Prognosis and treatment of polyneuropathy associated with IgM monoclonal gammopathy Jikke-Mien F. Niermeijer

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Prognose en behandeling van polyneuropathie geassocieerd met IgM monoclonale gammopathie

(met een samenvatting in het Nederlands)

ISBN 978-90-9024730-4

Subject headings: polyneuropathy, monoclonal gammopathy, treatment, controlled trial, prognosis, cyclophosphamide, fludarabine, rituximab

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Cover design and lay-out: Esther Beekman (www.estherontwerpt.nl)
Cover: photograph by Jikke-Mien Niermeijer©: Borobudur, Java, Indonesia
Printed by: Buijten en Schipperheijn, Amsterdam

Financial support of this thesis is gratefully acknowledged and was provided by:
Stichting het Remmert Adriaan Laan Fonds, Baxter B.V., Roche B.V.,
Boehringer Ingelheim, Sanofi Synthelabo, Genzyme, Glaxo Smith Kline, UCB Pharma,
Stichting Zeldzame Ziekten Fonds.

Proefschrift

ter verkrijging van de graad van doctor aan
de Universiteit Utrecht
op gezag van de rector magnificus,
prof.dr. J.C. Stoof,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op vrijdag 13 november 2009 des middags te 4.15 uur

door

Jikke-Mien Frédérique Niermeijer

geboren op 20 november 1973 te Rotterdam

Promotor: Prof. Dr. J.H.J. Wokke
Co-promotor: Dr. N.C. Notermans

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1

General introduction and aims of the thesis

Introduction

Polyneuropathy represents a clinical syndrome characterized by sensory symptoms and muscle weakness distally in the legs with a gradual progression to the more proximal regions and the upper extremities. The estimated incidence in the general population lies between 30 and 200 per 100.000 persons per year, with an estimated prevalence up to 3 per 1000.[1] The causes of polyneuropathy are manifold and can be toxic, metabolic, degenerative, genetic or immunological. In about 10-20% of these patients no underlying cause is identified after initial evaluation. At further analysis, a monoclonal gammopathy is found in about 10%.[2;3] Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the asymptomatic presence of a monoclonal protein (M protein) without an underlying hematological malignancy or other cause. MGUS is defined by 1) the presence of a serum monoclonal protein (M protein) concentration of less than 3 g/dL, 2) no M protein or only small amounts of monoclonal light chains in the urine, 3) absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M protein, and 4) less than 10% plasma cells in the bone marrow (if tested).[4;5] The monoclonal protein can be either of the IgG, IgA or IgM subclass.

Whereas the monoclonal gammopathy can be a coincidental finding (especially IgG), there is evidence for a causal relationship between IgM monoclonal gammopathy and polyneuropathy, as the presence of an IgM M protein in combination with polyneuropathy is more frequent than one would expect on the basis of age alone: 10% in patients with idiopathic polyneuropathy, opposed to 1% in the general population.[2;3] In patients with IgM MGUS and polyneuropathy (IgM MGUSP), the IgM M protein often shows reactivity to nerve epitopes, and hereby could serve as an auto-antibody.[6;7] About 50% of patients with IgM MGUSP have antibodies directed against myelin-associated-glycoprotein (MAG) which is part of the myelin sheath of the peripheral nerve.[8] In patients with polyneuropathy and IgM MGUS, IgM deposits have been observed in nerve biopsies and infusions of sera from patients with anti-MAG antibodies may cause polyneuropathy in animal models.[9-18]

Clinically, polyneuropathy associated with IgM monoclonal gammopathy (IgM MGUSP) is a distal symmetric sensorimotor polyneuropathy, sometimes with ataxic features, that runs in a progressive course.[19]

The clinical picture of polyneuropathy with IgM monoclonal gammopathy can be illustrated by the following case:

Patient 1 is a male, first seen in our center at the age of 51 years. Since the age of 49 years, he experienced tingling and numbness of his feet, followed by some weakness and instable gait. The past six months he had progressive difficulties with balance and walking, and necessitating closely watching his feet to prevent himself from falling over. Fine motor skills of the hands, like turning a key or closing buttons of his shirt had also become more difficult.

His wife had noticed that his lower legs had become thinner. She also sometimes had to help her husband with putting on his trousers, as he felt too unstable to stand on one leg and was not able to close buttons properly. The patient was only just able to fully perform his job that required physical strength.

Neurological examination showed marked symmetrical atrophy of the lower legs and feet, weakness of the foot dorsiflexors MRC grade 3, and of the toe extensors MRC grade 1, diminished tendon reflexes of the arms and absent tendon reflexes of the legs. Touch and pinprick sensation were diminished distal from the wrist and knee, vibration and joint position sense were absent in the legs.

The patient had a marked bilateral foot drop and an ataxic gait. Heel and toe gait were impossible; there was a positive Romberg's sign. There was a tremor of his arms and hands with some pseudoathetotic movements.

Nerve conduction studies showed a demyelinating polyneuro-pathy with signs of axonal degeneration.

Blood analysis showed normal blood count, albumin, electrolytes, liver, kidney and thyroid function. Immunologic analysis showed an IgM Kappa M protein with anti-MAG antibodies. The total M protein concentration was < 1 g/L, the IgM concentration was 10.3 g/L. Bone marrow showed no signs of a hematological malignancy.

Because of the disabling symptoms and the progressive course treatment was necessary. The patient had some very important questions that were difficult to answer: "What is my long term prognosis? What is the best treatment and what is the chance that my symptoms will improve after treatment with immunotherapy?" These are still unanswered questions that will form the main subject of this thesis.

Prognosis

The clinical management of a patient and his family demands optimal counseling about prognosis. It helps the patient and his partner or family to prepare for what could happen to them in the future. This is especially important in a disorder with limited therapeutic options. The determining factors for the rate of progression of IgM MGUSP however, are poorly understood. Previous studies have failed to identify a predictive role for the type of antibodies [20;21], the concentration of the IgM M protein, or the age at onset.

In order to find prognostic factors we studied the long-term disease course of IgM MGUSP in a well-defined, prospective cohort study of 140 consecutive patients. In addition, we developed a prognostic model for prediction of disease outcome. (**Chapter 2**)

Therapy

The severity of disability in IgM MGUSP finds its origin in diminished sensation, muscular weakness and disturbed balance, and may form a clear indication for treatment of IgM MGUSP.

The best treatment for IgM MGUSP is not known. Previous double blind randomized trials with intravenous immunoglobulin have shown only little and short-term effects in IgM MGUSP.[22] Plasma exchange was only of some effect in MGUSP with IgG/IgA M protein. [23]

Because IgM MGUSP is thought to be an immune-mediated neuropathy, in which the monoclonal protein produced by B cells plays an important role, it was hypothesized that treatment directed at depletion of the M protein-producing B-cells, comparable to the treatment of B cell malignancies or other immunological disorders, would be a good choice. Along this line of reasoning cyclophosphamide, fludarabine and later rituximab were presumed to be good candidate treatments.

When immunotherapy is successful, suppression of the immune reactions against the peripheral nerve are thought to enable neural regeneration and functional improvement. Ideally, the goal of therapy is functional improvement or stabilization, coinciding with improvement of sensory and muscular function. Clinically, this improved function can be measured as improvement of signs at neurological examination, sometimes coincided by electrophysiological improvements, although these may be delayed.

In the absence of a clearly effective immunotherapy for IgM MGUSP and their possible side effects, we decided to only treat patients with clear progression of symptoms. Progression was defined as a deterioration between two follow-up visits and it was monitored using quantified neurological examination of muscle strength and sensory function, disability scales and quantified measurements of ataxia [20;24;25] .

Cyclophosphamide with prednisone

As a combination of cyclophosphamide with prednisone seemed effective in IgM MGUSP in an open label trial in 1996, [24] we started a double blind randomized placebo-controlled study of pulsed oral cyclohosphamide with prednisone for IgM MGUSP with a progressive disease course in 1996. These results are described in **Chapter 3**.

Fludarabine

We started a second prospective open label trial in 2002 with fludarabine. This fluorinated purine analogue seemed effective in B cell malignancies and possibly in IgM MGUSP. [26] [27] In total, patients received six pulsed courses of oral fludarabine. Next to monitoring neurological outcome, hematological evaluation was performed in pre- and posttreatment bone marrow aspirates for documenting the B cell effects. We also investigated the relation between the hematological and neurological response to treatment, in order to find a confirmation for the working mechanism of the treatment **(Chapter 4)**.

While the studies of this thesis were were proceeding, no new effective treatment strategies were found [28]. In the meantime, a randomized controlled trial with interferon alpha showed no effect in IgM MGUSP.[29] In 2004, a Cochrane library review of different forms of immunotherapy found five randomized controlled trials and concluded that there was no sustainable evidence for any “best” treatment of IgM MGUSP with anti-MAG antibodies.[30]

Rituximab

With time, newer, biological drugs became available: monoclonal antibodies. Rituximab, directed against CD-20+ B cells, has proven to be effective in several inflammatory disorders in rheumatology such as idiopathic thrombocytopenic purpura and rheumatoid arthritis, as well as in several hematological B cell malignancies.[31;32] As this drug lowers CD 20 B cells, which possibly produce the monoclonal IgM, it seemed a good candidate for the treatment of IgM MGUSP. In addition, less side effects were expected because it specifically binds to B cells only and produces less collateral damage than other cytotoxic agents. We decided for an open label trial in a series of consecutive patients with prospective follow-up and studied the neurological and hematological responses to further prove the principle of this treatment strategy **(Chapter 5)**.

Factors related to treatment response

It is unknown which factors are associated with a good treatment response in IgM MGUSP. As this is important for selection of patients for future trials, it is a great challenge to identify predictive factors of treatment response. We hypothesized that disease duration, age at onset, presence of anti-MAG antibodies, classification of nerve conduction studies as demyelinating or axonal and concentration of the IgM M protein are possible factors that can be related to treatment response. These factors are further analyzed in the three treatment trials in **Chapters 3, 4, 5 and 6**.

Electrophysiological characteristics

Nerve conduction studies (NCS) in IgM MGUSP often reveal conduction slowing compatible with demyelination and may meet the research criteria for chronic idiopathic demyelinating polyneuropathy (CIDP).[33;34] However, there are some differences as there is often marked axonal degeneration in lower limb nerves and predominantly distal conduction slowing in IgM MGUSP. These findings suggest a length-dependent process, as opposed to a more diffuse or patchy form of demyelination in CIDP. [35;36]

It is unknown which factors are associated with a good response to immunotherapy in IgM MGUSP. Theoretically, one might expect that patients with more demyelination or less axonal degeneration have the best chances for improvement after immunotherapy as the regenerative capacity of myelin is better than that of the axon. We quantified the NCS findings into scores for demyelination and axonal degeneration and studied the relation of these quantified electrophysiological findings with disease severity and response to treatment in IgM MGUSP patients **(Chapter 6)**.

Aims of this thesis

Determination of the long-term course and possible prognostic factors for disability in IgM MGUS polyneuropathy in a large prospective cohort study (Chapter 2)

Evaluation of the efficacy of treatment with a combination of pulsed oral cyclophosphamide with prednisone in IgM MGUSP in a double blind randomized placebo-controlled trial (Chapter 3)

Evaluation of the neurological and hematological responses of treatment with oral fludarabine in a prospective open label trial (Chapter 4)

Evaluation of the neurological and hematological responses of treatment with intravenous rituximab in a prospective open label trial (Chapter 5)

Exploration of the electrophysiological findings and their relation to disease severity and treatment responses in IgM MGUS polyneuropathy (Chapter 6)

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Prognosis of IgM MGUS polyneuropathy: a prospective cohort study of 140 patients

J.M.F. Niermeijer[1], K. Fischer[2], M. Eurelings[3], H. Franssen[1], J.H.J.Wokke[1], N.C. Notermans[1]

[1] Rudolf Magnus Institute of Neuroscience, Department of Neurology, University Medical Center Utrecht, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
[3] Department of Neurology, Spaarne Hospital, Hoofddorp, the Netherlands

Neurology, under revision

Abstract

Background

The disease course of polyneuropathy associated with IgM monoclonal gammopathy (IgM MGUSP) can be highly variable. In order to identify factors that influence long term disease outcome, a prospective cohort study was performed of 140 patients with IgM MGUSP over a period of 23 years.

Methods

All patients with IgM MGUSP who were diagnosed in our tertiary referral center for polyneuropathy were eligible. All patients underwent nerve conduction studies and were tested for anti-MAG antibodies. The Modified Rankin Scale, MRC graded muscle strength, quantified sensory function, and laboratory testing were performed at 0,1,2,5 years and at last visit. The primary outcome measure was the risk of developing a modified Rankin Scale of ≥ 3 points.

Results

140 patients with IgM MGUSP fulfilled inclusion criteria (101(72%) demyelinating, 39 (28%) axonal, 63 (44%) MAG positive). The median age of onset was 59(IQR 52-67) years, median disease duration at baseline was 3,2(IQR1.9-6) years. Anti-MAG antibodies were associated with a lower risk of Rankin scale ≥ 3. Demyelination and a higher age of onset were associated with a higher risk for Rankin Scale ≥ 3. Based on these three factors, a web-based prognostic model was developed that directly allows clinicians to estimate the probability of developing disability .
http://www.umcutrecht.nl/subsite/Prognosis-MGUS-Neuropathy

Conclusion

Higher age of onset and demyelination increase the risk ,whereas anti-MAG antibodies decrease the risk, of developing Rankin scale ≥3 in IgM MGUSP. Our web-based prognostic model allows determination of prognosis in IgM MGUSP.

Introduction

Polyneuropathy associated with IgM monoclonal gammopathy (IgM MGUSP) is an immune-mediated polyneuropathy with distal symmetric sensorimotor and ataxic features. [1,2] The disease course of IgM MGUSP can be highly variable. As evidence-based treatment strategies for IgM MGUSP are still lacking, the individual disease course is the main parameter for initiation of therapy. [3] Insight into prognostic factors, and the possible definition of clinical subtypes, would not only enable early identification of those patients who require treatment, but also allow for correct stratification of future clinical treatment trials. [3;4]

About 50% of the patients with demyelinating IgM MGUSP have circulating antimyelin-associated glycoprotein antibodies (anti-MAG) [5]. Although previous studies have suggested that the presence of anti-MAG antibodies may play a role in the clinical course of IgM MGUSP, no convincing prognostic factors of IgM MGUSP have been described as most studies were small, retrospective, or both.[2;5-12]

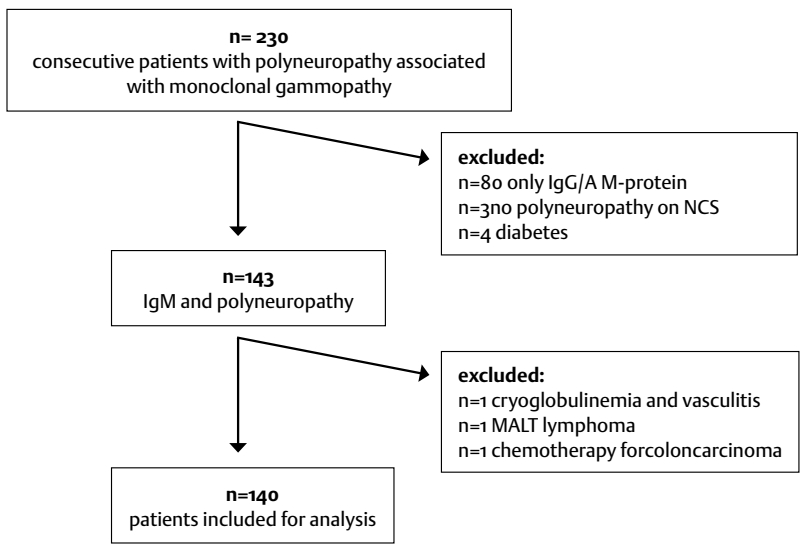
Practical classification, based upon clinical parameters and nerve conduction studies (NCS), has defined the distal acquired demyelinating symmetric (DADS) polyneuropathy. [4] A classification combining antibodies is another option, but DADS MAG-negative patients seem to be indistinguishable from DADS MAG-positive patients in several studies. [4,10;13, 14, 6;15]

This study investigates the prognostic role of clinical, electrophysiological and laboratory parameters in a large, long-term prospective cohort of 140 well-defined patients with IgM MGUSP. Based on these factors a prognostic model was developed.

Methods

A prospective cohort study was performed of 230 consecutive patients with a polyneuropathy and MGUS, seen between 1985 and 2007 at the neuromuscular clinic of the University Medical Center Utrecht (The Netherlands), a tertiary referral center for polyneuropathy. Excluded were patients with 1) IgG/A MGUS, 2) no confirmation of the polyneuropathy on NCS and 3) another cause for polyneuropathy or a hematological malignancy necessitating treatment.[16] The remaining 140 patients were included for analysis. (E-figure 1) Both treated and untreated patients remained in the study. Immunotherapy mostly consisted of prednisone with cyclophosphamide, fludarabine or rituximab as described elsewhere. [17-20]

E-Figure 1: Inclusion flowchart prospective cohort study IgM MGUS Polyneuropathy



Standard Protocol Approvals, Registrations and Patient Consents

The study was approved by the institutional medical ethics committee. Written informed consent was obtained from all patients.

Patient evaluation

Patients were seen every 6 or 12 months. Clinical data of the first visit, at 1, 2, and 5 years follow up and one visit after more than 5 years follow up were collected. Immunotherapy details and the use of walking aids or a wheelchair were documented. Every patient was followed by the same physician (NCN, ME or JMFN).

A complete neurological examination, including gait, balance and presence of tremor, was performed. Disability was measured using the modified Rankin Scale (Rankin Scale or MRS) ranging from 0-5 points (Appendix 1) [21] Manual muscle testing (MMT) was performed using the MRC graded scale (0-5), as described elsewhere. [20] The distal MRC sum score was composed of finger extensors, finger flexors, first interosseus, wrist extensors, anterior tibial, gastrocnemius, peroneal and extensor hallucis longus muscles. Both MRC sum scores are presented as a percentage of the maximum possible score of 140 (MRC sum score) or 80 (distal MRC sum score)(0-100%). (Appendix 4) Sensory function was measured using the Sensory Sum Score as described elsewhere (% of maximum possible score of 56 points).[2;20] (Appendix 5)

Electrophysiological assessment

All patients underwent nerve conduction studies (NCS) after their first visit to our center. NCS and concentric needle examination were carried out by the same investigator (HF) in all patients, according to a standardized protocol. The polyneuropathy was classified as demyelinating according to the AAN research criteria [22], with modification of the criteria for conduction block (segmental CMAP amplitude reduction > 30% for arm nerves or segmental CMAP area reduction > 50% of any nerve) and temporal dispersion (segmental CMAP duration increase > 30%); if these criteria were not fulfilled, the polyneuropathy was defined as axonal. [23]

Laboratory tests

Serum and urine M protein electrophoresis and immunofixation, full blood count, electrolytes, phosphate, calcium, glucose, thyroid function, liver enzymes, kidney function were performed in every patient at all visits. Serum IgM anti-MAG antibodies were tested at least once, as described elsewhere, by ELISA and Western blot. ELISA was regarded positive at titers of > 1,500 U. [24;25]

Bone marrow investigations

Bone marrow sampling was performed in all patients to rule out an underlying hematological malignancy. [17] The hematological disease was staged using criteria for MGUS, additional criteria for IgM MGUS and criteria determined at the Second International Workshop on Waldenstrom's Macroglobulinemia. [26;27] During follow-up, bone marrow investigations were only performed if this was prompted by clinical signs, increased M protein or other laboratory abnormalities.

Statistical Analysis

Patient characteristics were analyzed using descriptive statistics. Complete case analysis was used for all comparisons between visits and between subgroups. Several prognostic factors were considered based on previous literature: age at onset > 60 years, demyelinating neuropathy on NCS according to the AAN research criteria [22], presence of anti-MAG antibodies and total M protein concentration ≥ 1 g/l.

To analyze the rate of disease progression of IgM MGUSP, we computed delta scores (i.e. assessment at last visit compared to assessment at previous visit) of all outcome measures. Between groups delta scores were compared according to patient and disease characteristics using the Mann Whitney U test. All data as from the last follow-up visit were used for this analysis.

Within groups the Wilcoxon signed rank test was used to compare the difference of scores between the first and the last visit.

Survival analysis using Kaplan Meier statistics was performed for the probability of developing predefined fixed clinical endpoints. The primary endpoint was the development of a modified Rankin Scale ≥ 3. Secondary endpoints were the development of weakness in the lower extremities ≤ MRC grade 3, weakness in the upper extremities ≤ MRC grade 4, impaired sensation of the whole lower leg distal to the knee (i.e. sensory score = 1 on one of the sensory modalities), impaired sensation in the upper extremities (i.e. sensory score ≤ 3 on one of the sensory modalities), the start of the use of supportive walking aids, the initiation of immunotherapy for IgM MGUSP and the development of a hematological malignancy. Differences between groups based on presence of prognostic factors were analyzed by the log rank test. For the survival analysis and Cox regression analysis patients were followed until they reached an endpoint or until their last visit. Multivariate Cox regression analysis was performed to study the combined effects of different prognostic factors on disease progression and to develop a prognostic model. With these factors, stepwise logistic regression analysis was performed using $\alpha < 0.25$ as inclusion criterion. The predicted absolute risks for developing MRS ≥ 3 at 5, 10 and 15 years were calculated using the regression coefficient from the Cox regression analysis for calculation of the linear predictor, and the calculated baseline survival risk from the Cox regression analysis. Grouped means are presented with the standard deviation (SD) and grouped medians are presented with the interquartile range (IQR). For all test results p< 0,05 was regarded as significant. SPSS 15.0 was used for all statistical analyses.

Results

Neuropathy features at baseline

140 patients with IgM MGUSP fulfilled the inclusion criteria (101(72%) demyelinating, 39 (28%) axonal, 63 (44%) MAG positive).(E-figure 1) The median age of onset was 59(IQR 52-67) years; the median disease duration at baseline was 3.2(IQR1.9-6) years. The median scores of all outcome measures at baseline are shown in table 1. Sensory versus motor, and arm versus leg predominance, signs, symptoms and the use of walking devices are described in E-Tables 3, 4 and 5. Anti-MAG antibodies were present in 63(45%) patients (58 demyelinating). Anti-MAG titers were determined with ELISA in 75 patients. In the rest of the cases only Western blot analysis was used for detection of anti-MAG antibodies. The median anti-MAG titer was 10,938 U (IQR 862-96,786 U) (47/75 (63%) were MAG positive).

Table 1. Baseline characteristics and examinations in 140 patients with IgM MGUS polyneuropathy

	N patients(%) or median(IQR)
Patients	
median age at onset (y, IQR)	59 (52-67)
median disease duration (y,IQR)	3.2 (1.9-6)
median age first visit (y, IQR)	64.4 (56-71)
Disability	
median Modified Rankin Scale (0-5 points, IQR)	2 (2-2)
patients with Modified Rankin Scale =/>3 (n,%)	25 (18%)
Muscle strength	
median MRC sum score at baseline (%, IQR)	99 (94-100)
patients with weakness hand or arm muscles MRC =/<4 (n,%)	27 (19%)
patients with weakness anterior tibial muscles MRC =/<3 (n,%)	23 (16%)
Sensation	
median sensory sum score(%, IQR)	79 (68-88)
patients with diminished sensation distal from knee (n,%)	70 (50%)
patients with diminished sensation hands or arms (n,%)	71 (51%)
Nerve conduction studies	
patients with demyelinating NCS	101 (72%)
Antibodies	
patients with anti-MAG antibodies	63 (44%)
Monoclonal protein concentration	
patients with total M protein > 1 g/l	27 (19%)

Scores at baseline are expressed as median with IQR (interquartile range), disability is expressed as 0-5 points on the modified Rankin scale, MRC sum score is expressed as percentage of the maximum possible score of 140 points, sensory sum score is expressed as percentage of the maximum possible score of 56 points. NCS= nerve conduction studies. MAG= myelin associated glycoprotein.

