No Effect of Antiviral (Valacyclovir) Treatment in Fibromyalgia: A Double Blind, Randomized Study

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ABSTRACT. ***Objective***. To investigate the effect of an antiviral compound, valacyclovir, on pain and tenderness in patients with the fibromyalgia (FM) syndrome.

Methods. Sixty patients were randomized into a double blind, placebo controlled 6 week trial. Primary outcome was pain intensity change (on visual analog scale). Secondary outcome measures were tender points (myalgic score) and Fibromyalgia Impact Questionnaire (FIQ).

Results. Fifty-two patients completed the study. The numbers of dropouts due to adverse events were equal in valacyclovir (2) and placebo (2) groups. The effect of valacyclovir on pain and tenderness and FIQ did not differ from placebo.

Conclusion. Valacyclovir cannot be recommended as a therapy for FM at this point. (J Rheumatol 2004; 31:783–4)

Key Indexing Terms:
FIBROMYALGIA THERAPY VIROLOGY VALACYCLOVIR

The patient with fibromyalgia (FM) syndrome is characterized clinically by chronic widespread pain and tender points[1]. The etiology of FM is unknown. In one study, a substantial number of patients attributed the onset of FM symptoms to an acute viral illness[2]. In cross-sectional studies, a greater than expected prevalence of concomitant viral infection in the history of the disease onset has been observed for enterovirus[3], selected patients with human immunodeficiency virus[4], and hepatitis C[5] and Pogosta virus[6]. In previously pain-free patients with acute infectious mononucleosis (Epstein-Barr virus), 7% had persistent pain and widespread tenderness to pressure after 6 months[7].

In 1996 a case report published in Denmark[8], describing rapid symptom improvement in one patient after taking the dosage of acyclovir recommended for treatment of herpes zoster infection, led to pressure on physicians to prescribe the drug acyclovir to patients with FM. As a result of this pressure to prescribe a potentially longterm, unproven therapy without clear evidence of etiological connection of herpes zoster and FM, it was decided to test the evidence.

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We investigated the effect of acyclovir compared to placebo therapy on pain and tenderness in FM. Valacyclovir, which breaks down into acyclovir, was chosen because of its better bioavailability.

MATERIALS AND METHODS

Sixty adults with FM by the American College of Rheumatology (ACR) criteria[1] were recruited from patients known to the Rheumatology Clinic, Frederiksberg Hospital (a referral center for FM in Denmark). Patients with previous acyclovir treatment, blood, renal or hepatic function abnormalities, allergies to valine or lactose, pregnant or breast-feeding, or with central nervous system disorder or older than 70 years were excluded.

At baseline patients were randomized into valacyclovir or placebo group by computer generated lists. Age, height, weight, duration of symptoms, and year of FM diagnosis were recorded. The results of blood tests [blood status, thyroid, renal and hepatic function, herpesvirus antibodies (herpes simplex virus and human herpesvirus-6 titers), and pregnancy tests] were available at start and end of treatment.

Treatment. Patients received one 1 g tablet of valacyclovir (Zelitrex®, GlaxoSmithKline Pharma A/S, Copenhagen, Denmark) or one placebo tablet 3 times daily during a 6 week period. The placebo consisted of identical lactose tablets. Medication was delivered in 3 × 2 week supply packages.

Compliance to drug regime was monitored using a drug accountability schedule: the patient returns both opened and unopened drug packages to the examiner at start and end of treatment.

Primary outcome measure. Pain (general intensity previous week), was assessed on a 10 cm horizontal visual analog scale (VAS) anchored at 0 = no pain and 100 = very severe pain[9].

Secondary outcome measures. Global tenderness to moderate pressure of 4 kg was assessed by the myalgic score, the summary of scores at tender points, as 0 = no pain; 1 = slight pain, confirming response when questioned; 2 = moderate pain, spontaneous verbal comment or flinch/withdrawal; and 3 = severe pain, strong withdrawal reaction[10]. Overall function and symptom severity was assessed using the Fibromyalgia Impact Questionnaire (FIQ)[11].

