Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial

Mats Engström, Thomas Berg, Anna Stjernquist-Desatnik, Sara Axelsson, Anne Pitkäranta, Malou Hultcrantz, Mervi Kanerva, Per Hanner, Lars Jonsson

Summary

Background **Previous trials of corticosteroid or antiviral treatments for Bell's palsy have been underpowered or have had insufficient follow-up. The aim of this study was to compare the short-term and long-term effects of prednisolone and valaciclovir in the recovery of the affected facial nerve in a large number of patients.**

Methods **In this randomised, double-blind, placebo-controlled, multicentre trial, patients aged 18 to 75 years who sought care directly or were referred from emergency departments or general practitioners within 72 h of onset of acute, unilateral, peripheral facial palsy, between May, 2001, and September, 2006, were assessed. Patients were randomly assigned in permuted blocks of eight to receive placebo plus placebo; 60 mg prednisolone per day for 5 days then reduced by 10 mg per day (for a total treatment time of 10 days) plus placebo; 1000 mg valaciclovir three times per day for 7 days plus placebo; or prednisolone (10 days) plus valaciclovir (7 days). Follow-up was for 12 months. The primary outcome event was time to complete recovery of facial function, as assessed with a regional Sunnybrook scale score of 100 points. Analysis was by modified intention to treat. This study is registered with ClinicalTrials.gov, number NCT00510263.**

Findings **Of 839 patients who were randomly assigned, 829 were included in the modified intention-to-treat analysis: 206 received placebo plus placebo, 210 prednisolone plus placebo, 207 valaciclovir plus placebo, and 206 prednisolone plus valaciclovir. Time to recovery was significantly shorter in the 416 patients who received prednisolone compared with the 413 patients who did not (hazard ratio 1·40, 95% CI 1·18 to 1·64; p<0·0001). There was no difference in time to recovery between the 413 patients treated with valaciclovir and the 416 patients who did not receive valaciclovir (1·01, 0·85 to 1·19; p=0·90). The number of patients with adverse events was similar in all treatment arms.**

Interpretation **Prednisolone shortened the time to complete recovery in patients with Bell's palsy, whereas valaciclovir did not affect facial recovery.**

Funding **Uppsala University; GlaxoSmithKline (Sweden); Pfizer AB (Sweden); Acta Otolaryngologica Foundation; Rosa and Emanuel Nachmanssons Foundation; Stig and Ragna Gorthon Foundation; Torsten Birger Segerfalk Foundation; Margit Arstrups Foundation; County Council of Skåne; Helsinki University Central Hospital Research Funds.**

Introduction

Bell's palsy presents as unilateral weakness or paralysis of the face due to acute dysfunction of the peripheral facial nerve with no readily identifiable cause.[1] Bell's palsy accounts for 70% of peripheral facial palsies and the yearly incidence is about 30 per 100 000.[2,3] About 70% of patients with Bell's palsy recover completely within 6 months without treatment. The remainder have sequelae that include residual paresis, contracture, and synkinesis.[2] To minimise the time to recovery and sequelae from Bell's palsy, the most effective medical therapy has to be established.

A possible cause of Bell's palsy is inflammation of the facial nerve,[4–6] which might be related to the herpes virus;[7–10] this has led many investigators to study the efficacy of corticosteroids and antivirals to treat Bell's palsy. The Cochrane database report[11] on corticosteroid therapy concluded that trials[12–15] that met the inclusion criteria were too small (179 patients in total) to detect the benefits of corticosteroids. Another Cochrane report assessed the efficacy of aciclovir or similar antiviral drugs.[16] Three studies (246 patients) were reviewed,[17–19] and a need for adequately powered clinical trials of aciclovir and valaciclovir with a follow-up of 1 year was identified.[16]

Our aim was to study the short-term and long-term effects of treatment with prednisolone and/or valaciclovir on the recovery of the facial nerve in a large number of patients with Bell's palsy. We also studied the side-effects of the drugs and their effects on synkinesis. Valaciclovir was chosen because it has higher bioavailability than aciclovir. To improve reliability when assessing potential treatment effects, the regional Sunnybrook[20] and the gross House-Brackmann[21] scales were used to grade facial function.

Methods

Patients

Patients with acute, unilateral, peripheral facial palsy, who were referred from general practitioners or emergency departments, or who sought care directly, were screened by physicians at 16 public otorhinolaryngological centres in Sweden and one centre in Finland. Each study centre had at least one experienced

Lancet Neurol 2008; 7: 993–1000

Published Online October 11, 2008 DOI:10.1016/S1474-4422(08)70221-7

See Reflection and Reaction page 976

Department of Otorhinolaryngology and Head and Neck Surgery, Uppsala University Hospital, Uppsala, Sweden (M Engström MD, T Berg MD, L Jonsson MD); **Department of Otorhinolaryngology and Head and Neck Surgery, Lund University Hospital, Lund, Sweden** (A Stjernquist-Desatnik MD, S Axelsson MD); **Department of Otorhinolaryngology and Head and Neck Surgery, Helsinki University Central Hospital, Helsinki, Finland** (A Pitkäranta MD, M Kanerva MD); **Department of Otorhinolaryngology and Head and Neck Surgery, Karolinska University Hospital, Stockholm, Sweden** (M Hultcrantz MD); **and Department of Otorhinolaryngology and Head and Neck Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden** (Per Hanner MD)

