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Workshop report

151st ENMC International Workshop: Inflammatory Neuropathy Consortium 13th–15th April 2007, Schiphol, The Netherlands

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1. Introduction

Fourteen clinicians and scientists, a statistician, a representative of the European Medicines Agency (EMEA) and two representatives of the UK and International Guillain-Barré and CIDP patient support groups met at Schiphol Airport to discuss the published evidence for treatment of inflammatory neuropathies and the priorities for future trials of therapy for these conditions. Each participant presented an aspect of the current evidence, data supporting potential new therapies or proposals of trials of existing or novel treatments.

2. Goals of the meeting

There is a need for an international strategic approach to discover the best treatments for the inflammatory neuropathies. With notable exceptions, existing efforts have been intermittent and conducted at a single centre or national level. This has given rise to a start–stop programme which has been slow and inefficient. The consequence is that there are no current trials in Guillain-Barré syndrome and few in multifocal motor neuropathy (MMN) or paraproteinaemic demyelinating neuropathy (PDN). Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is for the first time the subject of pharmaceutical company interest. This workshop launched the international Inflammatory Neuropathy Consortium (INC) to establish an inflammatory neuropathy trial network led by investigators in partnership with the relevant professional and patient organisations, especially the Peripheral Nerve Society, the ENMC and the GBS-CIDP Foundation International, and eventually with the pharmaceutical industry.

The inflammatory or immune-mediated neuropathies are a diverse group of diseases which include Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with conduction block (MMN), and paraproteinaemic demyelinating peripheral neuropathy (PDN). The pathogenesis of the inflammatory neuropathies is still under investigation.

3. Guillain-Barré syndrome

Guillain-Barré syndrome is an acute inflammatory peripheral neuropathy with an incidence of 1–2 per 100,000 population per year. The results of the randomised trials of treatment in GBS are summarised in three Cochrane Systematic Reviews [1–3]. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the commonest underlying pathology in the Western world and the GBS variant for which most trials have been performed. For adults with severe GBS, plasma exchange (PE) is supe-

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rior to no treatment. In five trials, improvement with intravenous immunoglobulin (IVIG) was very similar to PE. Adding IVIG after PE did not produce significant extra benefit. Combining corticosteroids with IVIG leads only to possible minor short-term benefit, although the clinical significance of this result has been debated.

Despite these efforts and resulting evidence, there are many important issues which remain unresolved, with both therapeutic and economic implications. For example, despite the dissemination and implementation of best therapeutic practice 5–8% of patients die, 25% of patients require artificial ventilation at some time, and after one year 10 to 20% are left with severe disability requiring aids to walk, or worse [4]. In addition, more than half of patients are left with significant disabling levels of fatigue [5]. There are no data to guide the optimum dose of IVIG and in particular whether a second dose of IVIG, two weeks after the first course, for patients who are still severely affected, would reduce the residual disability. There is no information from randomised trials about whether IVIG is efficacious in adult patients with mild disease (able to walk unaided at inclusion, Hughes Disability scale 1 or 2) in patients with the axonal variants of GBS or Fisher syndrome [6] or in GBS in children.

The consortium agreed that high quality, coordinated multicentre randomised controlled trials are urgently needed to investigate these areas and that the following trials should be prioritised. The efficacy of IVIG in mild GBS and Fisher syndrome should be established and the use of a second IVIG dose in patients still bed bound two weeks after the first course should be trialed. A trial of plasma exchange *versus* IVIG in axonal (AMAN and AMSAN) forms of GBS is needed. Finally the use of novel but highly promising therapeutics including biologic complement inhibitors in acute severe GBS and sodium channel blockers in conjunction with standard therapies should be formally investigated.

4. CIDP

The prevalence of CIDP is about 2 to 4 per 100,000. The incidence is unknown. The pathogenesis is uncertain but may involve both T and B cell-mediated mechanisms [7]. CIDP leads to severe disability in a considerable number of patients. Diagnostic and management guidelines have been published recently under the auspices of the Peripheral Nerve Society (PNS) and the European Federation of Neurological Societies (EFNS) [8]. Trials have shown that corticosteroids, IVIG, and plasma exchange are superior to placebo. The results have been summarised in three Cochrane reviews which showed that corticosteroids, PE and IVIG are each beneficial in about two thirds of patients in the short-term but need to be continued or repeated to suppress disease activity [9–11]. Furthermore, some evidence is available that PE, corticosteroids and IVIG are equally effective. It is estimated that approximately 70–80% of patients with CIDP will respond to one or a combination of these treatment modalities. However, the general consensus is that, despite these available treatments, considerable numbers of patients have chronic severe disability and their needs are not met satisfactorily. According to another Cochrane review, there are no adequate randomised controlled trials (RCTs) to establish the possible value of other immunosuppressants and cytotoxic agents [12]. Many candidate agents have been tested in individual case reports or small series including azathioprine, ciclosporin, cyclophosphamide, mycophenolate, methotrexate, alemtuzemab, rituximab, etanercept, interferon-α, β-interferon-1α, and autologous peripheral blood cell transplantation. Trials in progress or recently completed but not yet reported are IVIG vs. placebo, IVIG vs. intravenous methylprednisolone, oral prednisolone vs. intermittent high oral dose dexamethasone, β-interferon-1α vs. placebo and methotrexate vs. placebo as add-on to IVIG or corticosteroid therapy.

