International Journal of Cardiology 112 (2006) 40–45

International Journal of Cardiology

www.elsevier.com/locate/ijcard

The role of intravenous immunoglobulin in the treatment of chronic heart failure

Pål Aukrust [a,b,*], Arne Yndestad [a], Thor Ueland [a,c], Jan Kristian Damås [a], Stig S. Frøland [a,b], Lars Gullestad [d]

[a] Research Institute for Internal Medicine, Rikshospitalet University Hospital, University of Oslo, N-0027 Oslo, Norway
[b] Section of Clinical Immunology and Infectious Diseases, Rikshospitalet University Hospital, University of Oslo, N-0027 Oslo, Norway
[c] Section of Endocrinology, Rikshospitalet University Hospital, University of Oslo, N-0027 Oslo, Norway
[d] Department of Cardiology, Rikshospitalet University Hospital, University of Oslo, N-0027 Oslo, Norway

Received 25 April 2006; accepted 10 May 2006

Abstract

Chronic heart failure (HF), including both ischemic and idiopathic dilated cardiomyopathies, is accompanied by a dysregulated cytokine network characterized not only by a rise in inflammatory cytokines, but also by an inadequate elevation of anti-inflammatory mediators. This dysregulation has been implicated in the development and progression of chronic HF, and in the last decade, attempts have been made to modulate this persistent inflammation. Failure of anti-tumor necrosis factor therapy in HF has led to further interest in a more general immunomodulatory approach, directed against the inflammatory imbalance rather than one particular cytokine. Treatment with intravenous immunoglobulin (IVIg) may represent such a broad-based approach trying to restore the dysregulated cytokine network through various mechanisms such as Fc receptor blockade, neutralization of microbial antigens and superantigens and more direct anti-inflammatory effects on the cytokine network. However, although one randomized placebo-controlled study in patients with chronic HF showed that IVIg improved left ventricular ejection fraction, accompanied by anti-inflammatory net effects, IVIg had no effect in another placebo-controlled study examining the effect of this medication in recent-onset cardiomyopathy. So far, few patients have been included in clinical trials, and there is clearly a need for larger placebo-controlled mortality studies involving a diverse group of patients with regard to cause and severity of HF.

Keywords: Chronic heart failure; Intravenous immunoglobulin; Cytokine network

Despite state-of-the-art cardiovascular treatment, chronic heart failure (HF) is a progressive disease with high morbidity and mortality, suggesting that important pathogenic mechanisms remain unmodified by the present treatment modalities. Persistent inflammation may represent such unmodified mechanisms. Thus, since the initial observation by Levine et al. [1], numerous studies have demonstrated that HF patients have raised plasma/serum levels of inflammatory cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)-1β, IL-6 as well as several chemokines, with increasing levels according to disease severity as assessed by clinical, hemodynamic and neurohormonal parameters [2,3]. Importantly, the rise in inflammatory mediators seems not to be accompanied by a corresponding increase in anti-inflammatory cytokines such as IL-10, resulting in an inflammatory imbalance [4]. Increased expression of inflammatory cytokines in HF patients has also been demonstrated in circulating leukocyte subsets at both protein and mRNA levels [5–7]. Moreover, these inflammatory mediators are not only increased in the circulation, but enhanced expression has also been found within the failing myocardium (e.g., adhesion molecules, TNFα, IL-6-related cytokines and chemokine receptors) [2],

* Corresponding author. Section of Clinical Immunology and Infectious Diseases, Medical Department, Rikshospitalet University Hospital, 0027 Oslo, Norway. Tel.: +47 23070000; fax: +47 23073630.
E-mail address: pal.aukrust@rikshospitalet.no (P. Aukrust).

0167-5273/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2006.05.015

suggesting a potential role for cytokine-related interactions in the pathogenesis of myocardial failure. Indeed, a series of experimental studies, including studies in gene modified animals, have revealed that the biological effects of cytokines may explain several aspects of chronic HF through mechanisms such as induction of cardiomyocyte apoptosis, enhanced matrix degradation and development of fibrosis, direct effects on Ca^{2+}-dependent processes and impaired β-adrenergic signal transduction [3]. Based on these issues, immunomodulating therapy has emerged as an option in the management of chronic HF.

