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Immunomodulatory Therapy to Achieve Maximum Efficacy: Doses, Monitoring, Compliance, and Self-infusion at Home

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Abstract
Introduction The Oxford Programme for Immunomodulatory Immunoglobulin Therapy has been operating since 1992 at Oxford Radcliffe Hospitals in the UK. Initially, this program was set up for patients with multifocal motor neuropathy or chronic inflammatory demyelinating polyneuropathy to receive reduced doses of intravenous immunoglobulin (IVIG) in clinic on a regular basis (usually every 3 weeks). The program then rapidly expanded to include self-infusion at home, which monitoring showed to be safe and effective. It has been since extended to the treatment of other autoimmune diseases in which IVIG has been shown to be efficacious.
Methods This review includes details of the program such as the training of patients, dosing with immunoglobulin, and monitoring and compliance for self-infusion at home, with cases to illustrate these points.
Results In addition, the Evidence for efficacy and the effects of confounding morbidities will be are included described. More recently, subcutaneous immunoglobulin therapy (SCIG) has been used in several chronic autoimmune peripheral neuropathies and in epidermolysis bullosa acquisita, with equally good effect. Trials of SCIG in other autoimmune diseases are planned.

Keywords Multifocal motor neuropathy · chronic inflammatory demyelinating polyneuropathy · intravenous immunoglobulin · subcutaneous immunoglobulin therapy

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Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are rare immune-mediated disorders. CIDP is characterized by sensory and motor symptoms that persist for over 6 months, usually without detectable autoantibodies against ganglioside antigens. The initial treatment consists of corticosteroids, and steroid-sparing agents are used as second-line therapies. Patients with resistant disease have a trial of high-dose, immunomodulatory therapeutic intravenous immunoglobulin (IVIG); about 20% of patients respond to such therapy [1]. MMN is characterized by an asymmetric, slowly progressive weakness of one or more limbs without sensory loss and is associated with autoantibodies to gangliosides in 30% to 80% of cases [2]. Immunomodulatory IVIG treatment is now recommended as a first-line therapy [3, 4] and more than 70% of patients respond to such therapy [3].

Once responsiveness to IVIG is proven for a given patient, using the standard immunomodulatory dose of 2 g/kg, the issue for chronic patients is how to maintain the therapeutic response. As yet, there are limited data regarding the use of a regular bolus given every 8 to 12 weeks or smaller maintenance doses given at shorter infusion intervals.

In the last 17 years, we have collected longitudinal data from patients referred to the Clinical Immunology Department at Oxford Radcliffe Hospitals to consider them for consider-

ation for the Self-infusion at Home Programme. The program was set up in 1987 for patients with primary immune deficiencies (PIDs) and in 1992 was modified for those requiring immunodulatory therapies. This extended the range of patients who were able to benefit from self-infusion at home as well as the ability of patients to take responsibility for their own disease and treatment [5]. Although the program initially focused on MMN and CIDP, it now includes diseases such as epidermolysis bullosa acquisita (EBA), the autoimmune blistering disease. Doses of immunoglobulin and the intervals between infusions have been tailored to each patient to achieve maximum efficacy and minimal interference with daily living.

Few data on the effect of immunoglobulin (Ig) therapy on disease progression in MMN or CIDP [6] are available. Furthermore, there are several outstanding issues regarding the long-term treatment of these conditions. Do regular Ig infusions slow or stop disease progression in MMN? Can we detect underlying progression in either the autoimmune diseases or the peripheral immunological neuropathies associated with low-grade malignancy? Does regular Ig therapy prove to be "curative" in some patients, as seen in selected patients with chronic ITP, or does successful discontinuation coincide with spontaneous remission of the disease? Can patients self-infuse safely at home and so contribute to maintaining clinical improvement? Finally, what is the best practice and benefit for patients who use subcutaneous immunoglobulin therapy (SCIG)?

In this review, we confirm the need for a home therapy program based on the increasing number of patients referred each year and discuss the new role of Ig therapy by the subcutaneous route in the maintenance of immunomodulation. We define the current protocols and procedures, discuss confounding factors and unexpected findings through the use of case histories, and summarize the outcomes of the program so far. In an attempt to provide some answers to the outstanding issues, we report anecdotal data regarding the size of Ig dose, infusion interval, half-life of the infused Ig, timing of the peak of efficacy, and relevance of the serum IgG trough level.