Correspondence to: Mats Engström, Department of Otorhinolaryngology and Head and Neck Surgery, Uppsala University Hospital, Akademiska Sjukhuset, SE-751 85 Uppsala, Sweden
mats.engstrom@akademiska.se

ear, nose, and throat physician with a special interest in facial palsy who was responsible for implementing the study. Patients aged 18 to 75 years with onset of palsy within 72 h were considered for inclusion. Exclusion criteria were systemic antiherpetic medication within the past 2 weeks, ongoing systemic steroid medication, allergy to aciclovir, valaciclovir, famciclovir, or ganciclovir, pregnancy, breastfeeding, being a woman of child-bearing age who was unwilling to use contraceptives during the medication period, other neurological diseases, diabetes, badly controlled hypertension, current or a history of serious heart disease, history of renal or hepatic disease, gastric or duodenal ulcer, history of glaucoma, acute otitis or history of ipsilateral chronic otitis, history of tuberculosis, history of immunodeficiency syndromes, recent head injury, psychiatric disease, or any other condition that was at risk of being influenced by the study medication or that might have affected completion of the study.

The study was approved by regional ethics review boards and done in accordance with the Declaration of Helsinki and good clinical practice guidelines. Written informed consent was obtained from all patients.

Procedures

Patients were recruited between May, 2001, and September, 2006, with final follow-up in September, 2007. Baseline assessments before the start of treatment included otorhinolaryngological examination, grading of facial function, measurement of ipsilateral pain, documentation of concurrent medication, and serum analysis for antibodies to *Borrelia burgdorferi*. Analyses for herpes viruses were not done.

Patients were randomly assigned to one of four treatment groups by use of a factorial method. The randomisation code was developed by Glaxo Wellcome GmBH (Bad Oldesloe, Germany), with a computer number generator to select random permuted blocks of eight. The randomisation code was double-blinded and kept by Glaxo Wellcome (London, UK). Study drugs were sealed in sequentially numbered, identical containers in accordance with the allocation sequence and distributed with numbered, sealed envelopes that contained the randomisation codes, to be opened only in the case of a serious adverse event. The physician allocated the next available number to patients on entry into the trial, and the patient received the corresponding container that contained the study drugs. All study personnel, participants, and data analysts were blinded to treatment allocation until all patients had completed follow-up. The distribution of study drugs to the study centres and destruction of returned containers was done by the Clinical Trial Unit at the Hospital Pharmacy of Uppsala University Hospital, Sweden.

Patients were randomised to treatment with placebo plus placebo, prednisolone plus placebo, valaciclovir plus placebo, or prednisolone plus valaciclovir within 72 h after onset of Bell's palsy. Prednisolone as 5 mg tablets (or placebo formulated to have the same smell and colour, and to be the same size) was given as a single dose of 60 mg daily for 5 days; the dose was then reduced by 10 mg per day, with a total treatment time of 10 days. Valaciclovir (or placebo formulated to have the same smell and colour, and to be the same size) was given as two 500 mg tablets three times per day for 7 days. All patients were given oral and written instructions to take the same number of tablets, regardless of their allocation group. There were 90 tablets in the prednisolone (or placebo) container and 45 tablets (three extra tablets) in the valaciclovir (or placebo) container. Patients received two containers: one with prednisolone or its placebo (90 tablets) and one with valaciclovir or its placebo (45 tablets). Thus, the patients were not able to deduce their treatment from the number of tablets given.

All patients received written information about Bell's palsy, the aim and design of the study, the possible adverse effects of prednisolone and valaciclovir, and instructions for taking the drugs. Patients were asked to return tablet containers at the first follow-up visit. Compliance was checked by counting the tablets that were left in the returned containers.

Follow-up visits were scheduled for between days 11 and 17, and at 1 month, 2 months, 3 months, 6 months, and 12 months after randomisation. If recovery was complete (Sunnybrook scale score of 100 points) at 2 or 3 months, the next follow-up was at 12 months. Otorhinolaryngological examination and registration of ipsilateral pain was done at each visit during the first 2 months. Pain around the ear, in the face, or in the neck was registered on a visual analogue scale that ranged from 0 to 10 points, where 0 was no pain and 10 very severe pain. Adverse events were registered between day 11 to 17, and at 1 month. Convalescent serum was taken at 2 months to test for antibodies to *Borrelia burgdorferi*.

Facial function was assessed at all visits with two grading systems. The Sunnybrook system is regionally weighted and assesses resting symmetry, the degree of voluntary movements, and synkinesis, to produce a composite score that ranges from 0 to 100 points, where 0 is complete paralysis and 100 normal function.[20] The House-Brackmann scale is based on a six-grade score, where I is normal function and VI is complete paralysis, for gross assessment of facial motor function and sequelae.[21] In this multicentre study, in vivo grading of facial function was done by many investigators, which might lead to between-assessor differences in facial gradings (ie, inter-rater variability). Another risk is that gradings done by the same assessor at different time points might vary. Therefore, variability in the assessment process was expected, and to reduce such problems two validated grading scales were used.[21]

The investigators were not given any specific training for facial grading. Most follow-up visits, however, were done at each study centre by one of two or three experienced ear,

nose, and throat doctors with a special interest in facial nerve disorders. Thus, 2094 of 2654 (79%) assessments at 1–12 month follow-ups were done by 49 assessors at 17 centres. For practical reasons, early-stage assessments were often done by doctors with less experience, with help available from a more experienced colleague at the clinic or via telephone to the study group (LJ). Case-report forms were clearly written and explained the House-Brackmann and Sunnybrook grading systems. The primary endpoint was time to complete recovery of facial function, defined as a Sunnybrook rating scale score of 100 points. Key secondary endpoints were facial function and synkinesis at 12 months, as assessed with the Sunnybrook scale. Adverse events were recorded. Time to complete recovery, defined as House-Brackmann grade I, and facial function at 12 months, were also analysed.

