Written consent for case report publication was obtained from the patient.

doi: 10.1136/jnnp.2006.090266

Competing interests: None.

References

1 **Whitley RJ**, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002;**359**:507–13.
2 **Cano F**, Mayo DR, Ballow M. Absent specific viral antibodies in patients with transient hypogammaglobulinemia of infancy. *J Allergy Clin Immunol* 1990;**85**:510–13.
3 **Garcia Rodriguez MC**, de la Concha EG, Fontan G, *et al*. Transient hypogammaglobulinemia in the adult. Functional assessment of T and B lymphocytes. *J Clin Lab Immunol* 1983;**11**:55–8.
4 **Sorrell TC**, Forbes IJ. Depression of immune competence by phenytoin and carbamazepine. Studies in vivo and in vitro. *Clin Exp Immunol* 1975;**20**:273–85.
5 **Spickett GP**, Gompels MM, Saunders PW. Hypogammaglobulinaemia with absent B lymphocytes and agranulocytosis after carbamazepine treatment. *J Neurol Neurosurg Psychiatry* 1996;**60**:459.
6 **Voutsinas D**, Foudoulaki L, Sofroniadou K, *et al*. Visceral leishmaniasis in a patient with acquired hypogammaglobulinemia. *Eur J Int Med* 2001;**12**:127–9.
7 **Aihara Y**, Ito SI, Kobayashi Y, *et al*. Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003;**149**:165–9.
8 **Galindo PA**, Borja J, Gomez E, *et al*. Anticonvulsant drug hypersensitivity. *J Investig Allergol Clin Immunol* 2002;**12**:299–304.
9 **Larcher C**, Gasser A, Hattmannstorfer R, *et al*. Interaction of HSV-1 infected peripheral blood mononuclear cells with cultured dermal microvascular endothelial cells: a potential model for the pathogenesis of HSV-1 induced erythema multiforme. *J Invest Dermatol* 2001;**116**:150–6.
10 **Joly P**, Autran B, Lauret P. Recurrent erythema multiforme associated with hypogammaglobulinemia of variable expression. *Ann Dermatol Venereol* 1990;**117**:33–4.

Treatment of Guillain–Barré syndrome with mycophenolate mofetil: a pilot study

Guillain–Barré syndrome (GBS) is a severe, acute, immune mediated polyneuropathy. Intravenous immunoglobulin (IVIg) is the preferred treatment.[1] The combination of methylprednisolone (MP) and IVIg does not provide significantly better improvement after 4 weeks if not adjusted for important prognostic factors.[2] GBS is associated with many longlasting residual deficits. Autoantibodies, and B and T cells are likely to play a role in the different stages of GBS.[3] Mycophenolate mofetil (MM) is a relatively new immune suppressive agent, suppressing mainly B and T lymphocytes, and is thought to be of additional value in immune mediated neurological conditions.[4–6]

We conducted an open label pilot study to assess the additional effect of MM, administered simultaneously with IVIg and MP. The aim was to investigate whether additional treatment with MM is safe in patients with GBS and, secondly, whether there is a tendency to improved outcome.

Patients and methods

The study was approved by the ethics committees of Erasmus Medical Centre and the nine participating centres. All patients fulfilled the criteria for GBS.[7] Eligibility criteria were onset of weakness within 2 weeks before inclusion and inability to walk independently for 10 m (GBS disability score ≥ 3). Exclusion criteria were age less than 18 years, GBS in the past, pregnancy, breast feeding, immunosuppressive treatment, antacids treatment, use of drugs interfering with the enterohepatic recirculation, suffering from immune mediated disease other than well regulated diabetes mellitus and severe concurrent disease.[2] The group of patients treated with IVIg and MP in the Dutch IVIg-MP trial was used as the historical control group.[2]

Treatment

All patients were simultaneously treated with 0.4 g IVIg/kg/day (Gammagard/S; Baxter BioScience, Westlake Village, California, USA) and 500 mg intravenous MP for 5 consecutive days. In addition, patients were treated with MM (Cellcept; Roche, Welwyn, UK), administered orally twice a day (1000 mg/ day), for 6 consecutive weeks. Treatment with MM had to start within 2 weeks after the onset of weakness and within 72 h after the start of IVIg and MP.