1. Negative results of the anti-TNF studies

Given the potential central role of TNFα in the pathogenesis of HF, therapeutic modulation targeting this cytokine has received particularly much attention. However, three clinical trials examining the effects of anti-TNF therapy in HF were recently discontinued because of lack of effect (i.e., RENAISSANCE, RECOVER) or higher rates of mortality and hospitalization (ATTACH) [8,9]. The lack of positive effects of anti-TNF treatment in these studies may have several explanations such as incorrect dosage, inclusion of too few patients with markedly raised TNF levels and inability of these drugs to modulate myocardial inflammation [2,10]. Moreover, the chimeric anti-TNF antibody (infliximab) directly binds to the transmembrane form of TNF, resulting in damage to TNF-expressing cells by both antibody- and complement-dependent cellular toxicity and by induction of apoptosis [11,12]. While such mechanisms may be beneficial in inflammatory disorders such as inflammatory bowel disease, it may result in deleterious effects in chronic HF, secondary to damage of TNF-expressing cardiomyocytes. Furthermore, while too much of inflammatory cytokines such as TNF may be harmful, too little of these mediators may also have adverse effects on the myocardium reflecting the involvement of these cytokines in both maladaptive and adaptive responses [3,13]. Finally, while several studies have focused on the possible pathogenic role of TNFα and targeted therapy against this molecule, further research in this area will also have to identify other actors in the immunopathogenesis of chronic HF. Thus, although the results of the placebo-controlled anti-TNF trials may seem disappointing, they do not mean the end of the cytokine era even before it has started. Nevertheless, failure of anti-TNF therapy has led to further interest in a more general immunomodulatory approach, directed against the imbalanced cytokine network rather than one particular cytokine. Treatment with intravenous immunoglobulin (IVIg) is one such broad based approach that has received particular attention.

2. IVIg—clinical use

IVIg was first demonstrated to be effective in idiopathic thrombocytopenic purpura (ITP) [14,15]. Thereafter, it has been established to be efficacious in the treatment of several other autoimmune disorders such as the Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, dermatomyositis, Kawasaki's syndrome and in the prevention of graft-versus-host disease in recipients of allogenic bone marrow transplants [14–16]. Benefits have also been reported in many other autoimmune and systemic inflammatory conditions such as autoimmune uveitis, various autoimmune skin disorders (e.g., toxic epidermal necrolysis and pemphigus), different neurological disorders (e.g., multifocal motor neuropathy and stiff-person syndrome), anti-phospholipid syndrome, anti-neutrophil cytoplasmic-autoantibody (ANCA) positive vasculitis, autoimmune haemolytic anaemia, severe group A streptococcal infection and hemophagocytic lymphohistiocytosis [14–16]. However, in most of these conditions controlled trials are lacking.

3. IVIg in heart failure

Beneficial effects of IVIg have also been suggested in acute and peripartum cardiomyopathy [17,18]. More recently, we carried out a double-blind, placebo-controlled study that examined the effect of intervention with IVIg in 40 ischemic and non-ischemic patients with a left ventricular ejection fraction (LV-EF) <0.40, categorized as NYHA functional class II to IV. The study showed that IVIg treatment for 6 months on a monthly basis, significantly increased LV-EF from 0.26 to 0.31 independent of the etiology of HF (i.e., idiopathic or ischemic cardiomyopathy) [19]. In contrast to this finding, McNamara et al., investigating 62 patients with recent-onset cardiomyopathy (<6 months) and an LV-EF <0.40, found no significant effect of IVIg compared with placebo [20]. There may be several reasons for the discrepancies between the results from these two placebo-controlled IVIg studies. First, while the former study only recruited patients with chronic HF (>6 months duration) in a stable phase, the latter study included patients with recent-onset IDCM of <6 months duration. In fact, while there were no changes in LV-EF during 6 months of follow-up in the placebo group in the study by Gullestad et al., the surprising finding of the other study was that the mean LV-EF in the placebo-treated patients changed from 0.23 at baseline to 0.42 at 6 months. With this dramatic improvement in the placebo group, there was no further effect observed in the IVIg-treated patients, possibly reflecting a spontaneous improvement in recent-onset IDCM. Moreover, it is noteworthy that the dosage schedule differed between the "recent-onset IDCM" and the "chronic HF" study. Thus, while both studies gave induction therapy (a total of 2 g/kg), maintenance therapy [monthly infusions (0.4 g/kg) for a total of 5 months] was only given in the "chronic HF" study. Notably, in the latter study there was a gradual decline in N-terminal pro-atrial natriuretic peptide throughout the study, with the most pronounced decline at the end of study period. Moreover, at follow-up 1 year after

