Comparison of oral antiviral therapy with valacyclovir or acyclovir after penetrating keratoplasty for herpetic keratitis

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ABSTRACT

Aims: To compare the outcome of prophylactic oral valacyclovir (VAL) or oral acyclovir treatment (ACV) in patients having undergone penetrating keratoplasty for herpetic keratitis (HK).

Methods: All patients having received a penetrating keratoplasty for HK and being treated postoperatively with either oral VAL or oral ACV (inclusion period from 12/97 to 3/06 and 5/92 to 9/96, respectively) were retrospectively evaluated. Records were analysed for postoperative reactivation of recurrent HK, graft rejection, endothelial cell loss, central corneal thickness and visual acuity after a follow-up of up to 5 years.

Results: Twenty patients received VAL and were compared with 19 patients being treated with ACV. Two patients developed clinical signs of recurrent herpetic disease in the VAL group compared with three patients in the ACV group. Two patients from both groups each developed an irreversible graft failure. Best corrected visual acuity improved in both treatment groups from baseline (logMAR) −1.97 (VAL), −1.47 (ACV) to −0.85, −0.72, respectively, at the 1-year follow-up and slightly deteriorated after 5 years in the ACV group (−0.71 VAL vs −1.14 ACV).

Conclusion: Prophylactic oral VAL treatment is at least as effective as ACV in preventing recurrence in patients who underwent corneal transplantation for HK. The tolerability of the two drugs is similar, but the dosing for VAL might be more comfortable for patients.

Corneal scarring due to recurrent herpetic keratitis (HK) is an important indication for penetrating keratoplasty. The survival rates and visual improvement of corneal grafts performed for herpetic eye disease are less favourable than for other forms of corneal disease, since recurrence of HK is a leading cause for graft failure in these cases. Prophylactic systemic acyclovir (ACV) treatment has become the treatment of choice for preventing recurrent infection and by this means indirectly also preventing graft failures following corneal transplantation for herpetic keratitis. Nevertheless, orally administered ACV has a poor absorption rate and therefore a limited bioavailability. Valacyclovir (VAL) is an L-valyl ester of ACV which is converted to ACV after oral administration. The resulting plasma levels of ACV are three to five times higher than those attainable with oral ACV itself.[1–3] Although VAL has clinically been available for several years, only very recently a pilot study on its use for preventing recurrent herpes simplex eye disease has been reported.[4] No studies to date have assessed the effect of postoperative prophylactic oral VAL on the survival of corneal grafts performed for herpetic keratitis.

We therefore retrospectively evaluated the long-term outcomes of oral VAL prophylaxis in a consecutive series of patients after penetrating keratoplasty (PKP) for herpetic keratitis and compared the results with controls having received the ACV treatment regimen (before VAL was available) for the same indication.

PATIENTS AND METHODS

We identified 43 patients having undergone penetrating keratoplasty for inactive or active HK. Thirty-nine patient records (four records were missing) with a documented follow-up of at least 1 year were retrospectively/historically reviewed. Two surgeons performed all PKPs for herpetic keratitis from May 1992 to March 2006 at the Inselspital Bern.

The diagnosis of herpetic keratitis was based on clinical grounds, that is history and clinical picture of corneal changes compatible with the diagnosis of recurrent infectious epithelial keratitis, neurotrophic keratopathy or stromal keratitis and the associated findings of recurrent dendritic or geographic epithelial keratitis.

Patients were examined according to our regular predefined quality control standard, preoperatively as well as postoperatively on the first postoperative day, after 1 and 4 months and after 1, 2, 3 and 5 years. Clinical evaluation included pachymetry of the graft using an ultrasonic pachymeter (AL-1000, or AL-3000, Tomey, Nagoya, Japan) and endothelial cell counting of the graft using a non-contact specular microscope (SP-1000, or SP-3000P Topcon, Tokyo). Fixed-frame counting technique was used to calculate endothelial cell densities according to the magnification and the instructions from the manufacturer. A donor endothelial cell count was performed with a fixed-frame counting technique after a photograph was taken on the day of surgery using a phase-contrast microscope.

