Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment

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ABSTRACT

Objective: Achieving long-term remission after a limited more intense treatment period would prevent prolonged use of corticosteroids or IV immunoglobulin (IVIg) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In this prospective cohort study we present long-term follow-up data on patients included in a multicenter randomized controlled trial comparing 6 monthly pulses of dexamethasone with 8 months of daily prednisolone.

Methods: Treatment effect was assessed with the Inflammatory Neuropathy Cause and Treatment disability scale and the Rivermead Mobility Index and was categorized using the CIDP Disease Activity Status (CDAS) scale.

Results: By March 2011, 39 out of 40 patients were included with a median follow-up of 4.5 years. Cure (>5 years off treatment) or remission according to the CDAS criteria after 1 or 2 courses of pulsed dexamethasone or daily prednisolone was achieved in 10 out of 39 patients (26%). Half of the patients who were in remission after initial treatment experienced a relapse (median treatment-free interval: 17.5 months for dexamethasone, 11 months for prednisolone). Alternative diagnosis was made in 7 out of 12 (58%) who did not respond to any therapy and in none of the treatment-responsive patients.

Conclusions: Cure or long-term remission can be achieved in about one-quarter of patients with CIDP after 1 or 2 courses of pulsed dexamethasone or 8-month daily prednisolone. In treatment-nonresponsive patients, the diagnosis CIDP should be reconsidered.

Classification of Evidence: This study provides Class IV evidence that pulsed dexamethasone or 8-month daily prednisolone can lead to long-term remission in CIDP. *Neurology*® 2012;78:1079–1084

GLOSSARY

CDAS = CIDP Disease Activity Status; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **INCAT** = inflammatory neuropathy cause and treatment; **IVIg** = IV immunoglobulin; **MRC** = Medical Research Council; **RMI** = Rivermead Mobility Index.

Current guidelines for treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) recommend both prednisolone and IV immunoglobulin (IVIg) as first-line therapies.[1] As CIDP often runs a relapsing-remitting course, long-term treatment is needed in many patients. Unfortunately, both prednisolone and IVIg maintenance treatment have their specific drawbacks such as serious long-term adverse events associated with long-term prednisolone treatment and high cost and inconvenience associated with IVIg. Choosing a first-line treatment and the proper dose for maintenance therapy is not guided by evidence. Furthermore, a recent trial showed that in 44% of patients with placebo add-on treatment, IVIg doses could be reduced or even discontinued, indicating that patients were treated too long with too high doses.[2] All treatment trials in CIDP, except for one trial with a 1-year follow-up,[3] have investigated improvement in the short term, while a long-term remission would be a much more

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Supplemental Data

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interesting outcome in a chronic disease. We performed a multicenter randomized controlled trial (PREDICT) comparing 6 monthly pulses of dexamethasone with 8-months daily prednisolone. Sixteen of 40 patients (42% in the dexamethasone and 38% in the prednisolone group) reached remission, defined as sustained improvement 1 year after start of treatment.[4] We now present long-term follow-up data on treatment and outcomes of these patients, with an emphasis on long-term remission.

METHODS

Design. The primary study objective was to determine the long-term remission rates in patients with CIDP after treatment with pulsed courses of dexamethasone or 8-month daily prednisolone. It was designed to provide Class IV evidence that limited treatment with corticosteroid can lead to a sustained remission. This prospective follow-up cohort study was conducted by the PREDICT study group.

Standard protocols approvals, registration, and patient consent. All participants gave written informed consent for the original trial including a possible follow-up. The trial protocol was approved by the ethics committees of all participating centers. The trial was registered in Current Controlled Trials, number ISRCTN07779236.

Participants. The PREDICT trial included 40 patients who had been newly diagnosed as having definite or probable CIDP according to the ENMC diagnostic criteria.[4] Participants had to have signs and symptoms sufficiently severe to warrant treatment and had to be treatment naive. Participants with subacute inflammatory demyelinating polyneuropathy or pure motor CIDP were excluded.

