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## CHAPTER 9

# Intravenous immunoglobulin in the treatment of neurological diseases

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### Background

Intravenous immunoglobulin (IVIG) has been successfully used to treat a number of immune-mediated diseases of the central and peripheral nervous system. Although the underlying mechanisms of the action of IVIG have not been fully explained, it is known that it can interfere with the immune system at several levels. The effect of IVIG in any particular disease may not be attributed to only one of its action mechanism, because the pathophysiology of these diseases is complex. IVIG has been used as a first-line therapy in Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and dermatomyositis (DM). It may be used also in diseases of neurotransmission, multiple sclerosis (MS) and in some rare neurological disorders of adults and children, including Rasmussen's encephalitis (RE), stiff-person syndrome (SPS) and post-polio syndrome (PPS). In this chapter we review the available literature on the use of IVIG in treatment of neurological diseases and offer evidence-based recommendations for its use in these disorders.

### Search strategy

The Task Force systematically searched Ovid Medline and several other sources to a set of predefined key questions. The final search was performed in December 2007. Recent papers of high relevance were reviewed. Consensus was reached by discussions during a Task Force meeting. Evidence was classified as Class I–IV and recommendations as Level A–C according to the current EFNS guidelines [1]. When only Class IV evidence was available the Task Force has offered advice as good practice points.

### Mechanisms of action of IVIG in neurological diseases

Despite over 25 years' usage in autoimmunity, how concentrated non-host immunoglobulins, delivered intravenously, produce their clinical effect remains unknown. Of many potential mechanisms of action [2], whether one (unlikely), all (also unlikely) or several in combination are important remains obscure. It is likely that different effects are relevant in different disorders. We here

consider the range of possible actions of IVIG, highlighting effects that appear especially pertinent in specific neurological disorders.

The possibility that IVIG works through non-immune mechanisms [3] (e.g., binding and removal of microbial toxins or targeting their surface antigens) is perhaps less relevant in neurology. However, direct actions on oligodendrocyte progenitors have been postulated to explain an effect in promoting experimental remyelination [4, 5], although alternative mechanisms are possible [6–9].

More direct, immune-modulating effects are generally considered more neurologically relevant. T-cell proliferation is reduced by IVIG [10], various pro-inflammatory cytokines are suppressed, including interleukin-1, tumour necrosis factor- $\alpha$  and  $\gamma$ -interferon, and lymphocyte and monocyte apoptosis is induced [11]. Endogenous immunoglobulin production and B-cell differentiation are suppressed, and IgG catabolism is accelerated by IVIG [3]. Therapeutic immunoglobulins exert Fc region-mediated inhibition of antibody production; they also modulate anti-idiotypic networks vital to immune tolerance.

In addition, IVIG contains anti-idiotypic antibodies that bind to F(ab) to neutralize autoantibodies – a mechanism involved in GM1-related neuropathy and perhaps GBS [12, 13]. Finally considering cytopathic immune effectors, IVIG interferes with the complement system: the beneficial effects of IVIG are associated with the disappearance of complement in the muscles [14], involved suppression of macrophage function through induction of increased  $\Phi$ Fc $\gamma$ RII-B expression, reducing phagocytic activity.

## Guillain-Barré syndrome

The proposed autoimmune aetiology led to the introduction of immunotherapy. Before its introduction, 10% of patients died and 20% were left seriously disabled [15]. Plasma exchange (PE) was introduced as a possible treatment in 1978 and was shown to offer significant benefit by a randomized trial published in 1985 [16, 17]. It became the gold standard against which other treatments were measured [18].

Intravenous immunoglobulin was introduced for GBS in 1988 [19]. In 1992, the first randomized trial compar-

ing IVIG and PE showed similar effects for each treatment [20]. In five trials (total 582 participants), the improvement on the disability grade scale with IVIG was very similar to that with PE, (95% CI 20.25–0.20) [20–24]. The effectiveness of IVIG has been shown in GBS patients unable to walk unaided (GBS disability score  $\geq 3$ ) who were started on IVIG within the first 2 weeks after onset of weakness. Results from PE studies indicate that PE is also effective when applied in patients less severely affected [25] and in patients who are treated within the first 4 weeks from onset [17]. This has not been investigated in studies of IVIG treatment. Although PE was more frequently discontinued, there was also no significant difference between IVIG and PE for other outcome measures [23]. One trial compared PE alone with PE followed by IVIG: the 128 patients who received both treatments did not have significant extra benefit after 4 weeks of treatment compared with the 121 patients who received PE alone [22].

In children, who may have a better prognosis than adults, limited evidence from three open trials suggests that IVIG hastens recovery compared with supportive care alone [26–28], a finding supported by a good quality observational study [29].

