Original
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Impact of suppressive antiviral therapy on the health related quality of life of patients with recurrent genital herpes infection

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Objective: To investigate whether suppressive antiviral therapy improves health related quality of life in patients with recurrent genital herpes.

Methods: Health related quality of life was measured using the disease specific recurrent genital herpes quality of life questionnaire (RGHQoL) as part of a randomised, double blind, 52 week, placebo controlled, dose ranging study of once and twice daily valaciclovir or aciclovir for the suppression of recurrent genital herpes in patients with six or more recurrences per year.

Results: Of 1479 participants, 1349 patients completed the baseline questionnaire. There were no significant baseline differences in RGHQoL score between any of the treatment groups. After 3 months there were significantly greater improvements in mean RGHQoL scores for all active treatment groups compared with placebo ($p < 0.05$). Mean RGHQoL score improvements from baseline remained significantly higher in the active treatment groups than in the placebo group after 6 and 12 months, indicating that the improved health related quality of life in patients receiving suppressive antiviral therapy was sustained over a prolonged period of time.

Conclusion: Suppressive antiviral therapy is an effective strategy for improving the quality of life of patients with recurrent genital herpes. These improvements in quality of life are sustained over time, thus enhancing the clinical benefit in the long term management of this condition.

(Sex Transm Inf 1999;75:398–402)

Keywords: genital herpes; quality of life; suppressive antiviral therapy

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Accepted for publication
22 September 1999

Introduction

Recurrent genital herpes is a common sexually transmitted disease caused by the herpes simplex virus. For those who have recurrent outbreaks, the frequency is likely to be on average four to six times a year, although about one third of patients who are seropositive to herpes simplex virus type II suffer more than 10 recurrences per year.¹ Recurrent episodes are not usually as severe as the initial episode but may be triggered by a variety of poorly defined physical, biochemical, and emotional stressors.² Often the psychological complications and stigma associated with genital herpes are as difficult to manage as the physical symptoms. Problems such as shock, anger, guilt, and depression are commonly reported, and these may be intensified by the lack of control that patients feel they have over the disease because of the unpredictable nature of recurrences. Problems with relationships ensue and feelings of low self esteem, fear of transmission, and impaired sexual function are common.²

Controlled clinical studies have demonstrated the marked reduction in genital herpes recurrence frequency with continuous aciclovir therapy,^{3,4} and uncontrolled trials have suggested an association between suppressive therapy and improvements in psychological wellbeing.⁵ Valaciclovir, the L-valine ester prodrug of aciclovir, increases aciclovir bioavailability and provides higher systemic exposure to permit less frequent dosing for most patients.⁶ In previous studies, a once daily dose of 500 mg/day of valaciclovir was shown to prevent or delay up to 85% of recurrences.^{7,8}

To investigate the impact of valaciclovir and aciclovir on patients' quality of life, a disease specific instrument called the recurrent genital herpes quality of life questionnaire (RGHQoL) has been developed. The need for a disease specific questionnaire based upon a tested model was reinforced by the unsuitability of existing generic instruments. The hospital anxiety and depression scale has been used to measure changes in levels of anxiety and depression associated with the treatment of recurrent genital herpes.⁹ In addition, the use of the general health questionnaire and Eysenck personality inventory have been reported.¹⁰ However, individuals with genital herpes are generally young and healthy with low levels of physical disability; hence, these instruments were not considered sensitive enough to detect problems which are particular to genital herpes. In contrast, the RGHQoL is a self completed, unidimensional, 20 item herpes specific questionnaire, which takes only several minutes to complete. The content of the RGHQoL is based on in-depth qualitative interviews with 33 patients with genital herpes. Interviews were designed to explore how the disease impacts on the patients' ability to fulfil everyday needs, and the instrument is founded on the hypothesis that quality of life relates to the ability and capacity of an individual to satisfy his or her human needs.¹¹ A pilot study was conducted in Denmark, which indicated that the instrument was sensitive to changes in quality of life associated with initiation of suppressive treatment for recurrent genital herpes.¹¹

