
INTRAVENOUS IMMUNOGLOBULIN AND MS

Intravenous globulins have been used for some time for treating diseases affecting the neuraxis, from brain to peripheral nerves and muscles. A comprehensive review of their use [1] examines the evidence in each of a number of clinical conditions. In most the trials were of limited quality, and results were hardly overwhelming, but in some conditions there was a modicum of evidence for effectiveness.

They are thought to work by halting, or even reversing, the process of demyelination that accompanies these diseases. Ways in which immunoglobulins might work to affect demyelination have been reviewed [2].

In multiple sclerosis intravenous immunoglobulins (IVIG) have been reported in a number of trials, and a large trial in secondary progressive MS is ongoing [3]. This is unlikely to report until mid 2002 or later, as the trial began in 1998 and the clinical part (recruitment?) finished in 2001, and there is a three year follow up. Bandolier decided a brief review of the available literature would help fill the gap.

Search

Searching PubMed and the Cochrane Library (February 2002) was done using free text terms. Review articles [1, 2] were examined, as were reference lists of retrieved papers. The intention was to be inclusive, and examine randomised studies where IVIG was used in treating any form of multiple sclerosis. It was not expected that endpoints of trials would be reported in consistent forms, perhaps other than mean EDSS scores. It was expected that the source of IVIG, dose, treatment schedule and duration, primary end points and duration of observations would be inconsistent between any trials found would make for a clinically heterogeneous set of trials, over and above any differences in patient characteristics, like type and severity of MS. Pooling of results was not expected to be likely.

Results and discussion

Table 1 shows the details of the papers we found [4-11]. They included a non-randomised study of electrophysiological data [8] and some early safety data from an ongoing trial [9]. Non-randomised trials looking at clinical outcomes were not included. The quality of the trials was generally good, with quality scores of the randomised trials 3 of 5 or above. One trial gave some electrophysiological results in which IVIG had no effect [8], and one was an early comment on safety in an ongoing trial [9].

Exacerbations

Some benefit was found in some outcomes in three trials [5-7], especially in terms of patients remaining free of exacerbations of MS, though that was not a clearly defined outcome. Two of these trials were of two year's duration [6,7], and it may be that if there is any effect of IVIG it will only be detected in longer duration trials, since shorter, and small, trials will have insufficient opportunity for enough events to have arisen for statistical or clinical significance to be achieved.

Using exacerbation or relapse free information from 230 patients in the three trials (Figure 1), overall 61/116 patients (53%) were relapse free with IVIG compared with 33/114 patients (29%) with placebo. The relative risk was 1.8 (95% confidence interval 1.3 to 2.5), producing a number needed to treat (NNT) of 4.2 (2.8 to 8.9).

The two US trials [10,11] did not give information in comparable ways to allow it to be combined, but there seemed to be no benefit there associated with IVIG.

EDSS

EDSS was used in a number of trials as an outcome. Mean changes in EDSS and number of patients with EDSS improvement of at least one point differed in direction between the European studies [6,7] and US studies [10,11]. The former showed some benefit, the latter no difference.

Adverse events

Rates of adverse events reported in these trials varied. Common themes were cutaneous adverse events (rash, eczema) and headache, associated more with IVIG infusion. One patient in one trial developed hepatitis C infection.

Comment

This is a difficult topic in a difficult clinical area. It would be premature either to embrace IVIG therapy, or to dump it. There is an intriguing hint that there may be some benefit in extending relapse or exacerbation-free periods.

Two problems present themselves.