All patients who completed the trial were asked to participate. Follow-up visits were scheduled between June 2009 and March 2011. Patients who had reached a remission were all contacted again in March 2011 to confirm that they still were in remission. If applicable, cause of death was sought in medical records and through contact with patients' general practitioner.

Treatment during trial phase and follow-up. In the trial, participants were randomly assigned to receive either dexamethasone 40 mg per day orally for 4 consecutive days, repeated for 6 cycles, or daily prednisolone for 32 weeks starting with 60 mg per day for 5 weeks and tapering ultimately to zero. The stratification, randomization, allocation, and blinding procedure is described elsewhere.[4] Patients were considered as treatment failures if there was no improvement or stabilization of disease, in case of occurrence of a relapse making immediate retreatment necessary, or serious adverse events. The choice of subsequent treatment after completion of the trial including when to start treatment after a relapse was at the discretion of the treating neurologists.

Treatment effect and definition of remission. In the PREDICT trial, remission was defined as improvement of at least 3 points on the Rivermead Mobility Index (RMI) and improvement of at least 1 point on the inflammatory neuropathy cause and treatment (INCAT) disability scale as compared with baseline or when the best possible score of a scale had been reached.[4–6] In this study, follow-up outcome was categorized according to the recently proposed CIDP Disease Activity Status (CDAS).[7] This scoring system defines long-term outcome in CIDP based on duration of disease, clinical response, duration of treatment, and neurologic examination (table 1). Patients who have a stable neurologic examination (muscle strength and sensory testing) and duration of follow-up without treatment of more than 5 years are considered cured (CDAS 1); those with less than 5 years are considered in remission (CDAS 2). In case of a relapse, duration of remission was determined by taking the time elapsed between last received treatment and the start of a new treatment. Patients requiring ongoing immunotherapy for a year or more to maintain clinical stability are considered to have stable active disease (CDAS 3). Patients responding to recently initiated treatment (more than 3 months and less than a year) are classified as improving (CDAS 4). All other patients are considered to have unstable active disease (CDAS 5). It is important to note that patients with a CDAS score of 1 or 2 may have neurologic deficit. Cure or remission reflects disease activity and does not imply a completely normal neurologic examination.

Table 1 Chronic Inflammatory Demyelinating Polyneuropathy Disease Activity Status[7]

1.	Cure: ≥5 years off treatment
2.	Remission: <5 years off treatment
3.	Stable active disease: ≥1 year on treatment
4.	Improvement: ≥3 months <1 year on treatment
5.	Unstable active disease: abnormal examination with progressive or relapsing course

CDAS categories were defined by 2 assessors (F.E. and I.v.S.) who independently scored all patients based on duration of disease and treatment, disability scores at last visit, and neurologic examination.

For all administered therapies after completion of the trial, treating neurologists were requested to score treatment effect with the following scores: 1) remission (good response and off treatment), 2) good response but no remission, 3) modest response, or 4) no response, based on improvement in disability on the INCAT disability scale and the RMI. Patients from the last 2 categories were grouped as nonresponders.

Measurements. All participating patients were invited to the trial center of inclusion where they were examined by their treating neurologist or, if patients were discharged from further follow-up, by F.E. Disability scores were filled in using the INCAT disability scale and the RMI.[5,6] The INCAT disability scale ranges from 0 to 10, from healthy to unable to make any purposeful movements with arms or legs; the RMI ranges from 0 to 15, from unable to mobilize to fully mobile.

Neurologic examination was performed by the treating neurologist or F.E. Muscle strength was tested in 12 predetermined muscle groups expressed as a maximum Medical Research Council (MRC) sumscore of 60 and bilateral grip strength was assessed with a handheld Vigorimeter in kPa.[8] Sensory involvement was scored with the INCAT sensory sumscore.[9,10] If a patient was not able to visit the treatment center, a telephone interview was held to collect the outcome data; neurologic examination was not performed in these patients.