We compared best spectacle-corrected Snellen decimal visual acuity (BCVA), graft rejection rates, herpes recurrence, graft vascularisation, graft endothelial cell density, pachymetry, anterior chamber reactions and endothelial precipitates of patients who underwent PKP for herpetic corneal disease and received oral VAL (Valtrex, GlaxoSmithKline, Brentford, UK) with those who underwent the same procedure and received oral ACV (Zovirax, GlaxoSmithKline). BCVA results from Snellen charts were converted into logMAR units for statistical analysis.[5]

Table 1 Characteristics for the acyclovir (ACV)- and valacyclovir (VAL)-treated groups (Fisher exact test, t test)

	ACV (n = 19)	%	VAL (n = 20)	%	p Value
Female	8	42	8	40	1.00
Mean (SD) age at penetrating keratoplasty (years)	54 (21)		65 (16)		0.07
Mean recurrence-free episode before keratoplasty (months)	16 (range 0 to 72)		13 (range 0 to 84)		
Re-keratoplastic	10	52	9	45	0.75
Herpetic complications before last keratoplasty					
Corneal vascularisation	13	68	11	55	0.51
Active herpes	4	21	5	25	1.00
Perforated ulcus	5	26	7	35	0.73
Mean follow-up time (years)	3.4 (range 1 to 5)		2.3 (range 1 to 5)		0.11

Corneal graft rejection episodes were defined on the basis of cellular anterior chamber reaction, keratic precipitates solely on the donor endothelium, stromal swelling and eventually the development of an endothelial rejection (Khodadoust) line or an epithelial rejection line. Herpes recurrence was diagnosed on clinical grounds, that is stromal swelling and infiltration, and the presence of endothelial precipitates not limited to the graft and in unclear cases confirmation attempted by diagnostic anterior chamber puncture. Graft failure was defined as irreversible loss of graft clarity.

Surgical technique, surgeon experience and postoperative management were similar in all patients. Monofilament 10–0 nylon interrupted sutures were used for fixation in all grafts. The donor diameter ranged in the VAL group the between 7.25 and 8.5 mm (mean 7.8 mm) and in the ACV group between 6.5 and 8.5 mm (mean 7.8 mm). The recipient bed was undersized by 0.25 mm.

All patients received postoperative topical steroids and antibiotics. The corneal grafts were all from our cornea bank and stored in organ culture medium at 36°C. The organ culture contained minimum essential medium and fetal calf serum, and was supplemented with penicillin, streptomycin and amphotericin B.[6] Before transplantation, the cornea stored in organ culture was deswelled with 6% dextran overnight, and the endothelium was examined with phase-contrast microscopy in the morning of surgery. Only corneas with a mean endothelial cell density of at least 2000 cells/mm^2 were transplanted (mean 2271 cells/mm^2 VAL and 2219 cells/mm^2 ACV).

Postoperative medications were used as follows: VAL 500 mg, two three times per day for 4 months. The dose was then tapered to a minimum of 2×250 mg according to the clinical response, with some patients being treated for up to 30 months.

A dosage of 800 mg of ACV, three to five times per day was given for 4 months, tapering slowly to at least 400 mg twice daily until 11 months postop and up to 36 months if needed. All patients from the VAL group were operated between December 1997 and March 2006, and the patients in the ACV group from May 1992 to September 1996.

Values are expressed as mean (SD). A clinical comparison between the two groups was performed using a two-tailed t test after confirmation of a normal distribution of results. A Kaplan–Meier survival estimate was calculated in order to determine graft survival rates for each treatment group and Fisher exact test applied to calculate p values for 2×2 frequency tables. Differences with a first-order error of $p \leqslant 0.05$ were considered statistically significant.

RESULTS

Thirty-nine patients who had undergone penetrating keratoplasty for herpetic keratitis and who had received oral VAL or ACV postoperatively were enrolled. Sixteen patients (eight in each group) were women. Patients ranged in age from 10 to 89 years (54 (SD 21) years for VAL and 65 (16) years in the ACV group; $p = 0.07$). The mean follow-up was 2.3 years in the VAL and 3.4 years in the ACV group (range 1 to 5 years, both groups).

Most patients were free from active inflammation for at least 6 months in both groups, four patients in the VAL group and five in the ACV group but presented with active herpetic keratitis at the time of surgery.

Eleven out of 20 patients in the VAL group had received 250–500 mg/day VAL in the immediate preoperative phase, whereas seven out of 19 patients in the ACV group had been treated with 200–800 mg/day ACV preoperatively. Twelve keratoplasties (5 VAL) were performed for corneal perforation due to necrotising keratitis and seven (4 VAL) for graft failure after previous PKP (table 1)

Two patients in the VAL and five in the ACV group graft rejection episodes were diagnosed. Two patients in the VAL group and three patients in the ACV group suffered recurrence of their herpetic keratitis at 5 and 21 months (VAL) and at 6, 8 and 25 months (ACV) after surgery. Two patients in both groups suffered total graft failure mostly after a series of graft rejection episodes (fig 1, table 2).

