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ORIGINAL ARTICLE

Multicenter randomized study of inosine pranobex versus acyclovir in the treatment of recurrent herpes labialis and recurrent herpes genitalis in Chinese patients

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ABSTRACT

The objective of the study is to evaluate the efficacy and safety of oral inosine pranobex as compared with acyclovir in the treatment of recurrent herpes labialis (RHL) and recurrent herpes genitalis (RHG). A multicenter double-blind, double-dummy, randomized, controlled, parallel group trial was conducted in 144 patients with RHL and 144 RHG. Patients were assigned to treatment in one of two groups: (i) inosine pranobex group (active inosine pranobex, 1 g four times daily, and acyclovir placebo); or (ii) acyclovir group (active acyclovir, 200 mg five times daily, and inosine pranobex placebo). The total symptom score (TSS) of patients with RHL did not differ in the inosine pranobex and acyclovir group on the 3rd or 7th day of treatment. There was also no difference in the efficacy rates between the two groups. No difference of TSS was observed between patients with RHG taking inosine pranobex and acyclovir on days 3 or 5 of the treatment, respectively. The short-term clinical recurrence rate of RHG at 3-month follow-up was much lower in the inosine pranobex group than acyclovir group. The incidence of hyperuricemia was higher in the inosine pranobex group than acyclovir group. In conclusion, inosine pranobex was as effective as acyclovir in treating RHL and RHG with significantly greater reduction of the short-term recurrence rate of herpes genitalis at 3-month follow up. Long-term recurrence rates at 6 months or longer remain to be determined. Hyperuricemia should be monitored during the treatment.

Key words: **acyclovir, clinical trial, inosine pranobex, recurrent herpes genitalis, recurrent herpes labialis.**

INTRODUCTION

Infections with herpes simplex virus (HSV) are ubiquitous worldwide and highly transmissible. HSV-1 usually causes orofacial infection, whereas HSV-2 is more often associated with genital infection. Both viruses can establish latent infection within the dorsal root and trigeminal sensory ganglia. Recurrence affecting the same dermatome may occur in an unpredictable fashion, causing painful recurrent diseases.[1,2] The prevalence of HSV-2 infection ranges 10–60% in the general population, being the major cause of sexually transmitted genital ulcers worldwide.[3] Acyclovir (ACV) was introduced in the 1980s and has become the standard therapy for all kinds of herpes simplex infections. Due to its hydrophilic nature and poor permeability across intestine and corneal tissues, new guanosine analogs such as valacyclovir and famciclovir have subsequently been developed to improve the oral bioavailabilities. Moreover, long-term use of ACV may cause emergence of resistant viral strains.[4] Inosine pranobex (Isoprinosine; Hainan Hualong Pharmaceutical, Haikou, China) is a synthetic compound consisting of the *p*-acetamido benzoate salt of *N*,*N*-dimethylamino-2-propanol and inosine in a 3:1 molar ratio. With an immunomodulatory effect, it has been shown to exert antiviral and antitumor activities in *vivo* and can be used to treat orolabial herpes, subacute sclerosing panencephalitis, influenza and type B viral hepatitis.[5] An effective delay in the progression of HIV infection in asymptomatic HIV-positive patients taking the drug has also been observed.[6] Available data about the therapeutic efficacy of inosine pranobex in mucocutaneous herpes are controversial. The aim of this study was to explore the

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efficacy and tolerance of the oral inosine pranobex in suppression of recurrent herpes labialis (RHL) and recurrent herpes genitalis (RHG) in comparison with acyclovir.

METHODS

Patients

The double-blind, double-dummy, randomized, controlled, parallel group trial was conducted in eight centers in China from September 2009 until December 2010, including the Southwest Hospital of Third Military Medical University; Institute of Dermatology, Chinese Academy of Medical Sciences; Affiliated Hospital of Nantong University; Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology; Xiehe Hospital, Tongji Medical College of Huazhong University of Science and Technology; First Hospital of Shanxi Medical University; Third Xiangya Hospital of Central South University; and the Affiliated Hospital of Xuzhou Medical College. The clinical trial was approved by the China Food and Drug Administration (2006L03426). The study protocol was also approved by the ethics committees of each participating hospital. All the patients were informed of the experimental nature of the treatment and were asked to give their written informed consent prior to entering the study.

