Immunoglobulins (antibodies) are plasma proteins produced by B cells, which are essential in the defence against bacterial and viral infections. Dysregulation of the immune system can lead to the formation of autoantibodies and subsequent autoimmune disease. Therapy with immunoglobulin was first studied in the late 19th century, when Von Behring and Kitasato showed that serum taken from rabbits immune to tetanus toxins could protect non-immune rabbits from infection. However, it was not until the 1960s that the first immunoglobulin preparations suitable for intravenous administration were formulated. Subsequently, intravenous immunoglobulin (IVIG) was introduced as replacement therapy in patients with primary immunodeficiencies. In the early 1980s, Imbach and colleagues were the first group to use IVIG in autoimmune disease. They gave patients with autoimmune thrombocytopenic purpura, who had been refractory to all conventional measures, an IVIG preparation as an experimental treatment. Their idea was that IVIG might interfere with the immune responses of the platelet-targeted autoantibody. Dramatic increases in platelet count were seen. Subsequently, the potential for using IVIG in autoimmune disease led to trials of its use in a wide variety of disorders (Table 1). There are large numbers of case reports and uncontrolled studies but few randomized controlled trials. This review provides a brief overview of the potential mechanisms of action and possible side-effects of immunoglobulin prior to highlighting the evidence for its use in autoimmune rheumatic diseases.

Preparation of intravenous immunoglobulin
IVIG is obtained from the plasma of large numbers (10,000–20,000) of healthy donors by cold ethanol fractionation. The cold ethanol fractionation process inactivates most viruses, including human immunodeficiency virus (HIV). To our knowledge, all of the reports of virus transmission with IVIG have involved hepatitis C virus prior to the mid-1990s. Subsequently, specific viral inactivation steps have been incorporated into the manufacturing of IVIG and there is no evidence that any of the IVIG products currently available (Table 2) transmit any known infectious agent. Aside from more rigorous purification techniques, each donor is selected according to strict criteria by medical interview and examination. Each plasma donation is then tested specifically for hepatitis B surface antigen, anti-hepatitis C antibodies, syphilis serology, HIV and normal liver function. The majority of commercial preparations contain predominantly polyclonal immunoglobulin G (IgG) (>90%) with a normal IgG subclass distribution and small amounts of immunoglobulins A and M (Table 2).

Administration and side-effects of intravenous immunoglobulin
There are very few studies comparing different regimes of administration. In general, an infusion of 2 g/kg/month is used in autoimmune disease. This is usually given in divided doses of 1 g/kg over 2 days or 0.4 g/kg over 5 days. The course is repeated monthly based on the rate of antibody clearance (the half-life of intravenous immunoglobulin is 4–6 weeks).

IVIG therapy is generally very well tolerated. Side-effects are usually mild and occur early during the infusion. The commonest are flu-like symptoms with myalgia, fever, headache, nausea and vomiting. Others include flushing, tachycardia and blood pressure changes. These minor complications can be managed by stopping the infusion temporarily or giving hydrocortisone prior to its start. There are a few rare but important side-effects. Anaphylaxis has been reported and is more common in IgA-deficient individuals. As the incidence of IgA deficiency in the general population is 1 in 700, this has led some authorities to advocate checking for deficiency prior to therapy. If this is confirmed, IgA-depleted commercial preparations can be used.

A second, rare complication is acute renal failure. This is much more common in individuals with pre-existing renal impairment. The mechanism is presumed to involve...
Mechanisms of action

The mechanisms of action of IVIG in autoimmune diseases are still not completely clear. They appear to be multifactorial and mediated either by the Fc portion of the IgG molecule or the variable (V) regions of the antigen-binding site of the molecule (Table 4).

**Fc-dependent mechanisms**

The Fc portion of the administered IgG can bind to the Fc receptors on splenic macrophages. This prevents the binding of autoantibody-coated targets to these receptors and hence reduces their subsequent clearance. This is an important mechanism in idiopathic thrombocytopenic purpura [15]. A second Fc-dependent mechanism is the inhibition of complement-mediated damage. Activation of the complement cascade leads to the formation of the membrane attack complex (MAC). The Fc portion of IVIG can bind to complement components C3b and C4b and hence reduce formation of the MAC [16]. This is thought to be important in dermatomyositis, which is characterized by intramuscular endocapillary deposition of the MAC, leading sequentially to loss of capillaries, muscle ischaemia and muscle fibre necrosis [17].

