Randomized Controlled Trial of Adjuvant Oral Dexamethasone Pulse Therapy in Pemphigus Vulgaris

PEMPULS Trial

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Objective: To determine the therapeutic effect of adjuvant dexamethasone pulse therapy when given in addition to conventional treatment of pemphigus vulgaris.

Design: A randomized, placebo-controlled trial.

Setting: International European, multicenter outpatient and inpatient study.

Patients: Of the 20 enrolled patients, 11 were randomized to the dexamethasone pulse (DP) group and 9 to the placebo pulse (PP) group.

Interventions: Oral dexamethasone in 300-mg pulses or PPs 3 days per month. During the intervention, the DP and PP groups received conventional treatment with prednisolone, 80 mg/d, which was tapered across 19 weeks, and azathioprine sodium, 3 mg/kg per day, until the end of the study. Monthly pulses were continued until prednisolone treatment was tapered to 0 mg.

Main Outcome Measures: Number of patients in remission, time to and duration of remission, cumulative prednisolone dose, and occurrence of adverse events during 1 year of follow-up.

Results: Eight of the 11 DP-treated patients and all 9 PP-treated patients achieved remission. Mean time to remission was 173 days with DP and 176 days with PP. The mean duration of remission within the first year was 151 days for DP and 141 days for PP. Mean cumulative prednisolone dose was 5300 mg for DP and 4882 mg for PP. Weight gain (>5% of baseline) occurred in 8 DP-treated patients compared with 1 PP-treated patient (P < .01). We found no statistically significant difference (P > .05) of an adjuvant effect of DP on remission of pemphigus vulgaris.

Conclusion: In patients with new pemphigus vulgaris disease activity, there was no benefit of oral DP therapy given in addition to conventional treatment.

Trial Registration: clinicaltrials.gov Identifier: NCT00127764.

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Pemphigus vulgaris is a potentially fatal, chronic, autoimmune mucocutaneous bullous disease, precipitated by IgG autoantibodies binding to desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1). Corticosteroids (CS) form the cornerstone in the treatment of pemphigus. To minimize the iatrogenic effects of CS therapy, adjuvant treatments by CS pulse therapy were used by Pasricha et al in a large open series of 300 patients. Pulse therapy, the “big shot,” refers to the discontinuous intravenous infusion of very-high-dose CS over a short time. Pulse therapy, which was initially used for the treatment of transplant rejection, began to be used to treat pemphigus in the 1980s. Many open studies differing in design, criteria, regimen, and concomitant drugs evaluated CS pulse therapy in pemphigus. For CS pulse therapy, 500- to 1000-mg shots of methylprednisolone acetate or, most often, 100- to 200-mg shots of dexamethasone are given intravenously divided during 3 consecutive days per month.

To our knowledge, there are no previous randomized controlled trials of CS pulse therapy in pemphigus. We performed a multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of adjuvant CS pulse therapy in addition to a conventional regimen of daily prednisolone and azathioprine in patients with new pemphigus vul-
giris disease activity. The therapeutic effect was measured by the time to remission, duration of remission, cumulative prednisolone dose, and occurrence of adverse events.

METHODS

STUDY PROTOCOL

The study was designed to find an additive therapeutic effect of adjuvant dexamethasone pulse (DP) therapy on remission rate and if DPs had a CS-sparing effect. The pulses were not administered as monotherapy but given in addition to an optimal conventional treatment schedule of medium-dose prednisolone plus high-dose azathioprine. The study was a European, multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial. The study was initiated and coordinated by the Center for Blistering Diseases of the University Medical Center Groningen, Groningen. It was conducted from 2000 to 2005.

Tablets containing dexamethasone were produced in our hospital pharmacy according to the European Pharmacopoeia. The dexamethasone was hydrophilized with methylcellulose 15 mPa·s. The tablets were prepared by direct compression using microcrystalline cellulose (Avicel PH 101; FMC Biopolymer, Philadelphia, Pa) and magnesium stearate. During pulse visits, 6 oral tablets of 50 mg of dexamethasone, or 6 tablets of placebo (which were both specially produced to be identical in taste and smell and were tested for this study) were given on 3 consecutive days every 4 weeks. The pulses were stopped when prednisolone treatment was tapered to 0 mg. If relapse occurred, prednisolone was administered (Table 1 and Figure 1). Pulse dosing was reintiated only when 80 mg of prednisolone was needed.

