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Intravenous Immunoglobulin Therapy in Primary Vasculitides

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1. Introduction

Vasculitis is defined as chronic blood vessel inflammation confirmed by histologic evidence. The typical course of the disease may lead to blood vessel stenosis/occlusion causing organ ischemia, or to thinning of the blood vessel which results in aneurysm formation or hemorrhage. Although in 1994 the American College of Rheumatology introduced morphological and histopathological classification criteria for the most common forms of vasculitides at the Chapel Hill Consensus Conference (CHCC) (Jennette et al., 1994), vasculitides are generally divided into two main categories. Primary vasculitides represent the first group, are the entities of unknown cause in which blood vessel inflammation is the pathologic basis of tissue injury. Secondary vasculitides constitute the second, heterogeneous and much bigger group, in which inflammatory process occurs in association with an underlying disease or exposure.

The pathophysiology of the vasculitides is based on immunologic mechanisms. These mechanisms appear to play an active role in mediating the inflammatory response, but precise mechanisms still remain poorly understood. Although the primary events that initiate this process remain largely unknown, recent investigations have brought us closer to understanding some of the critical pathways involved in disease and provided a rationale for the study of novel therapeutic agents (Langford, 2010).

Intravenous immunoglobulin (IVIG) represents one of the novel alternative choices for the treatment as the standard regimen and IVIG has now become an important option in a number of clinical indications beyond primary immunodeficiency, including vasculitides.

2. Mechanisms of action

When Burton in 1951 for the first time published experience with the use of immunoglobulins in the replacement therapy for patients with primary immunodeficiencies and later other authors for secondary immunodeficiencies, no one would have expected that it could lead to the contemporary wide use of IVIG. Immunoglobulins can be applied in several immunomodulatory and anti-inflammatory indications as well. However, the exact mechanisms of action are only tentative. Some pathogenetic aspects have been already described, but during last fifteen years of intensive research new perspectives in understanding immunologic mechanisms of IVIG effects were introduced.

Basic immunomodulatory mechanisms of IVIG in autoimmune and inflammatory diseases could be divided into two groups. The first group involves mechanisms of humoral

immunity and the second one involves mechanisms of cell-mediated immunity. Both groups interdependently involve modulation of expression and function of Fc receptors, interference with complement activation and the cytokine network, provision of antiidiotypic antibodies, modulation of dendritic cells, T and B-cell activation and differentiation and their effector functions (Negi et al., 2007).

Intravenous immunoglobulins are prepared from pooled normal polyspecific human IgG obtained from large numbers of healthy donors. IVIG thus contains the wide spectrum of natural antibodies that far exceeds spectrum present in individual subjects. Essential roles of natural antibodies in healthy subject are: first line defense against infection, clearance of aging cells, antigen presentation to T-cells, anti-tumoral surveillance, anti-inflammatory activity and selection of immune repertoires and homeostasis of autoreactivity (Lacroix-Desmazes et al., 1998).

2.1 Natural antibodies in IVIG

Immunomodulatory effect of IVIG is probably dependent on the content of natural antibodies in treatment preparations because it is hypothesized that the presence of natural antibodies in healthy subjects control autoreactivity and maintain immune homeostasis. IVIG preparations contain sampling from the entire array of variable regions of antibodies, so they play an important role in selection of autoreactive B-cells and prevent uncontrolled expansion of specific autoreactive clones in disease. In addition, natural antibodies may play a role in prevention of the occurrence of pathological autoimmune reactions by binding to microbial epitopes that are similar or identical to self antigens (Cohen & Cooke, 1986). Superantigens trigger the activation of autoreactive cells. IVIG contain anti-antibodies which could eliminate superantigens such as toxic shock syndrome toxin 1 and Staphylococcal enterotoxins. These superantigens are generally considered to be the triggers of exacerbation in Wegener's granulomatosis (WG) (Stegeman et al., 1994, Boros et al., 2005).

2.2 Effect on Fc receptor modulation and anti-inflammatory activity

In order to prevent intracellular degradation of immunoglobulins in normal conditions Fc-receptor (FcRn) binds the molecule IgG inside the lysosome. During IVIG treatment oversaturation of normal molecules result in the accelerated catabolism of IgG and therefore reduce the level of pathogenic autoantibodies. In addition such IgG saturation leads to downregulation of FcRn in lysosomes and amplifies the effect of such treatment (Yu & Lennon, 1999). This hypothesis was supported in an experimental model, where in FcRn knockout mice, IVIG did not increase the clearance of antibodies, while in the wild type animals it did (Hansen & Balthasar, 2002). Analogous to normal circulating immunoglobulins intravenous immunoglobulins have also anti-inflammatory properties which modulate systemic inflammation during various inflammatory pathologies. Kaneko et al., (2006) showed that distinct properties of the Fc segment of IgG result from differential sialylation of the Fc core polysaccharide. IgG acquires anti-inflammatory properties upon Fc sialylation, which is reduced upon the induction of an antigen-specific immune response.