Standardized questionnaires were filled in on signs and symptoms of CIDP, signs of long-term adverse events due to corticosteroids use (i.e., diabetes, hypertension, fractures due to osteoporoses, glaucoma, renal failure, Cushing appearance), and

current medication, specifically the use of blood pressure–lowering agents, oral antidiabetic agents, or insulin. Additionally, medical records of all patients were reviewed by F.E. for possible long-term corticosteroid adverse events.

Statistical analysis. Simple descriptive statistics were used to analyze the results. Due to the expected heterogeneity of treatments and treatment response results were not tested for significance.

RESULTS

Patients. Forty-one patients were randomized in the PREDICT trial, of whom 40 received treatment: 24 patients received dexamethasone and 16 patients received prednisolone. By March 2011, 39 patients were included in the follow-up study with a median follow-up of 54 months (range 9–100); 1 patient who was treated with prednisolone was lost to follow-up. The characteristics of the participants were published previously.[4] A total of 6 patients died during follow-up, 2 were in remission, 1 was improving on treatment, and 3 had unstable disease. Five patients died due to CIDP-unrelated causes: malignancy in 2 patients, heart failure, suicide, and hepatic failure in a transthyretin–associated hereditary amyloidosis. The sixth patient had significant respiratory and cardiac comorbidity and developed respiratory failure after plasma exchange and IVIg treatment.

Seven patients (18%) appeared to have an alternative diagnosis during follow-up. All patients were considered unresponsive to treatment. Six patients were treated with dexamethasone during the trial, while 1 patient was treated with prednisolone (table 2). In 3 patients, hereditary neuropathy was diagnosed after repeated electrophysiologic studies; this diagnosis was confirmed by DNA testing in 1 patient. In 2 patients, malignancy was found within months after the diagnosis of CIDP and start of treatment (testicular lymphoma and plasmacytoma). In one patient with previously absent monoclonal antibodies, immunoglobulin M paraproteinemia was found after repeated laboratory tests. One patient developed severe autonomic failure 1 year after his diagnosis of CIDP, which led to a further diagnostic workup and the diagnosis of transthyretin-associated hereditary amyloidosis. All patients who finally had another diagnosis fulfilled the criteria for CIDP at the time they were included in the PREDICT study.

Cure and remission. Using the CDAS classification, 13 patients (33%) reached a cure (3 patients) or a remission (10 patients) (table 2 and figure). Ten patients (26% of total) were considered to be responsive to dexamethasone courses or 8-month prednisolone treatment: 6 patients after a single course of dexamethasone given during the trial, 2 patients after a second course of dexamethasone given for a relapse following initial remission, 2 patients with 8 months prednisolone treatment given during the trial. By March 2011, median duration of remission was 41 months (range 7–95). One patient achieved remission after 4-year prednisolone treatment and 1 after 2-year IVIg treatment. One patient failed to respond to prednisolone, dexamethasone, and IVIg treatment but improved gradually several months after discontinuation of therapies to only minimal disability and fulfilled the CDAS criteria for cure.

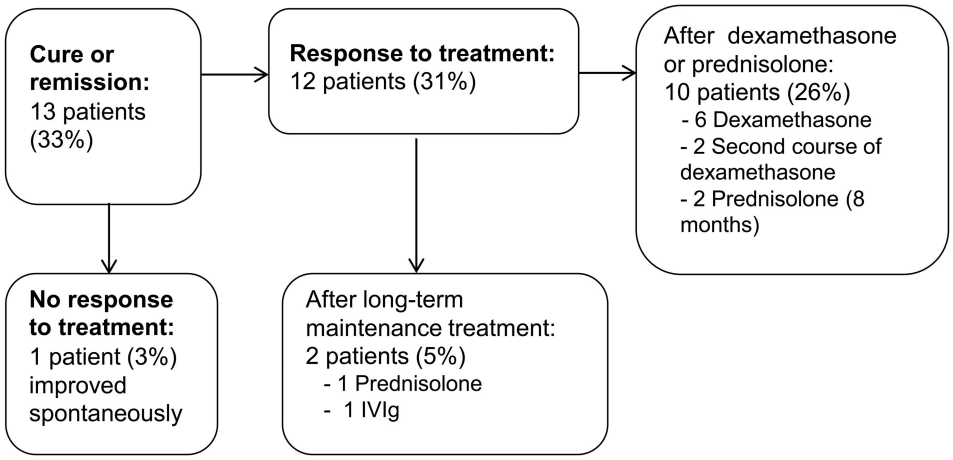
In the PREDICT trial, 16 patients (40%) reached remission. Four of 10 patients who were in remission