Patients were allowed to continue habitual medication throughout the study. They were encouraged not to change medication but it was not felt to be ethical to withdraw medication over the study period. All patients gave written consent, and the study was approved by the local ethics committee. The study was conducted in accord with the principles of the Helsinki Agreement, 1989.

Statistical analysis. Study power calculation was based on results of a previous study[12] in which pain VAS score change of 2 cm was considered a clinically relevant change. In a 2-arm, 2-sided study design with a clinical difference (Δ) = 2 and a test level (α) = 5%, an 80% power to detect a difference on VAS of 2 required 23 patients in each arm. The intention-to-treat population is the only analysis population. Pre and post-treatment scores for pain VAS and myalgic score were compared using the Student t test. ANOVA was used to examine change in pain or degree of tenderness (myalgic score change) with FM symptom duration (years) and age as covariables.

RESULTS

Thirty patients were enrolled into the valacyclovir (V group) and 30 into the placebo (P) group. There were no significant differences in characteristics at baseline (Table 1). No patient had clinical evidence of ongoing herpes or other viral infection (data not shown). Twenty-six patients in each group completed the study. Dropouts were due to adverse events, one headache, one vomiting in each group, one depression, one constipation, one family reasons, and one no reason given. Overall incidence of drug related adverse events was 6 in the V group and 8 placebo. Headache was most frequent in the V group, 5 events.

Pain VAS. There was no significant change before and after treatment (p = 0.45; Table 2). Including age and onset of symptoms as covariates gave a similar result (p = 0.64). The mean difference (improvement) was 0.16 in V group and 0.54 in P group.

Myalgic score. There was no significant change before and after treatment (p = 0.58; Table 2). Including age and onset of symptoms as covariates gave a similar result (p = 0.84). The mean difference (improvement) was 2.3 in V group and 3.5 in P group.

FIQ. There was no significant change in either total scores or subscale scores within or between groups (data not shown).

Table 1. Baseline characteristics of patients in the valacyclovir and placebo groups. Values are mean (SD). Herpes simplex virus (HSV) and human herpesvirus-6 (HHV-6): number with positive titers, i.e., patients with previous HSV or HHV-6 infection.

	Valacyclovir	Placebo
Female:male	28:2	30:0
Age, yrs	48.9 ± 7.0	50.2 ± 7.8
Height, cm	166.4 ± 8.1	164.0 ± 7.2
Weight, kg	71.6 ± 20.2	71.1 ± 15.3
FM diagnosis, yrs	2.4 ± 2.5	2.8 ± 2.6
FM symptom onset, yrs	10.3 ± 6.4	11.2 ± 7.0
HSV	26	25
HHV-6	28	28

Table 2. Pain and tenderness values pre and post-treatment. Values are mean (SD).

	Valacyclovir		Placebo	
	Pre	Post	Pre	Post
Pain, cm, VAS	7.9 ± 1.7	7.0 ± 2.3	7.8 ± 2.2	7.0 ± 2.3
Myalgic score	33.6 ± 5.4	31.7 ± 5.8	35.4 ± 6.6	32.4 ± 8.5

DISCUSSION

This study observed no effect difference between valacyclovir and placebo on overall pain intensity and global tenderness to moderate pressure in patients with FM not having current herpes infection. Study power was adequate to detect clinically significant changes in pain and tenderness and the dosage of valacyclovir was appropriate, and known to have clinical effect in herpes zoster infections[13].

However, we cannot exclude that valacyclovir might have an effect in patients with current viral infection and FM symptoms.

Immunological differences have been observed in a selected group of patients with a flu-like onset of FM[3] compared to those with acute onset. The FM diagnosis is presently based on case history and an objective examination[1]. Laboratory diagnosis verification in peripheral blood has not been found[14]. Future research in fibromyalgia may be directed toward distinguishing between patients with different immunological backgrounds.

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