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Management of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract

This review briefly describes current concepts concerning the nosological status, pathogenesis and management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). CIDP is an uncommon variable disorder of unknown but probably autoimmune aetiology. The commonest form of CIDP causes more or less symmetrical progressive or relapsing weakness affecting proximal and distal muscles. Against this background the review describes the short-term responses to corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange that have been confirmed in randomised trials. In the absence of better evidence about long-term efficacy, corticosteroids or IVIg are usually favoured because of convenience. Benefit following introduction of azathioprine, cyclophosphamide, cyclosporin, other immunosuppressive agents, and interferon-β and -α has been reported but randomised trials are needed to confirm these benefits. In patients with pure motor CIDP and multifocal motor neuropathy, corticosteroids may cause worsening and IVIg is more likely to be effective. General measures to rehabilitate patients and manage symptoms, including foot drop, weak hands, fatigue and pain, are important.

After a brief description of current concepts concerning the nosological status and pathogenesis this review considers the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Parts of this article are based on four Cochrane systematic reviews [1-4] and on another review written by the author.[5]

1. Diagnosis

CIDP began to emerge as a syndrome separate from Guillain-Barré syndrome with the description of recurrent corticosteroid-responsive neuropathy by Austin in 1958.[6] Thomas et al. described patients with a recurrent or chronic relapsing illness whose electrophysiological and pathological features resembled those of the acute inflammatory demyelinating polyradiculoneuropathy form of Guillain-Barré syndrome.[7] They compared it to chronic experimental autoimmune neuritis and suggested an autoimmune aetiology.

The description of increasingly large series of patients[8-11] led to a clearer clinical picture and eventually a consensus definition by an American Academy of Neurology committee.[12] This definition required fulfilment of clinical and electrophysiological criteria for a probable diagnosis and pathological criteria as well for a definite diagnosis (table I). Nerve biopsy may show characteristic macrophage-associated demyelination and lymphocytic infiltration. However, in the largest series, biopsies have more often shown only non-uniform loss of nerve fibres and ongoing axonal degeneration, which are the consequence of more proximal inflammation. Consequently, many consider nerve biopsy unnecessary.[13,14] Electrophysiological investigation on the other hand is crucial. The American Academy of Neurology electrophysiological criteria exclude many patients who would otherwise be considered to have CIDP.[14] Less strict European criteria have been shown to be more sensitive and adequately specific.[15] Briefly, these criteria require conduction block or temporal dispersion or abnormal nerve conduction values suggesting demyelination in at least one segment of three different nerves. At least one of the nerves must show abnormal nerve conduction values. The cerebrospinal fluid (CSF) protein is increased in at least 80% of patients with CIDP and has been proposed as a requirement for a definite diagnosis.[14]

Table I. Diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy[12]

Clinical
Progressive or relapsing motor and sensory (rarely only motor and sensory) dysfunction of the limbs developing over at least 2 months
Reduced or absent tendon reflexes
Absence of alternative cause, e.g. relevant toxin exposure, family history
Absence of CNS involvement
Neurophysiological
Neurophysiological studies indicating the presence of multifocal demyelination
Cerebrospinal fluid
Cell count <10/mm^3 or >10/mm^3 if HIV positive
(protein usually increased)[a]
Nerve biopsy[a]
Unequivocal evidence of demyelination or remyelination (inflammation, onion bulb formation, variation between fascicles)

a Supportive but not mandatory.

Diagnosis of CIDP is the first step in management. It is likely that patients with CIDP go unrecognised because it is so variable. Opportunities for missing the diagnosis abound and the steps necessary for making the diagnosis have recently been reviewed.[5] The diagnosis requires consideration in every patient with chronic peripheral neuropathy, in patients with Guillain-Barré syndrome with a prolonged onset phase or recurrence, and in patients with peripheral neuropathy resembling Charcot-Marie-Tooth disease but lacking a molecular genetic diagnosis or family history.