**V region-dependent mechanisms**

IVIG contains antibodies that can interact with the binding sites of disease-associated autoantibodies such as antineutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies [18]. This can prevent binding to target antigens, with a subsequent reduction in disease activity [19]. Similar idiotype–anti-idiotype interactions may occur on the surface of T cells, B cells and monocytes (via antibodies to cell surface receptors), leading to down-regulation of proinflammatory cytokines such as interleukin 1 and tumour necrosis factor α. Furthermore, anti-cytokine antibodies in IVIG can interact directly to modulate cytokine function [20].

**The evidence**

There has been progress in the use of IVIG in rheumatic disease since the initial observation in 1981 [3] of the beneficial effects in autoimmune thrombocytopenic purpura. However, most of the data stem from case reports and uncontrolled trials. Despite often impressive results in these studies, conclusive proof of benefit of IVIG in the form of randomized clinical trials is lacking in a number of the autoimmune rheumatic diseases. Below we discuss the data for the use of IVIG in inflammatory myositis, systemic lupus erythematosus, the antiphospholipid syndrome, vasculitis, rheumatoid arthritis and juvenile chronic arthritis.

**Inflammatory myositis**

Most of the data stem from case reports and uncontrolled trials. Of the uncontrolled trials, the majority have recruited patients with refractory myositis. These patients have all been on steroids and most have tried other immunosuppressive agents, such as methotrexate, azathioprine, cyclosporin A and cyclophosphamide; despite this, they continue to have active disease requiring further treatment. There are a handful of such uncontrolled trials in refractory juvenile dermatomyositis (DM) which suggest that monthly courses of IVIG lead to improvement in muscle strength and rash and allow a reduction in the dose of prednisolone [21–24]. The response can be unpredictable and inconsistent both between patients and between repeated

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**Table 1. Autoimmune diseases in which IVIG has been used**

<table>
<thead>
<tr>
<th>Proven</th>
<th>Unproven</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawasaki disease</td>
<td>SLE</td>
</tr>
<tr>
<td>Adult dermatomyositis</td>
<td>APS</td>
</tr>
<tr>
<td>Idiopathic thromboctypenic purpura</td>
<td>RA</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td>JCA</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathies</td>
<td>PM</td>
</tr>
<tr>
<td>Lambert–Eaton syndrome</td>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td></td>
<td>Churg–Strauss syndrome</td>
</tr>
<tr>
<td></td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td></td>
<td>Merosopic polyangiitis</td>
</tr>
<tr>
<td></td>
<td>Henoch–Schönlein purpura</td>
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</tbody>
</table>

**Table 2. Commonly used IVIG preparations currently available**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Amount of IgG (%)</th>
<th>Amount of IgA (mg/l)</th>
<th>Virus inactivation steps</th>
<th>Cost (5 g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandoglobulin</td>
<td>&gt; 90</td>
<td>720</td>
<td>pH 4/pepsin inactivation</td>
<td>£109.51 (6 g/100 ml)</td>
</tr>
<tr>
<td>Flebogamma</td>
<td>&gt; 90</td>
<td>15</td>
<td>Pasteurization/DEAE Sephadex/polyethylene glycol</td>
<td>£167.10</td>
</tr>
<tr>
<td>Gammagard</td>
<td>&gt; 90</td>
<td>5</td>
<td>Solvent/detergent (TNBP* Triton X-100)</td>
<td>£167.13</td>
</tr>
<tr>
<td>Octagam</td>
<td>&gt; 95</td>
<td>100</td>
<td>Unclear from product literature</td>
<td>£133.70</td>
</tr>
<tr>
<td>Vigam S</td>
<td>&gt; 98</td>
<td>5</td>
<td>Solvent/detergent (TNBP* Polysorbate 80)</td>
<td>£99.75</td>
</tr>
</tbody>
</table>

Data are from product literature and MIMS, April 2001.

TNBP, tri n-butyl phosphate.
courses, although the administration of IVIG in such children appears to be safe.

In adults with refractory myositis, uncontrolled studies [25, 26] suggest benefit in both polymyositis (PM) and DM. The largest open study was in 1991 [26] and involved 14 patients with PM and six with DM. They were given up to 12 infusions of IVIG. Ten patients with PM and five with DM improved in terms of muscle strength and a reduction in creatinine kinase. The improvement occurred within two infusions and was maximal after four infusions.

