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Acyclovir: an update of the clinical applications of this antiherpes agent

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Summary

This paper reviews the clinical evaluation of acyclovir in the treatment of herpesvirus infections, predominantly those due to herpes simplex and varicella-zoster viruses. Intravenous, oral and topical acyclovir have been reported to be effective in the therapy of a wide variety of established herpes simplex virus infections and the systemic drug has been shown to be capable of suppressing reactivation of that virus. Although acyclovir has less activity against varicella-zoster virus, infections caused by this agent are also susceptible to intravenous and possibly oral therapy. Clinical efficacy against Epstein-Barr virus and cytomegalovirus infections has not been demonstrated but several studies are currently in progress. Limited evidence of in vivo activity against hepatitis B virus also requires further evaluation. Continued studies on tolerance of the drug in clinical use has confirmed the early promise of this selective antiviral, whilst initial concern about the development of widespread resistance has not been borne out in practice.

acyclovir (Zovirax); herpes virus

Introduction

Following the first report in the literature by Elion et al. in 1977 [1] considerable progress has been made in the development of the antiviral agent acyclovir. Previously described in the literature as '248U' or 'acycloguanosine', the drug is 9-(2-hydroxyethoxymethyl)guanine and has the registered trade name 'Zovirax' (Wellcome). Many in vitro studies have been performed in order to elucidate the antiviral activity and mechanism of action of acyclovir. Extensive studies in animals have also been undertaken to evaluate the efficacy, pharmacokinetics and potential toxicity of the drug before its wide application to man.

Various systemic and local formulations of acyclovir have now been studied in man

and are licensed in many countries throughout the world. Although currently indicated for the treatment of herpes simplex virus (HSV) infections data will be presented supporting efficacy of acyclovir in the prevention of HSV disease and in the treatment of varicella-zoster virus (VZV) infections. This review is intended mainly as an update of the clinical applications of the drug. The possibility of its use in other virus diseases will also be briefly discussed. More detailed information about the preclinical and early clinical aspects are contained in a previous review by Brigden et al. [2].

Summary on preclinical data

Antiviral activity, as measured by in vitro systems, and pharmacokinetics of the drug in man probably have direct relevance to clinical efficacy. Table 1 gives the approximate sensitivity of herpesviruses to acyclovir as measured by a 50% inhibitory concentration in plaque-reduction assays. It is immediately apparent that HSV types 1 and 2 [3], and perhaps also Epstein-Barr virus (EBV) [4], are highly sensitive to the drug. VZV is moderately sensitive whilst cytomegalovirus (CMV) is variably less sensitive or insensitive to acyclovir. Virus-specific thymidine kinase such as that found in sensitive HSV and VZV strains is normally required to activate acyclovir. Whilst EBV and CMV lack this enzyme they show variable sensitivity to the small amounts of acyclovir triphosphate formed in infected cells [2]. The mode of action of acyclovir has been detailed in a previous review by Brigden et al. [2]. Simian B virus [5] is a very rare cause of disease in man and will not be discussed further.

Peak plasma levels of acyclovir in excess of the inhibitory dose-50% (ID_{50}) are easily achievable using intravenous therapy (Table 2). Peak levels following standard oral doses are also in excess of the ID_{50} values of HSV (and EBV) but only at or around the ID_{50} values of VZV. It is not yet possible to relate clinical efficacy to in vitro activity or plasma levels of acyclovir but it is to be hoped that this information will be forthcoming. For local therapy of HSV infections there are many animal models which are proving to be useful predictors of efficacy in man. Such models would include the

TABLE 1

Approximate mean 50% inhibitory dose (ID_{50}) values of acyclovir for different herpesviruses affecting man, intended as a rough guide of relative in vitro activity

Virus	Approximate ID_{50} values (μM)	Source of data (Ref.)
Herpes simplex type 1 (HSV-1)	$\leqslant 0.3$	[3][a]
Herpes simplex type 2 (HSV-2)	0.3	[3][a]
Epstein-Barr (EBV)	0.3	[4][b]
Varicella-zoster (VZV)	3.0	[3][a]
Simian B	3.0	[5]
Cytomegalovirus (CMV)	$\geqslant 30.0$	[3][a]

[a] A review of multiple studies using different cell lines.
[b] Measured by nucleic acid hybridization analysis.

TABLE 2

Peak and trough plasma acyclovir levels following intravenous and oral dosing at dosage levels currently employed

Dose	Mean plasma acyclovir level (μM)		Reference
	Peak	Trough	
Intravenous			
5 mg/kg 8 hourly	43.5	3.1	[110]
10 mg/kg 8 hourly	91.9	10.2	[110]
Oral			
200 mg 4 hourly	2.5	1.3	[111]
400 mg 4 hourly	5.2	2.8	[111]

rabbit eye for evaluation of ophthalmic formulations, and guinea pig skin for comparison of dermal preparations. In one such study Collins and Oliver [6] showed that acyclovir cream was superior to acyclovir ointment for treatment of cutaneous HSV infections. Unfortunately no such model infections exist for the other herpesviruses and so all evaluations must take place in man which may delay progress towards clinical application.