2.3 Immunomodulatory role of antiidiotypic antibodies

IVIG contains anti-idiotypes which are capable to neutralize pathogenic autoantibodies as described in antiphospholipid syndrome (Sherer et al., 2000) and idiopathic thrombocytopenic purpura (Hoffmann et al., 2000). Interaction between antiidiotypes (Fab

binding site) from IVIG and idiotype receptors on B-cells is probably responsible for the regulatory effect on autoreactive B-cell clones in patients with autoimmune and inflammatory disorders. Leucht et al., (2001) showed selective (VH gene origin) B-cell activation after IVIG treatment on patient with Kawasaki disease (KD). Sequence analysis has revealed that the most frequently used germ-line gene segments of all IVIG-bound Fabs were identical to those observed for many other autoantibodies and also represent the most frequently rearranged VH genes among human B-cells. It suggests that anti-idiotypic interactions may have an important role for the development and the control of the B-cell repertoire (Sib  ril et al., 2007).

2.4 Dendritic cells as a target of immunomodulatory effect

Defective functions of dendritic cells have also been attributed for predisposition in vasculitis pathology. Bayary et al. (2006) have shown that dendritic cells are influenced by IVIG at therapeutic concentrations (25 – 35 mg/ml) in terms of modulation of differentiation, maturation and function of dendritic cells. They observed that IVIG abrogates secretion of IL-12, downregulates the capacity of mature and immature dendritic cells to express costimulatory molecules (CD80, CD86, CD40) which results in inhibition of auto- and alloreactive T-cell activation and proliferation. Providing that the suppression of these signals is necessary for optimal antigen presentation and T-cell activation, it could be plausible explanation of the efficacy of IVIG in many immuno-inflammatory diseases including vasculitides.

2.5 Regulation of cytokine production

IVIG shows anti-inflammatory effect in vasculitis by modulation of cytokine antagonists and Th1 and Th2 cytokine production. Andersson et al. (1996) published that the addition of IVIG (6 mg/ml) to stimulated cell cultures of peripheral blood mononuclear cells caused a marked inhibition of proliferation and blast transformation despite unaffected cell survival. These cells exhibited a significant inhibition of production of T-cell derived cytokines IL-2, IL-10, TNF-beta, IFN-gamma. Gupta et al. (2001) found reduction of proinflammatory cytokines IL-6, IL-8 and TNF-alfa in patients with KD. Lau et al. (2009) confirmed in murine model of KD that IVIG in therapeutic concentrations, but not salicylate, effectively reduced the immune response leading to TNF-alpha expression. Possible mechanism published Siedlar et al. (2011) when in vitro exposure of the healthy individuals' monocytes to the IVIG preparation resulted in reduced TNF production, which was overcome by blockade of the Fc  RIIB in the CD14(+) CD16(++) CD32B(high) monocytes. Reduction in the number of CD14(+) CD16(++) monocytes and the blockade of their cytokine production via triggering CD32B can contribute to the anti-inflammatory action of IVIG. Regulation of cytokine and cytokine antagonists production is supposed to be one of the major anti-inflammatory mechanisms of intravenous immunoglobulins.

2.6 Attenuation of complement activation

Pathomechanisms of some vasculitides are closely associated with complement activation. Cryoglobulinemic vasculitis (glomerulonephritis) in patients with hepatitis C is associated with hypocomplementemia caused by its consumption (D'Amico & Fornasieri, 1995). In these patients various complement components such C3 and C1q has been detected in the different tissues (Haydey et al., 1980). IgA deposition, as well as complement factors (C3,

properdin, and complement membrane attack), were detected in mesangion in patients with Henoch-Schönlein purpura (HSP) complicated by nephritis (Bene & Faure, 1987). Deposition of C3, C4, MBL but no C1q were detected in an other study (Hisano et al., 2005). Association of complement activation in vasculitides is not clearly understood. The mentioned studies showed that the complement system could be activated both through the alternative and classical/lectin pathway in patients with HSP. In ANCA-associated vasculitides interaction among ANCA, neutrophils and complement suggests a role of these components in the development of the disease. The ANCA-activated neutrophils release factors that can directly damage the endothelium but also activate the alternative complement pathway with the generation of the powerful neutrophil chemoattractant C5a. C5a and neutrophil C5aR may thus compose an amplification loop for ANCA-mediated neutrophil activation. Complement activation amplifies neutrophil influx and activation eventually culminates in severe necrotizing inflammation of the vessel wall in ANCA-associated vasculitides (Chen et al., 2010).