Electrophysiological assessment

In 101 (72%) patients, NCS were consistent with a demyelinating polyneuropathy. In the remaining 39 patients, NCS were not consistent with a demyelinating polyneuropathy. These are referred to as axonal IgM MGUSP. However, 11/39 axonal patients showed demyelinating features at pressure points (10 prolonged DML of the median nerve and 1 demyelinative conduction slowing of the ulnar nerve at the elbow).

5/39 (13%) axonal IgM MGUSP patients were MAG-positive. Although being classified as axonal, all had a prolonged demyelinating DML(explain DML) of one or both median nerves.

E-Table 3: Distribution of signs and predominant signs in 140 IgM MGUS polyneuropathy patients

distribution signs 1st visit	n patients(%)
legs + arms	105 (75%)
legs only	31 (22%)
arms>legs	4 (3%)
predominant signs 1st visit	
sensory>motor	98(70%)
pure sensory	33(24%)
motor>sensory	9(6%)

E-Table 4: Signs and symptoms at baseline in 140 patients with IgM MGUS polyneuropathy

signs 1st visit neurological examination	n patients (%)
absent Achilles tendon reflex	121 (86 %)
absent Patellar Reflex	74 (53 %)
Romberg's sign	63 (45 %)
atrophy legs	62 (44 %)
heel walk impaired	58 (41 %)
absent triceps reflex	52 (37 %)
absent biceps reflex	48 (34 %)
walking straight line impaired	49 (35 %)
atrophy arms	32 (23 %)
toe walk impaired	30 (21 %)
tremor arms	27 (19 %)
legs ataxic	16 (11 %)
pseudo-athetosis arms	8 (6 %)
arms ataxic	7 (5 %)
symptoms 1st visit	**n patients (%)**
numbness	128 (91 %)
tingling	108 (77 %)
ataxia/ unsteadiness legs	95 (68 %)
weakness	92 (66 %)
pain	50 (36 %)
cramps	39 (28 %)
ataxia arms	32 (23 %)
autonomic symptoms	22 (16 %)

Hematological assessment

Mean total M protein concentrations at baseline was < 1 g/l in 113(81%) patients and > 1 g/l with a median of 8 g/l (IQR 5-11) in 27(19%) patients at baseline.

Bone marrow examination showed low grade malignant abnormalities in six patients (five lymphoplasmacytic lymphoma, one non-Hodgkin lymphoma) at baseline. As they did not necessitate further hematological treatment, these patients remained included in this study.

Disease progression

Disability, expressed by the Modified Rankin scale, progressed between the first and last visit, over a median period of 4 years, but not significantly.

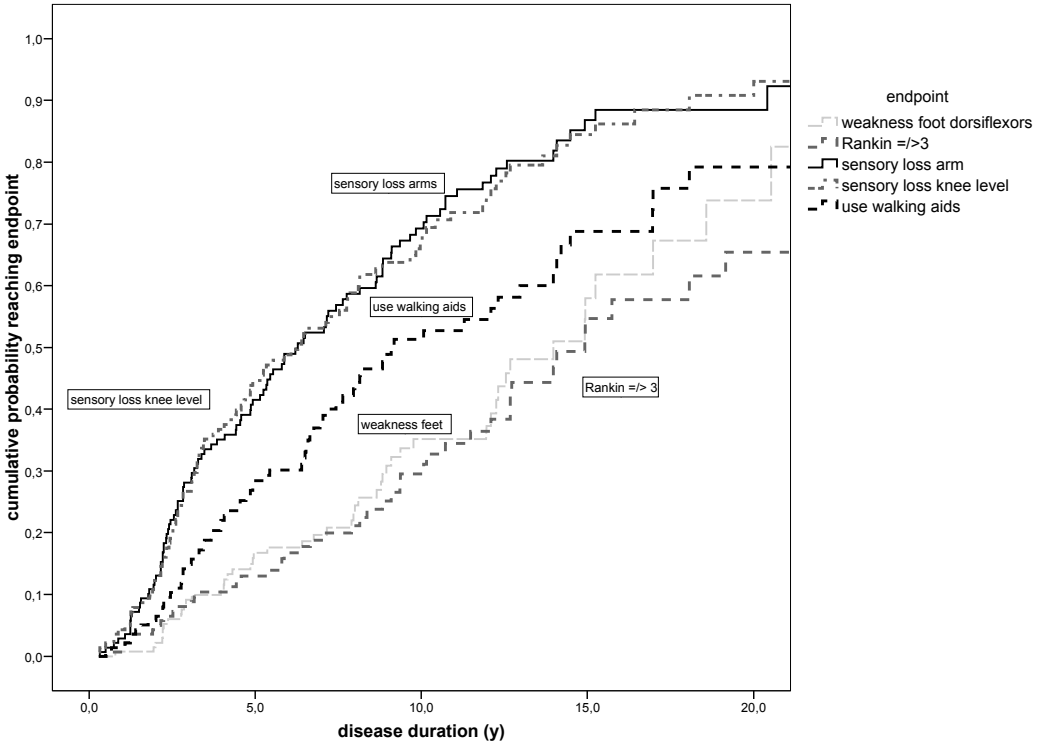
The use of walking aids increased during the disease course to 64/140(46%) at the last follow-up visit. (E-table 5). The median distal MRC sum score decreased between first and last follow-up visit from 98% to 95% (i.e. 4.2 MRC points) (n=116) (p<0.001) .

The median Sensory Sum Score declined from 79% to 75% (i.e. 2.2 sensory sum points) (n=116) (p=0.08). In 18/27 patients with a quantifiable M protein at baseline, the median decrease was 0.5g/l (IQR −5.5 - +1) (ns). The median IgM concentration remained unchanged and was 5.0 g/l (IQR 2.9-7.2) at baseline compared to 4.9 (IQR 2.9-7.4) at last follow-up visit in 83/140 patients (ns).Survival analysis shows the development of the different endpoints in time. (figure 1and E-figure 2). Early in the disease course, a large proportion of patients showed sensory signs and symptoms in the hands and sensory impairment of the whole lower leg up to the knee.

E-Table 5: Supportive walking devices in 140 patients with IgM MGUS Polyneuropathy

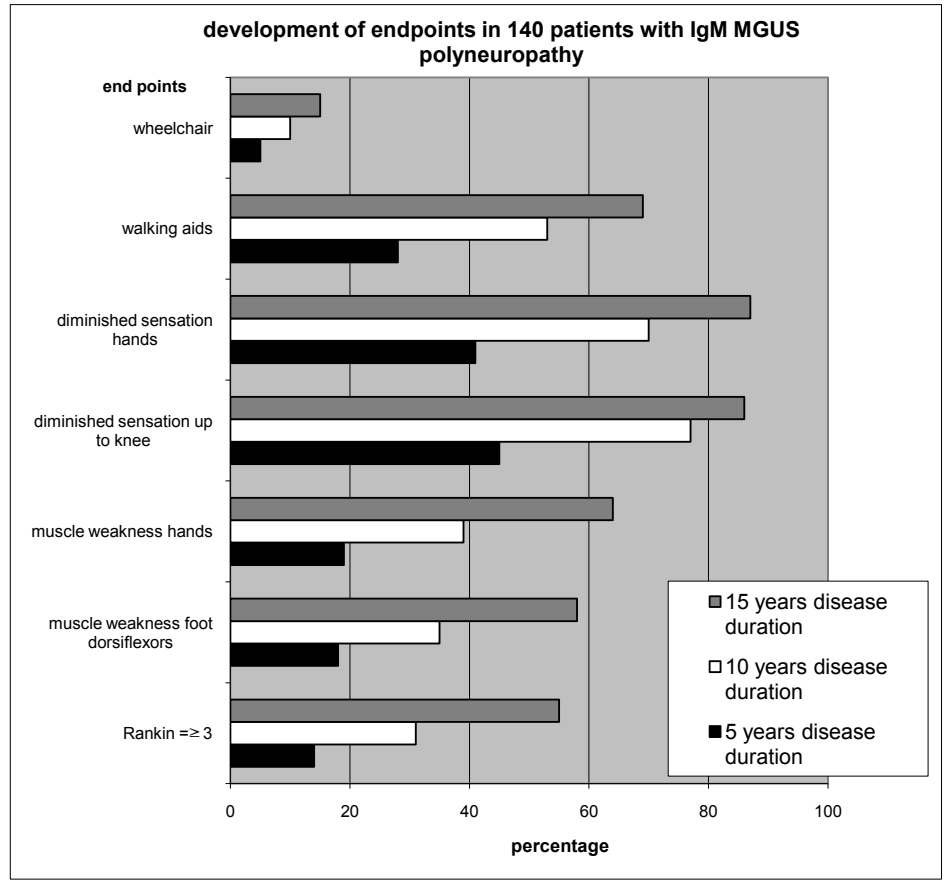
	baseline	last visit
total patients	140	123
cane	13 (9%)	23 (20%)
AFO	8 (6%)	14 (12%)
rollator	9(6%)	16 (14%)
wheelchair	4 (3%)	13 (11%)
scooter	2 (1%)	9 (8%)
all walking aids	36 (26%)	64 (55%)

Figure 1: Risk for development endpoints in 140 IgM MGUS polyneuropathy patients



The proportion of patients with muscle weakness of the foot dorsiflexors and hand muscles was smaller early in the disease course, but increased later during the disease course. The proportion of patients that needs supportive walking devices lies in between the proportion of patients with sensory and motor disturbances. (figure 1 and E-figure 2). New bone marrow abnormalities evolved in 17(12%) additional patients, leading to 23(16%) patients with hematological malignancies. There were 21 patients with LPL and two patients with NHL diagnosed at a mean disease duration of 7.5 years (SD 4.6). Treatment with chemotherapy was indicated for 5/23 patients; in the remainder the malignancy grade was low and there were no further clinical signs that prompted hematological treatment. Non-hematological malignancies evolved in eight(6%) patients: one colorectal carcinoma, one melanoma, one squamous cell carcinoma, three prostate cancer, one mamma carcinoma and one Grawitz tumor. Four of these patients had died at the end of the study. At the end of follow-up, 21 patients had died from diseases unrelated to IgM MGUSP.

E figure 2: Development of endpoints in 140 IgM MGUS polyneuropathy patients



Definition of endpoints:

Wheelchair= patients needing wheelchair for longer distances

Walking aids= use of any walking aids: crutches, rollator, ankle foot ortheses or a wheelchair

Diminished sensation of the hands= sensory score ≤ 3 = sensory disturbance distal from the wrist, of any of the sensory modalities touch/vibration/pinprick sensation

Diminished sensation up to the knee= sensory score=1 = sensory disturbance distal to the knee, comprising the whole lower leg

Muscle weakness hands= MRC grading ≤ MRC 4 in hand muscles

Rankin ≥ = Development of modified Rankin scale ≥ 3

Immunotherapy

Seventy-four patients were treated with immunotherapy during follow-up (38 patients once, 25 twice, 11 patients three or more times) at a median disease duration of 3.4 years (IQR 2.4-6.2). Mostly pulsed cyclophosphamide with prednisone (n=40), oral fludarabine (n=19), and intravenous rituximab (n=20) were administered as described elsewhere. [17-19] Treated patients were more disabled, showed lower MRC and sensory sum scores at baseline, and had a higher risk for development of Rankin Scale ≥ 3 (p=0.01) (E-table 6, E-figure 3). The delta scores were not different between the treated and untreated group. (E-table 6)

Univariate analysis delta scores

Delta scores of all outcome measures were similar between demyelinating and axonal IgM MGUSP, MAG-positive and MAG-negative patients, between groups with age of onset before or after 60 years or total M protein concentration > or < 1g/l.

Univariate survival analysis

Patients with demyelinating IgM MGUSP had a higher risk for development of weakness of foot dorsiflexors ≤ MRC grade 3 than axonal IgM MGUSP. Presence of demyelinating IgM MGUSP showed no difference for all other endpoints.

MAG-positive patients had a lower risk for developing a Rankin Scale ≥ 3 (p=0.04) (figure 2). Anti-MAG titers showed no association with disease severity as defined by development of a Rankin scale ≥ 3. Risks for development of all other endpoints were equal between MAG-positive and MAG-negative patients.

Age of onset >60 years was associated with a higher risk of developing a Rankin scale ≥ 3 (p=0.005).

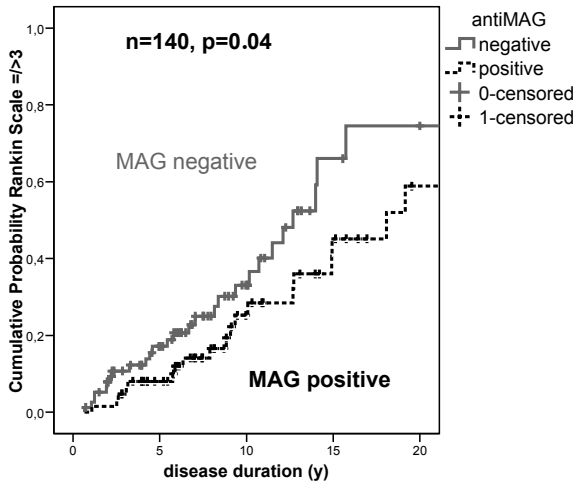
The presence of a total M protein concentration > 1g/l was not associated with a higher risk of development of any of the clinical end points (data not shown).

Multivariate analysis and prognostic model

Multivariate Cox regression analysis was performed with four possible relevant factors that were significant in the univariate Kaplan Meier survival analysis: presence of demyelination, presence of anti-MAG, total M-protein concentration > 1g/L and age of onset. (Table 2) Table 3 shows the calculated risk scores per patient category, depending on the age of onset, Demyelinating NCS and anti-MAG status. The table illustrates that the 5 year risk for developing a Rankin Scale ≥ 3 is 49% for a patient with age of onset between 40 and 50 years of age, with demyelinating NCS and with a presence of anti-MAG antibodies, opposed to 99% for patients with onset between 70 and 80 years, with demyelinating NCS and without anti-MAG antibodies.

In an additional nomogram, available at http://www.umcutrecht.nl/subsite/Prognosis-MGUS-Neuropathy it is possible to calculate an individual prognostic curve (with 95% confidence interval).

Figure 2: Risk of development of Modified Rankin scale ≥ 3 in a cohort of 140 IgM MGUS polyneuropathy patients



MAG positive= presence of antibodies against myelin associated glycoprotein (MAG),

MAG negative= absence anti-MAG antibodies

Number of patients at risk: at T=5 years: n=117,T=10 years: n=80,T=15 years:n=57,T=20 years:n=51

Table 2: Cox regression analysis for developing a Modified Rankin Scale score ≥ 3 in 140 IgM MGUS polyneuropathy patients

	unadjusted hazard ratio	95% CI	p	adjusted hazard ratio	95% CI	p
Age at onset (years)	1.042	1.01-1.077	0.014	1.040	1.007-1.074	0.017
demyelinating PNP (yes / no)	1.261	0.624-2.548	0.518	2.028	0.951-4.324	0.067
anti-MAG (yes / no)	0.549	0.308-0.980	0.043	0.453	0.242-0.849	0.013
M protein =>1g/l (yes / no)	0.711	0.365-1.386	0.316			

unadjusted hazard ratio = univariate analysis, adjusted hazard ratio = multivariate analysis

The factor “treatment” was also analyzed as factor for disease progression: a univariate Kaplan Meier survival curve shows that treated patients had a higher risk for developing MRS ≥3. (E-figure 3) The treated group was selected on the basis of progressive signs and symptoms, as this was an inclusion criterion for all our treatment trials. Hereby, obviously a group of patients with more severe disease course was selected. (E-table 6)

Figure 2: Risk of development of Modified Rankin scale ≥ 3 in a cohort of 140 IgM MGUS polyneuropathy patients

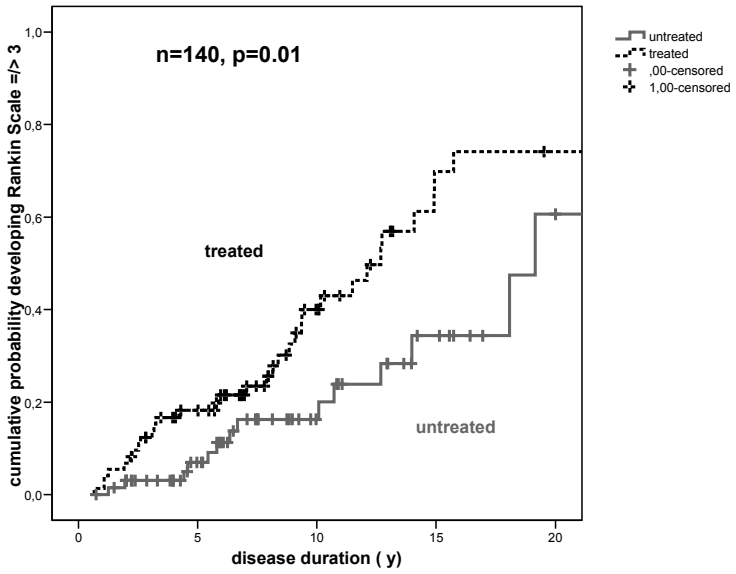


Table 3: Absolute risk of developing a Modified Rankin Scale score ≥ 3 in 140 patients with polyneuropathy associated with IgM monoclonal gammopathy

diagnostic work-up--> age at onset	NCS	antibodies	risk % 5y	risk % 10y	risk % 15y
onset 40-50 y	DEM +	MAG +	49	84	99
		MAG -	78	98	100
	AX	MAG +	28	60	91
		MAG -	52	87	100
onset 50-60 y	DEM +	MAG +	63	94	100
		MAG -	89	100	100
	AX	MAG +	39	74	97
		MAG -	66	95	100
onset 60-70 y	DEM +	MAG +	77	98	100
		MAG -	96	100	100
	AX	MAG +	52	86	99
		MAG -	80	99	100

-risks are calculated from linear predictors as calculated by Cox regression analysis
-risks are presented as % and derived from 1-survival at 5,10 and 15y disease duration
-NCS= nerve conduction studies, onset= age at onset in years, presented in 4 categories of 10 years, DEM= demyelinating,

E-Table 6: Treated versus untreated patients at baseline

	treated	untreated	p
total n patients	74	66	
Characteristics			
anti MAG	40 (55%)	22 (33%)	0.01
demyelinating	59 (81%)	40 (61%)	<0.01
IgM > 1 g/l	17 (23%)	10 (15%)	ns
median age of onset (IQR)	58,5 (50-66)	61(53-68)	ns
median disease duration (IQR)	2,8 (1,9-6,1)	3,6 (1,9-5,8)	ns
Baseline scores			
Median Rankin scale (IQR)	2 (2-2,25)	2 (2-2)	ns
Median MRC sum score (IQR)	96 (91-100)	99 (96-100)	0.02
Median Distal MRC sum score(IQR)	94 (86-100)	99 (93-100)	0.03
Median Sensory sum score (IQR)	71(61-82)	82 (75-93)	<0.001
Change scores			
Median delta MRS	0 (0-0)	0 (0-0)	0.50
Median delta distal MRC	0 (-5-0)	-3(-8-0)	0.15
Median delta sensory sum	-4 (-13-2)	0(-11-9)	0.16

Legend: anti-MAG= antibodies against myelin associated glycoprotein (MAG), MRC sum, distal MRC sum and sensory sum scores are in percentage (0-100%), MRS(Modified Rankin Scale) is in points (maximum=5 points)

Discussion

Based on this prospective cohort study of 140 patients, a prognostic model for the risk of disability in IgM MGUSP was developed. Three different prognostic factors were determined: the presence of demyelinating NCS, the absence of anti-MAG antibodies and a higher age of onset. Based on these three factors, the group of patients can be classified into three different subgroups: patients with demyelinating polyneuropathy with anti-MAG antibodies, patients with demyelinating neuropathy without anti MAG activity and patients with axonal neuropathy. Patients with demyelinating IgM MGUSP showed more severe sensory disturbances and muscle weakness at baseline than those with axonal IgM MGUSP. This difference has not been addressed very often before, probably because in most IgM MGUSP populations only 10-20 % of patients have axonal NCS. [5;5;13;28;29] Nevertheless, the previous studies also showed more severe symptoms in patients with demyelinating IgM MGUSP. [30] MAG-positive patients showed a lower risk for developing disability of MRS ≥ 3. This is contrary to previous studies, where MAG-positive and negative patients seemed clinically indistinguishable. [13] [6], [4], [10], [14], [15] It is possible that this difference has emerged because of the larger number of patients and hence larger statistical power of our study, or because of a difference in patient selection. The fact that the median MRC sum score was lower in the MAG-positive patients, may seem in contradiction with this finding, however, it is possible that there is no linear correlation between the modified Rankin scale and the MRC graded muscle strength and that in this subgroup sensory signs predominantly determine the level of disability.

A higher age of onset was associated with a higher risk or Rankin Scale ≥3. It is difficult to determine whether this can be attributed to ageing itself or to a different course of the neuropathy, or both. From a practical point of view, it shows that with later onset, patients will become dependent after a shorter disease duration, and can be prepared for this.

The prognostic table (table 3) shows that between 10 and 15 years of disease duration the risk percentages do not increase any longer, especially in the MAG negative patients. This may indicate that after 10 years a “plateau” phase is reached. This could even imply that modification of the disease course should take place in the first ten years of disease duration.

The occurrence of hematological malignancies was lower than in a previous study, probably because patients with IgG MGUSP were excluded from the present study. [31]

The prognostic model may be used in other, comparable populations with IgM MGUSP in a tertiary care setting. Unfortunately, the natural history of the disease cannot be distinguished from treatment effects. Patients who received treatment had more severe disease at presentation. This “confounding by indication” is to be expected in an observational cohort study. Unlike the risk for development of modified Rankin Scale ≥ 3, the rate of disease progression, expressed as delta scores, showed no difference between treated and untreated patients. Delta scores indicate the rate of disease progression. The modified Rankin scale is quite an insensitive scale to measure motor and sensory impairments. It is conceivable that treated patients were closer to a Rankin scale ≥ 3 than were untreated patients and therefore more likely to reach a Rankin scale ≥ 3 earlier with the same rate of progression, i.e. the same delta scores.

Another explanation for the fact that the delta scores were the same could be that the differences between the two groups were too small if measured as constant variables, and would have only emerged if dichotomous variables were compared. However, the influence of treatment on disease progression remains difficult to estimate, especially as previous treatment trials were not able to show clear or sustainable long term effects yet. [3;17;18;32] With the data from this study, one of the largest prospective cohort studies of the disease course in IgM MGUSP, individual prognostication of disability in IgM MGUSP is now possible. This is helpful in counseling and managing these patients

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Intermittent cyclophosphamide with prednisone versus placebo for polyneuropathy with IgM monoclonal gammopathy

J.M.F. Niermeijer [1], M. Eurelings [1], M.W. van der Linden[4], H.M. Lokhorst[2], H. Franssen[1], K. Fischer[4], L.L. Teunissen[5], L.H. van den Berg[1], F. Schobben[3], J.H.J. Wokke[1] and N.C. Notermans[1]

[1] Department of Neurology and Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands
[2] Department of Hematology University Medical Center Utrecht, the Netherlands
[3] Department of Pharmacology University Medical Center Utrecht, the Netherlands
[4] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
[5] Department of Neurology of the St Antonius Hospital, Mesos Medical Center, Nieuwegein, the Netherlands

Neurology, 2007;69(1):50-59

Abstract

Background

The best treatment for polyneuropathy associated with IgM monoclonal gammopathy (MGUS) is unknown. Oral cyclophosphamide combined with prednisone showed limited efficacy in a previous open label pilot study. We therefore performed a double-blind, randomized, placebo-controlled study of combined oral cyclophosphamide and prednisone in IgM MGUS polyneuropathy.

Methods

35 patients with progressive IgM MGUS polyneuropathy were included. After stratification for anti-MAG antibodies patients were randomized to oral cyclophosphamide 500 mg once daily for 4 days combined with oral prednisone 60mg once daily for 5 days (treatment) (n=16), or placebo (n=19), repeated every 28 days for 6 times. Primary outcome was improvement of the Rivermead Mobility Index (RMI). Secondary outcomes were improvement of the modified Rankin scale, MRC and sensory sum scores, levels of M protein, EMG and SF-36 scale after treatment. Patients were examined at 0, 6, 12, 18, and 24 months.

