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Current understanding and future directions

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Since immunoglobulin (Ig) replacement therapy was first used for the treatment of X-linked agammaglobulinaemia (XLA) [1], the therapeutic use of immunoglobulins has expanded to encompass not only many primary and secondary immunodeficiencies, but also vasculopathies, autoimmune diseases and numerous inflammatory disorders. The diversity of clinical topics covered at this 6th International Immunoglobulin Symposium was extraordinary, ranging from neurological indications, such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, Alzheimer's disease and multiple sclerosis, to blistering skin diseases, sepsis, transplantation and, of course, immunodeficiencies. The presentations featured reviews of current management strategies, as well as new clinical and basic science developments that will shape immunoglobulin therapy in the future.

Although intravenous immunoglobulin (IVIg) therapy has been used for essentially 30 years, there is much still to be learned about the mechanisms of action of immunoglobulins. New avenues of investigation in this field have opened and were covered in depth at the Symposium. These included novel insights into the interactions of IgG with Fc receptors and complement components, the importance of immunoglobulin Fc sialylation in inhibitory signalling and idiotype/anti-idiotype dimers, as well as natural antibodies and monomeric IgA in modulating the immune response.

Although much attention is given to the specificities of immunoglobulins, significant new findings have related to variability in interaction and function of the constant regions of immunoglobulin molecules. Single nucleotide polymorphisms and gene copy number variations of Fc receptors may affect the distribution and affinity of Fc receptors [2], as well as the balance between inhibitory and activating receptors. While creating a complex balance of influences, interindividual differences may also predispose individuals to particular autoimmune diseases. Genetic variations may additionally modulate the effects of therapeutically administered immunoglobulin and may be used as a future means of predicting clinical efficacy.

The complexity of immunoglobulin as a medicine is recognized increasingly and antibodies are perceived as multifaceted, multi-functional molecules that play important and varied roles in immune responses. An improved understanding of the different specificities and glycosylation states within antibodies may be harnessed for different uses and may not only increase further the efficacy of the therapeutic formulations, but could result in the development of new treatments.

It was discovered recently that a small, sialylated fraction of immunoglobulin is responsible for a disproportionate degree of anti-inflammatory effects when applied in certain model systems. In these settings, infusion of a low dose of sialylated Fc fragments (derived from IVIg) has been shown to result in the same effect as 10-fold higher doses of native IVIg [3]. Thus, it may be possible to reduce the amount of immunoglobulin needed for the treatment of selected inflammatory conditions if an enriched sialylated IgG could be provided. Moreover, because recombinant sialylated Fc seems to be as effective as native sialylated Fc molecules [4], arguing against a requirement for repertoire in this case, future opportunities deriving from this discovery may reduce the quantity of donor plasma needed to generate IVIg needed to treat certain autoimmune conditions. This could, in part, solve potential supply issues of IVIg that have been a fairly consistent concern.

Another mechanistic insight discussed regards the presence of idiotype/anti-idiotype dimers in preparations of IgG. These have been associated previously with reduced tolerability of IVIg products [5–7]. Novel findings relating to the dimeric fraction of IgG, however, have revealed that this fraction has an antigen specificity profile distinct from that of the monomeric fraction [8–10]. It is important that these specificities are not removed from IVIg products, as they may play an important immunoregulatory role.

Although efficacious and safe, immunoglobulin products in clinical use show batch-to-batch variation with respect to specific antibody content, and potentially other properties. Standardization and quality assessment of immunoglobulin products therefore remains an important consideration. The current methods of assessment of antibody function and repertoire are limited in scope and range and a more detailed understanding of specific antibodies and their functional characteristics, including complement activation ability and sialylation content, may need to be assessed in order to fill the knowledge gaps.

The issue of specificity of antibodies in IVIg preparations, in theory, applies directly to the treatment of primary antibody deficiencies, which are associated commonly with a relatively small number of pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphyllococcus aureus*, *Moraxella and Pseudomonas*) [11,12]. Thus, the question has arisen as to whether it may be feasible to target specifically or enhance antibodies with specificities for those pathogens or whether the full repertoire of antibody specificities is required for benefit. If only a certain subset of antibodies are needed to prevent the majority of infections, then a monoclonal antibody therapy approach may provide a targeted approach which would be affected less by potential supply shortages. Along similar lines, concentrated natural antibody fractions, such as anti-Fas and anti-CD40, which have been shown to have potent immunoregulatory effects [13,14], are also of interest. Experimentally, these have allowed for the development of 'super Ig' preparations, which are effective in an experimental model of systemic lupus erythematosus. Were these to be effective in human patients, they might contribute towards more efficient and individualized immunoglobulin therapies [15].