Rituximab and high dose methotrexate were considered the most promising agents and should be tried first, depending on the results of the ongoing methotrexate trial. Other promising agents considered were cyclophosphamide and ciclosporin.

In future trials, patient selection should be broad, and sub forms of the disease should be included. There is a need for better prognostic indicators (clinical and electrophysiological) predicting outcome. This could enable patient selection for treatment with more aggressive immunomodulatory agents.

5. Multifocal motor neuropathy with conduction block

Multifocal motor neuropathy with conduction block is a rare condition affecting no more than 1–2 persons per 100,000. It is more frequent in men than women with an approximate sex ratio of 2.6:1. In the past 4 years, several sets of diagnostic criteria for MMN for use in clinical trials have been proposed. The most recent criteria have been published in a guideline elaborated by a joint task force of the EFNS and the PNS [13]. Conduction block (CB) is considered as the gold standard for the diagnosis in MMN in these and other criteria. However, CB may be technically difficult to demonstrate in some patients meaning that some may be excluded from diagnosis and/or treatment. Recently, a new electrophysiological technique, the triple-stimulation technique (TST), has been proposed to objectively demonstrate very proximal CB in the motor roots, and the magnetic fatigue test has been considered for activity-dependent CB. The validation, acceptance and use of these tests may improve patient diagnosis in the near future.

The efficacy of IVIG in MMN has been assessed in four RCTs, whose results have been summarised in a recent Cochrane Review [14]. Impairment measures improve in approximately 80% of patients treated with IVIG but therapy needs to be repeated periodically and the cost-effectiveness and effect on long term disability are not known. Furthermore, questions still remain about the best therapy

in patients who are non-responders to first line IVIG. There are no randomised data on which to base decisions about the long term treatment of MMN patients either in terms of drug choice, dose or combination [15].

Parallel research streams are needed to improve the identification, diagnosis, treatment and follow-up of patients with MMN. Of the more common inflammatory neuropathies, the pathogenesis of MMN is probably least well understood [7]. The current electrodiagnostic and immunological criteria for MMN need refinement. A search for better biological markers of disease than anti-GM1 antibodies using a large serum bank should be undertaken. Trials of long term IVIG treatment to assess disability prevention are needed. Consensus was reached that methotrexate should be tested formally in a RCT whose primary outcome measure should be the reduction of IVIG maintenance infusions.

6. Paraprotein associated demyelinating neuropathy

The prevalence of clinically significant paraprotein (usually monoclonal gammopathy of undetermined significance) associated demyelinating neuropathy (PDN) is unknown. IgM paraproteins account for 60–70% of MGUS associated PDN, 60–80% of which have anti-MAG activity. Anti-MAG antibodies are implicated in the pathogenesis of PDN. The evidence for direct pathogenesis of other serum paraproteins is less strong.

There are only six randomised trials of PDN treatment [16,17]. A further large RCT rituximab treatment of patients with IgM anti-MAG PDN (RIMAG) is in progress. Two randomised trials of IVIG show benefit over the sort term. Interferon alpha had no significant effect in one trial in PDN [16]. There is insufficient evidence to judge the effectiveness of PE, steroids, cyclophosphamide, azathioprine, chlorambucil, mycophenolate mofetil, cladribine, melphalan, adriamycin, immunoadsorption, selective apheresis, bone marrow transplantation or combination treatments of the above. Chlorambucil was until recently the standard treatment for this condition but has not been subjected to a controlled trial.

Ten papers of nine studies (75 patients, 55 anti-MAG) describe the use of rituximab for treating PDN; one phase III study (RIMAG, France-Switzerland) may be near completion and one positive RCT (Dalakas, USA) awaits full publication. Two papers describe negative results of six patients but the remainder describe improvement in a variety of impairment, disability and handicap measures. Fludarabine is a purine nucleoside analogue which has been described in the treatment of 29 PDN patients in four studies (three published). Nine of twenty patients with published results improved assessed by a variety of outcome measures.

The treatment of IgA and IgG PDN has been reviewed by Allen et al. [18] but has been poorly studied. Observational and retrospective studies conclude that MGUS-CIDP may respond less well than idiopathic CIDP to treatment. Patients with demyelinating neuropathy respond better than patients with axonal damage.

The workshop agreed that IgG and IgA neuropathies should be included in trials of CIDP but analysed as a pre-specified subgroup. Trials of IgM PDN should preferably only include anti-MAG PDN patients or a specific subgroup analysis should be prospectively identified. Since many patients reach a plateau phase of their illness and do not deteriorate further, early and aggressive treatment may be unnecessary. There is a need to identify predictors of the course and likely natural history each patient's illness. The core outcome criteria set down by the 131st ENMC workshop [19] should be used but development of scales to assess tremor and unsteadiness should continue. Trial outcomes should be assessed after prolonged treatment (1–2 years) to be meaningful. Trials of treatment for other syndromes (CANOMAD and POEMS etc.) should be encouraged if resources are available.

