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# Intravenous Immunoglobulins in Neurological Diseases: Established and Novel Clinical Applications

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## 1. Introduction

Over the last decade, high-dose polyclonal intravenous immunoglobulin (IVIg) is used increasingly in the management of autoimmune conditions of the central and peripheral nervous system. Despite the expanded use of IVIg, the consensus on its optimal use is insufficient. Currently chronic idiopathic demyelinating polyneuropathy (CIDP), Guillain – Barre syndrome (GBS) and multifocal motor neuropathy (MMN) are the three major immune neuropathies, in which the latest evidence strongly supports the use of IVIg as a first-line therapy. In addition to these disorders, there is a rising number of other neurological indications in which IVIg has been used as a therapy, even though the available evidence-based data are relatively sparse and less convincing. Due to increasing costs of this treatment and relative shortage of products, careful selection of patients who will benefit from IVIg is extremely important (Elovaara & Hietaharju, 2010).

In this paper the current literature on the use of IVIG in treatment of neurological diseases has been reviewed and evidence-based recommendations, as well as less convincing data and future possibilities for its use in these disorders are presented.

## 2. IVIg in therapy of autoimmune neuropathies

Currently CIDP, GBS and MMN are the three major immune neuropathies, in which the latest evidence strongly supports the use of IVIg as a first-line therapy (level A recommendation). However, questions remain regarding the dose, timing and duration of IVIg treatment in these disorders. The efficacy of IVIg has been also proven in some paraneoplastic neuropathies (level B) (European Federation of Neurology Society [EFNS] task force, 2008; Elovaara & Hietaharju, 2010). There are other peripheral neuropathies in which there are reports of the efficacy of IVIg. These include diabetic amyotrophy, vasculitic peripheral neuropathy and painful sensory neuropathy associated with Sjogren's syndrome. The evidence for these conditions has been insufficient to earn a recommendation for the use of IVIg from national or international guidelines (Hughes et al, 2009).

### 2.1 Guillan-barre syndrome (GBS)

GBS is an autoimmune disorder of the peripheral nervous system. The incidence of GBS is approximately two per 100 000/year in adults. It may lead to respiratory failure requiring

artificial ventilation in up to 30% of patients and about 5% die in this disease (Hughes et al, 2006).

GBS consists of four major subtypes: acute inflammatory demyelinating polyneuropathy (AIDP); acute motor axonal neuropathy (AMAN); acute motor and sensory axonal neuropathy (AMSAN); and Fisher syndrome. The subtypes can be differentiated by clinical, electrophysiological and pathological findings. Diagnosis of GBS is made in the setting of the classic clinical scenario of a monophasic illness reaching a nadir within 4 weeks with symmetric weakness and sensory loss, areflexia and elevated cerebrospinal fluid (CSF) protein without pleocytosis. Presumed antecedent inciting events, such as infections, occur in up to 80% (van Doorn P.A. et al, 2008).

Molecular mimicry probably plays an important role in the pathogenesis. Infection with a pathological agent such as *Campylobacter jejuni* leads to the formation of cross-reacting antibodies. In AIDP, such cross-reacting anti-myelin or anti-ganglioside antibodies attack Schwann cell surface epitopes of motor and sensory fibres. Subsequent complement activation and macrophage infiltration leads to multi-focal inflammatory demyelination with conduction failure and secondary axonal degeneration. AMAN and AMSAN are characterized by axonal/nodal antibody binding, complement activation, macrophage attachment at nodes, opening of the periaxonal space and macrophage infiltration in motor axons in AMAN, or in motor and sensory axons in AMSAN (van Doorn P.A. et al, 2008).

The proposed autoimmune aetiology led to the introduction of immunotherapy. Before its introduction, 10% of patients died and 20% were left seriously disabled (EFNS task force, 2008). Plasma exchange (PE) was the first treatment of GBS that was shown to offer a significant benefit in randomized controlled trials (RCT) and became. The first RCT on the use of IVIg was published in 1992, followed later by other trials.