In efforts to understand more clearly and optimize immunoglobulin therapy specifically in primary immunodeficiency patients (PID), the utility of large databases and registries holds great potential. Initial experiences were presented at this Symposium regarding the evaluation of such registries in the United States and in Europe. They will certainly help us to understand the natural progression of these diseases and will probably reveal patterns in the incidences of complications and their impact on long-term outcomes. This may expose new areas to be examined more closely in the future and will drive future progress in immunoglobulin replacement therapy research.

Subcutaneous administration of immunoglobulins used as replacement therapy, which in some cases has been shown to be more convenient for PID patients and reduce the need for hospital resources [16], is already used widely in certain centres. New developments in this area may improve further the ease of administration and convenience to the patients. Higher-concentration (20%) products will allow for decreased infusion volumes, while the use of hyaluronidase [17] may increase potential volume and dose per site of subcutaneously administered immunoglobulins. Simple administration techniques such as 'daily subcutaneous push' using a syringe and a butterfly needle may also result in more patients choosing this route of administration in the future. Furthermore, research into new routes of administration, such as nebulized immunoglobulin, topical eye drops and local subcutaneous dermatological use, to deliver targeted, high doses of immunoglobulin require further studies, but may in the future allow expansion of non-intravenous administration into other therapeutic areas.

The potential use of immunoglobulins in currently 'off-label' indications, as mentioned above, as well as in previously underexplored fields such as systemic sclerosis and post-B cell ablation, may widen the need for immunoglobulin therapies. The potential expansion of clinical usage will probably lead to an increasing demand for immunoglobulin treatment in the future. Health systems will face increasing costs and pressure may rise on immunoglobulin as a finite resource. Strategies to reduce costs, optimize current use, improve therapeutic efficiency and address supply issues and the development of novel strategies arising from information from studies in this area are therefore warranted.

In addition to some of the potential theoretical improvements mentioned above in improving the immunoglobulin preparations themselves for use in particular indications, the use of adjunctive immunomodulatory therapies is also an important consideration. As experience accumulates, it is being appreciated increasingly that adjunctive therapies can provide an avenue for increasing the efficacy of immunoglobulin therapy, while potentially reducing the amount of IgG required. With advances in other fields, a new armamentarium of therapies, such as anti-B cell and anti-complement agents, will need to be evaluated in the context of immunoglobulin treatment in autoimmune or immunodeficient patients.

The use of IgM and IgA as immunomodulators is another area of intensive scientific research that could potentially alleviate some of the demand on therapeutic IgG. IgA has well-documented inhibitory effects in several inflammatory disease models, including asthma and glomerulonephritis [18,19]. Clinical trials with IgA remain to be performed, but the underlying mechanisms of IgA inhibition are being studied extensively. The fact that IgA can be extracted easily from plasma but is currently without a clinical use makes these issues all the more compelling. Similarly, IgM has tremendous potential in the treatment of human disease. It is known to interact with potentially self-reactive IgG in healthy individuals and is atheroprotective [20–22]. The use of IgM for immunomodulation or up-regulation of tissue homeostatic processes seems promising, with toxicology studies currently under way and a potential clinical trial set to start as soon as 2010.

New discoveries and developments in immunoglobulin therapy will drive the evolution of treatment guidelines, which are helpful in developing efficient, rationalized use of immunoglobulins. However, innovative use of immunoglo-

bulin for the benefit of patients should not be discouraged. It is important to remember that lack of evidence does not necessarily mean lack of efficacy, and specific guidelines for usage should not hinder further advances in immunoglobulin research and development of the evidence base for their use.

There is still much to be learned about immunoglobulin therapy, and many more clinical applications may yet emerge. These advances will stem from the enhanced basic and clinical science that drives forward our understanding and allows better management of a finite resource for those in whom the benefit is greatest. It is this juxtaposition of basic and clinical research that remains critical for effective translation for patient benefit.