Best spectacle-corrected visual acuity improved during the first year significantly in both treatment groups from baseline (logMAR) −1.97 to −0.85 (VAL) and −1.47 to −0.72 (ACV), respectively. In the further course until 5 years of follow-up, visual acuity deteriorated again in the ACV group, −0.71 (VAL) vs −1.14 (ACV) (fig 2)

The decline in mean endothelial cell counts was comparable between both groups over the 5 years' follow-up (from 2124 to 934 cells/mm^2 in the VAL-treated group and from 2043 to 851 cells/mm^2 in patients under ACV treatment; $p = 0.384$) (fig 3). The mean central corneal thickness remained unchanged throughout the follow-up period (fig 4) in both groups.

Two patients died between the 12- and 24-month control in the VAL group and one patient after the 3-year recall. They were all off the medication at that time, and their deaths were unrelated to their herpetic eye disease.

No serious adverse effects were attributable to either VAL or ACV treatment, but one patient in the VAL group suffered from nausea and headache, and another patient suffered from constipation. In the ACV group, one patient reported nausea.

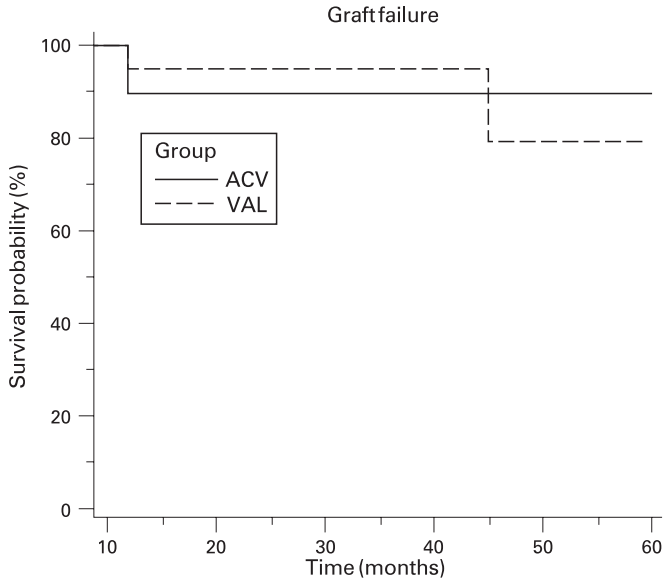

Figure 1 Kaplan–Meier survival estimates on graft failure for valacyclovir (VAL) and acyclovir (ACV) prophylaxis in patients having undergone penetrating keratoplasty for herpetic keratitis (p = 1.00).

No differences in recurrence rates, graft failure or side effects was found between the two groups (Fisher exact test) in this retrospective setting. Nevertheless, the posthoc power analysis (type I error alpha = 0.05; type II error beta = 0.2) to compare the two proportions of recurrence revealed a minimum total n = 1766 to ascertain statistical significance of non-inferiority.

DISCUSSION

Since herpes reactivation can be triggered by any type of local tissue trauma (eg, corneal transplantation),[7] and sufficient evidence exists that the trigeminus ganglion is the most important source for reactivation of herpetic keratitis,[8 9] the rationale for systemic rather than local treatment and prophylaxis of imminent recurrences for HK is evident.

Various studies have shown the efficacy of long-term oral prophylaxis with ACV in reducing the rate of recurrent infections in herpetic eye disease[10–12] or graft failures following corneal transplantation for herpetic keratitis. The herpes recurrences have substantially been reduced and hence the graft survival rates significantly enhanced since the introduction of its systematic use. VAL, an L-valyl ester of ACV extensively converted to ACV after oral administration reaches plasma levels of ACV three to five times higher than those attainable with oral ACV itself. ACV functions as a substrate for viral, but not cellular, DNA polymerase, competing with deoxyguanosine triphosphate for incorporation into the elongating chain. The incorporation of ACV in the growing chain of viral DNA results in chain termination, since ACV lacks the 3′-hydroxyl group necessary for subsequent elongation. In this retrospective comparative study, we showed that treatment with VAL after penetrating keratoplasty for herpetic keratitis is at least as good as the established ACV treatment.