Clinical trials

The natural history of herpesvirus infections differs depending on whether the patient has an intact or an impaired immune system and whether the infection is the first contact with the virus or a recurrence caused by reactivation of latent virus. Accordingly, the results of clinical studies with acyclovir will be discussed primarily with reference to the host's immune status.

The normal host

Initial genital herpes

Genital infections caused by HSV, particularly type 2, are an increasing problem in many parts of the world. Especially if there is no pre-existing HSV antibody the first or initial attack may be quite severe sometimes necessitating hospitalisation of the patient. The main problem with this disease, nevertheless, is its recurring nature. A summary of the various completed studies with acyclovir is given in Table 3. In 2 placebo-controlled trials with intravenously given acyclovir in severe primary genital herpes, Mindel et al. [7] and Corey et al. [8] demonstrated significant effects on the duration of viral shedding, duration of symptoms and progression of lesions. The total duration of the disease was more than halved from an average of 14–21 days in the placebo group to only 7–9 days in the acyclovir patients. Whether such therapy might effect subsequent recurrence rates is not yet known.

More recently, Nilsen et al. [9], Bryson et al. [10] and Mertz et al. [11] have

TABLE 3

Results of double-blind, placebo controlled trials of acyclovir in initial genital herpes

Reference	Route of administration	Dose	Antiviral efficacy[a]	Clinical efficacy[b]		
				H	NL	S
Mindel et al. [7]	Intravenous	5 mg/kg t.i.d.	+++	+++	+++	+
Corey et al. [8]	Intravenous	5 mg/kg t.i.d.	+++	++	++	+
Nilsen et al. [9]	Oral	200 mg 5×/day	+++	++	++	++
Bryson et al. [10]	Oral	200 mg 5×/day	+++	+	++	+
Kinghorn et al. [16]	Topical (cream)	5×/day	++	+++	+++	±
Fiddian et al. [12]	Topical (cream)	5×/day	+++	+++	++	+
Thin et al. [15]	Topical (ointment)	5×/day	+	+	+	++
Corey et al. [14]	Topical (ointment)	4×/day	+	+	-	±

+++, highly significant ($P < 0.001$); ++, very significant ($P < 0.01$); +, significant ($P < 0.05$); ±, strong trends ($P < 0.1$); -, not significant ($P > 0.1$).

[a] Effects on viral shedding.

[b] Effects on healing (H), new lesion formation (NL) and symptom duration (S).

demonstrated that orally administered acyclovir is also effective in the treatment of initial genital HSV infections. Comparison between the trials suggest that the two systemic formulations are equally effective in the treatment of the acute disease [12,13]. Topical treatment has been shown to have similar though perhaps slightly less impressive effects when used as the ointment [14,15], but as the cream [12,16] is probably as effective as systemic therapy. Oral and dermal formulations are obviously suitable for outpatient treatment of initial disease, but intravenous therapy may be useful for hospitalised patients with more severe attacks.

Recurrent genital herpes

Nilsen et al. [9], Reichman et al. [17,19], and Salo et al. [18] have all reported that orally administered acyclovir can reduce the duration of recurrent episodes of genital herpes (Table 4). Since the natural history of such infections is usually fairly short, major effects can only be expected if therapy is initiated as early as possible after the onset of prodromal symptoms. Reichman et al. [19] reported significantly better results from self-initiated therapy during the prodrome than when treatment was started in the clinic. Delayed treatment may still be worthwhile for the more severe episodes as demonstrated by Fiddian et al. [20]. In patients with frequent recurrences it may be justifiable to attempt prevention of attacks by using continuous therapy. An early report by Straus et al. [21] in immunodeficient patients suggested that suppression of infection was possible with acyclovir given orally. More recently, Straus et al. [22], Douglas et al. [23] and others (unpublished data) have reported successful suppression of recurrences in frequent sufferers (Table 5). Further work is in progress to determine optimal dosing and the long-term benefits and safety of continuous treatment.

Early reports of topical therapy of recurrent infections were not as encouraging.

TABLE 4

Results of double-blind, placebo controlled trials of acyclovir in the treatment of recurrent genital herpes

Reference	Route of administration	Dose	Antiviral efficacy[a]	Clinical efficacy[a]		
				H	NL	S
Nilsen et al. [9]	Oral	200 mg 5×/day	+++	+++	+	-[b]
Reichman et al. [17]	Oral	200 mg 5×/day	+++	+++	+	-[b]
Salo et al. [18]	Oral	200 mg 5×/day	+++	+	+	+
Reichman et al. [19]	Oral	200 mg 5×/day	+++	+++	+	±
Fiddian et al. [12]	Topical (cream)	5×/day	++	++	++	+++
Corey et al. [14]	Topical (ointment)	4×/day	+	±	+	±

[a] As for Table 3.
[b] Lack of effect on symptoms was probably due to delay in onset of therapy for up to 48 h.

