Management of Chronic Inflammatory Demyelinating Polyradiculopathy

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Abstract

Purpose of the review

To review the recent advances in the management and treatment of CIDP.

Recent findings

Recent studies confirm the efficacy/safety of long-term IVIg and short-term SCIg therapy in CIDP. New outcome measures have been recently proposed and further studies evaluated the properties of those already in use. The presence of antibodies against proteins at the node of Ranvier was associated with specific clinical features and treatment response. Fingolimod adds to the list of immunesuppressive agents that failed to be effective in a controlled trial.

Summary

Several studies on the best strategy to provide maintenance IVIg treatment in CIDP are in progress. SCIg were shown to be an alternative to IVIg for maitenance treatment while their efficacy as initial therapy should be further addressed. New outcome measures have been shown to be effective in detecting treatment response in clinical trials, but their use in clinical practice remains uncertain. Similarly unsettled is the role of nerve imaging techniques as biomarker in CIDP. The discover of antibodies against proteins at the node of Ranvier has rekindled a keen interest in the pathogenesis of CIDP and the potential therapeutic role of new agents.

Key words

CIDP, corticosteroids, immunoglobulin, outcome measure, fingolimod

Introduction

Chronic inflammatory demyelinating polyradiculopathy (CIDP) is a chronic and disabling neuropathy with a postulated immune pathogenesis [1]. Randomised controlled trials (RCT) have shown the efficacy of steroids, plasma-exchange (PE), and intravenous immunoglobulin (IVIg) in treating CIDP, with approximately 50-70% of the patients responding to each of these treatments [2•]. The efficacy of these therapies was confirmed in two recent Cochrane reviews [3••,4••] and in the Guidelines of the European Federation of Neurological Societies/Peripheral Nerve Society [5].

Text of the review

Intravenous immunoglobulin

Currently, IVIg is considered often the first-line treatment for CIDP given the less frequent side effects and the more frequent short-term efficacy than steroids [48 cambia di conseguenza]. Results of the largest trial proving short-term and long-term (24 weeks) efficacy and safety of IVIg in patients with CIDP (ICE study) [6] were recently confirmed by a single-arm, open trial, which also showed the efficacy of mantainance IVIg therapy for 52 weeks [7••]. The frequency of adverse events in this latter study (93.9%) was higher than that observed in the ICE study (75%), and two patients experienced cerebral infarction, a complication that did not occur in the ICE study. This difference might have reflected the longer period of treatment in the 52-week IVIg mantainance trial, although due to the lack of a placebo arm in this study it is difficult to reach conclusions about safety. A postmarket survey of Glovenin-I showed however that only 0.04% of 5587 CIDP patients developed cerebral infarction [7••], and a recent retrospective study showed that IVIg is safe also in patients over 60 year-old [8].

In the last few years, there has been a growing interest on mantainance IVIg therapy

in CIDP, particularly because of the lack of evidence-based guidelines on how IVIg maintenance treatment should be administered. In this regard, three main questions still unanswered can be indentified: what is the best IVIg treatment regimen, how to individualize IVIg treatment, and how to monitor treatment response and treatment dependency. The first question arises from the uncertainty whether more frequent, but lower IVIg dosing, leads to better efficacy and safety than less frequent, high IVIg dose infusions or viceversa. The importance of reaching high serum Ig level to obtain a better outcome was first noted in Guillain-Barré syndrome [9] and more recently also in CIDP [10]. Two clinical trials are currently underway to shed more light on this aspect: the ProCID study [11] that will compare the efficacy and safety of three different IVIg doses (0.5, 1.0, and 2.0 g/kg) administered every 3 weeks for 24 weeks, and the DRIP study [12] where grip strength will be used to measure whether high-frequent low-dosage of IVIg results in better efficacy and safety compared to low-frequent high-dosage treatment.

