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Review

Indications for IVIG in rheumatic diseases

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Abstract

The use of IVIG to treat a wide variety of immune-driven diseases has grown rapidly, although the mechanism of action is not completely understood. Increasing demand for IVIG coupled with concerns regarding potential transmissible agents has led to worldwide supply shortages. National agencies have therefore produced guidelines for its use, with the latest England and Wales guideline being published in 2011. Due to the rarity of the rheumatic diseases, the evidence for IVIG use has been shown to be lacking in some areas and promising in others. Conditions in which IVIG has been shown to have benefit include ITP, Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy occurring in the context of rheumatic disease, as well as in SLE, idiopathic inflammatory myopathies and ANCA-associated vasculitides. This review looks at current IVIG use and is designed to be an aid for rheumatologists when considering the use of IVIG in clinical practice.

Key words: rheumatic disease, lupus, vasculitis, myopathy, myositis, Kawasaki disease, intravenous immunoglobulin, IVIG, review.

REVIEW

Introduction

IVIG is a blood product prepared from the serum of a large number of donors. In recent years, its use has rapidly grown to treat a wide variety of immune-driven diseases. Although the mechanism of action is not completely understood, it is thought that IVIG is mediated via four pathways, including the actions of its many variable regions, known collectively as the antigen-binding fragments (Fab); the actions of its constant fragment (Fc) on host Fc receptors, which are widespread throughout the host immune system; the effects of host complement binding to the Fc fragment of IVIG, causing inhibition of the complement cascade; and other immunomodulatory agents that may be present in IVIG, such as cytokines, cytokine receptors and MHC molecules [1].

Increasing demand for IVIG coupled with concerns regarding potential transmissible agents has led to recent supply shortages. In the USA, the American Academy of Allergy, Asthma and Immunology first attempted to rationalize its use by publishing a comprehensive list of indications with supporting evidence. Concerning rheumatology, the authors reviewed the evidence for RA, SLE, APS and systemic vasculitis, although they did not offer any clear guidance for the use of IVIG in these diagnoses [2]. Similar guidance has also been published by Canada, Australia and other industrialized countries. The UK Department of Health set up the National Demand Management Programme (NDMP), which first published guidelines for IVIG use in England and Wales in 2008 with a revision in 2011 [3]. The NDMP requires each trust to set up an IVIG panel to approve the use of IVIG, depending on the priority given to each diagnosis, with red indications having the highest priority and blue indications as the next priority level. Grey indications have lower priority and indicate those conditions where evidence for IVIG use is lacking and therefore use is only considered and supported in exceptional circumstances and on a case-by-case basis (Table 1).

The aim of this review is to evaluate the current evidence for use of IVIG in rheumatological diseases with particular focus on blue and grey indications, as it is these indications for which rheumatologists will need to provide more justification for its use.

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Table 1 Some of the indications for the use of IVIG in the rheumatic diseases

Red (high priority)
Kawasaki disease
Chronic inflammatory demyelinating polyneuropathy
Guillain–Barré syndrome
Blue (medium priority)
Inflammatory myopathies
Congenital heart block
Autoimmune haemolytic anaemia
Grey (low priority)
SLE without secondary immunocytopenias
Stroke with APS
Catastrophic APS
Systemic vasculitides and ANCA disorders
CNS vasculitis
Systemic JIA
Complex regional pain syndrome
Black (no indication)
RA
Chronic fatigue syndrome

Red indications

Kawasaki disease

Kawasaki disease is the most common form of vasculitis in children and if left untreated a quarter will develop serious coronary artery aneurysms [4]. The first successful report of using IVIG for Kawasaki disease in 14 patients came in 1983 [5] and since then meta-analyses have confirmed that high-dose IVIG is highly efficacious in reducing coronary artery aneurysms when combined with aspirin [6]. More recently, a Cochrane review analysed 59 trials and found that a single high dose of IVIG (2 g/kg) led to a reduction in coronary artery aneurysms at 30 days [7]. It is therefore of high priority for Kawasaki patients to be treated with IVIG and aspirin within 10 days of onset.