The study population included 144 patients with RHL and 144 patients with RHG, aged 18–65 years. The diagnosis was based on the typical clinical manifestation and history, with viral culture or HSV polymerase chain reaction being conducted in the lesion of the patients whose diagnosis was in need of confirmation. The patients were eligible if they were reported within 48 h of the onset of symptoms and had not received any antiviral drugs in the last 4 weeks. Exclusion criteria were: (i) immunosuppression (e.g. systemic lupus erythematosus, HIV, long-term use of immunosuppressive agents); (ii) treatment with uricogenic medications; (iii) history of cardiovascular, gastrointestinal, kidney or renal disease; (iv) abnormal serum levels of creatinine, urea nitrogen and uric acid; (v) pregnancy or women who did not take adequate contraceptive measures; (vi) elevation of aminotransferase or alanine aminotransferase levels (>1.5 times the upper limit of normal); and (vii) participation in other clinical trials in the past 2 months.

Study design

Patients were randomly assigned to treatment in one of two groups: (i) inosine pranobex group, consisting of active inosine pranobex (1 g four times a day) and acyclovir placebo (200 mg five times a day); or (ii) acyclovir group, consisting of active acyclovir (200 mg five times a day) and inosine pranobex placebo (1 g four times a day). The treatment period of RHL and RHG was 7 and 5 days, respectively. A follow up at 3 months after cessation of treatment of RHG was conducted to assess post-treatment recurrence.

Assessments

A complete medical history, physical examination (including vesicle and rash assessment), electrocardiogram, blood routine, blood chemistry and urine routine were obtained before and at the end of the treatment. The total symptom score (TSS) of the patients with RHL and RHG was evaluated (Tables 1,2) on days 0, 3 and 7/5 by the doctor, respectively. The time index of the lesional changes was also recorded, including the time when the new vesicles stopped appearing, and when scabs began to form and fall off. All adverse events were noted and rated by the investigator at each visit for

Table 1. Total symptom score for recurrent herpes labialis patients

Symptom (score)	0	1	2	3
No. of papules	None	1–3	4–6	>6
No. of vesicles	None	1–3	4–6	>6
No. of erosions	None	1–3	4–6	>6
Diameter of erosions	None	<3 mm, mild effusion	3–5 mm, moderate effusion	>5 mm, obvious effusion
Erythema	None	Reddish, mild edema	Red, moderate edema	Obvious redness and edema
Burning and pain	None	Mild, felt occasionally	Moderate, tolerant	Severe, intolerable

Table 2. Total symptom score for recurrent herpes genitalis

Symptom (score)	0	1	2	3	4
Erythema	None	Reddish	Red, no edema	Red, mild edema	Crimson, obvious edema
Vesicle					
Diameter	None	≤2 mm	3–4 mm	5 mm	>5 mm
Morphology	None	Papulovesicle	Clear blister	Turbid blisters	Blood blister or pustule
Number	None	1–3	4–6	7–10	>10
Erosion	None	Not broken	No erosion	Mild	Shallow ulcer
Adjacent lymphadenectasis	None	<0.5 cm	0.5–0.9 cm	1.0–1.9 cm	≥2.0 cm
Pain	None	Mild, felt occasionally	Moderate, tolerant	Obvious, intolerable	Severe, with systemic symptom

severity and for the possible association with the study drug. The clinical trial was discontinued in the case of security issue, bad efficacy rate and major mistakes in the program.

Statistical analysis

The primary target for assessing efficacy and safety was the intent-to-treat population, involving all subjects randomized to treatment with at least one dose of investigational products. The mean ± standard deviation (SD) was used to describe the measurement outcomes of different treatment groups. Baseline demographic and clinical characteristics were compared by χ^2-test Student's *t*-test. Comparison of the two treatment groups was assessed by using group *t*-test, *t'*-test and Wilcoxon rank sum test. The χ^2-test and Fisher's exact test were used to compare the incidence of adverse events of the two groups after treatment. The magnitude of TSS change after therapy was calculated in percentage (pretreatment TSS − post-treatment TSS / pretreatment TSS × 100 (%). Change of 60% or more was defined as the efficacy rate.

RESULTS

A total of 300 patients were assessed for eligibility during the study period. Of these, 288 patients (144 patients with RHL and 144 with RHG) were randomized into the study (Fig. 1). The treatment groups did not differ in pretreatment demographic and clinical characteristics, as shown in Table 3.

