

GUIDELINES FOR THE USE OF INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF NEUROLOGIC DISEASES

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SUMMARY – The use of intravenous immunoglobulin (IVIg) in the management of patients with neuroimmune disorders has shown a progressive trend over the last few years. Despite the wide use of IVIg, consensus on its optimal use is deficient. The European Federation of Neurological Societies (EFNS) guidance regulations offer consensus recommendations for optimal use of IVIg. The effectiveness 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 and short-term treatment of severe myasthenia gravis (level A). As a second-line treatment, the use of IVIg is recommended in dermatomyositis in combination with prednisone (level B) and is considered as a treatment option in polymyositis (level C). As a second- or even third-line therapy, the use of IVIg should be considered in patients with 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). Finally, it appears that the use of IVIg has a beneficial effect also in stiff-person syndrome (level A), some paraneoplastic neuropathies (level B), and some acute-demyelinating diseases and childhood refractory epilepsy (good practice point).

Key words: Intravenous immunoglobulin; Neurologic diseases

Introduction

The use of intravenous immunoglobulin (IVIg) has increased in many institutions due to the rise in neu-

rologic diseases. The effect of IVIg in particular diseases may not be attributable to only one of its mechanisms of action because the pathophysiology of these diseases is complex. IVIg has been used as first-line therapy in Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and dermatomyositis. It may also be used in the diseases of neurotransmission, multiple sclerosis (MS), and in some rare neurologic disorders of adults and children including Rasmussen's encephalitis (RE), stiff-person syndrome (SPS) and post-polio syndrome (PPS)¹.

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Received September 1, 2012, accepted October 10, 2012

MECHANISMS OF ACTION OF INTRAVENOUS IMMUNOGLOBULIN IN NEUROLOGIC DISEASES

Although the underlying mechanisms of action of IVIg have not been fully explained, many experimental studies have shown, both *in vivo* and *in vitro*, that IVIg can interfere with the immune system at several levels². The key mechanisms include neutralization of activated complement (the beneficial effects are associated with disappearance of complement in the muscles³), modulation of proinflammatory cytokines (suppression of interleukin-1, tumor necrosis factor- α and γ -interferon), and exerting Fc region-mediated inhibition of antibody production⁴. The possibility that IVIg acts through non-immune mechanisms such as binding and removing microbial toxins or targeting their surface antigens is probably less relevant in neurology and neurologic disorders⁵.

INTRAVENOUS IMMUNOGLOBULIN IN GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome is an acute and usually progressive form of inflammatory polyradiculopathy, and is considered to be the most common acquired demyelinating neuropathy⁶. Before the introduction of IVIg in the treatment of GBS, 10% of these patients died and 20% were left seriously disabled⁷. In 1978, plasma exchange (PE) was introduced as a possible treatment and a randomized trial published in 1985 showed it to offer significant benefit, hence it became a gold standard against which other treatments were measured⁸⁻¹⁰. In 1988, IVIg was introduced for GBS treatment¹¹. In 1992, the first randomized trial comparing IVIg and PE showed both treatment options to yield similar effects¹². Although PE was more frequently discontinued, there was no significant difference in other outcome measures between IVIg and PE¹³. 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 alone¹⁴⁻¹⁶. Comparison of IVIg and PE showed no difference in long-term outcome. Neither IVIg nor PE or any other treatment could significantly reduce mortality, which ranged from 5% to 15% in hospital and population-based studies¹⁷. Limited data are available concerning the dosage of IVIg and there

is no evidence that it is better to administer IVIg in 2 or in 5 days.

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 less side effects than PE and this would favor IVIg over PE treatment (level B). IVIg treatment after PE, as a standard combination, does not produce significant extra benefit and cannot be recommended (level B). Combining high-dose intravenous methylprednisolone with IVIg may have a minor short-term benefit (level C). Children who generally have a better prognosis should be treated with IVIg as first-line treatment (level C). Patients who improve after IVIg and then relapse should preferentially be 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 patients with a mild form of GBS or patients with Miller Fisher syndrome should be treated with IVIg¹.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Therapeutic efficacy of IVIg in CIDP has been shown in several randomized, placebo-controlled studies that compared IVIg with plasmapheresis or steroids¹⁸⁻²⁰. The dosage of IVIg varied from 0.2 to 1.0 g/kg body weight, and duration of IVIg therapy ranged from 2 to 5 days¹⁹. In one study, IVIg was effective compared with placebo when given as primary therapy in untreated CIDP patients²⁰. Most experts in the field start treatment with IVIg as first-line therapy, and add immunosuppressants or steroids as needed⁴.