Other secondary endpoints evaluated the outcome of palsy in relation to the start of medication, the proportion of patients who developed severe palsy during the first week, the incidence of ipsilateral pain in the early stage of palsy (and the duration of this pain), the proportion of patients with severe pain, the occurrence of synkinesis, facial spasm or contracture, and the severity of residual facial symptoms during the study period. Owing to the size of this study, the results of these secondary endpoints will be published and discussed in a separate paper.

Statistical analysis

Before the study, we assumed that 70% of patients recover completely without treatment (placebo) compared with 80% of patients treated with prednisolone, valaciclovir, or both. This difference was regarded as a clinically significant improvement. To detect a statistically significant difference between the treatment groups with at least 80% power at a 5% significance level, we planned to include 880 patients, which included a 10% loss to follow-up. Analyses of primary and secondary endpoints were by intention to treat. All randomised patients who received at least one dose of study medication were included in the analysis, but patients who did not start therapy were excluded; therefore, the analysis should be regarded as a modified intention-to-treat analysis. Data analyses were done in accordance with a prespecified plan. The last-observation-carried-forward method was used for the modified intention-to-treat analysis, and missing data points were imputed in the post-baseline follow-up visits from the last observation available for each patient. To show any synergistic effect of the combination of prednisolone and valaciclovir, an interaction test was done on the primary endpoint. Results for continuous variables are given as median values with IQR, and results for dichotomous data are given as proportions with 95% CI, with the normal approximation approach. The Kaplan-Meier method was used to estimate survival curves. Categorical variables were compared with Fisher's exact test. Cox proportional hazards models were used to estimate the hazard ratio (HR) of recovery, including 95% CI. The assumption for proportional hazards was tested with Schoenfeld residuals (p=0·73). All computations were done with SAS software (version 9.1) and R (version 2.4.1).

The study is registered with ClinicalTrials.gov (number, NCT00510263).

Role of the funding source

GlaxoSmithKline (Sweden) and Pfizer AB (Sweden) supplied the study drugs, helped to design the study, and required confidentiality agreements with the study group investigators. None of the funding sources had a role in data collection, data analysis, or data interpretation. They were given access to the manuscript 1 month before submission for their comments. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From May, 2001, to September, 2006, 1953 patients (910 women and 1043 men) with acute peripheral facial palsy were screened and registered. At the initial examination, 1114 of the 1953 patients did not meet the inclusion criteria and were registered with separate

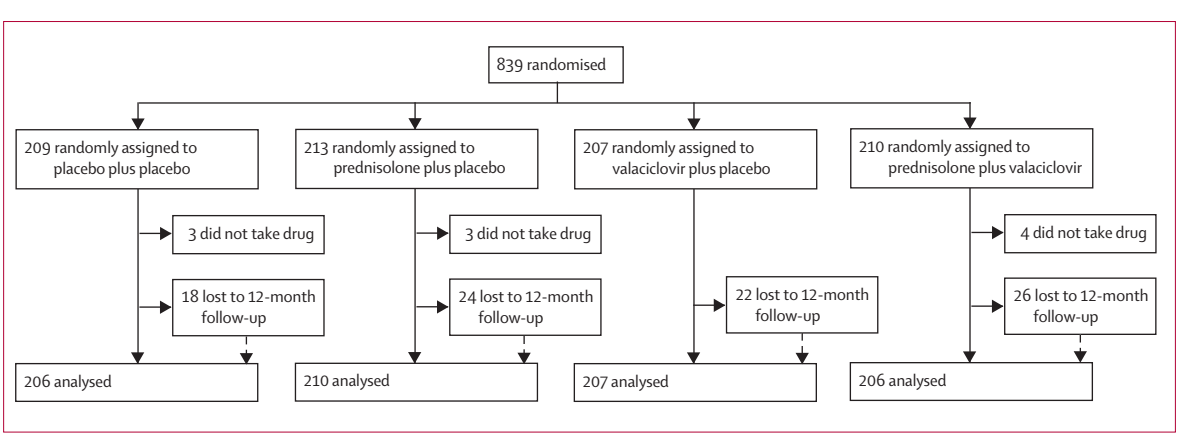
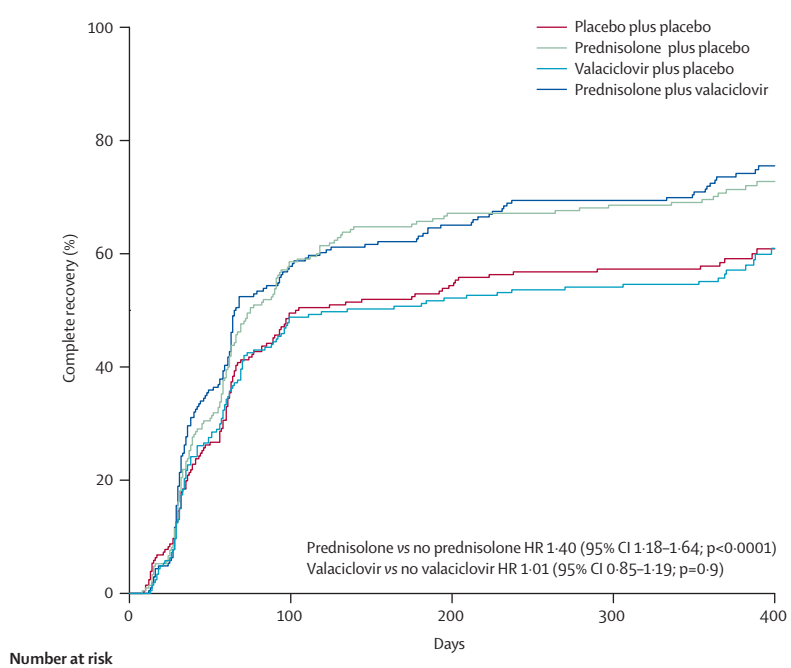