Treatment outcomes

After 3 and 7 days of treatment, the TSS of the inosine pranobex group did not differ from the TSS of the acyclovir group in the RHL patients (Table 4). Comparison of the number of

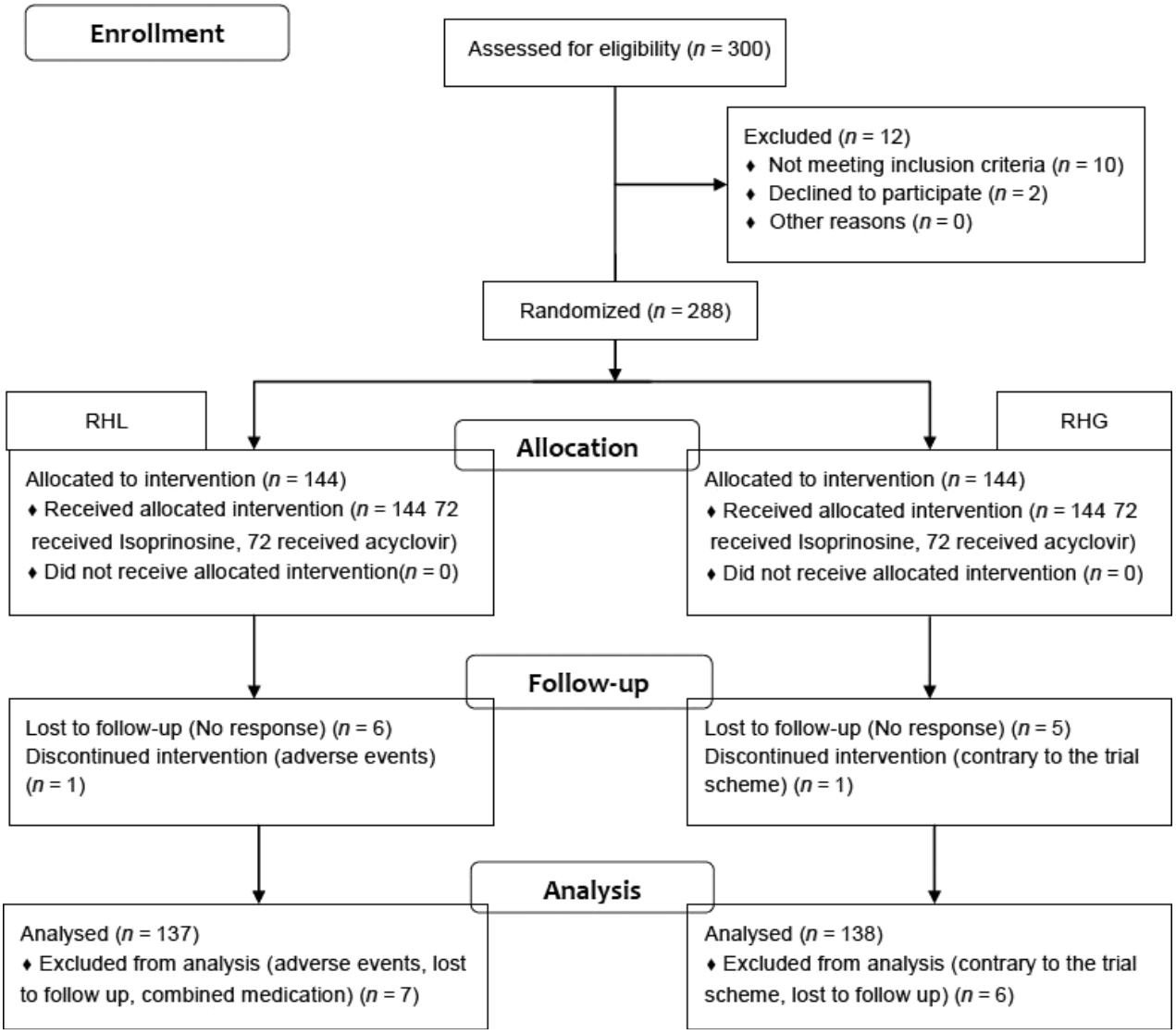

Figure 1. Flow diagram of the participants and numbers of the patients.

Table 3. Baseline characteristics of randomized patients (n = 275)

	RHL (n = 137)		RHG (n = 138)	
	Inosine pranobex (n = 69)	Acyclovir (n = 68)	Inosine pranobex (n = 69)	Acyclovir (n = 69)
Age				
Mean ± SD	40.93 ± 11.50	37.13 ± 12.71	37.23 ± 9.43	37.32 ± 8.821
Sex				
Male, *n* (%)	19 (27.54)	22 (32.35)	45 (65.22)	44 (63.77)
Female, *n* (%)	50 (72.46)	46 (67.65)	24 (34.78)	25 (36.23)
Duration of the disease (h, mean ± SD)	25.86 ± 10.89	22.78 ± 9.89	28.04 ± 12.41	27.74 ± 11.16
Symptom severity (TSS, mean ± SD)	8.81 ± 3.15	8.88 ± 3.05	10.45 ± 2.90	10.33 ± 3.13
Recurrence rate (monthly)				
<1 time (%)			29 (42.03)	30 (43.48)
1 time (%)			32 (46.38)	31 (44.93)
>1 time (%)			8 (11.59)	8 (11.59)

RHG, recurrent herpes genitalis; RHL, recurrent herpes labialis; SD, standard deviation; TSS, total symptom score.