Even though both IVIG and PE are considered as first-line therapy for GBS, IVIG is usually favored over PE due to its simplicity and better availability. Standard therapy of IVIG is 0.4 g / kg given for 5 days, but there is only limited evidence concerning the optimal dosage. There are also other unanswered questions. Additional primary treatments are needed, as up to 20% of patients with GBS die or are unable to walk after 1 year. Treatments to enhance nerve regeneration and to improve function in existing but partially repaired nerves are also required. The Inflammatory Neuropathy Consortium of the Peripheral Nerve Society defined a need for trials of IVIg treatment in mild GBS and Fisher syndrome, an IVIg dose-finding study in GBS and studies on the use of complement inhibitors and sodium channel blockers (Hughes et al, 2009). The most urgent question is whether patients who continue to deteriorate after a standard course of IVIG should receive a second course or receive some other additional treatment. An international study concerning this last issue is about to be launched in the near future (Elovaara & Hietaharju, 2010).

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 shortterm benefit (level C).
- Children, who generally have a better prognosis, should be treated with IVIg as firstline treatment (level C).

- Patients who improve after IVIg and then relapse should preferentially be retreated 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. (EFNS task force, 2008).

## 2.2 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP is a progressive or relapsing autoimmune disease that targets the myelin sheaths of the peripheral nerves, leading to weakness, sensory loss and impairment of gait and coordination. It has a variable clinical course causing both temporary and permanent disability. There is no definitive test for CIDP, and in most patients diagnosis is based on the clinical presentation and demonstration of demyelinating abnormalities in electrodiagnostic studies (Hughes et al, 2009).

It has been shown to respond to several therapies, including corticosteroids, PE and IVIg. The efficacy of IVIg has been assessed in five RCTs including 235 participants. In addition, there is one RCT, which has compared IVIg with PE, and one study, which has compared IVIg with prednisolone. A recently published Cochrane review summarizes the results of these studies and concludes that IVIg therapy improves disability for at least 2–6 weeks compared with placebo (Eftimov et al., 2009). During this induction period IVIg has an efficacy similar to PE and corticosteroids.

The ICE study (Hughes et al, 2008) that is included in this review is not only the largest but also the longest reported RCT ever performed in CIDP patients. Furthermore, it was the first trial aimed to assess the long-term efficacy of IVIg. The results of ICE study unequivocally demonstrated a beneficial effect on disability that is sustained up to 48 weeks.

The initial dose used in the ICE study (2 g/kg) was similar to that used in practice. This dose was shown to be more effective than 1 g/kg or 0.25 g/kg, although higher doses were not examined. The initial dose is usually given over one or several days, depending on tolerability or convenience. Patients who do not respond to an initial dose may respond to subsequent doses. In the ICE study, 44% of responders improved by 3 weeks after the initial treatment, and an additional 50% of patients responded only after a second dose of 1 g/kg at week 3, as measured at week 6 of the study. However, it is not known whether even more patients would have improved if additional treatments had been given, as patients who did not show improvement, including those who were stable, were crossed-over at week 6. In clinical practice, initial responses have been seen up to 3 months into the treatment, and stabilization of previously progressive disease is considered to be a positive response (Hughes et al, 2009).

IVIg responsive patients in the ICE trial were treated with 1 g/kg every 3 weeks for up to 24 weeks, with the responsive patients re-randomized to continue treatment or placebo in phase 2 of the study for an additional 24 weeks. Continued improvement was observed in some patients at up to 32 weeks into the study. Approximately 50% of the responders in the first phase of the study suffered a relapse during phase 2 when switched to placebo. Given the goal of achieving maximal improvement, a reasonable strategy would be to continue treatment until the improvement plateaus, before stopping to see whether additional treatments are still needed. Discontinuing the treatments prior to that point would risk leaving the patient with less than optimal function.

CIDP patients with very mild symptoms may not need any treatment at all. Approximately 20% of the CIDP patients seem to improve spontaneously. Treatment should be considered for patients with moderate or severe disability. IVIg (2 g/kg in 2–5 days) or corticosteroids (1 mg/kg or 60 mg daily) are recommended as first-line treatment in sensory and motor CIDP (EFNS task force, 2008). For pure motor CIDP, IVIg treatment should be the first choice and if corticosteroids are used, patients should be monitored closely for deterioration. In patients with relapsing–remitting CIDP responding to IVIg, attempts should be made to reduce the dose in order to find out if the patient still needs IVIg and what is the adequate dose. In addition to IVIg, PE can be considered as a treatment of choice in long-term therapy of relapsing–remitting CIDP. A number of immunosuppressant and chemotherapeutic agents have been reported to be effective in open studies, but only azathioprine and interferon beta have been investigated in RCT, with negative results (Hughes et al, 2004).