Table 1 Sample items from the RGHQoL questionnaire

Herpes affects my self confidence	
Yes, very much	☐
Yes, quite a lot	☐
Yes, a little	☐
No, not at all	☐
Herpes is affecting my sex life	
Yes, very much	☐
Yes, quite a lot	☐
Yes, a little	☐
No, not at all	☐
I get depressed about having herpes	
Very much	☐
Quite a lot	☐
A little	☐
Not at all	☐
I worry about giving herpes to someone	
Yes, I worry about it a great deal	☐
Yes, I worry about it quite a lot	☐
Yes, I worry a little	☐
No, I don't worry about it at all	☐

The present study was conducted within the framework of a randomised, placebo controlled clinical trial evaluating the safety and efficacy of once and twice daily valaciclovir or aciclovir for the suppression of recurrent genital herpes.⁸ The RGHQoL was used to measure the potential benefits of suppressive antiviral therapy on patients' quality of life. The clinical results of this study have confirmed all doses of valaciclovir and aciclovir were significantly better than placebo in preventing or delaying herpes simplex recurrences.⁸

Methods

STUDY DESIGN

This was an international, multicentre, randomised, double blind, placebo controlled, parallel group study conducted in adult immunocompetent patients with a history of recurrent genital herpes. All centres obtained ethics committee approval, and all patients gave written informed consent. To be eligible for inclusion into the study, patients had to have experienced at least six recurrences of genital herpes in the 12 months before screening. Alternatively, if they had previously received suppressive antiviral therapy for part of that period, they were to have experienced at least one recurrence since discontinuing suppressive treatment in the 3 months immediately before entry to the study. Patients were

randomised to one of the following six treatment arms on a 2:2:2:2:2:1 basis: valaciclovir 1000 mg once daily; valaciclovir 500 mg once daily; valaciclovir 250 mg once daily; valaciclovir 250 twice daily; aciclovir 400 mg twice daily; or placebo. Patients were assessed at the clinic every month for a period of 52 weeks. In addition, patients were required to visit the clinic on days 1 and 5 of a genital herpes recurrence, during which time they received treatment with open label valaciclovir (1000 mg twice daily for 5 days).

RGHQoL

The development of the RGHQoL is reported in detail elsewhere.¹¹ Patients respond to each statement by indicating the level of their limitation on a 4 point Likert scale which is scored from 0 (maximum level of limitation) to 3 (minimum level of limitation). Examples of items included in the RGHQoL are presented in table 1.

The RGHQoL was available in six validated translations (UK and US English, French, Italian, German, Danish) and the instrument was completed in all countries for which one of these translations was appropriate. The questionnaire was completed before study treatment (baseline) and at clinic visits at the end of month 1, 2, 3, 4, 6, 8, 10, and 12 or at discontinuation.

STATISTICAL ANALYSIS

Quality of life data are presented as the sum total of scores of the 20 questionnaire items, ranging from a worst score of 0 to a best possible score of 60. Data were included in the analysis for all patients who completed the RGHQoL at least at baseline. Summary statistics for all treatment groups were based on patients who were randomised and for whom RGHQoL data were available at each time point. The statistical significance of treatment related change in RGHQoL score from baseline for each active treatment group in comparison with placebo was tested at 3, 6, and 12 months using analysis of variance (ANOVA) adjusted for imbalances in frequency of genital herpes recurrences in the year before study and

Table 2 Summary of change from baseline in quality of life score at monthly evaluations—as treated population