Results

After 6 months of treatment and at later follow-up, no difference in change of the RMI between the two groups was observed. Change of the Rankin scale was similar in both groups. Other outcome parameters showed more improvement in the treatment group: the MRC sum score improved more from 6-24 months after treatment; tthe sensory sum score improved more at 6 months;the SF 36 mean health change score and physical role score improved more; and the median nerve distal conduction (abductor pollicis brevis muscle) improved more in the treatment group. The most common adverse event was nausea.

Conclusions

Compared with placebo treatment this first double blind randomized trial with cyclophosphamide and prednisone in IgM MGUS polyneuropathy showed no beneficial effect on the functional scales, however but a beneficial effect on muscle strength and sensation was observed

Introduction

Polyneuropathy associated with IgM monoclonal gammopathy of undetermined significance (IgM MGUS polyneuropathy) is a chronic progressive disorder that leads to a variable degree of functional impairment and disability. Most patients have a symmetric sensorimotor polyneuropathy and sensory ataxia. A causative role of the IgM M protein in the polyneuropathy is illustrated by the presence of circulating anti MAG antibodies or other antibodies directed at the myelin sheath of peripheral nerves. [1 2 3-6 7 8 9 10]

Immunotherapy is advocated if IgM MGUS polyneuropathy causes disabling symptoms [11]. However, there is no consensus about the best treatment strategy and the timing of initiation of treatment has not been established [11] Immunotherapy and chemotherapy may act through direct suppression or elimination of the B cell clone, or by suppression of the inflammatory cascade.

In an open study with oral cyclophosphamide and prednisone in MGUS polyneuropathy we could demonstrate a significant effect on functional outcome and EMG findings [12]. As a next step we conducted a double-blind, randomized, placebo-controlled trial to investigate the efficacy of combination treatment in patients with progressive IgM MGUS polyneuropathy.

Methods

Patients

Patients with IgM MGUS polyneuropathy were assessed for eligibility at the outpatient department for Neuromuscular Diseases at the University Medical Center Utrecht that is a tertiary referral center for patients with polyneuropathy in The Netherlands. Inclusion criteria were a diagnosis of symmetric motor and sensory polyneuropathy confirmed by electrophysiological examination; presence of a monoclonal IgM gammopathy, progression of symptoms defined as ≥1 point deterioration on the Modified Rankin scale or Rivermead Mobility Index, or ≥ 5% deterioration of the MRC sum score or sensory sum score in a time interval of 6 months ; no other causes for polyneuropathy; age over 25 years and completed family for reasons of fertility; no underlying hematological malignancies as excluded by a hematologist; no contra indications for the use of steroids or cyclophosphamide; no other immunotherapy for polyneuropathy in the previous 5 years.

The study was approved by the ethics committee of the University Medical Center Utrecht, The Netherlands. Patients gave written informed consent before inclusion in the study.

Study design

The study was conducted between January 1996 and July 2004. As the presence of circulating anti MAG antibodies could be a negative prognostic factor with respect to treatment response we stratified for presence of anti-MAG antibodies. [13] In all patients the presence of anti-MAG antibodies was determined as previously described. [4]

Phase 1: After stratification patients were allocated to treatment or placebo using a computer generated list with permuted blocks of randomly varying size.

Physicians and patients were unaware of treatment allocation throughout the study.

Patients were followed by the same physician throughout the whole follow-up period at 3, 6, 12, 18 and 24 months. To minimize interobserver variability the two co-investigators trained each other in the assessment methods. Adverse events were monitored according to the WHO criteria and registered on a separate form.[14] For ethical reasons it was decided to have an optional double blind cross over phase in this trial, so that in case the patients experienced progression of symptoms despite treatment during the first 6 months, they would still be able to receive potentially effective treatment thereafter. The second part of the trial is referred to as phase 2.

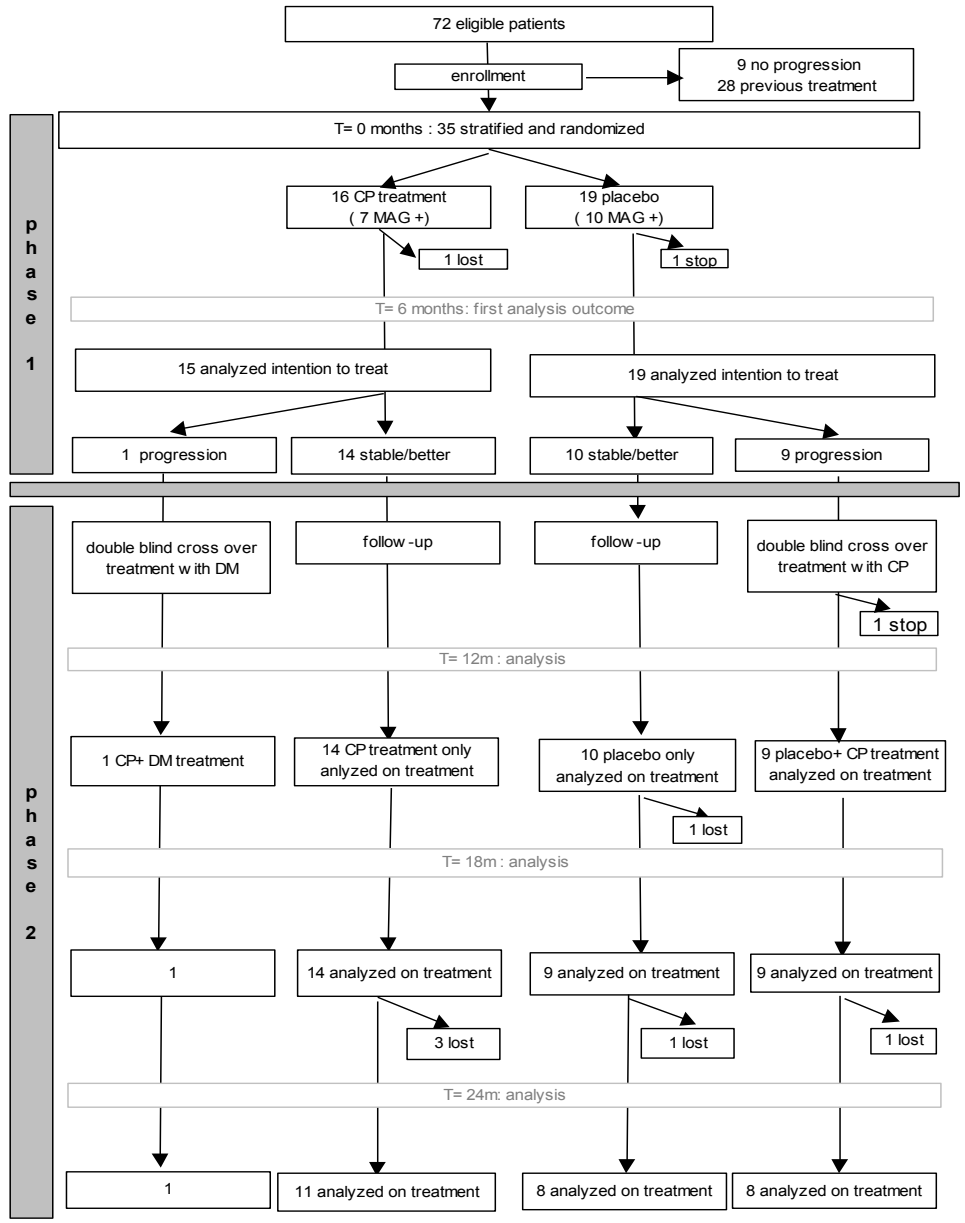
Phase 2: After the first six months, patients with progression of symptoms (see definition) were eligible for a second double blinded treatment regimen for six months. Patients with improvement or stabilization in phase I were not eligible for extra treatment. The hospital pharmacist randomized the patients in this second phase of the trial, so that physicians and patients remained unaware of treatment allocation throughout the study. Data analysis was performed after the treatment code was broken.

Treatment strategies

The treatment schedule was cyclophosphamide 500 mg orally once daily for 4 days with prednisone 60 mg orally once daily for 5 days (hereafter referred to as CP treatment), repeated every 28 days for 6 times, or placebo. For placebo we used dummy preparations identical in appearance to the treatment preparations.

If according to the criteria, patients were eligible for cross over therapy after phase I, the hospital pharmacist allocated the patient to CP treatment if the patient had received placebo in phase 1 (n=9), or to oral dexamethasone 40mg daily 4 days per every 28 days repeated 6 times if the patient had received CP treatment in phase 1 (n=1). (figure 1) Before the start of every new treatment cycle blood count was checked. For reasons of blinding this was done by the co-investigator who was not treating the patient. If leukocyte count was below $3x10^9$/l or thrombocyte count was below $100x10^9$/l, blood count was repeated and treatment was postponed until values returned to normal.

Figure 1: Trial profile



Primary outcome measure: We used the Revised Rivermead Mobility Index (RMI) on which 15 daily activities concerning mobility can be scored (0-15). For each item that can be performed 1 point is given. Items range from getting out of bed to walking outside independently, climbing stairs or at best run for 10 meters. [15] (see Appendix 2) Change from baseline on the RMI was compared between the treatment group and placebo group, as well as percentage responders from 6-24 months after start of treatment. Response was defined as ≥ 1 point improvement on the RMI.

Secondary outcome measures: Changes from baseline at 6, 12, 18 and 24 months were calculated and compared between the treatment and placebo group for the following secondary outcome measures:

-*Modified Rankin Scale* Ranging from 0=no symptoms at all to 5=severe disability, requiring constant nursing care and attention. [16]

-*MRC sum score* (0-140 points) . We did manual muscle testing (MMT) using the MRC scale in 28 muscles of both arms and legs (deltoid, biceps and triceps brachii, finger extensors, finger flexors, first interosseus, wrist extensors, iliopsoas, hamstrings, quadriceps femoris, anterior tibial, gastrocnemius, peroneal and extensor hallucis longus muscles). [12] (Appendix 5)

-*Sensory sum score* (0-56 points) was measured as follows: touch and pin prick sensation: 4= normal, 3= abnormal distal to wrist/ankle, 2= abnormal distal to half forearm/leg, 1= abnormal distal to knee/elbow, 0= abnormal distal to groin/ axilla. Vibration sense: 128Hz tuning fork perception on: 4=middle finger/ hallux, 3= ulnar styloid/medial malleolus, 2= elbow/knee, 1= clavicle/iliac crest, 0= absent. Joint position sensation of middle finger/ hallux: 2= normal, 1= diminished, 0= absent. [12;17] (Appendix 4)

-*Ataxia* was scored with a standardized tapping test of the dominant hand and foot measuring the number of taps using a device with 2 buttons attached to an automatic counter. [18]

-*Quality of life* was monitored with the Dutch version of the SF 36-item health survey Questionnaire that has been validated in immune mediated polyneuropathies. [19 20] (Appendix 6)

-*M protein levels* were determined with immunofixation and immunoelectrophoresis as described elsewhere. [21]

-*Electrophysiological studies* The EMG studies were performed before and 6 months after start of treatment and included motor conduction with stimulation up to the axilla of the median nerve to the forearm (flexor carpi radialis muscle) and the hand (abductor pollicis brevis muscle), ulnar nerve (abductor digiti quinti muscle), or stimulation up to the knee of the peroneal nerve (extensor digitorum brevis muscle and anterior tibial muscle), and tibial nerve (abductor hallucis brevis muscle). Sensory conduction of musculocutaneous, median, ulnar, radial and sural nerves on distal stimulation was measured as described elsewhere.[22] We used criteria for demyelination as described elsewhere. [23] EMG outcome measures were calculated changes between 0 and 6 months of the distal CMAP amplitude, distal motor latency (DML), motor conduction velocity (MCV) per segment, sensory conduction velocity, SNAP amplitude, ΣSNAP (= summated SNAP of median and sural nerve) and ΣCMAP (= summated CMAP of ulnar, median and peroneal nerve). [24] The terminal latency index (TLI) was determined to compare slowing in distal and adjacent segments. [25] In addition an improvement of ≥ 10% in the nerve conduction velocity within individual nerves after treatment was considered as electrophysiological response and response percentage was compared between both treatment groups. [26]

Statistical Analysis

Sample size was estimated in a pilot study reported elsewhere. [12] Briefly, assuming α=0.05, β=0.20 and mean difference in the Rivermead mobility index with a standard deviation of 2, a sample size of 16 patients per treatment group was considered adequate.

For every outcome measure, change over time was calculated. These change scores followed an approximate normal distribution and were compared by Student's t-test. At the end of phase 1 (T=6 months) univariate treatment effects were analyzed by intention-to-treat across the CP treatment group and the placebo group.

In Phase 2 cross over treatment strategy resulted in 2 extra treatment subgroups. As this could possibly lead to overestimation or underestimation of treatment effects in an intention to treat analysis, we performed a separate on treatment analysis for phase 2 (T=12- 24 months). We compared change scores by student's t-test between the CP treatment-only (n=14), placebo-only (n=9), and the placebo-and-CP treatment-group (n=9). (The only patient that received CP treatment followed by dexamethasone was excluded from this analysis.)

Being the primary outcome measure, we also compared the change in of the Rivermead Mobility Index scores over time between the two treatment groups in a repeated measurements ANOVA. For this analysis the dataset included single imputed values for RMI using a linear regression method incorporating the following covariates to estimate the imputed value: age at onset of symptoms, sex, anti-MAG protein status, and treatment group (treatment or placebo). In a second model we used cross-over therapy as a co-variate. Finally, we compared the proportion of patients who improved ≥ 1 point on the Rivermead Mobility Index between the two treatment groups using the chi square test. P values <0.05 were considered significant.

Results

Thirty-five patients could be included after informed consent from a cohort of 72 consecutive patients. Nine of 72 eligible patients did not meet the criterion of progressive polyneuropathy and 28/72 eligible patients had received previous treatment. Randomization with variable block size resulted in unequal groups within the anti-MAG positive stratum. (Figure 1) Baseline characteristics, primary and secondary outcome measures at baseline did not differ between the two groups. (Table1 and 2)

During phase 1 of the study one patient stopped CP treatment because of cardiac complaints (angina pectoris) and was lost to follow-up, and one patient stopped placebo because of rapid deterioration of the neuropathy. Only for this case the trial code was violated prematurely. This patient remained in follow-up.

At the end of phase 1, at six months, only one patient from the initial treatment group was eligible for cross-over therapy (7%) in contrast to 9 patients (47%) from the initial placebo group. (Figure 1)

During the optional cross over phase 2 from 7-12 months after start, one patient stopped CP treatment prematurely because of side effects. (Figure 1)

Table 1: Baseline characteristics of 35 patients with IgM MGUS polyneuropathy

Characteristics	Treatment (n=16)	Placebo(n=19)
Age (y)	64.3 (9.2)	64.2(8.5)
Onset (y)	60.7 (9.3)	59(9.8)
Duration (y)	2.7(1.7-12.2)	3.7(1.5-13.5)
Sex		
male	13(81%)	11(58%)
female	3(19%)	8(42%)
Clonality		
kappa	14(88%)	14(74%)
lambda	2(12%)	5(26%)
EMG		
axonal	3(19%)	4(21%)
demyelinating	13(81%)	15(79%)
Anti-MAG		
positive	7(44%)	10(53%)
negative	9(56%)	9(48%)

Data are mean (SD)/ median (interquartile range) or number of participants (%).
Patient characteristics were similar between groups

Table 2: Outcome measures at baseline

Outcome measures	Treatment (n=16)	Placebo (n=19)
Rivermead Mobility Index	13.5(12-14)	14(12-14)
Rankin scale	2(2-3)	2(2-3)
MRC sum score	133 (123-138)	136 (131-140)
Sensory sum score	39 (30-42)	40(33-47)
Tapping test arm	31(28-38)	31(28-36)
Tapping test leg	35(23-39)	36(30-40)
M protein concentration	0.5(0.5-0.5)	0.5(0.5-0.5)

Legend to table 2: data are median (interquartile range), outcome at baseline was similar between groups.

Adverse events

In total 45 sets of 6 treatment cycles were given: 19 placebo, 25 CP treatment (16 initial and 9 after cross over) and 1 dexamethasone (DM) (Figure 1). Treatment resulted significantly more often in nausea than placebo (p=0.001). Five years' follow up showed that 3/35 (8.6%) patients eventually developed immunocytoma, that did not necessitate further treatment until present. No other malignancies were reported.

Primary outcome measure Phase 1

The mean change on the RMI did not differ between both treatment groups at 6 months according to intention to treat analysis. (Table 3) At six months after start of treatment, 36% of patients (5 /15) in the CP treatment group versus 21% (4/19) in the placebo group showed improvement of ≥1 grade on the RMI (ns). (figure2)

Additional analysis with the repeated measurements ANOVA showed no difference in change of the RMI over time (p=0.459, F=0.561), nor did the second model, with cross-over therapy as a co-variate (p=0.390, F=0.758).

Secondary outcome measures Phase 1

Overall, secondary outcome improved more in patients with CP treatment according to intention to treat analysis.

The Modified Rankin scale improved more in the CP treatment group (-0.20 points) than in the placebo group (+0.11 points)(p=0.053).

The MRC sum score improved more in the CP treatment group (+1.87 points) CI:–1.88-5.61) than in the placebo group(-2.16 points)(CI-0.44- -0.12) (p=0.049) .

Table 3: outcome measures Phase 1: intention to treat analysis

	CP Treatment			Placebo			
	n	Mean change	95% CI	n	Mean change	95% CI	p value
RMI							
6 months	15	+0.47	-0.08-1.02	19	+0.05	-0.66-0.76	0.357
Rankin							
6 months	15	-0.20	-0.43-0.03	19	+0.11	-0.12-0.33	**0.053**
MRC sum							
6 months	15	+1.87	-1.88-5.61	19	-2.16	-4.44-0.12	**0.049**
Senssum							
6 months	15	+5.13	1.47-8.80	19	+0.36	-2.63-3.37	**0.039**

Legend to table 3: Groups are divided according to initial treatment during trial phase1.
Mean change from baseline scores with 95% CI= 95% confidence interval of Rivermead mobility index (RMI)(+= improvement, -= deterioration, score from 0-15), Rankin= Modified Rankin scale(+= deterioration, -= improvement score from 0-5), MRC sum= MRC sum score, Senssum= sensory sum score (+= improvement, -= deterioration). All significant p- values indicate more improvement in the group that received CP treatment

The Sensory sum score improved more in the CP treatment group (+ 5.13 points) compared to the placebo group (+ 0.63 points) (p=0.039).
Ataxia At six months, the quantified ataxia tests showed more improvement of the tapping test for the legs in the treatment group, with a mean increase of 5 taps/15 seconds (n=12) compared to a mean decrease of 3 taps/15 seconds (n=18) in the placebo group (p=0.04). (Data not shown).
SF 36 Quality of life scale The mean health change score improved +31 points in the treatment group, compared to +5 points in the placebo group (p=0.03) at 6 months.
M protein levels decreased more in the treatment group (-0.47 +/-1.25 g/l) compared with the placebo group (+1.03 +/-2.54 g/l) (p=0.045). During this period the mean change of IgM levels was -1.41(+/- 1.55) in the CP group and - 0.001 (+/-0.97), in the placebo group (p=0.048). (Data not shown).
EMG studies In the treatment group the median nerve DML (abductor pollicis brevis muscle) decreased more than after placebo (p=0.045).

Table 5: EMG findings in the median nerve (abductor pollicis brevis muscle)

	Treatment (n=15)			Placebo (n=18)			
	before	**after**	**change**	**before**	**after**	**change**	**P value**
DML wrist (ms)	6.94	6.4	-0.31(1.59)	7.21	8.23	+1.07(3.40)	**0.045**
MCV distal (m/s)	42.56	41.38	-1.67(4.03)	45.63	42.47	-3.27(8.04)	0.769
CMAP distal (mV)	7.94	8.42	+0.71(2.29)	7.97	8.11	+0.30(1.67)	0.612
TLI APB	0.27	0.28	+0.024(0.056)	0.25	0.23	-0.02(0.07)	**0.052**

Legend to table 5: Measurements performed before and after treatment with cyclophosphamide and prednisone or placebo in patients with IgM MGUS polyneuropathy.
DML= Distal Motor Latency, MCV= mean conduction velocity, CMAP= compound muscle action potential, TLI= terminal latency index, *values are mean(SD), for DML -= improvement and += deterioration, for MCV, CMAP and TLI+= improvement and - = deterioration, both significant p-values indicate improvement of distal nerve conduction in the group with treatment

Together with unchanged conduction velocity and increased TLI (p=0.052), this indicates faster distal conduction. (Table 5). Between groups the change of other variables or the response percentage of nerve conduction velocity was not different. (Data not shown)

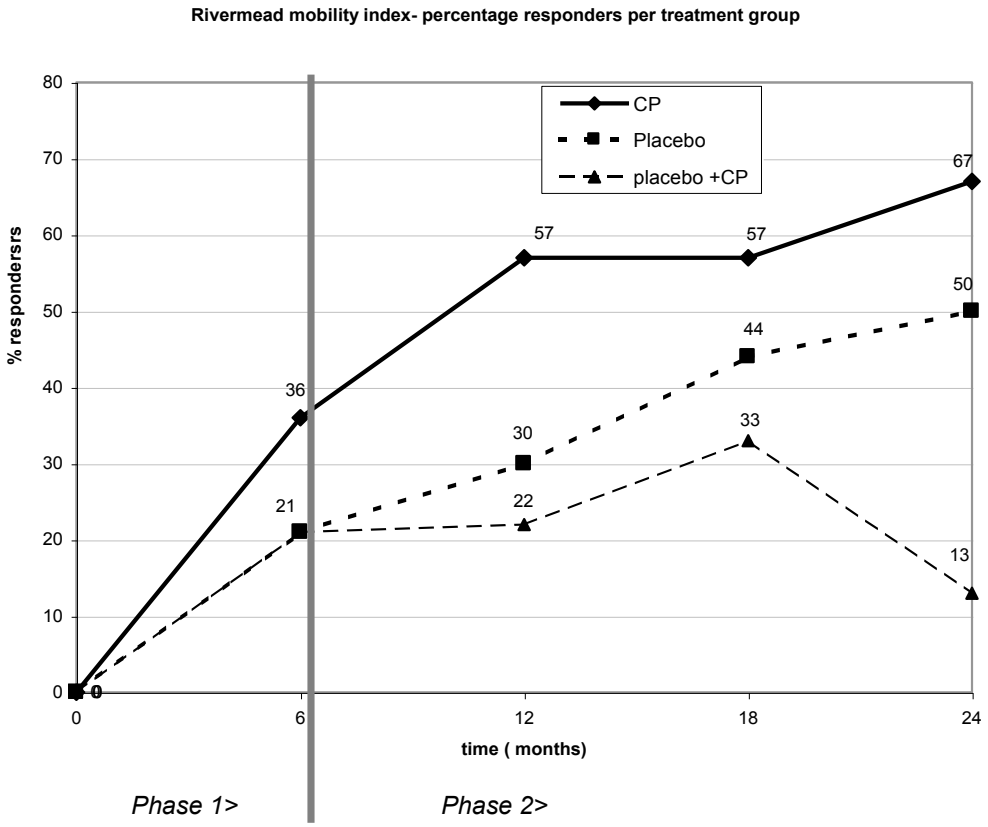
Primary outcome measure Phase 2

The response rate on the Rivermead Mobility Index was not different between the CP treatment only and placebo only group, nor between the placebo only and placebo and CP treatment group. After 24 months of follow up 8/14 patients (57%) in the CP treatment only group versus 5/10 (50%) patients in the placebo only group improved ≥1 point on the RMI (n.s.) (Figure 2).