TABLE 5

Recurrence rates of genital herpes during continuous therapy with oral acyclovir or placebo

Reference	Dose	% Patients with recurrences	
		placebo	acyclovir
Douglas et al. [23]	200 mg b.d.[a]	94	31
Straus et al. [22]	200 mg t.i.d.[a]	94	27
Unpublished data	200 mg q.i.d.[b]	95	16
Douglas et al. [23]	200 mg 5×/day[a]	94	22

[a] For 4 months.
[b] For 3 months.

With a 5% acyclovir ointment Corey et al. [24] reported only a reduction of viral shedding and new lesion formation compared with placebo. In a larger series Corey et al. [25] demonstrated a significant but modest shortening (from 9.7 to 7.6 days) of the healing time in male patients. When pooled with results from other centres the time to crusting in men and percent of new lesion formation in all patients were reduced, as reported by Corey et al. [14]. An alternative formulation, 5% acyclovir cream, has been evaluated. Using early patient-initiated therapy Fiddian et al. [12] have shown that the results achieved with the cream compare favourably with the oral formulation (Table 4). The apparent superiority of the cream over the ointment has already been demonstrated by Collins and Oliver [6] using an animal model of cutaneous HSV infections. In further studies Collins and Oliver (personal communication) also showed the cream formulation to be superior to 5% acyclovir in dimethyl sulphoxide.

Herpes labialis

Similar experiences have been reported with topical treatment of oro-labial HSV infections (Table 6). Spruance et al. [26] showed that acyclovir ointment reduced virus

TABLE 6

Results of double-blind, placebo controlled trials of topical acyclovir (cream or ointment) in herpes labialis

Reference	Formulation	Frequency of applications	Antiviral efficacy[a]	Clinical efficacy[a]		
				H	NL	S
Fiddian et al. [29]	Dermal cream (5%)	5×/day	NA[b]	++	-	±
van Vloten et al. [30]	Dermal cream (5%)	5×/day	NA	+	NA	-
Spruance et al. [26]	Dermal ointment (5%)	4×/day	+	-	-	-
Fiddian and Ivanyi [27]	Dermal ointment (5%)	5×/day	NA	+	NA	NA
Spruance et al. [28]	Dermal ointment (10%)	8×/day	+	-	NA	NA

[a] As for Table 3.
[b] NA, not analysed.

excretion from lesions of subjects with herpes labialis and this effect was enhanced in those in whom treatment was started early. They demonstrated no significant effects on the clinical course of the episodes but some trends in favour of acyclovir were seen in the patients treated early. Fiddian and Ivanyi [27] have reported that clinical benefit may be achieved with this formulation following patient-initiated therapy of recurrences in patients experiencing severe attacks. However, using early self-medication and even doubling the concentration of acyclovir in the ointment had no effect on the course of recurrent infections in healthy subjects as demonstrated by Spruance et al. [28]. The authors concluded that new formulations should be explored which enhance penetration through the skin.

Acyclovir cream has in fact been reported to be effective in the treatment of herpes labialis presumably because in the aqueous phase acyclovir can pass through the stratum corneum. In one study, Fiddian et al. [29] showed in healthy subjects that early self-initiated therapy reduced the duration of lesions from 6 to 4 days and, perhaps more importantly, increased the percentage of episodes that effectively aborted from 11% to 42%. In another trial van Vloten et al. [30] demonstrated similar effects on the course of established lesions of herpes labialis in patients attending a dermatology clinic. An anecdotal report by Kennedy et al. [31] indicated that prophylactic use of topical acyclovir could prevent most of the frequent recurrences of herpes labialis and the associated attacks of erythema multiforme experienced by one patient. Controlled trials are now in progress evaluating topical and oral therapy in this latter indication. Reviews of the treatment of herpes labialis with acyclovir have been prepared by Fiddian et al. [32] and Yeo and Fiddian [33].

Herpes keratitis

Numerous papers attest to the efficacy of acyclovir ophthalmic ointment in the treatment of HSV infections of the eye (Table 7). Jones et al. [34] first demonstrated in a controlled trial the potential of this formulation for the management of dendritic ulceration of the cornea. They showed that acyclovir completely prevented the early recurrences of lesions following minimal wipe dibridement compared with a more

TABLE 7

Results of comparative studies of 3% acyclovir ophthalmic ointment in herpes keratitis