Neuropathy occurring with diabetes mellitus, systemic lupus erythematosus and various cancers may resemble CIDP, and might be coincidental or represent aetiologically important associations. Of greater importance is the association with paraproteinaemia, which occurs in about 10% of patients with an acquired demyelinating neuropathy.[16] The paraproteinaemia may be monoclonal gammopathy of undetermined significance, Waldenstrom's macroglobulinaemia or solitary plas-

macytoma. A paraprotein should always be sought in a patient with CIDP. The management of such patients depends on the underlying cause of the plasma cell dyscrasia.[14,17]

2. Natural History

Minimum estimates of the prevalence of CIDP are 1–2 per 100 000.[18,19] It affects any age but is more common in the middle-aged and elderly, and in men than women. It is typically a symmetrical sensory and motor disorder pursuing a relapsing, progressive or monophasic course in which the progressive phase is greater than 2 months. Variants with purely sensory symptoms, purely motor symptoms and marked asymmetry have been described. The last was originally described by Lewis and Sumner[20] and has recently been called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).[21] It is characterised by sites of persistent conduction block persisting over many years. Another variant has similar persistent sites of conduction block but only affects motor nerve fibres. This is now called multifocal motor neuropathy (MMN) and may be a different condition rather than a variant because, unlike CIDP, it is associated with antibodies to ganglioside GM1 and, again unlike CIDP, it does not respond to corticosteroids and may be made worse by them.[22]

The clinical course is variable and unpredictable. In a population based study, 13% of 46 patients in the South East Thames region of England required aid to walk and 54% were receiving medical treatment on the prevalence date.[18] In large series 4–17% have died of their disease, usually as a consequence of respiratory failure or pulmonary embolism.[8,10,11,23,24] There are no obvious precipitants of most relapses but there are two reports of recurrent attacks occurring after tetanus toxoid immunisation.[25] Relapses were 3-fold more frequent during pregnancy than during non-pregnancy years in one series.[26] In a series of 21 patients with predominantly or purely motor CIDP, the prognosis was worse in the older patients (aged >50 years).[27] The prognosis and response to immunotherapy were also worse in another series in 35 patients over 64 years of age than in 89 younger patients.[28]

3. Pathogenesis

The evidence for inflammation in CIDP comes from the identification of endoneurial inflammation in active peripheral nerve lesions. Patients do not have an obvious systemic illness and generally feel well apart from their neuropathic symptoms. Although not proven, CIDP is generally considered to be an autoimmune disease caused by either humoral or cell-mediated immunity directed against myelin or Schwann cell antigens that have not been clearly identified.[29] Enhanced T-cell responsiveness to P0 and P2 myelin was somewhat greater than that in controls but not significantly so.[30] Increased concentrations of soluble interleukin (IL)-2 receptor and tumour necrosis factor (TNF)-α in the serum of patients with CIDP have been found in most,[31,32] but not all, series[29] suggesting the involvement of T cells. The inflammatory infiltrate consists of activated T cells and macrophages, which secrete cytokines and enzymes including TNFα and matrix metalloproteinase 9.[24,32-34] The T cells in the nerve have a heterogeneous Vβ gene repertoire, which does not favour an immune response to a restricted antigen.[35] However, this does not exclude an initially restricted T-cell response, such as occurs in blood T cells in Guillain-Barré syndrome,[36] followed by later epitope spreading.

The search for antibodies in the serum, which might cause and help diagnose CIDP, has not identified a single typical antibody. Antibodies to different individual myelin proteins or glycolipids are found in small percentages of patients. Antibodies to ganglioside GM1 are found in approximately 50% of patients with MMN, but only in 10% or less of patients with CIDP.[22] Antibodies to tubulin were proposed and then discarded as a helpful diagnostic test.[37-39] Antibodies to neuroblastoma cells were reported in 42% of 48 patients but their relevance to pathogenesis is obscure.[40] Antibodies to two myelin trans-membrane proteins seem more likely candidates. Antibodies to PMP22 were

found in 35% of 17 patients[41] and antibodies to the major myelin glycoprotein P0 were found in 16–29% of patients in two studies, [42,43] but not in two others.[44,45] Sera containing antibodies to P0 were shown to produce demyelination following injection into rat sciatic nerve.[43] Since no single antigen has emerged as being a common target in all patients with CIDP it seems likely that the antigenic target varies from patient to patient. Protein antigens expressed at the myelinating Schwann cell surface, such as PMP22 and P0, seem the most likely targets.