Table 4. TSS before and after treatment in RHL patients

Point	Inosine pranobex	Acyclovir	*P*
Before treatment			
n (missing)	69 (0)	68 (0)	0.894
Mean ± SD	8.812 ± 3.15	8.882 ± 3.045	
95% CI	8.055, 9.568	8.145, 9.619	
After 3 days			
n (missing)	69 (0)	68 (0)	0.899
Mean ± SD	4.348 ± 2.188	4.397 ± 2.364	
95% CI	3.822, 4.874	3.825, 4.969	
After 7 days			
n (missing)	69 (0)	68 (0)	0.514
Mean ± SD	0.826 ± 1.028	0.912 ± 1.033	
95% CI	0.579, 1.073	0.662, 1.162	

CI, confidence interval; RHL, recurrent herpes labialis; SD, standard deviation; TSS, total symptom score.

papules, vesicles, erosions and the degree of erythema and pain between the two treatment groups on the 3rd and 7th day of treatment showed no significant differences (Table 5). The course of the lesional changes was also identical. The treatment efficacy rate of both groups was also comparable (inosine pranobex group 98.55% vs inosine pranobex group 97.06%, P = 0.559).

The study on patients with RHG showed no significant difference in the TSS after 3 and 5 days of treatment between the inosine pranobex group and acyclovir group (Table 6). Neither was the change of the individual lesions nor the time index (Table 7).

Clinical recurrence rate

At 3-month follow up of the patients with RHG, a significantly lower rate of clinical recurrence was observed in the inosine pranobex group (26.56%) as compared with the acyclovir group (47.62%) (P = 0.015). (Table 8).

Table 5. Time index of the lesions in RHL patients

Time index (h)	Inosine pranobex	Acyclovir	*P*
Vesicles stopped	36.087 ± 21.125	41.412 ± 20.49	0.137
Lesions began to form scabs	53.657 ± 21.455	57.699 ± 21.968	0.283
All the scabs fell off	127.33 ± 24.331	133.481 ± 26.077	0.21

RHL, recurrent herpes labialis.

Table 6. TSS before and after treatment in RHG patients

Point	Inosine pranobex	Acyclovir	*P*
Before treatment			
n (missing)	69 (0)	69 (0)	0.822
Mean ± SD	10.449 ± 2.898	10.333 ± 3.128	
95% CI	9.753, 11.145	9.582, 11.085	
After 3 days			
n (missing)	69 (0)	69 (0)	0.173
Mean ± SD	4.609 ± 3.766	5.449 ± 3.616	
95% CI	3.704, 5.513	4.581, 6.318	
After 5 days			
n (missing)	69 (0)	69 (0)	0.534
Mean ± SD	1.029 ± 2.509	1.058 ± 1.714	
95% CI	0.426, 1.632	0.646, 1.47	

CI, confidence interval; RHG, recurrent herpes genitalis; SD, standard deviation; TSS, total symptom score.

Adverse events

All the adverse effects were invariably mild and self-limiting without serious adverse events related to the study medication. However, the incidence of hyperuricemia was shown to be higher in the inosine pranobex than in the acyclovir group (10% vs 2.92%, P = 0.017, Table 9).

Table 7. Time index of the lesion change in RHG patients

Time index (h)	Inosine pranobex	Acyclovir	*P*
Vesicles stopped	37.773 ± 22.235	44.406 ± 25.623	0.11
Lesions began to form scabs	62.308 ± 18.508	63.985 ± 20.116	0.619
All the scabs fell off	108.415 ± 20.875	108.06 ± 19.362	0.929

RHG, recurrent herpes genitalis.

Table 8. Recurrence rate after treatment in RHG patients

	Inosine pranobex, *n* = 64 (%)	Acyclovir, *n* = 63 (%)	*P*
No recurrence	47 (73.44)	33 (52.38)	0.015
Recurrence	17 (26.56)	30 (47.62)	

RHG, recurrent herpes genitalis.