A recent trial reported possible minor short-term benefit when high-dose intravenous methylprednisolone was combined with IVIG [30]. The significance of this benefit has been debated [31].

The comparisons of IVIG and PE showed no difference in the long-term outcome. Neither IVIG, PE nor any other treatment significantly reduces mortality, which ranged from 5% to 15% in hospital and population-based studies [32].

Only limited information is available concerning the dosage of IVIG. The usual IVIG regimen is 0.4 g/kg/day for 5 days. In a French trial, 3 days of 0.4 g/kg daily was slightly, but not significantly, less effective than 6 days of 0.4 g/kg daily [25].

In retrospective studies, patients with antibodies to ganglioside GM1 or GM1b treated with IVIG recovered faster than those treated with PE [33–35]. There is no evidence that it is better to administer IVIG (2 g/kg) in 2 or in 5 days. There is some indication that administration in 2 days may lead to a greater proportion of patients with a relapse [28].

Information is also lacking about how to treat patients who deteriorate or fail to improve after being treated with

IVIG or PE. It is common practice to re-treat patients who improve or stabilize and then relapse with IVIG (2 g/kg in 2–5 days) or PE. There is some indication that relapses occurring after 9 weeks may indicate that the patient had acute-onset CIDP [36]. Some centres treat patients again if they fail to improve after about 2–3 weeks, but evidence for this is lacking [37]. Whether mildly affected GBS patients (able to walk unaided) or patients with Miller Fisher syndrome should be treated with IVIG has not been studied. There is also no study available indicating that a second IVIG course is justified in patients who seem to be unresponsive to IVIG.

### Recommendations

IVIG 0.4 g/kg/day for 5 days or PE can be used as first-line treatment and are considered to be equally effective (Level A). IVIG has milder side-effects than PE and this would favour IVIG over PE treatment (Level B). IVIG treatment after PE, as standard combination, does not produce significant extra benefit and cannot be recommended (Level B). Combining high-dose intravenous methylprednisolone with IVIG may have a minor short-term benefit (Level C). Children, who generally have a better prognosis, should be treated with IVIG as first-line treatment (Level C). Patients who improve after IVIG and then relapse should preferentially be treated with a second course of IVIG (good practice point). In patients who seem to be unresponsive to the first course of IVIG a second course may be tried, but evidence supporting this is lacking (good practice point). No recommendations can be given for whether mildly affected GBS patients or patients with Miller Fisher syndrome should be treated with IVIG.

## Chronic inflammatory demyelinating polyradiculoneuropathy

Seven randomized controlled trials (RCT) with IVIG have been performed, including 284 patients with CIDP, and have been summarized in a Cochrane systematic review [38, 39, 40, 41, 42, 43, 44]. Four RCTs compared 2 g/kg bodyweight of IVIG [40, 42, 43, 44, 45], administered over 2 or 5 days with placebo, one compared IVIG with a 6-week course of oral prednisolone tapering from 60 to 10 mg daily [41], and one compared 1.8 g/kg bodyweight of IVIG in a course of 6 weeks with PE twice weekly for 3 weeks then once weekly for another 3 weeks [38]. Each study used different outcome measures impeding assessment.

Meta-analysis of the five placebo-controlled trials (232 patients) showed that IVIG produces significant improvement in disability lasting 2–6 weeks with a relative benefit of 2.0, 95% CI 1.48–2.71 (Class I) [39]. The benefit difference is 27%, which gives the number needed to treat (NNT) of 3.7, 95% CI 2.36–6.4. The two crossover trials comparing PE with IVIG and prednisolone with IVIG did not show a significant short-term difference, but the samples were too small to establish equivalence (both Class II) [39]. Both trials had other methodological issues. However, there are many observational studies reporting a beneficial effect from corticosteroids except in pure motor CIDP in which they have sometimes appeared to be harmful (Classes III and IV) [46, 47]. Apart from the treatment of pure motor forms of CIDP, there is no evidence to justify a different approach for other variants of CIDP [46].

Controlled long-term data on disability are available from the largest trial only ( $n = 117$ ) [45]. The initial loading dose of 2 g/kg was followed by a maintenance dose of 1 g/kg every 3 weeks. After 24 weeks of treatment, mean change from baseline disability was  $-1.1$  (SD 1.8) in the IVIG treatment group and  $-0.3$  (SD 1.3) in the placebo treatment group (weighted mean difference  $-0.8$  [95% CI  $-1.37$  to  $-0.23$ ]). In the second part of the study, after patients were again randomized for IVIG or placebo, a similar effect was found. A long-term, open follow-up in 84 CIDP patients responding to IVIG treatment reported remission in most patients. Seventy-three patients (87%) needed at least two courses; median time to remission was 2.1 years; and 10% of patients needed IVIG for more than 8.7 years [48].