There are no randomized controlled studies of the use of IVIG in PM or juvenile DM. There was one controlled study in refractory adult DM by Dalakas et al. in 1993 [27]. This was a double-blind placebo-controlled trial in which 15 patients were randomized to receive either IVIG or placebo for 3 months. Following this, they were given the option of crossing over to the other group for a further 3 months of treatment. After each infusion, patients were assessed on neuromuscular symptoms, muscle power and resolution of the rash. All but one of the patients who received IVIG improved on all three parameters assessed within one or two infusions. No patients in the placebo group showed improvement. Following crossover of the IVIG patients to placebo, all these patients deteriorated within 1–2 months.

There is only one trial of the use of IVIG as first-line therapy in myositis [28]. Five adults with PM and six adults with DM were given four infusions with IVIG. Only two patients with PM and one with PM improved in terms of muscle strength and creatinine kinase reduction. However, of the eight non-responders, four had underlying malignancy.

A key question is how IVIG therapy would compare in terms of efficacy with standard treatment with glucocorticoids and other immunosuppressants, particularly in view of the cost of IVIG. Unfortunately, this is not a question that can be answered currently, in view of the lack of randomized trials. Although prednisolone and methotrexate are widely used in myositis, there are no controlled trials and treatment has largely been established empirically. Head-to-head controlled studies comparing IVIG with standard therapy are necessary.

Thus IVIG has proven effectiveness in adult refractory DM. Open uncontrolled studies suggest benefit in adult refractory PM and juvenile DM but there are no controlled studies as yet. The response in improved muscle strength and enzymes is rapid (within 1–2 months) but short-lived (1–2 months). There is no good data in the literature regarding the use of IVIG as a first-line agent in either PM or DM.

Systemic lupus erythematosus
IVIG was first used in systemic lupus erythematosus (SLE) over 10 yr ago but there are still no randomized controlled studies, other than one very small pilot randomized trial in lupus nephritis (see below). The majority of the data comes from case reports and small uncontrolled series.

There are 25–30 case reports in the literature which suggest that SLE manifestations can respond to IVIG. These include pancytopenia, particularly thrombocytopenia [29], psychosis [30], pleural effusions [31], carditis [32] and vasculitis [33]. There are variable case reports on the use of IVIG in lupus nephritis, some suggesting benefit, especially for membranous nephropathy [29, 34, 35] whilst others show deterioration in renal function following its administration [36, 37].

There are a handful of small uncontrolled trials in the literature. Maier et al. [38], in a study of seven patients, showed that IVIG could induce a rapid rise in the platelet count in SLE-associated thrombocytopenia, although relapses were common and repeated courses not usually successful. Most authorities recommend high-dose steroids as the initial treatment in immune-mediated thrombocytopenia. A controlled trial [39] compared prednisolone alone, IVIG alone and combination therapy in idiopathic immune thrombocytopenia. There was a rise in the platelet count in a median of 5 days with each single therapy and in 3 days with combination treatment. Relapse rates were similar in all three groups.

The largest uncontrolled study to date [40] found a beneficial clinical response to IVIG in 17 out of 20 SLE patients with reductions in the Systemic Lupus Activity

| Proposed mechanisms of action of IVIG (for full discussion see text) |
|-------------------|-------------------|--------------------------|
| Mechanism         | Action             | Proposed disease example |
| Fc region-dependent| 1. Blockade of Fc receptor on splenic macrophages | Idiopathic thrombocytopenic purpura |
|                    | 2. Inhibition of complement-mediated damage by binding C3b and C4b | Dermatomyositis |
| V region-dependent | 1. Idiotype–anti-idiotype reaction | Systemic lupus erythematosus |
|                    | 2. Reduction in cytokines | Kawasaki disease |

Table 3. Adverse effects of IVIG

<table>
<thead>
<tr>
<th>Common (1–10%)</th>
<th>Uncommon (0.1–1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Fever</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Back pain</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Headache</td>
<td>Eczema</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
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</tbody>
</table>

*Percentage of patients taking IVIG.
Measures (SLAM). Each patient received between one and eight courses of treatment. Arthritis, fever, thrombocytopenia and neuropsychiatric lupus responded more to treatment than other clinical manifestations. Similar clinical benefit has been observed in other uncontrolled trials, usually within two cycles of therapy [41]. However, it appears that the clinical response has a limited duration (around 6 weeks [42]) and is only maintained by continuous monthly infusions [41]. This benefit has been associated with reductions in anti-DNA titres and the erythrocyte sedimentation rate and improvement in complement levels [41, 42]. Few adverse effects have been noted.