Methods

Clinical data from patients with autoimmune diseases who were seen in the Department of Clinical Immunology for more than 17 years were reviewed by a physician (K. Hugh-Jones) independently of the treating clinicians. The laboratory data were reviewed by the research coordinator (M. Lucas). These patients were receiving immunomodulatory doses of therapeutic Ig for one of several chronic autoimmune peripheral neuropathies. Data on each patient's clinical symptoms were collected from daily diaries in which patients self-reported scores for the strength of the muscle groups affected or sensory symptoms experienced. These measures were devised at the first outpatient visit, in consultation with medical and nursing staff to create suitable individual scoring methods [5].

No attempt was made to analyze the data statistically due to the variable nature of the scores (individualized for each patient) and the lack of baseline scores in patients with peripheral neuropathies before treatment.

Results and Discussion

Since 1992, 45 patients have entered the program. These include 15 patients with CIDP, 26 with MMN, 3 with chronic sensory and motor ataxia, and 1 patient (reported previously) with EBA [7]. In terms of outcomes, three have stopped therapy because of permanent remission (two CIDP, one MMN), four returned to hospital infusions for domestic reasons, and two died, both from unrelated causes. Currently, we expect four to six new patients each year. Although 16 patients were referred in the first 10 years this program was opened to immunomodulation (reflecting catch-up of longstanding patients), 29 have been referred so far in the last 7 years. In total, 45 patients have been followed for 364 patient-years (mean per patient was 8.1 years, with a range from 1 to 17 years).

Before patients enter into the program, it is essential that responsiveness to high doses of Ig therapy have has been demonstrated, usually on two separate occasions. Only 54% of patients with CIDP respond to the first dose of Ig [8], whereas another 23% respond to the second dose; 94% of those with MMN respond to the first dose [9]. Such a trial provides evidence of efficacy for Ig and justifies the use of this expensive drug.

It is important to start maintenance Ig therapy within 2 weeks of the last full dose of Ig, while the patient is in full remission, to achieve the maximum clinical effect. The dose to be used for maintenance is empirical. The maximum practical dose of IVIG (using either a 5% or a 10% product) in 1 day is 60 to 70 g. The dose and infusion interval to keep each patient asymptomatic is not predictable. From our experience, we have found that the dose is indicated by the length of clinical response, after an initial dose of 2 g/kg (see Table 1). As a result, equivalent doses varied vary from 30 to 12 g per week.

Table I Ig Starting Dose Depends on Length of Clinical Remission After Full Initial Test Dose

Response to initial dose (weeks)	Starting maintenance dose (approximate)
<6	1.0 g/kg every 3 weeks
6-8	0.5 g/kg every 3 weeks
≥9	0.25 g/kg every 3 weeks

Table II Infusion Intervals for 34 Patients Currently Receiving IVIG[a]

Infusion interval (weeks)	No. of patients
1	6
2	19
3	5
4	2
8	2

[a] Eleven patients receive SCIG and are not included in this table

Infusion intervals vary varied from once a week to every 4 weeks (Table 2). Traditionally, IVIG infusions have been given at 3- to 4-week intervals, consistent with the IVIG half-life of 21 to 28 days. A reduction in the interval between IVIG infusions results in more consistent and higher serum IgG trough levels (see Fig 1). Likewise, smaller doses of SCIG, given daily for convenience, raise the IgG trough level even higher. The IgG serum level for protection against infection in immune-deficient patients is individual to that patient [10].

On the assumption that the trough level is also important for immunomodulation, achieving consistent, higher IgG trough levels appears to be beneficial in autoimmune diseases, although each patient's case is unique. Because the initial IgG level is higher in immunocompetent patients with autoimmune diseases than in those with PIDs, the IgG trough levels are consequently also higher.

Patients are asked to keep records of their clinical symptoms in an attempt to correlate efficacy with serum IgG levels and to show that such measurements can be used as surrogates for effectiveness. Each patient diary is individualized to provide maximum information regarding the particular disability of the affected muscle groups. At regular outpatient department appointments (initially every 3 weeks, but once infusing at home, the visit intervals are lengthened to 3 monthly and then 6 monthly), diaries are reviewed for mention of any reduced function 1 to 2 days before the next infusion. In addition, intercurrent infections (e.g., influenza or recurrent bacterial infections due to bronchiectasis or secondary antibody deficiency) are noted, as are inflammation after surgery or trauma, serious life events (these include bereavement, blood loss such as hematuria or gastrointestinal bleeding), intercurrent therapies (e.g., bisphosphonates, anticoagulants), or any infusion reactions. It is also important to detect any development of a low-grade monoclonal lymphoproliferative state (e.g., non-Hodgkin's lymphoma). Blood is drawn for liver function tests (in view of the blood-product nature of Ig). Blood is also tested for serum IgG, IgA, IgM, and serum β_2 microglobulin levels (to detect any underlying low-grade lymphoproliferation).