Secondary outcome measures Phase 2

For phase 2 we compared the three eventual treatment groups in an on treatment analysis:
- *CP Treatment only versus placebo only group*:
When we compared patients who only received CP treatment (n=14) with patients who only received placebo (n=10) there was no difference in change of the Rankin scale or sensory sum score from 12-24 months.
At 12 months, the MRC sum scores improved more in the CP treatment only group (+4.62

Figure 2: Rivermead mobility index- percentage responders per treatment group



Legend to figure 2: Phase 1= from 0-6 months, initial treatment phase, phase2= from 7-24 months, after cross over, CP= group treated with cyclophosphamide and prednisone, PL= placebogroup, placebo+CP= group first treated with placebo, followed by CP treatment in phase 2 of trial.

(CI 95% 1.04-8.19) than in the placebo group (-3.70 (CI 95% -8.92-1.52) (p=0.006). At 18 months this change was +6.08 (CI 95% 1.56-10.60) in the CP treatment only group versus -4.33(-10.07-1.41) in the placebo group (p=0.004) and at 24 months +5.92 (CI 95% 0.83-11.00) in CP treatment only versus –1.88 (CI 95% -5-1.27) in the placebo only group (p=0.02).

-Placebo only group versus placebo and CP group:

Comparison of the change scores showed no difference between these 2 groups for Rankin, MRC sum score or sensory sum score from 12-24 months. (Table 4)

-CP treatment group versus placebo and CP group:

Comparison of the change scores showed no difference between these 2 groups for the change scores of the Rankin scale or sensory sum score from 12-24 months. (Table 4)

The MRC sum score improved significantly more in the CP treatment group than in the placebo and CP treatment group at 12, 18 and 24 months. (Table 4)

Before versus after cross-over: In the subgroup of patients who started with placebo and thereafter received CP treatment (n=9) we measured the effect of both placebo and treatment. We compared the change of the RMI, Rankin scale, MRC and sensory sum scores between 0 and 6 months (while on placebo) with the change between 7 and 12 months (while on CP treatment). The median change of the Rankin scale was 0 grades (IQ range: 0-1) from 0-6 months and -1 grade (IQ range: -1-0) in the period from 7-12 months (p=0.014), indicating improvement. We also found a difference in the median change of the MRC sum score between the period before and after start of treatment: 0 grades (IQ range: -5-0 grades) from 0-6 months and +2 grades from 7-12 months (IQ range 0-2.5) (p=0.05, data not shown)

Influence of anti-MAG, disease duration, age of onset or demyelinating EMG

As subgroups were small we could not establish a clear relation between the presence of anti-MAG antibodies, disease duration longer or shorter than 3 years, age of onset or EMG classification and response to treatment.

In the treatment group, 7/9 patients who responded on the RMI between 6 and 12 months after start of treatment, had a demyelinating EMG (4 with anti-MAG antibodies), versus 4/5 of the non-responders (2 with anti-MAG antibodies) (n.s.). Mean disease duration was 3.5 years among responders versus 3.1 years in non responders (n.s.)

Table 4: Phase 2: on treatment analysis: mean change from baseline scores compared between the three eventual treatment groups

		CP Treatment only		Placebo only		Placebo + CP treatment	CP vs PL	PL vs PL+CP	CP vs PL+CP
RMI	n	Mean change	n	Mean change	n	Mean change	p value	p value	p value
12 months	14	+0.46 (-0.41-1.34)	10	+0.20 (-0.86-1.26)	9	+0.11 (-0.60-0.82)	0.675	0.879	0.472
18 months	14	+0.54 (-0.47-1.54)	9	+0.67 (-0.27-1.61)	9	0 (-0.94-0.94)	0.846	0.265	0.373
24 months	12	+1.18 (0.40-1.97)	8	+0.86 (-0.07-1.82)	8	-0.25 (-0.99-0.49)	0.574	0.043	0.008
Rankin									
12 months	14	-0.15 (-0.49-0.18)	10	-0.20(-0.65-0.25)	9	-0.33 (-0.88-0.21)	0.854	0.670	0.470
18 months	14	-0.15 (-0.49-0.18)	9	-0.44(-0.85- -0.04)	9	0 (-0.54-0.54)	0.232	0.150	0.800
24 months	12	-0.18 (-0.45-0.09)	8	-0.50(-0.95- -0.05)	8	0 (-0.63-0.63)	0.157	0.149	0.523
MRC sum									
12 months	14	+4.29 (0.93-7.64)	10	-3.70 (-8.92-1.52)	9	+3.11 (-1.19-7.42)	**0.007**	0.366	**0.018**
18 months	14	+5.71 (1.49-9.94)	9	-4.33 (-10.07-1.41)	9	+2.11 (-2.41-6.63)	**0.004**	0.342	**0.013**
24 months	12	+5.91(0.83-11.00)	8	-1.88 (-5.0-1.27)	8	0 (-5.42-5.42)	**0.02**	0.562	**0.011**
Senssum									
12 months	14	+3.69 (0.88-6.51)	10	+2.60 (-2.48-7.68)	9	-1.22 (0.93-7.64)	0.661	0.865	0.937
18 months	14	+5.623.50-7.73	9	+2.67 (-1.80-7.13)	9	-1.56 (-4.68-1.57)	0.152	0.843	0.146
24 months	12	+62.46-9.54	8	+4.00 (-2.46-10.46)	8	-3.25 (-7.74-1.24)	0.510	0.281	0.064

Legend to table 4: Mean change from baseline scores with 95% confidence interval between brackets.RMI= Rivermead mobility index (+= improvement, -= deterioration), Rankin= Modified Rankin scale(+= deterioration, -= improvement), MRC sum= MRC sum score, Senssum= sensory sum score (+= improvement, -= deterioration). P values indicate comparison between the three different groups: CP= CP treatment only= cyclophosphamide with prednisone treatment, PL= placebo, PL+CP= placebo treatment followed by CP treatment. All significant p- values indicate more improvement in the group that received CP treatment.

Discussion

In this first double blind randomized placebo controlled trial with oral cyclophosphamide and prednisone treatment for IgM MGUS polyneuropathy we could not demonstrate an effect on the Rivermead Mobility Index that we chose as primary outcome measure for disability. However, more patients in the placebo group needed cross over therapy with cyclophosphamide and prednisone as their polyneuropathy progressed. Secondly, treatment did have a beneficial effect on the secondary outcome measures after 6 months. We showed more improvement of the MRC sum score both in the intention to treat analysis (phase 1) and in the on treatment analysis (phase 2) after switch from placebo to treatment. Furthermore, the physical domain and health change score of the SF 36 quality of life scale improved more in the treatment group after 6 months. Finally, some biological effects of treatment were measured such as improvement of distal nerve conduction in the median nerve and decrease of the M protein level. There were no major adverse events.

The lack of significant effect on the primary outcome measure may be explained by the cross-over strategy. Although performed double blinded, this resulted in additional treatment of 9 placebo patients with progressive disease, who received cyclophosphamide and prednisone from 7-12 months after start of the trial. In an intention to treat analysis according to initial treatment strategy, this has probably confounded the difference of the initial treatment effect between both groups: half of patients in the placebo group, all with clinically severe disease, eventually received treatment, resulting in confounding by indication. [27] On the other hand, those patients who remained in the placebo group showed clinically milder disease, resulting in underestimation of treatment effects. We attempted to resolve this by performing on treatment analysis for phase 2 of the trial hereby analyzing the patients that only received placebo versus those that only received treatment. Probably due to the small group size this post-hoc analysis did not show a treatment effect, except for the MRC sum score.

In retrospect, the Rivermead mobility index may not have been an adequate choice for primary outcome measure. When we designed our study the Rivermead Mobility Index had just been studied and found adequate in patients with polyneuropathy because it showed a high homogeneity (Crohnbach's alpha =0.91) and a high correlation with the physical dimension of the SIP (Sickness Impact Profile) in patients with peripheral neuropathy.[28] The RMI showed sensitivity to change in a pilot study with pulsed dexamethasone for chronic idiopathic demyelinating polyneuropathy.[29] Functions listed on this scale (Appendix 2) are mostly dependent on strength of large muscle groups, and to a minor degree on distal muscle strength. Thus the Rivermead mobility index may not be able to detect improvement of fine motor skills and hand function, disturbance of balance and decreased

sensation in the legs. Especially as, in retrospect, baseline scores on this scale were already on the high end of the spectrum in our study population and large improvements with this measure could therefore not be anticipated. This notion does not necessarily imply that all patients were minimally affected by their neuropathy or that treatment did not cause improvement. It may however explain why in our population there may have been an absence of sensitivity to change on this scale.

The fact that the other disability measures did not change either may be explained similarly. The Rankin scale was originally designed for patients with stroke, and does not measure more subtle changes in patients with distal weakness and sensory symptoms. Nevertheless, the Rankin scale was more widely applied in polyneuropathy trials, because at that time it was one of the most widely validated and applied disability scales.(Appendix 1) At present the Overall Disability Severity Scale, that comprises hand function and leg function, is advised as a measure of disability for immune mediated polyneuropathies.[30] (Appendix 3)

Previously we demonstrated a beneficial effect of cyclophosphamide and prednisone in an open label study of patients with MGUS polyneuropathy. Eight out of fourteen patients showed improvement for 3 years based on quantitative neurological examination, Rankin disability scale and electrophysiological studies.[12]. Patient selection in the present study was different as in the previous open label trial we also included IgG and IgA MGUS patients. Furthermore, any unintended influence on outcome due to an open label design has been avoided in the current setting.

In the present study, dosage and length/duration of treatment are assumed to be adequate, as they were based on experience in related hematological malignancies such as immunocytoma or multiple myeloma, where maximum tumor reduction is achieved within the first 6 months of therapy[31] Comparable to our pilot study, treatment effects could be measured long after cessation of therapy, until 2 years follow-up. So far IVIG has been the only drug that showed some efficacy in IgM MGUS polyneuropathy in a double-blind randomized trial with a short term follow-up of 4 weeks. [32] Rituximab and Fludarabine have again only proven effective in open label trials with follow up duration of 1 year or more [33-36] Another open label trial reported beneficial treatment effects of combined intravenous cyclophosphamide with plasma exchange.[37]

Another important question remains which patient characteristics could influence treatment response. In this trial we could not assign a prognostic role with respect to treatment response for anti-MAG antibodies or disease duration. This may be explained by small numbers of patients.

This trial has demonstrated that it was difficult to show a beneficial effect of 6 months treatment with cyclophosphamide and prednisone using the Rivermead Mobility Index as

a primary outcome measure for disability, but that there was a beneficial effect on most secondary outcome measures for impairment in addition to biological effects on the M protein concentration and nerve conduction after 6 months and on the MRC sum score thereafter. An important lesson is that the cross over strategy that was chosen for ethical reasons may have confounded results that could have otherwise been more positive. It remains therefore to be established whether cyclophosphamide with prednisone or other strategies of immunotherapy are effective for polyneuropathy associated with IgM monoclonal gammopathy. New treatments can only be evaluated using double–blind, randomized, placebo controlled trials. Future challenges could comprise treatment strategies that combine drugs that suppress the B cell clone, scavenge antibodies or promote neuronal regeneration.

Acknowledgements

We thank Prof. M. Vermeulen and Prof. P.A. van Doorn for their advice on the design of the study. We also thank them and many other neurologists for the referral of MGUS polyneuropathy patients to our center.

Part of this work was presented at the 58th meeting of the AAN, San Diego 2006.

The authors do not report any conflicts of interest.

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Neurologic and hematologic response to fludarabine treatment in IgM MGUS polyneuropathy

J.M.F. Niermeijer[1], M. Eurelings[1], H. Lokhorst[2], H. Franssen[1], R. Fijnheer[2], J.H.J. Wokke[1] and N.C. Notermans[1]

[1] Department of Neurology and the Rudolf Magnus Institute for Neuroscience, University Medical Center Utrecht, the Netherlands
[2] Department of Hematology, University Medical Center Utrecht, the Netherlands

Neurology 2006; 67:2076-9

Abstract

We studied the efficacy of fludarabine in 16 patients with immuunoglobulin M monoclonal gammopathy of unknown significance polyneuropathy in a prospective uncontrolled trial. The modified Rankin scale improved in 5/16 patients, all of whom had a demyelinating polyneuropathy and shorter disease duration. The motor conduction velocity improved >10% in two or more nerves for four of five of these patients. Hematological response in bone marrow occurred in three of five of these patients, whereas tw of five already had small polyclonal B cell populations. There were no serious side effects.

Introduction

Sensorimotor polyneuropathy associated with IgM monoclonal gammopathy (IgM MGUS) can lead to progressive disability. Treatment is directed at decreasing the M-protein concentration, thereby lowering the causative IgM anti-neural antibody reactivity. [1] The best treatment remains unknown. [2] In IgM MGUS polyneuropathy double blind randomized trials with intravenous immunoglobulin [3;4] [5] and plasma exchange show no long term efficacy. [6] Rituximab has resulted in conflicting reports. [7;8] Fludarabine, that is aimed at elimination of the monoclonal B cell population, showed promising results in small series of patients.[9;10]
We prospectively studied in a larger group of 16 patients with progressive IgM MGUS polyneuropathy the clinical efficacy of fludarabine in an uncontrolled trial . We also analyzed the relationship between a decrease of the clonal B cell population and clinical response to treatment.

Methods

Design

Prospective uncontrolled trial.

Patients

Sixteen patients with a progressive symmetrical sensorimotor neuropathy and IgM MGUS were enrolled between January 2000 and December 2004 at the Department of Neuromuscular Diseases of the University Medical Center Utrecht (table 1).
Inclusion criteria: IgM MGUS polyneuropathy with progressive symptoms between two follow-up visits with an interval of 6 months. Progression was defined as deterioration on the Rankin scale, Rivermead mobility index (RMI),and decrease of the MRC sum score or sensory sum score [11]. Exclusion criteria were other causes for polyneuropathy or a hematological malignancy.

Treatment strategy

Fludarabine 40mg/m^2 orally for 6 cycles of 5 days per 28 days. Fludarabine is approved in the Netherlands as a standard therapy for hematological disorders such as M Waldenstrom and Non Hodgkin Lymphoma. Antibacterial (cotrimoxazole 480 mg, twice daily) and antiviral (valaciclovir 500 mg, twice daily) prophylactics up to 3 months after the final course of fludarabine. Peripheral blood count was performed every four weeks. In case of leucopenia the next treatment cycle was postponed until leukocytes were > $3.0x10^9$.

Table 1: Characteristics of 16 patients with IgM MGUS polyneuropathy

	sex	age	onset	duration	anti MAG	IgM	EMG	Rankin	walking aids
1	m	69	68	1,4	-	κ	A	3	-
2	f	58	42	16,4	-	κ	D	3	wheelchair
3	m	53	45	8,1	-	κ	D	4	wheelchair
4	m	60	55	5,2	+	κ	D	3	AFO,stick
5	f	53	44	9,2	+	κ	D	3	AFO,stick
6	f	57	43	14,3	-	κ	D	3	stick
7	m	68	59	9,5	-	κ	D	4	crutches
8	m	68	60	8,3	+	κ	D	2	-
9	m	80	75	4,7	-	λ	A	2	-
10	f	61	44	17,8	+	λ	D	3	-
11	m	74	56	18,2	+	κ	D	2	-
12	m	77	66	11,3	-	κ	A	3	stick
13	f	68	64	4,6	-	κ	D	2	stick
14	m	68	57	11,6	+	κ	D	2	AFO, stick
15	m	58	50	7,7	-	κ	D	3	-
16	f	73	65	7,8	-	κ	D	2	-

Legend: Ages, age of onset and disease duration are defined in years, m=male, f=female, duration = disease duration, IgM = light chain isotype, anti-MAG = antibodies to myelin associated glycoprotein, D = demyelinating polyneuropathy, A =axonal polyneuropathy, AFO= Ankle foot ortheses.

Clinical evaluation

At 0, 6 and 12 months muscle strength and all sensory modalities were tested as previously described, leading to a maximal MRC sum score of 140 points and a maximal sensory sum score of 56 points.[12 11] Disability was scored with the Modified Rankin scale [13] and the revised Rivermead mobility index (RMI)[14]. Quality of life was monitored with the Dutch version of the SF 36-item health survey Questionnaire. [15]

Electrophysiological studies

Detailed methods and criteria for demyelination are described elsewhere. [11]

Laboratory and bone marrow analysis

Every 6 months the M-protein isotype and M-protein level was determined with immunofixation and immunoelectrophoresis techniques described elsewhere.[11] Before treatment all patients were screened for presence of anti myelin associated glycoprotein (anti-MAG) antibodies. [11] Bone marrow biopsies and aspirates were stained with May-Grunwald-Giemsa, and with hematoxylin-eosin and Congo red for the detection of amyloid deposits. Also we did immunophenotyping with CD138 (plasma cell specific), CD19 and CD20 (B cell specific) and IgM kappa and lambda antibodies. The monoclonal B cell population was identified by a predominance of kappa or lambda with a ratio > 3:1. Kyle's definition of MGUS was used. [16]

Outcome measures

Primary outcome measure was clinical response to therapy, defined as ≥ 1 point improvement on the Modified Rankin Scale.

Secondary outcome measures were: (1) ≥ 1 point improvement on the RMI; (2) ≥ 5% (to exceed the variability of repeated testing) improvement of the MRC sum score ; (3)> 5% improvement of the sensory sum score; (4) significant change of the grouped EMG variables, and improvement of the motor conduction velocity of > 10 % in individual nerves [17;18]; (5) significant change in one of the eight domains of the SF-36 score; and (6) adverse events.

Hematological response was defined as disappearance of the monoclonal plasma cell or B cell population in bone marrow, a significant decrease in M-protein level, or both. A significant decrease of the M protein level was defined as > 50 % reduction in the M-protein level, in cases where the initial M-protein was more than 5 g/l.

Statistical analysis

The Wilcoxon matched pairs test was used to compare values of the Rankin scale, RMI, MRC sum score and sensory sum score, before and 12 months after start of treatment. Next to this, outcome measures were dichotomized into "response" or "no response" as defined before. The distribution of responders among those with and without hematological response was compared using cross tabulation with the Chi square test. P values <0.05 were considered statistically significant.

Results

All 16 patients completed the study. There were no serious adverse events during or after treatment. One patient had a facial rash, which disappeared after switching to penicillin. Three patients (1, 4, 17) had mild gastrointestinal complaints. Patient 13 had a prolonged but reversible leucopenia without infections and stopped therapy after 4 cycles with good response to therapy.

Patients and disease progression before treatment

Before fludarabine treatment, 10 of 16 patients had received a combination of cyclophosphamide and prednisone, after a mean interval of 5 years (SD ± 2.3y).
Six months before treatment the median Rankin scale was 2 (IQR [interquartile range]: 2-3). It deteriorated to 3 (IQR: 2-3) at start of treatment (p=0.034). During that period the median MRC sum score decreased from 94% (IQR: 89.5-100) to 87% (IQR: 79-96) (p=0.016) (table 2).

Table 2: Median Rankin scale, RMI, MRC sum score and sensory sum score in 16 patients with IgM MGUS polyneuropathy at 6 months before, at start and 12 months after treatment with fludarabine

	Rankin			RMI			MRC sum score			Sensory sum score		
	-6m	0m	12m	-6m	0m	12m	-6m	0m	12m	-6m	0m	12m
Median	2	3	2	13	13	13	94	87	91	68	66	71
Min	2	2	2	9	7	7	53	66	66	43	29	18
25th	2	2	2	12	10	13	90	79	80	58	52	62
75th	3	3	3	14	13	14	100	96	99	80	75	83
Max	4	4	4	14	14	14	100	100	100	93	89	89
p-values												
-6m vs 0m		0.034			0.007			0.016			0.121	
0m vs 12m		0.025			0.042			0.010			0.112	

Legend: Rankin= modified Rankin scale (1-5), RMI= Rivermead mobility index (0-15),MRC sum score and sensory sum score in percentages (%), p-values indicate the difference between two measurements in time: -6m= 6 months before start of treatment, 0 months= at start of treatment, 12 m= 12 months after start of treatment.

Primary outcome

After one year of follow-up, the median Rankin scale had improved from 3 (IQR: 2-3) to 2 (IQR: 2-3) (p=0.025). In 5 of 16 patients (31%) (patients 5, 6, 7, 10, and 15), the Rankin scale improved; in all other patients it stabilized. All five responding patients (2 with anti-MAG antibodies) had a demyelinating polyneuropathy and their median age of onset was 44 years (43.5- 54.5 years) vs 60 years (IQR 55-68years) in the nonresponders (p=0.047). Median disease duration was 9.5 years (IQR 8.45-16.05 years) in responders and 8.1 (IQR 4.7-11.6years) in nonresponders (p=0.28).

Secondary outcome

Impairment and disability

Median RMI was 13 (IQR:10-13) before and 13(IQR:13 to 14) at 12 months after treatment (p=0.04). It improved in 31% (patients 1, 5, 6, 12, and 15) and stabilized in other patients.
Median MRC sum score was 87% before (IQR: 79 to 96%) and 91% (IQR: 80 to 99%) at 12 months after treatment (p=0.01). It improved ≥ 5% in 31% (patients 4, 6, 11, 12, and 16) after treatment. The median sensory sum score was 66% (IQR: 52 to 75%) before and 71% (IQR: 62 to 83%) after treatment (n.s.). It improved ≥ 5% in 56% (patients 2, 5, 6, 8, 10, 11, 12, 13, and 16) after treatment.

Hematological response and clinical association

At 1 year follow-up 15 of 16 patients agreed to have a bone marrow biopsy. There was a hematological response in 53% according to our definition (table 3). Median B cell infiltration declined from 15% (IQR: 2.75 to 20%) before to 3% (IQR: 1 to 5%) after treatment (p=0.005). The monoclonal B cell population disappeared in 7 of 10 patients.
A ≥ 50% decrease of the IgM M protein concentration ≥ 5g/L was measured in 31% patients. Median IgM concentration declined from 12 g/l (IQR: 4 to 16.7) to 5.9 g/l (IQR:2.63 to 9.33) after treatment (p=0.002). Median total M protein concentration declined from 5.5 g/l (IQR: 0.01 to 11.75) to 0.01g/l (= below level of detection) (IQR: 0.01 to 6.5) after treatment (p=0.02). We could not establish a clear relationship between clonal response and clinical response in this small series. Of the eight patients with a hematological response, three showed a clinical response on the primary outcome measure. Two patients who responded clinically had small polyclonal B cell clones (table 3).

Electrophysiological investigations (EMG)

The median values of EMG variables did not change significantly after treatment in the whole group. However, analysis of changes per patient indicated that in 11 of 14 patients, the MCV increased > 10 % in one or more nerves and in 6 of 14 patients in two or more nerves. Of the five patients with clinical response on the Rankin scale, four showed improvement of >10% of the MCV in 2 or more nerves.

Quality of life

The SF-36 questionnaire showed improvement of the median score for health change in the past year from 25 (0 to 50) to 50 (25 to 75) (p=0.059) suggesting subjective improvement after treatment. Median scores of physical, mental and general health and vitality increased marginally, social function and pain score decreased, but none statistically significant. Physical and mental role remained stable (data not shown).

Table 3: Hematological response of B cell clone in bone marrow and IgM and total M protein concentration in 16 patients with IgM MGUS polyneuropathy

Patient	%B cells		clonality		IgM g/L		M protein g/L		Hematological response
	before	after	before	after	before	after	before	after	
1	15%	0%	mono	poly	13.4	9	9	5	+
2	20%	5%	mono	mono	12	5.9	11	4	+
3	19%*	1%	mono	poly	23	14	20	8	+
4	1%	10%	poly	mono	6.4	3.7	<1	<1	-
5	20%	5%	mono	poly	16.7	5.9	<1	<1	+
6	6%	1%	mono	poly	5.6	2.4	<1	<1	+
7	2%	1%	poly	poly	4	3.3	3	<1	-
8	20%	5%	mono	poly	21.6	7	12	5	+
9	20%	3%	mono	mono	-	45.6	27	28	-
10	20%	4%*	mono	poly	12.3	5.5	8	<1	+
11	25%	3%	mono	poly	21.1	9.4	16	7	+
12	15%	15%	mono	mono	13.1	14.8	8	9	-
13	5%	5%	poly	poly	3.9	1.7	<1	<1	-
14	7%*	2%	poly	poly	7.7	7.1	<1	<1	-
15	2%	1%	poly	poly	3.7	2.1	<1	<1	-
16	1%	-	poly	-	1.8	1.7	<1	<1	-

Legend: % B cells= % B cells in bone marrow, mono=monoclonal B cell population, poly=polyclonal B cell population, IgM= concentration in plasma, M-protein= total M-protein concentration in plasma, *= result from bone marrow aspirate, <1= below threshold.