termination of the IVIg treatment, most of the HF patients had a decrease in LV-EF [21]. These findings suggest that maintenance therapy is needed for an extended period of time as in other chronic inflammatory disorders.

4. IVIg—mechanisms of action

Several non-mutually exclusive modes of action may be of importance for the clinical effects of IVIg in inflammatory disorders such as IDCM and other forms of chronic HF (Fig. 1). First, neutralization of microbial antigens and super-antigens have been observed after IVIg therapy [22,23], and these mechanisms could clearly be of relevance in patients with infection-induced myocarditis. In fact, in contrast to several other immunomodulators such as corticosteroids, IVIg has the potential both to dampen inappropriate immune activation and to enhance microbial specific immunity [22]. Second, IVIg is able to block the function of Fcγ-receptors on phagocytes by saturating, altering or down-regulating the affinity of the Fc receptors, a process that may render the sensitized phagocytic cells unable to exert their action [22]. Previous studies have demonstrated that the responses triggered by FcγRIII are counterbalanced by the inhibitory receptor FcγRIIB, and interestingly, it has been suggested that the beneficial effects of IVIg in ITP may primarily be caused by enhancing effects of this inhibitory Fc receptor [24,25]. Shioji et al. have recently shown that intact IVIg, but not F(ab′)$_2$ fragments, significantly ameliorated giant cell myocarditis, accompanied by down-regulation of inflammatory cytokines within the myocardium, suggesting that Fc-mediated effects also may be operating within the myocardium in IDCM [26]. Third, IVIg has been reported to impair leukocyte adhesion to endothelial cells, possibly mediated through antibodies against adhesion molecules [27]. Interestingly, such inhibitory effects on leukocyte recruitment was recently shown in vivo in an ischemia–reperfusion model, operating through inhibition of selectin and integrin function, further underscoring the relevance of these mechanisms in cardiovascular disorders [28]. Fourth, IVIg may also impair apoptosis by up-regulating the caspase inhibitor FLIP and by impairing Fas ligand-mediated apoptosis [29,30]. Hypoxia-induced cardiomyocyte apoptosis involves up-regulation of Fas and down-regulation of FLIP [31], but whether IVIg can counteract these pro-apoptotic events within the failing myocardium remains to bee proven. Sixth, recent studies suggest that dendritic cells (DC) are of major importance in the transition from an acute infectious myocarditis to a chronic autoimmune cardiomyopathy, involving both adaptive (e.g., CD40 ligand expressing T cells) and innate (e.g., toll-like receptor-mediated effects) immune responses [32]. IVIg has been found to impair DC function and maturation at least partly by down-regulating co-stimulatory molecules [33]. Notably, Shioji et al. showed that the IVIg-mediated suppression of giant cell myocarditis was associated with the suppression of DC, i.e., the suppression of the initial antigen-priming process in this experimental rat model of myocarditis [26].

