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

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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 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 Gorbon 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 5 which might be related to the herpes virus;6 7 this has led many investigators to study the efficacy of corticosteroids and antivirals to treat Bell’s palsy. The Cochrane database report8 on corticosteroid therapy concluded that trials9–10 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.9 11 Three studies (246 patients) were reviewed,9–11 and a need for adequately powered clinical trials of aciclovir and valaciclovir with a follow-up of 1 year was identified.10

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 Sunnybrook20 and the gross House-Brackmann21 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
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 antitherpetic 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 until all patients had completed follow-up. The participants, and data analysts were blinded to treatment contained the study drugs. All study personnel, the patient received the corresponding container that was 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. 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. 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.

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 1, 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
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 from onset of palsy to start of treatment, and facial nerve grading score.

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

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

Figure 2 shows 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.

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

Kaplan-Meier estimates of patients who made a complete recovery
- Prednisolone vs no prednisolone HR 1.40 (95% CI 1.18–1.64; p<0.0001)
- Valaciclovir vs no valaciclovir HR 1.01 (95% CI 0.85–1.19; p=0.9)

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.
67 patients were diagnosed with borreliosis, five with diseases that might have been the cause of the palsy; Sunnybrook and House-Brackmann scores.

829 patients (90%) attended the 12-month follow-up visit.

Included in the modified intention-to-treat analysis. 743 of disease, and parotid tumour). These 90 patients were (eg, sarcoidosis, multiple sclerosis, cerebrovascular herpes zoster oticus, and 18 with other diseases

Prednisolone plus placebo (n=210)

Sunnybrook scale 15, 7% (4% to 11%) 78, 38% (31% to 45%) 116, 56% (50% to 61%) 134, 65% (59% to 72%) 149, 72% (66% to 79%) 164, 80% (74% to 85%)

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 37%) 107, 51% (44% to 58%) 135, 64% (58% to 71%) 143, 68% (62% to 75%) 148, 71% (64% to 77%)

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

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 those who did not take prednisolone (1·01, 0·85 to 1·19; p=0·90). No interaction was found between the effects of prednisolone and 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 prednisolone (p=0·37; 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
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.

### Table 4: Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo plus placebo (n=201)</th>
<th>Prednisolone plus placebo (n=203)</th>
<th>Valaciclovir plus placebo (n=205)</th>
<th>Prednisolone plus valaciclovir (n=202)</th>
<th>Total (n=811)*</th>
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<td>6</td>
<td>5</td>
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<td>Headache</td>
<td>3</td>
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<td>7</td>
<td>4</td>
<td>17</td>
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<tr>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
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<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
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<tr>
<td>Insomnia</td>
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<td>0</td>
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<td>3</td>
<td>5</td>
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<td>Other events†</td>
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<td>26</td>
<td>23</td>
<td>37</td>
<td>114</td>
</tr>
<tr>
<td>Number of patients with adverse events</td>
<td>25 (12%)</td>
<td>21 (10%)</td>
<td>19 (9%)</td>
<td>27 (13%)</td>
<td>92 (11%)</td>
</tr>
</tbody>
</table>

*Data on adverse events are missing for 18 of the 829 patients in the modified 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.

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 peroperative5 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 started25 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 valaciclovir26 or aciclovir23,19 plus corticosteroids. Never-
theless, an additional effect of aciclovir or valaciclovir on corticosteroid treatment has been reported. However, the trial by Adour and colleagues followed up patients for only 4 months, and the study by Hato and co-workers 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 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.

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

Our recovery rates were lower than those previously reported. 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, 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.

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.

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 Rudhåd, I Augustsson (Orebro University Hospital, Orebro); T Ekström (deceased December, 2001), O Lind (Huddinge County Hospital, Huddinge); J Wingerstrand, J Grenner (Malmö University Hospital, Malmö); P Sadoan (Kristianstad County Hospital, Kristianstad); G Sættem (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, P Kekkari, 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 Westerstrom, L Falk (Göteborg County Hospital, Göteborg).

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.

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