Foster and Barney reported no HK recurrences and 2/14 graft failures after a mean of 16.5 months in patients receiving ACV initially dosed with 800–1000 mg/day and tapered over 12 months. In the untreated group, 4/9 patients experienced HK recurrence within 20.6 months and 5/9 suffered a graft failure.[13 14] Akova *et al* also retrospectively compared their herpetic PK patients and found 3/19 recurrences in the group

Table 2 Outcomes after acyclovir (ACV) and valacyclovir (VAL) prophylaxis for recurrent herpetic keratitis after penetrating keratoplasty

	ACV (n = 19)	%	VAL (n = 20)	%	Fisher exact test
Herpetic recurrence	3	15	2	10	p = 0.66
Graft rejection episodes	5	26	2	10	p = 0.24
Graft failure	2	10	2	10	p = 1.00
Adverse effects	1	5	2	10	p = 1.00

treated for 12 months with ACV 400 mg/day compared with 6/16 in untreated controls. Graft failure occurred in 1/19 in the ACV group versus 4/16 patients in the untreated control group.[15] Tambasco *et al* treated their herpetic PK patients for 12 months with ACV 800 mg/day and retrospectively compared them with an untreated group. None out of 20 patients in the ACV treated group experienced a HK recurrence or a graft failure in the first year compared with five recurrences and four graft failures in the 24 untreated patients.[16] The only prospective study by van Rooij *et al* on that subject compared herpetic PK patients being treated for 6 months with ACV 800 mg/day versus no treatment. Within 2 years, 3/35 treated patients experienced a recurrence and a graft failure compared with 9/33 recurrences and 3/33 failures in the untreated control group.[17] These results compare favourably with our findings of 2/20 recurrences and rejections among our VAL-treated patients and 3/19 recurrences and 2/19 failures in the ACV group.

Miserocchi *et al* recently compared the efficacy of VAL 500 mg/day versus ACV 800 mg/day during 12 months in preventing recurrent herpetic eye disease in non-transplanted patients and also found no difference between the two groups regarding herpes recurrence or adverse events in their proof-of-concept, pilot study.[18]

Only limited data on the ocular pharmacodynamics of VAL are available. Dias *et al* found higher aqueous levels after intravenous VAL treatment compared with intravenous ACV treatment in rabbits, which may be related to a functional transporter for small peptides.[19] Harding *et al* reported significantly higher aqueous concentrations in healthy cataract patients after single-day treatment with VAL (3000 mg) versus ACV (4000 mg).[20] Huynh found in a small group of three

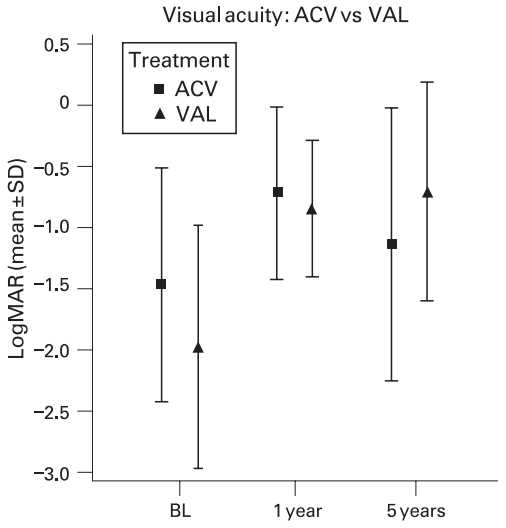

Figure 2 Mean (SD) best corrected visual acuity outcomes (logMAR) before transplantation (baseline, BL) at 1 year's and 5 years' follow-up for acyclovir (ACV) and valacyclovir (VAL).

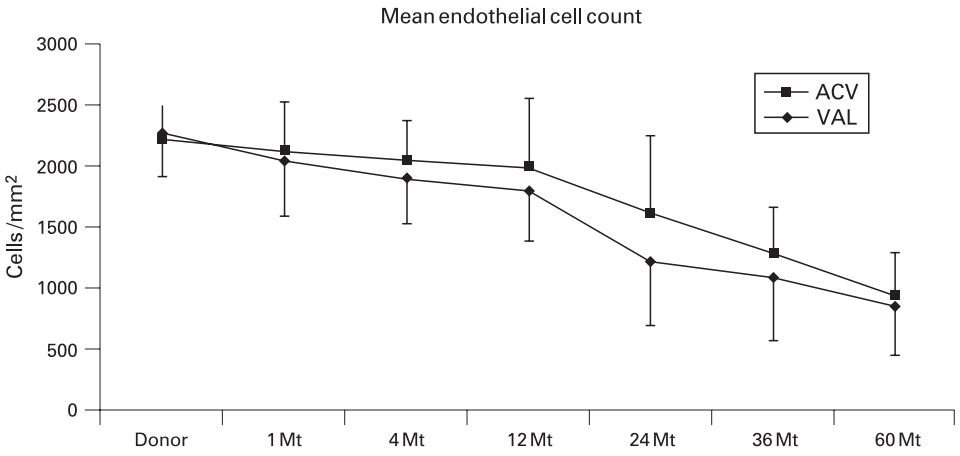

Figure 3 Mean (SD) endothelial cell count over time in months (Mt) for valacyclovir (VAL) and acyclovir (ACV).

