

Bromovinyldeoxyuridine and interferon treatment in ulcerative herpetic keratitis: a double masked study

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SUMMARY Bromovinyldeoxyuridine is a potent and safe antiherpes compound that in combination with a placebo treatment promoted the partial and complete healing of herpetic epithelial disease in 22 patients in average times of 4.6 days and 8.5 days respectively. However, when BVDU was combined with 1.5×10^6 IU of recombinant $\alpha 2C$ interferon, partial and complete healing times for keratitis in 19 patients were reduced to 2.6 days and 4.6 days respectively. No toxic effects of the medications were observed in any patient.

Bromovinyldeoxyuridine ((*E*)-5-(2-bromovinyl)-2'-deoxyuridine, BVDU) is a 5-substituted analogue of 2'-deoxythymidine (dThd),¹ like idoxuridine (5-iodo-2'-deoxyuridine, IDU) and trifluorothymidine (5-trifluoromethyl-2'-deoxyuridine, TFT). Studies *in vitro* have shown BVDU to possess a more potent and selective activity against herpes simplex virus type 1 (HSV-1) than IDU, TFT, and several other antiviral agents, namely, vidarabine (9- β -D-arabinofuranosyladenine, ara-A, Vira-A), acyclovir (9-(2-hydroxyethoxymethyl)guanine, acyclo-guanosine, ACV, Zovirax), and foscarnet (phosphonoformate).^{2,4} Other viruses sensitive to BVDU are varicella-zoster virus (VZV),^{5,6} simian varicella virus,⁷ Epstein-Barr virus, and some viruses of veterinary importance, namely, suid herpesvirus type 1 and bovid herpesvirus type 1.⁸

BVDU inhibits the replication of HSV-1^{2,4} and VZV^{5,6} at very low concentrations (0.001-0.01 mg/l), whereas the cell toxicity is observed only at drug concentrations of 50-100 mg/l. The selective antiviral activity of BVDU is based on its mechanism of action. In virus infected cells the HSV-1- and VZV-encoded thymidine kinases specifically phosphorylate BVDU.^{9,10} Once converted to its 5'-triphosphate form, BVDU inhibits viral DNA polymerases in a competitive fashion with regard to 2'-deoxythymidine triphosphate (dTTP). BVDU 5'-triphosphate (BVDUTP) has a much greater affinity for HSV-1 DNA polymerase than for the

cellular DNA polymerases α , β , and γ .¹¹ BVDUTP also serves as an alternative substrate for viral DNA polymerase,¹² which results in its incorporation, as BVDU 5'-monophosphate (BVDUMP), into the viral DNA.¹³ The HSV-2-encoded dThd kinase is less efficient in phosphorylating BVDU.^{10,14} Consequently the drug is less effective against HSV-2. BVDU is also inactive against dThd kinase-deficient (TK⁻) mutants of HSV.

Studies on experimental animals have shown topically administered BVDU to be significantly better than IDU in suppressing the development and promoting the healing of epithelial keratitis,^{15,16} and superior to TFT in suppressing the development of HSV-1 stromal disease.¹⁷ Iritis and endotheliitis, produced by directly inoculating the virus into the anterior chamber of rabbit eyes, responded better to BVDU eyedrops than TFT eyedrops.¹⁸ (¹²⁵I)IVDU, a radiolabelled analogue of BVDU, readily penetrates the normal rabbit cornea on topical application and attains therapeutic concentrations in the aqueous humour.¹⁹

Both short-term^{20,21} and long-term^{22,23} follow-up studies in a clinical setting have established that BVDU is a safe and efficacious compound for the treatment of HSV-1 dendritic keratitis, geographic ulcers, and stromal keratitis. The present study was aimed at investigating whether combined therapy of topical BVDU eyedrops and interferon would induce a faster healing of dendritic keratitis than BVDU eyedrops alone. Combination therapy of antiviral

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drugs (namely, TFT and ACV) with interferon has proved to promote faster healing of herpetic keratitis than the antiviral agents used alone.²⁴⁻²⁶

Materials and methods

Patients who presented with a recent recurrence of epithelial herpetic keratitis, without associated complications such as stromal disease, iritis, or secondary glaucoma, were included in the study. Typical dendritic ulcers were present in 30 patients, three patients had stellate lesions, and eight patients had small geographic ulcers. Informed consent was obtained from each patient, or from the parents in the case of children, following the declaration of Helsinki.