Figure 1: **Trial profile**

	Placebo plus placebo (n=206)	Prednisolone plus placebo (n=210)	Valaciclovir plus placebo (n=207)	Prednisolone plus valaciclovir (n=206)	Total (n=829)
Sex					
Women	93 (45%)	82 (39%)	86 (42%)	80 (39%)	341 (41%)
Men	113 (55%)	128 (61%)	121 (58%)	126 (61%)	488 (59%)
Age (years)*	39 (30–53)	40 (30–52)	40 (32–54)	42 (31–56)	40 (31–54)
Facial nerve grading score					
Sunnybrook scale†	38 (23–51)	38 (25–56)	41 (21–54)	38 (23–54)	39 (23–54)
House-Brackmann scale	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
Side of palsy					
Left	100 (49%)	111 (53%)	95 (46%)	109 (53%)	415 (50%)
Right	106 (51%)	99 (47%)	112 (54%)	97 (47%)	414 (50%)
Ipsilateral pain around the ear or in the face or neck‡	93 (46%)	107 (51%)	111 (54%)	101 (49%)	412 (50%)
Time from onset of palsy to start of treatment*	30 (24 to 48)	30 (22 to 48)	30 (20 to 48)	30 (24 to 48)	30 (22 to 48)
0 to 24 h	70 (34%)	79 (38%)	82 (40%)	77 (37%)	308 (37%)
25 to 48 h	96 (47%)	83 (40%)	81 (39%)	85 (41%)	345 (42%)
49 to 72 h	40 (19%)	48 (23%)	43 (21%)	44 (21%)	175 (21%)

Data are median (IQR) or number of patients (%). *Data missing for one patient. †Data missing for two patients. ‡Data missing for three patients.

***Table 1*: Baseline characteristics of the patients in the modified intention-to-treat analysis**



Number at risk

Placebo plus placebo	194	180	143	113	98	77
Prednisolone plus placebo	200	184	130	99	73	57
Valaciclovir plus placebo	202	181	138	115	102	84
Prednisolone plus valaciclovir	200	174	123	94	77	54

***Figure 2*: Kaplan-Meier estimates of patients who made a complete recovery**
Sunnybrook scale score of 100 points in the four treatment groups (n=829). The Kaplan-Meier estimates are based on the actual number of days from onset of palsy to the first follow-up visit when the patient had completely recovered. Follow-up visits not done on the exact day or time interval scheduled in the protocol are the cause of the zigzag shape of the lines.

forms. Patients who were screened but not included were not registered at the Helsinki centre; thus, the number of patients who were screened was greater than 1953. Reasons for ineligibility were: more than 72 h had elapsed since the onset of palsy (n=300); patients were aged less than 18 years or more than 75 years (n=164); unwillingness to participate (n=163); diabetes mellitus (n=76); previous facial palsy (n=73); signs of infection with borreliosis (n=67); pregnancy or breastfeeding (n=47); other neurological diseases (n=42); uncontrolled hypertension (n=40); psychiatric disease (n=26); systemic antiherpetic medication within the past 2 weeks or ongoing systemic steroid medication (n=24); ipsilateral otitis media (n=12); peptic ulcer (n=10); recent head injury (n=9); renal or hepatic dysfunction (n=9); immunodeficiency (n=7); glaucoma (n=5); and linguistic or geographical causes (n=40).

Figure 1 shows the trial profile. 839 of the 1953 patients (43%) who were screened met the inclusion criteria and were randomly assigned to one of the four treatment arms. Ten patients who were randomly assigned did not take any study drug and were excluded. Consequently, 829 patients were included in the modified intention-to-treat analysis: 206 received placebo plus placebo; 210 received prednisolone plus placebo; 207 received valaciclovir plus placebo; and 206 received prednisolone plus valaciclovir. Thus, 416 patients were given prednisolone and 413 received valaciclovir.

Our intention was to include 880 patients but the inclusion frequency was lower than expected. The study time was therefore prolonged, and enrolment of patients was ended in September, 2006; thus, fewer than 880 patients were included. Table 1 shows the baseline characteristics of the four treatment groups, which were similar in terms of median age, sex, side of palsy, time