Table 2 Results of long-term follow-up compared with PREDICT trial outcomes[a]

Follow-up	Cured CDAS 1	Remission CDAS 2	Stable active disease CDAS 3	Improvement on treatment CDAS 4	Unstable active disease CDAS 5	Alternative diagnosis	Lost to follow-up	Total
PREDICT trial, n (%)	3 (8)	10 (26)	13 (33)	2 (5)	4 (10)	7 (18)	1 (3)	(40 patients)
Dexamethasone								
Remission	2	4	3	1				10
Sustained improvement/ stable disease		1[b]	1	1	1	3[c]		7
Deterioration			3		1	3[d]		7
Prednisolone								
Remission		3[e]	3					6
Sustained improvement/ stable disease			2					2
Deterioration	1	2[f]	1		2	1[g]	1	8

Abbreviations: CDAS = CIDP Disease Activity Status; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IVIg = IV immunoglobulin.
[a] Follow-up categories are according to CDAS. Percentages are of total of 39 patients included in follow-up study.
[b] Patient improved after dexamethasone but experienced a relapse and was treated with a second course of dexamethasone, resulting in a remission.
[c] One patient had immunoglobulin M paraproteinemia, one had hereditary neuropathy, and one had transthyretin-associated hereditary amyloidosis.
[d] Two patients had hereditary neuropathy, one patient had plasmacytoma.
[e] One patient had a relapse and was treated with a course of dexamethasone, resulting in a remission.
[f] One patient achieved a remission after long-term IVIg treatment, one after long-term prednisolone treatment.
[g] Patient had testicular lymphoma.

Figure Treatment response in CIDP Disease Activity Status categories cure and remission (percentages are of total of included patients)



after dexamethasone treatment and 4 of 6 who were in remission after prednisolone treatment experienced a relapse requiring treatment (50% of all remissions). Median interval between start of remission to relapse was 17.5 months for dexamethasone (range 7–52 months) and 11 months for prednisolone (5–63 months). Five of these 8 patients (3 prednisolone, 2 dexamethasone) started to deteriorate within a year after ceasing therapy.

Stable active disease. At final follow-up, 13 patients (33%) had a stable active disease requiring maintenance treatment (table 2). Ten patients are currently being treated with IVIg (median duration 38 months, range 12–84 months). Three patients are being treated with prednisolone, 2 with monotherapy and 1 with a combination of prednisolone, plasma exchange, and azathioprine.

Improving on treatment. Two patients were categorized as improving on treatment (table 2). One patient was in remission for more than 4 years after his first course of dexamethasone and is currently being treated with a second course of dexamethasone (table 2). The other patient died of cancer while he was improving on IVIg treatment.

Unstable active disease. Four patients (10%) had an unstable active disease course, of which 2 are currently on treatment (table 2). Two patients had an initial improvement after dexamethasone during the trial while 1 patient had a moderate effect with high dose of IVIg (1 g/kg/week). Plasma exchange was used in 3 patients with a modest effect in only 1 patient. Immunosuppressive therapy was given in 4 patients including mycophenolate mofetil (3 patients), azathioprine (2 patients), methotrexate (2 patients), rituximab (2 patients), and cyclosporine (1 patient), all with only modest or no effect.