2.7 Regulation of T and B-cells

In normal condition T-cells and B-cells are important for the control of autoreactivity and induction of tolerance. In vasculitides, as well as in other autoimmune diseases, T-cells most likely play a role in delivering proper signals to autoreactive B-cells for the production of autoantibodies (Negi et al., 2007). T-cells probably also participate in granuloma formation in Wegener's granulomatosis (Heeringa et al., 2005). In granulomatous lesions of WG T-cells with phenotype CD4+, CD28- represents a major source of proinflammatory cytokines (TNF- α , IFN- γ) and may function as an essential driving force for perpetuating inflammation (Holle & Gross, 2009). These interactions indicate that an aberrant signaling cascade could be activated. Membrane molecules of T and B-cells could react with IVIG. In the last two decades many authors described that IVIG contain antibodies against variable membrane molecules variable such as CD4, CD5, CD40, CD95 and cytokine receptors and a variable amount of solubilised CD4, CD8, HLA-I and HLA-II molecules (Ephrem et al., 2005). Pool of antibodies stored in intravenous immunoglobulins directed to such functional molecules of lymphocytes is important for the immunomodulatory effects of IVIG and may interfere with antigen recognition by the T-cells (Blasczyk et al., 1993).

2.8 Modulation of Th17 cell function

Recently discovered regulatory Th17-cells and cell-derived cytokines play an important role in the pathogenesis of several autoimmune/inflammatory diseases including vasculitides. In Wegener's granulomatosis, regulatory T-cells display impaired suppressor activity potentially favouring inflammation and break of tolerance (Abdulahad et al., 2007). Th17 - cells produce several cytokines such as IL-17, IL-21, IL-22, CCL-20 which induce massive inflammatory tissue reactions and these cytokines also stimulate nonimmune cells (fibroblasts, endothelial and epithelial cells) to the production of other proinflammatory mediators (IL-6, TNF- α , prostaglandins, NO, MMP and chemokines (Miossec et al., 2009). Maddur et al. (2011) published their results concerning the inhibition of differentiation, amplification and function of Th17-cells by IVIG treatment. The inhibitory effect depends on Fab2 receptor on Th17-cells. Maddur concluded that inhibition of effector cytokine release (IL-17A, IL-17F, IL-21) by these cells could demonstrate efficacy of IVIG in patient with autoimmune diseases by newly discovered mechanism.

3. Clinical indications

Intravenous immunoglobulins contain many different types of immune globulins (differentiated on the basis of structure and biological activity) that target different specific immune functions of the body. In this way, immunoglobulins imparts several types of immune fighting antibodies simultaneously. Seeing that the precise mechanism of IVIG are still largely unknown, the therapeutic mechanism of low-dose and high-dose regimen, as well as the short-and long-term effects are not the same for each condition. In low-dose and long term regimen IVIG were initially used to treat immunodeficiencies. Controversial knowledge about effectivity of high-dose treatment regimens leads to organizing several scientific meetings where attempt for treatment guidelines has been emphasized. In 2007 EULAR recommendations for the management of primary vasculitides were published in two parts according to CHCC classification - recommendations for small & medium vessel vasculitides and recommendations for large vessel vasculitides. These recommendations have been developed according to standardized operating procedures by EULAR standing committees. The guidance needs to be tailored to meet individual requirements. It is intended for use by healthcare professionals, medical students and specialist trainees, and pharmaceutical industries and drug regulatory organizations (Mukhtyar et al., 2009a, b). The British Society for Rheumatology published by Lapraik et al. (2007) guidelines for the management of adult ANCA-associated vasculitides. The main need for guidelines was to review the current treatment protocols and to highlight where there is an evidence base for treatment protocols and where treatment is based on individual preference. Recommendations are classified according to the level of evidence and the strength of recommendation. For large vessel vasculitides there is no place for IVIG according to EBM recommended treatment choice. For small and medium vessel vasculitides in statement 11 – “Alternative immunomodulatory therapy” – for patients who fail to achieve remission and have persistent low activity intravenous immunoglobulin can be used to achieve remission. These patients should be referred to an expert centre for further management and enrolment in clinical trials (level of evidence 3, grade of recommendation C). Contraindications of such treatment protocol are patients with selective IgA deficiency who may develop an anaphylactic reaction and patients with hypergammaglobulinaemia with risk of hyperviscosity state. According to BSR guidelines (Lapraik et al., 2007) IVIG may be considered as an alternative therapy in patients with refractory disease or in patients for whom conventional therapy is contraindicated, for example, in the presence of infection, in the severely ill patient or in pregnancy (grade of recommendation B). In the management of refractory vasculitis it is important to identify drives for vasculitis, such as, intercurrent infection or malignancy, or non-compliance.