The trial was conducted in a double-masked randomised fashion. Before treatment was started material for virus culture was obtained from the corneal lesions by minimal wiping.

Treatment consisted of either BVDU 1% ointment in Fischer's ointment base and recombinant human α 2C interferon (rHuIFN) 1.5×10^6 IU IFN as a solid, soluble substance delivered by an ophthalmic rod, or BVDU 1% ointment and placebo in the form of 3% human serum albumin on an ophthalmic rod. BVDU ointment was applied five times a day. The first application was given after either the interferon or the placebo treatment and was administered daily in the outpatient department of the hospital. This treatment schedule was continued until complete healing of keratitis was achieved, whereafter BVDU ointment alone, five times a day, was applied for another six days.

Two criteria were used to define healing of keratitis, namely, partial healing, when the epithelial wound was closed, and complete healing, which meant an absence of intraepithelial cysts or epithelial oedema in addition to wound closure.

The time required to accomplish partial or complete healing by two treatment regimens was recorded, and the data were subjected to analysis of variance.

Results

The characteristics of the patients in the BVDU- α rHuIFN and the BVDU-placebo groups are shown in Table 1. The two treatment groups were comparable in terms of age and sex. The type and size of corneal lesions and the duration of symptoms before treatment was initiated did not differ significantly in the two groups (Table 2).

Nineteen patients received BVDU- α rHuIFN therapy (Table 3). Partial healing of keratitis occurred in this group in an average of 2.6 days and

Table 1 Patient characteristics of the bromovinyldeoxyuridine-recombinant human α 2C interferon (BVDU-rHuIFN) and the BVDU-placebo treatment group

Patient characteristics	BVDU+rHuIFN	BVDU+placebo	Significance
Sex male %	47	59	
female %	53	41	NS
Age median	32	45	
range	7-32	12-81	NS
Affected eye % OD	53	45	
OS	47	55	NS

NS: not significant.

Table 2 Interval in days between the occurrence of the first symptoms and the beginning of treatment

	BVDU-rHuIFN	BVDU-placebo
Mean (hours)	48	36
Average (days)	6.6	5.6
SD (n-1)	5.0	4.7
n	19	22

BVDU: bromovinyldeoxyuridine.

rHuIFN: recombinant human α -2C interferon.

SD: standard deviation.

n: number of patients.

Table 3 The average number of days for partial and complete healing of herpetic keratitis with BVDU-rHuIFN and BVDU-placebo treatment

		Healing	
		Partial	Complete
BVDU-rHuIFN	x	2.6	4.5
	n	19	19
	SD (n-1)	0.9	1.4
BVDU-placebo	x	4.6	8.5
	n	22	22
	SD (n-1)	1.3	2.2
Significance (p)		0.001	0.001

BVDU: bromovinyldeoxyuridine.

rHuIFN: recombinant human α -2C interferon.

x: mean.

n: number of observations.

SD: standard deviation.

complete healing in an average of 4.5 days. The 22 patients on the BVDU-placebo regimen showed partial healing in an average of 4.6 days and complete healing in an average of 8.5 days.

The distribution of days for partial healing in the BVDU-placebo group showed a tendency to right skewness ($\beta_1=0.23$), whereas this distribution was almost symmetrical ($\beta_1=0.0001$) in the BVDU-rHuIFN treatment group. Both of these distributions were platykurtic, that is, more widely dispersed from

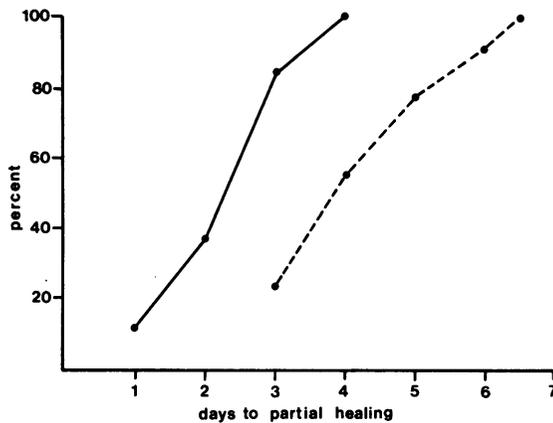


Fig. 1 Cumulative frequency distribution for partial healing of herpetic keratitis treated with bromovinyldeoxyuridine and recombinant human α 2C interferon (●—●) or with bromovinyldeoxyuridine and placebo (●---●).

