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PERSPECTIVE

Tailoring of therapy for chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a treatable immune-mediated disorder, which causes in its typical form, symmetric proximal and distal weakness with large fibre sensory impairment involving the four limbs. There are currently three main first-line therapeutic options for CIDP. These consist of corticosteroids, immunoglobulins and plasma exchanges (PE) which have all been found effective in a number of trials conducted over the past several years (Van den Bergh and Rajabally, 2013). No immunosuppressant therapy has shown benefit in CIDP, although they are utilized by many clinicians in various circumstances despite absence of an evidence base.

CIDP is a heterogeneous entity and also consists of so-called "atypical forms". These can be anatomical with focal and multifocal subtypes, or relate to the nerve fibre type involved, with pure sensory and pure motor variants. There are also forms co-existing with associated diseases. There are likely different pathophysiologic mechanisms for the different subtypes which may in turn affect best treatment to be offered for each variant. An example is the pure motor form of CIDP, for which there are a number of reports which have described deterioration on steroids, making immunoglobulins the favoured first-line treatment. The degree of electrophysiological, albeit asymptomatic, sensory involvement may hence also represent a marker of corticosteroid responsiveness, as may also the degree of focal electrophysiological demyelination (Eftimov et al., 2012). Co-existing disease, such as diabetes may make use of certain treatments such as corticosteroids unadvisable.

Corticosteroids themselves, administered intravenously, have recently been shown to be a less well-tolerated and/or effective treatment than immunoglobulins in a comparative Italian study (Nobile-Orazio et al., 2012), although importantly on long-term follow-up, offered a significantly longer remission-free period (Nobile-Orazio et al., 2015). In keeping with this finding, another retrospective study found steroids to be more likely to induce remission than immunoglobulins (Rabin et al., 2014). Also, the comparative Italian study also demonstrated a similar outcome with both treatments in terms of quality of life measures, somewhat contradicting the findings on the primary outcome (Nobile-Orazio et al., 2012). There has been furthermore a comparative trial of pulse oral dexamethasone *versus* the more conventional daily oral prednisolone regimen (PREDICT study) (Van Schaik et al., 2010). This analysis examined the remission rate at 12 months and showed no statistically different findings between the 2 groups. There was on the other hand importantly a significant difference in the median time to improvement on the disability scale (17.0 weeks for dexamethasone and 39.0 weeks for prednisolone; $P = 0.036$). The adverse effects profile was not different in the 2 groups although less sleeplessness and cushingoid facies occurred less frequently in the pulsed dexamethasone group. There consequently are currently different corticosteroid options for treating CIDP and the lengthy trial of daily oral prednisolone, with which assessment of treatment response was usually not advised before three months, may now have become the least attractive of those.

Intravenous immunoglobulins (IVIg) represent the favoured therapeutic avenue for many neurologists treating CIDP. Validated by a number of good quality studies, the effect of IVIg has been demonstrated on neurological function mainly in the short-term and by a single more recent study, in the longer term (Van den Bergh and Rajabally, 2013). IVIg is justifiably preferred when patients are severely disabled by the disease and require as quick improvement and recovery as possible with as low as possible risk of treatment withdrawal. IVIg should however be instigated with the possibility of monophasic disease being kept in mind and ideally, in case of full or near complete recovery, should be repeated only if re-deterioration occurs. Similarly, the need for continuing treatment should be regularly re-visited and questioned as disease remission can occur in as many as 25–40% of patients after variable lengths of time (Rajabally, 2015). How much IVIg to administer remains an unanswered question. Few studies have considered this issue, and immunological doses are still used as they have been in CIDP trials. Although the amount of data is limited, it is likely that weight, body mass index, level of disability play no role in IVIg dose requirements (Rajabally, 2015). In more recent years, there has otherwise been accumulating evidence for using subcutaneous immunoglobulin (SCIg) in replacement of IVIg in CIDP as well as multifocal motor neuropathy (Rajabally, 2014). In CIDP, after some small open-label studies, a double blind parallel group placebo-controlled trial demonstrated a significantly better result of SCIg than placebo on isokinetic strength change in previously IVIg-responsive subjects. Compared to the previous IVIg response, SCIg was at least as efficacious, even allowing some degree of significant isokinetic strength amelioration. The follow-up study of the patients subsequently maintained on SCIg demonstrated that SCIg importantly preserves muscle strength and functional ability in the longer term (Markvardsen et al., 2014).

PE are a proven treatment for CIDP although are frequently less practical and consequently less often used in clinical practice. It appears that the beneficial effects may be short-lived whereas side effects may be relatively common with PE (Van den Bergh and Rajabally, 2013) which makes also for that reason makes them a less attractive first-line option. PE represents however a very useful option in patients having failed to respond to IVIg or corticosteroids and should clearly be tried in this setting before any other non-evidence based alternatives. This may not always be the case in clinical practice.