Current guidelines for CIDP recommend to individualize IVIg treatment using the lowest effective mantainance dose and periodically attempting dose reduction or interval lengthening trials to establish the need for ongoing therapy [5]. There is however uncertainty on what is the best strategy to reach those goals. Recently, two different dosing algorithms to individualize IVIg treatment have been proposed [13•,14•]. Using one of these algorithms, the authors calculated an yearly saving of £661,415 at their institution [14•]. These two treatment algorithms however, have never been tested for superiority in RCT, where instead the most frequenly used IVIg mantainance protocol so far has been 1g/kg every 3 weeks. Several studies however suggested that the “IVIg dose per kilogram bodyweight” approach might not be fully appropiate [15,16].

Assessing treatment response and treatment dependency

Since there are no valid laboratory biomarkers for CIDP, objective outcome measures are recommended to optimize treatment. The GRIPPER study is currently investigating the role of daily monitoring of grip strength in IVIg treated patients with CIDP [17]. The daily self-monitoring of grip strength was shown to be helpful to optimize the dose and timing of IVIg in two CIDP patients [18] and to objectively confirm treatment-related fluctuations in some patients with chronic inflammatory neuropathies on long-term IVIg [19]. However, since grip strength measures only distal upper-limb strength while CIDP typically affects also lower limbs and causes sensory deficit and proximal weakness, it was suggested that it might not be completely adequate in clinical practice [20]. In addition, evidence for its validity is still unsufficient with conflicting results deriving from different studies [21,22]. Recently, a study examining the relationship between I-RODS and the vigorimeter (chosen as an objective tool) showed a significant correlating trend between the two measures [23]. The I-RODS is now considered the best outcome measure to assess disability in patients with inflammatory neuropathies although it is mainly a subjective self-reported scale and most of its items are not verifiable by the physician at the time of patient's assessment. It is also unclear what would be the best measure to assess quality of life (QoL) in patients with inflammatory neuropathies. Recently, a new disease-specific interval-based QoL questionnaire (IN-QoL) has been developed [24]. This measure demonstrated good validity, reliability and responsiveness [24], although it has not yet been tested prospectively in a large population with inflammatory neuropathies [24].

Despite the recent advances on this topic, there is still no consensus on how many and

which outcome measures should be used in routine clinical practice. Moreover, we still do not know which minumum clinical important difference (MCID) cutoff values should we use for individual patient assessment. In the ICE study, almost 26% of the patients treated with placebo showed improvement in their grip strength greater than the proposed MCID cutoff value of 8 kPa [6]. We are currently doing a study in our center aiming to determine the possible utility of different assessments performed at home before and after IVIg dose reduction in patients with chronic inflammatory neuropathies [25]. Preliminary results seem to show that the extended MRC (Medical Research Council) assessment (measured in 26 muscles) and the R-ODS have a greater sensibility than grip strength to detect significant clinical changes, although none of the assessment always catched clinical deterioration [25]. It is thus reasonable that on individual basis a multimodal approach may be the best way to monitor patients with chronic inflammatory neuropathies.

New potential applications of imaging techniques in inflammatory neuropathies have been recently evaluated, including the monitoring of disease progression, disease activity and treatment response. Most studies reported no more than a slight correlation among nerve enlargements detected with nerve ultrasound (US), nerve conduction studies (NCS) results and clinical impairment or disability [26-30]. Changes of nerve enlargements following treatment seem instead to correlate with treatment response [31-33], although increase of nerve enlargement under successful treatment has been reported [33]. A recent prospective study evaluated the role of US as a prognostic biomarker for therapeutic response [33]. Thirty-five treatment-naïve and 45 long-term treated patients were followed-up with US for 12 months. Three distinct pattern of nerve morphology abnormality were found, in line with Padua et al. [34]. Focal or diffuse enlargement with hypoechoic nerves/fascicles (Class 1) was the

predominant pattern in the untreated group whereas diffuse or focal enlargement with heterogeneous hyperechoic and hypoechoic fascicles (Class 2) and normal size nerve or minimal enlargement with iso-/hyperechoic fascicles (Class 3) were mostly found in treated patients [33]. Patients in Class 1 showed a significantly better improvement after treatment compared to those in Class 2 and 3 [33]. The authors concluded that nerve morphology may represent a marker for therapeutic susceptibility [33]. It is possible however that the better response to treatment in Class 1 patients might be also related to the fact that most of them had not yet received therapy (unlike instead of Class 2 and 3 patients), and that the prevalence of Class 1 in the untreated patients reflected a lower disease duration in this group compared to that of treated patients. A multicenter prospective studies using an homogeneous population is necessary to shed more light on the role of US morphology as a prognostic biomarker in chronic inflammatory neuropathies. Promising new methods to monitoring treatment response are emerging also for MR [27,35,36▪,37].