Table 9. Adverse events of the two treatment groups

	Inosine pranobex, *n* = 140 (%)	Acyclovir, *n* = 137 (%)	*P*
Gastrointestinal discomfort	1 (0.71)	4 (2.92)	0.354
Leukopenia	2 (1.43)	4 (2.92)	0.66
Hyperuricemia	14 (10)	4 (2.92)	0.017
Hyper-aminopherase	1 (0.71)	1 (0.73)	1
Other adverse events	7 (5)	4 (2.92)	0.375

DISCUSSION

Inosine pranobex can stimulate differentiation of T cells into cytotoxic T cells and T-helper cells as well as the production of lymphokine. It has also been reported to increase the production of interleukin (IL)-1, IL-2, γ-interferon and IL-12, to decrease the production of IL-3 and IL-4 *in vivo*, and to augment natural killer cell function. By stimulating differentiation of B lymphocytes into plasma cells and enhancing antibody production, inosine pranobex increases the humoral immune response.[7] Inosine pranobex has been reported to inhibit replication of several RNA and DNA viruses in tissue cultures, including orolabial herpes. The administration of inosine pranobex can increase the survival of mice experimentally infected with influenza A or B and hamsters with orolabial herpes simplex infection.[5] Inosine pranobex was used against a variety of viral infections in the early 1970s.[8] There were several randomized trials to evaluate the therapeutic effect of inosine pranobex on mucocutaneous herpes. Galli *et al.*[9] found that the mean number of recurrences was significantly lower in inosine pranobex-treated patients with labial herpes compared with controls, but not in patients with herpes genitalis. Inosine pranobex seemed to be capable of restoring the immune response which can hold off herpetic recurrences sometimes for longer periods. Talbot and Menday[10] also proved that the use of inosine pranobex in patients with primary or RHL produces a significantly beneficial effect in terms of overall response and in reducing the severity of associated symptoms. On the other hand, some previous studies showed that inosine pranobex was inferior to acyclovir for treating the first attacks and recurrences of herpes genitalis. A double-blind controlled trial conducted in patients with frequent RHG has shown that the time to the first recurrence was significantly longer and the frequency of recurrences significantly fewer in the recipients of acyclovir in comparison with the recipients of inosine pranobex.[11] Mindel *et al.*[12] showed that patients with first attack of herpes genitalis treated with acyclovir healed more quickly and had a shorter duration of viral shedding than those treated with inosine pranobex. Kinghorn *et al.* also reported lower proportion of recurrences in patients with RHG receiving acyclovir as compared with isoprinosin.[13]

The current study is the first multicenter randomized treatment study conducted to examine the safety and efficacy of inosine pranobex versus acyclovir in RHL and RHG in China. Our findings showed comparable TSS and efficacy rates in both treatment groups on the 3rd day and at the end of the treatment, both for RHL and RHG patients. Comparing the available reports, there were some differences in the patient composition and study design among these studies. In our study, the age of our patients was much older than that enrolled in Mindels *et al.*'s study regarding the first attack of herpes genitalis. Our patients were treated with much a higher dose of inosine pranobex (1 g four times a day) as compared with the patients treated in Kinghorn *et al.*'s study (0.5 g twice daily). The treatment period of 5 days for RHG in our study was also much shorter than that of 12 weeks in Mindel *et al.*'s study. It should be noted that the clinical cure rate does not mean microbiological eradication of the virus, and virological assessment should be performed to rule out asymptomatic viral shedding. On the other hand, as the degree of clinical symptoms does not always correlate with the amount of the virus in herpes and the inosine pranobex works mainly through immune regulation with certain anti-inflammatory effect, the measurement of viral shedding cannot fully reflect the clinical improvement and therapeutic efficacy.

As for the side-effects, a statistically significant increase in the serum uric acid concentration has been reported in male patients treated with inosine pranobex, which is due to the degradation of inosine pranobex to uric acid during the metabolism of natural purines.[5] In our study, 13 of the 14 patients with hyperuricemia caused by inosine pranobex showed normal uric acid levels in the follow-up period without any treatment, indicating that hyperuricemia is generally reversible.

The limitation of our study is that a single follow up at 3 months after treatment discontinuation cannot reflect the long-term recurrence rate of RHG. It is reported that approximately 70–90% people with symptomatic HSV-2 infection will have a recurrence within the 1st year, while nearly 25% of patients will experience an increase in recurrence after the 4th year of infection.[3] Three-month follow up can only reflect the short-term recurrence rate; long-term recurrence rates at

6 months or longer remain to be determined. In addition, the lack of a control group with placebo treatment cannot rule out spontaneous improvement in the observed patients.

In conclusion, oral inosine pranobex is as effective as oral acyclovir in the treatment of RHL and RHG. The short-term clinical recurrence rate at 3 months after treatment was significantly lower in the inosine pranobex than the acyclovir group. Transit hyperuricemia warrants attention during the administration of inosine pranobex. Long-term follow up is needed to confirm the long-term remission rate of inosine pranobex treatment for herpes infection.

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CONFLICT OF INTEREST: None declared.

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