	Valaciclovir				Aciclovir	Placebo
	250 mg twice daily	1000 mg once daily	500 mg once daily	250 mg once daily		
Baseline to month 3						
N	206	211	203	206	204	91
Mean change	7.9	7.2	8.0	8.2	9.1	4.1
Standard deviation	9.89	9.16	8.41	9.02	10.01	8.60
Mean difference from placebo*	4.0	3.3	4.3	4.3	5.1	
95% CI for difference	(1.7, 6.3)	(1.0, 5.6)	(2.0, 6.6)	(2.0, 6.6)	(2.9, 7.4)	
Baseline to month 6						
N	193	198	193	190	193	72
Mean change	9.7	8.8	8.8	9.1	10.8	4.6
Standard deviation	11.04	10.09	10.02	9.37	11.26	8.92
Mean difference from placebo*	5.2	4.3	4.5	4.6	6.3	
95% CI for difference	(2.4, 8.0)	(1.6, 7.1)	(1.7, 7.3)	(1.8, 7.4)	(3.5, 9.1)	
Baseline to month 12						
N	155	153	161	141	154	51
Mean change	9.9	9.3	9.7	9.4	12.0	4.8
Standard deviation	11.89	10.21	10.86	10.33	13.43	7.64
Mean difference from placebo*	5.3	4.6	5.3	4.8	7.4	
95% CI for difference	(1.8, 8.9)	(1.1, 8.2)	(1.1, 8.9)	(1.2, 8.4)	(3.8, 10.9)	

*Adjusted for imbalances between groups in prior suppressive antiviral therapy and HSV recurrence history.

Figure 1 Mean change (95% confidence interval) from screen in QoL measure at monthly evaluations.

experience of suppressive antiviral therapy before entering the trial. Observational data¹² have demonstrated that both of these factors can substantially reduce quality of life in genital herpes.

On analysis of the data, it became apparent that there were a substantial number of patients who had dropped out before the end of the study, particularly in the placebo group. In order to account for the differential patient dropout rate in the analysis and to substantiate findings from the initial ANOVA, further exploratory analyses were performed using two approaches. Firstly, a last observation carried forward (LOCF) approach was taken. For patients who did not complete the 12 month study period, the RGHQoL score recorded at their last observation was carried forward to all subsequent evaluations. The second exploratory analyses included only data from the subpopulation with a RGHQoL score calculable at the end of 6 months. A 6 month cut off point for this analysis was chosen, as it was anticipated that patients receiving placebo who were not progressing well and who were likely to dropout of the study would have done so by the 6 month assessment.

Results

The RGHQoL was completed in nine countries (United States, United Kingdom, Denmark, France, Australia, New Zealand, Italy, Austria, and Germany). Of the 1479 patients originally randomised into the clinical efficacy study (intent to treat population), evaluable RGHQoL baseline data were available from 1349 patients. Overall, 52% were women, with similar sex distributions across all treatment groups. The mean age of patients in each group was between 35 and 36 years.

Mean scores at baseline were similar for all six treatment groups; scores out of a possible maximum of 60 ranged from 30.2 to 33.9. Improvements from baseline were seen across the 12 month period in all groups. Adjusting for previous experience of suppressive antiviral therapy and frequency of genital herpes recurrences, mean RGHQoL score changes from baseline were significantly greater in the active treatment groups than in the placebo group at 3, 6, and 12 months (table 2). Mean changes in RGHQoL from baseline for patients who completed the study are also presented in figure 1. At 12 months, the adjusted mean improvement from baseline in the active treatment groups ranged from 9.4 to 12.0 compared with a mean improvement of 4.8 points in the placebo group. This indicates the sustained beneficial impact of these treatments on quality of life. No discernible differences in quality of life score were seen between the active treatments.