Reference	Comparative treatment[a]	Clinical efficacy (significant difference[b])
Jones et al. [34]	PCB	Recurrences: ACV = 0%, PCB = 58% (+)
Collum et al. [35]	IDU (0.5%)	Healing: ACV = 4.4 days, IDU = 9.2 days (++)
Colin et al. [36]	IDU (0.5%)	More rapid healing with ACV (+)
Klauber and Ottovay [112]	IDU (0.5%)	Cure rate: ACV = 94%, IDU = 70% (+)
McCulley et al. [113]	IDU (0.5%)	As effective, but less toxic than IDU(-)
Coster et al. [37]	IDU (1%)	At least as active as IDU (-)
Young et al. [38]	Ara-A (3%)	Healing: ACV = 6.4 days, Ara-A = 9.4 days (++)
McGill [39]	Ara-A (3%)	At least as good as Ara-A (-)
Laibson et al. [40]	Ara-A (3%)	As effective as Ara-A (-)
la Lau et al. [41]	TFT (2%)	Both highly effective (-)
Colin et al. [114]	ACV + INF	Faster healing after combination (++)
Wilhelmus et al. [115]	ACV + DEB	Combination gave more rapid healing (+)
Jensen et al. [43]	ACV + DEB	No differences were detected (-)

[a] PCB = placebo
IDU = idoxuridine
Ara-A = adenine arabinoside
TFT = trifluorothymidine
ACV = acyclovir
INF = interferon (drops)
DEB = mechanical debridement
} ointments

[b] ++, highly significant ($P < 0.01$); +, significant ($P < 0.05$); -, not significant ($P > 0.05$).

than 50% incidence in the placebo group. Since then acyclovir has been compared with the other available antiviral therapies for the treatment of herpes keratitis. Collum et al. [35] reported that acyclovir was superior to idoxuridine, producing a mean healing time of 4.4 days compared with 9.2 days, as did Colin et al. [36]. Several authors, including Coster et al. [37], showed that the drugs had comparable efficacy. Similar results have been demonstrated for acyclovir compared with adenine arabinoside; Young et al. [38] showed acyclovir to be more effective whilst McGill [39] and Laibson et al. [40] reported them to be roughly equivalent. In the only comparative trial with trifluorothymidine la Lau et al. [41] did not demonstrate any significant differences between the therapies.

Patients failing to respond to the other antiviral agents have shown favourable responses to acyclovir in open studies and this has been documented by Collum and Benedict-Smith [42] and Jensen et al. [43]. Particularly in the treatment of the more

severe ocular HSV infections the other existing antivirals are believed to be less than satisfactory, especially when the deeper tissues of the eye are involved. Since acyclovir has been shown by Poirier et al. [44] to penetrate the cornea and produce significant levels of drug in the aqueous humour, whereas the other agents do not, and also since acyclovir is devoid of toxicity even during long-term use, it is seen to have potential advantages. Topical acyclovir alone was reported to be superior to idoxuridine in controlling herpetic iridocyclitis [45] and superior to trifluorothymidine in controlling keratouveitis (Hoang-Xuan et al., personal communication). Collum et al. [46] reported a combination of acyclovir ointment and dilute steroid drops to be effective in the management of disciform keratitis. Acyclovir ointment and local corticosteroids were also effective in deep stromal herpetic keratitis as demonstrated by van Ganswijk et al. [47].

More recently, Hung and Patterson (personal communication) reported good penetration of acyclovir into the aqueous humour following oral administration. Hence oral administration could be useful in the long-term treatment of deep stromal keratitis and uveitis or in cases where compliance with local therapy is a problem. Topical treatment is extremely well tolerated as demonstrated by Morgan et al. [48] in a small placebo-controlled study. Also, unlike the other commonly used antivirals acyclovir does not inhibit corneal wound healing [49].

Herpes zoster

Little work has been done to evaluate acyclovir as a treatment for chickenpox, the primary infection caused by VZV: in otherwise normal children the disease is usually not severe enough to warrant therapy. However, in malnourished children in developing countries and in adults who have escaped infection during childhood the disease can be quite severe, sometimes with systemic involvement, particularly of the lungs. Al-Nakib et al. [50] reported from a placebo-controlled trial in young adults that intravenously given acyclovir was effective in reducing the duration of vesicle eruption and fever. Anecdotal reports have also suggested that this formulation might be useful for treatment of chickenpox pneumonia [51].

The major application of acyclovir in VZV infections has been in the treatment of herpes zoster (shingles). Controlled trials by Peterslund et al. [52], Bean et al. [53], McGill et al. [54] and Juel-Jensen et al. [55] have demonstrated the value of intravenously given acyclovir in relieving the acute pain and improving the healing rate of herpes zoster (Table 8). Such a treatment requires hospitalisation and may therefore have to be reserved for more severe cases or for patients who are at greater risk for complications, as is the case with the elderly or with facial zoster threatening the eye.

Several trials of acyclovir given by mouth or applied topically as a cream are in progress. Treatment by one or other of these routes may be effective and would obviously facilitate outpatient management of zoster. Peterslund et al. (personal communication) have compared intravenous and oral acyclovir in a double-blind, controlled study and reported that both are equally effective. Further studies are required to confirm this and to determine the optimum oral dose. For involvement of the eye with herpes zoster, McGill [39] has reported that the ophthalmic ointment is effective and so perhaps this formulation could be used to prevent spread of infection from the skin as well as for treatment of established disease of the eye.

