CURRENT RHEUMATOLOGICAL USES OF INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin therapy (IVIg) has emerged over the last decade since the seminal reports of Imbach [1] and Fehr [2] as a potentially useful immunomodulator in a number of rheumatological diseases. These include systemic vasculitis, SLE, refractory RA, systemic juvenile chronic arthritis (JCA), polymyositis, anticardiolipin antibody (ACA) associated recurrent miscarriage syndrome and Kawasaki's disease. At present the proven indications for IVIg are primary antibody deficiency, immune thrombocytopenic purpura (ITP) and Kawasaki's disease. There are relative indications for its use in the secondary immunodeficiency of AIDS and haematological malignancies. We review its rheumatological uses, proposed mechanisms of action and adverse reactions.

Injected gammaglobulins were first used in the 1950s to treat hypogammaglobulinaemia and in 1981 IVIg became available for clinical use [3]. IVIg is fractionated from normal plasma and contains over 90% IgG with trace quantities of IgA (depending on the preparation) which is screened for hepatitis B, C, HIV I and II and elevated amidotransferase. Each batch of IVIg is prepared from a pool of 10 000–20 000 healthy blood donors. IVIg thus contains a broad spectrum of the expressed normal human IgG repertoire of antibodies. No case of documented transmission of HIV or viral hepatitis has been reported with the new formulations which have additional viral inactivation processes like acid treatment and pasteurization.

An early report on the benefit of human placenta-eluted gammaglobulin [4] stimulated small clinical studies on the use of IVIg in RA [5–7]. These studies report initial improvement in clinical and biochemical parameters which do not persist when the treatment is stopped. Tumiati [7] reported that nine out of 10 patients who had failed on at least one DMARD had subjectively and objectively improved within 4 weeks of commencing IVIg and this improvement was maintained by monthly boluses for 6 months. After discontinuation of therapy all patients had a relapse of their disease within 12 weeks, suggesting the effect achieved was not disease remittive.

Emery and colleagues have reported on the first placebo-controlled study of IVIg in 32 patients with early RA who had not received second line agents [8]. The actively treated group had two consecutive days treatment at a dose of 0.5 g/kg/day followed by a single monthly treatment. While there was a significant fall in RF titre and an increase in immune complexes in the actively treated group there was no significant differ-
Glomerulonephritis is contentious. Schifferli [23] has reported that patients with the nephrotic syndrome may develop an asymptomatic reversible deterioration of renal function resultant from IVIg treatment while Jordan found that some patients with lupus nephritis deteriorated after IVIg, manifested by an increase in haematuria and proteinuria [24]. It cannot be excluded that the changes in renal function were due to the progression of the disease and other drugs used. A possible explanation for the deterioration observed in some patients may be the variable matching between solubilizing IgG in the IVIg infused and the nephritogenic immune complexes responsible for the disease. Some patients with lupus nephritis have improved clinically and in terms of renal biopsy findings following IVIg therapy [22] and while the numbers of patients treated in these studies have been small the balance of opinion favours a trial of IVIg in lupus patients with active renal disease unresponsive to cyclophosphamide and steroid.

IVIg has been used to treat pregnant women with the lupus anticoagulant and recurrent fetal loss [25, 26]. The authors have treated eight lupus anticoagulant-positive women in nine pregnancies with a total loss prior to treatment of 28 with IVIg [27]. There were six successful outcomes of pregnancy; in one the pregnancy was terminated at 8 weeks because of a blighted ovum giving an overall successful outcome rate of about 70%. Untreated the fetal loss is of the order of 90% [28].

Patients with poorly controlled polymyositis, despite aggressive immunosuppression, have improved clinically biochemically and in terms of muscle power as assessed by reproducible sphygmonometric increases following treatment with IVIg [29, 30]. In JCA patients Silverman et al. [31] reported that IVIg was effective in improving articular and extra-articular features of disease. In addition they were able to reduce the maintenance prednisolone dose and in seven out of eight patients followed for longer than a year steroid was discontinued. However, whether significant improvement is achieved is contentious as the first double blind placebo-controlled study of IVIg demonstrates no greater benefit in the IVIg-treated group [32]. IVIg has been shown to reduce the coronary artery lesions in Kawasaki's disease in a multicentre controlled clinical trial where the dosage used was 400 mg/kg body weight for 4 days [33]. Another trial showed that a single dose of 2 g/kg body weight was equally effective [34].