CIDP is a treatable disease whose manifestations can be prevented by early diagnosis and treatment with IVIg. Additional efforts are needed, however, to develop more reliable diagnostic tests, establish optimal treatment regimens and increase awareness of this condition.

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) (EFNS task force, 2008).

### 2.3 Multifocal motor neuropathy (MMN)

MMN is a rare autoimmune disorder which may cause prolonged periods of disability due to progressive weakness of one or more limbs.

There are four RCTs, which have examined the effects of IVIg vs placebo in patients with MMN. The total number of participants in these trials was only 34. A Cochrane review, however, showed that muscle strength improved in 78% of patients treated with IVIg and only in 4% of those who received placebo (van Schaik et al, 2005).

Because both prednisolone and PE have proved to be ineffective and even harmful, and cyclophosphamide, even though moderately effective, has significant side effects in long-term use, IVIg remains the only beneficial treatment for MMN.

Approximately one third of patients with MMN have a sustained remission (>12 months) with IVIg alone and approximately half of the patients need repeated IVIg infusions (Leger et al, 2008). The effect of IVIg declines during prolonged treatment, even if the dosage is increased, probably due to ongoing axonal degeneration (Terenghi et al, 2004).



There is only one RCT on the use of an immunosuppressive agent as an additional therapy (Piepers et al, 2007). This study with 28 patients showed that mycophenolate mofetil neither produced significant benefit nor reduced the need for IVIg.

Elevated anti-ganglioside GM1 antibodies and definite conduction block have been shown to be correlated with a favourable response to IVIg (class IV evidence) (EFNS task force, 2008). 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 (Vucic et al, 2004).

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) (EFNS task force, 2008).

## 2.4 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. In about 60% of patients with MGUS-related neuropathy the paraprotein belongs to the IgM subclass. In almost 50% of patients who have IgM MGUS and a peripheral neuropathy, the M protein reacts against myelin-associated glycoprotein. 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 RCTs with IVIg have been performed, encompassing 33 patients with IgM paraproteinaemic demyelinating neuropathy (class II). A third randomized study was an open parallel group trial with 20 patients which compared IVIg and recombinant interferon- $\alpha$  (class II). The results of these three trials have been summarized in a Cochrane review, which concluded that IVIg is relatively safe and may produce some short-term benefit (Lunn & Nobile-Orazio, 2006).

No RCTs are 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 (class IV). An open prospective trial of IVIg reported clinical improvement in two of four patients with IgG MGUS (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 (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 (Allen et al, 2007).

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. (EFNS task force, 2008).

## 2.5 Diabetic amyotrophy

Lumbosacral radiculoplexus neuropathy (LRPN) originally described in diabetic patients as diabetic amyotrophy is a distinct clinical condition characterized by debilitating pain, weakness and atrophy most commonly affecting the proximal thigh muscles asymmetrically. The syndrome is usually monophasic and preceded by significant weight loss (at least more than 10 lbs). Though a self-limited condition, recovery is gradual with some residual weakness (Bhanushai & Muley, 2008).

- There are reports and small open studies of the efficacy of IVIg in diabetic amyotrophy (Hughes et al, 2009).

Recommendations:

- The evidence for this condition has been insufficient to earn a recommendation for the use of IVIg.

## 2.6 Vasculitic peripheral neuropathy

Vasculitic neuropathy is routinely considered as a vasculitis associated with neuropathy. The consensus definition of pathologically definite vasculitic neuropathy requires that vessel wall inflammation is accompanied by vascular damage. A case definition of clinically probable vasculitic neuropathy in patients lacking biopsy proof incorporates clinical features typical of vasculitic neuropathy: sensory or sensory-motor involvement, asymmetric/multifocal pattern, lower-limb predominance, distal-predominance, pain, acute relapsing course, and non-demyelinating electrodiagnostic features (Good Practice Points from class II/III evidence). (Collins et al, 2010). There are reports of the efficacy of IVIg in vasculitic peripheral neuropathy (Hughes et al, 2009).