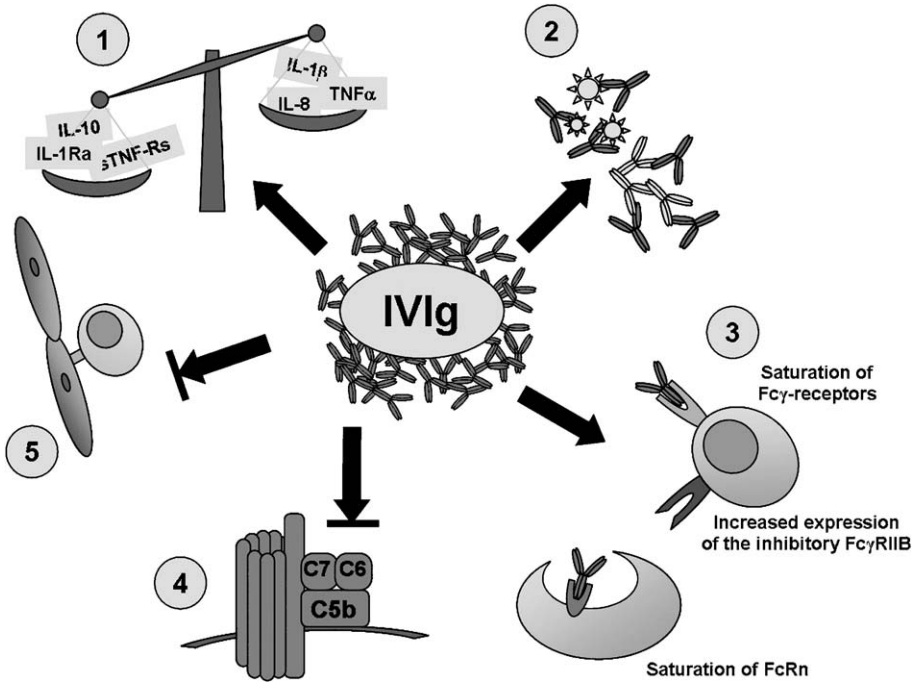

Fig. 1. Potential mechanisms for the beneficial effects of therapy with intravenous immunoglobulin in inflammatory and autoimmune disorders including idiopathic dilated cardiomyopathy and other forms of chronic heart failure. (1) Down-regulation of inflammatory (e.g., IL-1β, IL-8 and TNFα) and up-regulation of anti-inflammatory (e.g., IL-10, IL-1Ra and soluble TNF receptors) mediators, shifting the balance in the cytokine network towards anti-inflammatory net effects; (2) neutralization of microbial antigens, superantigens and autoantibodies; (3) inhibitory effects on Fc-receptor function through Fcγ-receptor blockade, increased expression of the inhibitory Fc-receptor FcγRIIB and through saturation of the neonatal Fc-receptor (FcRn) resulting in lack of protective effects on pathogenic autoantibodies; (4) inhibition of complement activation and deposition; and (5) impairment of leukocyte adhesion to endothelial cells.

5. Effects of IVIg on auto-antibodies

Auto-antibodies directed against β_1-adrenoreceptors or against other cardiac antigens such as troponin I may play a pathogenic role in IDCM [34]. It is therefore tempting to hypothesize that the beneficial effects of IVIg in IDCM may be secondary to inhibition or neutralization of such auto-antibodies. In fact IVIg may down-regulate or inhibit auto-antibodies in several ways. First, the high content of anti-idiotypes against auto-antibodies in immune globulin probably accounts for its ability to neutralize various antibodies and such mechanisms have been shown to be operating in the IVIg-mediated effects on autoimmune hemophilia due to auto-antibodies against factor VIII, ANCA positive vasculitis, myasthenia gravis and anti-body-mediated neuropathies [14,35]. Second, studies in animal models suggest that IVIg may down-regulate specific autoreactive B cells [35]. Finally, neonatal Fc-receptors (FcRn) are responsible for the maintenance of serum IgG levels by binding and protecting IgG against lysosomal degradation. However, these receptors may also protect pathogenic auto-antibodies, and notably, recent studies in ITP, serum-induced arthritis and pemphigus models all suggest that a high dose of IVIg saturates FcRn binding sites, and hence, pathogenic antibodies lose FcRn protection and are more rapidly degraded [24,36,37]. The faster degradation prevents pathogenic antibodies from reaching its tissue targets, e.g., the myocardium. However, we found no effects of IVIg on levels of cardiac β_1-adrenergic receptor auto-antibodies in the "chronic HF" study, suggesting that the beneficial effects of IVIg in that study was dependent on other mechanisms of action [38]. Interestingly, in contrast to IVIg, non-specific immunoad-sorption has been shown to remove auto-antibodies against cardiac β_1-adrenergic [39]. Although similarities, it is possible that these immunomodulatory treatment modalities may have different mechanisms of action with potential additive or even synergistic effects as a consequence.