### Recommendations

Patients with very mild symptoms which do not or only slightly interfere with activities of daily living may be monitored without treatment (good practice point). Treatment should be considered for patients with moderate or severe disability. IVIG (2 g/kg in 2–5 days) (Level A) or corticosteroids (1 mg/kg or 60 mg daily) (Level B) can be used as first-line treatment in sensorimotor CIDP. The presence of relative contraindications to either treatment should influence the choice (good practice point). For pure motor CIDP, IVIG treatment should be first choice and if corticosteroids are used, patients should be monitored closely for deterioration (good practice point). If a patient responds to IVIG, attempts should be made at intervals to reduce the dose to discover whether the patient still needs

IVIG and what dose is needed (good practice point). It is important to avoid deterioration sometimes seen just before the next IVIG course. The treatment intervals should be such that this does not occur. If a patient becomes stable on intermittent IVIG, the dose should be reduced before the frequency of administration is lowered (good practice point). These recommendations are in line with the EFNS guideline on the management of CIDP previously published [46].

## Multifocal motor neuropathy

There are few treatment options for people with MMN. MMN does usually not respond to steroids or PE, and patients may deteriorate when they receive these treatments [49, 50, 51, 52]. The efficacy of IVIG has been suggested by many open, uncontrolled studies; in 94 case reports (487 MMN pts), published between 1990 and 2004, an improvement of muscle weakness was seen in 81% of patients and an improvement of disability was seen in 74% (Class IV) [53]. Four RCTs of IVIG for treating MMN have been performed [54, 55, 56, 57]. These four trials encompass 45 patients, of whom 34 were randomly assigned to IVIG or placebo and have been summarized in a Cochrane systematic review [53]. Different disability scales were used, making the primary end-point of change in disability difficult to assess. Disability showed a trend for improvement with IVIG, however this was not significant ( $P = 0.08$ ). IVIG treatment was significantly superior to placebo in achieving an improvement in muscle strength ( $P = 0.0005$ ; NNT 1.4, 95% CI 1.1–1.8) (Class I). As weakness is the only determinant of disability in patients with MMN, it is to be expected that in patients whose muscle strength improves after IVIG treatment, disability will improve as well.

Elevated anti-ganglioside GM1 antibodies and definite conduction block have been shown to be correlated with a favourable response to IVIG (Class IV) [58]. Approximately a third of patients have a sustained remission (>12 months) with IVIG alone; approximately half of patients need repeated IVIG infusions and, of them, half need additional immunosuppressive treatment [59]. The effect of IVIG declines during prolonged treatment even when dosage is increased, probably due to ongoing axonal degeneration [60, 61]. However, in one retrospective study, treatment with higher than normal maintenance

doses of IVIG (1.6–2.0 g/kg over 4–5 days) promoted re-innervation, decreased the number of conduction blocks and prevented axonal degeneration in 10 MMN patients for up to 12 years [62].

### Recommendations

As there is no other treatment of proven benefit, the recommendation is to use IVIG (2 g/kg in 2–5 days) as a first-line treatment (Level A). If the initial IVIG treatment is effective, repeated infusions should be considered (Level C). A considerable number of patients need prolonged treatment, but attempts should be made to decrease the dose to discover whether a patient still needs IVIG (good practice point). Furthermore, the frequency of maintenance therapy should be guided by the individual response, whereby typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks (good practice point). A recent European guideline on the management of MMN summarizes the other treatment options [63].

## Paraproteinaemic demyelinating neuropathy

Paraproteinaemia, also known as monoclonal gammopathy, is characterized by the presence of abnormal immunoglobulin (M protein) produced by bone marrow cells in blood. The different types of immunoglobulin are classified according to the heavy chain class as IgG, IgA or IgM. The non-malignant paraproteinaemias are generally referred to as monoclonal gammopathy of undetermined significance (MGUS).

Paraproteins are found in up to 10% of patients with peripheral neuropathy not secondary to another primary illness [64]. In about 60% of patients with MGUS-related neuropathy the paraprotein belongs to the IgM subclass [65]. In almost half of patients who have IgM MGUS and a peripheral neuropathy, the M protein reacts against myelin-associated glycoprotein [66]. The most common type of IgM MGUS-related peripheral nerve involvement is a distal, symmetrical demyelinating neuropathy. Patients with IgG or IgA paraproteinaemic neuropathy usually have both proximal and distal weakness and sensory impairment that is indistinguishable from CIDP.