A trial of chlorambucil should be performed. If the Dalakas and RIMAG trials using rituximab are positive then a trial with rituximab giving a second dose at either standard or double (750 mg/m^2) dose given 8–12 months after the first was favoured. If negative, then a double dose trial should be considered and trials of other agents proposed. However, Fludarabine was considered too toxic at present to trial in IgM PDN.

7. Clinical outcome measures

In the last eight years, efforts have been made by the Inflammatory Neuropathy Cause and Treatment (INCAT) group to scientifically approach the standardisation of outcome measures for clinical studies in GBS, CIDP, MMN, and PDN. These efforts and the remaining needs for optimal standardisation of outcome measures were addressed by the 131st European Neuromuscular Centre workshop in 2004 [19]. This new workshop recommended a comparative study between outcome measures of impairment, activity and participation limitations, and quality of life in these conditions. The peripheral neuropathy outcome measures standardisation (*P*eri*N*omS) study was conceived and presented by the Rotterdam–Maastricht group. PeriNomS aims to expand the clinimetric knowledge of peripheral neuropathy outcome measures, particularly in terms of scale responsiveness. At the pathology level, intra-epidermal nerve fibre density will be assessed in GBS, CIDP, and PDN, and its correlation with other outcome measures will be investigated. At the impairment level, comparative studies will be performed between the MRC sumscore and INCAT sensory sumscore vs. NIS motor and sensory subsets, and between the Jamar dynamometer and the Martin Vigorimeter. Also, the general applicability of an autonomic symptoms scale plus some selected activity limitation (ODSS, ONLS) scales will be examined. Furthermore, a new polyneuropathy-specific calibrated activity scale (C-ODSS) is being constructed based on a modern scientific statistical approach, known as Rasch analysis,

Table 1
Electrophysiological indices sensitive to change in inflammatory neuropathies

Condition	Parameter	Characteristic for quantitation
GBS and CIDP	Distal CMAP	CMAP amplitude increase or reappearance reduction of CMAP duration prolongation (dispersion)
	Proximal CMAP	Reduction or disappearance of conduction block Reduction or disappearance of abnormal temporal dispersion
	DML	Reduction
	MCV	Increase
	F-wave latency	Reappearance, greater persistence
	SNAP amplitudes	Increase
MMN	Distal CMAP	CMAP amplitude increase or reappearance
	Proximal CMAP	Reduction or disappearance of conduction block Reduction or disappearance of abnormal temporal dispersion
	DML	reduction
	MCV	Increase
	F-wave latency	Reappearance, greater persistence

CMAP, compound muscle action potential; DML, distal motor latency; MCV, motor conduction velocity; SNAP, sensory nerve action potential.

which will include weighted linearly scaled items. Disease-specific and generic quality of life measures will be compared to each other. The ultimate goal of the *P*eri*N*omS study will be the presentation of a *specific* minimum core set of outcome measures to be used in future clinical and follow-up studies in patients with inflammatory polyneuropathies. The collaborative study will be performed in European and USA neurological centres experienced in dealing with inflammatory neurological disorders.

8. Electrophysiological outcome measures

Numerous sets of criteria have been published for the categorisation of electrophysiological divergence from normal as predominantly axonal or demyelinating. The main features of primary demyelination are maximal conduction velocity slowing, abnormal temporal dispersion, and conduction block. Since axonal degeneration may lead to varying degrees of conduction slowing and temporal dispersion with "pseudo-conduction block" due to interphase cancellation, there is a grey zone where it is virtually impossible to differentiate primary axonal from primary demyelinating neuropathies. The currently used electrophysiological criteria for the inflammatory neuropathies can be difficult in their application in individuals and trial groups, especially in forced dichotomous decisions and the inverse correlation of sensitivity and specificity. Possible solutions to these difficulties were proposed that included the optimization of the number of required electrophysiological abnormalities, the introduction and application of levels of probability (definite, probable, possible), and computerised optimization and validation of proposed criteria. The first two of these solutions have been presented in the EFNS/PNS guideline for management of CIDP [8].

An overview of known electrodiagnostic predictors of treatment response in GBS, CIDP, and MMN was given as a basis for the development of electrophysiological outcome measures (Table 1). A consensus was reached that further coordinated and focussed work is needed to develop and refine new and existing electrophysiological criteria in inflammatory neuropathies.

9. Conclusion

The workshop members developed plans for taking forward each of the prioritised trials and resolved to meet again in July 2007 at the Peripheral Nerve Society meeting in Utah. They thank the ENMC for providing the launching platform for INC.

In addition to the specific projects described above, the workshop recognised the need for more research into the pathogenesis of inflammatory neuropathy to enable the more rational design of new treatments. They also recognised the need for better education of health care professionals to enable the earlier diagnosis of these potentially treatable diseases.

10. Participants

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