Subcutaneous immunoglobulin

Most patients with CIDP require regular IVIg infusions to prevent relapses [2▪]. This inconvenience can be solved with home infusion of subcutaneous immunoglobulin (SCIg) whose efficacy as maintenance treatment was shown to be similar to IVIg in a small controlled study [38] and its extension [39]. These data have been recently confirmed by a RCT on a large population of patients that provided evidence that SCIg is significantly more effective than placebo in preventing relapse within 6 months after suspending effective IVIg therapy, even if one third of the patients relapsed within six months after passing from IVIg to SCIg [40▪▪]. The results of these trials are also confirmed by one multicenter prospective real-life study [41] and its

extension [42]. SCIg was recently shown to have a similar, but delayed efficacy compared to IVIg as initial treatment in CIDP, with improvement in muscle strength occuring after a median time of 5 weeks compared to the 2 weeks after IVIg [43]. The number of patients included in this study was however relatively small and notably one severely disabled patient deteriorated after SCIg and required switch to IVIg [43]. An increase in patients satisfaction [38,41,42], disability [41], and muscle strength [38] after switching from IVIg to SCIg have been reported. In addition, some studies report a more favourable systemic side-effect profile of SCIg compared to IVIg [40▪▪,41,44,45]. A recent meta-analysis concluded that the use of SCIg was associated with a 28% reduction in the risk of moderate and/or systemic adverse effects compared with IVIg, with a similar efficacy [46]. An alternative to SCIg could be home-based IVIg therapy [47], although this possibility is not yet allowed in all countries.

Steroid therapy

Steroids are also considered as first-line therapy for CIDP although evidence for their use is inferior to that of IVIg [5], maily because of a lower number and quality of RCT [3▪▪]. This contrasts however with the extensive use of steroids in clinical practice. A RCT (IMC study) comparing the efficacy of therapy with IVIg or intravenous methylprednisolone (IVMP) showed that IVIg were more frequently effective than steroids during the first six months of treatment [48]. The more rapid efficacy of IVIg compared to steroids is supported by the results of the PREDICT study [49] where the median time to improvement in patients treated with pulsed oral dexamethasone was 17 weeks and of 39 weeks for daily oral prednisolone, while in the ICE trial IVIg showed to be effective in most patients within the first two months

of therapy [6]. In the IMC study and its extension, it was also shown that steroids discontinuation was associated with a lower frequency and greater latency of deterioration appearance compared to IVIg discontinuation [48,50]. A similar difference also derives from the PREDICT study where the median time to relapse after therapy discontinuation was 17.5 months after pulsed dexamethasone and 11 months after oral prednisolone [49], while in the ICE trial 45% of the patients relapsed within 6 months after suspending therapy with IVIg [6]. Similar conclusions were reached from a large retrospective study [51].

Steroids are known to carry a long-term risk of serious side effects and for this reason IVIg are generally preferred in developed countries for treating CIDP. In the IMC trial, there were not significant differences regarding safety between the IVIg-treated and the IVMP-treated group, and the frequency of adverse events in both groups was very low [48]. These findings however, may reflect the short duration of treatment, as also suggested by a retrospective study showing significantly more frequent adverse reactions after steroids (13%) than after IVIg (4%) [52]. Pulsed high dose steroid therapy seems howeber to have less side effects than daily steroid dose therapy [49]. Based mainly on the results of the IMC and PREDICT trial, a recent systematic review concluded that in case of motor-dominant CIDP, fastly progressive course, and contraindications to steroids, IVIg therapy should be preferred rather than steroids [53].

Immunesuppressive and immunemodulator agents

Most of the available data on immunesuppressive and immunemodulator agents in CIDP derives from observational studies and RCT have not shown that they are effective [54-58▪▪]. Immunosuppressive are still however frequently used in CIDP.