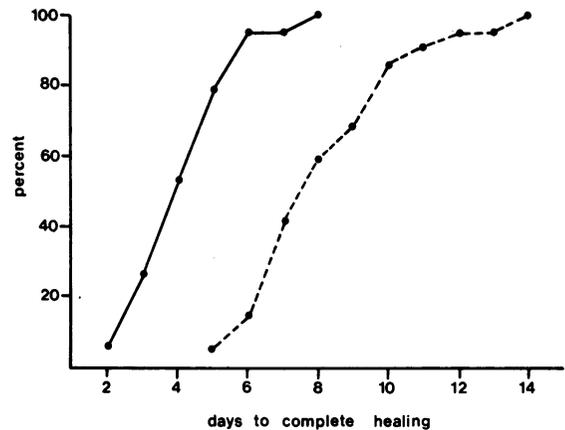


Fig. 2 Cumulative frequency distribution for complete healing of herpetic keratitis treated with bromovinyldeoxyuridine and recombinant human α 2C interferon (●—●) or with bromovinyldeoxyuridine and placebo (●---●).

the mean than normal, resulting in a broad and flattened distribution curve. As regards complete healing, the distributions of days for BVDU-placebo and BVDU-rHuIFN treatments were slightly skewed to the right (β_1 value 0.59 and 0.23, respectively) and leptokurtic—less widely dispersed from the mean than normal—resulting in a higher and narrower distribution curve.

Graphic presentation of the cumulative frequency distributions for the partial and complete healing times are shown in Figs. 1 and 2. Statistical analysis of the data showed a highly significant difference (Table 3, $p < 0.001$) between both the complete and partial healing times of the two treatment groups.

Discussion

The present study shows that a combination therapy of α rHuIFN and BVDU leads to the healing of herpetic keratitis in about half the time required on combined BVDU-placebo treatment. Interferon in combination with other antiviral drugs (TFT^{24,25} or ACV²⁶) has been reported to promote a significantly faster healing than these antivirals used alone. It is still not clear how interferon achieves this beneficial effect when given in combination therapy, as interferon monotherapy does not seem to have any clinical value in the treatment of herpetic dendritic ulcers.²⁷

The average healing time of 8.5 days obtained with BVDU-placebo therapy in the present study is similar to the healing time (average 8.6 days in 76 cases of dendritic ulcers) obtained from treatment with BVDU 0.1% eyedrops, instilled nine times a

day, in a large series of patients.²³ The use of BVDU 1% ointment did not promote a shorter healing time than BVDU 0.1% eyedrops, which confirms the experimental data that increasing the concentration of BVDU in ointment from 0.1% to 2.5% did not improve the therapeutic efficacy of the drug.¹⁶ These observations also suggest that at a 0.1% concentration BVDU appears to be adequate to achieve an optimal therapeutic effect, whether the drug is delivered in the form of eyedrops or ointment.

In our trial we included only those patients who had uncomplicated herpetic epithelial disease of recent onset and had not been treated with other antiviral drugs. In a reported study²³ 44 of 76 patients with dendritic keratitis failed to respond to other antiviral drugs, namely, IDU, TFT, Vira-A, Zovirax, before their treatment was switched to BVDU eyedrops. Since all these patients healed rapidly (average 8.6 days) under BVDU topical eye drops it appears that this drug is an efficacious compound whether the treatment is started early, as in our study, or late, as reported previously.²³

Except for hypersensitivity reactions to the topical drug formulation in a small number of patients, which may be attributed to the vehicle rather than the drug, no other toxic side effects have been reported.²³ In the present investigation no toxic effects, including drug allergy, were observed.

Since BVDU is a selective, safe, and effective compound, it may be used in combination with interferon to achieve a rapid healing of herpetic epithelial disease. Our patients accepted the dispensing of freeze-dried recombinant human α -2C interferon delivered by an ophthalmic rod readily

and rapidly learned how to administer the drug combination. This is of great practical importance, as the patients would not have to visit the ophthalmologist daily if such treatment was prescribed on a routine basis.

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