Discussion

Our study demonstrates that at one year of follow-up oral treatment with fludarabine may induce stabilization and improvement in patients with progressive IgM MGUS polyneuropathy. Furthermore it was safe, and showed no serious side effects.

Because untreated IgM MGUS polyneuropathy , runs a progressive course and spontaneous improvement has not been documented [19], we suggest a therapeutic effect of fludarabine.

We have chosen the modified Rankin scale as a primary outcome measure because it is an appropriate measure of handicap according to our experience and that of others.[11 2 20]

The five patients who showed clinical response on the Rankin scale had a demyelinating polyneuropathy, and a younger age of onset compared to the non-responders.

In four of these five patients the EMG showed improvement of the MCV>10% in two or more nerves. In one patient with very long disease duration of nearly 18 years, the MCV did not improve.

Patients who did not show clinical response had been older at onset. Three had an axonal polyneuropathy, which could explain the absence of clinical response or improvement of motor nerve conduction velocity, because axonal repair in the elderly is usually disappointing.

We noticed a clinical response in five patients (31%) and a hematological response in eight patients (53%), three showed both. We found no relationship between clinical and hematological response. This could be explained by the fact that in two clinical responders the B cell clone was already small and could not further decrease.

In conclusion, our results suggest that treatment with fludarabine, aimed at lowering the B cell clone, may result in improvement in a proportion of patients with progressive IgM MGUS polyneuropathy. However, it is necessary to obtain more robust evidence from double blind randomized trials. It is also worthwhile to further explore the characteristics of those patients who will respond to treatment.

This work was presented in part at the Annual Meeting of the European Neurological Society in Barcelona, Spain, July 2004.

Acknowledgements: The authors would kindly like to thank Dr. M.W. van der Linden who has advised on the methodological section.

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Rituximab for polyneuropathy with IgM monoclonal gammopathy

J.M.F. Niermeijer[1], M. Eurelings[1], H.L. Lokhorst[2], W.-L. van der Pol[1], H. Franssen[1], J.H.J. Wokke[1], N.C. Notermans[1]

[1] Department of Neurology and the Rudolf Magnus Institute for Neuroscience, University Medical Center Utrecht, the Netherlands
[2] Department of Hematology, University Medical Center Utrecht, the Netherlands

Journal of Neurology, Neurosurgery and Psychiatry 2009;80:1036-39

Abstract

Background

Polyneuropathy with IgM monoclonal gammopathy can be a disabling disorder necessitating treatment.

Methods

In a prospective open label trial 17 patients with disabling IgM MGUS polyneuropathy were treated with rituximab, a chimeric anti CD-20 monoclonal antibody.

Results

Rituximab induced an improvement of ≥ 1 point on the Overall Disability Sum Score in 2/17 patients, an improvement of ≥ 5% of the distal MRC sum score in 4/17 and the sensory sum score in 9/17 patients. Bone marrow investigations showed CD 20 B cell depletion in all patients. There were no serious adverse events. Compared to treatment with intermittent cyclophosphamide with prednisone or treatment with fludarabine, it shows a comparable response percentages but less side effects. Presence of anti-MAG and a disease duration shorter than 10 years may predict treatment response

Conclusion

Rituximab is a candidate for treatment of IgM MGUS polyneuropathy and should be further investigated in a double blind randomized trial.

Introduction

Polyneuropathy associated with IgM monoclonal gammopathy (IgM MGUS) is a disabling immune mediated neuropathy. Evidence based effective treatment strategies are still lacking.[1]

Rituximab is a chimeric monoclonal antibody directed at the CD 20 surface antigen found on most normal and neoplastic B cells. It is efficacious for the treatment of some haematological malignancies [2] and inflammatory diseases [3] including a number of neurological disorders such as multiple sclerosis.[4] Open label trials and preliminary results of a placebo-controlled trial suggest that it may be of value for the treatment of IgM MGUS polyneuropathy.[5-8]

In this prospective open label trial we studied if rituximab safely induces improvement of disability scores, muscle strength and sensory function, and depletion of CD20-positive B cells in bone marrow in IgM MGUS polyneuropathy.

Methods

A prospective open label trial was performed in a tertiary referral center for polyneuropathy.

The study was approved by the local medical ethics committee and written informed consent was given by all participants.

Seventeen patients (3 female, 6 anti MAG antibodies) with disabling or progressive symmetric sensorimotor polyneuropathy associated with IgM monoclonal gammopathy were included . Progression was defined as ≥ 1 point deterioration on Modified Rankin scale (MRS) (Appendix1) or Overall disability sum score (ODSS)[9] (Appendix 3), or ≥ 5% deterioration of the distal MRC sum score (Appendix 4) or sensory sum score (Appendix 5) in 6 months. Disabling was defined as ≥ 2 points on the MRS.

Median age of onset was 55 years (Interquartile Range (IQR): 50-60y) and median disease duration 7 years (IQR:4-12y).

Five patients had been previously treated for their polyneuropathy: patients 3, 10, 13, 16, and 17 with intermittent cyclophosphamide and prednisone, and patients 16 and 17 with fludarabine. As previous treatment had resulted in stabilization or improvement, and was given more than 4 years previous to rituximab treatment, they were considered as candidates for this trial.

Treatment consisted of intravenous rituximab 375 mg/m² once weekly for 4 weeks and the median follow up was 12 months (IQR 12-26m).

Nerve conduction studies were performed before and 9 months after treatment as described elsewhere [10]. Polyneuropathies were classified as demyelinating if features of demyelination were found in at least 2 nerve segments and as axonal if otherwise [11].

Bone marrow biopsies and aspirates were stained with May-Grunwald-Giemsa, and with hematoxylin-eosin and Congo red for the detection of amyloid deposits, and immunophenotyping with CD138 (plasma cell specific), CD19 and CD20 (B cell specific) and IgM kappa and lambda surface antibodies was performed. The monoclonal B cell population was identified by a predominance of kappa or lambda with a ratio > 3:1. Kyle's definition of MGUS was used. [12]

Outcome measures

The primary outcome measure was ≥ 1 point improvement of the ODSS. (Appendix 3) The secondary outcome measures were: (1) ≥ 1 point improvement of the Modified Rankin Scale (MRS, (2) ≥ 5% improvement of the distal MRC sum score (a composite score of 8 distal muscle groups in arms and legs calculated into a percentage of the maximum score of 80 points) or (3) ≥ 5% improvement of the sensory sum score (a composite score of touch, pinprick, vibration and position sense, calculated into a percentage of the maximum score of 56 points) [10], (4) disappearance of CD 20 positive B cells in bone marrow biopsy or ≥ 50% decrease of M protein concentration (hematological response), (5) ≥10% improvement of conduction velocity (NCV), (6) adverse events.

Statistical analysis

Outcome measures of first and last visit were compared by the Wilcoxon matched pairs test. Pooled data analysis for characteristics associated with treatment response was performed by Mann Whitney U test and Chi square test . P < 0.05 was considered statistically significant.

Results

There were no adverse events, except for 1 patient with transient facial erythema.

Primary outcome: The ODSS improved in 2/17, remained unchanged in 14/17 and deteriorated in 1/17 patients .

The median ODSS changed from 4 (IQR= 2.5-5) to 3 (IQR= 2-5.5). (ns) (Table 1)

Secondary outcome: The MRS improved in 5/17 patients. The grouped median MRS changed from 2 (2-3) to 2 (1.5-2.5) (p=0.025). The distal MRC sum score improved ≥ 5% in 4/17 patients, and improved <5% in 11/17 . The grouped median distal MRC sum score increased from 90 % to 93% after treatment (p= 0.006). The sensory sum score improved ≥ 5% in 9/17 and deteriorated in 4/17 patients. The grouped median sensory sum score of the legs improved from 57% to 71% after treatment (p=0.03). The median IgM concentration decreased from 6,31 g/l (3,67-9,85) before to 3,91g/l (2,87-7,42) after treatment (p<0,001). (Table 1)

Bone marrow investigations in 17 patients did not show haematological malignancy. After treatment 10/13 evaluated bone marrow samples showed complete disappearance of CD 20+ B cells, and 3/13 a significant decrease. The median CD20+ B cell percentage decreased from 5% (2-6) before to 0% (0-0,5%) after treatment (p=0,002) (Table 1) In all cases disappearance of CD 20+ B cells coincided with a decrease in CD19+ B cells. In one patient (5) the B cell population was further specified before and after rituximab treatment showing elimination of the CD20+sIgM+B cells leaving predominantly pre- and pro B cells.

Nerve conduction studies showed ≥10% improvement of NCV in 4/17 patients (1, 5, 12, and 14) in 2 or more nerves and in 2/17 patients (6, 7) in 1 nerve (data not shown).

Comparison to data from previous trials performed in our center:

Response to rituximab treatment was compared with response to double blind cyclophosphamide with prednisone (CP) (n=25) [10] and open label fludarabine (n=16) [13]treatment in other IgM MGUS polyneuropathy patients. All three treatment strategies resulted in an equal percentage of responders: response on the MRS was 31% after fludarabine, 29% after rituximab and 36 % after CP. Response on the MRC sum score was 31 % after fludarabine, 24 % after rituximab and 32 % after CP, on the sensory sum score 56 % after fludarabine, 53% after rituximab and 20 % after CP. Response of NCV was 43 % after fludarabine and rituximab, 60% after CP. Intermittent CP and fludarabine treatment both resulted in a higher frequency (56% after CP and 25 % after fludarabine) and severity of side effects compared to rituximab (6%). After analysis of pooled data, specific patient characteristics associated with treatment response could not be identified. Age at onset, disease duration, number of MAG positive patients, number of patients with a demyelinating EMG were equal between responders and non-responders. (data not shown) .

Table 1: Outcome after treatment with rituximab in 17 IgM MGUS polyneuropathy patients

patient nr	sex	MAG	EMG	onset (y)	duration (y)	FU (m)	ODSS (0-10) first	ODSS (0-10) change	Rankin (0-5) first	Rankin (0-5) change	MRCsum distal (%) first	MRCsum distal (%) change	Sensory sum (%) first	Sensory sum (%) change	NCV response	CD 20% before	CD 20% after	M protein g/l before	M protein g/l after	IgM g/l before	IgM g/l after
1	f	neg	D	52	4	12	4 (2/2)	**-1**	2	0	100	-1	57	**18**	**yes**	2	0	<0.5	<0.5	3.95	2.49
2	m	pos	D	61	12	18	5(3/2)	0	3	**-1**	89	**5**	75	**14**	no	5	0	5	3	10.7	7.19
3	m	neg	D	46	7	12	3 (1/2)	0	2	0	89	**7**	71	**11**	no	1	<1	<0.5	<0.5	3.12	3.07
4	m	pos	D	49	3	24	3 (1/2)	0	2	0	58	**22**	61	**23**	no	6	0	6	4	9.96	8.84
5	m	neg	A	66	4	24	5 (2/3)	**-3**	2	**-1**	99	0	89	-5	**yes**	10	x	7	<0.5	9.52	5.82
6	m	neg	D	64	5	12	2 (0/2)	0	2	**-1**	99	**1**	82	**11**	**yes**	2	0	<0.5	<0.5	3.85	1.91
7	m	neg	D	55	4	12	3 (1/2)	0	2	**-1**	90	**1**	63	**2**	**yes**	5	<1	<0.5	<0.5	5.22	3.28
8	m	neg	D	54	2	30	2 (1/1)	0	2	**-1**	96	**2**	68	**14**	no	5	x	<0.5	5	1.38	1.03
9	f	neg	D	53	6	12	2 (1/1)	0	2	0	99	**1**	88	**13**	no	6	x	8	<0.5	7.18	3.61
10#	m	neg	D	50	14	24	3 (1/2)	0	2	0	90	0	86	0	no	5	0	9	5	14.7	9.22
11	m	pos	D	67	2	21	5 (2/3)	1	2	0	84	**1**	46	**20**	no	2	0	<0.5	<0.5	12.1	10.2
12	m	neg	D	52	6	12	5 (3/2)	0	3	0	83	**2**	13	**16**	**yes**	x	x	<0,5	<0,5		
13	m	neg	D	46	4	12	5 (2/3)	0	2	0	66	**11**	50	-20	no	4	0	<0.5	<0.5	2.86	2.8
14	m	pos	D	56	2	12	2(1/1)	0	2	0	95	**2**	89	-13	**yes**	10	<1	<0.5	<0.5	5.44	4.21
15 #	m	neg	D	59	12	12	6(3/3)	0	3	0	93	0	66	0	no	1	0	<0.5	<0.5	3.61	3.18
16 #	f	pos	D	44	14	14	6(3/3)	0	3	0	38	-1	71	-18	no	x	0	<0.5	<0.5	8.57	7.5
17 #	m	pos	D	55	11	12	7(3/4)	0	3	0	90	0	32	0	no	30	9	<0.5	<0.5	7.25	7.05
Wilcoxon test								**ns**		**p=0.025**		**p=0.006**		**p=0.03**			**p=0.002**				**p<0.001**

Legend to table 1:
m=male, f=female, light chain = M-protein light chain, k= kappa, l= lambda, MAG= anti- MAG (myelin associated glycoprotein) antibodies, neg = negative, pos=positive, NCS = nerve conduction studies, D = demyelinating, A = axonal, onset= age at disease onset defined as date of first complaints, duration = disease duration at start study, ODSS = Overall Disability Sum Score presented as total score with separate score for arms and legs between brackets, first = score at baseline, change = change of score in comparison with first score, ODSS: - = improvement), Rankin = modified Rankin scale (- = improvement), MRC sum distal = distal summed MRC score of 4 arm and 4 leg muscle groups (0-80 points) presented as % of the maximum score of 80, sensory sum score (0-56 points) presented as % of the maximum score of 56, NCS response = nerve conduction velocity improved >10% in 1 or more nerves, **bold**= improvement of score, **#** =no improvement in this patient after treatment, CD 20 = percentage CD 20 positive B cells, M protein (g/L) total = total M protein concentration (g/l), IgM= concentration IgM in g/l, x =not done.

Discussion

Improvement of the ODSS occurred in 2/17 patients with polyneuropathy associated with IgM monoclonal gammopathy after treatment with rituximab. However, in 11/17 patients the MRC sum score improved and in 10/17 the sensory sum score improved

This may suggest that improvement in strength or sensory function does not coincide with reduced disability, or that the disability scores we used lack sensitivity. Because the trial was unblinded, the observed improvement of exam scores could be caused by a placebo effect, however, spontaneous improvement has not been observed in IgM MGUS polyneuropathy.

The lack of treatment response may be explained by the long disease duration of more than 10 years in some patients (10,15,17) . This suggests that early treatment, at the moment when axonal degeneration supposedly is not yet a prominent feature, increases chances of treatment response. This concept is supported by the finding that improvement of nerve conduction velocity occurred primarily in patients with shorter disease duration, suggesting that nerve dysfunction is partly reversible early in the disease course.

Three-out-of-six patients with anti-MAG IgM showed clear improvement, indicating that anti-MAG antibodies may predict treatment response. However the small numbers preclude sound statistical analysis.

Deterioration of scores in some patients in this study was not treatment related, as reported by others[14;15], but, in our opinion, reflects the ongoing deterioration of the polyneuropathy itself.

Elimination of CD 20 + B cells occurred in all patients, and was paralleled by decreased M protein concentrations. Knowledge emerges that rituximab may be effective through a set of different hematological and immunological mechanisms. Next to depletion of CD 20+ B cells to lower the level of circulating auto-antibodies, rituximab may also lower CD 20 negative plasma cells that produce auto-antibodies, through suppression of memory-B-cells. It may also directly inhibit binding of auto-antibodies to the neural antigen by scavenging the circulating anti-neural antibodies, which may explain early treatment effects [3].

There is debate about what dosage of rituximab is most effective for polyneuropathy associated with IgM monoclonal gammopathy. [7] Considering the level of suppression of the CD 20 and CD 19 B cell clones in the investigated bone marrow biopsies, and the decline in IgM concentrations, the dosage that was used in this study is presumed to be adequate.

Analysis of pooled data of this trial with those from previous trials examining the effects of intermittent cyclophosphamide combined with prednisone [10] and fludarabine[13] found no difference in treatment effects, nor identification of predictive factors for good clinical treatment response. Importantly, rituximab treatment was safe and caused less side effects than fludarabine and cyclophosphamide with prednisone.

In this open label trial individual patients experienced benefit by reduction of disability scores and more than half showed improved neurological examination after rituximab treatment that was well tolerated. Presence of anti-MAG and a disease duration shorter than 10 years may predict treatment response. Our data suggest that efficacy of rituximab for polyneuropathy associated with IgM monoclonal gammopathy should be further investigated in a double-blind randomized trial.

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Electrophysiology in polyneuropathy associated with IgM monoclonal gammopathy: correlation with clinical severity and response to treatment

J.M.F. Niermeijer[1], N.C. Notermans[1], L.L. Teunissen[2], J.H.J. Wokke[1], H. Franssen[1]

[1] Department of Neurology and Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands
[2] Department of Neurology of the St Antonius Hospital, Mesos Medical Center, Nieuwegein, the Netherlands

submitted

Abstract

Background

Polyneuropathy associated with IgM monoclonal gammopathy (IgM neuropathy) is characterized by demyelination and axon loss which are more prominent in longer nerves and by demyelination which is more prominent distally, suggesting a unique length dependent process. Since IgM neuropathy may lead to substantial disability, treatment with different types of immunotherapy was tried. Because patient selection based on predictors of treatment response seems worthwhile, we aimed to identify electrophysiological features which determine a clinical response to immunotherapy.

Methods

Fifty-one patients with IgM neuropathy treated with either cyclophosphamide with prednisone (n=26), fludarabine (n=14), or rituximab (n=12) were investigated. Standardized nerve conduction studies (NCS) after warming were performed. Axonal degeneration and demyelination were scored per nerve and patient. Treatment response was defined as improvement of the modified Rankin scale, or MRC sum score, or sensory sum score.

Results

Median age of onset was 55 years and median disease duration 4.4 years. A Rankin scale response was found in 31%, a distal MRC response in 33% and a sensory response in 75% of patients. Patients with a distal MRC sum score < 93% had more severe demyelination and more nerves with axon loss. NCS classified as demyelinating (35 patients) were associated with a distal MRC response in 41% of patients and NCS classified as axonal (16 patients) with a distal MRC response in 8% of patients (p=0.04). The percentages of: demyelinated segments, demyelinated nerves, and nerves with axon loss per patient were all higher in patients with a distal MRC response. In patients with a Rankin scale response or a sensory response there was no difference in scores for demyelination or axon loss. Length dependence was present in 15 out of 29 patients with demyelinating NCS and in 1 out of 9 patients with axonal NCS (p=0.004).

Conclusion

Our study showed that patients with IgM neuropathy and pronounced motor NCS abnormalities are more likely to improve on immunotherapy than patients with less pronounced abnormalities. In the future, this finding may be used to select patients for treatment.

Introduction

Polyneuropathy associated with IgM monoclonal gammopathy (IgM neuropathy) is an acquired immune-mediated neuropathy with progressive distal sensory disturbances, ataxic features and weakness. IgM neuropathy has features of both demyelination and axon loss [1]. Demyelination and axon loss are more prominent in longer nerves and demyelination is more prominent distally; previous studies suggested that these features reflect a unique length dependent process [2;3].

Because IgM neuropathy may lead to substantial disability, treatment with different types of immunotherapy was tried [4-7] Debate remains about the best treatment regimen since only a proportion of patients improved.[4-7] Although patient selection based on predictors of treatment response, seems worthwhile, it is unknown which characteristics are associated with response to treatment.

Our aim is to identify electrophysiological features which determine a clinical response to immunotherapy in IgM neuropathy. From nerve conduction studies, performed before treatment, the differences between responders and non-responders were determined, with special attention for the amount of demyelination and axon loss.

Methods

Patients

Between 1990 and 2007, 51 patients with IgM neuropathy were included for treatment. The patients had to have a slowly progressive symmetrical sensorimotor polyneuropathy, no hematological malignancy [6] and a monoclonal IgM M protein. The patients received immunotherapy because of progressive or disabling symptoms. [5-7] Immunotherapy either consisted of 6 four-weekly cycles of oral cyclophosphamide with prednisone (n= 27 (53%), six four-weekly cycles of oral fludarabine (n=12 (23.5%), or 4 weekly cycles of rituximab (375 mg per m^2) in 12 patients (23.5%).[5-7] Prior to medication all patients underwent standardized nerve conduction studies. All patients were seen and investigated at the outpatient department of the Neuromuscular department of the University Medical Center Utrecht, a tertiary referral center for polyneuropathy in the Netherlands.

Nerve conduction studies

Nerve conduction studies (NCS) that were performed prior to the start of the first cycle of immnunotherapy were analyzed. NCS were performed by the same investigator (H.F.) according to a standardized protocol. Before the investigation, the forearm, upper arm,

and lower leg were continuously warmed for at least 30 minutes in water kept at 37°C by a thermostat valve coupled to an electronic water thermometer; thereafter they were kept at 37°C by infrared heaters [8].

Motor conduction was studied in the median (stimulation: wrist, elbow, axilla; recording: m. abductor pollicis brevis and m. flexor carpi radialis), ulnar (stimulation: wrist, 5 cm below the elbow, 5 cm above the elbow, axilla; recording: m abductor digiti V), peroneal (stimulation: ankle, 5 cm below the fibular head, popliteal fossa; recording: m. extensor digitorum brevis and m. tibialis anterior) and tibial (stimulation: ankle and popliteal fossa; recording: m. abductor hallucis) nerves. F-waves were recorded after 20 distal stimuli to nerves with a distal CMAP amplitude above 0.5 mV. Responses were only scored if supramaximal stimulation was possible (at least 20% above the strength yielding the maximum compound action potential (CMAP). Measurements were taken from the negative CMAP part. We analyzed: distal CMAP amplitude, distal CMAP duration, distal motor latency (DML), terminal latency index (TLI), segmental motor conduction verlocity (MCV), segmental duration prolongation (proximal CMAP value - distal CMAP value) x 100% / (distal CMAP value), segmental area and amplitude reduction (distal CMAP value - proximal CMAP value) x 100% / distal CMAP value) and shortest F-M interval. For polyphasic waveforms, duration was measured to the last baseline crossing. Sensory conduction in the median, ulnar, radial and sural nerves was performed to establish the diagnosis of polyneuropathy but was not analyzed.

Demyelination and axon loss

Demyelination was assessed in the following nerve segments: median nerve to m. abductor pollicis brevis (distal, forearm and upper arm), ulnar nerve (distal, forearm, elbow and upper arm), median nerve to m. flexor carpi radialis (distal and upper arm), peroneal nerve (distal, lower leg, fibular head), peroneal nerve to m. tibialis anterior (fibular head), tibial nerve (distal and lower leg). Distal refers to the segment between the most distal stimulation site and the muscle from which the CMAP was recorded.

Demyelination was defined as: DML, MCV, F-M interval or segmental duration prolongation fulfilling criteria for demyelination established at 37°C [9], segmental CMAP amplitude reduction in an arm nerve exceeding 30% (possible block) [10], and segmental CMAP area reduction in any nerve exceeding 50% (definite block)[11]; decreased TLI was regarded as distal demyelination. Criteria for decreased TLI were for the median nerve (recording m. abductor pollicis brevis) <0.27, median nerve (recording m. flexor carpi radialis) <0.31, ulnar nerve <0.29, peroneal nerve (recording m. extensor digitorum brevis) < 0.34, and tibial nerve <0.48. [3] Axon loss in a nerve was defined as distal CMAP amplitude < 1 mV, or signs of denervation or reinnervation on concentric needle EMG.