Which of the three available options should be used as first-line treatment in CIDP? The practical choice clearly lies between IVIg and corticosteroids although the ultimate answer may not be straightforward. IVIg appears to offer a greater chance of rapid improvement and may be therefore preferred when disability is severe. Corticosteroids, preferably in the pulse form, oral or intravenous, are on the other hand a good option in absence of contraindications, if the history is already long and functional impairment relatively mild. In both cases, consideration should be given to the possibility as well as potential seriousness, of side effects. IVIg is usually well-tolerated but the risk of thromboembolic events should not be overlooked, particularly in patients with multiple vascular risk factors. There are unfortunately no proven effective preventative measures for such complications which may of course, and be life-threatening. With corticosteroids, when treatment is prolonged, prevention of osteoporosis and gastric protection represent adequate precautions. Other rarer side effects should not be ignored and represent good reasons to be cautious with regular close monitoring.

Treatment of patients who have failed to respond to any one of the first three evidence-based therapies requires careful thought. First, ascertaining that the appropriate dose and length of treatment was used is essential before considering it as ineffective. Also, whether adequate evaluation scales were utilized is of paramount importance. INCAT (Inflammatory Neuropathy Cause and Treatmtment) Scores or ONLS (Overall Neuropathy Limitation Scores) as well as the more recently-introduced R-ODS (Rasch-built Overall Disability Scale), offer more precise and relevant evaluation than previously used Rankin scales (Rajabally, 2015). In addition, and not infrequently, whether there is

objective definite unresponsiveness or, instead, persistent mainly subjective fatigue, decreased stamina or sensory symptoms, poses obviously different problems as may make the impression of treatment-refractoriness erroneous. Only about half of newly IVIg-treated patients respond after a single course (Latov et al., 2010), and while two courses may be needed for the majority, it is also possible that a third course is warranted in initial non-responders. Furthermore, several further courses may be required for maximum benefit in those who have improved only partially (Latov et al., 2010). Combination of treatments represents, in our experience a good way forward and can be a very effective solution (Van den Bergh and Rajabally, 2013). IVIg and pulse steroid therapy represents probably the easiest to use and monitor for improvement in clinical practice. PE combined to pulse steroids can also represent an effective course of action.

No immunosuppressant or other immunomodulatory agents has shown to date benefit in CIDP in randomized controlled trials (Van den Bergh and Rajabally, 2013). The only other tried therapies in the setting of RCTs, have been azathioprine, interferon beta-1a and methotrexate and all these trials were negative. Many other agents including cyclophosphamide, cyclosporine, rituximab and mycophenolate have been used with success anecdotally.

It is possible that the rarity of CIDP may pose difficulties in conducting appropriately-sized studies, underestimating the value of immunosuppressant agents. In practice, for completely refractory patients, using non-evidence-based therapies in order to attempt improving function may however justified, particularly as it appears a proportion of these patients have a reasonable chance of significant improvement. This requires clear discussion particularly of side effects risks and should involve obtaining clear informed consent from patients. The most useful agent in severely weak and disabled patients would appear to be high-dose pulse cyclophosphamide, usually administered concurrently with high-dose intravenous methylprednisolone, at the dose of 1 g/m^2, on a monthly basis, for six months. Cyclophosphamide has shown impressive results in a number of cases (Good et al., 1998). Although these data date back 17 years, with no recent confirmatory randomized controlled trial evidence, we have found it highly effective in severe refractory cases. It is clear that this treatment has to be used very selectively, by units familiar with it and with all adequate precautions being taken. More recently, an autologous hematopoietic stem cell transplant (AHSCT) has been described as highly efficacious in a small series of patients. The place of this therapy requires further study particularly as may avoid an initial unsuccessful exposure to Cyclophosphamide, which is also used for mobilization and conditioning during the AHSCT (Press et al., 2014). It is nevertheless debatable whether AHSCT has a place in treating CIDP, as it may be argued it would be best avoided in many patients who would respond well to Cyclophosphamide, and also as is not always effective in the long-term anyway with relapses described in nearly 30% of cases (Press et al., 2014).

In conclusion, therapeutic decision-making in CIDP requires consideration of a number of different factors, relating principally to the individual patient's circumstances. Disease severity, disease subtype, age, comorbidities, all play a significant role in the process. First-line therapies most frequently suffice alone and in combination, and effects should be carefully evaluated using appropriate validated scales. Immunosuppressant treatment, although without an evidence base, should not be excluded in selected, albeit exceptional cases. The task of tailoring CIDP therapy for each patient is important, with often long-term implications. The right decision may not be easy but is crucial both in order to offer the maximum chances of remission and/or cure, while offering the justifiably most adequate therapeutic option for every affected individual in relation to risk exposure and side effect profile.

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