	11–17 days	1 month	2 months	3 months	6 months	12 months
Placebo plus placebo (n=206)						
Sunnybrook scale	16, 8% (4% to 11%)	56, 27% (21% to 33%)	88, 43% (36% to 50%)	105, 51% (44% to 58%)	117, 57% (50% to 64%)	118, 57% (51% to 64%)
House-Brackmann scale	16, 8% (4% to 11%)	63, 31% (24% to 37%)	94, 46% (39% to 52%)	111, 54% (47% to 61%)	127, 62% (55% to 69%)	133, 65% (58% to 71%)
Prednisolone plus placebo (n=210)						
Sunnybrook scale	14, 7% (3% to 10%)	65, 31% (25% to 37%)	107, 51% (44% to 58%)	135, 64% (58% to 71%)	143, 68% (62% to 75%)	148, 71% (64% to 77%)
House-Brackmann scale	18, 9% (5% to 12%)	71, 34% (27% to 40%)	111, 53% (46% to 60%)	137, 65% (59% to 72%)	150, 71% (65% to 78%)	160, 76% (70% to 82%)
Valaciclovir plus placebo (n=207)						
Sunnybrook scale	12, 6% (3% to 9%)	60, 29% (23% to 35%)	89, 43% (36% to 50%)	104, 50% (43% to 57%)	111, 54% (47% to 61%)	119, 58% (51% to 64%)
House-Brackmann scale	13, 6% (3% to 10%)	65, 31% (25% to 38%)	94, 45% (39% to 52%)	113, 55% (48% to 61%)	120, 58% (51% to 65%)	133, 64% (58% to 71%)
Prednisolone plus valaciclovir (n=206)						
Sunnybrook scale	12, 6% (3% to 9%)	71, 35% (28% to 41%)	109, 53% (46% to 60%)	124, 60% (53% to 67%)	141, 69% (62% to 75%)	152, 74% (68% to 80%)
House-Brackmann scale	15, 7% (4% to 11%)	78, 38% (31% to 45%)	116, 56% (50% to 63%)	134, 65% (59% to 72%)	149, 72% (66% to 79%)	164, 80% (74% to 85%)

Complete recovery was defined as Sunnybrook scale score of 100 points or House-Brackmann scale score of I at follow-up. Last-observation-carried-forward method was used for missing data points. Data are number of patients, % (95% CI).

***Table 2*: Patients in the modified intention-to-treat analysis with complete recovery per follow-up visit**

	3 months			6 months			12 months		
	Number	Difference	p	Number	Difference	p	Number	Difference	p
Prednisolone (n=416) *vs* no prednisolone (n=413)	259, 62% (58% to 67%) *vs* 209, 51% (46% to 55%)	12% (5% to 18%)	0·0007	284, 68% (64% to 73%) *vs* 228, 55% (50% to 60%)	13% (7% to 20%)	p=0·0001	300, 72% (68% to 76%) *vs* 237, 57% (53% to 62%)	15% (8% to 21%)	<0·0001
Valaciclovir (n=413) *vs* no valaciclovir (n=416)	228, 55% (50% to 60%) *vs* 240, 58% (53% to 63%)	–3% (–9% to 4%)	0·48	252, 61% (56% to 66%) *vs* 260, 63% (58% to 67%)	–2% (–8% to 5%)	0·07	271, 66% (61% to 70%) *vs* 266, 64% (59% to 69%)	2% (–5% to 8%)	0·66
Prednisolone plus placebo (n=210) *vs* valaciclovir plus placebo (n=207)	135, 64% (58% to 71%) *vs* 104, 50% (43% to 57%)	14% (5% to 24%)	0·004	143, 68% (62% to 75%) *vs* 111, 54% (47% to 61%)	15 (5% to 24%)	0·003	148, 71% (64% to 77%) *vs* 119, 58% (51% to 64%)	13% (4% to 22%)	0·006

Data are number of patients, proportion with complete recovery for each treatment modality (95% CI), and % differences (95% CI).

***Table 3*: Rates of complete recovery**

from onset to start of treatment, and the median Sunnybrook and House-Brackmann scores.

During follow-up, the investigating physicians diagnosed diseases that might have been the cause of the palsy: 67 patients were diagnosed with borreliosis, five with herpes zoster oticus, and 18 with other diseases (eg, sarcoidosis, multiple sclerosis, cerebrovascular disease, and parotid tumour). These 90 patients were included in the modified intention-to-treat analysis. 743 of 829 patients (90%) attended the 12-month follow-up visit.

The time to complete recovery was significantly shorter for the 416 patients who received prednisolone compared with the 413 not treated with prednisolone (HR 1·40, 95% CI 1·18 to 1·64; p<0·0001). Time to recovery did not differ between the patients who took valaciclovir and the patients who did not take valaciclovir (1·01, 0·85 to 1·19; p=0·90). No interaction was found between the effects of prednisolone and those of valaciclovir (p=0·59).

Figure 2 shows the median time to complete recovery (Sunnybrook score of 100 points): 75 days in the prednisolone plus placebo group, 104 days in the placebo plus placebo group (p=0·04), and 135 days in the valaciclovir plus placebo group (p=0·03). Tables 2 and 3 show that patients who received prednisolone had significantly higher recovery rates at 3, 6, and 12 months than the patients who did not take prednisolone. At 12 months, 300 of 416 patients (72%) in the prednisolone group had recovered compared with 237 of 413 patients (57%) who did not take prednisolone (p<0·0001). The outcome for the 413 patients who were treated with valaciclovir did not differ from that for the 416 who did not receive valaciclovir (p=0·66; table 3).

Of the patients who were treated with prednisolone plus placebo, 148 of 210 patients (71%) had recovered at 12 months, which was significantly more than the number who had recovered in the valaciclovir plus placebo group (119 of 207 [58%]; p=0·006; tables 2 and 3).