We scored: percentage of demyelinated segments per nerve, percentage of demyelinated segments per patient, percentage of demyelinated nerves per patient, and percentage of nerves with axon loss per patient. Per patient the polyneuropathy was scored as demyelinating (at least two nerves had features of demyelination) or axonal (at least two nerves had features of axon loss and none of the nerves had features of demyelination).

Treatment response

The following treatment responses were defined: (1) Rankin Scale response: improvement ≥1 points on the modified Rankin scale[12] (Appendix 1), (2) distal MRC response: improvement of ≥ 5% (≥ 4/80 points) in the distal MRC sum score (the distal MRC score was taken from eight distal muscle groups in arms and legs on both sides, maximum = 80 points = 100%) (Appendix 4), and (3) sensory response: improvement of ≥ 5 % (≥ 3/56 points) in the sensory sum score.[5-7]

Length-dependence

We assessed length-dependence by comparing the DML and distal CMAP amplitude in nerves with short axons (median to the m. flexor carpi radialis), medium-length axons (median to the m. abductor pollicis brevis) and long axons (tibial). DMLs and amplitudes in each patient were normalized with respect to their median in a normal control population by determining (index value*100%) / (normal median value). [3]

Per patient, the polyneuropathy was scored as length-dependent if: short nerve DML < medium-length nerve DML, and if: short nerve CMAP > medium-length nerve CMAP > long nerve CMAP. Each difference had to be at least 10%.

Statistical analysis

Chi square tests were used to compare the number of features of demyelination and axon loss between responders and non responders. Mann-Whitney U-tests were used to compare scores for demyelination, scores for axon loss, and median values of NCS between responders and non responders. P values < 0.05 were considered statistically significant. SPSS version 15.0 was used for data processing and analysis.

Results

Patient characteristics

The median disease duration at the moment of the NCS was 4.3 years (2.3-7.9), the median age of onset was 56 years (50-65), median IgM concentration was 5.0 g/l (3.3-10.3). Twenty-nine patients (57%) had anti-MAG antibodies.

A Rankin scale response was found in 31%, a distal MRC response in 33% and a sensory response in 75% of patients. In patients with a distal MRC response, the median distal MRC sum score at baseline was 62% (53-73); in patients without distal MRC response, it was 78% (72-80) (p=0.0001). The median baseline scores of the modified Rankin scale and the sensory sum score were not different at baseline between responders and non-responders on any of these outcome scales.

Electrophysiology at baseline (before treatment)

Patients with a modified Rankin Scale of >2 had more often demyelination in the ulnar nerve (47% versus 21%, p=0.05) and signs of axonal degeneration in the first interosseus muscle (38% versus 6%, p=0.01).

Patients with a distal MRC sum score < 93% had more segments with demyelination, more nerves with demyelination, more nerves with axon loss, a longer DML of the median nerve to the m. flexor carpi radialis (median 3.8 ms versus 2.7 ms, p=0.001), and a longer DML of the ulnar nerve (median 5.0 ms versus 3.5 ms, p=0.002) than patients with a distal MRC sum score > 93% (Table 1).

Patients with a sensory sum score of more than 70% at baseline and patients with a sensory sum score of less than 70 % did not differ with respect to electrophysiological features.

Axon loss was associated with a longer disease duration: the median number of nerves with axon loss was 3 (IQR1-3) in patients with a disease duration of ≥ 7 years versus 2 (IQR 0-2) in patients with a shorter disease duration (p=0.02).

NCS were classified as demyelinating in 35 patients and as axonal in 16 patients. Patients with demyelinating NCS had more often axon loss in the tibial nerve than patients with axonal NCS (79% versus 43%, p=0.01).

Table 1: Demyelination and axon loss in relation to distal MRC score at baseline

No. of segments with demyelination / total no. of segments	Distal MRC < 93%	Distal MRC ≥ 93%	p value
Median nerve, m APB	25/29 (86%)	12/22 (55%)	0.01
Wrist	24/29 (83%)	12/22 (55%)	0.03
Forearm	16/29 (55%)	2/22 (9%)	0.001
upper arm	12/25 (48%)	1/21 (5%)	0.001
Median nerve, m FCR	13/23 (57%)	1/17 (6%)	0.001
Forearm	13/23 (57%)	1/17 (6%)	0.001
Ulnar nerve, m ADV	23/29 (79%)	13/22 (59%)	n.s.
Wrist	18/29 (62%)	7/22 (32%)	0.03
Forearm	13/29 (45%)	3/22 (14%)	0.02
Elbow	19/26 (73%)	11/22 (50%)	n.s.
upper arm	9/26 (34%)	3/21 (14%)	n.s.
Peroneal nerve, m EDB	8/9 (89%)	9/16 (56%)	n.s.
ankle	5/9 (56%)	9/16 (56%)	n.s.
lower leg	7/9(78%)	5/16 (31%)	0.03
Peroneal nerve, m TA	22/23 (96%)	16/17 (94%)	n.s.
lower leg	22/23 (96%)	16/17 (94%)	n.s.
Tibial nerve, m AH	11/13 (85%)	8/18 (44%)	0.02
Ankle	10/13 (77%)	8/18 (44%)	n.s.
lower leg	7/13 (54%)	2/18 (11%)	0.01
No. of nerves with axon loss / total no. of nerves			
Median nerve, m APB	1/29 (3%)	0/22 (0%)	n.s.
Median nerve, m FCR	0	0	n.s.
Ulnar nerve, m ADV	6/23 (26%)	1/21 (5%)	0.05
Peroneal nerve, m EDB	26/29 (90%)	10/22 (46%0	0.001
Peroneal nerve, m TA	14/21 (67%)	2/17 (12%)	0.001
Tibial nerve, m AH	25/28 (89%)	8/20 (40%)	<0.001

Distal MRC= distal MRC sum score, m APB = abductor pollicis brevis muscle. m FCR = flexor carpi radialis muscle. m ADV = abductor digiti quinti muscle. m EDB = extensor digitorum brevis muscle. m TA= tibialis anterior muscle. m AH= abductor hallucis muscle.

Electrophysiology and treatment response

Of the seventeen patients with a distal MRC response, 16 had demyelinating NCS and one an axonal NCS. Demyelinating NCS were associated with a distal MRC response in 41% and axonal NCS with a distal MRC response in 8% of patients (p=0.04).
In patients with a distal MRC response, NCS variables were slower (Table 2).

Table 2: NCS values in IgM MGUS Polyneuropathy patients with and without distal MRC response after treatment

	Distal MRC Response (17)		No distal MRC response (34)		
	Median	**IQR**	**Median**	**IQR**	**p**
Median Nerve, m APB					
MCV forearm	39	19.5-42	47.5	39.5-52.3	0.003
MCV upper arm	42	27-49	50.5	44.8-57.3	0.009
Duration CMAP elbow	9.6	8.8-12.5	7.8	6.6-9.0	0.004
Duration CMAP shoulder	10	9.7-13.4	8	7.1-9.7	0.002
Median Nerve, m FCR					
DML	4.35	3-6	2.85	2.58-3.40	0.005
MCV	44	27-52	58	49-65	0.008
Tibial Nerve, m AH					
MCV	24	19-30	37.5	30-42	0.02

Distal MRC response= ≥ 5% improvement of distal MRC sum score after treatment, IQR= interquartile range. DML= distal motor latency (m/s). MCV= motor conduction velocity (m/s). CMAP = compound muscle action potential (mV), m APB = abductor pollicis brevis muscle. m FCR= flexor carpi radialis muscle. m AH= abductor hallucis muscle. Only statistically significant results are shown.

The percentage of demyelinated segments per nerve, the percentage of demyelinated segments per patient, the percentage of demyelinated nerves per patient, and the percentage of nerves with axon loss per patient were higher in patients with than in patients without a distal MRC response (Table 3). The median disease duration did not differ significantly between responders and non-responders.
In patients with an Rankin scale response or a sensory response, the NCS variables, demyelination scores, and axonal degeneration score were not different from those in patients without Rankin scale response or sensory response.

Table 3: Demyelination and axon loss in patients with and without distal MRC response

	distal MRC response (17)		no distal MRC response (34)		
% demyelinated segments per nerve	**median**	**IQR**	**median**	**IQR**	**P value**
Median, m APB	67	33-100	33	0-38	0.007
Median, m FCR	100	0-100	0	0-0	0.005
Ulnar, m ADV	63	25-100	25	0-50	0.02
Peroneal, m EDB	100	50-100	50	0-100	0.05
Peroneal, m TA	100	100-100	100	100-100	n.s.
Tibial, m AH	50	50-100	0	0-50	0.009
% demyelinated segments per patient	46	27-61	27	8-40	0.006
% demyelinated nerves per patient	100	66-100	75	31-100	0.02
% nerves with axon loss per patient	50	33-67	33	0-50	<0.001

m APB = abductor pollicis brevis muscle, m FCR = flexor carpi radialis muscle, m ADV = abductor digiti quinti muscle, m EDB = extensor digitorum brevis muscle. m TA = tibialis anterior muscle. m AH = abductor hallucis muscle. Distal MRC response = at least 5% improvement of the distal MRC sum score. IQR= interquartile range. Only statistically significant results are shown.

Length dependence

Length dependence could be calculated in 38 patients (Table 4). According to our criteria, it was present in 15 out of 29 patients with demyelinating NCS and in 1 out of 9 patients with axonal NCS (p=0.004). Fifty-five percent of MAG positive patients had length dependence and 28% of MAG negative patients had length dependence (p=0.09). The presence of length dependence was not significantly associated with any treatment response. However, the normalized values showed that patients with distal MRC response had more demyelination in short nerves and more axon loss in long nerves (Table 4).

Table 4: Length dependence in 51 IgM MGUSP patients

	Distal MRC response (n=17)		No distal MRC response (n=34)		
Normalized DML	**median**	**IQR**	**median**	**IQR**	**p**
Short nerve	198	(135-274)	130	(117-155)	0.0054
Medium-length nerve	233	(171-307)	189	(126-283)	0.1288
Long nerve	213	(174-245)	141	(111-252)	0.1169
Normalized CMAP amplitude					
Short nerve	84	(68-99)	80	(64-110)	0.8115
Medium-length nerve	50	(31-78)	66	(52-83)	0.1313
Long nerve	0	(0-6)	6	(0-32)	0.0390

Distal MRC response = at least 5% improvement of the distal MRC sum score. Normalized values were calculated as (measured value / normal median value) * 100%. Short nerve = median nerve to m flexor carpi radialis. Medium-length nerve = median nerve to m abductor pollicis brevis. Long nerve = tibial nerve to m abductor hallucis. DML = distal motor latency. CMAP = compound muscle action potential.

Discussion

The present study comprises a detailed analysis of the electrophysiological findings in 51 patients with IgM neuropathy who were treated with different forms of immunotherapy. Features of demyelination and axon loss were found more often and were more pronounced in: patients with reduced distal muscle strength and patients with improvement in distal muscle strength after immunotherapy. More axon loss was found in patients with a disease duration of ≥ 7 years. Length dependence of electrophysiological features of demyelination and axon loss was associated with demyelinating NCS.

In our previous studies, a simple classification of NCS into demyelinating or axonal did not help to predict a treatment response to cyclophosphamide with prednisone, fludarabine or rituximab.[5-7] This may have been due to the small number of patients investigated. Evaluation of responses to various treatments, including rituximab, by others showed that a response was associated with high anti-MAG titers and more severe sensory deficits, but not with disease duration, age, or IgM level, or electrophysiology.[13-17] Contrary to these findings, our study may indicate that a standardized assessment of motor NCS in two upper extremity and two lower extremity nerves, may be suitable to predict a treatment response. This difference may have been the result of different methodologies in the analysis of electrophysiological studies.

Our finding that a response to treatment was found in patients with more extensive demyelination and axon loss may indicate that these patients have a relative active disease process, possibly due to a more aggressive IgM monoclonal protein. Immunological suppression of such a protein may account for a relatively marked treatment response. Another suggestion, which was not investigated in our study, is that treatment induces restoration of lost myelin and axons. Restoration of damaged Schwann cells may have occurred by mechanisms described for Guillain-Barre syndrome and experimental allergic neuritis. [18] The possible restoration of axon loss is more difficult to explain. Axonal structures, such as medium and heavy chain neurofilaments, are controlled by Schwann cell molecules, including MAG. [19]. MAG normally maintains axon caliber by neurofilament sidearm phosphorylation and loss of MAG function results in neurofilament clustering and loss of axon diameter. Removal of anti-MAG IgM activity may therefore possibly result in neurofilament sidearm rephosphorylation, restoration of axon diameter, and restoration of conduction in previously non-functional but viable axons.

Although the intervention in this study consisted of three different forms of immunotherapy, the treatment methods and follow-up methods were standardized and the same for all three. Moreover, the study group was clinically well characterized and the methods for NCS were standardized, so that comparison of treatment results and electrophysiological data did not lead to any biased findings. However, the patients were treated because of progression of their disease, so that our results apply for patients with a relatively severe disease course.

In conclusion, our study showed that patients with IgM neuropathy and pronounced motor NCS abnormalities are more likely to improve on immunotherapy than patients with less pronounced abnormalities. In the future, this finding may be used to select patients for treatment.

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7

General Discussion

General discussion

IgM MGUSP is a rare immune mediated mostly demyelinating sensorimotor polyneruopathy. Thanks to the collaboration with other University departments of neurology and many neurologists in The Netherlands and the willingness of patients to participate in clinical studies it has been possible to collect a very large cohort of IgM MGUSP patients. Many patients were referred to our center for further diagnosis, or advice about therapy. As determinants of progression are mostly unknown in IgM MGUSP we decided to perform a prospective follow-up study of IgM MGUSP patients. Patients were extensively analyzed at regular, six monthly visits. The decision to initiate therapy that could consist of cytotoxic or immunosuppressant agents depended upon the progression of their signs and symptoms.
During the standardized follow-up study we collaborated with the department of hematology. The multidisciplinary approach has generated many new data as well as new research questions. The collaboration with the departments of hematology and rehabilitation, physiotherapist and neuromuscular nurse practitioner has improved the care for IgM MGUSP patients. Before the results of the studies that are presented in this thesis are discussed, I would like to emphasize that this centralized way of patient care and clinical research is pivotal for the evaluation of new treatment strategies. It also helps to gain insight into pathophysiological mechanisms of this rare disorder.

Prognosis of polyneuropathy with IgM monoclonal gammopathy

In the prospective cohort study of the largest population of IgM MGUSP published this far, we could demonstrate that the neuropathy associated with IgM monoclonal gammopathy is a predominantly distal sensory or sensorimotor neuropathy with a gradual progression. Eventually, the majority of patients experience disability up to a level that they need help with activities of daily life. The risk for reaching this level of disability was highest for patients without anti-MAG antibodies, with nerve conduction studies classified as demeylinating and with a higher age at onset. (**Chapter 2**)
Variation in the rate of disease progression like we have found has been described before. [1]
Our results showed that patients with anti-MAG antibodies have a lower risk for disability. If IgM MGUSP with and without anti-MAG antibodies should be regarded as separate disease entities is unclear. Some have found that IgM MGUSP patients with and without anti-MAG antibodies are indistinguishable [2-7], while others have found differences. [8-14]
From a theoretical viewpoint it can be hypothesized that the difference in disease severity between patients with and without anti-MAG antibodies is explained by the presence of other, yet unidentified, anti-neural antibodies that impair nerve fiber function through different mechanisms.

Levels of anti-MAG plasma titer were not associated with disease severity. (Chapter 2) As we measured the anti-MAG antibody titer only in 75 patients (54%), we cannot totally exclude the possibility of an association between the anti-MAG titer and disease severity. However, in auto-immune myasthenia gravis this relationship does not exist either. [15]
Demyelinating nerve conduction studies (NCS) are another determinant of disease severity. (**Chapter 2**) This finding could be explained by the observation that, interestingly, demyelinating IgM MGUSP patients have more severe axon loss than patients with pure axonal NCS, as was found in the study of electrophysiological characteristics. (**Chapter 6**)
Higher age at onset is a third factor that determinates disease severity. It is difficult to distinguish whether this is an effect of ageing itself, or if other processes are involved. It could for instance be explained by loss of neuronal plasticity in the elderly. (**Chapter 2**)
One of the limitations of the prospective cohort was that we included both treated and untreated patients as daily practice demands treatment of certain patients. To explore the effect of treatment on prognosis, we analyzed treatment as a prognostic factor. It seemed that treated patients showed a higher risk for disability. As treated patients showed more severe symptoms at baseline, we concluded there was an overrepresentation of more severe patients in the treated group, and excluded the factor treatment from the multivariate model.
A prognostic model was developed that was based on the three significant factors: presence of anti MAG bodies, presence of demyelinating NCS and age of onset as a continuous factor. The challenge was to develop a presentation of the model that could be used in daily practice, and would be available to those who work with IgM MGUSP patients. Therefore we decided to develop a risk calculator that will be made available on a website on the internet. (www.umcutrecht/Prognosis-MGUS-Neuropathy)
When using the model, one should bear in mind that the risks that can be calculated with this model should be interpreted with some caution. Our cohort consisted of patients that were seen in a tertiary referral center for polyneuropathy and may therefore have a more severe disease course. We cannot exclude that mildly affected, or very old patients have not been referred. The collaboration with may Dutch neurologists from all over the country and many consultations about referral make referral bias unlikely. Our study comprised a large number of patients that were followed prospectively in a standardized manner for a long period, it should be able to give direction to counseling and treatment of IgM MGUSP patients.

Hematological outcome

Twelve percent of the IgM MGUSP patients developed a hematological malignancy in a mean follow-up period of 4.9 years, leading to a 2.5 % per patient year risk for development

of a hematological malignancy. This risk is higher than that of 1.5% as measured in a large population of IgM MGUS patients without polyneuropathy.[16;17] The observation, that patients with MGUSP have a higher risk for malignant transformation has been previous done by our group. [18] In a large follow up study of MGUS patients presence of polyneuropathy was not investigated as a risk factor, so further comparison remains difficult. [17;19] The reasons for the increased risks for malignant transformation in patients with IgM MGUS and polyneuropathy are not known. This finding may be caused by selection and referral bias, as in a tertiary referral center the more severe and complicated cases are seen.

Treatment trials

Even after three trials that were performed in order to study which treatment regimen is most effective in IgM MGUSP, we can give no conclusive answer about therapy in individual patients. This is the pessimistic interpretation of our trial results.

A more optimistic interpretation can be that improvement of quality of life disability, muscle strength, sensory function, and nerve conduction velocity was achieved in a proportion of patients with disabling IgM MGUSP. (**Chapters 3,4,5**) For these individuals slight improvements in the mentioned outcome measures could for instance improve balance, or hand function. That in turn could cause improvement of daily functioning, including the ability to stay at work. This notion warrants further research for treatment strategies in IgM MGUSP.

The limitations of the cross-over design and choice of the primary outcome measure have complicated the interpretation of the results of the double blind placebo controlled trial with cyclophosphamide and prednisone. (**Chapter 3**) The cross over design led to subdivision of patients into four different treatment arms. Reduction of the numbers of patients per group hampered measurement of possible treatment effects. This problem was partly tackled by using intention to treat analysis, that compared the two initial treatment groups, with larger numbers of patients. Although both analyses showed the same results.

A second problem was the choice of the Rivermead Mobility Index as a primary outcome measure. This index was not able to detect change of function, even when muscle strength improved more in the treated group compared to placebo. The measured treatment effects were also supported by more improvement of distal conduction velocity in the median nerve and more improvement of the physical component of the SF-36 quality of life scale in the treated group. (**Chapter 3**) If we had chosen another primary outcome measure, the trial results could have been positive. At the onset of the study there were no better clinical scales for measurement of disability in polyneuropathy. The problem of identification of good clinical outcome measures for trials in neuromuscular diseases has been recognized before and could impair clinical studies in other neuromuscular disorders as well. [20-22] As we were unable to show more improvement on a functional level after cyclophosphamide, we had to conclude that the trial results were negative.

In the open label trial with fludarabine the modified Rankin scale was used as the primary outcome measure of disability. Although the median Rankin scale after treatment significantly improved for the whole group, the individual MRC sum score and the sensory sum score improved more often than the Rankin scale after treatment. **(Chapter 4)** Effect of treatment may thus remain unnoticed. At the time of the rituximab trial a novel scale for immune mediated neuropathy, the Overall Disability Sum Score had been developed (ODSS). [23;24] Yet, it seems that to improve one or more points, a lot has to happen. For example: rituximab induced an improvement of the Overall Disability Sum Score in only 2/17 patients, whereas the distal MRC sum score improved >5% in 4/17 and the sensory sum score improved > 5% in 9/17 patients.

The difficulty with IgM MGUSP is, that in contrast to other immune mediated neuropathies such as Guillain Barré Syndrome or its chronic variant chronic idiopathic demyelinating polyneuropathy, severe muscle weakness and fluctuating course are no features. IgM MGUSP runs a more gradually evolving, monophasic course. Differences in functioning are more subtle and outcome scales need to be more sensitive.

Comparison of the three treatment strategies

Comparison of the three treatment strategies showed equal response percentages. (**Chapter 5**) If side-effects were considered, these were most prominent in cyclophosphamide and significantly less observed after rituximab.

Based on these findings, we now mainly treat patients with rituximab. This is further supported by results of a small double blind randomized trial of rituximab for IgM MGUSP with anti-MAG antibodies. This trial showed a good response in 4/13 patients after 8 months, which was significantly better than in the placebo group. [25]. Further long term results and results of another double blind trial with rituximab are awaited.

Timing of treatment

In previous years we postponed treatment of IgM MGUSP as it was experimental, expensive and potentially toxic. Treatment was initiated when the point was reached that disability was moderate-severe and patients became more dependent on their caregivers. In addition the quantified neurological examination had to deteriorate between two following visits.

However, over years the notion has emerged that it may be better to treat patients right at the beginning of the disease course, at the stage in which axonal degeneration has not started yet, or is still minimal. In this way chances of response to treatment may increase. This

notion is supported by the findings in the electrophysiological studies. We demonstrated increased axonal loss in patients with a disease duration of ≥ 7 years. Others also found decreased treatment responses after a longer disease duration. [26] (**Chapter 6**).
The prognostic study showed that risk percentages for development of disability do not change much more after a disease duration of 10 years. This "plateau" phase may indicate that a maximum loss of function is reached after ten years. This may implicate that modification of the disease course should take place in the first ten years of disease duration.

Predictors for treatment response
We failed to identify predictors of treatment response in our three clinical trials. However, with regards to the rituximab study, it appeared that in patients with a long disease course of more than 10 years did not benefit at all. (**Chapter 5**) Others shared this experience [26]

Duration of treatment effect and repeated treatment
From clinical data we estimated that the duration of treatment effects in responders may vary between 6 months and several years. The effects seem wean off after several years. As a result, a proportion of patients from our cohort received repeated treatment cycles after secondary deterioration.(**Chapter 2)** Furthermore, it is difficult to study the disease modifying effect in our cohort, as due to the inclusion criteria for treatment, treated and untreated patients form a different group in matters of disease severity.
The ideal dosage scheme of rituximab in IgM MGUSP is still unknown. In, rheumatological, immunological and hematological disorders a repeated dosage scheme is used, as the effects on the B cell population last 9-12 months. It is not known, whether in IgM MGUSP repeated dosage is of extra benefit or if clinical progression should be followed for timing of a follow-up treatment, or if a schedule with fixed intervals should be used. [27-29] . As proof of principle study we treated one IgM MGUSP patient (IgM kappa, anti-MAG antibodies, disease duration 3 years) with several rituximab courses that were separated by 9-12 months. Every new cycle was initiated after clinical deterioration and always resulted in improvement. Hereby this patient was still able to continue his work.

