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REVIEW

Voclosporin as a Treatment for Noninfectious Uveitis

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Abstract: Voclosporin is a relatively new calcineurin inhibitor that has been used successfully in humans for the treatment of plaque psoriasis. Available data indicate a good safety profile for this treatment and a significant increase in quality of life for psoriasis patients. More recently, voclosporin has been used to treat ophthalmic conditions such as uveitis. The limited data available indicate at least comparable results relative to current therapy with a better safety profile. Here, we analyze data from human and animal studies and the mode of action of voclosporin. Available safety profile data are also discussed.

Keywords: voclosporin, uveitis, transplantation, drug, eye

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Introduction

Voclosporin (Luveniq™, Lux Biosciences, Inc, Jersey City, NJ, USA) is a next-generation calcineurin inhibitor (CNI). which has shown efficacy when evaluated as a therapy for renal allograft rejection, psoriasis, and autoimmune uveitis.[1–3] CNIs were originally used as antifungal agents; they are immune suppressive agents that reversibly inhibit T-cell proliferation and function and prevent the release and/or function of proinflammatory cytokines. These molecules block the activity of calcium-regulated serine-threonine phosphatase calcineurin. Cytokine production is impaired when CNIs enter a lymphocyte and bind to immunophilins. This binding action inhibits calcineurin, which ultimately results in impaired cytokine transcription, particularly of interleukin (IL)-2, a molecule essential for T-cell proliferation. CNIs have been used as transplant rejection agents and more recently in ophthalmology, particularly as a treatment for uveitis. Ophthalmic indications for voclosporin have been recent, and most have been for treating uveitis. Voclosporin has been more extensively used as a psoriasis treatment with good success.

Uveitis is a broadly descriptive term, which may encompass the iris in the anterior segment to the choroid in the posterior segment of the eye. Symptoms of uveitis include general inflammation caused by a number of sources, which may be infectious such as in syphilis or noninfectious such as in sarcoidosis. The most common cause of inflammation is acute anterior uveitis, which is often associated with HLA-B27 acute anterior uveitis and can be organ-specific or systemic in humans. The first course of treatment for uveitis in the United States and in most of Europe is corticosteroids, which are available orally or as eye drops. Corticosteroids may also be administered via intravitreal injection or implant, although the first two methods are more common.

Voclosporin has a number of synonyms in addition to Luveniq, including ISA247, ISA(TX)247, and E-ISA247, all of which are referenced below depending on the author and the year of publication of a study.

Chemistry and Mechanism of Action

Voclosporin is a cyclosporine A analog with a molecular mass of 1214.6. The molecular formula is $C_{63}H_{111}N_{11}O_{12}$ and the chemical name is cyclo{[(6E)-(2S,3R,4R)-3-hydroxy-4-methy-2-(methylamino)-6,8-nonadienoyl]-L-2-aminobutyryl-N-methyl-glycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}. Voclosporin is a cyclicundecapeptide fungal metabolite with the same structure as cyclosporine A, except that the amino acid-1 residue of the molecule is modified to have a higher binding efficiency to calcineurin. This modification alters the metabolism away from the amino acid, leading to higher potency of voclosporin compared to other cyclosporines.

Cyclosporines, such as voclosporin, act as reversible inhibitors of competent lymphocytes (particularly T-lymphocytes). They exert their effect during the early phases of the cell cycle by binding to the intracellular protein cyclophilin. These types of cyclosporines exert their immunosuppressive effect by forming a complex with peptidyl-prolyl cis-trans isomerase cyclophilin A.[4] This complex then inhibits calcium-dependent phosphatase calcineurin, preventing de-phosphorylation of the transcriptional activator of T-cells. Thus, translocation of the protein from cytoplasm to the nucleus is prevented and cytokine signaling is disrupted or prevented. This results in delay, disruption, or prevention of an immune response.

In Vitro Studies of Voclosporin

Aspesiet et al[5] evaluated voclosporin as an immunosuppressive drug using a calcineurin assay with human whole blood. The assay showed that the in vitro activity of voclosporin (referred to as ISA(TX)247 in this paper) was 2.5 times greater than that of cyclosporine compared to controls.

Stadler et al[6] used whole blood from cynomolgous monkeys to assess in vitro lymphocyte stimulation. Monkeys were treated orally for 7 days with 25 mg/kg of either cyclosporine or ISATX247 or with 50 mg/kg of ISATX247. Drug levels were analyzed using liquid chromatography/mass spectroscopy. Following stimulation of lymphocytes, cell proliferation was measured by measuring [3H]-TdR incorporation and by flow cytometry. Cytokine production was also measured using this technique.

Lymphocyte proliferation and cytokine production (in vitro) was assessed using whole blood from cynomolgus monkeys by measuring

[3H]-TdR incorporation and by flow cytometry. The concentration of voclosporin necessary to attain an EC_{50} value similar to that of cyclosporine was statistically significantly lower.[7]

Cunningham et al[8] showed that voclosporin was effective for suppressing a wide range of cytokine activities in vitro. Human T-cells incubated with different concentrations of voclosporin showed that voclosporin was effective for decreasing Th1, Th2, and Th17 cytokine release. This activity was directly correlated to the amount of voclosporin administered.