ITP, chronic inflammatory demyelinating polyneuropathy and Guillain–Barré syndrome associated with lupus

It was first observed in 1981 that a young patient with both congenital hypogammaglobulinaemia and ITP had unexpected increases in his platelet count after being given IVIG [8]. This also prompted its use in other autoimmune disorders. Currently the British Society for Haematology suggests IVIG as first-line therapy in ITP patients where the platelet count has to be raised to prevent predictable bleeding or in emergencies [9]. In lupus-associated immune thrombocytopenia, 65% of patients treated with high-dose IVIG responded by an increase in platelets to $>50 \times 10^9$ per litre, although this effect was transient [10]. IVIG should therefore be considered in severe and resistant cases of lupus-associated thrombocytopenia where recovery of platelets needs to be achieved quickly before long-term measures are available.

IVIG treatment for Guillian–Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) has been recommended at level A in recent evidence-based guidelines by the American Academy of Neurology [11], although no controlled trials exist that have specifically examined IVIG for use in lupus patients with these conditions. One case series of six patients with lupus-associated CIDP reported improvement in three of the patients if treatment was started within 3 months of symptoms [12]. There is also a large body of evidence supporting IVIG use in primary GBS, but only a small number of reports that describe favourable outcomes in lupus-associated GBS [13, 14]. It is therefore recommended that IVIG be used in lupus patients presenting with CIDP or GBS when treatment is started within 3 months of onset (Table 2).

Blue indications

Idiopathic inflammatory myopathies

The idiopathic inflammatory myopathies consist of PM, DM, juvenile myositis and IBM. The main outcomes for treatment of PM and DM include improvement of muscle strength, normalization of muscle enzymes and reduction of skin disease. The cornerstone of therapy has been i.v. or oral glucocorticoids with the introduction of steroid-sparing agents such as MTX, AZA and HCQ [15].

Resistant DM/PM is refractory to high-dose glucocorticoids and disease-modifying drugs. In 1993 a small trial found that 9 of 12 patients receiving IVIG showed major improvement compared with 3 of 11 patients receiving placebo only [16]. Patients who benefited from IVIG required repeat infusions every 6 weeks. Also, an open-label trial found that 25 of 35 resistant PM patients treated with two infusions per month (1 g/kg/day) for 4–6 months showed significant improvement, with all patients being able to reduce their glucocorticoid dose by >50% [17]. Of those 25, 12 responders remained in complete remission after the follow-up period, with no treatment or low-dose glucocorticoids required. No major side effects were reported and the authors concluded that IVIG is safe and effective for the long-term treatment of resistant PM. The most recent randomized controlled trial (RCT) comparing IVIG with placebo found no significant differences between treatment and control groups, with both groups of patients showing much improvement [18], although in this trial each cohort was crossed over to the other treatment arm after only 8 weeks, which may be too short a period to allow IVIG to be fully effective.

Regarding IBM, only modest improvements in the power of certain muscle groups have been found [19]. This conclusion was confirmed in a double-blind RCT of 22 patients with IBM that found no significant differences between the treatment and placebo arms of the trial after 3 months, suggesting that the treatment of IBM with IVIG may only be marginally effective [20].

Current guidelines are in place for the use of IVIG in DM/PM by the European Dermatology Forum (EDF) and

Table 2 Recommendations for IVIG use in the red indications

Indication	Circumstance	Recommendation; level of evidence[a]
Kawasaki disease	All confirmed cases. Single IVIG infusion at a dose of 2 g/kg over 8–12 h with aspirin 80–100 mg/kg in three or four divided doses [6].	A; Ia
Lupus-associated ITP	IVIG to be used at a dose of 1 g/kg/day for 2 days if steroids and other treatments have failed or are contraindicated and if platelet count needs to be raised to prevent predictable bleeding or in emergencies [9].	C; III
Guillain–Barré syndrome	Five infusions at a dose of 400 mg/kg/day, although insufficient data to offer a dosing regimen [13].	C; III
Chronic inflammatory demyelinating polyneuropathy	If treatment started within 3 months, then monthly courses of 2 g/kg over 5 days, although more robust experimental data are needed [12].	C; III