Recommendations

Patients with very mild symptoms that 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 the 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. Treatment intervals should be such that this deterioration does not happen. If the patient becomes stable on intermittent IVIg, the dose should be reduced before the frequency of administration is lowered (good practice point)²¹.

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 treatments²²⁻²⁴. The overall therapeutic efficacy of IVIg in MMN has been confirmed in several double-blind, placebo-controlled studies. The number of cases in each study was in the range of 5-18 patients. IVIg was administered at a dosage of 0.4 g/kg body weight on five consecutive days. The response rate was between 58% and 100%. Clinical improvement could generally be seen after 1 week, although in some cases it was only seen after 4 weeks²⁵⁻²⁷. 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 years²⁸.

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 the 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)²⁹.

PARAPROTEINEMIC DEMYELINATING NEUROPATHY

Paraproteinemia is also known as monoclonal gammopathy and is characterized by the presence of M protein, which is an abnormal immunoglobulin produced by bone marrow cells in the blood. There are three different types of immunoglobulin classified according to the heavy chain class as IgG, IgM and IgA. The non-malignant paraproteinemias are generally referred to as "monoclonal gammopathy of undetermined/unknown 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 subclass³⁰. The most common type of IgM MGUS-related peripheral nerve involvement is a distal, symmetric demyelinating neuropathy. The results of two randomized placebo-controlled crossover trials and one randomized open parallel group trial have been summarized in a Cochrane review³¹, which concludes that IVIg is relatively safe and may produce some short-term benefit. In EFNS guideline article, the use of IVIg in IgM paraproteinemic demyelinating neuropathy is recommended only in patients with significant disability or rapid worsening³². No controlled trials are available on the effects of IVIg in IgG or IgA paraproteinemic neuropathy. A Cochrane review states that observational or open trial data provide limited support for the use of immunotherapy, including IVIg, in patients with IgG and IgA paraproteinemic neuropathy³³. EFNS guideline document concludes that the detection of IgG or IgA MGUS does not justify a different approach from CIDP without a paraprotein³².

Recommendations

IVIg should be considered as initial treatment for 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 paraproteinemia does not justify a different therapeutic approach from CIDP without a paraprotein¹.

PARANEOPLASTIC SYNDROMES

Due to the rarity of immune mediated paraneoplastic diseases, there are very few prospective, randomized, double-blind and placebo-controlled studies. Paraneoplastic syndromes involving peripheral nervous system, such as Lambert-Eaton myasthenic syndrome (LEMS) and neuromyotonia, are considered to respond best to immunosuppressive treatment. A Cochrane review has concluded that limited data from one placebo-controlled study show improvement in muscle strength after IVIg³⁴. The IVIg response regarding improvement of muscle strength probably does not differ in paraneoplastic and non-paraneoplastic LEMS. Only one case report describes the beneficial effect of IVIg in a patient with neuromyotonia³⁵, whilst another case report notified worsening after IVIg therapy³⁶. Symptoms in paraneoplastic opsoclonus-ataxia syndrome in pediatric neuroblastoma patients are declared to improve, although data concerning long-term benefits of the treatment are lacking (class IV evidence)³⁷. In adult patients, the response is less immunosuppressive, although IVIG is suggested to accelerate recovery (class IV evidence)³⁸. Evidence for the effect of IVIg in paraneoplastic cerebellar degeneration, limbic encephalitis and sensory neuropathy is scarce.

Recommendations

Intravenous immunoglobulin therapy may be tried in paraneoplastic LEMS and opsoclonus-ataxia, especially in pediatric neuroblastoma patients (good practice point). No clear recommendations considering the effect of IVIg in paraneoplastic neuromyotonia, cerebellar degeneration, limbic encephalitis or sensory neuropathy can be made due to the lack of data¹.

