Update in therapy of chronic inflammatory demyelinating polyradiculoneuropathy

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1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired disease of the peripheral nervous system, characterized by proximal and distal muscle weakness and sensory loss in the four limbs [1,2]. The concept of the disease has grown since Austin reported cases of recurrent steroid responsive neuropathy, followed by the description of remittent and progressive subtypes. In the absence of a definite diagnostic biomarker, selected clinical, neurophysiological, and pathological criteria have been published, found excessively restrictive and made more liberal. The more used guideline on the management of CIDP has been revised in 2010 [3]. CIDP is the more frequent of the so-called chronic dysimmune neuropathies, whose spectrum mainly encompass CIDP, multifocal motor neuropathy (MMN), and demyelinating neuropathy associated with IgM monoclonal gammopathy (MG) and antibodies to anti-myelin associated glycoprotein (MAG). All of them are rare but potentially treatable diseases.

The prevalence of CIDP is estimated within 2.0 – 3.0 per 100.000 people in the scarcely published epidemiologic studies, with a classical male predominance [1,2]. In a recently reported epidemiological study, mean age of onset was 57.7 years, prevalence increased with age and reached a maximum in the age group of 70-79 years.

Randomized controlled trials (RCT) have firstly investigated whether prednisone, plasma exchange (PE), or intravenous immunoglobulin (IVIg) are effective as first-line therapy of CIDP. More recent trials have aimed to evaluate different regimens of one single treatment, or combination of treatments [4]. Lastly, very few trials have evaluated the efficacy of immunomodulatory agents as a long-term treatment option.The aim of the present article is to provide an overview of the challenges in the treatment of CIDP.

2. Diagnosis of CIDP

Based on consensus expert opinion, diagnosis of CIDP leads to distinguish typical CIDP from other atypical presentations including sensory CIDP, multifocal acquired demyelinating sensory and motor (MADSAM) and distal acquired demyelinating sensory (DADS) neuropathy. Although there may be overlap between these presentations, this distinction seems appropriate as natural history and response to treatment may be different among each.

2.1 Typical CIDP

CIDP is believed to have an autoimmune etiology. However, the criteria for diagnosis are often vague, and there are no specific and reliable biomarkers to establish the diagnosis. In 1991, a first attempt for the diagnosis of CIDP was based on clinical, electrophysiologic, pathological and CSF features. The more used guideline for CIDP has been revised in 2010, and aimed to propose new criteria [3]. These criteria have at least 81% of sensitivity and 96% of specificity. The usual clinical picture is made of symmetrical motor weakness in both proximal and distal muscles of the 4 extremities for at least 2 months, sensory involvement predominant in large myelinated fibers, and hypo or areflexia. Electrophysiologic investigations show demyelinating features, ie slowed motor nerve conduction velocities (MNCV), prolongation of motor distal latencies (DL), absence or prolongation of F-waves, and conduction blocks (CB) on motor nerves. In addition, supportive criteria obtained from CSF examination and MRI of the peripheral nerve roots may be helpful for diagnosis.

The presence on nerve biopsies of « onion bulb » formations, perivascular inflammatory infiltrates, and patterns of demyelination/remyelination are hallmarks of

CIDP. The mechanisms that lead to demyelination of peripheral nerves are poorly understood, but are believed to be mediated by both cellular and humoral immune factors. No clear correlation has yet been demonstrated between CIDP and specific serum autoantibodies, although antiganglioside antibodies are found in a proportion of patients. Recent challenges have focused on finding new serological biomarkers for CIDP. Antibodies binding to contactin-1 and contactin associated protein 1 (CNTN1/CASPR) seem to correlate with older age and more aggressive onset, predominantly motor involvement with early secondary axonal degeneration, and poor response to IVIg [for reference see 2]. Similarly, patients with autoantibodies binding to neurofascin 155 (NF155) of IgG4 isotype could constitute a specific subgroup with severe deficit, poor response to IVIg, and disabling tremor [for reference see 2].

CIDP has an unpredictable course, although the majority of patients have a severe motor, sensory or sensorimotor disabling status after years. In a recent population-based study, nadir overall neuropathy limitation scale score (ONLS) was 5, and 58% of patients were unable to walk independently at some point of their illness. Between 3% and 7% of patients have died during follow-up in one of the largest reported studies.

*2.*2 Atypical CIDP

2.2.1 Sensory CIDP

Patients with CIDP who present with purely sensory neuropathy may either exhibit the typical electrophysiologic changes of CIDP, including (asymptomatic) CB, or a cryptogenic sensory polyneuropathy [5]. In the last situation, somatosensory evoked potentials, MRI of peripheral nerve roots or nerve biopsy may help defining the diagnosis.

