclosporin in patients with active noninfectious intermediate, posterior, or panuveitis. The mean change in vitreous haze from baseline to 12-week follow-up and time to treatment failure is the primary outcome measure of this trial. Secondary outcome measures are mean daily systemic corticosteroid dose during weeks 12–24, time to augmentation with corticosteroid therapy, and mean change from baseline in the Vision Specific Role Difficulties subscale of the National Eye Institute Visional Functioning Questionnaire. If successful, voclosporin may become the first corticosteroid-sparing agent approved by the Food and Drug Administration for the treatment of noninfectious uveitis.

Conclusion

Voclosporin, a novel immunomodulatory drug inhibiting the calcineurin enzyme, may significantly reduce inflammation and prevent recurrences of inflammation in patients with noninfectious uveitis. If the additional Phase III study confirms its effectiveness, voclosporin may become the first immunosuppressive drug approved by the Food and Drug Administration for the treatment of noninfectious uveitis.

Disclosure

The authors report no conflicts of interest in this work.

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