Disability and neurologic examination. At final follow-up mean INCAT disability score was 1 in the CDAS 1 group (range 0–3), in the CDAS 2 group (range 0–2), and in the CDAS 3 group (range 0–3). All patients were independent in daily activities. The mean improvement of INCAT disability score between trial baseline and final follow-up was 2 in the CDAS 1 group and 3 in both the CDAS 2 and the CDAS 3 group. The mean INCAT disability score in the CDAS 5 group was 5 (range 4–5). The mean RMI was 13 (range 11–14) in the CDAS 1 group, 14 in both the CDAS 2 group (range 13–15) and the CDAS 3 group (range 9–15), and 11 (range 10–12) in the CDAS 5 group. The mean improvement of the RMI was 3 in the CDAS 1 group, 4 in the CDAS 2 group, and 3 in the CDAS 3 group. Only 3 patients (8%) had a complete normal neurologic examination (1 patient was in remission and 2 had stable active disease).

Corticosteroid adverse events during follow-up. The most important adverse events during the trial are listed in table 3. A more extensive overview has been published previously.[4] No new cases of diabetes or glaucoma were identified during follow-up. Three patients developed hypertension (defined as blood pressure above 140 mm Hg systolic or 90 mm Hg diastolic) during the follow-up period. All 3 had dexamethasone during the trial of which 2 were subsequently treated with prednisolone (1 patient was on maintenance prednisolone treatment). Four patients had a Cushing face; all received maintenance prednisolone treatment. Two patients treated with dexamethasone experienced a fracture. One of these patients had osteopenia while the other had a normal bone densitometry at baseline visit in the trial. In both patients bone densitometry was not repeated at final

Table 3 Adverse events during trial and follow-up[a]

	Trial period (40 patients) (dexamethasone/prednisolone)	Follow-up[b] (39 patients)	
		No active steroid treatment at final follow-up visit (35 patients) (dexamethasone/prednisolone)	Maintenance prednisolone at final follow-up visit (4 patients) (dexamethasone/prednisolone)
Trial treatment (dexamethasone/prednisolone)	24/16	21/14	3/1
Diabetes	0/2	0	0
Impaired glucose tolerance	1/1	0	0
Hypertension	2/1	2[c]/0	1/0
Cushing appearance	8/11	0	3/1
Increase osteopenia at bone densitometry	1/0	Not performed	Not performed
Fractures	0	2/0	0
Acute glaucoma	1/0	0	0

[a] One patient (prednisolone) was lost to follow-up.
[b] Eight patients were treated with prednisolone and 6 patients with dexamethasone during the follow-up period. Another 4 patients had prednisolone maintenance treatment at last follow-up visit.
[c] One patient was also treated with prednisolone during follow-up.

trial visit. One patient who was treated with long-term prednisolone in combination with azathioprine developed Kaposi sarcoma. After switching to IVIg, a remission of the Kaposi sarcoma was observed.

DISCUSSION Cure or long-term remission was achieved after 1 or 2 courses of pulsed dexamethasone treatment or 8-month daily prednisolone treatment in 10 out of 39 patients (26%). Only 2 more treatment-responsive patients went into remission after long-term prednisolone or IVIg treatment. These results are comparable with the CDAS validation cohort of 106 patients in which 11% were classified as cured and 20% were considered in remission.[7] Half of the patients who initially reached remission experienced a relapse warranting treatment. However, in some patients this relapse followed a long treatment-free interval of remission.

About half of the patients who did not respond to corticosteroids had a satisfactory response to IVIg treatment. In our study, treatment with plasma exchange or immunosuppressives was of limited value in patients who failed to respond to both corticosteroids and IVIg. To our surprise, 7 of the 12 (58%) treatment nonresponsive patients turned out to have an alternative diagnosis during follow-up, while no patients had an alternative diagnosis in the treatment responsive group. All patients who finally had another diagnosis fulfilled at the time they were included in the PREDICT study the ENMC criteria for CIDP and the more recent EFNS criteria, illustrating the fact that different conditions can cause a neuropathy that mimic idiopathic CIDP.[1] Our results show that the diagnosis of CIDP should be reconsidered if patients do not respond to first-line treatments, especially before other immunosuppressive therapies are considered which can have potentially serious adverse events.