Recommendations:

- The evidence for this condition has been insufficient to earn a recommendation for the use of IVIg.

## 2.7 Painful sensory neuropathy of Sjogren's syndrome

Primary Sjogren's syndrome is associated with seven forms of neuropathy: sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic

neuropathy and radiculoneuropathy, based on the predominant neuropathic symptoms. The majority of patients are diagnosed with Sjogren's syndrome after neuropathic symptoms appearance. Painful sensory neuropathy without sensory ataxia is the second more frequent form of neuropathy associated with Sjogren's syndrome. It is characterised by chronic progression of sensory symptoms without substantial motor involvement, although the affected sensory modalities and distribution pattern vary. Autonomic symptoms, like abnormal pupils and orthostatic hypotension are often seen. Unelicited somatosensory evoked potentials and spinal cord posterior column abnormalities in MRI are observed. Sural nerve biopsy specimens reveal variable degrees of axon loss, predominantly small fibre loss (Mori et al, 2005). Patients usually suffer from severe neuropathic pain, with small-fiber neuropathy causing lancinating or burning pain which can disproportionately affect the proximal torso or extremities, and the face (ie, in a "non-length-dependent distribution") (Birnbbaum, 2010).

There are reports and small open studies of the efficacy of IVIg in painful sensory neuropathy associated with Sjogren's syndrome (Hughes et al, 2009).

Recommendations:

- The evidence for this condition has been insufficient to earn a recommendation for the use of IVIg.

### 3. IVIg in therapy of myasthenia gravis (MG)

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. A direct induction of muscle weakness by the autoantibodies has been shown.

The efficacy of IVIg in the treatment of MG has been confirmed by five controlled, prospective studies that are summarized in a Cochrane review. In acute exacerbations of MG, IVIG and PE have roughly the same efficacy, but when using IVIg the effect is slightly slower and there are less side effects (Gajdos et al, 2006).

The optimal dose of IVIG in MG has also been debated. So far no marked superiority of IVIg 2 g/kg over 2 days compared to 1 g/kg in a single day has been detected. The dose used has mostly been 2 g/kg resulting in the improvement after 3–6 days. Although IVIg is an effective treatment for acute exacerbations of MG, it is not recommended as maintenance therapy. Importantly, IVIg is often used in preparing MG patients for thymectomy or other types of surgery in case they have severe weakness, bulbar symptoms, poor pulmonary function, or a thymoma, even though there are no controlled studies justifying this practice. IVIg therapy has also been considered as rescue therapy in worsening MG, exacerbations of the disease during pregnancy and before giving birth, and neonatal MG. IVIg is considered safe in children and in elderly patients (EFNS task force, 2008).

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 (EFNS task force, 2008).



## 4. IVIg in therapy of inflammatory myopathies

The inflammatory myopathies are rare autoimmune diseases characterized by muscle weakness, which is usually proximal, painless and of insidious onset. The three groups of autoimmune myopathies are dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM). There are some controlled trials on the use of IVIg in patients with dermatomyositis (DM) and inclusion body myositis (IBM), and only one with polymyositis (PM) (EFNS task force, 2008; Hughes et al, 2008).

### 4.1 DM

DM is an inflammatory disease, affecting skin and muscle and causing varying degrees of muscle weakness, ranging from mild to severe. Prominent inflammation is observed usually at the periphery of the fascicle, leading to atrophy of the fibres around the fascicle (Hughes et al, 2008).

In a majority of DM patients a favourable response has been reported and therefore IVIg is recommended as a second line treatment in combination with prednisone for those who have not improved with corticosteroids alone. A total dose of 2 g / kg given over 2–5 days for adults and over 2 days for children is a safe initial treatment option. In severe, life-threatening DM, IVIg can be considered as the first line treatment together with other immunosuppressive therapy (Elovaara et al, 2010; EFNS task force, 2008).

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) (EFNS task force, 2008).

### 4.2 IBM

IBM is a progressive inflammatory skeletal muscle disease that presents with a distinctive pattern of weakness in the wrist and finger flexors and quadriceps muscles. It is characterized by inflammatory cells surrounding myofibres and rimmed vacuoles.