Of the 743 patients who had 12-month follow-up, synkinesis was reported in 51 of 370 patients (14%) treated with prednisolone compared with 107 of 373 (29%) in those who did not receive prednisolone (difference –15%, 95% CI –21% to –9%; p<0·0001). Of the 369 patients who received valaciclovir, 73 (20%) had synkinesis compared with 85 of the 374 patients (23%) who did not have valaciclovir (difference –3%, –9% to 3%; p=0·37). Of the patients treated with prednisolone plus placebo, 32 of 186

	Placebo plus placebo (n=201)	Prednisolone plus placebo (n=203)	Valaciclovir plus placebo (n=205)	Prednisolone plus valaciclovir (n=202)	Total (n=811)*
Gastrointestinal complaints	12	6	5	14	37
Headache	3	3	7	4	17
Fatigue	2	3	2	2	9
Dizziness	0	3	1	2	6
Insomnia	0	0	2	3	5
Increased appetite	0	2	0	0	2
Polyuria	0	1	0	1	2
Paraesthesia	0	1	1	0	2
Palpitations	0	0	0	2	2
Raised blood glucose concentration	0	0	0	1	1
Exanthema	2	1	0	0	3
Other events†	9	6	5	8	28
Number of events‡	28	26	23	37	114
Number of patients with adverse events	25 (12%)	21 (10%)	19 (9%)	27 (13%)	92 (11%)

*Data on adverse events are missing for 18 of the 829 patients in the modifed intention-to-treat analysis. †Adverse events reported by only one patient. Placebo plus placebo: general body pain, chest pain, oral pain, dysphoria, fall on stairs, hypertension, pruritus, slight loss of memory, and external otitis. Prednisolone plus placebo: back pain, external otitis, haematuria, haemorrhoid bleeding, urticaria, and metastasis of temporal bone. Valaciclovir plus placebo: abdominal/thoracic pain, fever, tongue swelling, vesicles, and weight gain. Prednisolone plus valaciclovir: arthralgia, common cold, coughing, peripheral oedema, pustule on right wrist, rash, sweating, and transient atrial fibrillation. ‡More than one adverse event was reported by 15 patients.

Table 4: **Adverse events**

had synkinesis at 12 months, which was significantly less than the 54 of 185 patients in the valaciclovir plus placebo arm (17% *vs* 29%, difference –12%, –21% to –3%; p=0·007).

728 of 829 patients (88%) returned no prednisolone/placebo tablets and three or fewer valaciclovir/placebo tablets, which indicated complete compliance. 68 patients (8%) returned between 0 and 20% of the study drugs (compliance ≥80%) and 17 (2%) returned more than 20% (compliance <80%). Compliance data were missing for 16 patients (2%). Thus, 796 of 829 patients (96%) were more than 80% compliant. Non-serious adverse events were reported by 92 patients: 25 who received placebo plus placebo; 21 who received prednisolone plus placebo; 19 who received valaciclovir plus placebo; and 27 who received prednisolone plus valaciclovir. The numbers of patients with adverse events as estimated with Fisher's exact test did not differ between the prednisolone plus placebo and placebo plus placebo groups (difference –2%, 95% CI –8% to 4%; p=0·53), the valaciclovir plus placebo and placebo plus placebo groups (difference –3%, –9% to 3%; p=0·34), or the prednisolone plus valaciclovir and placebo plus placebo groups (difference 1%, –6% to 8%; p=0·88). The number of non-serious events was 114 (15 patients reported more than one adverse event). Table 4 shows the adverse events. One man with a history of recurrent atrial fibrillation had a transient relapse on prednisolone plus valaciclovir.

Discussion

This large, double-blind, placebo-controlled trial assessed corticosteroid and antiviral treatment for Bell's palsy. The patients who received prednisolone had a shorter time to complete recovery, and outcomes at 12 months were more favourable in these patients than in those who did not receive prednisolone. Valaciclovir was not proven to be effective and did not affect prednisolone treatment.

In 2001, the American Academy of Neurology concluded in their practice guideline meta-analysis that although the benefit of steroids has not been established, they probably are effective for improving facial functional outcomes.[22] This postulation is supported by our results on the efficacy of prednisolone and by the results of a recent trial in Scotland, UK, of 551 patients randomly assigned to either 10 days of 25 mg prednisolone twice daily, 400 mg aciclovir five times daily, both drugs, or placebo.[23] The investigators of that trial concluded that early treatment with prednisolone significantly improved the chances of complete recovery at 3 and 9 months.

The effect of prednisolone indicates that inflammation and oedema of the facial nerve is part of the pathogenesis in Bell's palsy, which agrees with previous findings in peroperative[5] and MRI studies.[4,6]

In this study, the dose of valaciclovir used gave a concentration that was well above the inhibitory level for herpes simplex virus but that was maybe only partially inhibitory for varicella zoster virus.[24] The ineffectiveness of valaciclovir might also be because the rate of virus replication had declined before treatment started[25] or that herpes viruses are not the main cause of Bell's palsy.

As seen in figure 2, prednisolone plus valaciclovir was not more effective than prednisolone alone. This result is in accordance with previous findings with either valaciclovir[26] or aciclovir[19,23] plus corticosteroids. Never-

theless, an additional effect of aciclovir[17] or valaciclovir[27] on corticosteroid treatment has been reported. However, the trial by Adour and colleagues[17] followed up patients for only 4 months, and the study by Hato and co-workers[27] was not double-blinded; therefore, the results of both trials should be interpreted with caution.

