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Antiviral prophylaxis may not provide benefit in patients with Posner-Schlossman Syndrome

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ABSTRACT A critical appraisal and clinical application of Chee SP, Jap A. Cytomegalovirus anterior uveitis: outcome of treatment. *Br J Ophthalmol.* 2010 Dec;94(12):1648-52. <https://doi.org/10.1136/bjo.2009.167767> for a patient on antiviral prophylaxis for recurrent episodes of Posner-Schlossman Syndrome.

Keywords: *Posner-Schlossman, antiviral, cytomegalovirus, uveitis*

Clinical Context

Maryam Davis [pseudonym] is a 32 year-old female of Middle-Eastern ethnicity with a diagnosis of Posner-Schlossman Syndrome (PSS). She has had several visits to the clinic due to episodes of elevated intraocular pressure, blurry vision, and conjunctival injection in the left eye. Previous episodes have always occurred similarly in the same eye and have been resolved successfully with topical Brimonidine and steroids, with normal visual acuity and visual fields between episodes. OCT imaging has shown mild retinal thinning in the left eye. During a previous visit, Mrs. Davis was started on oral valganciclovir as prophylaxis, but she has continued to experience episodes. Mrs. Davis presents to the clinic today with similar symptoms and is concerned regarding the efficacy of the Valtrex in decreasing the frequency of these episodes. She is highly motivated to trying anything to protect her vision but does not want to take any long-term medications if they do not achieve this goal.

PSS was initially described in 1948 as a pattern of recurrent unilateral attacks of severe intraocular pressure (IOP) elevations and mild anterior uveitis in relation to the IOP elevations.¹ The syndrome is a clinical diagnosis with an unknown cause, though it has been suggested that PSS is an acute-relapsing pattern of presentation of CMV Anterior Uveitis.² Thus, antiviral therapy has been proposed as a prophylactic therapy for patients with PSS. However, the basis for this treatment is largely theoretical.

Clinical Question

Are antivirals effective as a long-term prophylaxis for Posner-Schlossman Syndrome?

Research Article

Chee SP, Jap A. Cytomegalovirus anterior uveitis: outcome of treatment. *Br J Ophthalmol.* 2010 Dec;94(12):1648-52. <https://doi.org/10.1136/bjo.2009.167767>

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Related Literature

A review of the literature was conducted utilizing Pubmed, using the terms “Antiviral”, and “Posner-Schlossman” or “Cytomegalovirus Anterior Uveitis”. 101 results were returned, with only 7 being accessible studies in English regarding the effect of an antiviral medication on multiple patients with either PSS or CMV Anterior Uveitis.

The majority of studies regarding the subject matter are case series suggesting possible effects of antiviral therapy on the disease. Articles by Accorinti et al.³, Touhami et al.⁴, Sobolewska et al.⁵, Harada et al.⁶, and Hwang et al.⁷ all reported that antiviral administration in patients with PSS or Cytomegalovirus (CMV) Anterior Uveitis was well-tolerated, and that the majority of patients saw a resolution of symptoms after administration of therapy. However, these studies all shared several significant weaknesses. First, none of these studies include a direct comparison between treated and untreated patients, limiting the conclusions that can be drawn regarding whether a change in episode frequency is due to the therapy provided or the natural course of the disease. At most, comparisons in several of these studies were only made to the patients’ episodes before the treatment was begun. Additionally, most of these reports did not differentiate whether patients suffering from CMV anterior uveitis exhibited the acute relapsing pattern of disease characteristic of PSS, limiting the applicability of this data to Mrs. Davis’ condition, as a chronic form of CMV anterior uveitis without the characteristic episodes seen in PSS can occur.

Su et al. reported a retrospective series on the effects of topical 2% ganciclovir treatment on the frequency of intraocular pressure spikes in 126 PSS patients found to have CMV positivity in the aqueous humor.⁸ The authors compared the clinical outcomes of these treated patients against CMV-negative PSS patients, who did not receive therapy and were considered as a control group. The authors concluded that antivirals cleared viral load, controlled IOP, and maintained corneal endothelial cell counts. However, it is difficult to know whether these effects are due to the antiviral therapy, or a difference in the course of disease in patients who had higher CMV DNA counts in the aqueous humor. Additionally, the intervention in this study utilized 2% ganciclovir drops, while Mrs. Davis has been using oral valganciclovir, limiting the applicability of the data.

Chee et al. conducted a retrospective cohort study regarding the effects of ganciclovir on 70 CMV anterior uveitis patients (72 eyes).⁹ Recurrence rates were similar between patients treated with antivirals versus those who had refused treatment. Due to the inclusion of a nontreated group, stratification of CMV anterior uveitis patients into those with acute recurrent or chronic subtypes, and inclusion of data utilizing multiple forms of antiviral therapy, including oral valganciclovir, this study was chosen for critical appraisal.

Critical Appraisal

This nonrandomized retrospective cohort study by Chee et al. evaluates the effect of various antivirals in CMV anterior uveitis patients. Patients were selected through a review of the records for all CMV anterior uveitis cases seen in the Singapore National Eye Centre clinic from Jan 2002 to Aug 2008. Only those patients found to have CMV-positive aqueous humor were offered treatment. While Mrs. Davis has serum CMV-positivity, aqueous humor testing has not been performed, so we can only definitively diagnose her with PSS, but not CMV anterior uveitis. Moreover, the study is conducted in Singapore, drawing from a population with a different ethnicity from Mrs. Davis.