The reason for the development of autoimmunity in CIDP is not known. One study showed that suppressor cell function is defective in CIDP, a defect that was corrected by interferon (IFN)-β.[46] There are old reports of a weak association with HLA class I antigen Cw7 and HLA class II antigen DR3 or DW3.[47-49] These would be worth investigating further since genetic immunosusceptibility is likely to be the underlying cause for the development of autoimmunity.

4. Treatment

4.1 Corticosteroids

Austin in 1958 established the existence of recurrent steroid-responsive neuropathy with repeated comparisons of response to corticosteroids or placebo in a single patient.[6] Dalakas and Engel treated 25 patients with CIDP in a large, uncontrolled study with corticosteroids alone, and 'the majority' improved. They emphasised that a lag period usually of 1–4 weeks, but occasionally up to 5 months, occurred from onset of therapy to the first sign of improvement.[50] They recommended high doses of corticosteroids for about 1 year, then cautious tapering to avoid pharmacorelapses and long-term, low maintenance doses to prevent spontaneous relapses. McCombe et al. reported a study of 92 patients of all ages.[10] Sixty patients (65%) had a relapsing course and 32 patients (35%) a progressive or monophasic course. Seventy-six patients were treated with corticosteroids. Forty-nine patients (65%) made a good recovery and became independent. Similarly Barohn et al. studied 60 patients aged 10–77 years.[11] Patients were started on a regimen of prednisone 100 mg/day for 2–4 weeks and then switched to prednisone 100mg as a single dose on alternate days. This regimen was continued until the clinical improvement plateaued. If the patient's response was poor or a relapse occurred, either azathioprine or plasma exchange was added to the treatment. Fifty-six (95%) of 59 treated patients showed initial improvement with immunosuppressive treatment. The mean (±SD) time for improvement was 1.9 (±3.6) months. The mean time to reach a clinical plateau was 6.6 (±5.4) months. Molenaar et al. treated 10 patients with dexamethasone 40 mg/day for 4 consecutive days every 28 days for six cycles.[51] Five had previously improved with intravenous immunoglobulins (IVIg), one with corticosteroids and azathioprine, and three had not been treated. One patient stopped treatment because of vomiting and weight gain. Six patients went into sustained remission, one improved but then relapsed, one continued to worsen and one (with pure motor CIDP) worsened dramatically. A randomised, controlled trial (RCT) of this regimen is in progress. Beneficial effects of corticosteroids have also been documented in children with CIDP.[52-54] The experience from published series uniformly suggests that corticosteroids induce at least short-term improvement in two-thirds to 95% of adult patients with CIDP.

The only available RCT of corticosteroids in CIDP compared prednisone, starting with 120 mg/day and tapering over 12 weeks, with no treatment and included 35 evaluable patients.[55] The methodological quality of this trial was reduced by the failure to conceal allocation and any use of blinding. Nevertheless, in other respects the trial was meticulously performed. The authors concluded that corticosteroids significantly reduced impairment and improved measures of nerve conduction. The interpretation of the results of the trial is critically dependent on how the withdrawn patients are analysed. On the one hand, one withdrawn prednisone recipient died and another re-

mained ventilated, which argues against prednisone. On the other hand, two withdrawn control patients worsened and then improved on prednisone, which favours prednisone. The trial did show a strong trend towards improvement in several measures of impairment and nerve conduction, but the absence of a true intention-to-treat analysis weakens the strength of the evidence that corticosteroids are beneficial.[2]

The overall conclusion from the only available trial, case series and published opinion is that corticosteroids are beneficial in CIDP. There may be a lag period usually of 1–4 weeks, but occasionally up to 5 months, from the onset of therapy to the first sign of improvement. Care must be exercised in starting treatment because occasional patients deteriorate, especially those with pure motor forms of CIDP or with multifocal motor neuropathy with conduction block.[56] The exact mechanism by which corticosteroids cause worsening in these CIDP variants is not known. The serious adverse effects of prolonged corticosteroid treatment are a major disadvantage.