[a]Recommendation and level of evidence: grade A recommendation: requires level Ia or Ib evidence specific to the recommendation being made; grade B: requires well-conducted clinical studies but not necessarily RCTs on the topic of recommendation; grade C: evidence from expert committee reports and/or from respected authorities usually indicates the absence of firm evidence. Evidence level Ia is from meta-analyses, Ib from at least one RCT, IIa includes well-designed non-RCTs, IIb includes well-designed experimental trials, III includes case or correlation studies and IV from expert panels. RCT: randomized controlled trial.

the European Federation of Neurological Societies (EFNS) [21, 22]. The EFNS recommends IVIG in resistant DM as second-line therapy or as a steroid-sparing agent and as first-line therapy in life-threatening DM. They suggest IVIG as second-line therapy in PM if immunosuppression fails and they do not recommend its use in IBM. Similarly the EDF suggests that IVIG be considered for use as second-line therapy in resistant DM/PM or as first-line therapy in severe DM/PM. In contrast to the EFNS, the EDF also recommends its use for IBM. They suggest a dose of 2 g/kg spread over 2–5 days each month for at least 6 months and that if no improvement is seen, IVIG should be stopped [21].

Autoimmune haemolytic anaemia associated with lupus

Autoimmune haemolytic anaemia (AIHA) is found in 12% of SLE patients [23]. AIHA does not respond as dramatically to IVIG as does ITP. One study found that only 40% of patients improved after IVIG as defined by an increase in haemoglobin of 20 g/l within 10 days [24]. Those who responded best to IVIG were those with hepatomegaly or severe anaemia. Most recent guidelines on the use of IVIG suggest that IVIG only be used in severe life-threatening cases of AIHA [25], although evidence is limited to a small number of case reports. One report found that IVIG was able to stabilize haemoglobin levels in patients who were refractory to glucocorticoids [26], but a further case series of 28 patients found only 3 patients improved with IVIG and that this improvement was transient [27]. Therefore there is too little evidence to support the use of IVIG for lupus-associated AIHA.

Congenital heart block associated with lupus

Congenital heart block (CHB) is the most serious manifestation of neonatal lupus and can cause permanent damage to the neonate. Only 1–2% of Ro/La-positive mothers have pregnancies complicated by CHB [28]; however, the recurrence rate in subsequent pregnancies is 15–20% [29]. A recent open-label trial studied 20 patients with previous CHB pregnancies but found no reduction in recurrence rates when compared with baseline [30], a finding that was confirmed in a further cohort study [31]. In these trials, the dose of IVIG may not have been high enough, as both studies used 400 mg/kg of IVIG, compared with the higher immunomodulatory dose of 2 g/kg. Indeed, when mothers' serum was analysed in the trial reported by Friedman *et al.* [30], mothers whose fetuses developed CHB had a significantly higher idiotypic to anti-idiotypic antibody ratio when compared with the sera of unaffected mothers [32], suggesting that there may have been an inadequate response due to the actual constitution of individual IVIG courses or from subtherapeutic IVIG doses being administered. Although the UK Department of Health recommends IVIG for CHB prophylaxis at a dose of 400 mg/kg, on the basis of these open trials, we would recommend that IVIG be used at the immunomodulatory dose of 2 g/kg and that further study of this increased dose be undertaken (Table 3).

