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EFNS TASK FORCE/CME ARTICLE

EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases

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Despite high-dose intravenous immunoglobulin (IVIG) is widely used in treatment of a number of immune-mediated neurological diseases, the consensus on its optimal use is insufficient. To define the evidence-based optimal use of IVIG in neurology, the recent papers of high relevance were reviewed and consensus recommendations are given according to EFNS guidance regulations. The efficacy of IVIG has been proven in Guillain-Barré syndrome (level A), chronic inflammatory demyelinating polyradiculoneuropathy (level A), multifocal mononeuropathy (level A), acute exacerbations of myasthenia gravis (MG) and short-term treatment of severe MG (level A recommendation), and some paraneoplastic neuropathies (level B). IVIG is recommended as a second-line treatment in combination with prednisone in dermatomyositis (level B) and treatment option in polymyositis (level C). IVIG should be considered as a second or third-line therapy in relapsing–remitting multiple sclerosis, if conventional immunomodulatory therapies are not tolerated (level B), and in relapses during pregnancy or post-partum period (good clinical practice point). IVIG seems to have a favourable effect also in paraneoplastic neurological diseases (level A), stiff-person syndrome (level A), some acute-demyelinating diseases and childhood refractory epilepsy (good practice point).

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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 underlying mechanisms of action of IVIG have not been fully explained, it is known that IVIG can interfere with the immune system at several levels. The effect of IVIG in one of particular diseases may not be attributed to only one of its mechanisms of action, 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

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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 paper we have reviewed the available literature on the use of IVIG in treatment of neurological diseases and are offering evidence-based recommendations for its use in these disorders.

Materials and methods

Search strategy

The task force systematically searched Ovid Medline and several other sources to a set of predefined key question. 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 (likewise) or several together are important remains obscure. Probably, different effects are relevant in different disorders. We here consider the range of possible actions of IVIG, stressing effects that appear especially pertinent in specific neurological disorders.

The possibility that IVIG works through non-immune mechanisms [3] – e.g. binding and removing 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-α and γ-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 disappearance of complement in the muscles [14], involved suppression of macrophage function through induction of increased Φ FcγRII-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 comparing IVIG and PE showed similar effects from each treatment [20]. In five trials with altogether 582 participants, the improvement on the disability grade scale with IVIG was very similar to that with PE, WMD 20.02 (95% CI 20.25–0.20) [20–24]. This 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 on 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 had 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], which is 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. IVIG nor PE or any other treatment does significantly reduce 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 administrate 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 worsen 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 again. 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 or 3 weeks but evidence for this practice 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 lesser 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 can not 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 re-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 such a strategy is lacking (good practice point). No recommendations can be given 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 [38–44]. Four RCTs compared 2 g/kg bodyweight of IVIG [40,42–45], 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 encumbering assessment.

Meta-analysis of the five placebo-controlled trials with altogether 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 evidence) [39]. The benefit difference is 27% which gives a 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 evidence) [39]. Both trials had also some 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 have a harmful effect (class III and IV evidence) [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 only available from the largest trial with 117 patients [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 re-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, 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 deterioration does not happen. 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 only few treatment options for people with MMN. MMN does usually not respond to steroids or PE, and patients may worsen when they receive these treatments [49–52]. 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 evidence) [53]. Four RCTs of IVIG for treating MMN have been performed [54–57]. These four trials encompass 45 patients. Thirty-four patients 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 under IVIG that however was not significant ($P = 0.08$). IVIG treatment was superior to placebo in inducing an improvement in muscle strength which was significant ($P = 0.0005$; NNT 1.4, 95% CI 1.1–1.8) (class I evidence). 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 evidence) [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 given 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 which is 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 50% 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-α [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 [71–76] with altogether 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 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 eight of them [78] (class IV). An open prospective trial of IVIG reported clinical improvement in two of four 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 provides limited support for the use of immunotherapy, including IVIG, in patients with IgG and IgA paraproteinaemic neuropathy [80]. EFNS guideline document 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 initial treatment of demyelinating IgM MGUS-related neuropathy (level B recommendation). As long as long-term effects and cost-benefit aspects are not known, 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 rarity 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 immunosupressive treatment. However, there is only one report showing the beneficial but short-term effect of IVIG on the muscle strength in LEMS (class II evidence) [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 does probably not differ in paraneoplastic and non-paraneoplastic LEMS. Only one case report describes the beneficial effect of IVIG in patient with neuromyotonia [83], whilst another case report demonstrated worsening after IVIG therapy [84]. Symptoms in paraneoplastic opsoclonus-ataxia syndrome in paediatric neuroblastoma patients are stated to improve, although data concerning the long-term benefits of the treatment is lacking (class IV evidence) [85]. In adult patients the response is less immunosuppressive, although IVIG is suggested to accelerate recovery (class IV evidence) [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 immunosupressive (pp) or immunomodulatory drugs, including IVIG, with a poor response (class IV evidence) [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 ($P = 0.018$) (evidence class II). One retrospective chart review [89] and two case series [90,91] tried IVIG as add-on therapy (evidence class III). Taken 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 (evidence 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 lower the dose of steroids in patients with DM (level C). IVIG is not recommended as 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-moderate numbers of patients were published. Two were crossover trials comparing IVIG to placebo in 19 patients [94] and 22 patients [95] (evidence 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] (evidence class II). Also here the outcome was negative.

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

Recommendation

IVIG can not be recommended for the treatment of sporadic IBM (level A).