TABLE 8

Results of double-blind, placebo controlled trials of intravenous acyclovir in acute herpes zoster

Reference	Dose	Antiviral efficacy[a]	Clinical efficacy[a]		
			H	NL	S
Peterslund et al. [52]	5 mg/kg t.i.d.	NA[c]	+	NA	+
McGill et al. [54]	5 mg/kg t.i.d.	NA	++	+++	±
Bean et al. [53]	10 mg/kg t.i.d.[b]	+	++	+	+
Juel-Jensen et al. [55]	10 mg/kg t.i.d.	NA	±	±	±

[a] As for Table 3.
[b] Actually 500 mg/m^2 t.i.d.
[c] NA, not analysed.

Other infections

The fortunately rare but very serious systemic complications of HSV infections in children and adults, namely neonatal HSV disease and herpes encephalitis, merit some attention. Difficulty in recruiting adequate numbers of patients into controlled trials implies that it will take some time before definitive results will be available. Interim results presented by Whitley [56] suggest that effective antiviral therapy may result in a reduced mortality from these diseases. Results of case series of treated infections in neonates by Gould et al. [57] and Yeager [58], and anecdotal observations in herpes encephalitis from Chapman and Brigden [59] and Harrington et al. [60] are also encouraging. It should be noted that twice the normal dose of acyclovir is usually given for these conditions and treatment is continued for 10 days or more. When considering chemotherapy for these infections the potential benefits of an early onset of treatment should be realised.

Another complication of HSV infection is eczema herpeticum and reports by Gould et al. [57] and Swart et al. [61] suggest that acyclovir is useful in the management of this condition.

Several other manifestations of herpes virus infections require further evaluation. These include primary HSV stomatitis or proctitis, and EBV and CMV infections in non-immunocompromised patients. Quite recently, Sixby et al. [62] reported a small placebo-controlled, double-blind, randomised study of intravenously given acyclovir in hospitalised patients with acute infectious mononucleosis. Acyclovir appeared to exert a beneficial clinical effect on regaining of weight, which may reflect pharyngitis and anorexia, and which began on day 4 compared with day 10 in the placebo group. An apparent suppression of viral excretion in the throat was documented. The value for the sensitivity of EBV in vitro (Table 1) from Pagano et al. [4] suggests that it would be reasonable to study oral therapy in the treatment of early acute infectious mononucleosis.

Another DNA virus that may be susceptible to acyclovir is hepatitis B virus (HBV). Although HBV DNA polymerase is only sensitive in vitro to extremely high concentrations of acyclovir [3] it has been reported that acyclovir triphosphate is quite active (Hantz et al., personal communication). Weller et al. [63] first reported in vivo

inhibition of HBV replication in 2 patients with chronic infection treated with high doses of intravenous acyclovir for 5 or 7 days. Similar effects were seen by Smith et al. [64] in 3 patients given several short courses of therapy. The effects were only transient and further work is required to explore the use of longer periods of treatment. In one such study Trepo et al. (personal communication) demonstrated inhibition of viral replication in 10 patients given acyclovir at 45 mg/kg/day for 21 days by continuous infusion, but permanent loss of activity occurred in only one. The use of high dose intermittent intravenous infusions is now being investigated.

Despite initial enthusiasm expressed by Bauer [65] for the treatment of chronic plantar warts, a controlled trial by Gibson et al. [66] revealed a lack of effect from topical acyclovir. Ongoing studies in the treatment of genital warts are expected to show similar ineffectiveness.

The immunocompromised host

HSV infections

In a large multicentre, double-blind, placebo-controlled study, Meyers et al. [67] reported that intravenously administered acyclovir was effective and safe in the treatment of mucocutaneous HSV infections in immunocompromised patients. Significant effects on the duration of virus shedding from lesions, the duration of pain, the time to scabbing and the time to healing of lesions were demonstrated. The latter was reduced by almost one week, from a median of 20.1–13.7 days. Different groups of patients many of whom were included in this overall trial report, have been documented separately (Table 9). Wade et al. [68] presented similar data for infected patients following bone marrow transplantation and several renal transplant patients were included in a paper by Mitchell et al. [69]. A separate report by Chou et al. [70] showed dramatic effects in a small number of acyclovir-treated patients after cardiac transplantation compared with placebo-treated controls.

TABLE 9

Results of double-blind, placebo-controlled trials of intravenous acyclovir in HSV infections in immunocompromised patients

Reference	Major underlying disease	Dose[a]	Antiviral efficacy[b]	Clinical efficacy[b]		
				H	NL	S
Meyers et al. [67]	Marrow transplant; lymphoma; leukaemia	5 mg/kg t.i.d.	+++	+	NA[c]	++
Wade et al. [68]	Marrow transplant	5 mg/kg t.i.d.	+++	+	NA	+
Mitchell et al. [69]	Renal transplant; marrow transplant	5 mg/kg t.i.d.	++	±	±	+
Chou et al. [70]	Cardiac transplant	5 mg/kg t.i.d.	++	±	NA	±

[a] Actually 250 mg/m^2 t.i.d.