Outcome measures

The primary end point was improvement by one or more grades on the GBS disability score after 4 weeks. Secondary end points included the percentage of patients able to walk independently after 8 weeks, median time to independent walking, median time to improvement by ≥ 1 disability grade, improvement by ≥ 1disability grade after 6 months and need for artificial respiration. Adverse events were monitored daily and evaluated every next visit.

Analyses

Percentages in the group of patients treated with IVIg-MP-MM were compared with the group of 112 patients treated with IVIg-MP using the χ^2 test (without correction for continuity), the method of Kaplan and Meier and the log rank test.[2] Two important secondary end points (the proportion of patients that improved by 1 or more grades on the GBS disability score and the proportion of patients that improved to independent walking (GBS disability ≤ 2) over 52 weeks of follow-up) were also compared with the group of 113 patients treated with IVIg alone in the Dutch IVIg-MP trial.[2] Analyses were performed using STATA version 8.0.

Results

Between July 2002 and January 2005, 26 GBS patients were included in the study.

There were no significant differences in baseline characteristics, including age, GBS disability score, onset of weakness until randomisation and antecedent infections between this group of patients and the historical control group (table 1).

Primary end point

In the IVIg-MP-MM treatment group, 16 (62%) of the 26 patients reached the primary end point compared with 76 (68%) of the 112 control patients treated with IVIg-MP (OR 1.3, 95% CI 0.6–3.2, p = 0.54).[2]

Secondary end points

No significant differences between the two treatment groups were found for the secondary end points (see fig 1A, 1B and table 2; fig 1 and table 2 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). To further assess possible differences in treatment modalities, we compared the results of two important secondary end points with the results of the group of 113 patients who received IVIg only in the Dutch IVIg-MP trial (fig 1A, 1B; fig 1 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).[2] No significant differences between the three groups were found for both end points. A comparison of the differences in MRC sum scores and sensory signs between the treatment groups also did not show significant differences.

Adverse events

None of the reported side effects, including urinary or respiratory tract infections, thrombosis, gastrointestinal bleeding and renal failure, differed significantly between the groups. One patient interrupted MM treatment because of abdominal complaints. Two (8%) of 26 patients treated with IVIg-MP-MM died compared with 6 (5%) of 112 patients treated with the combination IVIg and MP. There is no indication that the two patients in the IVIg-MP-MM died of drug related complications (see table 3; table 3 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

Table 1 Baseline characteristics

Characteristic	IVIg+MP+MM (n = 26)	IVIg+MP[2] (n = 112)
Male (%)	19 (73%)	73 (65%)
Age (y) (median (95% CI))	46 (23–76)	58 (50–61)
Age ≥50 y (%)	12 (46%)	68 (61%)
GBS disability score (F score) at baseline (%)		
F = 3	4 (15%)	26 (23%)
F = 4	21 (81%)	77 (69%)
F = 5	1 (4%)	9 (8%)
Onset weakness–randomisation ≤4 days	13 (50%)	64 (57%)
Diarrhoea (%)	10 (39%)	30 (27%)
Upper respiratory tract infection (%)	7 (27%)	39 (35%)
Positive *C jejuni* serology (%)	6 (23%)	29 (28%)

GBS, Guillain–Barré syndrome; IVIg, intravenous immunoglobulin; MM, mycophenolate mofetil; MP, methylprednisolone.

Comment

The combination of IVIg-MP-MM was found to be safe but demonstrated no tendency for improved outcome compared with the historical control group from the Dutch IVIg-MP trial.[2] Side effects did not differ significantly between the two groups. Secondary outcome measures, mainly related to long term effects, were not significantly different between the groups. We performed survival analyses to compare the time to independent walking and the time to improve at least one grade on the GBS disability scale. The IVIg treatment group from the Dutch IVIg-MP trial was included in the analyses to rule out the possibility of a negative effect of the combination of MM with MP and IVIg. This comparison also did not reveal any significant differences. It is possible that another methodological approach could have led to different results. Comparing a small group of non-randomised patients with historical data from a large group of patients is mainly useful to detect major differences between groups. Although the dose of MM used was a standard dosage, a delayed start of MM or an inadequate duration of therapy might contribute to the lack of efficacy. It is possible that MM does not interfere with, or does not act rapidly enough, within the crucial immunopathological pathways in GBS.[3] Severe nerve damage, possibly due to complement activation and the presence of antiganglioside antibodies, could have occurred even before MM was administered and lymphocyte proliferation was inhibited.