Preclinical Studies

Voclosporin has been compared to cyclosporine in a cynomolgous monkey model in several in vivo and in vitro studies. There have also been a few studies in lower animals, including nonhuman primates, examining the effects of voclosporin, referred to as ISATX247 in these studies.[9] A renal transplantation and bilateral nephrectomy study in male adult cynomolgus monkeys was conducted using either ISATX247 or cyclosporine to prevent rejection. Administration was performed twice daily to ensure that a 150 ng/mL level of drug was maintained. The ISTAX247 treatment group survived significantly longer than the cyclosporine group ($P = 0.0036$).[9] Calcineurin inhibition levels were 80% ± 11% for ISTAx247 and 48% ± 12% for cyclosporine. The longer survival times indicate that ISTAX247 is somewhat more potent than cyclosporine as an immunosuppressive agent in this model.

Cunningham administered voclosporin subcutaneously to treat autoimmune uveitis in male Lewis rats.[8] These animals were injected with concentrations of 2.5 mg/kg, 10 mg/kg, and 40 mg/kg. The positive control included cyclosporine administered at 40 mg/kg. All drugs were administered in the dorsal region. Further, the animals were segregated into preventative and therapeutic treatment groups. The preventative group received daily injections of both interphotoreceptor binding protein and voclosporin. The therapeutic group also received daily injections, but these began 7 days after inoculation with interphotoreceptor binding protein. Animals in the voclosporin preventative treatment groups did not exhibit signs of experimental autoimmune uveitis, even in the low-dose group (2.5 mg/kg).[8] Animals in the therapeutic treatment groups also responded to voclosporin after disease onset. However, the effects were not as dramatic. Low-dose voclosporin was not effective for preventing or reversing disease onset. The high dose of voclosporin (40 mg/kg) was comparable to cyclosporine in reversing disease onset.

Stadler et al[6] used cynomologus monkeys to evaluate ISATX247 versus cyclosporine in terms of lymphocyte proliferation, T-cell activation surface antigen, and general cytokine production. Measurements were taken from whole blood of the animals. The authors concluded that ISATX247 suppressed T-cell functions to a greater degree than cyclosporine in this animal model. Bîrsan et al[7] obtained similar results using an in vitro system by measuring whole blood from cynomologus monkeys. Whole blood samples withdrawn from the animals were used for detection. Thus, data from two different investigators demonstrated similar findings using a similar model.

Toxicological Reactions

Aspesiet et al[5] performed some of the initial toxicological studies using ISA(TX)247. They studied rats, rabbits, and dogs and found that ISA(TX)247 was well-tolerated compared to cyclosporine. The in vitro activity of ISA(TX)247 was significantly greater (2.5 times) than that of cyclosporine in a blood calcineurin assay.[5] ISA(TX)247 prolonged graft survival by a factor of three compared to cyclosporine. These authors reported that morphological changes observed in the kidneys of animals receiving cyclosporine were not observed in animals that received ISA(TX)247. ISA(TX)247 given to rats at concentrations up to 80 mg/kg/day for 28 days did induce significant morbidity or mortality. In rabbits and rats given this same concentration, no change in serum creatinine levels was observed.

Much of the more comprehensive toxicity data comes from psoriasis patients. Voclosporin was reported by various investigators to be well-tolerated in single and multiple dose Phase I trials, with dosages ranging up to 4.5 mg/kg. The most commonly reported adverse events were similar to those reported with other CNIs, including headache, hypertension, upper respiratory tract infections, and diarrhea. Adverse events were dose-dependent.[10] Renal functions appeared to remain stable even at

higher dosage levels. The highest mean change in serum creatinine levels (0.4 mg/kg) were 5.6% above baseline (week 12). The authors considered this value to be within the normal range.[10] After 60 weeks, serum creatinine remained stable.

In 2006, Bissonnette et al[11] reported that side effects including nausea, headache, and increased creatinine levels, as well as changes in electrocardiograms were observed in some patients. This was in contrast to other CNIs that exhibited a narrower therapeutic range (tacrolimus) and showed more side effects, which were generally more severe.

Systemic use of Voclosporin

The PROMISE study was multicenter, randomized, open label study of three groups receiving voclosporin at low, medium, and high doses. The study was conducted over a six-month period at 40 sites in the United States and Canada.[12] Volunteers were similar in terms of age, gender, and race. The comparator drug in this study was tacrolimus and was administered to 334 low-risk renal transplant patients.[12] Their data showed that adverse events were similar for all treatment groups (voclosporin and tacrolimus). There were no significant differences in the treatment groups in terms of total cholesterol or the triglycerides high-density lipoprotein or low-density lipoprotein. There was a significantly lower difference in new onset of diabetes following transplantation (6 months) in the low-voclosporin group compared to in the tacrolimus group (1.6% vs. 16.4%). The results of this study indicated that the incidence of new onset diabetes increased with increasing voclosporin dosage. These data have not been confirmed by other studies. The study also showed that voclosporin as well as tacrolimus prevented acute rejection for up to 6 months.