4.2 Plasma Exchange

Plasma exchange was reported to offer at least short-term benefit in patients with CIDP in the late 1970s and early 1980s by several authors.[57-61] Subsequently its efficacy was confirmed in two RCTs. Dyck and colleagues at the Mayo clinic undertook a double-blind trial comparing twice weekly plasma exchange or sham exchange for 3 weeks. They showed significantly greater improvement in impairment and motor nerve conduction measurements in 15 patients randomised to plasma exchange than in 14 patients randomised to sham.[62] Hahn and colleagues in London, Ontario, Canada, undertook a crossover trial comparing plasma exchange with sham exchange in 18 treatment naïve patients of whom 16 completed the crossover period. Patients received four exchanges in the first week, three in the second, two in the third and one in the fourth. There were significant improvements in impairment, disability, grip strength and proximal compound muscle action potential amplitude with plasma exchange which were not seen with sham exchange.[63] A Cochrane systematic review is in progress and is likely to conclude that plasma exchange produces short-term improvement.

In order to maintain improvement, plasma exchange has to be repeated at variable intervals, but often as little as four weeks, which is inconvenient and eventually gives rise to difficulties with venous access. Bromberg et al. reported one patient who responded to regular plasma exchange after failing to respond to vigorous immunosuppressive regimens.[64] In a follow-up study of 105 patients we treated 33 with plasma exchange and 23 responded: seven patients required repeated treatment for between 8 months and 5 years.[65] These patients were eventually transferred to IVIg, but one did not respond to IVIg and continued to receive plasma exchange for 6 more years. In this patient, an n-of-1 trial showed that plasma exchange was more effective than immunoabsorption.[66] The usefulness of plasma exchange as a treatment for CIDP is limited by its inconvenience, requirement for hospital attendance and specially trained staff, and the occurrence of adverse events. Complications, usually from the use of a central venous catheter, were reported in 17% of 381 procedures in one series and one was fatal.[67]

4.3 Intravenous Immunoglobulin

Maas et al. reported that infusion of fresh frozen plasma was as effective as plasma exchange in a patient with CIDP.[68] Vermeulen et al. showed that plasma and then IVIg infusion appeared to benefit patients with CIDP.[69] This observation was replicated in many case series and eventually confirmed in three randomised trials in IVIg-naïve patients[70-72] but not in a fourth.[72,73] The evidence from these trials has been summarised in a meta-analysis.[3] For three of the trials, including 87 patients for whom the data were available, the authors found that a significantly higher proportion of patients improved one point on the Rankin scale after IVIg compared with placebo (relative risk 2.47, 95% CI 1.02–6.01). Unfortunately the

benefit is short-lived. It commonly lasts only 4 weeks and seldom more than 12 weeks, so that treatment, which is very expensive, has to be repeated.

A crossover trial in 20 patients did not find a significant difference between the short-term effects of IVIg and plasma exchange courses of similar cost.[74] Finally, our own crossover trial in 32 patients did not detect any significant difference between the short-term benefits from IVIg and oral prednisolone.[75]

In case series approximately two thirds of patients respond to treatment with IVIg, of whom one third improve and do not require further treatment and two thirds require repeated courses at intervals. The intervals vary between 2 and 12 weeks, and doses between 0.4 and 2.0 g/kg.[65,76,77]

4.4 Azathioprine

Azathioprine is a broad spectrum immunosuppressive agent and is probably the one most commonly used in CIDP. Uncontrolled observations from case reports and case series in the literature provide little hard information about the value of azathioprine in CIDP. In 1981 Dalakas and Engel[50] described azathioprine as their immunosuppressive drug of choice. They used a 3 mg/kg single daily dose and considered that a clinical effect could be detected in between 1 and 12 weeks. They reported improvement in three of four patients with steroid-resistant CIDP to almost 90–95% of normal. They also considered that azathioprine has a steroid-sparing action in patients who responded to corticosteroids. In a series of 59 treated patients, 56 (95%) responded to immunosuppressive treatment which started with prednisone and then included azathioprine in the event of a relapse or poor response: the number who received azathioprine was not stated.[11] Seven of a series of 92 patients with CIDP were treated with azathioprine and four improved by at least one point on a six point disability scale.[10] One widely respected textbook recommends azathioprine as a substitute for prednisone in patients with CIDP who have contraindications to corticosteroids.[78] In a disease with a relapsing remitting course and a drug that has a slow onset of action conclusions are particularly difficult to draw from anecdotal observations.