Both study arms received conventional treatment with prednisolone and medium-high-dose azathioprine. The initial prednisolone dose was 80 mg. Tapering was performed in response to disease activity according to a predetermined schedule (Table 1 and Figure 1). Azathioprine treatment was started at a dosage of 50 mg/d for 1 week and increased to 3 mg/kg per day for the rest of the study, depending on thiopurine methyltransferase activity. If the thiopurine methyltransferase level was lower than 37.5 nmol per gram of hemoglobin per hour, then the azathioprine dose was lowered to 1.5 mg/kg. The azathioprine dose was halved if leukopenia developed, decreased by 50 mg if the liver enzyme levels more than doubled, or stopped if severe thrombocytopenia developed. Prophylactic ranitidine hydrochloride and a combination of etidronate disodium and calcium carbonate or cholecalciferol (vitamin D) were given as long as CS was administered.

PARTICIPATING CENTERS

In Europe the following centers participated: University Medical Center Groningen; Albert Szent-Gyorgyi Medical University Szeged, Szeged, Hungary; Instituto Dermopatico dell’Immacolata–IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico spe-
to conclude significance at a level of 5% with a power of 90%.

Exclusion Criteria
Exclusion criteria were treatment with CS within the past 2 months, treatment with adjuvant therapy other than azathioprine or having contraindications for the use of high-dose CS or azathioprine, concomitant disease treated with CS, or no ability to attend follow-up.

Patients were withdrawn from the study if a serious adverse event occurred, if the investigator considered it in the best interest of the patient for safety reasons, if they withdrew their consent, or if the randomization code was broken. Patient data have been used only if the required variable data set was complete. Eligible volunteer patients signed an informed consent before entering the study.

METHODS OF ASSIGNING PATIENTS TO TREATMENT GROUPS
Computer-generated random numbers were used to randomize patients to the DP group or the placebo pulse (PP) group in blocks of 8. A sealed box containing the previously computer-randomized blinded study medication and case report form was provided via express mail shortly after inclusion.

DETERMINATION OF SAMPLE SIZE
For this proof-of-concept study, effectiveness was defined as a difference of at least 5 weeks in the duration of remission, the primary variable. From a clinical perspective, this criterion was considered very strict, but it was chosen to achieve a more robust sample size for this multicenter study. To be able to detect this difference with a power of 90% at a 5% level of significance and an estimated standard deviation of 6 weeks, 30 patients were needed in both treatment groups.

When we considered 10 weeks as the more clinically relevant difference in duration of remission for the assessment of superiority of adjuvant DP therapy compared with the conventional regimen, 9 patients in both groups would have been sufficient to conclude significance at a level of 5% with a power of 90%.

SAFETY ANALYSIS
All eligible patients underwent assessment of safety before inclusion in the trial. Extensive medical histories were obtained, and physical examinations were performed. A complete blood cell count, electrolyte levels, and blood glucose levels were measured and urinalysis and renal and liver function tests were performed at the initial visit, every pulse visit, and the end of study.

Heart rate, blood pressure, body weight, and body temperature were recorded before and after every pulse therapy. During the first pulse visit, a chest radiograph and electrocardiogram were obtained, and blood samples for indirect immunofluorescence pemphigus titer, thiorurine methyltransferase activity, and rhesus and blood group analysis were collected. Bone density measurement for osteoporosis was performed by means of dual-energy x-ray absorptiometry scans at the first pulse and end-of-study visits.

Efficacy Variables
The baseline time point was the time the patient entered the trial. The time to remission was the time between the first dose of prednisolone and the day that prednisolone treatment was tapered to 0 mg. The duration of remission was defined as the time between the prednisolone treatment taper to 0 mg and the time when there was new disease activity requiring additional prednisolone administration. The total use of prednisolone was calculated from the data in the case report form. The total number of pulses represents the number of months that dexamethasone was used during the study.

Disease Monitoring
During the 1-year follow-up, assessment visits were planned every 2 weeks when pemphigus was active and every 4 weeks when the disease was in remission. Prednisolone dose was adjusted according to disease activity.

Disease activity is defined as indicated in Table 1.

At each visit the disease activity, compliance, medication dose and adjustment, adverse events, and safety measurements were recorded in the case report form.

In each participating center, 1 trial physician recorded all of the case report forms for their patients. Prednisolone and azathioprine dose tables were faxed monthly to the trial coordination center. The adverse and serious adverse events, if any, were recorded at every visit, and appropriate action was taken, if necessary. The weight gain was calculated by comparing the initial weight with the maximum weight measured during the study.

To evaluate the effect of therapy on pemphigus titer activity, serum specimens were collected at the beginning, first remission, and end of the study and were examined on antibody index level by the central coordinating laboratory at the Center for Blistering Diseases in Groningen. Therefore, the IgG indexes to Dsg1 and Dsg3 were determined by the enzyme-linked immunosorbent assay (ELISA) MESACUP desmoglein tests for Dsg1 and Dsg3 according to the protocols of the manufacturer (MBL, Nagoya, Japan).