Polymyositis

Only one non-RCT [97] (evidence class III) and two case series (evidence class IV) (see above DM) on IVIG therapy for polymyositis have been published. Only the first one used IVIG exclusively in patients with polymyositis. This study reported clinical improvement in 71% of patients with significant improvement in muscle power, 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 amongst 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. Three larger studies represent class I evidence [99–101], the two smaller ones class II evidence [102,103]. The only placebo-controlled study examined short-term treatment of 51 MG patients with worsening 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 evidence). It was a tendency for a slightly slower effect of IVIG, and also less 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 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 class IV evidence). The dose used has mostly been 2 g/kg. These studies show a significant improvement after IVIG in

all muscle groups, the improvement starting after 3–6 days [104–109].

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 evidence).

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 if PE has a more rapid effect than IVIG for MG crisis, but this has not been convincingly proven 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 maintenance, long-term therapy for MG. Such treatment has only been examined in open-label studies, including only small number of patients with severe MG. These studies report significant improvement starting after a few days and remaining for up till 2 years [114–116] (class IV evidence). 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, 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 effect. This treatment is safe also for children, during pregnancy and for elderly patients with complicating disorders. There is not sufficient 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 European countries the last big epidemics occurred in the 1950s, mainly affecting small children. Present prevalence of polio sequelae in most European countries is probably 50–200 per 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 contribute. Immunological and inflammatory signs have been reported in the cerebrospinal fluid and central nervous tissue [119].

There are two RCTs of treatment with IVIG in PPS (class I evidence) [120,121] including 155 patients. In addition, there is one open and uncontrolled study of 14 patients [122], and one case report [123] (class IV evidence). In the study with highest power, a significant increase of mean muscle strength of 8.3% was reported after two IVIG treatment cycles during 3 months. Physical activity and subjective vitality also differed significantly in favour of the IVIG group [121]. The smaller study with only 20 patients and one-cycle IVIG found a significant improvement of pain but not 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 short-term, nothing is known about 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 evidence). As long as responding subgroups, long-term effects, dosing schedules and cost-benefit aspects are not known, 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

Until recent, four randomized double-blind studies have all shown a beneficial effect on disease activity in relapsing–remitting multiple sclerosis (RRMS) [124–127]. All four studies have been rated class II because of limitations in methodology or size. IVIG 0.15–0.2 g/kg every 4 weeks during 2 years showed a pronounced reduction in relapse rate in two placebo-controlled trials, 59% in the 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 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 2.0 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 evidence) [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 amongst 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 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 clinical definite MS ($P = 0.03$) and reduced new T2 lesions in MRI compared with placebo (class II evidence) [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 evidence). 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 evidence) [133]. Small studies with historical controls suggested that IVIG might reduce relapse rate after childbirth (class IV evidence) [134–136].

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 evidence) [139–141].

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 clinical practice point). IVIG cannot be recommended for treatment in secondary progressive MS (level A). IVIG does not seem to have any valuable effect as 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 not sufficient evidence to make any recommendations.

Other demyelinating diseases of central nervous system

Neuromyelitis optica termed also Devic's disease, is a demyelinating disease of the spinal cord and optic nerves that may manifest by 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 evidence) [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 post-partum may result partial neurological improvement (class IV evidence) [143].

Acute-disseminated encephalomyelitis (ADEM) is a monophasic immune-mediated demyelinating disease of the central nervous system that 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 evidence) [144–148]. IVIG may have beneficial effects also as second-line therapy (class IV evidence) [149–152] especially in patients who could not receive or failed to respond to steroids (class IV evidence) [153–155] or in patients with peripheral nervous system involvement and steroid failure (class IV evidence). Alternatively combination therapy by steroids and IVIG (class IV evidence) [156–161] or steroids, IVIG and PE were suggested to have favourable effects especially if given early in the course of disease (class IV evidence) [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 with lack of response to high-dose steroids (good practice point). The cycles may be repeated. PE could also be considered in patients with a lack of response to high-dose steroids.

Stiff-person syndrome

Published data are available on one randomized, double-blind, placebo-controlled, cross-over trial (class I evidence) [164], on one national experts opinion (class IV evidence) [165], on three non-controlled studies (class IV evidence) [166–168], on two case series (class IV evidence) [169,170], on 16 case reports (class IV) and five adequately powered systematic review of prospective randomized controlled clinical trials (class I evidence) [171–175].

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 another 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 to 12 weeks or up to a 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 quality of life in six patients with SPS [166] and resulted in substantial objective improvement in two groups, each composed of three patients with SPS [167,168]. Two case series showed clinical improvement in five of six patients treated with IVIG [169,170].

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 in 2–5 days) (level A based on class I evidence).

Drug-resistant epilepsy

Drug-resistant infantile epilepsy (DRIE) include a number of diseases such as Landau-Kleffner syndrome (LKS), West syndrome, Lennox-Gastaut syndrome, severe myoclonic epilepsy or RE that 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) [176,177].

Approximately a hundred patients with West or Lennox-Gastaut syndromes have been treated with IVIG with widely varying results [177,178]. The treatment has resulted reduction in the number of seizures with improvement in the EEG in about half of the cases. The positive effects were noted few days to several weeks to months after treatment. Relapses have been common.

Successful use of IVIG as initial monotherapy in LKS has been reported in case studies [179,180] and after initial therapy by steroids [181] or antiepileptic drugs and steroids [182,183] in only few patients [184].

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 interval followed by monthly maintenance IVIG) may ameliorate disease in patients who are refractory to antiepileptic drugs [185] or steroids and PE [186].

Recommendation

IVIG seems to have a favourable effect in RE and may be tried in selected patients that 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.

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 [187]. Headache occurred during 30% of treatment courses. Severe adverse events leading to discontinuation of the treatment were noted in ca. 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 aspartate-amino transferase. None of these laboratory changes were clinically relevant. Based on these data IVIG can generally be regarded as relatively safe treatment. However, to avoid these complications careful monitoring of laboratory findings like full blood count, liver enzymes and renal functions should be mandatory [187].

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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