Grey indications

Lupus

IVIG has been used experimentally as last-resort therapy to treat organ-specific manifestations of lupus, and case studies have reported positive outcomes in specific areas such as neuropsychiatric lupus [33], panniculitis [34], immune cytopenias [35] and severe serositis [36]. Recently, with the advent of biologic agents, there have been cases where the monoclonal antibody has been efficacious where IVIG has not [37]. It is well known that positive case reports that describe favourable outcomes

TABLE 3 Recommendations for IVIG use in the blue indications

Indication	Circumstance	Recommendation; level of evidence[a]
DM/PM	IVIG can be used in resistant cases of DM or as a steroid-lowering agent or as first-line therapy in those with life-threatening DM at a dose of 2 g/kg/month over 2–5 days for at least 6 months [17, 21, 22].	B; IIa
IBM	IVIG not recommended [20].	A; Ib
Lupus-associated AIHA	IVIG not recommended [25–27].	B; IIb
Lupus-associated CHB	IVIG may be considered as prophylaxis against CHB at an immunomodulatory dose (2 g/kg) in Ro/La-positive mothers who have previously had fetuses with CHB [30–32].	C; IIa

[a]Recommendation and level of evidence: grade A recommendation: requires level Ia or Ib evidence specific to the recommendation being made; grade B: requires well-conducted clinical studies but not necessarily RCTs on the topic of recommendation; grade C: evidence from expert committee reports and/or from respected authorities usually indicates the absence of firm evidence. Evidence level Ia is from meta-analyses, Ib from at least one RCT, IIa includes well-designed non-RCTs, IIb includes well-designed experimental trials, III includes case or correlation studies and IV from expert panels. AIHA: autoimmune haemolytic anaemia; CHB: congenital heart block; RCT: randomized controlled trial.

for treatments are more likely to be published than those that do not and therefore the results of case reports where IVIG is used as a last resort with success should be interpreted with caution.

Two small RCTs tested the efficacy of IVIG in SLE as well as four open trials and one retrospective study. These studies include 150 patients in total. The most recent RCT investigated the response of pregnant SLE patients to IVIG compared with those given prednisolone and NSAIDs alone [38]. Patients in the treatment group had a total of 11 infusions of IVIG (500 mg/kg every 3 weeks to 33 weeks gestation). The lupus activity in pregnancy score fell significantly, from 0.72 to 0.13, and there was no significant change in the control group (0.88–0.66). All 12 IVIG patients went to term, compared with 9 of 12 of the control group with no serious side effects, leading the authors' to conclude that IVIG improves pregnancy outcome and reduces lupus disease activity. A second RCT looked at IVIG use in LN compared with CYC [39]. Fourteen LN patients who had already been induced into remission with i.v. CYC were randomized to receive monthly IVIG (400 mg/kg) or i.v. CYC. After a follow-up period of 18 months, there was no significant difference between IVIG and CYC in maintaining remission, leading the authors to conclude that IVIG could be an alternative treatment to CYC. However, it is recognized that significant differences between LN treatment outcomes may take 5 years to become apparent [40, 41]. Therefore larger-scale RCTs with longer periods of follow-up are required to accurately compare the two treatments.

Uncontrolled open trials all report positive results for IVIG. Francioni *et al.* [42] looked at the treatment of chronically active lupus rather than acute flares and administered IVIG (400 mg/kg) for 5 days every month for 6–24 months. Of 12 patients, 11 showed clinical and serological improvement after treatment, although no comment was made on concurrent medication changes. Schroeder *et al.* [43] also demonstrated a significant improvement in mild flares of lupus as measured by a reduction in their SLAM scores from 7.33 to 5.25 ($P < 0.001$) with a total of 10 infusions 20 days apart, although this improvement was only very modest considering the intensity of the infusion protocol. Levy *et al.* [44] describe 20 patients with various manifestations of SLE treated with monthly IVIG (400 mg/kg/day for 5 days). Of the 20, 17 responded fully after one to eight courses of monthly IVIG, with a mean reduction in SLAM score from 19.3 to 4.0 ($P < 0.0001$). Encouragingly, 8 of 15 patients taking glucocorticoids were able to reduce their dose by the end of the trial. Hundt *et al.* [45] studied the treatment of lupus exacerbations in 13 patients with 5 consecutive days of IVIG (400 mg/kg/day) as measured by mECLAM scores. Although concurrent glucocorticoid dose was increased in six of these patients, it was noted that the remaining seven patients, in whom the glucocorticoid dose was kept constant, were full responders with a median reduction in their mECLAM score of 8 points. When these results are taken together, they suggest that IVIG may be useful in acute flares of SLE, with most benefit seen during severe flares. They also suggest that the most common symptoms to improve are those of fatigue, fever and pain.