The results of this non-controlled study would not encourage conducting a large scale, randomised, controlled trial of the additional value of MM in the treatment of patients with GBS.

Acknowledgements

We thank Professor Dr LH van den Berg for being a member of the Steering Committee, Dr ISJ Merkies for suggestions concerning the protocol and methodological considerations, Dr BC Jacobs and M Kuijf for help with the GM1 antibody assay and *C jejuni* serology, Dr J Meulstee for suggestions concerning the study protocol, the participating neurologists for including their patients (see appendix), and Mrs MM de Kimpe for administrative support. The study was supported by Baxter and Roche.

M P J Garssen, R van Koningsveld, P A van Doorn
Erasmus Medical Centre, Rotterdam, the Netherlands

Correspondence to: P A van Doorn, Erasmus MC, Department of Neurology, Room BA450, PO Box 1738, 3000 DR Rotterdam, the Netherlands; p.a.vandoorn@erasmusmc.nl

The study was approved by the Ethics Committee of Erasmus Medical Centre in May 2002 and subsequently by the Ethics committees of the participating centres. Informed consent was obtained.

doi: 10.1136/jnnp.2006.102731

Competing interests: None.

Figs 1A and 1B, and tables 2 and 3 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental

References

1 **Hughes RA**, Raphael JC, Swan AV, *et al*. Intravenous immunoglobulin for Guillain–Barré syndrome. *Cochrane Database Syst Rev* 2004;**1**:CD002063.
2 **Van Koningsveld R**, Schmitz PI, Meché FG, *et al*. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain–Barré syndrome: randomised trial. *Lancet* 2004;**363**:192–6.
3 **Willison HJ**. The immunobiology of Guillain–Barré syndromes. *J Peripher Nerv Syst* 2005;**10**:94–112.
4 **Vermersch P**, Stojkovic T, de Seze J. Mycophenolate mofetil and neurological diseases. *Lupus* 2005;**14**(Suppl 1):S42–5.
5 **Cauchy V**, Cornblath DR, Griffin JW, *et al*. Mycophenolate mofetil: a safe and promising immunosuppressant in neuromuscular diseases. *Neurology* 2001;**56**:94–6.
6 **Gorson KC**, Amato AA, Ropper AH. Efficacy of mycophenolate mofetil in patients with chronic immune demyelinating polyneuropathy. *Neurology* 2004;**63**:715–17.
7 **Asbury AK**, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. *Ann Neurol* 1990;**27**(Suppl):S21–4.

Appendix

Members of the Dutch GBS study group: MPJ Garssen, R van Koningsveld and PA van Doorn (writing group), ISJ Merkies, M Scheltens-de Boer, Erasmus Medisch Centrum, Rotterdam; JA van Leusden, Medisch Centrum Alkmaar, Alkmaar; IN van Schaik, Academisch Medisch Centrum, Amsterdam; WHJP Linssen, Sint Lucas Andreas Ziekenhuis, Amsterdam; F Visscher and AM Boon, Stichting Oosterscheldeziekenhuizen, Goes; CG Faber, Academisch Ziekenhuis Maastricht, Maastricht; J Meulstee and MJJ Prick, Nijmeegs Interkonfessioneel Ziekenhuis Canisius-Wilhelmina, Nijmegen; LH van den Berg and H Franssen, Universitair Medisch Centrum Utrecht, Utrecht; JAP Hiel, Sint Joseph Ziekenhuis, Veldhoven, the Netherlands; PYK van den Bergh and CJM Sindic, Clinique Universitaire St Luc, Brussels, Belgium.