The following case histories demonstrate the ways in which such intercurrent events can reduce the efficacy of the therapeutic immunoglobulin as well as the need to consider reducing Ig doses to ensure that the most cost-effective doses are used. In view of the uncertainty of both remission and disease progression in CIDP and MMN, it is important to review the dose and infusion frequency on a regular basis. In the first two cases, sudden or even rapid cessation of maintenance therapy was not successful in treating either of the patients. Gradually increasing the infusion interval, while using the same dose of IVIG

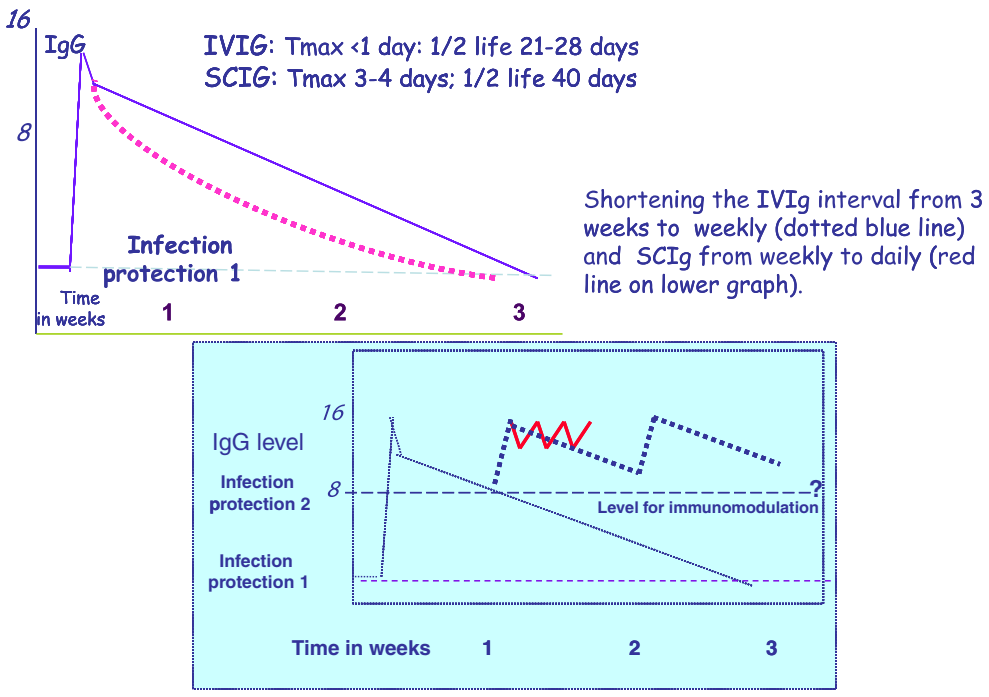

Fig. 1 The effect of shortening the infusion interval in terms of serum IgG trough level for IVIG and SCIG. The beta phase of catabolism depends on the IgG concentration; thus, the curve is steeper initially. Shortening the interval to weekly enables smaller doses of IVIG or SCIG to be given to achieve a higher serum IgG trough level, which appears to correlate with clinical efficacy

for convenience, however, proved successful in these 2 patients.

Case 1. Cessation of IVIG Therapy

- 15-year-old girl presented with weakness in all limbs. CIDP diagnosed; corticosteroid therapy was not effective. Started IVIG at 2 g/kg with improvement in symptoms that lasted 3 weeks.
- 17 years: started infusing at home with 0.8 g/kg at four weekly intervals, with no increase in symptoms between infusions.
- 19 years: attempted to stop IVIG abruptly—not successful; continued regimen of four weekly infusions.
- 20 years: planned increase in interval between infusions by 1 week every second infusion. Stopped IVIG once interval was >3 months. Nerve conduction studies were normal.
- 23 years: continuing well without IVIG; normal pregnancy.
- 26 years: second pregnancy—symptomatic during puerperium; IVIG restarted at 0.8 g/kg every 4 weeks, with reduction of symptoms. Plan to lengthen interval between infusions with intention to discontinue once patient is was stable.
- 29 years: achieved 3 months between infusions without relapse. Normal nerve conduction studies on two occasions. IVIG stopped again.