The only RCT compared 14 adult patients randomised to azathioprine 2 mg/kg and prednisone with 13 patients treated with prednisone alone.[79] The trial had a parallel group design and treatment lasted 9 months. The observers and participants were not blinded. Follow-up data were not available for one azathioprine and prednisone recipient and three prednisone alone recipients. There were no significant differences after 4–9 months in any of 16 variables including a neuropathy impairment score, other measures of impairment, motor nerve conduction and CSF protein. The trial lacked power to detect or exclude any but very large treatment effects. Furthermore, it only tested a dose of 2 mg/kg, whereas a dose of 2.5 mg/kg or sometimes 3.0 mg/kg has been used in other conditions such as multiple sclerosis and Crohn's disease.[80] The trial also only continued treatment for 9 months, whereas in a similar trial in myasthenia gravis a treatment effect did not become evident until after 12 months.[81] Consequently, it would be premature to draw conclusions about the efficacy of azathioprine from this trial and the drug is often used as a first line immunosuppressive treatment when corticosteroids and IVIg are inadequate.

Adverse effects from azathioprine include nausea, vomiting, diarrhoea and allergic reactions including rash, which prevent its continuation in about 10% of patients. It also causes leucopenia, altered liver function and increased susceptibility to infection. It carries a theoretical risk of inducing neoplasia.[82,83] Azathioprine is metabolised by thiopurine methyl transferase, and 10% of the population are heterozygotes and 0.3% homozygotes for deficiency of this enzyme. Measurement of the enzyme levels before starting treatment allows detection of the heterozygotes, whose dose should be halved, and homozygotes, who should probably not be given the drug.[84] It should also not be used with allopurinol.

Azathioprine is less expensive than most immunosuppressive drugs. In 2002, the UK National Health Service (NHS) cost of giving 150 mg/day for a year was £300. To this cost must be added the costs of monitoring the haematological and liver function, which are required for as long as treatment is continued, and the costs of treating adverse effects. However, if the drug is effective it might result in savings because of reduced healthcare costs arising from the disability which CIDP causes and especially from the reduced usage of IVIg.

4.5 Cyclophosphamide

Cyclophosphamide is an alkylating agent which can be given orally or by intravenous injection. Oral cyclophosphamide 2 mg/kg was reported to be beneficial in one patient with CIDP.[50] Another report described benefit in four of five patients but did not mention the dose or route.[10] A series of 36 patients were treated in turn, depending on response, corticosteroids, IVIg, plasma exchange and finally oral cyclophosphamide 2 mg/kg/day for 6–12 months.[24] Three patients who had not responded to previous agents also failed to respond to this cyclophosphamide regimen. A series of 15 patients were treated with intravenous pulses of 1 g/m^2 monthly for a maximum of 6 months with careful precautions to avoid dehydration and premedication to reduce nausea.[85] Twelve patients showed marked improvement, 11 improving to normal. Three did not improve and one worsened. All patients developed a drug-induced leucopenia. Six patients had minor adverse effects and two developed alopecia. None developed haematuria, prolonged bone marrow depression or neoplasia, all of which are serious adverse effects associated with high-dose cyclophosphamide. Additional likely adverse effects are increased susceptibility to infection and ovarian failure, but neither were not reported in this series. Brannagan et al. induced long-term remissions in four patients with high dose cyclophosphamide without stem-cell rescue.[86] The impressive results in these case series strongly suggest treatment benefit. The risk of serious adverse effects discourages many patients and their neurologists from using this drug.

4.6 Cyclosporin

Another drug that has been used quite frequently in patients with CIDP is cyclosporin, which particularly inhibits the proliferation of T cells. In one patient its use combined with plasma exchange appeared successful when corticosteroids and then plasma exchange alone had failed.[87] The largest series is that of Pollard and McLeod[88,89] who treated 19 patients with CIDP but five had a paraprotein which excludes them from consideration in this review. At the beginning of their series they used a high dose of cyclosporin, 10 mg/kg/day reduced to 8 mg/kg/day after 1 month and 5 mg/kg/day after 3 months, but later they reduced the starting dose 3–7 mg/kg and the maintenance dose to 2–3 mg/kg. All 14 patients without a paraprotein improved either with a reduction in disability by at least one grade or by a reduction in the annual relapse rate. Eleven of the 19 patients experienced adverse effects, nephrotoxicity in four, hypertension in four, nausea in three, oedema in three and hirsutism in four. These are the common adverse effects of cyclosporin, which, together with expense, have precluded its more widespread use. The adverse effects were less with lower doses. This series suggests but does not prove that cyclosporin is beneficial in CIDP: there is no doubt that it causes potentially serious adverse effects.