In IBM, the available evidence based on trials with small to moderate numbers of patients suggests an overall negative outcome even if a small number of patients reported improvement in swallowing difficulties. Therefore, IVIg cannot be recommended for the treatment of sporadic IBM (Hughes et al, 2008).

Recommendation:

- IVIg can not be recommended for the treatment of sporadic IBM (level A) (EFNS task force, 2008).

### 4.3 PM

Polymyositis is an inflammatory myopathy with no rash. It is defined by symmetric proximal muscle weakness, elevated serum muscle enzymes, myopathic changes on electromyography, characteristic muscle biopsy abnormalities and the absence of histopathologic signs of other myopathies. Muscle weakness is indeed the most common

presenting feature of polymyositis. The onset is usually insidious and the distribution of weakness is typically symmetric and proximal. Myalgias occur in less than 30% of the patients (Dalakas & Hohlfeld, 2003).

Only one non-RCT (evidence class III) and two case series (evidence class IV) 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 ( $P < 0.05$ ) (Hughes et al, 2008).

Recommendation:

- IVIg may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment (level C).

## 5. IVIg in therapy of demyelinating diseases of central nervous system

### 5.1 Multiple sclerosis (MS)

Multiple sclerosis (MS) is a central nervous system chronic inflammatory disease that is characterized by an extensive and complex immune response. It is the most common demyelinating disease of the central nervous system in young adults. MS can cause a variety of symptoms, including changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, cognitive impairment, problems with balance, overheating, and pain. MS will cause impaired mobility and disability in more severe cases. Multiple sclerosis may take several different forms, with new symptoms occurring either in discrete attacks or slowly accruing over time. Between attacks, symptoms may resolve completely, but permanent neurologic problems often persist, especially as the disease advances. MS currently does not have a cure, though several treatments are available that may slow the appearance of new symptoms (Baumstarck-Barrau et al, 2011)

Although earlier trials on the efficacy of IVIg in Relapsing Remitting MS (RRMS) have demonstrated a reduction in relapses, a recent study investigating the prevention of relapses with IVIg (PRIVIG trial) failed to confirm these earlier observations (Fazekas et al, 2008). In this study 127 patients with RRMS participated in a double blind, placebo-controlled trial, in which 44 and 42 patients received treatment with 0.2 or 0.4 g / kg of IVIg and 42 patients received placebo every 4 weeks for 48 weeks. After 1 year, the proportion of relapse-free patients did not differ between the groups, and there was no difference in MRI activity assessed 6-weekly. The authors of the study suggested that the obtained results may be related to short disease duration and overall disease activity of the study population that was more like that observed in a population with a clinically isolated syndrome.

The efficacy of IVIg in the treatment of MS exacerbations has been addressed in small add-on type studies that could not demonstrate any additional benefits due to addition of IVIg to conventional treatment of acute exacerbations with high-dose IV methylprednisolone. However, a recent study reported that IVIg might have a beneficial effect in patients with insufficient recovery from optic neuritis, if treatment with high-dose IV methylprednisolone fails (Achiron, 2008). No clinically significant effects were seen in progressive forms of MS, and consequently IVIg is not recommended in these conditions (Elovaara et al, 2010).

Currently the main indication for the use of IVIg in MS is to reduce relapses during pregnancy or breastfeeding when other therapies may not be used safely (Haas & Homes, 2007).

Recommendations:

- 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)
- IVIg 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.

### 5.2 Neuromyelitis optica (NMO)

Neuromyelitis optica (NMO) 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) (Bakker & Metz, 2004).

### 5.3 Balo's concentric sclerosis

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) (Airas et al, 2005).

### 5.4 Acute disseminated encephalomyelitis (ADEM)

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). 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) or in patients with peripheral nervous system involvement and steroid failure (class IV evidence). Alternatively combination therapy by steroids and IVIG (class IV evidence) or steroids, IVIg and PE were suggested to have favourable effects especially if given early in the course of disease (class IV evidence) (EFNS task force 2008).

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.

## 6. IVIg in therapy of paraneoplastic syndromes

Due to the rarity of immunologically mediated paraneoplastic diseases, there are very few prospective, randomized, double-blind and placebo-controlled studies.