Statistical Analysis
Characterization of Patient Sample
Comparability between groups was evaluated with respect to the demographic and baseline data. Baseline descriptive statistics are given as the mean (range) for continuous variables and as counts for categorical variables. To calculate differences between groups, we used the Mann-Whitney test for nonparametric continuous data and the Fisher exact test for categorical data. Kaplan-Meier survival analysis (with the log-rank test) was performed on time to remission, duration of remission, and relapses over time in the study population. In all analyses, a value of $P<.05$ (2 sided) was considered statistically significant. We used SPSS software, version 12 (SPSS Inc, Chicago, Ill), for statistical analysis.
Sample Size

During the 4½ years that the study was open to accrual, we were confronted with financial and legal limitations of this trial, so that the aim of recruiting 60 patients was not reached. We decided to stop accruing patients after 4½ years and evaluate the European Randomised Placebo-Controlled Trial of Adjuvant Oral Glucocorticoid Pulse Therapy in Pemphigus (PEMPULS) using the 20 patients who were included at that time.

After analysis, no statistically significant differences were observed between conventional treatment and the adjuvant regimen, raising the question of a sufficiently powered study. To further evaluate this issue, a post hoc power analysis was performed. Instead of a post hoc power estimation for differences as small as those observed in our study, we chose the clinically relevant perspective. Our small study was sufficiently powered to detect a clinically relevant difference after at least 10 weeks at a significance level of 5%.

RESULTS

PATIENTS

From January 1, 2000, to June 1, 2004, 28 patients were contacted, 24 were eligible, and 20 gave informed consent and were included (Figure 2). The distribution per center was as follows: 7 patients from Groningen, 4 from Rome, 4 from Belgrade, 2 from Szeged, 1 from Utrecht, 1 from Barcelona, and 1 from Ghent. The final study follow-up assessment was performed in June 2005.

Eleven patients received DP therapy and 9 received PP therapy. Baseline characteristics are shown in Table 2. Both groups were comparable regarding the number of lesions, age, and sex.

Five patients were withdrawn from the study, including 3 from the DP group and 2 from the PP group. In the DP group, 1 patient was withdrawn because of Epstein-Barr viral hepatitis, 1 because of onset of muscle weakness and myalgia, and 1 because of cognitive impairment after pulses (steroid dementia syndrome), which was completely reversible shortly after the last pulse.20 In the PP group, 2 patients prematurely discontinued the study. One of these dropped out because of a newly diagnosed lung carcinoma. In retrospect, the carcinoma was not visible on the chest radiograph at the start of the study and could not be attributed to the medication in the trial. The other withdrew because of insurance problems.

TIME TO REMISSION

In the DP group, 8 of 11 patients achieved remission within 1 year. In the PP group, all 9 patients achieved remission. The mean time to remission was 173.2 days in the DP group and 175.6 days in the PP group, with a median of 141 and 140 days, respectively (Table 3).

An optimal response of remission within 19 weeks was found in 4 patients receiving DP therapy and 6 patients receiving PP therapy. The difference between the times each group took to achieve remission (1-2 days) was not significant (P=.76).

DURATION OF REMISSION

The mean number of days in remission until day 365 was 151 (range, 0-233) in the DP group, and 141 (range, 8-232) in the PP group. The difference of 10 days in duration of remission was statistically not significant (P=.82) (Table 3). Within the follow-up period, relapses after remission occurred in 4 patients in the DP group and 3 patients in the PP group. The mean time from remission to relapse before the end of the study was 102 days (range, 62-166 days) in the DP group and 26 days (range, 6-65 days) in the PP group. The trend of a longer relapse-free remission in the DP group was not statistically significant owing to the very small numbers of patients in this subset.
The mean cumulative prednisolone dose was 5300 mg in the DP group and 4882 mg in the PP group (Table 3) \( (P = .78) \). The number of days of prednisolone use in the DP group was 198; in the PP, group 224. The average daily dose of prednisolone was 24.8 mg in the DP group and 21.8 mg in the PP group (Figure 3).

The mean dose of prednisolone needed to achieve remission was lower in the DP group (3654 mg) than in the PP group (4329 mg), counting only those patients who achieved remission. The trend was statistically not significant. Patients in the DP and PP groups received a mean of 5.44 and 6.44 pulse courses, respectively, before the first remission.