Two randomized placebo-controlled crossover trials with IVIG have been performed, encompassing 33

patients with IgM paraproteinaemic demyelinating neuropathy [67, 68] (Class II). A third randomized study was an open parallel group trial with 20 patients, which compared IVIG and recombinant interferon- $\alpha$  [69] (Class II). The results of these three trials have been summarized in a Cochrane review [70], which concluded that IVIG is relatively safe and may produce some short-term benefit. There are six Class IV studies [71, 72, 73, 74, 75, 76] with 56 patients treated with IVIG. Of these, 26 showed improvement ranging from transient relief of paraesthesiae to a clear-cut response with a marked gain in daily activities. In an EFNS guideline article the use of IVIG in IgM paraproteinaemic demyelinating neuropathy was recommended only in patients with significant disability or rapid worsening [77].

No controlled trials were available on the effects of IVIG in IgG or IgA paraproteinaemic neuropathy. There is one retrospective review of 20 patients with IgG MGUS neuropathy treated with IVIG; beneficial response was found in 8 [78] (Class IV). An open prospective trial of IVIG reported clinical improvement in 2 of 4 patients with IgG MGUS [72] (Class IV). In a review which included 124 patients with IgG MGUS neuropathy, 81% of the 67 patients with a predominantly demyelinating neuropathy responded to the same immunotherapies used for CIDP (including IVIG) as compared with 20% of those with axonal neuropathy [79] (Class IV). A Cochrane review states that observational or open trial data provide limited support for the use of immunotherapy, including IVIG, in patients with IgG and IgA paraproteinaemic neuropathy [80]. The EFNS guideline concludes that the detection of IgG or IgA MGUS does not justify a different approach from CIDP without a paraprotein [77].

### Recommendations

IVIG should be considered as the initial treatment of demyelinating IgM MGUS-related neuropathy (Level B). While the long-term effects and cost-benefit aspects are unknown, routine use of IVIG cannot be recommended in patients without significant disability (good practice point). However, in patients with significant disability or rapid worsening, IVIG may be tried, although its efficacy is not proven (good practice point). In patients with CIDP-like neuropathy, the detection of paraproteinaemia does not justify a different therapeutic approach from CIDP without a paraprotein.

## Paraneoplastic syndromes

Due to the low incidence of immunologically mediated paraneoplastic diseases, there are very few prospective, randomized, double-blind and placebo-controlled studies. Paraneoplastic syndromes involving peripheral nervous system, such as Lambert-Eaton myasthenic syndrome (LEMS) and neuromyotonia, are considered to respond best to immunosuppressive treatment. However, there is only one report showing the beneficial but short-term effect of IVIG on the muscle strength in LEMS (Class II) [81]. Nevertheless, a recent Cochrane review has concluded that limited data from one placebo-controlled study show improvement in muscle strength after IVIG [82]. The IVIG response regarding improvement of muscle strength probably does not differ in paraneoplastic and non-paraneoplastic LEMS. Only one case report describes the beneficial effect of IVIG in patient with neuromyotonia [83], while another demonstrated worsening after IVIG therapy [84]. Symptoms in paraneoplastic opsoclonus-ataxia syndrome in paediatric neuroblastoma patients are stated to improve, although data on the long-term benefits of the treatment are lacking (Class IV) [85]. In adults the response is less immunosuppressive, although IVIG is suggested to accelerate recovery (Class IV) [86]. Evidence for the effect of IVIG in paraneoplastic cerebellar degeneration, limbic encephalitis and sensory neuropathy is scarce. In previously published reports, patients were treated with a combination of immunosuppressive or immunomodulatory drugs, including IVIG, with a poor response (Class IV) [87].

### Recommendations

Intravenous immunoglobulin therapy may be tried in paraneoplastic LEMS and opsoclonus-ataxia, especially in paediatric neuroblastoma patients (good practice point). No clear recommendations of the effect of IVIG in paraneoplastic neuromyotonia, cerebellar degeneration, limbic encephalitis or sensory neuropathy can be made due to lack of data.

## Inflammatory myopathies

Three categories of inflammatory myopathy are reviewed based on published IVIG trials: DM, polymyositis and sporadic inclusion body myositis (IBM). Common

diagnostic criteria based on neuropathological muscle biopsy findings are widely accepted in DM and in s-IBM, whereas there are diverging opinions regarding nosology of polymyositis.

### Dermatomyositis

Published data are available on one RCT, one non-RCT, one retrospective chart review and four case-series. One 3-month, randomized crossover trial compared IVIG and prednisone to placebo and prednisone in 15 therapy-resistant patients [88]. Patients on IVIG significantly improved by symptom scale ( $P = 0.035$ ) and a modified MRC scale ( $P = 0.018$ ) (Class II). One retrospective chart review [89] and two case-series [90, 91] tried IVIG as an add-on therapy (Class III). Together, 82% improved clinically in these studies. One non-randomized trial and one case-series included patients with DM or polymyositis [92, 93]. The outcome in both was positive but as these were pooled data results on patients with DM could not be separated (Class IV).