6. Effects of IVIg on complement activation

Several studies suggest that IVIg inhibits complement activation involving mechanisms such as binding of C1q and activated C3 and C4 as well as C3b inactivation, and IVIg has also recently been shown to bind the potent inflammatory anaphylatoxin C5a [15,40]. However, in the "chronic HF" study we found that IVIg markedly enhanced complement activation in plasma [41]. Although this finding could reflect deviation of complement activation and deposition from the target tissue (i.e., myocardium) towards the fluid phase, we found that those with the most marked increase in complement activation in the fluid phase had only a slight increase or a decrease in LV-EF during IVIg therapy, challenging "the complement deposition" hypothesis [41]. A reasonable interpretation could be that although a certain complement activation, deviating C1q, C3, or C4 from the target may be beneficial, a fluid phase activation over a certain limit may by itself generate inflammatory products that overcome the protecting effect of a modest activation [42–44]. These findings also suggest a potential role for specific complement inhibitors in addition to IVIg in HF and IDCM.

7. IVIg—effects on matrix degradation

Recent data indicate that a complex regulation of matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) may significantly contribute to myocardial remodeling during various conditions [45]. Thus, myocardial overexpression of inflammatory cytokines such as TNFα leads to an early increase in MMP activity, possibly causing derangement of fibrillar collagen and ventricular dilation [46]. Such an up-regulation of MMP levels have also been demonstrated within the failing myocardium in humans both in ischemic and idiopathic dilated cardiomyopathy, and therapy targeting these processes has been suggested as an interesting approach in IDCM and other forms of HF [45]. It is noteworthy that IVIg has been found to inhibit MMP-9 activity in macrophages [47], and MMP-9 was also reported to be down-regulated in vivo during IVIg therapy in children with Kawasaki's syndrome [48]. More recently, we showed that etanercept and in particularly IVIg down-regulated the myocardial expression of MMP-2 as well as collagens I and III in a rat model of post-myocardial infarction (MI) HF [49]. If such IVIg-mediated effects also are operating within the myocardium in patients with chronic HF, they could contribute to the beneficial effects of IVIg on myocardial remodeling in these patients.

8. IVIg—anti-inflammatory net effects on the cytokine network

In our opinion, particular attention should be drawn towards the effects of IVIg on the cytokine network. Thus, we and others have demonstrated that IVIg may influence the levels of several cytokines and cytokine modulators, resulting in down-regulation of inflammatory responses. For example, IVIg has been shown to trigger the production of IL-1 receptor antagonist (IL-1Ra) in monocytes, without concomitant effects on the production of its inflammatory counterparts IL-1α and IL-1β [50]. Moreover, in vitro studies have shown that IVIg is a potent inducer of IL-10 in DC [33], further underscoring its anti-inflammatory potential. Also, IVIg preparations contain natural antibodies against several cytokines such as IL-1 and IL-6 contributing to their anti-inflammatory properties [15]. Importantly, these anti-inflammatory effects seem not only to be an in vitro phenomenon. Thus, IVIg administration in vivo has been found to markedly enhance plasma levels of IL-10 as well as IL-1Ra and the soluble decoy receptor IL-1 receptor type II, without any increase in IL-1 [51–53]. Furthermore, we showed that the improvement in