Retrospective analysis of patients according to the frequency of herpes recurrences during the year before the trial showed that at baseline, those who had suffered >10 recurrences had lower mean RGHQoL scores than patients who had experienced ≤10 recurrences. In general, mean scores for the active treatment groups improved by approximately 9–12 points over the 12 month period. Improvements in those patients who had experienced ≥10 recurrences were marginally higher. These findings are summarised in table 3. When data were analysed according to whether patients had experienced suppressive therapy before the

Table 3 Baseline and 12 month quality of life scores according to baseline characteristics

		Valaciclovir				Aciclovir	Placebo
		250 mg twice daily	1000 mg once daily	500 mg once daily	250 mg once daily		
Prior suppression	Baseline	N	35	34	30	29	40
		Mean	32.2	27.8	32.2	31.2	31.4
	12 months	N	25	23	20	16	25
		Mean	43.4	39.3	43.0	38.9	39.3
No prior suppression	Baseline	N	214	221	210	218	204
		Mean	31.5	31.3	33.1	32.8	30.0
	12 months	N	131	131	143	125	129
		Mean	41.4	41.5	43.5	42.9	42.9
≥10 recurrences	Baseline	N	118	110	79	100	119
		Mean	31.0	29.8	30.5	30.7	27.7
	12 months	N	70	72	50	61	76
		Mean	41.6	41.3	41.7	40.2	42.9
<10 recurrences	Baseline	N	131	136	161	147	125
		Mean	32.2	31.8	34.1	33.8	32.7
	12 months	N	86	82	113	80	78
		Mean	41.8	41.0	44.3	44.2	41.7

Table 4 Summary of change from baseline in quality of life score at monthly evaluations—last observation carried forward (LOCF) approach

	Valaciclovir				Aciclovir	Placebo
	250 mg twice daily	1000 mg once daily	500 mg once daily	250 mg once daily		
Baseline to month 3						
N	245	240	234	244	240	123
Mean change	7.0	6.7	7.1	7.5	8.2	3.4
Standard deviation	9.47	8.86	8.26	9.27	9.88	7.90
Mean difference from placebo*	3.7	3.4	3.9	4.2	4.8	
95% CI for difference	(1.7, 5.6)	(1.4, 5.3)	(1.9, 5.9)	(2.2, 6.1)	(2.9, 6.8)	
Baseline to month 6						
N	245	242	234	244	241	119
Mean change	8.4	7.9	7.9	8.2	9.4	3.5
Standard deviation	10.43	9.87	9.72	9.54	11.03	8.13
Mean difference from placebo*	4.9	4.4	4.6	4.7	5.9	
95% CI for difference	(2.7, 7.1)	(2.2, 6.6)	(2.4, 6.8)	(2.5, 6.9)	(3.7, 8.1)	
Baseline to month 12						
N	249	245	240	247	243	123
Mean change	8.8	8.2	9.2	8.2	10.1	4.2
Standard deviation	11.24	10.52	10.56	10.54	12.45	7.90
Mean difference from placebo*	4.6	4.0	5.2	4.0	5.9	
95% CI for difference	(2.2, 6.9)	(1.7, 6.3)	(2.8, 7.5)	(1.7, 6.4)	(3.6, 8.3)	

*Adjusted for imbalances between groups in prior suppressive antiviral therapy and HSV recurrence history.

study, similar improvements were seen for all active treatment groups, while patients allocated to placebo who had experienced prior suppression did not show RGHQoL improvements. In contrast, those placebo patients who had no previous experience of suppressive therapy also showed improvements in RGHQoL score over time (table 3).

With application of the LOCF approach, examination of change in mean scores from baseline revealed improvements of approximately 10 points in the active treatment groups and 4 points in the placebo group (table 4, fig 2). The LOCF approach did not alter the results to any noticeable extent but did reinforce the inference that suppressive therapy caused greater improvements in RGHQoL than did placebo. Analysis of data from those patients who had a RGHQoL score available at 6 months resulted in evaluable data for 190–198 patients in each of the active treatment groups and 72 patients in the placebo group. This analysis re-emphasised the above findings, demonstrating mean RGHQoL score improvements of between 8.8 and 10.8 points for the active treatment groups at 6 months compared with an improvement of 4.6 for placebo.

Figure 2 Mean change (95% confidence interval) from screen in QoL measure at monthly evaluations. Last observations carried forward (LOCF) approach applied.

