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Advances in the understanding of the mechanism of action of IVIg

Abstract 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 the immune response; many of which may be relevant to neuromuscular disorders and immune neuropathies.

Key words IVIg · immune · neuropathies · antibodies · mechanism.

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All persons gave their informed consent prior to their inclusion in the study.

Advances in the understanding of the mechanism of action of IVIg

The birth of antibody therapy dates back to the late 19th century when the Nobel Laureate Emil von Behring and his colleague Shibasaburb Kitasato described antibodies to diphtheria as the important component of immunity. IVIg was first used against infections, either as a prophylactic therapy or following exposure to pathogens, and later it became used as a replacement therapy in patients with immunodeficiencies. In 1981, the use of IVIg for the treatment of autoimmune diseases was first described [11].

The field of neurology had been leading the way in investigating the therapeutic uses of IVIg; in fact, trials of IVIg have been conducted in over 20 neurological conditions. Neuromuscular diseases are one of the best studied therapeutic applications of IVIg, and the most extensive trial data are available for Guillain-Barré Syndrome. The most commonly studied disorders are:

- Guillain-Barré Syndrome (GBS)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal Motor Neuropathy (MMN)
- Paraproteinemic (IgM) polyneuropathy
- Myasthenia gravis
- Lambert-Eaton Syndrome.

The IgG molecule, which is the main component of the

IVIg product, can be divided into two important subunits: 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-thyreoglobulin, 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].

The complement system

The complement system, an important component of innate immunity, is also affected in a therapeutically relevant fashion by IVIg. There are several mechanisms by which the complement system can be activated, and IVIg acts to interrupt steps in the complement activation cascade and prevent assembly of the terminal complement complex (which can damage the myelin sheath of nerve cells). For example, components of IVIg bind to C1q, C4b, C3b, while also promoting the degradation of C3b [4].

Experiments in GBS have shown the prevention of complement activation after administration of IVIg. A monoclonal antibody to a specific ganglioside (considered a relevant auto-antigen for GBS) was added to a peripheral nerve culture, and activation of the complement system was detected by presence of the activation product C3b. When IVIg was added, no activation of the complement system was detected and the cytotoxic effect of the anti-ganglioside antibody was diminished [6]. Of interest, recently evidence was advanced for a protective role of IVIg in experimental stroke in an ischemic brain damage model. IVIg was shown to target neuronal complement expression which led to decreased caspase-3 activation and neuronal cell death [3].

Fc receptors

Fc receptors – expressed on a broad range of hematopoietic cells, including macrophages, dendritic cells, microglia and neutrophils – occur in many different subtypes, some of which are activating and others inhibitory. Several studies have shown that IVIg may influence the effect of Fc receptor-mediated activity of immunologically relevant cells. Although some controversy remains, it is generally thought that IVIg acts to block activating receptors, induce inhibitory factors and, as mentioned earlier, block the neonatal Fc receptor involved in the catabolism of IVIg. The net result of these effects is the down-regulation of the damaging activity of macrophages [1, 16–18].

Two key studies of the connective tissue disease dermatomyositis have clearly identified the targets described here and serve to illustrate the multiple effects of IVIg. In 1993, Dalakas *et al.* studied diseased tissue pre and post-IVIg therapy and observed clear differences in ICAM and MHC I expression following IVIg treatment [7]. A subsequent study by the same group also demonstrated that cytokines, adhesion molecules and complement factors were significantly down-regulated by IVIg, providing convincing evidence that IVIg targets these injurious components of the immune response [15].

Conclusion

In conclusion, IVIg has numerous modes of action, all or many of which may be relevant to neuromuscular disorders and immune neuropathies (Fig. 1).

IVIg has been shown to inactivate, silence or drive auto-reactive T-cells into apoptosis, while acting to restore the balance of anti-inflammatory and pro-inflammatory cytokines. In addition, IVIg is thought to interfere with the passage of auto-immune cells across the blood-nerve barrier. The effects of exogenous antibodies on B-cells are well studied and IVIg is thought to down-regulate the production of antibodies by B-cells, interfere with the proliferation of B-cells via cell surface receptors and block the activity of certain B-cell subtypes. IVIg may also contain numerous anti-idiotypes

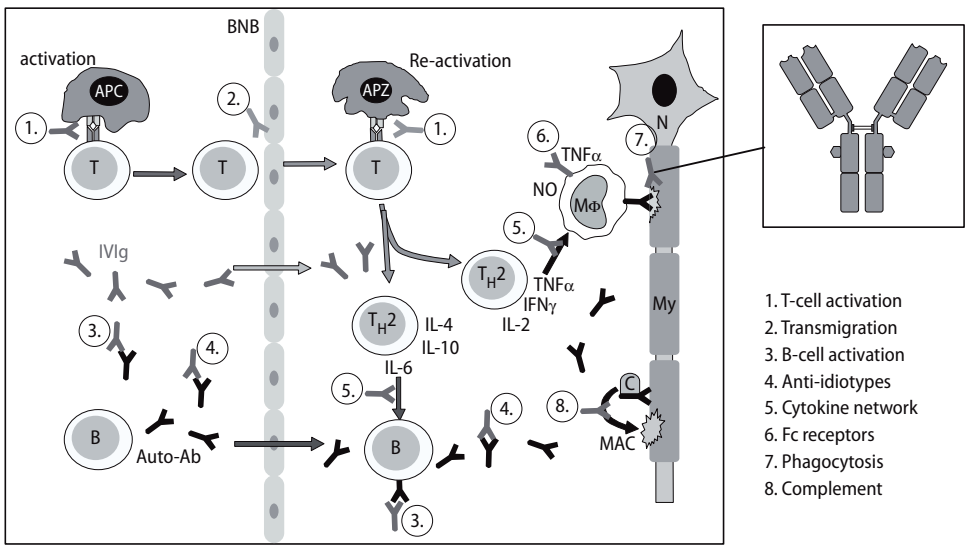

Fig. 1 Modes of action of IVIg in immune neuropathies

to neutralise pathogenic antibodies. Finally, it has been shown that IVIg therapy interrupts several steps in the complement activation cascade, and influences the effect of Fc receptor-mediated activity.

Conflict of interest H.-P. Hartung received fees for consulting and speaking at scientific symposia from Bayer Vital, Talecris, Octapharma, and Baxter, all with approval by the University hospital CEO and President of Heinrich-Heine-University. He served on the stering committee of the ICE trial in CIDP sponsored by Bayer Vital/ Talecris.

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