[b] As for Table 3.

[c] NA, not analysed.

Whitley et al. [71] demonstrated in a controlled trial that topically applied acyclovir was also effective in reducing viral shedding and pain associated with mucocutaneous HSV infections in immunocompromised patients, mostly renal transplant recipients. Numerous uncontrolled series and anecdotal reports of apparently successful topical and intravenous therapy with acyclovir have also been published. More notable amongst these are papers by Selby et al. [72], O'Meara and Hillary [73], van der Meer and Versteeg [74], Spector et al. [75] and Straus et al. [21]. In the latter report the authors suggest that orally administered acyclovir is also effective in the treatment of mucocutaneous HSV infections.

If therapy is initiated after the onset of lesions then significant tissue damage may have occurred and so only partial benefit may be achieved. Where it is possible to predict a high risk of recurrent HSV infections, as for instance following organ or marrow transplantation, prophylaxis may be more appropriate (Table 10). Saral et al. [76] were the first to show in a controlled trial that intravenous acyclovir could successfully prevent HSV infections in susceptible patients immediately after bone marrow transplantation. They used a standard dose of drug given every 8 h and this gave complete protection. Hann et al. [77] treated both bone marrow transplant patients and patients with acute leukaemia undergoing induction chemotherapy with 2 daily administrations of acyclovir or placebo. All the marrow recipients and most of the leukaemic patients receiving the drug were prevented from developing HSV infections. The acyclovir group of transplant patients also had fewer days of fever and a shorter duration of leukopenia (i.e., more rapid engraftment). Saral et al. [78] have now also studied acute leukaemics and again found complete protection with 3 daily infusions of acyclovir.

More recently, there have been several reports of successful prophylaxis with oral acyclovir in placebo-controlled trials as well as in open studies. Wade et al. [79] and

TABLE 10

Rates of HSV infection in patients receiving intravenous or oral acyclovir prophylaxis following transplantation or induction chemotherapy

Reference	Dose/route	Underlying disease	% Compliant patients with HSV infections	
			placebo	acyclovir
Saral et al. [76]	5 mg/kg t.i.d.[a], i.v.	Marrow transplant	70	0
Saral et al. [78]	5 mg/kg t.i.d.[a], i.v.	Leukaemia	73	0
Hann et al. [77]	5 mg/kg b.d., i.v.	Marrow transplant	50	0
Hann et al. [77]	5 mg/kg b.d., i.v.	Leukaemia	50	11
Wade et al. [79]	400 mg 5×/day p.o.	Marrow transplant	68	4
Prentice and Hann [82]	400 mg 4×/day p.o.	Marrow transplant	50[b]	20
Gluckman et al. [80]	200 mg 4×/day p.o.	Marrow transplant	68	0
Fiddian [81]	200 mg 4×/day p.o.	Cardiac transplant	80[b]	0

[a] Actually 250 mg/m^2 t.i.d.

[b] Historical control group.

Gluckman et al. [80] conducted formal trials in bone marrow transplant patients demonstrating that doses of 400 mg 4 hourly or 200 mg 6 hourly are effective in preventing reactivation of HSV during treatment. Others, including Straus et al. [21], Fiddian [81] and Prentice and Hann [82] have reported similarly dramatic results in open studies of patients with immunodeficiency syndromes, cardiac transplants or bone marrow transplants, respectively. It has been noted that recurrences of HSV infections still occur after arresting prophylactic therapy with acyclovir. Further studies have been initiated to evaluate long-term treatment for periods of up to 6 months or more.

Systemic infections caused by HSV are fortunately not very common and concern about the life-threatening nature of such infections has in any case precluded placebo-controlled trials. There are several anecdotal reports in which intravenous acyclovir was believed to have had a beneficial effect in such situations. Amongst these are Many et al. [83] for HSV oesophagitis, Selby et al. [72] and Goldman et al. [84] for HSV pneumonia and Heaton et al. [85] for HSV encephalitis. It seems likely that the greatest benefits from acyclovir will be achieved by preventing dissemination of infection in patients at risk rather than in treating already widespread disease.

VZV infections

With the common practice of using zoster immune globulin for the prevention of primary infections in susceptible patients at risk, large controlled trials of acyclovir in this indication have not been possible. In a small double-blind, placebo-controlled study on chickenpox Prober et al. [86] showed that intravenous acyclovir prevented dissemination of the disease to the lungs. None of 7 acyclovir-treated patients developed pneumonia compared with 5 of 11 placebo recipients. In addition, there have been several anecdotal reports of efficacy in the treatment of cutaneous and visceral varicella. Amongst these, studies by van der Meer and Versteeg [74], Kinney et al. [87] and Shulman et al. [88] indicate that acyclovir may be useful in the management of primary VZV infections. The possible role of acyclovir in the prophylaxis of such infections is currently under evaluation.