The largest uncontrolled study in lupus nephritis found that three out of nine patients had clinical improvement following one course of IVIG [43]. These three patients had WHO class IV nephritis and showed a reduction in proteinuria within 2 weeks of IVIG administration and decreased IgG deposits on follow-up biopsy. The remaining patients had partial response but none had worsening of renal function.

The most recent study in seven patients with membranous or membranoproliferative lupus nephritis given one to six courses of IVIG found that all showed a reduction in proteinuria, the benefit lasting at least 6 months [44].

There has been one small pilot randomized trial [45] which enrolled 14 patients with grade III or IV nephritis. These patients had all received cyclophosphamide and prednisolone for 6 months and were then randomized to IVIG monthly for 18 months or cyclophosphamide initially every 2 months for 6 months and then every 3 months for a year. Prednisolone was allowed to continue. At the end of follow-up there were no statistically significant differences between the two groups in terms of changes in proteinuria and creatinine clearance.

In summary, there are no double-blind randomized trials with IVIG in SLE. Currently, the main situation where it appears to be useful is in severe thrombocytopenia, in which the rapid rise in platelets can buy time for other treatments to take effect, particularly if the patient is bleeding. Otherwise, as the evidence currently stands we would not support the use of IVIG in SLE.

**Antiphospholipid syndrome**

IVIG has been used in pregnancy in patients with both primary antiphospholipid syndrome (APS) and in APS secondary to SLE. Its first use in APS was in 1988, when a pregnant woman with a history of early miscarriages successfully gave birth following monthly treatment with IVIG [46]. Subsequently, early case reports and series [47–50] suggested similar benefits of the use of IVIG in similar patient groups. Unlike the initial report, these studies used subcutaneous heparin and low-dose aspirin as additional therapy to IVIG during the pregnancy.

There has been a recent multicentre, randomized, double-blind pilot study [51] which compared treatment with heparin, low-dose aspirin plus monthly IVIG with the more conventional treatment of heparin, low-dose aspirin plus placebo in 16 pregnant women with APS and a history of foetal death. Seven patients received IVIG monthly until week 36. Obstetric outcomes were excellent in both groups. However, IVIG did not achieve any statistically significant benefit beyond that achieved with heparin and low-dose aspirin.

In summary, as the evidence stands currently, IVIG cannot be recommended for initial therapy in pregnant women with ALS. However, it is possible that, because the randomized trial recruited only 16 patients, there was not sufficient power to show significant differences between conventional treatment and additional IVIG treatment. Furthermore, it is still not known whether IVIG is beneficial in pregnant women with a history of miscarriages who continue to abort despite standard treatment with aspirin and heparin.

**Vasculitis**

One of the earliest rheumatic conditions in which IVIG was used was the childhood vasculitic disorder Kawasaki disease. The coronary arteries can be affected, and approximately 20% of untreated patients develop coronary aneurysms, an important cause of mortality. The usefulness of IVIG in this condition has been demonstrated in both uncontrolled and controlled trials [52–54]. In 1986, a randomized controlled trial [53] compared treatment with aspirin plus one course of IVIG with the conventional treatment of aspirin alone. Treatment was instituted early (within 10 days of illness onset). Echocardiography at 7 weeks found a much lower frequency of coronary artery abnormalities in the IVIG group (4 vs 18%). IVIG has now become a standard therapy for this condition.

Subsequently, various case reports and small open studies suggested beneficial effects of IVIG in other vasculitides. There have been a few isolated case reports suggesting improvement in renal function following single courses of IVIG in Henoch–Schönlein purpura [55] and classical polyarteritis nodosa [56]. Most of the studies have concentrated on the ANCA-positive vasculitides (Wegener’s granulomatosis [57], microscopic polyangiitis [57] and Churg–Strauss syndrome [58]). There have been a number of open studies suggesting beneficial effects of a single course of IVIG, full clinical remission lasting over a year in some patients [59, 60], and corresponding reductions in levels of ANCA of up to 50% of pretreatment values [61].

There has been only one prospective, double-blind, randomized controlled trial [62] using IVIG in ANCA vasculitis. Patients with Wegener’s or microscopic polyangiitis were included who had ongoing disease activity despite at least 2 months of treatment with prednisolone and one other immunosuppressant. One course of IVIG led to significant clinical improvement and a fall in the C-reactive protein concentration lasting up to 3 months. After this time, however, there were no differences between the experimental and placebo groups.