Six of 7 patients in whom the diagnosis was changed were using dexamethasone during the trial. In a post hoc per-protocol analysis of only idiopathic CIDP cases, about a third would have had cure or remission after 1 or 2 courses of corticosteroids in this long-term follow-up study (40% after dexamethasone and 12% after prednisolone treatment). In the PREDICT study, this would have resulted in a higher remission rate (56% after dexamethasone and 40% after prednisolone treatment, difference in remission rate is not significant).

Most adverse events occurred during treatment and not during follow-up, suggesting that long-term adverse events are probably not of major importance after discontinuation of short periods of corticosteroid treatment.

Due to the small numbers of included patients and the overall low frequency of adverse events it is difficult to compare pulsed dexamethasone and daily prednisolone with regard to side effects. In a larger study with 125 patients with chronic idiopathic thrombocytic purpura who were treated with cycles of dexamethasone, no patient had to stop treatment due to severe side effects.[11] However, patients need to be instructed for transient adverse events such as mood changes, insomnia, and excitation during and days after pulse therapy.

There are some limitations in this study. First of all, for pragmatic reasons treatment protocol was at

discretion of the treating neurologist once patients had reached an endpoint in the trial. This led to various treatment regimens. However, this variation plays a role only in patients on maintenance treatment and in nonresponders (CDAS 3 to 5) and less in patients who went into remission or a cure (CDAS 1 to 2) which was the primary objective of this study.

Furthermore, although this is a relatively large group of prospectively followed patients with CIDP, the numbers of patients in combination with the rate of remissions are too small to draw firm conclusions on difference between dexamethasone and prednisolone in inducing remission. Finally, data on adverse events were collected retrospectively, which could lead to an underestimate of these events. However, we focused on long-term adverse events such as diabetes and hypertension, which are less prone to recall bias.

These results suggest that remission and cure can be achieved with a relatively short course of corticosteroid therapy. If corticosteroids are chosen as first-line treatment dexamethasone pulsed therapy seems to be a more appropriate choice because it led to a faster improvement, slightly longer remissions, relatively fewer relapses, and less adverse events when compared to continuous prednisolone treatment. If a patient in remission experiences a relapse, one may consider repeating the course of corticosteroids, especially if the first course led to a long-term sustained remission.

Possible directions for further research are studies predicting patients' response to treatment and a head-to-head comparison of steroids to IVIg in achieving long-term remission. Guidelines on long-term treatment once on maintenance therapy are needed.

AUTHOR CONTRIBUTIONS

Dr. Eftimov: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript. Dr. Vermeulen: acquisition of data, interpretation of data, revising manuscript. Dr. van Doorn: acquisition of data, interpretation of data, revising manuscript. Dr. Brusse: acquisition of data, interpretation of data, revising manuscript. Dr. van Schaik: study concept and design, analysis and interpretation of data, drafting/revising manuscript, supervision study.

DISCLOSURE

Dr. Eftimov received payment from Sanquin Blood Supply Foundation for a single lecture to nurses providing home-care immunoglobulin therapy. Dr. Vermeulen reports no disclosures. Dr. van Doorn has served on scientific advisory boards for Octapharma AG and Talecris Biotherapeutics (ICE trial); has received funding for travel and speaker honoraria from Baxter International Inc.; serves on the editorial board of the *Journal of the Peripheral Nervous System* and the *Journal of Neurological Sciences*; received a departmental research grant from Baxter International Inc. and from Sanquin; and has received research support from Baxter International Inc., Talecris, the Dutch Prinses Beatrix Fonds, the GBS-CIDP Foundation International, and the Dutch National Institute of Health (ZonMW). Dr. Brusse reports no disclosures. Dr. van Schaik received departmental honoraria for serving on scientific advisory boards and a steering committee for CSL-Behring; and received departmental research support from The Netherlands Organisation for Scientific Research and from the Dutch Prinses Beatrix Fonds. All lecturing and consulting fees for INS were donated to the Stichting Klinische Neurologie, a local foundation that supports research in the field of neurological disorders. He serves on the editorial board of the *Cochrane* neuromuscular disease group.

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