First is an apparent conflict between the superb and methodologically rigorous trials from the Mayo Clinic that give

Table 1: Details of trials

Reference	Condition	Treatment	Design	Outcome
Sørensen et al, 1997 Sørensen et al, 1998	Relapsing/remitting, relapsing/progressive MS Patients aged 20-50 years, within 10 years of diagnosis, two or more exacerbations in previous year, EDSS 2-7, at least five cerebral lesions, no corticosteroids or immunosuppressive treatment	IVIg 1g/kg daily for 2 days every four weeks for 24 weeks, or placebo	Randomised, double blind, placebo (human albumin), crossover with three month wash out. ITT and per-protocol analysis	Primary outcome was new lesions on serial MRI performed every four weeks. A number of secondary outcomes were used
Fazekas et al, 1997	Relapsing/remitting, EDSS 1-6, two clearly defined relapses in previous two years. Age 15-64 with first manifestation below 60 years. No immunosuppressive therapy with three months.	IVIg 0.15-0.2 g/kg every month for two years, or saline placebo.	Randomised, double blind, parallel, placebo controlled. Intention to treat and per protocol analysis, two years duration	Primary outcome was absolute change in EDSS, and improved, stable or worse clinical disability (change of at least 1 point on EDSS) by end of study.
Achiron et al, 1998	Relapsing/remitting MS, confirmed by MRI, age 18-60 years, EDSS 0 to 6, 0.5 to 3 exacerbations per year in prior period	IVIg 0.4 g/kg per day for five days and once every two months for 2 years, or saline placebo	Randomised, double blind, parallel, placebo controlled. Intention to treat and per protocol analysis, two years duration	Primary outcome was yearly exacerbation rate. Relapse clearly defined
Stangel et al, 2000	Relapsing/remitting MS with EDSS 2.0-4.5, no clinical relapse within three months, no beta-interferon or immunosuppressives.	IVIg 0.4 g/kg on five consecutive days. Placebo was identical except IVIG.	Double-blind, non-randomised, with placebo treatment followed by IVIG, six weeks each treatment	Electrophysiological studies, neurological assessment
Poehlau et al, 2000	Primary and secondary chronic progressive MS	IVIg 0.4 g/kg every four weeks, or placebo	Randomised, double blind,. Placebo controlled	Not given. Early report on safety
Noseworthy et al, 2000	Relapsing/remitting or secondary progressive MS between ages 18 and 60, with apparent irreversible motor deficit (weakness of at least one limb with more than 25% loss of power).	IVIg 0.4 g/day for five days and every two weeks thereafter for three months, with 11 infusions in total	Randomised, double blind, placebo controlled, six months duration, ITT analysis	Primary outcome was six month change in affected muscle strength
Noseworthy et al, 2001	Patients with demyelination optic neuritis and MS, younger than 50 years, with stringent optic criteria	IVIg 0.4 g/day for five days and ever two weeks thereafter on three occasions at monthly intervals, with 8 infusions in total	Randomised, double blind, placebo controlled, six months duration, ITT analysis over 12 months	Visual function tests, clinical activity, with primary endpoint of visual acuity at 6 months