We did baseline assessments before medication was started. Sullivan and co-workers[23] assessed facial function within 8 days of the onset of palsy; consequently, 7% of these patients were graded as House-Brackmann grade I at baseline. Our complete compliance rate was 88%, whereas compliance data for the trial in Scotland were reported for only 426 of 551 randomly assigned patients, of whom 383 had complete compliance.[23]

In most trials of treatments for Bell's palsy,[12,15,23] facial function is evaluated with the House-Brackmann scale.[21] The Sunnybrook system reports facial function in a continuous manner and has a wider response range than the House-Brackmann scale.[20] The intra-rater and inter-rater reliability of the Sunnybrook scale is high when applied by either a novice or expert assessor[28] and is more reliable than the House-Brackmann scale.[29] We therefore used the Sunnybrook scale as the main scale to assess facial nerve function.

Our recovery rates were lower than those previously reported.[2,23] Although the overall results were similar between the two grading systems, we found lower complete recovery rates with the Sunnybrook scale than with the House-Brackmann scale. This probably shows the higher sensitivity of the Sunnybrook scale for sequelae.

The analysis methods used in a trial also affect the results for complete recovery rates. In the revised CONSORT statement for the reporting of randomised trials,[30] all randomised patients are to be included in the intention-to-treat analysis. Consequently, our modified intention-to-treat population was based on all 839 patients who were randomised, with the exception of the ten patients who did not take any study drug. The last-observation-carried-forward method, which was used when follow-up data were missing, most certainly reports lower recovery rates. Furthermore, the severity of palsy at baseline, differences in follow-up time, grading done on the basis of photos or interviews and questionnaires instead of clinical examination, the grading scales used, and the definition of complete recovery all affect the final recovery rates.[2,17,23,27]

On the basis of the results of an acute serological test, the investigating physician diagnosed infection with *Borrelia burgdorferi* in 67 patients (8%). This incidence is most probably overestimated because paired assessment of the sera or assessment of the CSF is needed for a definite diagnosis. Another shortcoming is that some centres discontinued follow-up in patients who were randomised but were diagnosed with other diseases. Consequently, 30 of these 90 patients (33%) had no 12-month visit. Furthermore, when this study was being planned we considered screening for herpes viruses; such analyses would have extended this treatment trial and, for practical reasons and the uncertainty about the results of viral tests to identify the aetiopathological causes of Bell's palsy, analyses for herpes were not done.[7,8,10,25]

In conclusion, we found significant short-term and long-term treatment effects of prednisolone in patients with Bell's palsy, whereas valaciclovir did not affect facial recovery. Analysis of the severity of palsy at baseline related to outcome might give information on which patients would benefit the most from treatment with corticosteroids.

Contributors

All authors participated in the design, or implementation, analysis, and interpretation of the study. ME was the coordinating principal investigator. AP was the principal investigator for Finland, and LJ was the study director. ME, TB, AS-D, SA, and LJ were responsible for the input of the data from the case report forms on to the database.

Investigators and participating centres

In addition to the authors, the following physicians and otorhinolaryngological centres participated in this multicentre trial. M Svensson, T Ekberg (Uppsala University Hospital, Uppsala); M Karlberg, S Lindberg (Lund University Hospital, Lund); S Rudblad, I Augustsson (Örebro University Hospital, Örebro); T Ekstrand (deceased December, 2001), O Lind (Hudiksvall County Hospital, Hudiksvall); J Wingerstrand, J Grenner (Malmö University Hospital, Malmö); S Padoan (Kristianstad County Hospital, Kristianstad); P Gissén (Karlstad County Hospital, Karlstad); I-L Sjölin (Helsingborg County Hospital, Helsingborg); B Nilsson-Helger (Borås County Hospital, Borås); L Aziz (Sahlgrenska University Hospital, Göteborg); A Granath, S Blomberg, K Strömbäck, M Pekkari, P Stammler, W Jäger (Karolinska University Hospital, Huddinge); M Jessen, I Nordbladh (Växjö Central Hospital, Växjö); R Isholth, N Lönnbro (Kalmar County Hospital, Kalmar); P Gunnarsson (Sundsvall County Hospital, Sundsvall); S-A Westerström, L Falk (Gävle County Hospital, Gävle).

Conflicts of interest

ME was paid by GlaxoSmithKline for a lecture on Bell's palsy in 2001. The other authors have no conflicts of interest.

Acknowledgments

This trial was supported by grants from Uppsala University, GlaxoSmithKline, Sweden, Pfizer AB, Sweden, Acta Otolaryngologica Foundation, Rosa and Emanuel Nachmanssons Foundation, Stig and Ragna Gorthon Foundation, Torsten Birger Segerfalk Foundation, Margit Arstrups FoundatioIn memory of Tom Ekstrand (Hudiksvall County Hospital, Hudiksvall), one of the initiators of this study. We also thank Matti Anniko (Uppsala University Hospital, Uppsala) for encouraging support; Mats Holmström (Uppsala University Hospital, Uppsala) for support and educational discussions; Elisabeth Aurelius (Karolinska University Hospital, Stockholm) for valuable scientific advice; Nermin Hadziosmanovic, Lars Berglund, and Niclas Eriksson (Biostatisticians, Uppsala Clinical Research Centre) for help with the statistics; Pär Lundqvist (Systems developer, Uppsala Clinical Research Centre) for developing the database; Adam Taube (Department of Information Science-Statistics, Uppsala University, Uppsala) for help with planning and the final analysis of the study; Per Engervall and Gunnar Dahl (GlaxoSmithKline, Sweden) for help to initiate and implement this study; Markku Pulkkinen (GlaxoSmithKline, Finland) for practical help with the study drugs; Eva Dahl (Pfizer AB, Sweden) for supporting this study; Charlotte Cervin-Hoberg (Lund University Hospital, Lund) for help in monitoring; Annette Johansson (Uppsala University Hospital, Uppsala) for administrative help; and all the physicians, nurses, and personnel at the participating centres for their help with the study. The results of this study were partly presented at the Annual Meeting of the Swedish Association of Otorhinolaryngology and Head and Neck Surgery in Örebro, Sweden, May 7–9, 2008, and at the 30th Congress of the Nordic Association of Otolaryngology in Trondheim, Norway, June 11–14, 2008.