More recently, Zandman-Goddard *et al.* [46] reported that 9 of 11 lupus patients given IVIG (400 mg/kg/day for 5 days) over 2–42 months had a full or partial response as measured by a significant reduction in SLEDAI score. Background therapy in this open study was not controlled, which of course may confound interpretation of these observations. In addition, >10% developed pulmonary embolism, representing an unacceptably high rate of serious side effects.

Finally, a larger retrospective study by Sherer *et al.* [47] looked at 62 patients given IVIG as part of their treatment for lupus. Patients were treated for a variety of symptoms, including mucosal ulcers, fever, rash, pleurisy and pericarditis, with a single dose of IVIG (500 mg/kg). Good responses were noted with a reduction in SLEDAI score

Table 4 Recommendations for IVIG use in the grey indications

Indication	Circumstance	Recommendation; level of evidence[a]
Lupus flare	IVIG may be considered for use in refractory disease where other treatments have failed (400 mg/kg/5 days).	C; III
	IVIG should be considered for acute severe flares of lupus, particularly with fever, pain and fatigue. It could be considered in critically unwell patients who are unable to tolerate immunosuppression (400 mg/kg/5 days).	C; III
LN	IVIG may have a role as maintenance therapy after induction (400 mg/kg/month), although more trial data are needed and over longer follow-up periods [39].	A; Ib
Lupus in pregnancy	IVIG may be considered for use (500 mg/kg/21 days up to week 33 gestation) as a steroid-sparing agent, especially in those with recurrent pregnancy loss [38].	A; Ib
Catastrophic APS	IVIG does not add any further benefit to the combination of plasma exchange, glucocorticoids and anticoagulation except where severe thrombocytopenia coexists [48].	B; III
Cerebral infarction	No convincing evidence on the use of IVIG in cerebral infarction [49].	C; IV
Systemic JIA	IVIG of uncertain use in initial treatment of systemic JIA with other, newer biologic agents showing proven efficacy [50].	C; Ib, IV
ANCA-associated vasculitis	IVIG may be considered as an alternative therapy in patients with refractory disease or in patients for whom conventional therapy is contraindicated (500 mg/kg/4 days/month), e.g. in the presence of infection, in the severely ill patient or in pregnancy [51].	B; IIa

[a]Recommendation and level of evidence: grade A recommendation: requires level Ia or Ib evidence specific to the recommendation being made; grade B: requires well-conducted clinical studies but not necessarily RCTs on the topic of recommendation; grade C: evidence from expert committee reports and/or from respected authorities usually indicates the absence of firm evidence. Evidence level Ia is from meta-analyses, Ib from at least one, IIa includes well-designed non-RCTs, IIb includes well-designed experimental trials, III includes case or correlation studies and IV from expert panels. RCT: randomized controlled trial.

from 15 to 5. Overall, the results from this study were promising, although there was no information about the dosing regimen of IVIG for each patient or other treatments they were receiving, and it is clear that a more rigorous study design is required. A summary of indications for IVIG use in lupus can be found in Table 4.

APS

APS can present as early pregnancy loss and stillbirth or arteriovenous thromboses. As of May 2012, the NDMP updated its clinical guidelines and no longer permits IVIG use in pregnancy-related problems related to APS, although its use is still permitted in catastrophic APS (CAPS) and stroke.