3.1 Kawasaki disease

Clinical criteria and the exclusion of other conditions, including sepsis define the diagnosis of Kawasaki disease (Brogan et al. 2002). After the estimation of correct diagnosis the treatment regimes are focused on reducing inflammation and preventing vascular complications. Coronary artery abnormalities develop within 8 weeks of Kawasaki disease onset. Males and young children are most at risk. No IVIG treatment is considered to be one of the positive risk factor for Kawasaki disease cardiac complications (Phillip & Luqmani, 2008). So that, besides the standard regimes IVIG represent approved choice of treatment in KD with one basic aim – directly reduce the risk of developing coronary artery

abnormalities. The highest doses of IVIG were associated with the lowest risk late coronary complications. Meta-analysis study (Durongpisitkul et al., 1995) of treatment studies showed that a single high-dose of IVIG ($>1\text{g/kg}$) in combination with aspirin reduced coronary artery abnormality formation from 23% to 2.3%. Japan research committee reported one trial using low-dose of IVIG (100 mg/kg as a single dose) which showed no significant difference between the treatment groups in term of the occurrence of coronary artery abnormalities. It should emphasized that high-dose IVIG treatment in acute phase of KD have to start as soon as possible after diagnosis (Newburger et al., 1986).

3.2 Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium or small arteries characterized by a wide variety of clinical features including fever, constitutional symptoms, and systemic involvement (muscles, joints, intestines, nerves, kidneys, and skin). Asano et al. (2006) postulated that the effect of IVIG therapy on PAN is temporary, but in situation that PAN is induced by infections, IVIG therapy leads to a complete remission of the disease due to the neutralization of immune activation triggers, such as Parvovirus B19 and Streptococcus. Also Girisgen et al. (2011) based on the case report of 7 years old girl with polyarteritis nodosa and Henoch-Schönlein purpura nephritis suggested that IVIG might be an important adjunct therapy in selected patients with polyarteritis nodosa, especially in the lack of response to steroids and immunosuppressive drugs. On the contrary González-Fernández & García-Consuegra (2007) published the case-report of a child with polyarteritis nodosa that was unresponsive to conventional treatment, as well as IVIG treatment during her first and second hospitalizations. Treated child was successfully improved after the addition of iloprost and bosentan.

3.3 Wegener's granulomatosis and microscopic polyangiitis

Wegener's granulomatosis is a rare disorder which is characterized by necrotizing granulomatous vasculitis of small vessels. WG mainly affects the upper and lower respiratory tract, the kidneys, joints, skin and eyes in contrary to microscopic polyangiitis (MPA) which is characterized by pauci-immune, necrotizing, small-vessel vasculitis without clinical or pathological evidence of necrotizing granulomatous inflammation. MPA usually affects the kidneys, nervous system (particularly the peripheral nerves), skin, and lungs. Some authors mention that WG, MPA even the Churg-Strauss syndrome (CSS) form a part of a spectrum of one disease rather than entirely different entity (Kallenberg, 2005) and PAN. In a view of such classification more accurately criteria are expected. Watts et al. in 2007 published reclassification of ANCA-associated vasculitides and PAN which would be applied into clinical research in the future. This classification allows less unclassified patients and overlapping diagnosis in epidemiological studies as well as in pharmacological trials of various treatment regimes. Until present no study was realized by using this criteria and the evaluation of IVIG treatment in ANCA-associated vasculitides allows us to join WG and MPA under one condition. Moreover the role of IVIG for the treatment of ANCA associated vasculitides has not been clearly defined. IVIG treatment of these entities is frequently discussed subject of many scientific contributions. Jayne et al. (2000) published the only randomized placebo controlled trial of 34 patients with WG/MPA and found that a single course of IVIG reduced disease activity in persistent ANCA associated vasculitides, but this effect was not maintained beyond three month. Side effects were frequent, but mild

and reversible. Authors advise IVIG as an alternative treatment in persistent disease after standard therapy. Martinez et al. (2008) published results of multicenter, prospective, open-label study of 22 patients (19 with WG and 3 with MPA) and concluded that IVIG induced complete remissions of relapsed ANCA-associated vasculitides in 13 of 22 patients at nine months. Because of the good safety and tolerance profiles of IVIG, these agents can be included in a therapeutic strategy with other drugs used to treat relapses of WG or MPA. In 2009 Fortin et al. reanalyzed data from 187 publications and found the only randomized controlled trial published by Jayne et al. in 2000. The main aim of Fortin's review was to determine if intravenous immunoglobulin adjuvant therapy provides a therapeutic advantage over treatment with systemic corticosteroids in combination with immunosuppressants for the treatment of WG. After data extraction and statistical analysis Fortin concluded that there were no significant differences between adjuvant IVIG and adjuvant placebo in mortality, serious adverse events, time to relapse, open-label rescue therapy and infection rates. The fall in disease activity score, derived from patient-reported symptoms, was slightly greater in the IVIG group than in the placebo group after one month. Total adverse events in the IVIG group were increased 3.5 times (relative risk (RR) 3.50; 95% CI 1.44 to 8.48, $P < 0.01$). General conclusion from published Cochrane review is that there is insufficient evidence for comparing the advantages of IVIG adjuvant therapy to the treatment using the combination of steroids and immunosuppressants for patients with WG. Hiemstra & Jayne (2009) recommended in situations where glucocorticoids and immunosuppressives are contraindicated or represent an unacceptably high infection risk that IVIG may be considered; these include the presence of sepsis, a patient in intensive care unit or in pregnancy. IVIG cannot be recommended for routine use in ANCA-associated vasculitides, but can be considered where conventional agents are ineffective or contraindicated. Chung & Seo (2009) in general evaluation of advances in use of biological agents for the treatment of systemic vasculitides summarized that IVIG is not a panacea but play a role as adjunctive therapy for disease refractory to routine immunosuppression. IVIG may also be useful for patients in whom immunosuppression is undesirable or contraindicated (pregnancy).