2.2.2 MADSAM neuropathy (Lewis-Sumner syndrome)

Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) consists of a subgroup of CIDP patients with a chronic asymmetric sensorimotor neuropathy mostly affecting the upper extremities, with multifocal involvement of peripheral nerves.

2.2.3 DADS neuropathy

Distal acquired demyelinating symmetric (DADS) neuropathy is a predominantly sensory neuropathy with ataxia. Patients with DADS neuropathy frequently have IgM monoclonal gammopathy with anti-MAG antibodies. On the other hand, non-anti MAG DADS patients may be considered as a variant of CIDP [6].

3. First-line treatment for CIDP

Corticosteroids, PE and IVIg have proven efficacy for CIDP.Up to 80% of patients responded to at least one of three first-line therapies in a recent study. Patients with high relapse rates may become treatment dependent, which leads to search for factors associated with treatment dependence or successful withdrawal. In addition, response may differ in patients with atypical presentations, favoring the hypothesis that different pathogenetic mechanisms may underlie the heterogeneity of CIDP [1,2].

3.1. Corticosteroids

Corticosteroids likely exert their benefits via several mechanisms. They act as inhibitors of T-cell proliferation and T-cell dependent immunity. They also have been shown to interfere with the activity of cytokines, decreasing the expression of several proinflammatory cytokines such as interleukin-1 (IL-1), IL-2, IL-6 and tumour necrosis factor, and increasing the expression of anti-inflammatory cytokines such as IL-4 and IL-10.

Corticosteroids have been shown to be more effective than no treatment in a historical RCT. A recently reported trial compared pulsed high-dose dexamethasone (40 mg per day for 4 days followed by placebo 24 days; 6 cycles) with standard prednisolone treatment (60 mg per day for 5 weeks and tapering to alternate day doses and then zero over the next 27 weeks), in 40 patients [7]. Twenty four patients received dexamethasone and 16 received prednisolone. At 12 months, 16 patients were in remission (40% of patients - 10 in the dexamethasone group, 6 in the prednisolone group) without a significant difference between the 2 groups. Most adverse events were minor and did not differ substantially between groups. In long-term evaluation of these patients, median time for relapse ranged from 11 months for

oral prednisolone to 17.5 months to pulsed dexamethasone. In a subset of patients that presented an early deterioration after treatment initiation, significantly higher frequency of pure focal distribution of demyelination was disclosed.

In pure motor CIDP, corticosteroids have been associated with clinical majoration of motor deficit. In these cases, corticosteroids should not be first treatment option and if they are used, close monitoring for deterioration is strongly recommended.

In summary, although corticosteroids are well-documented and inexpensive treatement option for patients with CIDP, the serious complications that may arise during its prolonged use, are a major limitation. In addition, some of these side effects (ie aseptic necrosis of the head, sepsis) may add substantially to the total cost of this therapy.

3.2 Plasma exchanges

It has been emphasized that humoral effector mechanisms may underlie or at least participate in the pathogenesis of CIDP. Removal of these pathogenic humoral factors may therefore be responsible for the recovery of nerve conduction velocity in CIDP patients after PE, thereby providing a rationale for the use of PE in CIDP. PE is therefore a well-established and well-tolerated treatment of patients with CIDP [8]. However, as with corticosteroids, relapses occur in a majority of patients, and PE has severe limitations: it is invasive, time-consuming, expensive, can be performed only in special centers, and requires special equipment and well-trained personnel.

3.3 Intravenous imunoglobulins

The mechanism by which IVIg exerts its immunomodulatory effect in CIDP is poorly known. Several theories include neutralization of pathogenic autoantibodies by anti-idiotypes, attenuation of complement-mediated tissue damage, saturation and functional blockade of Fc receptors on macrophages, modulation of proinflammatory cytokines/T cell mediators and decrease in autoantibody production through the binding of anti-idiotypes to antigen receptors on B-cells.

In the ICE study, 10% IVIg (10% caprylate-chromatography purified immune globulin – IGIV-C) efficacy and safety has been studied in 117 CIDP patients, enrolled in a randomized, double-blind, placebo-controlled, response-conditional crossover trial.

IGIV-C or placebo was given at the initial dose of 2g/kg, then 1g/kg every 3 weeks for up to 24 weeks. Absence of improvement in adjusted INCAT disability score of 1 point or more conducted to switch into the alternate treatment in a crossover period. Primary outcome was the percentage of patients who had maintained an improvement from baseline through to week 24 of follow-up in adjusted INCAT disability score of 1 point or more. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (p=0·0002). Significant improvements from baseline to endpoint were also recorded for grip strength in the dominant and non-dominant hand (p=0·0008 and 0.005, respectively). Similar results were observed during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than placebo-treated patients (p=0·011). The incidence of serious adverse events per infusion was 0·8% (9/1096) with IGIV-C versus 1·9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypertension. Moreover long-term therapy with IGIV-C, showed a maintened improvement in health-related quality of life in CIDP patients. The PRIMA study confirmed these results with another IVIg 10% brand.