A large placebo-controlled trial in herpes zoster has been conducted in the U.S.A. and the results have recently been reported by Balfour et al. [89]. The most important finding was that intravenous acyclovir halted progression of the disease as measured by cutaneous or visceral dissemination. Three patients in the placebo-treated group died from visceral zoster developing during the study. The rates of pain and cutaneous resolution were accelerated by acyclovir. Greatest overall effects were seen in patients treated within 72 h of onset of the rash. Significant effects on cutaneous healing and the duration of acute pain were reported in a smaller controlled trial by Rocchi et al. (personal communication) where therapy was initiated early after the onset of the rash. Again there are numerous anecdotal reports in the literature. O'Meara and Hillary [73], Serota et al. [90], Selby et al. [72], Spector et al. [75], and others all treated several patients with localised zoster. In many cases it was felt that acyclovir was beneficial and most impressive were the rapid effects on pain and the way progression of the disease was arrested. Acyclovir was also thought to be potentially useful in the treatment of disseminated cutaneous zoster, as reported by Balfour et al. [89], van der

Meer and Versteeg [74], O'Meara and Hillary [73] and Cupps et al. [91]; and possibly for the visceral complications of zoster such as pneumonia [72,89], and meningoencephalitis [74,89,92,93]. As with HSV infections it was felt that the greatest impact from acyclovir might be in prevention of dissemination, whether locally or systemically. However, it should be noted that a higher dose of acyclovir was often employed in the treatment of these VZV infections (10 mg/kg or 500 mg/m^2 every 8 h for 7 days). Novelli et al. (personal communication) suggest that high oral doses of acyclovir may also be useful in the treatment of VZV infections in immunocompromised children. Oral administration of acyclovir has also been considered for the prevention of reactivation of VZV in susceptible patients following transplantation and either oral or topical administration for treatment of established infections. A number of clinical trials are in progress to explore these possibilities.

Other infections

There are few published data and some apparent discrepancy with the findings relating to acyclovir treatment of EBV infections in immunocompromised patients. Hanto et al. [94] reported antiviral and clinical effects in a patient with an EBV-associated lymphoma following renal transplantation. On the other hand, Sullivan et al. [95] showed no such effects in 2 children with life-threatening EBV infections. Further work is required to determine whether acyclovir will have any role to play in the treatment of EBV disease. At the present time more emphasis is being placed on evaluating the drug in EBV-infected patients with reasonably intact immune systems.

Finally, for treatment of CMV infections there is also some disagreement between reports from different centres, although this again may be due to differences in the immune status of the patients involved. In a controlled trial reported by Balfour et al. [96], the authors concluded that acyclovir may be useful for treatment of CMV disease in certain immunosuppressed patients, particularly renal allograft recipients. Nunan et al. (personal communication) also report benefit in renal transplant patients, and in a single patient case report Ashraf et al. [97] stated that acyclovir may also be useful for treatment of CMV pneumonia after cardiac transplantation; whereas Wade et al. [98] and Meyers et al. [99] reported that acyclovir was not effective for CMV pneumonia after marrow transplantation. It is worth noting that Plotkin et al. [100] demonstrated a definite but transient antiviral effect in congenitally infected children. It is reasonable to suppose that prophylaxis would be the most likely situation in which acyclovir might offer hope against CMV infections. The findings of Gluckman et al. [80] appear to support this view. They report an incidence of 7 out of 19 patients (37%) clinically infected by CMV after bone marrow transplantation in the placebo group compared with 0 out of 20 patients receiving acyclovir by the oral route. Since CMV is not very sensitive, efficacy with acyclovir by mouth does seem surprising and so confirmation of these results is eagerly sought. Controlled trials in renal transplant patients, using intravenous therapy early in the course of CMV disease, are also in progress.

Tolerance in clinical use

There has now been extensive experience with all the various formulations of acyclovir. In an earlier review by Keeney et al. [101] this subject was discussed. Following intravenous injection the major adverse reaction is a transient impairment of renal function. This is generally avoidable if adequate hydration of the patient is ensured and if the drug is given as a slow infusion over 1 h, rather than as a bolus injection, as reported by Chapman and Bridgen [59]. In the presence of pre-existing renal impairment dosage modification should be performed as recommended. Brigden et al. [102] have given detailed information on this topic and demonstrated that, in animals, the problem is caused by transient crystal deposition in the collecting tubules of the papilla associated with minimal and reversible histological changes of the epithelial cells.