Case 2. Discontinuation of IVIG Despite Requirement for High-Dose Maintenance

- 34-year-old man presented with weakness in legs, which progressed rapidly to arms, and led to difficulty standing and poor hand grip. Diagnosis of MMN (though GM1 Ab negative). Treated with IVIG at 2 g/kg on several occasions, with total resolution lasting for 6 weeks before deterioration.
- 35 years: referred for home therapy. Maintenance infusions were started 2 weeks following last high-dose immunoglobulin. Stabilized on IVIG at 70 g weekly (0.8 g/kg weekly).
- 36 years: rapid attempts to reduce dosage failed on frequent occasions.
- 38 years: Planned gradual reduction by lowering the dose by 10 g every fourth infusion.
- 39 years: finally stopped therapy. Nerve conduction studies normal.

The role of underlying low-grade lymphoproliferation, particularly in older patients in whom benign paraproteins are not uncommon, is obscure [11]. This is demonstrated by the patient (case 3), in whom there was no traditional evidence of lymphoma (no lymphadenopathy, splenomegaly, or abnormal bone marrow despite low levels of IgA and IgM). The difficulties in detecting progression of Waldenstrom's macroglobulinemia are exemplified in the patient (case 4), in whom progression was revealed by the increase in IgM and serum β_2 microglobulin levels only; the response to rituximab therapy confirmed this.

The associations between intercurrent infections or inflammation due to surgery and loss of efficacy were unexpected (case 3), and one can only speculate that inflammation increases the catabolic rate of IVIG, reducing the availability of the effective immunomodulatory components. Whether or not this provides clues about efficacy mechanisms, or whether SCIG will prove to be superior for maintenance of remission, is not clear. Drug interactions are less surprising, particularly in regard to warfarin (case 3), which depends on stable liver enzymes to sustain effectiveness. The efficacies of both warfarin and IVIG were affected by concurrent administration, although this has not been reported previously and the mechanisms involved are unknown. It was reassuring to find that the plasma viscosity levels were not clinically concerning, even with high-dose immunoglobulin therapy (case 4).

Case 3. Effects of Intercurrent Events

- 50-year-old man presented with paresthesia in fingers and mouth, and numb feet. Diagnosis CIDP. Cyclosporin therapy unsuccessful. Deep vein thrombosis (DVT).
- 56 years: a stable monoclonal IgG band (13 g/L) found in serum, with relatively low IgA (0.9 g/L) and IgM (0.3 g/L) levels. Bone marrow trephine normal.
- IVIG at 2 g/kg given with improvement in symptoms lasting for 5 weeks.
- Referred for home therapy. Started 60 g every 10 days (0.5 g/kg weekly).
- 57 years: DVT and pulmonary embolism; warfarin long-term results in need to increase IVIG dose for maximal efficacy to 72 g every 10 days.
- 58 years: chest infection delays infusion by 7 days, resulting in need for extra 12 g at next infusion to restore full function.
- 60 years: surgery for repair of hernia complicated by wound infection, resulting in need for extra 12-g IVIG at next infusion.
- 61 years: recurrent chest infections in winter. Develops secondary antibody deficiency (IgA 0.8, IgM 0.2 g/L) results in need for several additional IVIG doses.

- 62–68 years: winter infections prevented by prophylactic antibiotics; no need for extra IVIG.

Case 4. Underlying Low-Grade Lymphoid Malignancy

- 33-year-old man presented with paresthesia and ataxia. Diagnosis of MADSAM; treated with prednisolone 60 mg once daily with effect.
- 47 years: treated with IVIG, 90 g every 3 weeks (0.25 g/kg week) as a steroid-sparing measure.
- 49 years: bisphosphonate started (Didronel), resulting in rapid loss of function after 1 dose. IVIG restarted at 2 g/kg to ensure efficacy; higher 120-g Ig maintenance dose needed over 2 days, every 3 weeks.
- 51 years: gradual loss of efficacy of IVIG. Investigated and found small IgM band noted in serum. Bone marrow trephine showed excess plasmacytoid cells indicating Waldenstrom's. Chlorambucil therapy for 7 months with improved response to IVIG.
- 54 years: further exacerbation of Waldenstrom's, with rise in serum IgM (6–16 g/L) and serum β_2 microglobulin (5–10 mg/L), treated with rituximab. Corticosteroids withdrawn permanently. Well for 4 years but then fludaribine required and gradual improvement again over 4–6 months.