How IVIg works is not completely understood. As a result of clinical and experimental studies several mechanisms have been identified and implicated in explaining IVIg's immunomodulatory effects. Interactions between the Fc fragments of infused IgG and Fc receptors on inflammatory cells, lymphocytes and complement components have been described [35]. Fehr has shown that following IVIg treatment of ITP patients there is Fc receptor blockade of splenic macrophages. This may play a critical role in the short-term decrease in platelet clearance, which is one of the mechanisms of action of IVIg in these patients [2].

Anti-inflammatory effects of IVIg includes an ability to down-regulate cytokine production and release by activated macrophages resulting from Fc receptor...
There is a measurable difference between pre- and post-IVIg blood samples in terms of antibody activity assessed in vitro [44]. The authors have noted a 5-yr-old child with IgA and IgG subclass immunodeficiency with hypergammaglobulinaemia treated with IVIg replacement therapy in whom following treatment the total IgG and IgM decreased to age-related normal ranges.

An observed immunomodulatory effect of IVIg in RA [7] that is possibly important has been previously discussed. The peripheral blood of RA patients has a relatively low 'naive' CD45RA+ T cell subset compared with their CD4+ CD29+ 'memory' subset. IVIg has resulted in a peripheral blood increase in the 'naive' subset paralleling a clinical response. A similar increase in 'naive' cells has been found in the synovial cells of a small RA cohort responding to slow-acting antirheumatic drugs [45]. Further studies of the synovial 'naive' cell subset should clarify if IVIg treatment is associated with a similar increase in this T cell subset.

IVIg is relatively safe to use. However, side effects of varying severity may occur. Some batchs of the earlier IVIg preparations were associated with the transmission of non A non B hepatitis (most probably hepatitis C). Headache is not an uncommon occurrence during or after IVIg infusion. It may occur with chills, myalgia and fever. The vast majority of these reactions can be prevented by a slower rate of infusion, pre-treatment with aspirin or in the case of previous reactions concomitant administration of hydrocortisone. IgA-deficient individuals receiving IVIg may develop anaphylaxis due to the development of antibodies to the administered IgA. IVIg is used in much higher dosage in rheumatological disorders than in IVIg replacement therapy. The passively acquired antibodies may interfere with red cell grouping and antibody testing and cause haemolytic anaemia [46]. Patients receiving high dose IVIg should be cross-matched with the IVIg preparation to be used and a batch with low titre haemagglutinins selected in order to reduce the risk of haemolytic anaemia. Aseptic meningitis has been reported to rarely complicate high dose IVIg [47].

At present the primary antibody immunodeficiencies, immune thrombocytopenic purpura and Kawasaki's disease are the conditions for which there is a proven role for IVIg use. IVIg appears to be effective in a number of rheumatological diseases. However, the studies reported to date contain small numbers of patients and most have been uncontrolled. It is clear that there is a need for well-designed controlled trials of IVIg and in systemic vasculitis these are already underway. The novel mechanisms of action of IVIg suggest that further research on IVIg treatment of rheumatological disease will improve our understanding of the immunopathogenesis of these conditions, which may have therapeutic implications.

Acknowledgements

The authors sincerely thank Mrs B. Dibb at the Rheumatology and Rehabilitation Research Unit and Mrs J. Hagger at the Yorkshire Regional Blood Transfusion Centre for their assistance in preparing the manuscript.

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[BRITISH JOURNAL OF RHEUMATOLOGY VOL. 33 NO. 11]
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### APOLOGY

The publishers regret that because of an error at the printers the new editorial board referred to in the editorial announcement on p. 797 of the September issue did not appear on the front inside cover as stated.