Studies using repeated courses of IVIG in ANCA vasculitis have all been open. Some suggest a beneficial clinical effect of monthly IVIG courses [63], whilst others have found no difference between repeated and
single courses [64]. Currently, a randomized controlled trial is under way (IVISTAT) [65] to compare standard treatment in ANCA vasculitis in one arm with standard treatment plus repeated courses of IVIG in the other arm.

In summary, the usefulness of IVIG in Kawasaki disease is well recognized. In ANCA vasculitis, a single course of IVIG has been shown to have beneficial effects in the short term but this benefit was not maintained beyond 3 months. Whether repeated courses of IVIG (i.e. every 3 months) can sustain benefit is not known, but answers should be forthcoming over the next year.

Rheumatoid arthritis and juvenile chronic arthritis

IVIG appears to be ineffective in adult rheumatoid arthritis (RA) despite early reports of favourable outcomes [66]. There have been two randomized controlled trials: one included 32 patients with early active sero-positive RA [67] and the second included 20 patients with treatment-refractory RA [68]. In both trials, patients in the experimental arm received six courses of IVIG. Neither trial found significant differences in clinical or biochemical response when compared with the placebo arm.

The use of IVIG in juvenile chronic arthritis (JCA) is more controversial. In the largest of the uncontrolled studies [69], 27 patients with active systemic-onset JCA received monthly courses of IVIG. There was a significant improvement in systemic features, with resolution of fever and a reduction in steroid dosage. The effect on altering the course of arthritis was less clear. Two other uncontrolled studies [70, 71] have also shown beneficial clinical effects in systemic-onset JCA, improvements occurring after the first infusion of IVIG and becoming maximal after five or six infusions. However, the study by Prieur et al. [72] on 16 patients found no clinical benefit, although there were improvements in laboratory abnormalities, with a drop in the erythrocyte sedimentation rate and an improvement in thrombocytosis and haemoglobin. The only randomized controlled trial using IVIG in systemic-onset JCA was by Silvermann et al. in 1994 [73]. Patients with active refractory JCA were treated with IVIG or placebo for 6 months. No statistically significant differences in systemic symptoms or laboratory abnormalities were detected, although there was a trend towards greater clinical improvement in the IVIG group. The authors concluded that IVIG has limited usefulness in systemic onset JCA; however, the numbers recruited for the study were small and hence the results must be considered indefinite.

Data on the use of IVIG in polyarticular JCA is much more limited. There has been one study [74], which recruited 25 patients with rheumatoid factor-positive, active polyarticular JCA. All patients were initially given eight courses of IVIG and 76% improved clinically, as assessed by physician’s global assessment, a reduction in the number of active joints and improvement in functional capacity. The patients were then randomized to placebo or IVIG for a further 4 months and the IVIG group continued to improve whilst the placebo group deteriorated rapidly. Numbers were small.

In summary, there is no evidence to support the use of IVIG in adult RA. Some studies suggest beneficial effects in systemic-onset and polyarticular JCA, but further controlled trials are necessary. IVIG should still be considered experimental in juvenile arthritis and its use should be considered only if conventional treatment fails.

Future directions

This review illustrates how IVIG has been subjected to few randomized controlled trials in autoimmune diseases. Where good data exist, the effects have been relatively small. In most autoimmune conditions (including SLE, APS, polymyositis and the vasculitides) randomized controlled trials remain essential if IVIG is to be convincingly shown to be efficacious.

In view of the cost of IVIG, randomized trials comparing its potential efficacy with that of more standard, and less costly, immunosuppressant agents are necessary in the future. One potential avenue worth exploring to increase the potency of IVIG would be the addition of IgM to IVIG preparations. One study in support of this, using a rat model of acute renal inflammation, demonstrated that IgM was more efficient than IVIG in preventing the inflammatory reaction [75]. In this model, IgM bound activated components of complement more effectively compared with IgG. IgM has also been shown to suppress the binding of auto-reactive IgG antibodies to host tissues, possibly through an idiotypic interaction [76]. Compatible with this observation, mice deficient in serum IgM have an increased propensity to develop IgG autoantibodies and autoimmune disease [77, 78].

Reduced serum levels of IgM have been found in lupus patients [79] and it is possible that the administration of pooled IgM to rectify this deficiency could suppress the autoimmune response in these patients. Studies have shown the safety and efficacy of IgM in bone marrow transplantation and sepsis [80, 81]. We therefore propose that IgM-enriched IVIG should be tried in patients with autoimmune rheumatic diseases and, if preliminary results are encouraging, a randomized controlled trial should be initiated.

References