CAPS is a rare complication of APS that causes microthrombi and occlusions in the small vessels of multiple organs and carries a high mortality rate. Due to the rarity of CAPS, the European Forum on Antiphospholipid Antibodies set up the CAPS registry with the aim of increasing our understanding of CAPS and developing treatment strategies. The registry has shown that patients who receive prompt anticoagulation, glucocorticoids and plasma exchange with or without IVIG make the best recovery, with 75% of patients surviving, compared with ~20% with anticoagulation and glucocorticoids alone [48]. Regarding IVIG, patients who received anticoagulants, glucocorticoids and plasma exchange had a survival rate of 78%, compared with 69% of those who also received IVIG, although this difference was not significant. As already mentioned, IVIG has been associated with thromboembolism, with an incidence rate of up to 2% [52]. Most patients who developed thromboembolism were given high-dose IVIG at a fast rate and had multiple risk factors. It has therefore been suggested that a high dose (2 g/kg) be given over 5 days and each infusion over a minimum of 8 h, as this has been shown to reduce the risk of thromboembolism [52]. On this basis, the current evidence does not support the use of IVIG in CAPS unless it is complicated by severe autoimmune thrombocytopenia.

Ischaemic stroke is a well-recognized complication of APS, with one in five young stroke sufferers having aPLs [53]. No RCTs exist evaluating the use of IVIG in preventing or treating stroke associated with APS. One case study reports positive findings stating that 'the temporal association between IVIG and reversal of . . . neurological impairment . . . strongly indicates a specific effect of IVIG administration in this patient' [54]. Tincani *et al.* [49] canvassed the opinions of six experts at the International Advisory Board of the 10th International Congress on Antiphospholipid Aantibodies. Most respondents had little or no experience of using IVIG and it was mainly used where other treatments had failed or where severe thrombocytopenia coexisted. Furthermore, the British

Committee for Standards in Haematology guidelines do not mention of the use of IVIG and only endorse a target international normalized ratio (INR) of 2.0–3.0 for APS prophylaxis [55]. The lack of evidence for IVIG use certainly warrants more research in this area. However, currently, anticoagulation should only remain the mainstay of prophylaxis against arterial thrombosis in APS. IVIG should be reserved only for those severely affected by coexistent thrombocytopenia.

Systemic-onset JIA

Systemic-onset JIA (sJIA) causes fever, arthritis, serositis and a characteristic salmon-pink macular rash. Traditional therapies have included NSAIDs, corticosteroids and MTX. A number of findings led investigators to postulate that sJIA is driven by the interleukin IL-6 [56]. These findings were confirmed by a placebo-controlled double-blind RCT comparing the anti-IL-6 antibody tocilizumab with placebo, where a significant improvement was seen over 12 weeks [57]. The anti-IL-1β antibody canakinumab has also recently been shown to be effective in two RCTs [58]. Other biologic therapies found to be effective include the IL-1 receptor antagonist anakinra [59] and the anti-TNF agents adalimumab and etanercept [60, 61].

IVIG has occasionally been used alongside glucocorticoids in resistant cases of sJIA, with good anecdotal evidence of efficacy from a number of studies [62, 63], although the only RCT comparing IVIG with placebo in sJIA had negative results [50]. Today its use has largely been superseded by the newer biologics, and recent guidance released by the ACR states that the use of IVIG in sJIA with fever but without active arthritis is ‘uncertain for initial management’ [64].

ANCA-associated vasculitis

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophillic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome) make up the ANCA-associated vasculitides (AAVs). Induction of remission usually involves intensive treatment with CYC combined with high-dose glucocorticoids. However, CYC is associated with a risk of ovarian failure and infertility even when given in courses as short as 6 months [65]. Rituximab has recently been shown in the Rituximab for ANCA-associated Vasculitis (RAVE) trial [66] to be non-inferior to CYC in inducing remission. Maintenance therapy usually involves corticosteroids as well as AZA, MTX or LEF.