4.7 Other Immunosuppressive Regimens

The successful use of tacrolimus (FK-506) in a single patient with treatment-resistant CIDP has been reported.[90] It was ineffective in a similar patient in whom I tried it.

Mycophenolate is becoming popular as an alternative to azathioprine and cyclosporin in prevention of renal transplants and reports are beginning to appear of its use in neurological disease. For instance, there is a recent report of benefit from mycophenolate in two patients with CIDP.[91] However, Chaudhry et al. reported benefit in only

two of three patients[92] and I have not found it helpful in five, admittedly treatment-resistant, patients.

Although methotrexate is very commonly used in rheumatoid arthritis there appear to be no substantial series of patients with CIDP having been treated with this drug. Molenaar et al. briefly mention benefit in one patient[51] and I have used it as an adjunct to corticosteroids and IVIg in two patients with apparent benefit. Its use would merit further study.

Etanercept is a recombinant dimeric fusion protein consisting of part of the TNF receptor linked to the IgG Fc component. It is expected to inhibit the action of TNF and is an efficacious treatment for rheumatoid arthritis. There is a single report of its successful use in treatment resistant CIDP.[93] Of concern is that there are more than 20 reports of its use in rheumatoid arthritis triggering the onset of multiple sclerosis.[94]

There is a single report of substantial improvement following autologous stem cell transplantation in a single treatment-resistant patient.[95] The reason that more patients have not been treated with this regimen is that it still carries a 5% mortality because of the risks associated with extreme immunosuppression.

4.8 Interferons

IFNβ is a naturally occurring cytokine, which down regulates inflammatory responses and has been shown to reduce relapse frequency and blood-brain barrier leakage in multiple sclerosis. IFNβ-1a is a recombinant protein manufactured in mammalian cells that exactly replicates human IFNβ. We found an apparently beneficial effect in one patient with treatment-resistant CIDP.[96] In a prospective, open study four patients with moderately severe CIDP received a 6-month course of IFNβ-1a 22μg three times weekly for 3 weeks and then 44μg three times weekly for 8.5–10.3 months.[97] There was no statistically significant benefit, two patients showed moderate improvement and one relapsed on treatment with IFNβ-1a alone. When the treatment was combined with IVIg improvement did occur but this might have been due to the known beneficial effect of IVIg. An open study claimed benefit from IFNβ-1a 22μg three times weekly in one patient with pure motor CIDP and three with multifocal motor neuropathy.[98]

Encouraged by our own experience we undertook a randomised trial comparing IFNβ-1a with placebo in a crossover design.[99] Ten adult patients with treatment resistant CIDP were randomised to receive IFNβ-1a (Rebif®[1]) 11μg subcutaneously three time weekly for 2 weeks and then 22μg three times weekly for 10 weeks or a similar appearing placebo. After a 1-week wash-out period patients were started on the opposite treatment to that which they had received during the first treatment period. There was no significant difference between improvement on measures of disability, impairment or quality of life comparing the IFNβ-1a and placebo treatment periods. The negative result has to be considered in the context of the facts that the patients were resistant to other treatments, only received treatment for 12 weeks and received a low dose, maximum 22μg subcutaneously three times weekly. In subsequent trials in patients with multiple sclerosis IFNβ-1a (Rebif®) 44μg three times weekly has been more effective on most parameters than 22μg three times weekly.[100,101] In a subsequent series of five patients with CIDP, treatment with IFNβ-1a (Rebif®) 44μg three times a week (combined with IVIg in four) for between 5 and 29 months appeared effective.[102]

IFNβ often causes minor skin reactions and alterations of liver function and white cell counts, but serious adverse effects are rare. Its main disadvantage is expense. In 2002, the UK NHS price is £7000–£12 000 per year.