Discussion

In view of the increasing prevalence of genital herpes and the current lack of a cure for this chronic disease, it is important to look at ways of minimising the associated long term psychological morbidity.¹³ A survey that included 5000 herpes sufferers in the United States provided insight into the significant non-medical impact of herpes.¹⁴ Over half the respondents reported feelings of depression and fear of rejection. Respondents also noted decreased sex drive and self destructive feelings. While numerous clinical studies have confirmed that antiviral therapy with aciclovir or valaciclovir is highly effective in reducing the frequency of genital herpes outbreaks,^{7 8 15 16} there have been no previous controlled studies that have examined the impact of suppressive therapy on patients' quality of life.

The RGHQoL is a new questionnaire for the investigation of quality of life associated with genital herpes. The RGHQoL covers relevant aspects of quality of life such as self esteem, social and sexual functioning, personal relationships and mental health. It is easy for patients to complete, generally requiring no more than 5–10 minutes.¹¹ Using this disease specific measure, the present study has confirmed that suppressive antiviral therapy significantly improves health related quality of life compared with placebo. This effect was sustained throughout this 12 month study.

The high dropout rate of patients in the placebo group made analysis and interpretation of the results more difficult. However, several analytical measures employed to overcome this problem have further confirmed the favourable impact of active suppressive therapy over placebo on health related quality of life. There were no discernible differences between the active treatment regimens, which was expected given the significant efficacy demonstrated for all regimens compared with placebo.⁸ The current results confirm that the RGHQoL is able to measure improvement in herpes specific quality of life over time, although further work is required to improve our understanding of

what constitutes a clinically meaningful improvement in RGHQoL score.

In conclusion, this is the first well controlled clinical trial to demonstrate that suppressive antiviral therapy is an effective strategy for improving the quality of life of patients with recurrent genital herpes. These improvements are sustained over time, indicating an additional value of suppressive therapy in long term management of the disease.

The authors gratefully acknowledge the contribution of the following participants in the quality of life section of this study: D Whiting, Dallas, Texas, USA; M Levin, Denver, Colorado, USA; M Reitano/J Stern, New York, New York, USA; B De Gregorio/C Thoming, Portland, Oregon, USA; S Spruance, Salt Lake City, Utah, USA; K Beutner, Vallejo, California, USA; D Campbell, St. Louis, Missouri, USA; K Fife, Indianapolis, Indiana, USA; J Powers, Scottsdale, Arizona, USA; W Lang, San Francisco, California, USA; M Lebowitz, New York, New York, USA; S Biback, Seattle, Washington, USA; P Lee, Nassau Bay, Texas, USA; T Kurtz, Des Moines, Iowa, USA; L Corey, Seattle, Washington, USA; D Baker, Stony Brook, New York, USA; T Appel, Boulder, Colorado, USA; F Dunlap, Tucson, Arizona, USA; M Weinstein, San Antonio, Texas, USA; A Pandya, Dallas, Texas, USA; C Hicks, Durham, North Carolina, USA; C Bowman, Nottingham, UK; G Luzzi, High Wycombe, UK; G Kinghorn, Sheffield, UK; B Goh, London, UK; M Shahmanesh, Birmingham, UK; S Barton, London, UK; J Soltz-Szots, Vienna, Austria; H Kerl, Graz, Austria; J Roed-Petersen, Hellerup, Denmark; A-M Worm, Copenhagen, Denmark; J Esmann, Aarhus, Denmark; G Vejlsgaard, Copenhagen, Denmark; J-P Ortonne, Nice, France; J-E Malkin, Paris, France; C Duncombe, NSW, Australia; C Law/N Doong, NSW, Australia; J Patten, Queensland, Australia; R Franklin, Auckland, New Zealand; M Sparrow, Wellington, New Zealand; M Negosanti, Bologna, Italy; S Borelli, Munich, Germany.

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