#### Recommendations

IVIG is recommended as a second-line treatment in combination with prednisone for patients with DM who have not adequately responded to corticosteroids (Level B). IVIG is recommended, in combination with immunosuppressive medication, as a measure to reduce the dose of steroids in patients with DM (Level C). IVIG is not recommended as a monotherapy for DM (good practice point). In severe, life-threatening DM, IVIG can be considered as the first-line treatment together with other immunosuppressive therapy (good practice point).

### Inclusion body myositis

Three RCTs with small-to-moderate numbers of patients were published. Two were crossover trials comparing IVIG to placebo in 19 patients [94] and 22 patients [95] (Class II). The outcome was negative even if some symptomatic positive effects were recorded. In one RCT, IVIG plus prednisone was compared with placebo plus prednisone in 35 patients [96] (Class II). Here too the outcome was negative.

The available data provide results of three fairly small randomized trials. The overall outcome was negative even though a small number of patients reported benefits regarding swallowing difficulties.

#### Recommendation

IVIG cannot be recommended for the treatment of sporadic IBM (Level A).

### Polymyositis

Only one non-RCT [97] (Class III) and two case-series (Class IV) (see above, DM) on IVIG therapy for polymyositis have been published. Only the first used IVIG exclusively in patients with polymyositis. This study reported clinical improvement in 71% of patients, with significant improvement in muscle strength, muscle disability scores and creatinine kinase levels ( $P < 0.01$ ). Steroid doses could be reduced after IVIG ( $P < 0.05$ ).

Intravenous immunoglobulin can apparently be considered as an alternative in patients who do not respond to conventional immunosuppressive treatment. Dose and duration of the treatment are as recommended for DM.

#### Recommendation

IVIG may be considered among the treatment options for patients with polymyositis not responding to first-line immunosuppressive treatment (Level C).

### Myasthenia gravis

Myasthenia gravis (MG) is caused by autoantibodies against antigen in the post-synaptic neuromuscular membrane; in most patients against the acetylcholine receptor (AChR), in 5% against muscle-specific tyrosin kinase (MuSK) and in 5% against undefined antigen(s). A direct induction of muscle weakness by the autoantibodies has been shown. PE with removal of autoantibodies has a well-documented effect [98].

An improvement of muscle weakness in MG by IVIG treatment has been documented by five controlled, prospective studies, comprising 338 patients. The three largest studies represent Class I evidence [99, 100, 101], the other two smaller studies Class II evidence [102, 103]. The only placebo-controlled study examined short-term treatment of 51 MG patients with increasing weakness. A significant improvement of a quantitative MG score for disease severity was found due to an effect in the patients with more severe disease. The effect was present after 2

weeks and was maintained after 4 weeks. The other four studies showed that IVIG had roughly the same efficacy as PE as acute treatment for MG exacerbations (Class I). It has a tendency for a slightly slower effect of IVIG, and also fewer side effects. No MG-specific side-effects were reported. There was no significant superiority of IVIG 2 g/kg over 2 days compared with 1 g/kg on a single day, but a trend for the slight superiority for the higher dose [100]. The changes of anti-AChR antibody titre were not significant [99, 102].

There are several additional reports on prospective or retrospective MG patient materials treated with IVIG for acute exacerbations, some of them comparing with other treatments (Class III and IV). The dose used was mostly 2 g/kg. These studies show a significant improvement after IVIG in all muscle groups, the improvement starting after 3–6 days [104, 105, 106, 107, 108, 109].

For MG patients with anti-MuSK antibodies there are case reports of a positive effect of IVIG [110, 111]. In the only placebo-controlled prospective study, 14 patients with anti-MuSK antibodies and 13 patients without detectable antibodies were included [101]. Results were not reported for antibody subgroups, but overall results indicate an improvement also in the non-AChR antibody positive MG patients (Class IV).

A recent EFNS guideline document and two recent Cochrane reviews concluded that IVIG is a well-documented, short-term treatment for acute exacerbations of MG and for severe MG [98, 112]. It has been discussed whether PE has a more rapid effect than IVIG for MG crisis, but this has not been convincingly established in controlled studies.

Intravenous immunoglobulin is often used to prepare MG patients for thymectomy or other types of surgery. This is especially recommended for those with severe weakness, bulbar symptoms, poor pulmonary function or a thymoma. There are no controlled studies for this practice. However, the well-documented, short-term effect of IVIG in acute exacerbations is useful in the post-operative situation (good practice point). IVIG is widely recommended for severe MG or MG exacerbations during pregnancy and also before giving birth. This is partly due to its effect on muscle strength, partly to its safety profile. Similarly, IVIG has been recommended for neonatal MG [113] (good practice point).