LV-EF in patients with chronic HF was correlated with a marked rise in the anti-inflammatory mediators IL-10, IL-1Ra and soluble TNF receptors (sTNF-Rs), accompanied by a slight decrease in TNFα and IL-1β, suggesting an anti-inflammatory net effect with potentially beneficial results on the myocardium [19]. Thus, IL-10 was been found to have protective effects on the development of atherosclerosis and viral myocarditis in mice [54–56], and IL-1Ra has been found to protect against hepatic and cerebral ischemic injury in rats [57,58] and may provide cardioprotection against ischemia–reperfusion injury in rat cardiomyocytes [59]. We have also recently reported that IVIg therapy, but not placebo, down-regulated chemokines and their corresponding receptors in peripheral blood mononuclear cells in HF patients [5]. Based on the important role of these mediators in attracting and activating leukocytes into inflamed tissues such as the myocardium during IDCM or other forms of chronic HF, this effect could contribute to the beneficial results of IVIg in HF. IVIg appears therefore to have a balanced and dual effect on the cytokine network with a down-regulation of certain inflammatory mediators (e.g., IL-8 and IL-1) combined with an up-regulation of anti-inflammatory mediators (e.g., IL-10 and IL-1Ra). In fact, enforcing the anti-inflammatory pathways might be as important as reducing the inflammatory cytokines.

9. IVIg during post-MI remodeling

Due to natural shortcomings of the product (expensive and limited supply), it is doubtful that long-term IVIg therapy could be routine in chronic HF. Post-MI remodeling is an important cause for the development of chronic HF, and an attractive hypothesis is that acute intervention with IVIg could prevent the remodeling process that takes place among patients with acute MI followed by HF. Indeed, we have recently showed that early intervention with IVIg, targeted against the inflammatory response following MI, attenuates the left and right ventricular remodeling processes [49]. Based on the balanced effect of IVIg on the cytokine network, it is conceivable that the use of this medication also will avoid potential harmful effects of more aggressive immunosuppressive therapy during MI (e.g., impairment of wound healing). These findings raise the possibilities that short-term immunomodulating therapy with IVIg could delay or inhibit the development of HF after MI by inhibiting the remodeling process.

10. Conclusion

Chronic HF, including both ischemic and idiopathic dilated cardiomyopathies, is accompanied by a dysregulated cytokine network characterized not only by a rise in inflammatory cytokines but also by an inadequate elevation of anti-inflammatory mediators. This dysregulation has been implicated in the development and progression of chronic HF, and in the last decade, attempts have been made to modulate this imbalance in the cytokine network. IVIg may represent such a therapeutic approach trying to restore the inflammatory imbalance in the cytokine network. However, so far, few patients have been included in clinical trials, and there is clearly a need to confirm the results of the small studies in larger placebo-controlled mortality studies involving a diverse group of patients with regard to cause and severity of HF.

References

[1] Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236–41.
[2] Aukrust P, Gullestad L, Ueland T, Damås JK, Yndestad A. Inflammatory and anti-inflammatory cytokines in chronic heart failure: potential therapeutic implications. Ann Med 2005;37:74–85.
[3] Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 2002;91:988–98.
[4] Aukrust P, Ueland T, Lien E, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1999;83:376–82.
[5] Damås JK, Gullestad L, Aass H, et al. Enhanced gene expression of chemokines and their corresponding receptors in mononuclear blood cells in chronic heart failure-modulatory effect of intravenous immunoglobulin. J Am Coll Cardiol 2001;38:187–93.
[6] Yndestad A, Damås JK, Eiken HG, et al. Increased gene expression of tumor necrosis factor superfamily ligands in peripheral blood mononuclear cells during chronic heart failure. Cardiovasc Res 2002;54:175–82.
[7] Yndestad A, Holm AM, Müller F, et al. Enhanced expression of inflammatory cytokines and activation markers in T-cells from patients with chronic heart failure. Cardiovasc Res 2003;60:141–6.
[8] Mann DL, McMurray JJV, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
[9] Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
[10] Anker SD, Coats AJS. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123–30.
[11] Haraoui B. Differentiating the efficacy of tumor necrosis factor inhibitors. J Rheumatol Suppl 2005;74:3–7.
[12] Van den Brande JM, Braat H, van den Brink GR, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology 2003;124:1774–85.
[13] Meldrum DR. Tumor necrosis factor in the heart. Am J Physiol 1998;274:R577–95.
[14] Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med 2001;345:747–55.
[15] Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol 2005;142:1–11.
[16] Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. JAMA 2004;291:2367–75.
[17] Bozkurt B, Villaneuva FS, Holubkov R, et al. Intravenous immune globulin in the therapy of peripartum cardiomyopathy. J Am Coll Cardiol 1999;34:177–80.