The toxicity of these drugs has led to IVIG being considered among other treatments. Jayne *et al.* [67] reported positive results in seven treatment-resistant GPA patients who were given IVIG, with symptoms improving within 2 days–3 weeks. In another open trial by the same author, 13 of the 26 patients with GPA had complete remission and another 13 of the 26 had partial remission after 8 weeks that was maintained 12 months after treatment started [68]. In contrast, Richter *et al.* [69] found that only 6 of 15 patients had a partial response to IVIG after 4 weeks, with none going into complete remission. Subtle differences between the responders and non-responders in this trial led the authors to hypothesize that IVIG may have an effect on the vasculitic but not the granulomatous component of the disease. The first RCT examining the effect of IVIG in persistent systemic AAV found a significant response at 3 months, with a reduction of >50 % in BVAS in 14 of 17 treated patients [70], although this benefit did not persist beyond 3 months as the BVASs of the placebo-treated patients gradually came down to meet those of the IVIG group.

Regarding EGPA, Tsurikisawa *et al.* [71] describe five patients with EGPA-associated myocarditis and heart failure who received five doses of IVIG and subsequently increased their left ventricular ejection fraction significantly. In a further open-label prospective study, 22 patients with a diagnosis of relapsed systemic AAV were induced into remission by administering six courses of monthly IVIG (500 mg/kg/day for 4 days) [72]. All patients initially responded well, with 59% remaining in remission after 9 months, suggesting that IVIG might be an important adjunct in AAV patients with refractory or relapsing disease. Recently a Cochrane review evaluated IVIG as an adjuvant therapy to glucocorticoids and immunosuppression in GPA and found insufficient evidence to support its use given its high cost and the need for repeat courses [73]. Current guidance from the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology regarding AAVs is that IVIG ‘may be considered as an alternative therapy in patients with refractory disease or in patients for whom conventional therapy is contra-indicated, for example, in the presence of infection, in the severely ill patient or in pregnancy’ [51]. IVIG may therefore be an important and safe bridging therapy during severe active vasculitis with coexisting immunosuppression.

Black indications

The NDMP will not approve the use of IVIG for RA and chronic fatigue syndrome. This is either because evidence has shown that IVIG is ineffective in these conditions or that there are better treatments available. In the case of RA, the effect of IVIG on cytokines is conflicting and the evidence for disease alleviation is based on anecdotal reports [74]. Likewise, in the 1990s there was interest in using IVIG to treat chronic fatigue syndrome, but in 1997 a well-designed double-blind RCT with 99 patients found no benefit of IVIG over a placebo of 1% albumin [75]. With the dawn of monoclonal antibody therapies for RA and the wealth of clinical data from well-designed RCTs in this area, the case for the use of IVIG in RA will not be discussed here.

Conclusion

IVIG has been shown to be effective in treating Kawasaki disease, ITP, CIDP and GBS with good supporting evidence. There is also evidence for its second-line use in DM/PM and as a bridging therapy in some cases of AAV. Certain subsets of SLE patients may also benefit from

IVIG during acute flares. The overall safety profile for IVIG is good, with only minor transfusion reactions being reported throughout the literature. That said, and of relevance in rheumatological practice, there is an increased risk of thromboembolism of up to 2% when given in high doses [52]. For this reason, slow infusion with the lowest concentration available is warranted.

It has been difficult to gather conclusive results on the efficacy of IVIG in the rheumatic diseases due to the rarity and heterogeneity of these diseases. The shortage of robust research has led to the NDMP placing many of these diseases in a category that requires more justification before IVIG use can be authorized, the main intention of the NDMP being that IVIG use is allocated to those conditions where the benefit has been demonstrated to be greatest. This review has provided justification for the use of IVIG in some of the rheumatic diseases by summarizing the current available evidence.

It is obvious that there is a clear need for further study in rheumatic conditions, including setting up national RCTs for the rheumatic indications of IVIG. Although this review has focused on summarizing the evidence for the rheumatic conditions that may benefit from IVIG, it is hoped that it may also act as a guide for future areas of research and help to standardize IVIG dosing and use in the treatment of these rare and less well-understood diseases.

Rheumatology key messages

- IVIG has proven efficacy in treating a number of rheumatic conditions; however, it remains poorly understood.
- The overall safety profile of IVIG is excellent.
- A better coordinated approach is needed to study the efficacy of IVIG in rheumatic conditions.

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