A Cochrane recently summarized IVIg studies in CIDP, pointing to an improvement of disability, for at least two to six weeks, compared with placebo, and having a similar efficacy to PE, oral prednisolone and intravenous methylprednisolone [9].

Despite efficacy, a high proportion of CIDP patients remain dependent on IVIg treatment . This fact justifies the search of new forms of IVIg administration intending to maximize the benefits of therapy and render side effects, social and economic impacts, minimal. In that sense, some studies regarding the use of subcutaneous immunoglobuline (SCIg) have been reported. SCIg has no established difference in half-life, usually at lower doses and more frequent intervals than IVIg. The consequence is a higher and more stable immunoglobulin G level which may prevent end-of-dose reduction in efficacy and minimizes side-effects. A double-blind placebo-

controlled RCT of SCIg, performed in 30 CIDP patients previously responders to IVIg, showed that there was no significant difference in MRC sum score or grip dynamometry, but there was a significant improvement in isokinetic muscle strength in SCIg-treated patients. Moreover, 70% of patients preferred SCIg administration. Finally, SCIg seems to contribute to a significant reduction in non-drug costs of up to 85%.

In summary, the efficacy and safety of IVIg have been documented in several RCT for CIDP. However, IVIg remains a time-consuming and expensive therapy, In addition, it is not recommended in patients presenting severe kydney disease and must be used with caution in patients with cardiovascular disease.

3.4 Comparative trials

A recent comparative study has been published , comparing efficacy and tolerability of IVIg (0.5g/kg per day for 4 consecutive days) and high dose intravenous methylprednisolone (0.5g in 250 mL sodium chloride solution per day for 4 consecutive days) given every month for 6 consecutive months. This double-blinded, placebo controlled RCT was completed in 45 patients (24 IVIg; 21 methylprenisolone). Methylprednisolone was more frequently stopped (p=0.0085) because of lack of efficacy, adverse events or voluntary withdrawal, when compared with IVIg. On the other hand, after therapy discontinuation, IVIg treated patients had a higher frequency of worsening and more frequently required further treatment (p=0.0317). In a follow-up study, the authors looked at the proportion of patients and the duration of relapse after therapy discontinuation with a median follow up of 42 months (1-60) Twenty-four out of 28 patients (85.7%) treated with IVIg worsened after therapy discontinuation, with a comparable number in the methylprednisolone group (10 out of 13 patients, 77%). Interestingly, the median time to relapse in the IVIg group was 4.5 months compared to 14 months in the methylprednisolone group (p=0.013) suggesting that when effective, methylprednisolone might have a longer beneficial effect in CIDP, when compared to IVIg.

4. Long-term therapy in CIDP

The usual lack of long-term response to the first-line treatments leads immunosuppressive drug to be tried. Unfortunately, no immunomodulatory treatment has proven efficacy for CIDP. However, in clinical practice, these drugs are often used for CIDP. A retrospective study including 110 patients refractory to conventional therapies intended to verify if immunossupressors/immunomodulators (IA) could increase the number of CIDP patients responding to treatments. Thirty seven percent of the 110 patients responded to one IA; the rate of response to each IA was 17-38%, with the exception of interferon beta-1a that was not effective in any treated patient. There was no significant difference in the clinical response to the different IA. Cyclosporine was significantly associated with more adverse events (p=0.01). Moreover, no relation of IA response was found with either the presence of axonal damage, age at CIDP onset, disease duration or response to conventional therapies. We selected in the following the main reported results in trials with IA.

4.1 Interferon beta 1a

Interferon beta 1a (IFN beta) has proven efficacy in the treatment of MS. The immunomodulatory properties of IFN beta that are believed to mediate its beneficial effects in MS suggest that it could also be effective in CIDP. A prospective, open-label clinical trial studied the safety, tolerability, and efficacy of once-weekly IFN beta (Avonex®) in a cohort of 20 IVIg resistant CIDP patients. It showed an improvement in clinical grading but not in grip strength scores. Then, a large RCT was conducted in 67 IVIg-dependent CIDP patients, followed for 32 weeks. IVIg was maintained until 16th week of follow-up and reintroduced in worsened patients. IFN beta did not provide significant benefit at different regimens, but was seemingly beneficial for patients requiring higher doses of IVIg (p=0.005) or with a greater baseline weakness (MRC< 51) (p=0.025).