### 6.1 Lambert – eaton myasthenic syndrome (LEMS)

Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated disorder of the presynaptic neuromuscular transmission, which more frequently occurs as the remote effect of a neoplasm. The clinical features described are proximal weakness, especially in the lower limbs, with diminished tendon reflexes and post-tetanic potentiation. Autonomic symptoms are often reported, including pupil abnormalities, dry eyes and mouth, and erectile dysfunction (Maddison & Newsom-Davis, 2005).

LEMS is 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 evidence) and there is also a recent Cochrane review that has concluded that limited data from one placebo-controlled study show improvement in muscle strength after IVIg (Maddison & Newsom-Davis, 2005).

The IVIg response regarding improvement of muscle strength does probably not differ in paraneoplastic and non-paraneoplastic LEMS.

Recommendations:

- IVIg therapy may be tried in paraneoplastic LEMS (good practice point).

### 6.2 Neuromyotonia

Acquired neuromyotonia is a condition associated with muscle hyperactivity that includes muscle stiffness, cramps, myokymia, pseudomyotonia and weakness, most common in the limbs and trunk. The typical finding on electromyography is spontaneous motor unit discharges occurring in distinctive doublets, triplets, or longer runs with high intraburst frequency (Hart et al, 2002).

Only one case report describes the beneficial effect of IVIg in patient with neuromyotonia, whilst another case report demonstrated worsening after IVIG therapy (EFNS task force, 2008).

### 6.3 Paraneoplastic opsoclonus ataxia syndrome (OMS)

Opsoclonus refers to involuntary, conjugate, multivectorial, saccadic eye movements. It can occur as an isolated neurologic anomaly but, when it occurs with involuntary multifocal jerking movements of the skeletal musculature, the phenomenon is known as opsoclonus-myoclonus syndrome (OMS). The syndrome often includes features of ataxia, or incoordination with voluntary movements. In the setting of malignancy, opsoclonus is linked most clearly to neuroblastoma, occurring in 3% of childhood cases. Anti-neuronal antibodies, usually to nuclear antigens, are considered markers of immune system activation in this disorder, detected in 81% of pediatric patients (Pittock et al, 2003).

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). In adult patients the response is less immunosuppressive, although IVIg is suggested to accelerate recovery (class IV evidence) (EFNS task force, 2008).

Recommendation:

- IVIg therapy may be tried in opsoclonus-ataxia especially in paediatric neuroblastoma patients (good practice point).

### 6.4 Paraneoplastic cerebellar degeneration

Cerebellar dysfunction is one of the most common paraneoplastic presentations of cancer. The tumours more commonly involved are small-cell lung cancer, gynaecological and breast

tumours, and Hodgkin's lymphoma. Neurological deficits are sometimes preceded by prodromal symptoms, such as a viral-like illness, dizziness, nausea, or vomiting that might be attributed to a peripheral vestibular process. These symptoms are followed by gait unsteadiness that rapidly develops into ataxia, diplopia, dysarthria, and dysphagia. Some patients have blurry vision, oscillopsia, and transient opsoclonus. Initial MRI is normal in most patients, although over time, MRI shows cerebellar atrophy and PET demonstrates hypometabolism (Dalmau & Rosenfeld, 2008).

### 6.5 Limbic encephalitis

Autoimmune limbic encephalitis (LE) can arise both by paraneoplastic and non-paraneoplastic mechanisms. Patients with LE usually have a subacute onset of memory impairment, disorientation and agitation, but can also develop seizures, hallucinations and sleep disturbance. The following investigations may aid the diagnosis: analysis of cerebrospinal fluid (CSF), electroencephalography, magnetic resonance imaging, fluorodeoxyglucose positron emission tomography and neuronal antibodies in the serum and CSF. Neuronal antibodies are sometimes, but not always, pathogenic. Autoimmune LE may respond to corticosteroids, intravenous IgG (IVIG) or plasma exchange. The cornerstone of paraneoplastic LE therapy is resection of the tumour and/or oncological treatment. Several differential diagnoses must be excluded, among them herpes simplex encephalitis (Vedeler & Storstein, 2009)