3.4 Churg-Strauss syndrome

Churg-Strauss syndrome (CSS) is characterized by the presence of asthma, eosinophilia, and small vessel vasculitis with granuloma. Hamilos & Christensen first reported in 1991 that a 33-year-old man with CSS, who was resistant to conventional steroid treatment, showed a marked improvement of vasculitis symptoms and normalization of eosinophil count after IVIG therapy. However, there have been only a few reports on the use of IVIG therapy for CSS (Taniguchi et al., 2007). In 2004 Tsurikisawa et al. reported that neurological and cardiac manifestations in 15 patients with CSS, who were not responsive to corticosteroids with or without cyclophosphamide, were significantly improved after IVIG therapy. Intravenous immunoglobulin therapy may also be considered as a second-line treatment for CSS patients, particularly in the case of neuropathy or cardiomyopathy, which are resistant to conventional therapy. There is not much evidence supporting the effectiveness of IVIG in CSS, however, the mechanisms underlying the action of IVIG remain unclear. (Baldini et al., 2010). In 2004 Danieli et al. published the long term effectiveness of intravenous immunoglobulin and plasmapheresis associated with prednisone and cyclophosphamide in Churg-Strauss syndrome. Complete clinical and functional recovery with a long term stable remission and a low incidence of side effects can be achieved by intravenous

immunoglobulin associated with plasmapheresis in patients with Churg-Strauss syndrome. Churg-Strauss syndrome (CSS) is an extremely rare disease, and even less common in women of childbearing age. Hot et al. (2007) in their case report not only supports the beneficial effect of IVIG in CSS, but also illustrates its successful and safe use in a patient who was pregnant. They concluded alternative indication of IVIG in ANCA associated vasculitides during the pregnancy.

3.5 Behçet's syndrome

Behçet's syndrome is a systemic vasculitis with an unknown etiology affecting the small and large vessels of the venous and arterial systems. Recent European League Against Rheumatism guidelines are useful for the management of the disease in organ systems distinct from the vascular, neurological, and gastrointestinal systems. This is because of a lack of controlled studies evaluating such vascular, neurological, and gastrointestinal complications (Yazici et al., 2010). Seider et al. (2001) reported their results in the group of four patients in which the use of an immunoglobulin had brought the acute inflammation, uncontrolled by corticosteroids and/or cyclosporine A, under control and preserved the remission for a period of at least 1 year. Beales (1998) reported a case report of Behçet's colitis. Such gastrointestinal involvement in Behçet's syndrome is relatively rare, but could bring significant complications (Yurdakuk et al. 1996). Treatment may be difficult and published report suggests intravenous immunoglobulin to be beneficial. Behçet's colitis rapidly responded to IVIG, initially when the patient had failed steroid and immunosuppressive therapy and subsequently when IVIG was used as primary therapy. Leong et al. (2008) according to various reviewing american organisations calculated score for treatment of Behçet's syndrome to zero (not recommended), but above mentioned reports advise IVIG treatment in specific situations.

3.6 Henoch-Schönlein purpura

Most studies concerning IVIG treatment in Henoch-Schönlein purpura are case reports and bring repugnant conclusions. Orbach et al. (2004) reported that IgA nephropathy and HSP with poor prognosis may improve with IVIG, but 5/15 patients suffered from progressive renal failure after treatment. Hamidou et al. (1996) reported the efficacy of intravenous immunoglobulin in severe gastrointestinal manifestations. Fagbemi et al. (2007) described one patient with massive gastrointestinal haemorrhage in isolated intestinal Henoch-Schönlein purpura with prompt response to intravenous immunoglobulin infusion. They concluded that in severe cases where there is significant gastritis, IVIG provides an effective alternative to corticosteroids that may be employed as first-line therapy. In an open prospective cohort study Rostoker et al. (1994) treated 2 patients with HSP (from the group of 11 patients with IgA nephropathy) and concluded for all eleven patients that IVIG should protect renal function. On the contrary, other authors reported 3 more cases of HSP who did not show improvement in renal function, but rather deterioration (Orbach et al., 2004).