INFLAMMATORY MYOPATHIES

Three categories of inflammatory myopathy are reviewed based on the published IVIg trials: dermatomyositis, polymyositis and sporadic inclusion body myositis (IBM).

Dermatomyositis

Published data are available on one randomized controlled trial, one non-randomized controlled trial, one retrospective chart review and a few case series. It is shown that patients on IVIg significantly improved by symptom scale and a modified MRC Scale (evidence class II). One retrospective chart review and two case series tried IVIg as add-on therapy (evidence class III)³⁹⁻⁴¹. Taken together, 82% of cases improved clinically in these studies.

Recommendations

IVIg is recommended as a second-line treatment in combination with prednisone for patients with dermatomyositis 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 dermatomyositis (level C). IVIg is not recommended as monotherapy for dermatomyositis (good practice point). In severe, life-threatening dermatomyositis, IVIg can be considered as first-line treatment together with other immunosuppressive therapy (good practice point)¹.

Inclusion body myositis

Three randomized controlled trials with small to moderate numbers of patients have been published. The overall outcome was negative even if a small number of patients reported benefits regarding swallowing difficulties⁴²⁻⁴⁴.

Recommendation

IVIg cannot be recommended for the treatment of sporadic inclusion body myositis (level A)¹.

Polymyositis

Only one non-randomized controlled trial 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. Steroid doses could be reduced after IVIg⁴⁵. IVIg can apparently be considered as an alternative in patients who do not respond to conventional immunosuppressive treatment. The dose and duration of the treatment are as recommended for dermatomyositis.

Recommendation

IVIg may be considered among treatment options for patients with polymyositis not responding to first-line immunosuppressive treatment (level C)¹.

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 tyrosine kinase (MuSK), and in 5% against undefined antigen(s). Direct induction of muscle weakness by the autoantibodies has been shown. PE with removal of autoantibodies has a well-documented effect⁴⁶. An EFNS guideline document and two Cochrane reviews conclude that IVIg is a well-documented short-term treatment for acute exacerbations of MG and for severe MG^{46,47}. 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. IVIg 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 postoperative situation (good practice point). IVIg is widely recommended for severe MG or MG exacerbations during pregnancy and also before delivery. This is partly due to its effect on muscle strength and partly to its safety profile. Similarly, IVIg has been recommended for neonatal MG⁴⁸ (good practice point). IVIg has been proposed as maintenance, long-term therapy for MG. Such treatment has only been examined in open-label studies including a small number of patients with severe MG. EFNS task force guidelines, Cochrane

review and other guideline documents conclude that there is insufficient evidence to recommend IVIg as maintenance therapy for MG patients⁴⁶⁻⁴⁸.

Recommendations

IVIg is an effective treatment for acute exacerbations of MG and for short-term treatment of severe MG (level A). IVIg has similar effect as PE. 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 drugs¹.

POST-POLIO SYNDROME

Post-polio syndrome is a syndrome developing several years after acute polio, characterized by new muscle weakness, muscle atrophy, fatigue and pain. The other potential causes of the weakness have to be excluded^{49,50}. The prevalence of PPS in patients with previous polio is 20% to 60%. According to geography, the prevalence of previous polio shows great variation. The last big epidemic in Europe occurred in the 1950s, mainly affecting small children. The current prevalence of polio sequels in Europe is probably 50-200 *per* 100,000. PPS is caused by an increased degeneration of enlarged motor units, and some motor neurons cannot maintain all their nerve terminals. Muscle overuse may contribute. Immune and inflammatory signs have been reported in the cerebrospinal fluid and central nervous tissue⁵¹. There are two randomized controlled trials on the treatment with IVIg in PPS (class I evidence)^{52,53}, one open and uncontrolled study⁵⁴, and one case report⁵⁵ (class IV evidence). In the study with highest power, a significant increase in the mean muscle strength of 8.3% was reported after two IVIg treatment cycles over 3 months. Physical activity and subjective vitality also differed significantly in favor of the IVIg group⁵³. PPS is a chronic condition. Although a modest IVIg effect has been described at 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. The

optimal dose and IVIg cycle frequency have not been examined. Cost-benefit evaluation has not been performed⁴⁹.

Recommendations

IVIg has a minor to moderate positive effect on muscle strength and some aspects of the quality of life in PPS (class I evidence). As long as the 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 rigorous follow-up of muscle strength and quality of life can be undertaken (good practice point)¹.