### 6.6 Paraneoplastic sensory neuronopathy (SSN)

Paraneoplastic sensory neuronopathy (SSN) is characterized by primary damage of the sensory nerve cell body of the dorsal root ganglia. A paraneoplastic origin is only one of the causes of SSN. The most common low associated tumor is small cell lung carcinoma. The main clinical complaints at onset are pain and paresthesias with asymmetric distribution that involves the arms rather than the legs. Later, pain is replaced by numbness, limb ataxia, and pseudoathetotic movements of the hands. The neurologic examination shows abolition of the deep tendon reflexes and involvement of all modalities of sensation with clear predominance of the joint position. Electrophysiologic studies show marked, but not restricted, involvement of the sensory fibres (Dalmau & Rosenfeld, 2008).

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 evidence) (EFNS task force, 2008).

Recommendations:

- No clear recommendations of the effect of IVIG in paraneoplastic neuromyotonia, cerebellar degeneration, limbic encephalitis or sensory neuronopathy can be made due to lack of data (EFNS task force, 2008).

## 7. IVIg in therapy of Stiff-Person Syndrome (SPS)

Stiff-person syndrome (SPS) is characterized by muscle stiffness and episodic spasms. A significant decline of the stiffness scores was found in a randomized trial of 16 SPS patients treated with IVIg. Based on this study IVIg may be considered as a safe and effective second-line therapy for patients with SP incompletely responding to diazepam and / or baclofen and who have 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) (EFNS task force, 2008).

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).

## 8. IVIg in therapy of post-polio syndrome (PPS)

Post-polio syndrome (PPS) is characterized by new muscle weakness, muscle atrophy, fatigue and pain developing several years after acute polio. The prevalence of PPS in patients with previous polio is 20–60%.

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 (EFNS task force, 2008).

There are two RCTs of treatment with IVIg in PPS (class I evidence) including 155 patients. 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 (Farbu et al., 2007).

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.

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) (EFNS task force, 2008).

## 9. IVIg in therapy of drug resistant epilepsy (DRIE)

Drug-resistant infantile epilepsy (DRIE) syndromes 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).

Approximately a hundred patients with West or Lennox-Gastaut syndromes have been treated with IVIg with widely varying results. The treatment has resulted in 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 and after initial therapy by steroids or antiepileptic drugs and steroids in only few patients. 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 or steroids and PE (EFNS task force, 2008).

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.

## 10. IVIg in therapy of narcolepsy with cataplexy (NC)

Narcolepsy with cataplexy (NC) is caused by substantial loss of hypocretin neurons. NC patients carry the HLA-DQB1\*0602 allele suggesting that hypocretin neuron loss is due to an autoimmune attack.

There are some case studies that report that IVIg treatment initiated before 9 months disease duration has some clinical efficiency. The unaffected CSF hypocretin-1 levels and lack of autoantibodies suggest that any autoimmune process occurs very early in NC. The final IVIg effect needs to be investigated in RCTs (Knudsen et al, 2010).

## 11. IVIg in therapy of Alzheimer's disease (AD)

Alzheimer's Disease (AD) is the most common neurodegenerative disorder leading to dementia. The pathological hallmarks of AD are extracellular accumulation of Ab peptides, as senile plaques and intracellular neurofibrillary tangles composed of tau proteins.

Clinical studies of active immunization in humans with AD were complicated by the development of meningoencephalitis in 6% of the patients treated with vaccine AN1792 in a phase II clinical trial. Furthermore, only 20% of the patients immunized with AN1792 developed a twofold increase in anti-Ab antibodies.

However, progress was made with the discovery that peripheral administration of antibodies against Ab peptide could reduce amyloid burden to a similar extent as active immunization. Passive immunization had the advantage that the potentially harmful activation of host T cells could be avoided.

Based on the finding that externally administered antibodies were able to protect mice from AD, it was hypothesized that high titres of natural anti-Ab antibodies may protect humans from AD, while low levels may predispose certain individuals to the development of AD. Studies have found reduced levels of anti-Ab antibodies both in the serum and CSF of

patients with AD. Autoantibody-decorated plaques were found frequently in patients with AD and patients with low antibody-levels were shown to harbour more diffuse plaques than patients with high levels. Autoantibodies against Ab may therefore be important for maintaining plaque homeostasis.

