Neuromuscular Disorders 18 (2008) 85–89

www.elsevier.com/locate/nmd

Workshop report

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

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Received 29 June 2007

Keywords: Inflammatory neuropathy; Controlled trials; Chronic inflammatory demyelinating polyradiculoneuropathy; Guillain-Barré syndrome; Multifocal motor neuropathy; Paraproteinaemic demyelinating neuropathy; Clinical scales; Electrophysiology

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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[1] List of members of the workshop appears at the end of this report.

0960-8966/$ - see front matter
doi:10.1016/j.nmd.2007.08.004

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