MULTIPLE SCLEROSIS

In multiple sclerosis, IVIg has not fulfilled the promise indicated by the results of many well-designed studies. Four randomized double-blind studies have all shown a beneficial effect on disease activity in relapsing-remitting multiple sclerosis (RRMS)⁵⁶⁻⁵⁹. 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. A meta-analysis of four studies showed a significant reduction of the annual relapse rate and of disease progression (class I evidence)⁶⁰. 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 RRMS⁶¹. Thus, this trial failed to support earlier observations of a beneficial effect of IVIg in RRMS. 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 Expanded Disability Status Scale (EDSS), and change in lesion volume on T2 weighted images (class I evidence). The only beneficial effect was reduction in brain atrophy⁶². Small studies with historical controls suggested that IVIg might reduce relapse rate after childbirth (class IV evidence)^{63,64}.

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 recommendations¹.

OTHER DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM

Neuromyelitis optica, also known as 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 pointing that monthly IVIg was associated with cessation of relapses (class IV evidence)⁶⁵.

Baló's concentric sclerosis is a severe demyelinating disease, also with poor prognosis. There is a case report indicating that IVIg (0.4 g/kg/daily for 5 days) and interferon-beta-1a given postpartum may result in partial neurologic improvement (class IV evidence)⁶⁶.

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 accessible. 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 favorable effects when used as an initial therapy in both adults and children (class IV evidence)^{67,68}. IVIg may have some beneficial effects also as a second-line therapy (class IV evidence)^{69,70}, particularly in patients who could not receive or failed to respond to steroids (class IV evidence)⁷¹, or in patients with peripheral nervous system involvement and steroid failure (class IV evidence).

Recommendations

IVIg may have a favorable effect in the treatment of ADEM and therefore it should be tried (0.4 g/kg/day for 4-5 consecutive days) in patients unresponsive to high-dose steroids (good practice point). The cycles may be repeated. PE could also be considered in patients unresponsive to high-dose steroids¹.

STIFF-PERSON SYNDROME

Stiff-person syndrome is a disabling central nervous system disease with no gratifying treatment. It is characterized by muscle rigidity, episodic muscle spasms, anti-GAD65 antibodies, and frequent association with autoimmune or neoplastic disorders. In one controlled study with 16 patients with SPS and anti-GAD65 antibodies, IVIg significantly decreased the stiffness and heightened-sensitivity scores; patients were able to walk more easily or independently⁷². The study suggested IVIg as a second-line therapy for patients with SPS.

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)¹.

DRUG-RESISTANT EPILEPSY

Drug-resistant infantile epilepsy (DRIE) includes various diseases such as Landau-Kleffner syndrome (LKS), West syndrome, Lennox-Gastaut syndrome, severe myoclonic epilepsy or Rasmussen's encephalitis (RE). They all typically manifest in childhood or adolescence and are labeled by epilepsy and progressive neurologic dysfunction. Standard treatment of RE consists of antiepileptic drugs, high-dose steroids; also, surgical treatment 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)^{73,74}. Some patients had reduction in the number of seizures^{74,75}, and improvement in the EEG. The positive effects were noted a few days to

several weeks to months after treatment. Relapses have been common.

Recommendation

IVIg seems to have a favorable 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 weeks¹.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) poses an important socioeconomic challenge in many countries. Amyloid β ($A\beta$ peptide) is considered to be the major pathogenic element in plaque formation in the brains of individuals with AD. Some data from transgenic mouse models indicate that clearance of $A\beta$ *via* immune mediated pathways might have an important impact on the development of plaques. In a study where seven patients with AD were treated with IVIg (0.4g/kg *per* day) over three days, the levels of antibodies against $A\beta$ were found to be increased in serum and cerebrospinal fluid⁷⁶. In another uncontrolled follow-up study, five patients were treated with IVIg and as a result, decreased levels of $A\beta$ were observed⁷⁷. Hence IVIg or specific purified $A\beta$ antibodies might have potential utility as a therapy for AD, but larger controlled studies are needed to confirm these findings.