Electrophysiological characteristics
The study of electrophysiological characteristics in relation to disease severity showed that IgM MGUSP patients with more severe muscle weakness show more signs of demyelination. In addition, patients with demyelinating NCS have more severe axonal loss. (**Chapter 6**) It seems that demyelination and axon loss are a combined finding in this disease, and cannot be interpreted as separate processes. This could be explained by studies of the function of MAG, that seems to play a role in linking myelinating Schwann cells to the axon and regulation of

the axon caliber.[29] MAG may be involved in the maintenance of the structure and function of axons. It is suggested by several observations that axonal atrophy is a primary effect that is mediated by anti-MAG antibodies. (see appendix figs 1 and 2) Delaying or preventing axonal degeneration could alleviate the clinical symptoms of anti-MAG neuropathy. [29].
Patients with a higher percentage of demyelination showed a higher chance of improvement of muscle strength after treatment with immunotherapy. As these patients also showed more profound axon loss, signs of axonal degeneration do not decrease the a priori chance of treatment response as was theoretically assumed.
Longer disease duration was associated with more severe axon loss. This confirms the concept that axon loss progresses with time in IgM MGUSP, as in other demyelinating polyneuropathies. [30;31] It is unknown if the patients with NCS that did not fulfill criteria of demyelination have a different disorder or are in a different stage of the same disorder. Either way, we have decided that they remained included in the studies, as eventually the development of a prognostic model would mean that a subdivision into clinical subtypes based on prognostic factors would emerge. We hypothesized that this was correct because the axonal patients showed a clinical picture that fitted well into that of IgM MGUSP

Future directions for research
The degree of disability of IgM MGUSP patients and individual successes with various treatments should motivate neurologists to consider and help to develop new treatment strategies for IgM MGUSP.
As a next step we propose a double blind randomized trial with rituximab- including patients with minimal handicap and short disease duration. Treatment schemes must be more prolonged and with repeated dosing comparable to rheumatological disorders.
Rituximab can be either compared to placebo or to cyclophosphamide, as this was effective in individual patients in a placebo controlled trial and in a previous open label trial. [32] (Chapter 3) Furthermore, cyclophosphamide is successfully used in other neuro-immunological disorders such as pediatric multiple sclerosis, dermatomyositis and myasthenia gravis.[33-37]
Other important issues that need to be addressed in future studies are:

- What are the factors associated with good treatment response?
- What are the long term effects of treatment with rituximab?
- Does treatment with immunotherapy act as a disease modifier, comparable to immunotherapy in multiple sclerosis?
- What are antibodies and underlying mechanisms of nerve damage are involved in IgM MGUS polyneuropathy and can we direct treatment at these mechanisms?
- And: do they help to understand clinical and electrophysiological differences?

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Summary

Summary

Summary

Introduction (Chapter 1)

Polyneuropathy represents a clinical syndrome characterized by sensory symptoms and muscle weakness distally in the legs with a gradual progression to the more proximal regions and the upper extremities. The causes of polyneuropathy are manifold and in about 10-20% of these patients no underlying cause is identified after initial evaluation. At further analysis, a monoclonal gammopathy is found in about 10%.

Polyneuropathy associated with IgM monoclonal gammopathy of undetermined significance (IgM MGUS polyneuropathy) is an immune mediated polyneuropathy. Antibodies directed against myelin associated glycoprotein (MAG), a component of the myelin sheath of the peripheral nerves, are present in about 50% of the patients.

Clinically, IgM MGUS polyneuropathy is a distal symmetric sensorimotor polyneuropathy, sometimes with ataxic features, that runs in a highly variable but progressive course. Substantial levels of disability may develop during the first years or after decades and therefore treatment is warranted in a proportion of patients. The therapy aims at lowering the M protein and suppressing the immune system.

Monoclonal gammopathy of undetermined significance (MGUS) can transform to B cell malignancies like immunocytoma, or non-Hodgkin lymphoma at an annual rate of 2,7% in IgM MGUS polyneuropathy compared to 1,5% in MGUS without polyneuropathy. Since this risk is continuous, these patients need regular lifelong surveillance.

The Outpatient Department for Neuromuscular diseases at the University Medical Center Utrecht monitored during the last decades 140 patients with IgM MGUS polyneuropathy, which is one of the largest documented groups of patients in a single academic institution by standardized clinical, neurophysiological and laboratory methods.

This thesis develops a new prognostic model for IgM MGUS polyneuropathy, using the longterm observations of the large cohort of cases. The impact of such a model is obvious both for the patient and his family, to prepare for the near future, but also for monitoring and testing new therapies and comparing them with earlier approaches.

As the basic mechanism of the disease remains elusive and its therapeutical interventions only partially effective, properly recorded and analyzed clinical observations remain fundamental, as shown in the evaluation of three treatment trials and of the electrophysiological manifestations in relation to clinical severity and treatment response.

A prognostic model for IgM MGUS polyneuropathy (Chapter 2)

The 140 patients in the cohort were followed for a median period of 5 years (range: several months to 23 years) and had either no or various forms of immunotherapy. Central in the periodical patient evaluation is the standardized neurological exam and reporting of disability with standardized scales.

A substantial part of patients develop disability up to a level that they need assistance with daily activities (Rankin scale $\geq$ 3). In a multivariate model the presence of anti-MAG antibodies reduced the risk of such disability (Rankin scale $\geq$3). However, a higher age at onset and demyelination gave a higher risk for that level of disability.

With these three factors we developed a prognostic model for development of disability in IgM MGUS polyneuropathy. For practical application of the model, a risk table and a web-based risk calculator were designed. These two tools allow clinicians to directly estimate the probability of disability developing in individual patients with IgM MGUS polyneuropathy. **http://www.umcutrecht.nl/subsite/Prognosis-MGUS-Neuropathy**

A double blind, randomized trial with cyclophosphamide-prednisone in IgM MGUS polyneuropathy (Chapter 3)

Various forms of immunotherapy were proposed for IgM MGUS polyneuropathy, but in the absence of clear effectivity of any individual therapy and their wide range of side effects, our institute decided to treat only patients with clear progression of symptoms, as observed between two follow-up visits by quantified neurological exam and disability scales. The primary goal of therapy is functional improvement, with improvement of sensory and muscular functions.

An earlier open label trial in our center with oral pulsed cyclophosphamide and prednisone showed limited efficacy and was the stimulus for a more informative double-blind, randomized, placebo-controlled trial of that combination in 35 patients. The primary outcome measure, the Rivermead mobility index (RMI), and the secondary outcome (the Rankin scale) were similar in both groups. However, improvement was observed in the treatment group on the MRC sum score; the sensory sum score at 6 months, the SF 36 quality of life mean health change and the physical role score. Also, the median nerve distal conduction improved more in the treatment group. There were no serious adverse events, the most common being nausea. We concluded that, as the primary outcome was not better after treatment with cyclophosphamide and prednisone, this combined treatment can not be advised as a standard therapy for IgM MGUS polyneuropathy.

A prospective open label trial with fludarabine (Chapter 4)

Fludarabine is a fluorinated purine analogue shown as effective in B cell malignancies

and possibly in IgM MGUS polyneuropathy. We studied the efficacy of fludarabine in 16 IgM MGUS polyneuropathy patients in a prospective uncontrolled trial. Improvement on the modified Rankin scale was present in 5/16 patients, who all had a demyelinating polyneuropathy and shorter disease duration. The motor conduction velocity improved ≥10% in two or more nerves of 4/5 of these patients. Hematological response in bone marrow occurred in 8/16 patients, and in 3/5 of the patients with a neurological response. There were no serious side effects. We concluded that fludarabine is effective in individual patients, but should be further tested in a controlled trial.

A prospective open label trial with rituximab (Chapter 5)

Rituximab is a chimeric monoclonal antibody (mab) directed against the CD20 surface component of normal and neoplastic lymphocytes. As the M protein in IgM MGUS polyneuropathy is produced by B cells, and reports emerged of its efficacy in IgM MGUS polyneuropathy, rituximab seemed a promising candidate.

We performed a prospective open label trial of 17 patients with disabling IgM MGUS polyneuropathy. The Overall Disability Sum Score (ODSS) showed an improvement of ≥ 1 point in 2/17 patients, the distal MRC sum score an improvement of ≥ 5% in 4/17 and the sensory sum score improved ≥ 5% in 9/17 patients. Bone marrow investigations showed CD 20 B cell depletion in all patients. There were no serious adverse events.

The response rates were comparable to those of combined intermittent cyclophosphamide with prednisone, fludarabine or rituximab schedules, but with fewer side effects. Presence of anti-MAG antibodies and a disease duration shorter than 10 years may predict rituximab treatment response.

We conclude that rituximab is a candidate for treatment of IgM MGUS polyneuropathy and a double blind randomized trial seems indicated, also to confirm the positive responders in a recent controlled trial of 13 patients in the USA.

Correlation of electrophysiology with clinical severity and response to treatment (Chapter 6)

IgM MGUS polyneuropathy is characterized by demyelination and axon loss which are more prominent in longer nerves and by demyelination which is more prominent distally, suggesting a unique length dependent process. Since IgM MGUS polyneuropathy may lead to substantial disability, different types of immunotherapy were tried, as described in the previous chapters. Because patient selection based on predictors of treatment response seems worthwhile, we aimed to identify electrophysiological features which determine a clinical response to immunotherapy.

Improvement of muscle strength after treatment was found to be associated with high

percentages of demyelinated segments, demyelinated nerves and nerves with axonal loss. Our study shows that patients with IgM MGUS polyneuropathy and pronounced motor nerve conduction abnormalities are more likely to improve on immunotherapy than patients with less pronounced abnormalities. It also showed that patients with more severe muscle weakness have a higher percentage of demyelinated nerves and segments. In this way, the neurophysiological assessment may support the clinical severity grading and optimize the selection of patients likely to benefit from treatment with immunotherapy.

Implications for future research (Chapter 7)

This single center, long term study of a large group of patients with IgM MGUS polyneuropathy, that is a rare, chronic and incapacitating neurological disorder, shows that an interdisciplinary collaborative effort is essential to obtain clinically relevant results on the disease mechanism, diagnosis and therapy. In this way, the present results are a tribute to the Dutch patients, their neurologists, the Utrecht University Medical Center departments of Hematology, Rehabilitation Medicine and Physiotherapy and many others.

The size of the cohort and the length of observation enabled the construction of the prognostic model and the formation of trial groups for testing several new medications.

The prognostic model learned us to exploit the documented variability of the disease as a predictive tool for individual prognosis. As that model will be openly available on the net, its validation in larger samples will become possible.

As most forms of immunotherapy are only beneficial to a certain fraction of patients, and can only modify rather than cure, trials of new forms of intervention, like rituximab, remain essential.

Measuring disease progression in a disorder like IgM MGUS polyneuropathy can be influenced by a scale's capacity to pick up the changes in the specific problems of a disease. We experienced differences in outcome measures when ranking patient-data on different scales, like Rivermead Mobility index, Rankin Scale, Overall Disability Sum Score, which will need future choices especially in monitoring trial outcomes.

Timing of therapy will certainly become another area of study, since rituximab related outcomes seemed to be more favourable after shorter disease duration (≤ 10 years). That might be a reason to reconsider our policy of only giving treatment to patients showing advanced stages of disability and rapid progression during two clinic visits 6 months apart.

Most of all, research into the fundamental causes of this enigmatic, chronic neurological and immunological disease seems needed, to develop a more causal intervention.

Samenvatting

Samenvatting

Inleiding (Hoofdstuk 1)

Polyneuropathie is een klinisch syndroom dat wordt gekenmerkt door sensibele symptomen en spierzwakte distaal in de benen, met een geleidelijke progressie naar meer proximale regio's en de armen. Er zijn zeer veel verschillende oorzaken voor polyneuropathie. Bij ongeveer 10-20-% wordt geen duidelijke oorzaak gevonden na de initiële evaluatie. Bij 10% hiervan wordt bij verdere evaluatie een monoclonale gammopathie vastgesteld.

Polyneuropathie geassocieerd met IgM monoclonale gammopathie van onduidelijke betekenis (IgM MGUS polyneuropathie) is een immuun gemedieerde polyneuropathie. Antilichamen gericht tegen myelin associated glycoprotein (MAG), een component van de myelinelaag van de perifere zenuwen, zijn aanwezig bij ongeveer 50% van de patiënten.

Klinisch presenteert IgM MGUS polyneuropathie zich als een distale sensomotorische polyneuropathie met soms atactische verschijnselen, met een variabel, maar progressief beloop.

Patiënten kunnen een zekere mate van invaliditeit ontwikkelen gedurende de eerste jaren, of na tientallen jaren, waarvoor behandeling geïndiceerd is van een gedeelte van de patiënten. De behandeling is gericht op het verlagen van de productie van het paraproteine (M proteine) en het onderdrukken van het immuunsysteem.

MGUS (monoclonal gammopathy of undetermined significance) kan maligne ontaarden in onder andere immunocytoom of non-Hodgkin lymphoom met een jaarlijks risico van 2,7% bij patiënten met IgM MGUS polyneuropathie ten opzichte van 1.5% bij patiënten met IgM MGUS zonder polyneuropathie. Omdat dit risico continu is, is levenslange follow-up hiervoor geïndiceerd.

De polikliniek Neuromusculaire ziekten van het Universitair Medisch Centrum Utrecht heeft gedurende de laatste tientallen jaren een populatie van 140 IgM MGUS polyneuropathie patiënten prospectief vervolgd met gestandaardiseerd neurologisch en neurofysiologisch onderzoek.

Dit is een van de grootste gedocumenteerde groepen IgM MGUS polyneuropathie patiënten, uit één academisch centrum, tot nu toe beschreven,

Dit proefschrift ontwikkelt een nieuw prognostisch model voor IgM MGUS polyneuropathie, gebruik makend van de langdurige observatie van een groot aantal patiënten. De impact van een dergelijk model is duidelijk zowel voor het voorlichten van de patiënt en zijn familie, als voor het monitoren en testen van nieuwe behandelingen ten opzichte van eerdere behandelingen.

Omdat het exacte ziektemechanisme van IgM MGUS polyneuropathie onopgehelderd blijft en de therapeutische interventies vaak gedeeltelijk effect hebben, blijven goed gedocumenteerde en geanalyseerde klinische observaties fundamenteel. Dit blijkt zowel uit de evaluatie van de drie therapeutische trials, als uit die van de electrofysiologische bevindingen in relatie tot ernst van de klinische verschijnselen en behandelresponse.

Een prognostisch model voor IgM MGUS polyneuropathie (Hoofdstuk 2)

De 140 patiënten in het cohort werden gevolgd voor een mediane periode van 5 jaar, variërend van enkele maanden tot 23 jaar. Een gedeelte van de patiënten werd behandeld met immunotherapie. Centraal in de periodieke patiënten evaluatie is het gestandaardiseerd gekwantificeerd neurologisch onderzoek en het gebruik van gestandaardiseerde handicapschalen door alle onderzoekers en clinici. Een substantieel gedeelte van de patiënten bereikt een mate van invaliditeit waarbij hulp nodig is bij dagelijkse activiteiten (Rankin schaal ≥ 3). In een multivariaat model verlaagde anti-MAG antilichamen het risico op Rankin Schaal ≥ 3. Hogere leeftijd van ontstaan van de ziekte en demyelinisatie gaven een hoger risico op het ontwikkelen van dat niveau van invaliditeit. Met deze drie factoren maakten wij een voorspellend model voor handicap in IgM MGUS polyneuropathie. Voor de praktische toepasbaarheid van het model werden naast een risicotabel ook een risico-calculator op een website ontwikkeld. Deze twee middelen geven clinici de mogelijkheid om direct de kans op invaliditeit in te schatten voor individuele patiënten met IgM MGUS polyneuropathie. **http://www.umcutrecht.nl/subsite/Prognosis-MGUS-Neuropathy**

Een dubbelblinde gerandomiseerde studie met cyclophosphamide en prednison in IgM MGUS polyneuropathie (Hoofdstuk 3)

Door de jaren heen werden verschillende vormen van immunotherapie voor IgM MGUS polyneuropathie onderzocht. Omdat duidelijke effectiviteit van de verschillende vormen van behandeling niet was bewezen, en er bijwerkingen waren, hebben wij besloten om alleen patiënten te behandelen met duidelijke progressie van symptomen, zoals gemeten tussen twee afzonderlijke polikliniekbezoeken met gekwantificeerd neurologisch onderzoek en handicapschalen. Het primaire doel van behandeling is verbetering van functioneren zoals gemeten met handicapschalen en verbetering van spierkracht en sensibiliteit.

Een eerdere open label trial in ons centrum met orale cyclophosphamide en prednison stootkuren liet goede resultaten zien en was een stimulans voor een dubbelblinde gerandomiseerde placebo gecontroleerde trial bij 35 patiënten. De primaire uitkomstmaat, de Rivermead mobility index, en de secundaire uitkomst (Rankin Schaal) waren gelijk in beide groepen. De spierkracht, de sensibele somscore na 6 maanden en de kwaliteit van leven verbeterden meer in de behandelde groep. Ook de geleidingssnelheid in de distale nervus medianus verbeterde meer in de behandelde groep. Er waren geen ernstige bij-

werkingen. Het meest kwam misselijkheid voor. Omdat de primaire uitkomstmaat niet gehaald was, concludeerden we dat de combinatie van cyclophosphamide en prednison niet als standaard therapie voor IgM MGUS polyneuropathie geadviseerd kan worden.

Een prospectieve open label trial met fludarabine (Hoofdstuk 4)

Fludarabine is een purine analoog, die effectief was gebleken in B cel maligniteiten en een serie IgM MGUS patiënten.We bestudeerden de effecten va fludarabine in een prospectieve open label studie in 16 patiënten. Verbetering van de primaire uitkomstmaat, de modified Rankin schaal trad op bij 5/16 patiënten, die allemaal een demyeliniserende polyneuropathie hadden. Bij 4/5 van deze patiënten verbeterde de motorische zenuwgeleidingssnelheid met >10%. Bij 8 van alle 16 patiënten en bij 3 van de 5 patiënten met een goede neurologische respons trad een hematologische respons op. Er waren geen ernstige bijwerkingen. We concludeerden dat fludarabine effectief was bij individuele patiënten, maar dat het verder getest moest worden in een placebogecontroleerde studie.

Een prospectieve open label trial met rituximab (Hoofdstuk 5)

Rituximab is een monoclonaal antilichaam gericht tegen het CD20 antigen op de celmembraan van normale en neoplastische lymfocyten. Omdat het IgM paraproteine wordt geproduceerd door B cellen, lijkt rituximab een geschikte kandidaat voor behandeling van IgM MGUS polyneuropathie.

Rituximab werd getest in een open studie bij 17 patiënten met invaliderende IgM MGUS polyneuropathie. De primaire uitkomstmaat, de overall disability sum score (ODSS), verbeterde in 2/17 patiënten. De MRC som score verbeterde in 4/17 en de sensibele som score verbeterde in 9/17 patiënten met ≥ 5%. Beenmergonderzoeken toonde B cel depletie in alle patiënten. Er traden geen ernstige bijwerkingen op.

De response percentages waren vergelijkbaar aan die in de cylophosphamide en prednison en fludarabine studies, maar rituximab toonde minder bijwerkingen.

Anti-MAG antilichamen en een ziekteduur korter dan 10 jaar zijn mogelijk geassocieerd met een goede klinische respons op behandeling met rituximab.

We concludeerden dat rituximab een kandidaat was voor een placebo gecontroleerde dubbelblinde studie in IgM MGUS polyneuropathie, ook om de effecten zoals beschreven in een later verschenen placebo gecontroleerde studie verder te bevestigen.

Electrofysiologie in IgM MGUS polyneuropathie: correlatie met klinische ernst en respons op behandeling (Hoofdstuk 6)

IgM MGUS polyneuropathie wordt electrofysiologisch gekenmerkt door demyelinisatie en axonaal verlies die meer prominent zijn in lange zenuwen en door demyelinisatie die meer

uitgesproken is in distale zenuwsegmenten. Deze bevindingen suggereren een uniek lengte afhankelijk proces. Omdat IgM MGUS polyneuropathie kan leiden tot een substantiële mate van invaliditeit, werden er verschillende vormen van immunotherapie onderzocht, zoals beschreven in de voorgaande hoofdstukken.

Patiëntenselectie voor behandeling op basis van factoren die positief zijn geassocieerd met een goede behandelresponse lijkt zeer de moeite waard. Het doel van deze studie was om vast te stellen wat de electrofysiologische kenmerken zijn van patiënten die verbetering toonden van hun symptomen na behandeling met immunotherapie.

Patiënten met ernstiger spierzwakte hadden een hoger percentage demyeliniserende zenuwsegmenten en zenuwen. Verbetering van spierkracht na behandeling was geassocieerd met hogere percentages zenuwen met demyelinisatie en axonale degeneratie. De studie toonde dat patiënten met IgM MGUS polyneuropathie en zeer geprononceerde afwijkingen van de motorische zenuwgeleiding een hogere kans hebben om goed te reageren op immunotherapie, dan patiënten die minder tekenen van demyelinisatie vertonen. Op deze manier kan het klinisch neurofysiologisch onderzoek bijdragen aan de selectie van patiënten die een optimale kans hebben om op behandeling met immunotherapie te reageren.

Consequenties voor toekomstig onderzoek (Hoofdstuk 7)

Deze studie van een groot cohort van patiënten met IgM MGUS polyneuropathie die werden gevolgd in één centrum, toont dat een interdisciplinair samenwerkingsverband met verwijzende specialisten uit het hele land essentieel is om klinisch relevante studieresultaten te bereiken over het ziektemechanisme, de diagnose en de behandeling van IgM MGUS polyneuropathie, een zeldzame chronische en invaliderende neurologische aandoening.

Op deze manier zijn wij voor de resultaten in dit proefschrift dank verschuldigd aan de Nederlandse MGUS polyneuropathie patiënten,hun neurologen, de afdelingen hematologie, revalidatiegeneeskunde en fysiotherapie in het UMC Utrecht, en vele anderen.

De grootte van het cohort en de follow-up duur maakten de ontwikkeling van een prognostisch model en selectie van patiëntengroepen voor behandelstudies mogelijk. De gedocumenteerde gegevens over de variabiliteit van het ziektebeeld werden met een prognostisch model verwerkt en leverden een hulpmiddel op voor het stellen van een individuele prognose. Omdat dit model open beschikbaar wordt op het internet, behoort validatie in een groter cohort tot de mogelijkheden in de toekomst.

Omdat de meeste vormen van immunotherapie uitsluitend effectief zijn bij een gedeelte van de patiënten, en eerder modificatie van het beloop geven, dan genezen, blijven trials met nieuwe vormen van behandeling, zoals rituximab essentieel.

Het meten van de ziekteprogressie in een aandoening als IgM MGUS polyneuropathie kan beïnvloed worden door het vermogen van de gebruikte schaal om ziektespecifieke

verandering op te pikken. Wij hebben verschillen bemerkt tussen de gebruikte schalen zoals de Rivermead mobility index, de modified Rankin schaal, en de Overall Disability Sum Score, die verder geëvalueerd moeten worden bij het opzetten van toekomstige studies.

Timing van behandeling zal zeker een ander onderwerp van studie vormen, aangezien in de rituximab studie en de electrofysiologische studie is gebleken dat behandeluitkomsten na een kortere ziekteduur (<10 jaar) gunstiger zijn. Dit is een reden om onze policy om patiënten pas te behandelen bij duidelijke invaliditeit en/of ziekteprogressie, die meestal na verloop van jaren optreden, te heroverwegen.

Verder is er vooral meer onderzoek nodig naar de fundamentele oorzaken van deze chronische neurologische en immunologische aandoening, om een meer causale interventie te ontwikkelen.

Dankwoord

Allereerst ben ik zeer veel dank verschuldigd aan **alle patiënten** met MGUS polyneuropathie (en hun verwijzers) die reeds jarenlang de polikliniek neuromusculaire ziekten in het UMC Utrecht bezoeken. Zij vormen een voortdurende bron van informatie over hun eigen ziektebeeld, waardoor wij als dokters in staat gesteld worden observaties te doen die vervolgens leiden tot een beter inzicht in het ziektebeloop, de mogelijke ontstaansmechanismen en een betere behandeling.