[18] McNamara DM, Rosenblum WD, Janosko KM, et al. Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. Circulation 1997;95:2476–8.
[19] Gullestad L, Aass H, Fjeld JG, et al. Immunomodulating therapy with intravenous immunoglobulin in patients with chronic heart failure. Circulation 2001;103:220–5.
[20] McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001;103:2254–9.
[21] Gullestad L, Aukrust P. Review of trials in chronic heart failure showing broad-spectrum anti-inflammatory approaches. Am J Cardiol 2005;95:17C–23C [discussion 38C-40C].
[22] Ballow M. Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. J Allergy Clin Immunol 1997;100:151–7.
[23] Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. J Clin Invest 1993;91:602–7.
[24] Jin F, Balthasar JP. Mechanisms of intravenous immunoglobulin action in immune thrombocytopenic purpura. Hum Immunol 2005;66:403–10.
[25] Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 2001;291:484–6.
[26] Shioji K, Kishimoto C, Sasayama S. Fc receptor-mediated inhibitory effect of immunoglobulin therapy on autoimmune giant cell myocarditis: concomitant suppression of the expression of dendritic cells. Circ Res 2001;89:540–6.
[27] Vassilev TL, Kazatchkine MD, Van Huyen JP, et al. Inhibition of cell adhesion by antibodies to Arg–Gly–Asp (RGD) in normal immunoglobulin for therapeutic use (intravenous immunoglobulin, IVIg). Blood 1999;93:3624–31.
[28] Gill V, Doig C, Knight D, Love E, Kubes P. Targeting adhesion molecules as a potential mechanism of action for intravenous immunoglobulin. Circulation 2005;112:2031–9.
[29] Arredondo J, Chernyavsky AI, Karaouni A, Grando SA. Novel mechanisms of target cell death and survival and of therapeutic action of IVIg in pemphigus. Am J Pathol 2005;167:1531–44.
[30] Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 1998;282:490–3.
[31] Yaniv G, Shilkrut M, Lotan R, et al. Hypoxia predisposes neonatal rat ventricular myocytes to apoptosis induced by activation of the Fas (CD95/Apo-1) receptor: Fas activation and apoptosis in hypoxic myocytes. Cardiovasc Res 2002;54:611–23.
[32] Eriksson U, Ricci R, Hunziker L, et al. Dendritic cell-induced autoimmune heart failure requires cooperation between adaptive and innate immunity. Nat Med 2003;9:1484–90.
[33] Bayry J, Lacroix-Desmazes S, Carbonneil C, et al. Inhibition of maturation and function of dendritic cells by intravenous immunoglobulin. Blood 2003;101:758–65.
[34] Mobini R, Maschke H, Waagstein F. New insights into the pathogenesis of dilated cardiomyopathy: possible underlying autoimmune mechanisms and therapy. Autoimmun Rev 2004;3:277–84.
[35] Lemieux R, Bazin R, Neron S. Therapeutic intravenous immunoglobulins. Mol Immunol 2005;42:839–48.
[36] Akilesh S, Petkova S, Sproule TJ, et al. The MHC class I-like Fc receptor promotes humorally mediated autoimmune disease. J Clin Invest 2004;113:1328–33.
[37] Li N, Zhao M, Hilario-Vargas J, et al. Complete FcRn dependence for intravenous Ig therapy in autoimmune skin blistering diseases. J Clin Invest 2005;115:3440–50.
[38] Larsson L, Mobini R, Aukrust P, et al. Beneficial effect on cardiac function by intravenous immunoglobulin treatment in patients with dilated cardiomyopathy is not due to neutralization of anti-receptor autoantibody. Autoimmunity 2004;37:489–93.
[39] Felix SB, Staudt A, Landsberger M, et al. Removal of cardiodepressant antibodies in dilated cardiomyopathy by immunoadsorption. J Am Coll Cardiol 2002;39:646–52.
[40] Basta M, Van Goor F, Luccioli S, et al. F(ab)′2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. Nat Med 2003;9:431–8.