3.7 Mixed cryoglobulinaemia

Mixed cryoglobulinemia type II causes small vessel vasculitis. Vasculitis in skin, peripheral nerve, kidneys, gastrointestinal tract and joints is evoked by presence of circulating cryoglobulins of both polyclonal IgG and a monoclonal IgM rheumatoid factor that are directed against the IgG. The use of IVIG in mixed cryoglobulinaemia type II has been

reported without favorable effect and could lead to the induction of cryoglobulinaemia (cryoglobulinemic vasculitis) (Odum et al., 2001). In the presence of peripheral neuropathy vasculitis IVIG treatment showed beneficial effect (Almog et al., 2010). Until present, there is lack of supporting information, but according to Levy et al. (2005) IVIG may be beneficial in cases of resistant vasculitic peripheral neuropathy usually connected with cryoglobulinaemia. IVIG should probably be considered as a sole or adjuvant treatment in patients for whom conventional treatment is contraindicated, or for patients in whom conventional treatment is failed.

4. Economic, supervising and supply implications

IVIG is an expensive blood product that has been used in clinical praxis. IVIG preparations are derived from donor blood with potential risk of such infections as hepatitis and HIV. The process used to prepare final products for use in humans is monitored by the manufacturer and the supervising institutions of particular countries for the presence of dangerous infectious agents. The monitoring starts with the screening of potential donors. Under processing, a multi-step approach that extracts the desired immunoglobulins and attempts to remove all other substances is used. At the end, samples of each batch are tested for the presence of infectious particles. While all attempts are taken to reduce the risk of infection, some small risk still exists.

In last recent years, there was a marked limitation in their supply from manufacturers. This can be caused by several reasons, but main reason is supposed to be the increased use of immunoglobulin for the treatment of assorted new clinical indications, often used without evidence of benefit in the literature. Other liable factory which have affected supply and production costs have been are lack of donors and possible contamination of these human plasma products by infectious agents. It may carry a risk of transmitting infectious agents, e.g. viruses (hepatitis C) (Bjoro et al., 1994) and theoretically, the Creutzfeldt-Jakob disease caused by prions (Will et al., 1996).

For example, UK Department of Health published from November 2007 to May 2008 the programme related to manufacturing, distribution and use of intravenous immunoglobulins in the country. The Demand Management Programme is a three-part initiative that consists of: 1) National Clinical Guidelines for the appropriate use of IVIG, 2) Demand Management Plan and 3) National Immunoglobulin Database. Published material also includes requirement for the major UK supplier of immunoglobulin to buy plasma from the USA. This fact significantly increased production costs. Plasma was previously sourced within the UK as a by-product of voluntary blood donations. Second requirement was to close a UK manufacturer, Scottish National Blood Transfusion Service, also resulting in reduced local supply. Some additional problems increasing the price of IVIG is shortage availability of therapeutic immunoglobulin due to reduced imports by commercial companies who market intravenous immunoglobulins and acute shortages caused by unexpected withdrawals of batches of immunoglobulin for safety reasons e.g. the introduction of further measures to reduce the risk of disease transmission by immunoglobulin infusions (Department of Health UK, 2008). The UK demand management plan restricts IVIG use where benefit is unproved (Vaitla & McDermott, 2010).

In many European countries use of IVIG is mostly limited for treatment primary immune deficiencies where such treatment has been known to be life saving. Even though use of intravenous immunoglobulins in inflammatory diseases has been increased and a recent

literature search revealed more than 150 off-label usages of IVIG, which included 6781 patients in clinical trials and 362 patients in case reports (Leong et al., 2008). Due to shortage at the same time also in the USA, prices for IVIG have been on an upward trend, most notably in the secondary market. Many medical professionals have reported that the majority of their IVIG use was applied for off-label indications. Off-label use seems to be increased, contributing to rising demand.

Name	Producer	Indications	Last update EMA
Flebogamma	Grifols	RT, BMT, KD, ITP,GBS	09/2010
Kiovig	Baxter	RT, BMT, KD, ITP,GBS	05/2008
Privigen	CSL Behring	RT, BMT, KD, ITP,GBS	03/2008
*Orfagen	Orfagen	PM	10/2003

Table 1. a. IVIG indications exceeded RT in EU (EMA)