NARCOLEPSY

In narcolepsy, hypocretin (orexin) deficiency seems to be a consistent feature and it is thought to involve an autoimmune mechanism – a hypothesis also supported by linkage to human leukocyte antigen genes⁷⁸. Four patients with hypocretin-deficient narcolepsy were treated with IVIg within a few months after acute onset of narcolepsy⁷⁹. Clear improvement in the frequency and severity of cataplexy was assessed by repeated polysomnographies and questionnaires. The beneficial effect, with greater than 90% reduction in the frequency of cataplectic attacks, persisted in three patients for at least 2 years without any additional IVIg treatment⁸⁰. Controlled studies early in the disease onset are certainly needed.

SIDE EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN

Several studies have reported side effects of PE and IVIg therapy^{11,12}. More cases of pneumonia, atelectasis, thrombosis and hemodynamic difficulties were related to PE than IVIg. Side effects related to IVIg included hypotension, dyspnea, fever and hematuria, nausea or vomiting, meningism, exacerbation of chronic renal failure, possible myocardial infarction, and painful erythema at the infusion. Severe adverse events leading to discontinuation of the treatment included thrombosis of the jugular vein, allergic reaction and retrosternal pressure. The changes in blood laboratory findings included abnormalities of liver enzymes, changes of leukocytes, erythrocytes, hematocrit, hemoglobin, alanine aminotransferase and aspartate aminotransferase. None of these laboratory changes were clinically relevant. Based on these data, IVIg can generally be considered as a relatively safe treatment. However, to avoid these complications careful monitoring of laboratory parameters like complete blood count, liver enzymes and renal functions should be obligatory⁸¹.

Conclusion

Treatment with IVIg is effective for many neurologic diseases but it has only been established as first-line therapy for a few of them. Some new indications are emerging but well-designed, controlled trials are still needed to prove the efficacy of IVIg in these settings. Besides, a targeted use of IVIg will be required in the future also because of high costs and limited resources. In chronic conditions, it remains to determine whether the administration of immunoglobulins subcutaneously (possibly at home) would be as effective in maintaining clinical response as in-hospital IVIg administration.

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Sažetak

SMJERNICE ZA PRIMJENU INTRAVENSKOG IMUNOGLOBULINA U LIJEČENJU NEUROLOŠKIH BOLESTI

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Posljednjih nekoliko godina pojavio se pozitivan trend u liječenju bolesnika oboljelih od neuroimunoloških poremećaja intravenskom primjenom imunoglobulina. Unatoč učestalosti i širokoj upotrebi imunoglobulina intravenskim putem nema zadovoljavajućeg konsenzusa o njihovoj optimalnoj primjeni. U cilju definiranja intravenske upotrebe imunoglobulina u neurologiji temeljene na znanstvenim dokazima i u skladu sa smjernicama EFNS-a donesene su preporuke za konsenzus. Učinkovitost intravenske upotrebe imunoglobulina dokazana je u liječenju bolesnika s Guillain-Barréovim sindromom (stupanj A), kroničnom upalnom demijelinizirajućom polineuropatijom (stupanj A), multifokalnom mononeuropatijom (stupanj A), akutnom egzacerbacijom mijastenije gravis te kao kratkotrajna terapija u bolesnika s teškim oblikom mijastenije gravis (stupanj A). Kao druga linija liječenja intravenski imunoglobulini preporučuju se u liječenju bolesnika oboljelih od dermatomiozitisa, ali u kombinaciji s prednizonom (stupanj B) te u liječenju polimiozitisa. Kao druga ili treća linija liječenja intravenski imunoglobulini uzimaju se u obzir kod bolesnika s relapsno-remitirajućom multiplom sklerozom pri nepodnošenju konvencionalne imunomodulatorne terapije (stupanj B) te u relapsima za vrijeme trudnoće ili u postpartalnom razdoblju (rezultat dobre kliničke prakse). Naposljetku, doima se da bi upotreba intravenskih imunoglobulina također mogla imati povoljan učinak u liječenju sindroma ukočene osobe (stupanj A), nekih paraneoplastičnih neuropatija (stupanj B) i akutno demijelinizirajućih bolesti te refraktorne epilepsije u djetinjstvu (rezultat dobre kliničke prakse).

Ključne riječi: Intravenska primjena imunoglobulina; Neurološke bolesti