While the authors directly compare untreated versus treated patients, another weakness of the study is that the untreated group consisted of those patients who refused treatment. The authors themselves demonstrated that this group consists of healthier patients, with significantly decreased glaucoma, cataract, and follow-up duration compared to those who elected to be treated with antiviral therapy.

The treatment group was provided with several antiviral options, including intravenous, implantable, intravitreal, topical ganciclovir, or oral valganciclovir. It was noted that oral valganciclovir became available sometime during the middle of the study and all patients on the intravenous form were switched to the oral form. It is unclear when this occurred during the study, and potentially affects whether these results can be extrapolated to Mrs. Davis’ condition, as she has only used the oral antiviral medication.

Both groups also received topical NSAIDs (ketorolac) and anti-glaucoma medications. However, while some patients in the treatment group received topical prednisolone, those in the untreated group did not. It is unclear whether the small difference

between treated and untreated patients could be due to the presence of the steroid drops. Further complicating this is the fact that patients utilizing different forms of antivirals were also offered different concentrations of prednisolone, with those on systemic antivirals receiving 0.12% prednisolone twice a day, those using intravitreal injection or gel forms receiving either topical ketorolac or 0.12% prednisolone, and those with the implant given 1% prednisolone four times a day. Each eye may have received more than one mode of therapy, with patients being offered to change if treatment failure occurred, or if cost or adverse effects became a consideration. In our case, the risks and difficulties associated with some of these modes of treatment over a long-term duration for a younger patient such as Mrs. Davis must be taken into consideration. While she states that has no problem taking oral medications, constant travel for intravitreal injections may affect compliance with treatment. Prolonged systemic therapies may also introduce increased morbidity as well as cost, and the authors suggest that these factors may influence some results due to compliance issues.

Endpoints evaluated in this study included best-corrected visual acuity, IOP, and anterior chamber inflammation. Notably however, an assessment of visual field was not performed. The characteristic progression of glaucoma often involves the peripheral vision, leading to a restricted visual field in the periphery while central visual acuity remains intact until late in the disease. Mrs. Davis herself expressed concern regarding whether she could be impacted by these early changes without her own knowledge.

Of total CMV-positive patient group, 49 patients (50 eyes) were found to have the acute recurrent pattern of uveitis, which was similar to the course experienced by Mrs. Davis. 22 of these patients (23 eyes) agreed to antiviral treatment. There were 27 treatment episodes in these eyes, with resolution of the episode in 21 eyes (77.8%). However, 16 eyes (76%) showed recurrence. In contrast, 72.7% of untreated eyes showed recurrence, suggesting a risk ratio of 1.05, though the decreased follow-up time in the untreated group suggests that the number of eyes with recurrent during the study period may be lower than expected. Interestingly, in comparison between systemic versus gel treatment, it was found that 80% (8/10) of treatment episodes with systemic therapy resulted in recurrence, compared to 57% (4/7) of treatment episodes with gel therapy. However, only 9% (1/11) of treatment episodes with systemic therapy resulted in initial failure, compared to 36% (4/11) of treatment episodes with gel therapy. The small sample sizes limit the conclusions that can be made from these findings, but the authors suggest that those who respond initially to systemic therapy but cannot comply with maintenance therapy may instead benefit from gel application. Unfortunately, this situation doesn't apply to Mrs. Davis, who had recurrences of PSS even while taking systemic antiviral medication. Moreover, Mrs. Davis voiced complaints regarding utilizing topical gel medications for dry eye in the past, as they resulted in blurry vision that interfered with her day.

The study does not disclose competing interests.

Overall, the study suffers from several weaknesses that limit its applicability to Mrs. Davis' condition. As a cohort study that is historically controlled, this places the study at an evidence level of 4 according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence Table.¹⁰ However, there are no superior studies regarding the clinical question posed by Mrs. Davis, and the data demonstrated here is crucial for designing a future trial on the subject.

Clinical Application

There is a lack of high-quality evidence supporting the role of antiviral therapy in patients suffering from Posner-Schlossman Syndrome. The authors of this study appropriately concluded that their data suggests that while administration of antivirals may increase the chance of resolution of the elevated IOP and anterior chamber inflammation in PSS crises, there is little benefit in its use in decreasing the recurrence of these episodes, with the exception of topical gel ganciclovir. However, the low sample size and lack of a proper control group in this study limit these conclusions.

In the specific clinical context of our patient, the morbidity and cost associated with long-term antiviral therapy in a relatively young patient further argues against use of oral valganciclovir. Additionally, previous episodes had all been promptly resolved to her satisfaction with a short-term course of a combination of topical antiglaucoma and steroid eye drops. The patient was highly motivated and demonstrated a history of following up immediately upon noticing any signs of inflammation in the left eye. She did not endorse any difficulty in continuing to do so. Thus, the patient was given the same combination of eyedrops and it was suggested that the oral antiviral was not

providing long-term benefit to her. In a discussion of these decisions, the patient agreed, and stated that she felt it was not worth continuing her dose of oral antiviral in light of the low-quality evidence for doing so, and the fact that she herself continued to experience recurrent symptoms.

New Knowledge Related to Clinical Decision Science

When faced with a rare disorder or a difficult to treat condition, it is natural for physicians to see what information is available in the medical literature. In this case, the critical appraisal records the thought process of the clinician when trying to match the limitations of the study to the clinical evidence that might be important to the patient—how to connect the patient to the evidence. Thus, it is the cognitive processes highlighted in this paper that hint at how doctors should read medical literature with a specific patient in mind, rather than developing a decision rule to be used on all patients.

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