Name	Producer	Indication	Last update FDA
Gammagard S/D	Baxter	RT, KD, ITP	10/2008
Gammagard Liquid	Baxter	RT	04/2005
Iveegam E/N	Baxter	RT, KD	N/A
Polygam S/D	Baxter	RT, ITP	N/A
Carimune	CSL Behring	RT, ITP	10/2008
Privigen	CSL Behring	RT, ITP	07/2007
Panglobulin NF	CSL Behring	RT, ITP	N/A
Gamamr-P I.V.	CSL Behring	RT	N/A
Flebogamma DIF	Grifols	RT	07/2010
Venoglobulin-S	Gfrfols	RT, ITP, KD	N/A
Gammaplex	Bio Products	RT	10/2009
Octagam	Octapharma	RT	02/2006
Gamunex - C	Talecris	RT, ITP, CIDP	09/2008

Table 1. b. IVIG indications exceeded RT by FDA in USA. (N/A – without actual FDA approval)

Unexpected development in last years led all responsible representatives (EMA, FDA, medical professional societies, manufacturers) to coop with arose situation and postulate exact indications in Europe and USA respectively (Table 1a and 1b). There are less IVIG products with limited indications in summary of product characteristics at present market in comparison with the eighties. Uncertain role of IVIG in unlabeled indications is well established in UK Department of Health Clinical Guidelines for Immunoglobulin Use. The goal of submitted material is to ensure best practice across all indications, based on available evidence and expert opinion. Table 2 shows approved, potentially approved (grey) indications of IVIG in vasculitis treatment in UK (Department of Health UK, 2008).

5. Dosage implications

Generally accepted dosing regimes can be divided into two main groups. The first labeled group represents substitution (replacement) therapy used in primary and secondary

immunodeficiencies and the second group represents immunomodulatory therapy in idiopathic thrombocytopenic purpura, Kawasaki disease, Gullain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and polymyositis. All these indications are approved by EMA and FDA in Europe and USA respectively (Table 2 and 3). In replacement therapy (low-dose) group recommended dosis ranges from 0,2 to 0,8 g per kg of body weight and in immunomodulatory (high-dose) group ranges from 1,0 to 2,0 g/kg. The labeled use of IVIG is at present widely overlapped by unlabeled indications. These indications include the treatment of many immunological and idiopathic diseases involving nearly all organ systems. Man could say “gunshot into the unknown”. Leong et al. (2008) analyzed over 150 unlabeled uses of IVIG, including the most studied indications (e.g. multiple sclerosis, antiphospholipid syndrome in miscarriage, ...) and concluded that evidence for unlabeled use of IVIG has been interpreted in different ways by various reviewing subjects.

Condition	Recommended - short term	Recommended - long term	Evidence (grade)	Alternatives
KD	Yes	No	A, Ia	None
DM, JDM	Selected	Seleted	B, IIa	CS, IS, PE
CNS vasculitis	N/A	N/A	IIb	CS, IS
PM	N/A	N/A	III	CS, IS, PE
SV, AAV	N/A	N/A	III	IS
SLE, JSLE	N/A	N/A	III	CS, IS

Table 2. UK Department of Health guidelines for using IVIG in vasculitis (adapted).

Indication	Ratko	Orange	Ahmed	Aetna	BC	MLD T	Score
KD (labeled)	NI	2	NI	2	2	2	2,0
Unlabeled							
Behçet’s syndrome	0	NI	NI	0	NI	NI	0,0
CCS	NI	NI	NI	2	NI	NI	2,0
PAN	NI	NI	NI	0	NI	NI	0,0
Systemic vasculitides	1	1	NI	0	NI	NI	0,7
Secondary vasculitides	NI	NI	NI	0	NI	NI	0,0
WG	NI	NI	NI	0	NI	NI	0,0

Table 3. Indication score of various US guidelines for using IVIG in vasculitis (adapted according to Leong et al., 2008).

Until present immunological mechanisms of immunomodulatory effect of IVIG are not clearly known. In such context a question of adequate dosage appears in the relation of cost/benefits of unlabeled treatment. We published (Lukán et al., 2008) an adequate response in a case of Wegener’s granulomatosis after lower “high-dose” regimen (1 g/kg) which lasts until present without any therapy, only with mild increase of cANCA and no clinical recurrency. Many authors published effectiveness of such lower dose regime also in other rheumatological and hematological indications. Genevay et al. (2001) published effective use of IVIG in lower doses (0,8 g/kg) but only for maintenance treatment in polymyositis and concluded considerable reduction in treatment costs without a negative