Voclosporin has also been used primarily and initially as an immunosuppressive agent and for treating psoriasis.[13] Treatments for psoriasis typically include a measurement of the quality of life change in patients. Results of a Phase II psoriasis study showed that quality of life was improved ($P < 0.05$) in the pooled patient group compared to in the control group.[1] Seventy-seven patients received 0.5 mg/kg/day of voclosporin in the low-dose group and 83 patients who received 1.5 mg/kg/day in the high-dose group in this randomized, double blind, multicenter study. The overall results of this study showed that voclosporin improved quality of life for chronic, moderate, and severe plaque psoriasis. These results for plaque psoriasis were confirmed by Papp et al[14] who showed that quality of life was improved following treatment with ISA247 (voclosporin). These authors reported that during a 24-week period, the drug was safe and effective for psoriasis treatment. However, Naidoo and Rambiritch[15] disputed the ethical aspects of the study, including the use of a placebo group and stated that the 24-week treatment period was too short.

Relative to quality of life issues with plaque psoriasis, Kunynetz et al[2] performed a randomized, multicenter, double-blind, placebo-controlled study in Canada involving 451 patients. Patients were enrolled in a range-finding study consisting of placebo and 0.2 mg/kg, 0.3 mg/kg, and 0.4 mg/kg twice a day voclosporin treatment for up to 12 weeks. Quality of life was measured using two indices, including dermatology life quality index and psoriasis disability index. At the end of 12 weeks, patients who received 0.4 mg/kg voclosporin had significantly improved quality of life indices for all domains of both indices. The data obtained from the other treatment groups was significant but less dramatic compared to the placebo control group. These results are in addition to the ophthalmic indications, which will be discussed below.

Ophthalmic use of Voclosporin

CNIs have gained attention in the ophthalmic community over the past decade.[15–17] Concerns regarding their use for ophthalmic conditions involve the lack of a safety profile that practitioners can use to specifically relate to uveitis or other eye conditions. However, since voclosporin has been used for psoriasis treatment, several studies have been conducted related to efficacy and quality of life.[1,2] Unlike some other ophthalmic indications, these studies provide some evidence for the safety profile. Uveitis, which includes a complex group of ocular disorders, is a T_H1-mediated condition that classified according to location and dry eye syndrome, which is a chronic disease of the lacrimal gland; these diseases have been postulated as potential targets for CNI therapy.[17]

Treatments for these conditions have included lubricating drops and corticosteroids, specifically small molecule steroids with molecular weights of approximately 500.[18]

Voclosporin has been used in the ophthalmic setting primarily as a treatment for uveitis.[15,19] The Lux Uveitis Multicenter Investigation (LUMINATE) clinical program was initiated by a product development company (Lux) in an attempt to demonstrate the usefulness of voclosporin for treating uveitis.[17,18] The program consisted of three double-masked, randomized, placebo-controlled (combination) Phase II/III trials and included patients that had been diagnosed with sight-threatening uveitis. The primary enrollment criterion for all reported clinical work was the presence of noninfectious uveitis that was either uncontrolled or controlled only with corticosteroid or other immunosuppressive treatments.

The three studies may be described by study number. Study 1 was active LUMINATE Active; Study 2 was designated as LUMINATE Maintenance and Study 3 was designated as LUMINATE Anterior.[20] In volunteers with active intermediate, posterior, and panuveitis, voclosporin delivered at 0.4 mg/kg and 0.6 mg/kg reduced inflammation by 50% if administered twice daily compared values in placebo groups (29%) as measured at 16 and 24 weeks. Quiescent uveitis recurrences were reduced by 50%. All three studies demonstrated that for patients taking oral prednisolone, the dosage could be reduced to ≤5 mg/day. However, 20% of patients in the 0.6 mg arm experienced decreased retinal function as compared to 8.2% in the 0.4 mg groups. Hypertension was experienced in both groups at rates of 7.5% in the 0.4 mg group and 10.3% in the 0.6 mg group.

Conclusion

While these results are promising, there is much work with this drug that remains to be done. It should also be noted that much of the data come from Lux supported research and some level of independent verification would be helpful in establishing this drug as an ophthalmic therapeutic agent.[21] However, taken as a whole it seems clear that Voclosporin will be useful drug in the arsenal of uveitis treatments. It will also be useful to know how this drug interacts with other small molecule steroids, if it does.

Author Contributions

Conceived and designed the experiments: CLS. Analyzed the data: CLS. Wrote the first draft of the manuscript: CLS. Contributed to the writing of the manuscript: CLS. Agree with manuscript results and conclusions: CLS. Jointly developed the structure and arguments for the paper: CLS. Made critical revisions and approved final version: CLS. All authors reviewed and approved of the final manuscript.

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