  Serum IgG level at peak (immediately postinfusion) was 40 g/L while infusing 120 g every 3 weeks. Plasma viscosity measured to ensure no risk of hyperviscosity (>3.8 relative to water [rel.]) and found to be <2.8 rel.

Additional issues include how to devise the appropriate immunoglobulin dose and infusion interval for an individual patient. We have found that the patients in the Oxford cohort have needed a wide range of immunoglobulin doses. Although it has not been possible to determine the exact efficacious maintenance dose, a rough guide is given in Table 3.

We have not found any differences in the efficacy of the five IVIG products used in these 45 patients over 17 years. We have not seen significant infusion-related adverse events, provided that infusions are not given during an intercurrent infection. Hence, we recommend that patients self-infusing at home who experience such an infection either consult the expert nursing staff running the program or seek medical attention to commence antibiotic therapy (if appropriate) and delay the infusion for 48 hours. We also have not seen adverse reactions related to infusion rates provided to that patients who infuse at the recommended rate for their product, whether it is a 5% or a 10% product.

Table III Immunoglobulin Doses and Infusion Intervals

The maximum dose IV (5%/10%) in 1 day is 60–70g
Weekly maintenance doses vary from 0.25 to 1 g/kg
Infusion intervals vary from one to four weekly
The precise dose and infusion interval to keep each patient asymptomatic is not predictable but a rough guide, from experience, indicates that:
Patients in whom responses last <6 weeks may need 1 g/kg infusions once every 3 weeks
Those patients with responses lasting 6-8 weeks need approximately 0.5 g/kg infusions every 3 weeks
Those patients with longer lasting responses can go to 0.25 g/kg every 3 weeks

It has been shown recently that immunoglobulin therapy by the subcutaneous route is equally efficacious as IVIG. Three comparative trials have shown that SCIG therapy is equally successful as IVIG for sustaining muscle strength in patients with MMN [12, 13] (S. Misbah, oral communication, 2009). In a randomized, single-blinded crossover trial in which nine IVIG responsive patients crossed over to SCIG with equivalent dose for three IVIG infusions (18-56 days), increases in muscle strength and decreases in conduction defects were about the same in each therapeutic arm of the trial. GM1 autoantibody levels were not significantly different for either therapy. At the end of the trial, five patients preferred SCIG and four patients preferred IVIG [13]. It is important to note that because of the costs of pumps required for the administration of SCIG and the need to monitoring of both types of therapy at home, the expenses of IVIG and SCIG are largely the same. In a similar study from the Netherlands [12], the same equivalence in efficacy was found with Sanquin products. The study's authors also pointed out that maintenance therapy, in this case SCIG treatment, should be started within 1 week of a full dose of IVIG (2 g/Kg). Initially, five patients started on a dose of SCIG that was 50% of the IVIG dose, divided into weekly doses. One patient withdrew due to localized redness and pain; the four remaining patients deteriorated and had to restart regular IVIG. Subsequently, these patients entered a new protocol with SCIG at the same dose as IVIG, divided into weekly doses; this therapy was found to be equally efficacious. Three patients remained on SCIG and one returned to IVIG infusions. These two trials have been confirmed by a recent trial in Oxford (S. Misbah, oral communication) and are supported by the finding that SCIG has been used successfully for maintenance immunomodulatory therapy in another autoimmune disease [7, 14].

All self-infusion at home programs require resources in terms of staff. The provision of specialist nurse support for

teaching and training for patients at home is essential [5]. To justify the cost-effectiveness of these programs and obtain funding for patient care, monitoring for ongoing efficacy is essential. The variability of affected muscle groups makes monitoring difficult in MMN and CIDP. We have asked our patients to keep a regular (usually daily) record of specific symptom measurements to ensure that the minimal dose for efficacy is used. The UK IVIG Demand Management Programme requires such data collection for funding on a regular basis. It also requires that patients are reviewed at least once a year to confirm the ongoing need for this expensive therapy.

Conclusions

Maintenance therapy is essential for patients with immunoglobulin-responsive chronic diseases. This can be delivered with IVIG or SCIG, but self-infusion at home with either type of route improves the feasibility and convenience for both hospitals and patients. The dose of Ig and the serum IgG trough level are individual to each patient, and it is essential that patients are monitored for clinical efficacy. This includes reviewing the patient's symptoms on a regular basis, taking note of inflammation due to intercurrent infections, newly prescribed drugs, and monitoring for progression of underlying disease due to low-grade lymphoproliferation.

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