influence on patient's health conditions. Sherer et al. (2008) reported a retrospective analysis of the medical records of 62 patients who received low-dose of IVIG and concluded that low-dose IVIG is a possible therapeutic option which is associated with lower cost, however treatment did not improve vasculitis in analyzed patients. Authors recommend IVIG only as an add-on therapy. Mori et al. (1988) concluded that in the treatment of acute idiopathic thrombocytopenic purpura there was no difference in therapeutic efficacy between the high and the low-dose IVIG regimen. Boman et al. (1995) achieved dramatic responses to IVIG in two cases of cerebral vasculitis even after the administration of the first dose (1 g/kg). One of the patients improved within 24 h of the administration, treatment continued at 4-week intervals and the patient was stable for 13 months, in spite of halving the dose of IVIG. Gedalia et al. (1995) reported in cutaneous polyarteritis nodosa combined with streptococcal infection in a dose 1 g/kg and Asano et al. (2006) in female patient with polyarteritis nodosa without any infection in a dose of 0,5 g/kg rapid and dramatic improvement after the first administration of IVIG. Monova et al. (2002) collected data on 116 patients with lupus nephritis who were treated with intravenous immunoglobulins. IVIG was applied in a dose of 0,255 g/kg. Depending on the clinical improvement afterwards the courses were repeated after 1 month (and every 3 months for maintenance of remission) to 7 years. Full remission was achieved in 36 patients. Partial remission was present in 48 patients. 32 patients went into end-stage renal failure and/or died. In 13/34 patients with impaired renal function serum creatinine levels returned to normal after treatment. Recher et al. (2010) reported a case report on unexpectedly successful a low-dose regimen (0,6 g/kg) in female patient with inclusion body myositis which costs approximately fourfold less than high-dose IVIG. In Henoch-Schönlein purpura some authors (Heldrich et al., 1993, Rostoker et al., 1995, Ruellan et al., 1997) administered low-dose or lower limit of high-dose regimens, others (Rostoker et al., 1994, Lamireau et al., 2001, Fagbemi et al., 2007) strictly apply 2 g/kg. Apart from the dose applied all authors emphasize dramatic improvement of IVIG treatment already after 24 hours after beginning (Girisgen et al., 2011).

It could be supposed that patients who respond to high-dose IVIG therapy would probably also respond to much lower doses, in many rheumatological indications vasculitides not excluded. In addition to economic reasons, low-dose regimen would likely help to reduce treatment related side effects. The lack of validated and generally accepted outcome measures as well as prospective clinical studies, makes it difficult to compare the effect of different interventions in different cases (Yu & Lennon, 1999).

6. Conclusion

Biological complexity of vasculitides and their contemporary nomenclature complicates not only the estimation of appropriate diagnosis but also hampers effective treatment. Intravenous immunoglobulins represent one of the very often discussed alternative treatment modality of vasculitides. For patients who fail to achieve remission, have persistent low activity of inflammation and relapse, intravenous immunoglobulins could be used as an alternative/adjuvant immunomodulatory therapy. Mechanism of action of intravenous immunoglobulins is complex and its effects are not clearly understood.

Even though many questions remain unanswered, intravenous immunoglobulins could be considered as an effective treatment regimen in many "off label" indications particularly in the cases when standard immunosuppressive regimes fail or could be harmful. In spite of

evidence of efficacy, dosage and timing IVIG therapy, questions of costs/benefits still remain insufficiently documented and controlled trials with consecutive formation of common guidelines are required.

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8. Abbreviations used in text and tables (in alphabetic order)

BMT – bone marrow transplantation, BSR - British Society for Rheumatology , CHCC - Chapel Hill Consensus Conference, CIDP – chronic inflammatory demyelinating polyneuropathy, CS- corticosteroids, CSS – Churg-Strauss syndrome, EBM – evidence based medicine, EULAR - European League Against Rheumatism, GBS – Gullain-Barré syndrome, HSP - Henoch-Schönlein purpura, IS – immunosuppressives, ITP – idiopathic thrombocytopenic purpura, IVIG – intravenous immunoglobulin(s), KD – Kawasaki disease, MPA – microscopic polyangiitis, PAN – polyarteritis nodosa, PE – plasma exchange, PM – polymyositis, RT – replacement therapy, WG – Wegener's granulomatosis.

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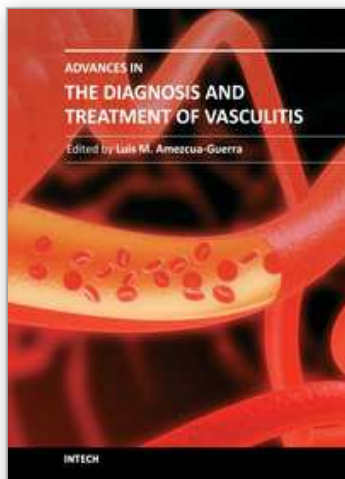
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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to draw themselves into this volume by keeping both the text and the accompanying figures and tables lucid and memorable. The book provides practical information about the screening approach to vasculitis by laboratory analysis, histopathology and advanced image techniques, current standard treatment along with new and more specific interventions including biologic agents, reparative surgery and experimental therapies, as well as miscellaneous issues such as the extra temporal manifestations of "temporal arteritis" or the diffuse alveolar hemorrhage syndrome. The editor and each of the authors invite you to share this journey by one of the most exciting fields of the medicine, the world of Vasculitis.

How to reference

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