Recently, Fingolimod has been tested against placebo in a RCT in CIDP but the trial was stopped prematurely for futility [59▪]. According to the trial design, patients received their first trial medication on the day after the last IVIg infusion cycle and then received no further IVIg treatment, while patients receiving oral steroids on the day of randomization began tapering their steroid dose to zero over up to an 8-week period [59▪]. By the time the pre-planned interim analysis, there was no difference between the groups in the primary outcome and time to confirmed worsening [59▪]. It is possible, although speculative, that the negativity of the study might derive from the suspension of IVIg immediately after starting Fingolimod, with the possibility that some patients might have worsened before fingolimod become effective. It is advisable that further RCTs will be performed in the next few years in CIDP to assess the efficacy of the recently developed immune suppressive and modulator agents.

Rituximab and antibodies to nodal and paranodal proteins

Recently, there is a growing interest in the possible beneficial effect of Rituximab, whose efficacy attained around 70% in a review of uncontrolled studies [58▪▪]. The interest on the efficacy of Rituximab in CIDP was also boosted by the recent studies showing that some patients with CIDP have detectable antibodies targeting node of Ranvier proteins such as contactin-1 (CNTN1), contactin-associated protein 1 (CASPR1) and neurofascin 155 (NF155) [60-62▪▪-64], whose pathogenetic relevance has been recently reviewed [65▪]. These patients share a poor response to IVIg which has been related to the fact that these antibodies are predominantly or exclusively IgG4 and therefore unable to activate complement and bind to Ig Fc receptor [65▪]. However, response to other therapies, including prednisone –PE - and Rituximab, has been reported in these patients [60-62▪▪-64,66], with many of them requiring a

combined long-lasting treatement [63,67]. Testing for these antibodies may have important clinical implications as they may represent a valuable biomarkers for patients with specific clinical features and treatment response [65•]. Moreover, periodic assessment of antibodies level may help monitor treatment response and disease activity [67]. More recently, five patients with a severe phenotype and antibodies against the nodal isoforms of neurofascin (NF186 and NF140) have been reported [68••]. In most of these patients IVIg were effective despite the fact that most of them had IgG4 antibodies not fixing C1q *in vitro*, [68••], suggesting that IVIg response might not be only related to its effect on the complement pathway.

Conclusion

In the last few years there has been a growing interest on how to optimize mantainance IVIg treatment in CIDP and several ongoing studies are addressing the problem. The new disease-specific outcome measures have shown to have good clinimetric properties and promising results are waited from studies investigating the possible role of US and MR in monitoring disease activity and treatment response in CIDP. There is still, however, uncertainty on which and how many outcome measures should we use in routine clinical practice for CIDP. In addition, we still do not know whether the MCID cutoff values used in RCT are appropriate for individual patient assessment. Recent studies suggest that SCIg may be an alternative to IVIg for mantainance treatment with respect to efficacy, tolerability and quality of life even if their efficacy over the long-term should be further verified. Larger studies are also needed to evaluate the efficacy of SCIg as initial therapy in CIDP. Studies on the immune response to proteins at the node of Ranvier suggest that the small proportion of patients bearing these reactivities may have some specific clinical features and a

less frequent response to IVIg, even if this needs to be confirmed in a larger series of patients. It would be also advisable that future RCT will be mainly focused at assessing the efficacy of the newly developed immune suppressive agents in CIDP.

Key points

- Optimal IVIg maintenance treatment is still mostly empirically-based but ongoing studies will hopefully shed more light on this aspect.
- There is still uncertainty about how to decline the use of modern outcome measures in individual patients in routine clinical practice.
- SCIg are effective as maintenance therapy in the majority of patients with CIDP and improve the quality of life of the patients.
- IVIg are more frequently effective than corticosteroids in CIDP but are more frequently associated with treatment dependence.
- Testing for antibodies against proteins at the node of Ranvier may help in the choice of therapy and in the monitoring of disease activity.
- Even if immune suppressive agents are widely used in CIDP their efficacy still needs to be proved in RCTs.

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Conflicts of interest

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This complete and updated review analyzes all the studies with immune suppressive therapy in CIDP.

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