Results	Adverse effects	Quality score
Of 25 randomised (mean EDSS 3.5) 17 completed the crossover. Median of half a new lesion fewer in IVIG (ITT, p=0.002). 15/21 patients were exacerbation free with IVIG and 7/21 with placebo. There were 3 severe exacerbations with IVIG and 7 with placebo.	Eczema, urticaria and headache appeared to be more common with IVIG. One patient developed hepatitis C infection with IVIG. Severe eczema was most common cause of withdrawal from study, and affected palms of hands, arms, legs and face. Four withdrawals were on IVIG and four on placebo. 21 completing at least one month of second arm made up ITT population.	R = 1 DB=1 WD=1 Total=3/5
148 patients participated, well matched at baseline. Mean change in EDSS was -0.23 for IVIG and +0.12 for placebo. Improvement of EDSS of 1 or more in 23/75 with EDSS (31%) and 10/73 (14%) with placebo. Deterioration occurred in 12/75 (23%) with IVIG and 17/73 (23%) with placebo. With IVIG 40/75 (53%) were relapse free compared with 26/73 (36%) with placebo.	Adverse event withdrawal occurred in 11/75 (15%) with IVIG and 17/73 (23%) with placebo, more often because of lack of efficacy.	R = 2 DB=1 WD=1 Total=4/5
40 patients were included. Significantly lower exacerbation rates with IVIG than placebo (39% reduction in relapses). 6/20 IVIG were relapse free, 0/20 with placebo. EDSS decreased by 0.3 with IVIG and rose by 0.15 with placebo.	Side effects associated with 19/630 infusions. Two discontinuations, one in each group, after one year	R = 2 DB=2 WD=1 Total=5/6
No major changes	Headache in 6/10 with IVIG and 3/10 with placebo	Not appropriate
Not given	In 600 IVIG infusions in 131 patients there were 25 severe adverse events in 25 patients. None of these was considered to be drug-related, and included worsening (9), relapse (5), UTI (3), Seizure (2, both with epilepsy), pneumonia, appendectomy, dyspnoea, dysaesthesia and tremor (1 each)	Not appropriate
No effect of IVIG on muscle strength, or EDSS improvement at least 1 point (3/29:3/29), new MS activity, or new MS attacks, or patient global.	Rash in 8/34 IVIG and 2/33 on placebo.	R = 1 DB=2 WD=1 Total=4/5
55 patients were randomised, and two groups were comparable at baseline. There was no difference in the primary outcome, or EDSS worsening of at least 1 point (3/28 placebo 4/27 IVIG), or change in EDSS or active MS, at six or 12 months	Adverse events described in detail, with rash and headache perhaps associated with IVIG	R = 1 DB=2 WD=1 Total=4/6

virtually no hint of any benefit, whether for the particular topics they sought to address (muscle weakness or optic neuritis) or for the disease in general. At least one of the European trials [7] was large and well done, and lasted two years, and showed benefit. There's no easy explanation for this with the data we have. Caution is the watchword, especially when the intervention, a blood product, has no clear chemical definition and where we cannot be sure that there is not a difference between products used in different trials. They may be immune globulins, and have a certain protein content and electrophoretic pattern, but presumably it is what these proteins bind to that is crucial.

The second problem is that of cost and availability. This is not a cheap treatment option, and availability of human immune globulin is not straightforward. Transmission of blood-borne disease, real (hepatitis) or theoretical (CJD), is not to be ignored, nor are the adverse events that may accompany treatment.

Intravenous immune globulin is no miracle cure for MS, much as we may like it to be. There will be few patients for whom its use is warranted outside a randomised trial.

References

- 1 N Latov et al. Use of intravenous gamma globulins in neuroimmunologic diseases. *J Allergy Clin Immunol* 2001 108: S126-132.
- 2 M Stangel et al. Mechanisms of high-dose intravenous immunoglobulins in demyelinating diseases. *Archives of Neurology* 1999 56: 661-663.
- 3 OR Hommes & M Maas-Enriquez. ESIMS – An ongoing clinical trial in secondary progressive multiple sclerosis. *Multiple Sclerosis* 2000 6 Suppl 2: S27-S32.
- 4 PS Sørensen et al. A double-blind, cross-over trial of intravenous immunoglobulin G in multiple sclerosis: preliminary results. *Multiple Sclerosis* 1997 3: 145-148.
- 5 PS Sørensen et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998 50: 1273-1281.
- 6 F Fazekas et al. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Lancet* 1997 349: 589-593.
- 7 A Achiron et al. Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. *Neurology* 1998 50: 398-402.
- 8 M Stangel et al. Placebo controlled pilot trial to study remyelination potential of intravenous immunoglobulins in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000 68: 89-92.
- 9 D Poehlau et al. Treatment of chronic progressive multiple sclerosis with intravenous immunoglobulins – interim results on drug safety of an ongoing study. *Multiple sclerosis* 2000 6 Suppl 2: S21-S23.
- 10 JH Noseworthy et al. IV immunoglobulin does not reverse established weakness in MS. *Neurology* 2000 55: 1135-1143.
- 11 JH Noseworthy et al. A randomised trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 2001 56: 1514-1522.