References

1 May M, Hughes GB. Facial nerve disorders: update 1987. *Am J Otol* 1987; **8:** 167–80.

2 Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. *Acta Otolaryngol Suppl* 2002; **549:** 4–30.

3 Yanagihara N. Incidence of Bell's palsy. *Ann Otol Rhinol Laryngol Suppl* 1988; **137:** 3–4.

4 Engström M, Thuomas K-Å, Naeser P, Stålberg E, Jonsson L. Facial nerve enhancement in Bell's palsy demonstrated by different gadolinium-enhanced magnetic resonance imaging techniques. *Arch Otolaryngol Head Neck Surg* 1993; **119:** 221–25.

5 Fisch U, Esslen E. Total intratemporal exposure of the facial nerve. Pathologic findings in Bell's palsy. *Arch Otolaryngol* 1972; **95:** 335–41.

6 Schwaber MK, Larson TC III, Zealear DL, Creasy J. Gadolinium-enhanced magnetic resonance imaging in Bell's palsy. *Laryngoscope* 1990; **100:** 1264–69.

7 Adour KK, Bell DN, Hilsinger RL Jr. Herpes simplex virus in idiopathic facial paralysis (Bell palsy). *JAMA* 1975; **233:** 527–30.

8 Furuta Y, Fukuda S, Suzuki S, Takasu T, Inuyama Y, Nagashima K. Detection of varicella-zoster virus DNA in patients with acute peripheral facial palsy by the polymerase chain reaction, and its use for early diagnosis of zoster sine herpete. *J Med Virol* 1997; **52:** 316–19.

9 McCormick DP. Herpes-simplex virus as a cause of Bell's palsy. *Lancet* 1972; **299:** 937–39.

10 Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* 1996; **124:** 27–30.

11 Salinas RA, Alvarez G, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2004; **2:** CD001942.

12 Lagalla G, Logullo F, Di Bella P, Provinciali L, Ceravolo MG. Influence of early high-dose steroid treatment on Bell's palsy evolution. *Neurol Sci* 2002; **23:** 107–12.

13 May M, Wette R, Hardin WB Jr, Sullivan J. The use of steroids in Bell's palsy: a prospective controlled study. *Laryngoscope* 1976; **86:** 1111–22.

14 Taverner D. Cortisone treatment of Bell's palsy. *Lancet* 1954; **267:** 1052–54.

15 Ünüvar E, Oğuz F, Sidal M, Kiliç A. Corticosteroid treatment of childhood Bell's palsy. *Pediatr Neurol* 1999; **264:** 814–16.

16 Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2004; **1:** CD001869.

17 Adour KK, Ruboyianes JM, Von Doersten PG, et al. Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: a double-blind, randomized, controlled trial. *Ann Otol Rhinol Laryngol* 1996; **105:** 371–78.

18 Antunes ML, Fukuda Y, Testa JRG. Clinical treatment of Bell's palsy: comparative study among valaciclovir plus deflazacort, deflazacort and placebo. *Acta AWHO* 2000; **19:** 68–75.

19 De Diego JI, Prim MP, De Sarria MJ, Madero R, Gavilan J. Idiopathic facial paralysis: a randomized, prospective, and controlled study using single-dose prednisone versus acyclovir three times daily. *Laryngoscope* 1998; **108:** 573–75.

20 Ross BG, Fradet G, Nedzelski JM. Development of a sensitive clinical facial grading system. *Otolaryngol Head Neck Surg* 1996; **114:** 380–86.

21 House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985; **93:** 146–47.

22 Grogan PM, Gronseth GS. Practice parameter: steroids, acyclovir, and surgery for Bell's palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001; **56:** 830–36.

23 Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007; **357:** 1598–607.

24 Lycke J, Malmeström C, Ståhle L. Acyclovir levels in serum and cerebrospinal fluid after oral administration of valacyclovir. *Antimicrob Agents Chemother* 2003; **47:** 2438–41.

25 Stjernquist-Desatnik A, Skoog E, Aurelius E. Detection of herpes simplex and varicella-zoster viruses in patients with Bell's palsy by the polymerase chain reaction technique. *Ann Otol Rhinol Laryngol* 2006; **115:** 306–11.

26 Kawaguchi K, Inamura H, Abe Y, et al. Reactivation of herpes simplex virus type 1 and varicella-zoster virus and therapeutic effects of combination therapy with prednisolone and valacyclovir in patients with Bell's palsy. *Laryngoscope* 2007; **117:** 147–56.

27 Hato N, Yamada H, Kohno H, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. *Otol Neurotol* 2007; **28:** 408–13.

28 Hu WL, Ross B, Nedzelski J. Reliability of the Sunnybrook Facial Grading System by novice users. *J Otolaryngol* 2001; **30:** 208–11.

29 Kanerva M, Poussa T, Pitkäranta A. Sunnybrook and House-Brackmann facial grading systems: intrarater repeatability and inter-rater agreement. *Otolaryngol Head Neck Surg* 2006; **135:** 865–71.

30 Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; **134:** 663–94.