IFNα is another naturally occurring cytokine, which has complex, incompletely understood immunoregulatory actions. It is used to enhance immune reactions and so treat hepatitis C. It up-regulates immune responses and has been reported to cause autoimmune diseases including CIDP.[103,104] Despite this, IFNα has been used to treat CIDP. In

1 Use of tradenames is for identification purposes only and does not imply endorsement.

the largest series,[105]16 patients, of whom two had a paraprotein, were treated with IFNα-2a at a dosage of 3 million IU subcutaneously three times a week for 6 weeks. Of the 14 without a paraprotein, nine responded to IFNα: five had a sustained improvement, one improved, received plasma exchange and then had sustained improvement, and three relapsed. Minor adverse effects consisting of fatigue, fever, malaise, myalgia and arthralgia were common. In another series, six of 12 patients treated with 2–3 million IU improved, allegedly without any adverse effects.[106] Like IFNβ, IFNα is very expensive.

5. Multifocal Motor Neuropathy

One of the principal differences between MMN and CIDP is the absence in MMN of the response to corticosteroids that is usual in CIDP. In fact, in MMN and pure motor forms of CIDP, corticosteroid treatment may cause serious worsening.[56] A Cochrane systematic review listed anecdotal reports of treatment with corticosteroids which were often followed by deterioration and rarely caused improvement.[4] There have also been a few reports of the use of plasma exchange which has usually had little effect, sometimes been followed by improvement and sometimes by deterioration. By contrast IVIg is often dramatically and rapidly effective, experience that is supported by three small trials.[107-109] Unfortunately the improvement is short-lived and not invariable, and disability progresses despite repeated treatment. Many different immunosuppressive drugs, but principally cyclophosphamide, have been tried but without any randomised trials. The evidence from non-randomised studies is inadequate to conclude whether any particular immunosuppressive agent is effective.[4] As for patients with CIDP, repeated treatment is usually needed in patients with MMN.

6. General Management

Preventive and palliative treatments are as important in CIDP as in other forms of neuropathy. Foot care, appropriate shoes or boots, ankle-foot orthoses, wrist splints, weight reduction, physiotherapy, occupational therapy and counselling about prognosis and coping with disability are obviously important in different patients. Their prescription depends on common sense and experience more than evidence from randomised trials. Autonomic involvement is relatively uncommon in CIDP, but erectile impotence does occur and in my experience will usually respond to sildenafil. In the 20% of patients with pain from their CIDP the use of tricyclic antidepressants, anti-epileptic drugs and tramadol has been endorsed by systematic reviews or randomised trials of treatment for neuropathic pain (not undertaken specifically in CIDP).[110] Because of reports of relapse of CIDP after immunisation, more than usual caution should be observed before recommending immunisation, especially with tetanus toxoid.[25,111] Finally, fatigue is a significant problem for many patients[112] and there are no trials to determine whether tricyclic antidepressants, exercise programmes or other treatments are helpful.

7. Patient Support Groups

The US-based Guillain-Barré Syndrome Foundation International (http://www.guillain-barre.com) and the UK-based Guillain-Barré Syndrome Support Group (http://www.gbs.org.uk) are both sites that provide well edited information and support to people with Guillain-Barré syndrome, CIDP and related conditions.

The Peripheral Neuropathy Trust site (http://www.neuropathy-trust.org) provides information about all forms of neuropathy, especially chronic idiopathic axonal neuropathy and painful neuropathy.

8. Conclusions

CIDP is heterogeneous: the most common form causes more or less symmetrical progressive or relapsing weakness affecting proximal and distal muscles. Its prevalence is at least 1–2 per 100 000. Its severity is variable. Half require persistent treatment, 13% are permanently disabled and 5–17% die from the disease.

Corticosteroids, IVIg and plasma exchange all have similar short-term efficacy. In the absence of better evidence about long-term efficacy, corticosteroids or IVIg are usually favoured because of convenience.

Benefit following introduction of azathioprine, cyclophosphamide, cyclosporin, other immunosuppressive agents and IFNβ and IFNα has been reported, but randomised trials are needed to confirm these benefits.

In patients with pure motor CIDP and multifocal motor neuropathy, corticosteroids may cause worsening and IVIg is more likely to be effective.

General measures to cope with foot drop, weak hands, fatigue and pain are important.

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