Another adverse reaction definitely related to acyclovir administration is inflammation at the local injection site but with care this can be kept to a minimum. In addition, several other events have been reported in patients receiving intravenous injection including occasional nausea and vomiting, reversible neurological reactions, raised liver enzymes, rashes and decreased haematological indices. The incidence of these reported adverse events does not cause concern about the toxicity of the drug in normal usage. However, at higher doses there have been increased reports of nausea and vomiting associated with rises in serum creatinine [53] which may have been related to more rapid or frequent infusion of acyclovir [103] and neurologic symptoms in marrow recipients which may have been due to concurrent therapies [104].

Expectedly, since with oral administration the plasma levels of acyclovir are much lower, the incidence of side effects occurring during oral therapy is very small. Indeed when the experience gained from treating over 1 000 patients in controlled trials is pooled then the nature and severity of such events do not differ between the acyclovir and placebo groups. In fact rather more events occurred in patients receiving placebo, particularly elevation of liver enzymes. Nilsen et al. [9] have reported some of this experience. During long-term oral therapy for 3 or 4 months the drug has also been reported to be well tolerated by Halsos et al. (personal communication) and Straus et al. [22] respectively.

With dermal applications of acyclovir cream or ointment the majority of adverse events are the result of physical contact with raw surfaces. Corey et al. [14] reported transient pain or burning on application of the ointment in 24% of initial and 11% of recurrent cases of genital herpes compared with 36% and 16% of placebo recipients respectively. With acyclovir cream more patients with initial genital herpes had adverse events (11% acyclovir and 32% placebo) than with recurrent disease (7% acyclovir and 2% placebo) but the authors conclude that topical treatment was well-tolerated overall (Fiddian et al. [12]).

Use of acyclovir ophthalmic ointment may be associated with transient stinging and the development of superficial punctate keratopathy. This latter adverse effect is found with the administration of other antivirals to the eye and as discussed by McGill and Tormey [105] is not considered serious. Otherwise the lack of toxicity of acyclovir to the cornea [48], even after long-term use, reflects the exceptional tolerance of this

drug compared with other antivirals. Lass et al. [49] have also shown that acyclovir does not delay corneal wound healing whereas the other antivirals do.

Resistance in clinical practice

Despite the ease with which 'resistance' of HSV to acyclovir and other nucleoside analogues can be produced in vitro rapid emergence of less sensitive strains has not been seen in experimentally infected animals [106] or in the treatment of HSV infections in man [107]. The majority of acyclovir-resistant strains produced in vitro and the only clinical isolates with reduced sensitivity have been defective in thymidine kinase induction. Such strains have been shown to have reduced pathogenicity in vivo and be less likely to become latent or reactivate [106]. Experience in clinical practice has supported these findings. The sensitivity to acyclovir of more than 1 000 HSV isolates from over 400 patients have been reported recently by Dekker et al. [107] and Oliver and Collins (personal communication). In most cases therapy with acyclovir had not significantly altered the sensitivity of the isolates. The few patients in whom resistant viruses were detected were normally severely immunocompromised at the time with asymptomatic or indolent infections. The sensitivity of subsequent recurrent HSV isolates have always been found to be similar to that of the original infecting virus.

Whilst continued efforts to monitor the possible emergence of resistance from even wider use are in progress it seems particular vigilance must be maintained in centres treating severely immunocompromised patients. To date it would appear that therapy of established infections in these patients is a greater risk than is prophylaxis [108]. The latter approach may, therefore, become an accepted part of their clinical management. In the meantime there is no reason to restrict the use of the drug in immunocompetent patients as the risk of development of resistance is remote.

Conclusions

In summary, acyclovir is already playing an important role in the management of infections caused by at least some of the herpesviruses. Certainly most HSV infections, whether in the immunocompromised host or in otherwise normal patients, can be satisfactorily controlled with one or other formulation of acyclovir. Much of the initial impact of the drug in HSV infections has been with treatment of established disease, particularly in severely ill patients. In an earlier review by Fiddian [81] the potential use of prophylaxis in patients at risk of developing HSV infections was discussed. The wider application of the drug for long-term prevention of HSV disease in all groups of susceptible patients now appears to be emerging as a real possibility as evidence is gained about the efficacy and safety of orally administered acyclovir.

For treatment of VZV infections the case for the use of intravenous acyclovir is also well proven. Alternative methods of treatment are being explored and, although the virus is less sensitive than HSV, it is possible that topical or oral therapy may be

successful. Research into the enhancement of acyclovir plasma levels by use of orally administered pro-drugs such as the one reported by Krasny et al. [109] may offer a solution to this problem should the need arise. It is also rather less certain whether prophylaxis will be useful in the management of VZV infections since prediction of those at risk is less easy than with HSV. Nevertheless research is continuing.

Finally, for EBV, CMV and HBV infections it remains to be seen whether acyclovir will have any serious part to play in the treatment or prevention of these diseases. For whichever indication acyclovir is used, it is reassuring to know that the drug will cause little harm to the uninfected host cells because of its targeted activity. The development of acyclovir hopefully heralds a new era of safe and effective antiviral chemotherapy.

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