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References

1 Bruton OC. Agammaglobulinemia. Pediatrics 1952; **9**:722–8.
2 Breunis WB, van Mirre E, Geissler J *et al.* Copy number variation at the FCGR locus includes fcgr3a, fcgr2c and fcgr3b but not fcgr2a and fcgr2b. Hum Mutat 2009; **30**:E640–50.
3 Kaneko Y, Nimmerjahn F, Ravetch JV Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science 2006; **313**:670–3.
4 Anthony RM, Nimmerjahn F, Ashline DJ *et al.* Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 2008; **320**:373–6.
5 Tankersly DL. Dimer formation in immunoglobulin preparations and speculations on the mechanism of action of intravenous immune globulin in autoimmune diseases. Immunol Rev 1994; **139**:159–72.
6 Vassilev TL. Variable region-connected, dimeric fraction of intravenous immunoglobulin enriched in natural autoantibodies. J Autoimmun 1995; **8**:405–13.
7 Sultan Y, Rossi F, Kazatchkine MD. Recovery from anti-VIII : C (antihemophilic factor) autoimmune disease is dependent on generation of antiidiotypes against anti-VIII : C autoantibodies. Proc Natl Acad Sci 1987; **84**:828–31.
8 Schaub A, Wymann S, Heller M *et al.* Self-reactivity in the dimeric intravenous immunoglobulin fraction. Ann NY Acad Sci 2007; **1110**:681–93.
9 Wymann S, Ghielmetti M, Schaub A *et al.* Monomerization of dimeric IgG of intravenous immunoglobulin (IVIg) increases the antibody reactivity against intracellular antigens. Mol Immunol 2008; **45**:2621–8.
10 VonGunten S, Simon HU. Natural anti-Siglec autoantibodies mediate potential immunoregulatory mechanisms: implications for the clinical use of IVIG. Autoimmun Rev 2008; **7**:453–6.
11 Su J, Georgiades A, Wu R *et al.* Antibodies of IgM subclass to phosphorylcholine and oxidized LDL are protective factors for atherosclerosis in patients with hypertension. Atherosclerosis 2006; **188**:160–6.
12 Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med 1993; **86**:31–42.
13 Matsuno H, Yudoh K, Nakazawa F *et al.* Antirheumatic effects of humanized anti-Fas monoclonal antibody in human rheumatoid arthritis/SCID mouse chimera. J Rheumatol 2002; **29**:1609–14.
14 Bayry J, Lacroix-Desmazes S, Donkova-Petrini V *et al.* Natural antibodies sustain differentiation and maturation of human dendritic cells. Proc Nat Acad Sci 2004; **101**:14210–5.
15 Shoenfeld Y, Rauova L, Gilburd B *et al.* Efficacy of IVIG affinity-purified anti-double-stranded DNA anti-idiotypic antibodies in the treatment of an experimental murine model of systemic lupus erythematosus. Int Immunol 2002; **14**:1303–11.
16 Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs 2007; **21**:105–16.
17 Bookbinder LH, Hofer A, Haller MF *et al.* A recombinant human enzyme for enhanced interstitial transport of therapeutics. J Control Release 2006; **114**:230–41.
18 Wolf HM, Fischer MB, Puhringer H *et al.* Human serum IgA down-regulates the release of inflammatory cytokines (tumor necrosis factor-a, interleukin-6) in human monocytes. Blood 1994; **83**:1278–88.
19 Pasquier B, Launay P, Kanamaru Y *et al.* Identification of FcalphaRI as an inhibitory receptor that controls inflammation: dual role of FcRgamma ITAM. Immunity 2005; **22**:31–42.
20 Rossi F, Guilbert B, Tonnelle C *et al.* Idiotypic interactions between normal human polyspecific IgG and natural IgM antibodies. Eur J Immunol 1990; **20**:2089–94.
21 Hurez V, Kazatchkine MD, Vassilev T *et al.* Pooled normal human polyspecific IgM contains neutralizing anti-idiotypes to IgG autoantibodies of autoimmune patients and protects from experimental autoimmune disease. Blood 1997; **90**:4004–13.
22 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999; **92**:34–48.