Intravenous immunoglobulin has been proposed as long-term maintenance therapy for MG. Such treatment

has only been examined in open-label studies, including a small number of patients with severe MG. These studies report significant improvement starting after a few days and continuing for up to 2 years [114, 115, 116] (Class IV). Maintenance IVIG treatment was given every 1–4 months. However, no control groups were included, the number of patients was low and the patients received other immunoactive and symptomatic therapy as well. Recent EFNS Task Force guidelines, a Cochrane review and other guideline documents conclude that there is insufficient evidence to recommend IVIG as maintenance therapy for MG patients [98, 112, 113].

### Recommendations

Intravenous immunoglobulin is an effective treatment for acute exacerbations of MG and for short-term treatment of severe MG (Level A). IVIG is similar to PE regarding its effect. The treatment is safe for children, during pregnancy and for elderly patients with complicating disorders. There is insufficient evidence to recommend IVIG for chronic maintenance therapy in MG alone or in combination with other immunoactive drugs.

### Post-polio syndrome

Post-polio syndrome is characterized by new muscle weakness, muscle atrophy, fatigue and pain developing several years after acute polio. Other potential causes of the new weakness have to be excluded [117, 118]. The prevalence of PPS in patients with previous polio is 20–60%. The prevalence of previous polio shows great variation according to geography. In Europe the last major epidemics occurred in the 1950s and mainly affected small children. Present prevalence of polio sequelae in most European countries is probably 50–200/100,000.

Post-polio syndrome is caused by an increased degeneration of enlarged motor units, and some motor neurones cannot maintain all their nerve terminals. Muscle overuse may be a contributory factor. Immunological and inflammatory signs have been reported in the cerebrospinal fluid and central nervous tissue [119].

There are two RCTs ( $n=155$  patients) of treatment with IVIG in PPS (Class I) [120, 121]. In addition, there is one open and uncontrolled study of 14 patients [122] and one case report [123] (Class IV). In the study with

highest power, a significant increase of mean muscle strength of 8.3% was reported after two IVIG treatment cycles over 3 months. Physical activity and subjective vitality also differed significantly in favour of the IVIG group [121]. The smaller study of 20 patients and one-cycle IVIG found a significant improvement of pain but not of muscle strength and fatigue in the active treatment group [120]. The open study reported a positive effect on quality of life [122]. The report of an atypical case with rapid progression of muscle weakness described a marked improvement of muscle strength [123]. IVIG treatment reduced pro-inflammatory cytokines in the cerebrospinal fluid [119, 120].

Post-polio syndrome is a chronic condition. Although a modest IVIG effect has been described in the short term, nothing is known about its long-term effects. Responders and non-responders have not been defined. Any relationship between the clinical response to IVIG treatment and PPS severity, cerebrospinal fluid inflammatory changes and cerebrospinal fluid changes after IVIG is unknown. Optimal dose and IVIG cycle frequency has not been examined. Cost–benefit evaluation has not been performed. Non-IVIG interventions in PPS have recently been evaluated in an EFNS guideline article [117].

### Recommendations

IVIG has a minor-to-moderate positive effect on muscle strength and some aspects of quality of life in PPS (Class I). As long as responding subgroups, long-term effects, dosing schedules and cost–benefit aspects are unknown, routine use of IVIG for PPS cannot be recommended (good practice point). However, in the very few patients with especially rapid progression of muscle weakness and atrophy, especially if there are indications of ongoing low-grade inflammation in the spinal cord, IVIG may be tried if a rigorous follow-up of muscle strength and quality of life can be undertaken (good practice point).

## IVIG in multiple sclerosis

Four randomized double-blind studies have all shown a beneficial effect on disease activity in relapsing–remitting multiple sclerosis (RRMS) [124, 125, 126, 127]. All four studies have been rated as Class II due to limitations in methodology or size. IVIG 0.15–0.2 g/kg every 4 weeks

for 2 years showed a pronounced reduction in relapse rate in two placebo-controlled trials, 59% in a study by Fazekas et al. [125] and 63% in the study by Achion et al. [124]. In the largest 2-year study of 150 patients, IVIG showed a significant beneficial effect on the expanded disability status scale (EDSS) change from baseline compared with placebo ( $P = 0.008$ ) [125]. A small study of two different doses of IVIG (0.2 or 0.4 g/kg every 4 weeks) showed a reduction in relapse rate compared with placebo, but no difference between the two IVIG doses [126]. A crossover study in RRMS patients showed a beneficial effect of IVIG 2 g/kg every 4 weeks on new gadolinium-enhancing lesions in MRI compared with placebo [127].

