Advances in the understanding of the mechanism of action of IVIg

The IgG molecule is the main component of IVIg. Commercial preparations of IVIg are derived from a pool of donors and subsequently, IVIg products contain smaller amounts of IgA and IgM antibodies as well as Th2 cytokines and cytokine antagonists that may also contribute to therapeutic effects. Numerous targets for IVIg include: T-cells, cytokines, immune cell trafficking, B-cells, complement and Fc-receptors. IVIg has been demonstrated to inactivate auto-reactive T-cells by competing for and interrupting their interaction with antigen presenting cells. The balance of cytokines also appears to be restored by IVIg, with studies showing that IVIg contains antibodies and antagonists to pro-inflammatory cytokines. In addition, IVIg is thought to interfere with and prevent the passage of auto-immune T-cells into the blood–nerve barrier. The effects of exogenous antibodies on B-cells have been well studied; IVIg is thought to down-regulate antibody production by B-cells, interfere with B-cell proliferation via a blockade of cell surface receptors and prevent the activation of certain subtypes of B-cell. In addition, IVIg can affect innate immunity by interrupting the steps in the complement activation cascade and blocking Fc-receptor mediated activity, which results in down-regulation of macrophage activity. In conclusion, IVIg has numerous modes of action, which culminate in the down-regulation of immune response; many of which may be relevant to neuromuscular disorders and immune neuropa-thies.

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All human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study.

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IVIg product, can be divided into two important sub-units: the antigen binding regions, which are involved in adaptive immunity, and the Fc fraction, which is involved in innate immunity. In addition to IgG, different commercial preparations, which are derived from a pool of 5,000–10,000 blood donors, usually contain smaller amounts of IgA and IgM antibodies and other molecules that may also contribute to the therapeutic effects of the product. Antibodies are mostly present in monomeric form, but are also found as dimers and polymers.

The effects of IVIg can be broadly categorized as relating to either the action of the IgG molecule proper or to immunomodulatory components other than IgG. Numerous potential targets for these effects of IVIg have been identified within the immune system:

**T-cells**

T-cells play a crucial role in the adaptive immune response. The interaction between the antigen-presenting cell (APC) and the T-cell is mediated by a number of molecules, such as MHC molecules, CD4/CD8 and T-cell receptors (TCR). Various components of IVIg, such as soluble CD4/CD8, soluble HLA and anti-TCR, may inactivate auto-reactive T-cells by competing for and interrupting this interaction with APCs. Other factors present in the IVIg preparation may also drive auto-reactive T-cells into apoptosis. In summary, IVIg may inactivate, silence or bring about programmed T-cell death [10].

**Cytokines**

Cytokines are important therapeutic targets of IVIg. A complex ensemble of cytokines, including IFN-γ, IL-4, and IL-5 is released when T-cells are activated. These molecules can be classified as Th1 cytokines, which are pro-inflammatory, or Th2 cytokines, which are anti-inflammatory. In many autoimmune disorders, it has been shown that the balance of Th1 and Th2 cytokines is disrupted and Th1 cytokines predominate over counter-regulatory Th2 cytokines. Several groups have demonstrated that IVIg can help to restore the balance because it contains antibodies to Th1 cytokines, a number of Th2 cytokines, as well as antagonists of pro-inflammatory Th1 cytokines [9].

**Immune cell trafficking into the peripheral nervous system**

The passage of auto-immune cells from the systemic circulation through the blood-nerve barrier can lead to destruction of myelin in the peripheral nervous system. Auto-reactive T and B-cells are thought to adhere to the blood-nerve barrier, pass through and exert their deleterious pathogenic effects. Factors on the T-cells themselves and in the endothelium and its basement membrane are important for trafficking across the blood-nerve barrier to occur. Evidence suggests that important components of the extracellular matrix around the endothelium are blocked by IVIg, thereby interrupting the migration of T-cells from the blood into the peripheral nerve. In this way, IVIg may interfere with the build up of inflammatory lesions in target organs of the aberrant immune response [2, 19].

**B-cells**

Many auto-immune diseases are caused by B-cell production of auto-antibodies. Several modes of action of have been proposed for how IVIg may counteract this problem:

- IVIg has been shown to down-regulate production of antibodies by B-cells
- IVIg may contain numerous anti-idiotypes – these are naturally occurring auto-antibodies which act to neutralise pathogenic antibodies. The following anti-idiotypic antibodies have been identified in IVIg preparations: anti-Factor VIII, anti-DNA, anti-thyroglobulin, anti-neuroblastoma and anti-laminin.
- Anti-CD5 antibodies found in IVIg preparations block the activity of a specific sub-population of B-cells proven to release naturally occurring auto-antibodies
- IVIg may block receptors on the surface of B-cells that are responsible for stimulating their proliferation [5, 8].

IVIg may also produce its beneficial effects by enhancing catabolism of pathogenic auto-antibodies. This effect is mediated through a specific receptor, the FcRN (neo-natal Fcγ receptor) which plays a crucial role in the catabolism of IgG. Exogenous IgG saturates the FcRN, thus accelerating the catabolism of pathogenic IgG in the circulation [20].

It was demonstrated in a recent study that IVIg may neutralise a crucial factor (B-cell activating factor, BAFF), which is important for the differentiation of B-cells. Found within commercial IVIg preparations are antibodies to BAFF, which interrupt the further differentiation of B-cells, preventing generation of auto-antibodies [12, 13].

Finally, interesting results were seen in a recent study where the authors investigated the serum antibodies that are relevant to the pathogenesis of rheumatoid arthritis (rheumatoid factor, RF). Oral application of IVIg led to reduced serum RF titers i.e. the generation of auto-antibodies was diminished [14].