Prof. Dr. J.H.J. Wokke, beste John, het beste wat mij kon overkomen naast de opleiding neurologie in Utrecht, was om gevraagd te worden voor promotieonderzoek bij de neuromusculaire groep. Mijn eerste kennismaking met neurologie was namelijk die met kinderen met neuromusculaire aandoeningen, in Londen. Eén om nooit te vergeten. Toen kinderneurologisch onderzoek in Utrecht even plan B werd, was het geweldig dat neuromusculair plan A mocht zijn. Met groot plezier heb ik de afgelopen jaren onder je supervisie gewerkt zowel in de kliniek als in het onderzoek. Heel veel dank voor je begeleiding als promotor en opleider.

Dr. N.C. Notermans, beste Nicolette, de dagen met jou als poli-supervisor vlogen voorbij: er was altijd een snelle analyse en meteen een helder plan van aanpak. Samen nog even terug naar de patiënt, en dan was eigenlijk alles geregeld. Ik herinner mij nog als de dag van gisteren dat je die ene keer nog even wat langer in de kamer bleef om mij vervolgens te vragen of ik geïnteresseerd was in onderzoek naar de behandeling van MGUS polyneuropathie: het betrof een inmiddels rijdende trein, met resultaten van een trial die nog moesten worden verwerkt en opgeschreven. Ik sprong stilletjes een gat in de lucht. De rest is geschiedenis. Als co -promotor wist je steeds weer haarfijn de hoofdlijnen van het onderzoek aan te geven, met tussen de regels door de minstens even belangrijke lessen, namelijk over het stellen van prioriteiten, carrière- en gezinsplanning. Heel veel dank voor je doortastende begeleiding, het is een groot plezier met je samen te werken.

Dr. H. Franssen, beste Hessel, als klinisch neurofysioloog of seinwachthuisbeheerder moet je over stalen zenuwen beschikken - alles moet neurotisch goed kloppen - de wissels moeten goed staan voor een gestroomlijnde reis of analyse van een focaal, dan wel distaal verdeelde demyelinisatie met een meer of minder op de voorgrond staande vorm van axonale degeneratie met of zonder temporele dispersie. Je enorme betrokkenheid bij het onderwerp van mijn promotieonderzoek heeft zeer bijgedragen aan de stukken die we schreven, met als sluitstuk het artikel over de relatie tussen EMG karakteristieken en de respons op behandeling. Het was een groot plezier steeds weer even op de bank te ploffen om een volgende versie voor te bereiden, met of zonder treinenfilmpjes voor Olivier op de

achtergrond. Heel veel dank voor de plezierige samenwerking.

Prof. Dr. L.H. van den Berg, beste Leonard, je betrokkenheid bij mijn promotieonderzoek was divers: je stond tijdens jouw onderzoek in de VS mede aan de wieg van de ontdekking van de werking van anti-MAG antilichamen. Je dacht mee over het trial artikel en legde mij het verschil uit tussen de Amerikaanse manier van interpreteren, en de Nederlandse: op zijn Amerikaans wordt hetzelfde studieresultaat als positief geïnterpreteerd, waar wij nog terughoudend zijn. Met enthousiasme stimuleerde je het inleveren van zoveel mogelijk abstracts voor zoveel mogelijk meetings. Met veel plezier denk ik terug aan de AAN meeting in San Diego, met als detour het strand van La Jolla met een kleine Utrechtse delegatie. Heel veel dank voor je bijdrage.

Dr. K. Fischer, beste Kathelijn, als epidemioloog heb jij mij als geen ander weten te motiveren om ook de meer ingewikkelde statistische analyses zelf uit te voeren, en met de juiste mix van klinisch en epidemiologisch denken kon jij als kinderarts steeds toch weer iets begrijpelijks maken van wat die neurologen nu weer hadden bedacht. “Dan is het net of je het cadeau mag uitpakken!” was een van je gevleugelde uitspraken als we de resultaten van een analyse bekeken. Hierdoor werden alle uren van data-invoer opeens helemaal de moeite waard, en begreep ik mijn eigen voorspellende model plotseling zo goed dat ik in staat was deze kennis over te dragen aan epidemiologen in de dop. Je enthousiasme en gedrevenheid zijn aanstekelijk en een voorbeeld, heel veel dank voor al je hulp.

Dr. M. Eurelings, beste Marijke, van jou heb ik het MGUS- stokje overgenomen, jij was al expert toen ik net kwam kijken in 2004. Het was beslist geen straf warm te lopen in Barcelona in 2004. Het was een feest dagelijks langs Lake Michigan naar de AAN Meeting in Chicago in 2008 te fietsen, om vervolgens onze fietsen naast de rolstoelen te stallen, en een sessie over neuropathie in te duiken. Tussen de congresbedrijven door stond powershopping voor man en kinderen op de verlanglijst. Je belangstelling en hulp bij het schrijven van de stukken waardeer ik bijzonder, heel veel dank hiervoor.

Dr. H. Lokhorst, beste Henk, als hematoloog was je altijd bereikbaar voor patiëntenoverleg en gaf hematologische input voor de behandelstudies. Dit heeft een grote bijdrage geleverd aan de kwaliteit van het onderzoek van de bijzondere en grote Utrechtse MGUS polyneuropathie populatie. Heel veel dank hiervoor.

Dr. L. Teunissen, beste Laurien, als voorgangster in het MGUS onderzoek werd je aan het einde van mijn opleiding mijn supervisor op de afdeling klinische neurofysiologie in het

Antonius Ziekenhuis in Nieuwegein. Uiteindelijk is, na veel andere, Nieuwegeinse, EEG en EMG beschrijvingen, het artikel over de relatie tussen EMG- karakteristieken en behandelrespons nu tot stand gekomen . Heel veel dank voor het meedenken hierover.

Dr. W-L. van der Pol, beste Ludo**,** heel veel dank voor je pijlsnelle frisse blik en het helpen down-sizen van het rituximab artikel voor een betere verteerbaarheid door reviewers.

Nienke de Goeijen, nurse practitioner neuromusculaire ziekten, dankjewel voor je enorme inzet bij de begeleiding van de MGUS patiënten op de poli neuromusculaire ziekten.

Prof. Dr. J. van Gijn, heel veel dank voor het in mij gestelde vertrouwen door mij in 2000 aan te nemen voor de opleiding neurologie in Utrecht. Het was een plezier en voorrecht door U te worden opgeleid in een kliniek waar zowel de patiënt als de wetenschap centraal staan. Wat ontzettend jammer dat U vandaag niet achter de tafel kunt zitten, maar de gedachte dat U zich op Rotterdamse grond bevindt om belangrijk onderzoeksgeld te verdelen maakt het goed.

Een gedeelte van dit proefschrift is tot stand gekomen in wat men ook wel de microprocessor van de afdeling neuromusculaire ziekten zou kunnen noemen: de **kopkamer.** Aangezien het in het huidige tijdperk mede door de voortschrijdende technologie en de veranderende richting van het neuromusculaire onderzoek niet alleen om mega maar nu ook om gigabytes gaat, is inmiddels ruimere behuizing gezocht in een voormalige patiënten kamer op C3 Oost. Hier werkte ik aan de laatste loodjes en hangen de beeldbuizen al klaar voor het geval de patiëntenzorg de wetenschap ooit zal verdringen…. Maar met veel plezier heb ik daarvoor in die veel te kleine en te warme kopkamer alle perikelen mogen delen die het doen van medisch wetenschappelijk onderzoek met zich meebrengt, alsmede de niet verwante zaken. Nadia, Sonja en ook Frans: " licht aan/uit? Wel/geen UV lamp? Wel/geen chemisch ruikende muismat? Deur open/dicht? Fan aan/uit? Mag ik nu even de telefoon? Koffie nummertje 4?" Dank voor de gezelligheid en heel veel succes met het afronden van jullie proefschriften!

Beste ASAS, Monique Timmer, Jeanine Buttolo en Marjolein de Groot, jullie hebben mij als onderdeel van jullie wetenschappelijke stages enorm geholpen met het verzamelen en invoeren van data voor met name de prospectieve cohort studie, heel veel dank voor jullie inzet, ik heb jullie met veel plezier begeleid en wens jullie veel succes in jullie verdere carrière, alle drie neurologie en onderzoek, daar mogen jullie trots op zijn!

Oud collega-assistenten Neurologie, heel veel dank voor alle samen gewerkte uren bij nacht en ontij tijdens de opleiding in Utrecht. De Utrechtse assistentengroep neurologie

is als volgt te typeren: *Zeer gedreven*: iedereen promoveert. *Enigszins xenofoob*: angst om in een perifeer ziekenhuis een deel van de opleiding te moeten volgen, met als gevolg een slepende sessie vergaderingen over KNF in St. Elsewhere. *Lenig en flexibel*: hangend aan touwen met kampvuur en disco in de Ardennen. *Trouw*: een steeds uitdijende Utrecht tafel op de Biemond cursus. *Losbandig*: na de vrijdagmiddagoverdracht- met chips en cassis-lange borrelavonden- met iets anders. Hier denk ik met veel plezier aan terug. Het wordt tijd voor een Utrechtse Neuro-Alumni borrel!

De afdeling kindergeneeskunde van het Emma Kinderziekenhuis AMC heeft mij naast een stimulerend werkklimaat voor mijn opleiding tot kinderneuroloog de ruimte en souplesse geboden voor het afronden van mijn promotie over een "volwassen" neurologische aandoening.

Mijn paranimfen, **Marieke Wermer en Ynte Ruigrok**,
Lieve Marieke: op C3 Oost begon het: hier werden wij als kersverse assistenten losgelaten, en al dicterend tot in de kleine uurtjes, terwijl wij nog puntjes op de i probeerden te zetten door MO-tjes en labformulieren voor de afdeling in te vullen, leerden wij elkaar al snel goed kennen. Inmiddels hebben wij al 9 keer gevierd weer een jaar verder te zijn in onze neurologische ontwikkeling. Lieve Ynte: Ook onze opleiding begon ongeveer tegelijkertijd. Ik herinner mij kleine uurtjes in Havanna en lachpartijen op de Biemond. Ons uitwisselingsprogramma van werksters en oppassen zorgt ervoor dat we deze fase van een intensief gezin en carrière goed door kunnen komen. Marieke en Ynte, ik bewonder jullie beiden om wat jullie al bereikt hebben naast man en gezin en ben trots dat jullie vandaag naast mij staan als paranimf.

Lieve vriendinnen en vrienden, "Een helling oogt minder steil met een vriend. Mensen nemen niet de objectieve, maar de subjectieve werkelijkheid waar – daarin zit ingecalculeerd hoeveel energie er nodig is om de helling in kwestie te beklimmen. Wie zich door vriendschap weet gesteund, voelt extra energie en ziet een minder steile helling."
Dit stond voor mij al vast, en blijkt nu ook wetenschappelijk bewezen. (Bericht NRC n.a.v. artikel in Journal of Experimental Psychology juni 2008). Heel veel dank voor jullie vriendschap, aandacht en steun de afgelopen jaren, ik verheug mij op weer meer tijd en gezellige afspraken met jullie!

Lieve pappie en mammie, zonder jullie niet aflatende steun en motivatie was het afronden van dit promotietraject nooit zo soepel verlopen. Naast alles wat ik van jullie heb meegekregen, hebben jullie de afgelopen drie jaar geen kans voorbij laten gaan om eens een middag, dagje of week voor Olivier te zorgen, waardoor ik weer even aan de slag kon. Dank jullie wel voor alles.

Dankwoord

Lieve Robbert, het antwoord op je vraag wat je nu concreet zou hebben bijgedragen aan dit proefschrift moge duidelijk zijn: al was het alleen maar de reis naar de foto op de kaft en je rol als belangrijkste “vriend” in het verhaal van de helling. Thank you for being there. We gaan een heerlijke tijd tegemoet samen met Olivier.

Lieve Olivier, mamma heeft een boekje geschreven, nu is het klaar.

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*both authors contributed equally

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Meeting of the Peripheral Nerve Society, Würzburg, Germany, July 2009.

Biography

Biography

Biography

Jikke-Mien F. Niermeijer was born November 20, 1973 in Rotterdam, the Netherlands.
In 1992 she graduated at the Erasmiaans Gymnasium in Rotterdam.

She studied medicine at the University of Utrecht and obtained her medical degree in May 2000. During her studies she was an active member, and in 1995-1996 secretary of the Board of the Utrechtsche Vrouwelijke Studenten Vereeniging (Utrecht Women Students Association).

In 1998 she visited the Neuromuscular Unit of the Pediatric Department at the Hammersmith Hospital in London (Imperial College) for a clinical and research internship (grant: Prinses Beatrix Fonds). She participated in a study on the long term outcome of patients with spinal muscular atrophy type III (Professors V. Dubowitz and F. Muntoni). That experience was a strong motivation for her decision to obtain a specialization in pediatric neurology and neuromuscular diseases.

In 2000 she started her neurology training at the University Medical Center Utrecht (Professors J. van Gijn and J.H.J. Wokke). From 2000 to 2003 she participated in a PhD project on treatment strategies for benign pediatric epilepsy (Wilhelmina Children's Hospital, University Medical Center Utrecht).

In 2004 she was invited for a PhD project on the prognosis and treatment of polyneuropathy associated with IgM monoclonal gammopathy by Dr. N.C. Notermans and Professor J.H.J. Wokke at the neuromuscular department of the University Medical Center in Utrecht. Their group studies the largest cohort worldwide of patients with this chronic disease. The recent results are presented in this thesis.

In 2008 she finalized her neurology specialization to start a 2 year fellowship in pediatric neurology at the Academic Medical Center in Amsterdam, the Netherlands.

She is married to Robbert Lunsingh Scheurleer, with whom she has a 2 year old son Olivier.

Appendix

Appendix 1: The Modified Rankin Scale

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

Appendix 2: Rivermead mobility index (RMI)

RIVERMEAD MOBILITY INDEX
Patient's name:
Hospital number:

1. Do you turn over from your back to your side without help?
2. From lying in bed, are you able to get up to sit on the edge of the bed on your own?
3. Could you sit on the edge of the bed without holding on for 10 seconds?
4. Can you (using hands and an aid if necessary) stand up from a chair in less than 15 seconds, and stand there for 15 seconds,
5. Observe patient standing for 10 seconds without any aid.
6. Are you able to move from bed to chair and back withoutany help?
7. Can you walk 10 metres with an aid if necessary but with nostandby help?
8. Can you manage a flight of steps alone, without help?
9. Do you walk around outside alone, on pavements?
10. Can you walk 10 metres inside with no caliper, splint or aidand no standby help?
11. you drop something on the floor, can you manage to walk5 metres to pick it up and walk back?
12. Can you walk over uneven ground (grass, gravel, dirt, snowor ice) without help?
13. Can you get in and out of a shower or bath unsupervised, andwash yourself?
14. Are you able to climb up and down four steps with no rail butusing an aid if necessary?
15. Could you run 10 metres in 4 seconds without limping?(A fast walk is acceptable.)

TOTAL

Copyright: rivermead rehabilitation centre,
Abingdon road, oxford oxi 4xd.
(Reproduce freely but acknowledge source.)
Score 0 = No 1 = Yes

DATE

Appendix 3: Overall disability sum score (ODSS)

From:

Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies, I S J Merkies, P I M Schmitz, F G A van der Meché, J P A Samijn, P A van Doorn, for the Inflammatory Neuropathy Cause and Treatment (INCAT) group

J Neurol Neurosurg Psychiatry 2002;72:596–601

Arm disability scale – function checklist	**Not affected**	**Affected but not prevented**	**Prevented**
Dressing upper part of body (excluding buttons/zips)	O	O	O
Washing and brushing hair	O	O	O
Turning a key in a lock	O	O	O
Using knife and fork (/spoon—applicable if the patient never uses knife and fork)	O	O	O
Doing/undoing buttons and zips	O	O	O

Arm grade

0 = Normal

1 = Minor symptoms or signs in one or both arms but not affecting any of the functions listed

2 = Moderate symptoms or signs in one or both arms affecting but not preventing any of the functions listed

3 = Severe symptoms or signs in one or both arms preventing at least one but not all functions listed

4 = Severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible

5 = Severe symptoms and signs in both arms preventing all purposeful movements

Leg disability scale – function checklist	**No**	**Yes**	**NA**
Do you have any problem with your walking?	O	O	O
Do you use a walking aid?	O	O	O
How do you usually get around for about 10 metres?			
Without aid	O	O	O
With one stick or crutch or holding to someone's arm	O	O	O
With two sticks or crutches or one stick or crutch and holding to someone's arm	O	O	O
With a wheelchair	O	O	O
If you use a wheelchair, can you stand and walk a few steps with help?	O	O	O
If you are restricted to bed most of the time, are you able to make some purposeful movements?	O	O	O

Leg grade

0 = Walking is not affected

1 = Walking is affected but does not look abnormal

2 = Walks independently but gait looks abnormal

3 = Usually uses unilateral support to walk 10 metres (25 feet) (stick, single crutch, one arm)

4 = Usually uses bilateral support to walk 10 metres (25 feet) (sticks, crutches, two arms)

5 = Usually uses wheelchair to travel 10 metres (25 feet)

6 = Restricted to wheelchair, unable to stand and walk few steps with help but able to make some purposeful leg movements

7 = Restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs (eg, unable to reposition legs in bed)

Overall disability sum score = arm disability scale (range 0–5) + leg disability scale (range 0–7); overall range: 0 (no signs of disability) to 12 (maximum disability).

For the arm disability scale: allocate one arm grade only by completing the function checklist. Indicate whether each function is "affected," "affected but not prevented," or "prevented."

For the leg disability scale: Allocate one leg grade only by completing the functional questions.

From: I S J Merkies, P I M Schmitz, F G A van der Meché, J P A Samijn, P A van Doorn, for the Inflammatory Neuropathy Cause and Treatment (INCAT) group, Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. J Neurol Neurosurg Psychiatry 2002;72:596–601

Appendix 4: Medical research Council (MRC) graded muscle strength

Adapted from: Medical research council. Aids to the examination of the peripheral nervous system, Memorandum No 45, Her Majesty's stationary office, London, 1981

0 No visible contraction
1 Visible contraction without movement of the limb
2 Active movement of the limb, but not against gravity
3 Active movement against gravity over (almost) the full range
4 Active movement against gravity and resistance
5 Normal power

The **MRC sum score** that was used in this thesis is composed of the following muscle groups: leading to a maximum total score of 140 points. In all studies, the MRC sum score will be expressed as a percentage of the maximum score of 140 points.

The following muscle groups are tested manually:

Arms:
deltoid (shoulder abduction)
biceps (arm flexion)
triceps (arm extension)
*finger extensors
*finger flexors
*interossei (finger spreading)
*wrist extensors

Legs:
iliopsoas (hip flexion)
quadriceps (knee extension)
hamstrings (knee flexion)
*anterior tibial (foot dorsiflexioin)
*gastrocnemius (foot extension)
*peroneal (foot eversion)
*extensor hallucis longus (toe extension)

*muscle groups that are marked with an asterix form the **distal MRC sum score** with a maximum of 80 points. This will also be used as an outcome measure in all studies.

Appendix 5: Sensory Sum Score

Scoring system per modality tested:

Vibration sense
4 = perception on the finger tip / hallux,
3 = perception on the ulnar styloid / malleolus, but not more distal
2 = perception on the elbow / knee,
1 = perception at the clavicle / iliac crest,
0 = no perception at all

Joint position sense
2 = normal at the middle finger / hallux
1 = diminished at the middle finger/ hallux
0 = absent.

Touch sensation and pinprick sensation
4 = normal
3 = distal impairment to the wrist / ankle
2 = distal impairment to the second half of the forearm or lower leg
1 = distal impairment to the elbow / knee
0 = distal impairment to the axilla / groin

Summation of all sensory modalities leads to a total sensory sum score of 56 points.

Appendix 6

SF-36 questionnaire

Name:_____ Ref. Dr:_____ Date: _____

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?

- Much better now than one year ago
- Somewhat better now than one year ago
- About the same
- Somewhat worse now than one year ago
- Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Were limited in the kind of work or other activities

Yes No

Had difficulty performing the work or other activities (for example, it took extra effort)

Yes No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Didn't do work or other activities as carefully as usual

Yes No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all Slightly Moderately Severe Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

None Very Mild Mild Moderate Severe Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

Definitely true Mostly true Don't know Mostly false Definitely false

I am as healthy as anybody I know

Definitely true Mostly true Don't know Mostly false Definitely false

I expect my health to get worse

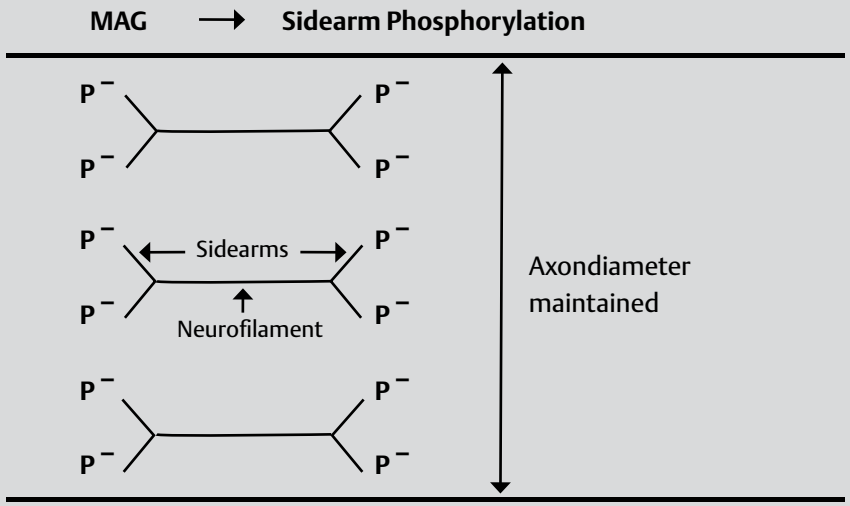
Definitely true Mostly true Don't know Mostly false Definitely false

My health is excellent

Definitely true Mostly true Don't know Mostly false Definitely false

Appendix 7, figure 1:

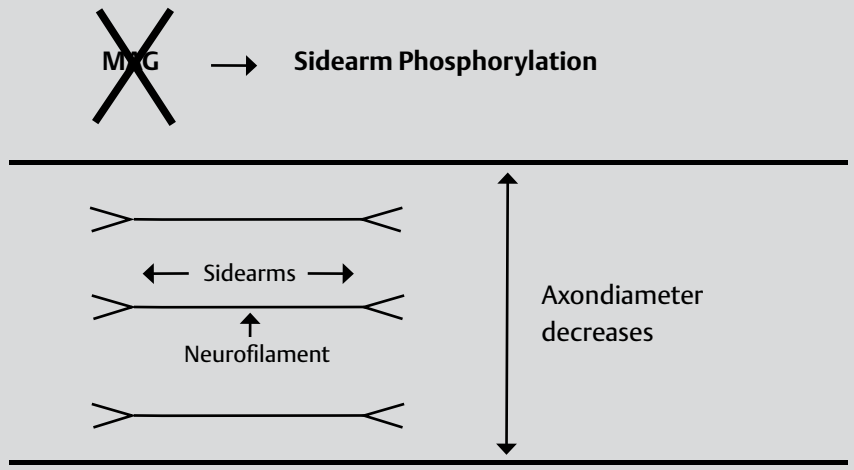
Role of myelin associated glycoprotein (MAG) in the peripheral nerve in a normal situation :
MAG plays a role in the maintenance of axon diameter through phosphorylation of the sidearms of neurofilaments



Dr. H. Franssen

Appendix 7, figure 2:

The role of myelin associated glycoprotein (MAG): in IgM MGUS polyneuropathy with anti-MAG antibodies:
in the absence of MAG, the sidearms of the neurofilaments remain dephosphorylated. It is presumed that this leads to decrease of the axon diameter.



Dr. H. Franssen