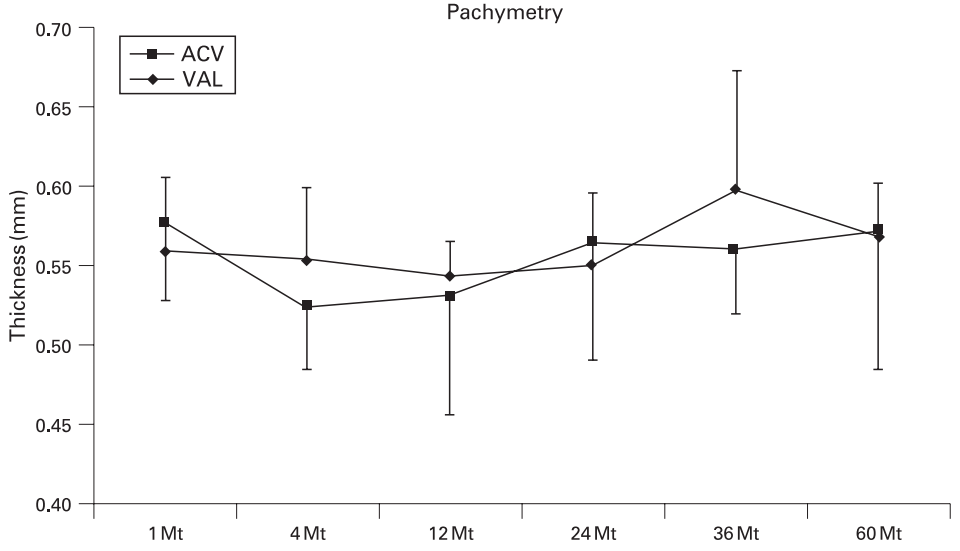

Figure 4 Mean (SD) central corneal thickness over time in months (Mt) for valacyclovir (VAL) and acyclovir (ACV).

elective vitrectomy patients therapeutic antiviral vitreous concentrations after oral VAL treatment (total dose 4000 mg; 3000 mg/day).[21]

The daily costs for the long-term maintenance therapy in Switzerland actually are 6.94 CHF (1 CHF≅1 U$) for 2×250 mg VAL (Valtrex) and 4.38 CHF for 2×400 mg ACV (Zovirax). We must recognise that it is difficult to judge the soft factors (different shapes of tablets, possibility of once daily dosing, etc) without a proper analysis of the quality of life or quality-adjusted life years between the two groups for a 37% more expensive therapy. We recognise that the prices will vary, and the cost differences might be less (but also more) pronounced in other countries. Lairson *et al* calculated a cost-effectiveness analysis for the prevention of herpes simplex virus eye disease. They concluded that from an economic viewpoint, a prolonged oral ACV is a relatively expensive preventive strategy.[22]

In summary, we were able to show that a long-term herpes recurrence prophylaxis with VAL after penetrating keratoplasty for herpetic keratitis was in this retrospective setting at least as effective as the established ACV treatment in reducing both the rates of recurrences and of graft failures.

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Competing interests: None.

Ethics approval: Retrospective analysis of the data was approved by the cantonal ethical committee of the University of Bern.

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Video report

Single incision wagon wheel phaco

ABSTRACT

Soft-to-semisoft cataracts may be challenging to remove with conventional sculpting and chopping phaco techniques. There are risks to intracameral structures during excessive and prolonged instrumentation. At a paracentesis site, corneal trauma may lead to wound leakage and astigmatism. We describe a technique for soft-to-semisoft lens extraction that minimises the mechanical stresses within the eye and utilises low phaco energy during surgery. The endonucleus is positioned in the vertical plane at the level of the capsulorhexis, and then removed in a centrifugal manner. Our single site wagon wheel technique uses the flow dynamics associated with high vacuum and burst phaco to safely remove soft-to-semisoft cataracts.

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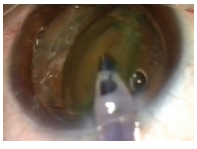

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