[41] Aukrust P, Gullestad L, Lappegård KT, et al. Complement activation in patients with congestive heart failure: effect of high-dose intravenous immunoglobulin treatment. Circulation 2001;104:1494–500.
[42] Basta M, Fries LF, Frank MM. High doses of intravenous Ig inhibit in vitro uptake of C4 fragments onto sensitized erythrocytes. Blood 1991;77:376–80.
[43] Mollnes TE, Andreassen IH, Hogasen K, Hack CE, Harboe M. Effect of whole and fractionated intravenous immunoglobulin on complement in vitro. Mol Immunol 1997;34:719–29.
[44] Mollnes TE, Hogasen K, Hoaas BF, et al. Inhibition of complement-mediated red cell lysis by immunoglobulins is dependent on the IG isotype and its C1 binding properties. Scand J Immunol 1995;41:449–56.
[45] Li YY, McTiernan CF, Feldman AM. Interplay of matrix metalloproteinases, tissue inhibitors of metalloproteinases and their regulators in cardiac matrix remodeling. Cardiovasc Res 2000;46:214–24.
[46] Sivasubramanian N, Coker ML, Kurrelmeyer KM, et al. Left ventricular remodeling in transgenic mice with cardiac restricted overexpression of tumor necrosis factor. Circulation 2001;104:826–31.
[47] Shapiro S, Shoenfeld Y, Gilburd B, Sobel E, Lahat N. Intravenous gamma globulin inhibits the production of matrix metalloproteinase-9 in macrophages. Cancer 2002;95:2032–7.
[48] Senzaki H, Masutani S, Kobayashi J, et al. Circulating matrix metalloproteinases and their inhibitors in patients with Kawasaki disease. Circulation 2001;104:860–3.
[49] Gurantz D, Yndestad A, Halvorsen B, et al. Etanercept or intravenous immunoglobulin attenuates expression of genes involved in post-myocardial infarction remodeling. Cardiovasc Res 2005;67:106–15.
[50] Ruiz de Souza V, Carreno MP, Kaveri SV, et al. Selective induction of interleukin-1 receptor antagonist and interleukin-8 in human monocytes by normal polyspecific IgG (intravenous immunoglobulin). Eur J Immunol 1995;25:1267–73.
[51] Muller F, Aukrust P, Nordoy I, Froland SS. Possible role of interleukin-10 (IL-10) and CD40 ligand expression in the pathogenesis of hypergammaglobulinemia in human immunodeficiency virus infection: modulation of IL-10 and Ig production after intravenous Ig infusion. Blood 1998;92:3721–9.
[52] Aukrust P, Frøland SS, Liabakk NB, et al. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. Blood 1994;84:2136–43.
[53] Aukrust P, Muller F, Svenson M, et al. Administration of intravenous immunoglobulin (IVIG) in vivo down-regulatory effects on the IL-1 system. Clin Exp Immunol 1999;115:136–43.
[54] Pinderski Oslund LJ, Hedrick CC, Olvera T, et al. Interleukin-10 blocks atherosclerotic events in vitro and in vivo. Arterioscler Thromb Vasc Biol 1999;19:2847–53.
[55] Mallat Z, Besnard S, Duriez M, et al. Protective role of interleukin-10 in atherosclerosis. Circ Res 1999;85:e17–24.
[56] Nishio R, Matsumori A, Shioi T, Ishida H, Sasayama S. Treatment of experimental viral myocarditis with interleukin-10. Circulation 1999;100:1102–8.
[57] Shito M, Wakabayashi G, Ueda M, et al. Interleukin 1 receptor blockade reduces tumor necrosis factor production, tissue injury, and mortality after hepatic ischemia–reperfusion in the rat. Transplantation 1997;63:143–8.
[58] Yang GY, Zhao YJ, Davidson BL, Betz AL. Overexpression of interleukin-1 receptor antagonist in the mouse brain reduces ischemic brain injury. Brain Res 1997;751:181–8.
[59] Suzuki K, Murtuza B, Smolenski RT, et al. Overexpression of interleukin-1 receptor antagonist provides cardioprotection against ischemia–reperfusion injury associated with reduction in apoptosis. Circulation 2001;104:308I–13.