IVIg has been shown to contain autoantibodies against many states of Ab peptide aggregation including monomers, oligomers and fibrils and may therefore have a distinct advantage over monoclonal anti-Ab until the precise pathogenic state(s) of the Ab peptide is known (Hughes et al, 2008).

Recently, commercially available IVIg have been used in small pilot trials for the treatment of patients with AD, based on the hypothesis that IVIG contains naturally occurring autoantibodies (nAbs-Abeta) that specifically recognize and block the toxic effects of Abeta. Furthermore, these nAbs-Abeta are reduced in AD patients compared with healthy controls, supporting the notion of replacement with IVIg. Beyond the occurrence of nAbs-Abeta, evidence for several other mechanisms associated with IVIg in AD has been reported in preclinical experiments and clinical studies. In 2009, a phase III clinical trial involving more than 360 AD patients was initiated and may provide conclusive evidence for the effect of IVIg as a treatment option for AD in 2011 (Dodel et al, 2010).

## 12. Conclusion

IVIg is used increasingly in neurological diseases.

Its efficacy has been proved in GBS, CIDP and MMN, where it is considered as the first-line treatment. However, questions remain regarding the dose, timing and duration of IVIg treatment in these disorders.

It is also successfully used in acute exacerbations of MG and as a short-term treatment of severe MG. It is recommended in SPS, in some paraneoplastic syndromes and as a second-line treatment in combination with prednisone in dermatomyositis and a treatment option in polymyositis.

In MS, IVIg is indicated mainly in reducing disease activity during pregnancy and breastfeeding.

In addition to these major indications, IVIg is increasingly used even in such conditions where the strong evidence is currently lacking, like refractory epilepsy, narcolepsy, post polio syndrome.

According to preliminary data, IVIg might be a promising candidate for the treatment of (AD). Large-scale randomized trials are under way, and the results of these studies are awaited eagerly worldwide.

When considering treatment options, it is important to notify that uncontrolled use may lead to high costs and limited availability of IVIg. Careful selection of patients who will benefit from IVIg is extremely important.

### ABBREVIATIONS:

AChR: acetylcholine receptor

AD: Alzheimer's Disease

ADEM: Acute-disseminated encephalomyelitis

AIDP: acute inflammatory demyelinating polyneuropathy

AMAN: acute motor axonal neuropathy

AMSAN: acute motor and sensory axonal neuropathy

CIDP: chronic idiopathic demyelinating polyneuropathy

CSF: cerebrospinal fluid  
 DM: dermatomyositis  
 DRIE: Drug-resistant infantile epilepsy  
 GBS: Guillain – Barre syndrome  
 IBM: inclusion body myositis  
 IVIg: intravenous immunoglobulin  
 LEMS: Lambert-Eaton myasthenic syndrome  
 LRPN: Lumbosacral radiculoplexus neuropathy  
 MGUS: monoclonal gammopathy of undetermined significance  
 MMN: multifocal motor neuropathy  
 MG: Myasthenia gravis  
 MS: Multiple Sclerosis  
 MuSK: muscle-specific tyrosin kinase  
 NC: Narcolepsy with cataplexy  
 NMO: Neuromyelitis optica  
 OMS : opsoclonus-myoclonus syndrome  
 PE: Plasma exchange  
 PM: polymyositis  
 PPS: Post-polio syndrome  
 RCT: randomized controlled trials  
 RRMS: Relapsing Remitting Multiple Sclerosis  
 SPS: Stiff-person syndrome  
 SSN: Paraneoplastic sensory neuronopathy

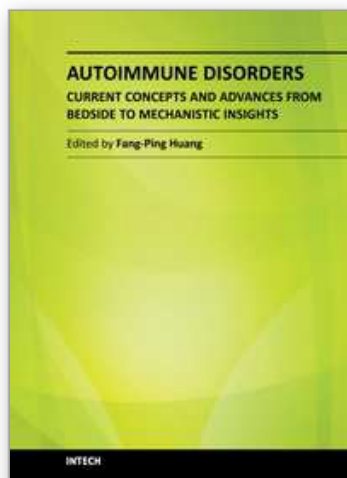
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## **Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights**

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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