4.2 Methotrexate

Possible other immunomodulators to be tried in CIDP include methotrexate which is a widely used disease modyfing drug by rheumatologists, on account of efficacy and safety profile. A multicentre, double-blind RCT aimed to compare methotrexate with placebo. Response to treatment was considered if there was more than 20% of IVIg

or corticosteroid dose reduction. There was no significant difference between methotrexate and placebo groups.

4.3 Rituximab

Rituximab is a chimeric (mouse/human) monoclonal antibody against CD20+ B lymphocytes, that was mainly used in haematological diseases, and more recently in IgM anti-myelin associated neuropathy (anti-MAG neuropathy). A retrospective study in 13 CIDP patients (8 with an haematological associated condition) showed that treatment with rituximab may clinically improve patients (at least 2 points in clinical scales) or reduce previous necessary therapies (9 patients; 7 with haematological diseases). This study pointed also to a significative correlation of response with shorter disease duration. It was then suggested that rituximab might be an option, especially in CIDP associated with haematological diseases.

4.4 Alemtuzumab

Alemtuzumab is a monoclonal antibody against CD52 antigen. Scarce information is reported in CIDP patients. A study in 7 patients pointed to a a prolonged remission or partial response in 4 patients. On the other hand, 3 out of 7 patients developed an autoimmune condition (high levels of anti-thyroperoxidase antibodies in 2 patients, one of which was later diagnosed with Graves' disease, 1 patient with autoimmune haemolytic anaemia).

5. Improvement in assessment of CIDP for clinical trials: outcome measures

The selection of outcome measures for use in trials of treatment is difficult for CIDP. The disability in CIDP affects upper and lower limbs but is usually predominant in the lower limbs. In addition, outcome measures should also cover impairment and quality of life. They should be simple, valid, reliable and responsive, and correlate with disease severity. They should also allow comparison with those used in previous trials to facilitate systematic reviews.

A Workshop (196th ENMC international workshop) organized by the European Neuromuscular Centre (ENMC) was held in February 2013 and edited recommendations on behalf of a group of experts coming from Europe and

USA/Canada, for the best clinical (and non-clinical) outcome measures in polyneuropathies, to be used as tools in their evaluation for RCT. It pointed to a better evaluation of data analysis with Rasch method which enabes to transform ordinal data into an interval metric ones, increasing the level of precision in the assessment. In that sense, primary outcomes for CIDP should be at the participation and activity levels measured by the Rasch-built overall disability scale (R-ODS) since it has higher responsiveness compared to the modified inflammatory neuropathy cause and treatment – overall neuropathy limitation scale (INCAT-ONLS). Other outcomes for trials for CIDP should include Martin Vigorimeter, the RT-mISS and the manual muscle testing for impairement; the R-ODS and the INCAT for activity and participation and the 5-points patient global impression of change and the SF-36 for quality of life (Table 1).

6 Conclusion

This overview aimed to summarize the last issues in improving the diagnosis, the outcome measures and the treatment options for CIDP, in line with previous reviews. The challenges for the future are mainly 1) To look for potential new biomarkers for the diagnosis of CIDP, including autoantobodies in line with defined subsets of the disease 2) To improve the outcome measures for clinical trials for CIDP, with specific attention to disability scales, mainly R-ODS 3) To develop animal models as there is a lack of consistent ones 4) To test new immunomodulatory.immunosuppressive agents in the long-term treatment for CIDP, as it was recently proposed for mycophenolate mofétil and for fingolimod [10].

Table 1: Overview of the minimum core set, recommendation and future needs (adapted from 44)

	CIDP	MGUSP
Minimal core set		
Impairment level	Martin Vigorimeter	Not yet defined; further study required
	RT-mISS	
	Manual muscle testing	
Activity and participation level	R-ODS	See above
	Original INCAT disability score	
Quality of life level	5-PGIC	See above
	SF-36	
Recommendations		
Impairment level	11-PI-NRS	RT-mISS
	RT-FSS	
Activity and participation level	-	R-ODS
		Original INCAT 10-point
Quality of life level	-	PIGC
		SF-36 or Euro-QoL
Future needs		
Impairment level	RT-MRCss	Define core set
	Pain	Pain
	Walking test	Ataxia
	-	Tremor
	-	9-hole PEG test
Activity and participation level	Cross cultural R-ODS	Define core set
Quality of life level	RT-QoL scale	RT-QoL scale

RT, Rasch transformed; mISS, modified INCAT sensory sumscore; R-ODS, Rasch-built overall disability scale; MRCss, Medical Research Council sum score; FSS, fatigue severity scale; 5-PGIC, 5-points patient global impression of change; 11-PI-NRS, 11-point pain intensity numerical rating scale; QoL, quality of life

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