A meta-analysis of four studies showed a significant reduction of the annual relapse rate (effect size divided by 0.5;  $P = 0.00003$ ) and of disease progression (effect size divided by 0.25;  $P = 0.04$ ) (Class I) [128].

Based on these studies IVIG was recommended as a second-line treatment in RRMS if s.c. or i.m. injectable therapies were not tolerated [129]. IVIG could not be included among first-line therapies, because of the limited evidence for clinical efficacy and because the optimum dose of IVIG had not been established.

Recently, the prevention of relapses with IVIG trial (PRIVIG) re-evaluating the effects of IVIG given 0.2 and 0.4 g/kg monthly failed to show an effect on the proportion of relapse-free patients and MRI activity in a placebo-controlled study of 127 patients with RRMS [130]. Thus, this trial failed to support earlier observations of a beneficial effect of IVIG in RRMS.

In a study of 91 patients with clinically isolated syndromes, IVIG significantly reduced the risk of conversion to clinically definite MS ( $P = 0.03$ ) and reduced new T2 lesions in MRI compared with placebo (Class II) [131].

In secondary progressive MS, a large placebo-controlled trial of IVIG 1 g/kg monthly in 318 patients failed to show any beneficial effect on relapse rate, deterioration in EDSS and change in lesion volume of T2-weighted images (Class I). The only beneficial effect was a reduction in brain atrophy [132]. Very recently, however, a placebo-controlled trial of IVIG 0.4 g/kg monthly for 2 years in 231 patients with either primary progressive MS ( $n = 34$ ) or secondary progressive MS ( $n = 197$ ) showed a borderline significant delay in time to sustained progression on EDSS ( $P = 0.04$ ), although the effect was limited to patients with primary progressive MS (Class II) [133].

Small studies with historical controls suggested that IVIG might reduce the relapse rate following childbirth (Class IV) [134, 135, 136].

Two studies of 76 and 19 patients with acute exacerbations showed that IVIG had no effect on recovery from acute relapses when given as add-on to i.v. methylprednisolone (Class II studies) [137, 138]. Chronic deficits in visual acuity or persistent stable muscular weakness were not affected by IVIG compared with placebo (Class I) [139, 140, 141].

### Recommendations

The negative results of the PRIVIG study challenge recommendations for IVIG as a second-line treatment for RRMS. However, IVIG could still be considered as a second- or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated because of side-effects or concomitant diseases (Level B), and in particular in pregnancy where other therapies may not be used (good practice point). IVIG cannot be recommended for treatment in secondary progressive MS (Level A). IVIG does not seem to have any beneficial effect as an add-on therapy to methylprednisolone for acute exacerbations (Level B) and cannot be recommended as treatment for chronic symptoms in MS (Level A). In clinically isolated syndromes and in primary progressive MS there is insufficient evidence to make any recommendations.

## Other demyelinating diseases of the central nervous system

Neuromyelitis optica, also called Devic's disease, is a demyelinating disease of the spinal cord and optic nerves which may manifest as recurrent attacks and tends to have a poor prognosis. There is only one case-type study suggesting that monthly IVIG was associated with cessation of relapses (Class IV) [142].

Balo's concentric sclerosis is a severe demyelinating disease with poor prognosis. There is a case report suggesting that IVIG (0.4 g/kg/daily for 5 days) and interferon- $\beta$ -1a given postpartum may result in partial neurological improvement (Class IV) [143].

Acute-disseminated encephalomyelitis (ADEM) is a monophasic immune-mediated demyelinating disease of the central nervous system and is associated with significant morbidity and mortality. Controlled studies on therapy in ADEM are not available. Standard treatment is high-dose steroids. The use of IVIG (0.4 g/kg/day for 5

days or 1 g/kg/2 days) has been reported in case reports and small series suggesting that IVIG may have favourable effects when used as an initial therapy in both adults and children (Class IV) [144, 145, 146, 147, 148]. IVIG may have beneficial effects also as second-line therapy (Class IV) [149, 150, 151, 152], especially in patients who cannot receive or fail to respond to steroids (Class IV) [153, 154, 155] or in patients with peripheral nervous system involvement and steroid failure (Class IV). Alternatively, combination therapy by steroids and IVIG (Class IV) [156, 157, 158, 159, 160, 161] or steroids, IVIG and PE were suggested to have favourable effects, especially if given early in the course of disease (Class IV) [162, 163].

### Recommendations

IVIG may have a favourable effect in the treatment of ADEM and therefore it should be tried (0.4 g/kg/day for 4–5 consecutive days) in patients who fail to respond to high-dose steroids (good practice point). The cycles may be repeated. PE could also be considered in patients who do not respond to high-dose steroids.