**ADVERSE EVENTS AND TOLERABILITY**

In the DP group, 30 adverse events occurred in 10 of 11 patients compared with 14 adverse events in 5 of 9 patients in the PP group (Table 4). Three patients in the DP group discontinued the study because of adverse events in the form of infection, myalgia, high blood glucose levels, and cognitive dysfunction. All adverse events disappeared after discontinuation of medication therapy. A greater than 5% weight gain was encountered by 8 of 9 patients in the DP group and in 1 of 9 patients in the PP group. The mean increase in body weight compared with the initial weight was 12.4% in the DP group compared with 2.9% \( (P = .01) \) in the PP group. After discontinuation of Cs therapy, weight gain had the tendency to resolve. Adjustment of azathioprine dose, treatment of infection, and use of elastic stockings and antithrombotic agents controlled or prevented many of the adverse effects.
compared with a conventional regimen of prednisolone, 80 mg, with a tapering schedule, and azathioprine, 3 mg/kg per day, in terms of time to remission, duration of remission, or cumulative prednisolone dose. The number of patients included in this study was only one third that of the preplanned number of patients; therefore, small benefits of less than 10 weeks’ extension of remission might have been missed. However, we believe that from a clinical perspective, these differences would not have altered the decision to choose not to initiate oral DP therapy. In addition, a post hoc power analysis showed that our small study was sufficiently powered for a clinically relevant difference of at least 10 weeks.

The trend of a longer relapse-free remission time in the DP group (102 days) vs the PP group (26 days) was based on subsets of only 4 and 3 patients, respectively. We did not see any relapses in the 12 patients who achieved remission at least 141 days of prednisolone treatment, most likely because of the short follow-up period of 365 days. It is therefore hard to judge whether the difference in duration of the remission between the groups is a trend or merely a coincidence.

A positive trend, which was statistically not significant, was the lower mean prednisolone dose used to achieve remission in the DP group. We should remember, however, that in this trial a very quick tapering of the prednisolone dose to 0 mg within 19 weeks was chosen to detect early relapses in the control group. The positive trends in the DP group might have been leveled if prednisolone treatment had not been tapered to less than 10 mg/d in both groups, as is often used in practice. However, relapses occurring in this quick tapering schedule could be controlled with stepped-up doses of 20 or 40 mg of prednisolone.

The results of this randomized controlled trial cannot directly be compared with those of other open patient series in which DP was used in combination with cyclophosphamide, usually called dexamethasone-cyclophosphamide pulse (DCP) therapy. In DCP therapy, patients receive low daily doses of oral prednisolone and cyclophosphamide, 50 mg/d. We chose azathioprine instead of cyclophosphamide as the CS-sparing agent because the latter has the potential to induce malignancies and might result in permanent sterilization in women. The surprising good results of the PP (control) group in this study might be attributed to the continued azathioprine administration during the study at a higher dosage (3 mg/kg per day) than is commonly used (<2 mg/kg per day). Randomized placebo-controlled studies addressing the effect of azathioprine in pemphigus are lacking, although its CS-sparing effect has been shown in other autoimmune bullous diseases. A second difference compared with the DCP study is that we stopped pulses after tapering prednisolone treatment to 0 mg, whereas DCP therapy was continued for 6 months. A third difference is that we used oral instead of intravenous CS pulses. Oral pulses are more convenient and serve as a more acceptable blinding method for placebo. Oral dexamethasone pulsing has a bioavailability of 60%. In this study, only patients with newly diagnosed pemphigus vulgaris or those in complete remission with a new flare-up were included, so the results do not extend to patients with refractory disease that is resistant to conventional therapy. Adjuvant pulse therapy may have a value for severe or refractory cases of pemphigus.

We saw a significantly larger weight gain in patients in the DP group. This weight gain was probably due to cushingoid obesity, which is known to be an adverse effect of CS therapy. In this study, a small number of adverse events were probably caused by azathioprine, such as liver and kidney dysfunction, anemia, and leukopenia. These effects were reversible after lowering the azathioprine dose. The end-of-study dual-energy x-ray absorptiometry scans showed no signs of osteoporosis in any patient.

With regard to the anti-Dsg1 and anti-Dsg3 ELISA results, both study groups showed a significant decline between the start and remission levels of Dsg1 antibodies, and also, but to a lesser extent, in Dsg3 antibodies. After discontinuation of CS therapy, a slight increase in Dsg3 antibody levels was seen in both groups, but in Dsg1 antibody levels only in the PP group. We could not find a statistically significant difference in reduction of antibody levels between the groups.

As we stated, the conclusions that can be drawn from this study for the treatment of patients with pemphigus vul-
argas are somewhat restricted because of the small number of patients (n = 20), the relatively short follow-up period (365 days), and the restriction to patients with new disease activity. However, we believe that when the observed treatment differences are considered from a clinical respective, these restrictions do not alter our overall recommendation against using DP therapy in this patient group. The results from both groups imply that conventional treatment with prednisolone, 80 mg/d, on a tapering schedule to 0 mg in 19 weeks, and azathioprine sodium, 3 mg/kg, continued for 1 year after tapering, is an effective therapy for new disease activity in patients with pemphigus vulgaris, and that adding DP therapy to this regimen has no benefit.

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