## Stiff-person syndrome

Published data are available on one randomized, double-blind, placebo-controlled, crossover trial (Class I) [164], one national experts opinion (Class IV) [113], three non-controlled studies (Class IV) [165, 166, 167], two case series (Class IV) [168, 169], 16 case reports (Class IV) and five adequately powered systematic review of prospective randomized controlled clinical trials (Class I) [170, 171, 172, 173, 174].

The randomized trial [164] enrolled 16 SPS patients who were treated with 2 g/kg IVIG, divided in two consecutive daily doses of 1 g/kg, or placebo for 3 months. After a washout period of 1 month, the patients crossed over to the alternative therapy for a further 3 months. All patients were followed for at least 3 months after the infusions. The results of the trial showed a significant decline of the stiffness scores in the IVIG-randomized patients from month 1 through 4, and rebound when they crossed to placebo. The scores in the placebo-randomized group remained constant from month 1 to 4 and dropped significantly after crossing to IVIG. Eleven

of 16 patients who received IVIG became able to walk unassisted. The duration of benefit varied from 6–12 weeks to up to 1 year. The serum titres of anti-GAD antibody declined after IVIG, but not after placebo. This study has demonstrated that IVIG is a safe and effective therapy for patients with SPS.

According to uncontrolled studies IVIG improved the quality of life in six patients with SPS [165] and resulted in substantial objective improvement in two groups, each composed of three patients with SPS [166, 167]. Two case-series showed clinical improvement in five of six patients treated with IVIG [168, 169].

### Recommendations

In patients with SPS incompletely responding to diazepam and/or baclofen and with significant disability requiring a cane or a walker due to truncal stiffness and frequent falls, the recommendation is to use IVIG (2 g/kg for 2–5 days) (Level A, based on Class I).

## Drug-resistant infantile epilepsy

Drug-resistant infantile epilepsy (DRIE) includes such diseases as Landau-Kleffner syndrome (LKS), West syndrome, Lennox-Gastaut syndrome, severe myoclonic epilepsy and RE which typically manifest in childhood or adolescence and are characterized by epilepsy and progressive neurological dysfunction. Standard treatment of RE consists of anti-epileptic drugs, high-dose steroids or PE. Surgical treatment also may be considered. Case studies and small series have reported that some patients with RE respond in some measure to treatment with IVIG (Class IV) [175, 176].

Approximately 100 patients with West syndrome or Lennox-Gastaut syndrome have been treated with IVIG with widely varying results [176, 177]. The treatment has resulted in a reduction in the number of seizures with improvement in the EEG in about half the cases. The positive effects were noted a few days to several weeks to months after treatment. Relapses have been common.

Successful use of IVIG as the initial monotherapy in LKS has been reported in case studies [178, 179] and after initial therapy by steroids [180] or antiepileptic drugs and steroids [181, 182] in few patients [183].

Case studies on the use of IVIG in RE have suggested that monthly IVIG therapy (0.4 g/kg for 5 days at 4-week

intervals followed by monthly maintenance IVIG) may ameliorate disease in patients who are refractory to antiepileptic drugs [184] or steroids and PE [185].

### Recommendation

IVIG seems to have a favourable effect in RE and may be tried in selected patients who are refractory to other therapies (good practice point). IVIG has been administered at doses of 0.4 g/kg/day for 4–5 consecutive days; the cycles may be repeated after 2–6 weeks.

## Side-effects of IVIG

Side-effects in PE and IVIG therapy have been reported in several studies (20–24). They reported more instances of pneumonia, atelectasis, thrombosis and haemodynamic difficulties related to PE than IVIG. The incidents related to IVIG included hypotension, dyspnoea, fever and haematuria, nausea or vomiting, meningism, exacerbation of chronic renal failure, possible myocardial infarction and painful erythema at the infusion site. The side-effects of IVIG in the treatment of neurological autoimmune diseases have been studied prospectively during 84 treatment courses with a total 341 infusions under routine clinical conditions [186]. Headache occurred during 30% of treatment courses. Severe adverse events leading to discontinuation of the treatment were noted in approximately 4% of all treatment courses. They included thrombosis of the jugular vein, allergic reaction and retrosternal pressure. The changes in blood laboratory findings included abnormalities of liver enzymes, changes for leucocytes, erythrocytes, haematocrit, haemoglobin, alanine aminotransferase and aspartateaminotransferase. None of these laboratory changes was clinically significant. Based on these data IVIG can generally be regarded as a relatively safe treatment. However, to avoid these complications careful monitoring of laboratory findings, including full blood count, liver enzymes and renal functions, should be mandatory [186].

## Conflicts of interest

Irina Elovaara has lectured on IVIG and participated in a trial on efficacy of IVIG in exacerbations of MS sponsored by Baxter.

None of the other Task Force members reported any conflict of interest.

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