

## THERAPEUTIC APPLICATION OF INTRAVENOUS HUMAN NATURAL IMMUNOGLOBULIN PREPARATION

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### 1. ABSTRACT

Human natural immunoglobulin (HunIg) preparation for intravenous use has been used in various diseases. The most typical application of this preparation is agammaglobulinemia. Currently, however, this preparation is being used in the therapy of many other disorders. These include thrombocytopenia, Kawasaki disease, systemic vasculitis, several other disorders of autoimmune origin and systemic inflammation such as sepsis. In some diseases, the clinical improvement following use of HunIg has been dramatic, while in others its effect is not striking. Due to rarity of the side effects, the range of application of HunIg has been recently broadened. Such side effects include transmission of several diseases such as hepatitis and retroviral infections. Before it is recommended for use, however, and primarily due to expense, the efficacy of this drug should be carefully evaluated. The mechanism of action of HunIg is not fully understood. However, it has been suggested that its action may involve blockade of Fc-receptor, an anti-cytokine effect, or inhibition of

complement activation. In this review, the mechanism of action of HunIg and its application in human diseases are discussed.

### 2. INTRODUCTION

Human intravenous natural immunoglobulin preparation has been used for supplementation of immunoglobulin in the blood (1, 2, 3). This preparation has also been used for modulation of immune reactions in a variety of disorders (3, 4). This preparation contains natural immunoglobulins mostly IgG which includes antibodies against various entities such as bacteria, viruses, proteins, glycosides and numerous self antigens (5). Many theories exist regarding the mechanism of action of these proteins (5, 7), however, their role is far from clear. These proteins may play a role in defense against infecting microorganisms and are constituents of the immunoglobulin network (6).

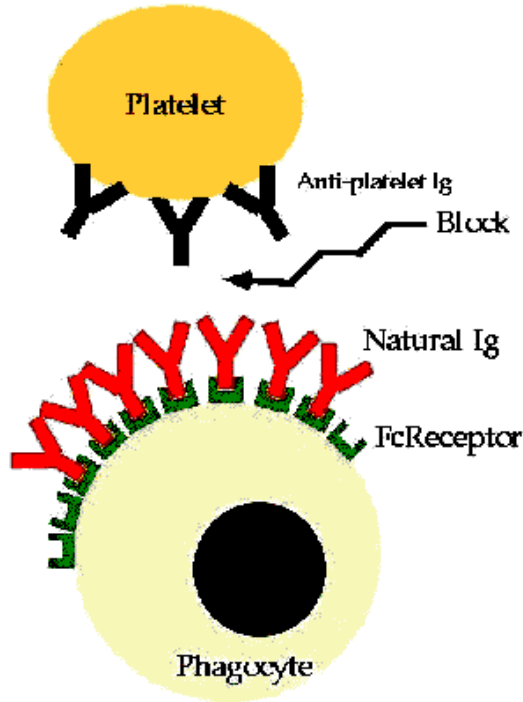
Deficiency of natural immunoglobulin in human blood is associated with undesirable effects. Patients with agammaglobulinemia such as Severe Combined Immunodeficiency (SCID) exhibit various clinical features, some of which are attributable to the deficiency of immunoglobulin in the blood (8). These patients are prone to opportunistic infections by many microorganisms which are not virulent in healthy individuals (8, 9). Similar to the primary form of the disorder, patients with secondary hypogammaglobuli-

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Received 5/15/96, Accepted: 6/12/96.

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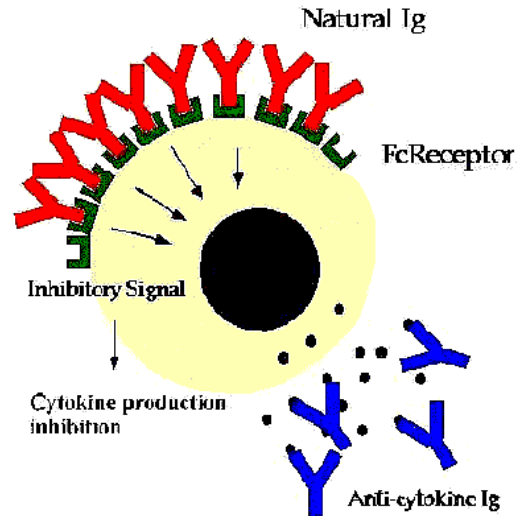
**Figure 1.** Blocking the Fc-receptors (FcR) on monocytes/macrophages or neutrophils by human natural immunoglobulin preparation. Natural immunoglobulin non-specifically binds to the FcR and blocks the binding of immune complexes such as platelet-anti-platelet to the FcR.

nemia also exhibit clinical features and are prone to infections (2, 8).

The most typical application of the human natural immunoglobulin preparation is agammaglobulinemia. In addition, this preparation, is now being widely used for many other disorders. In this review, the mechanisms of action of this preparation and its applications to human diseases will be presented.

### 3. MECHANISMS OF ACTION

The role that natural immunoglobulin plays in the blood is still unclear, and its composition has not been completely elucidated. However, it is well known that presence of natural immunoglobulin in the blood is required for the maintenance of human life. The most plausible mechanisms of its action include blockade of Fc-receptors on monocytes/macrophages and neutrophils (Figure 1)(10, 11, 12), and suppression of cytokine production and neutralization of cytokines (Figure 2)(13, 14, 15). Several other mechanisms of action for these proteins have been proposed that include inhibition of complement activation (16), anti-idiotypic suppression (17), downregulation of B- and T-cell functions (10), and neutralization of superantigens (18). In view of these



**Figure 2.** Suppression of cytokine production and neutralization of cytokines by human natural immunoglobulin preparation. Natural immunoglobulin generates an intracellular inhibitory signal to the cytokine production system through binding FcR, and anti-cytokine autoantibodies in the natural immunoglobulin preparation bind to cytokines directly.

proposed effects, HunIg has been used in hypogammaglobulinemia, thrombocytopenia, auto-immune diseases, allergic disorders and systemic inflammation. HunIg has also been used in other disorders such as seizures, neuropathy, and acute renal failure. However, the mechanism of action of HunIg in these disorders remains completely obscure. Considering the cost/benefit ratio, some of these diseases are "good" indications for the natural immunoglobulin treatment whereas other diseases are not.

## 4. APPLICATION TO DISEASES

### 4.1. Hypogammaglobulinemia

The most reasonable application of HunIg is primary as well as secondary agammaglobulinemia (2, 19-21). Positive results have been observed in X-linked agammaglobulinemia with more than 400 mg/kg every three weeks (9). HunIg has been used in multiple myeloma, chronic lymphocytic leukemia and life threatening infections in patients with multiple myeloma (20-21). In these diseases, 150 to 300 mg/kg every three weeks for periods longer than 3 years have been used (19). Use of HunIg along with antibiotics has been associated with protection against recurrent bacterial infections in patients who suffer from IgG subclass deficiency such as IgG3 (2, 22). In addition, dramatic clinical improvements in symptoms such as those associated with hepatitis have been reported in these patients (23-24).

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### 4.2. Idiopathic Thrombocytopenic Purpura (ITP)

HunIg has been successfully used in ITP with dramatic clinical effects (4, 25). The elevation of platelet number has been repeatedly observed (25). Applications for its use include episodes of severe bleeding, prophylaxis of intraoperative bleeding during major surgeries and delivery (10). The increase in platelet number may be the result of the blocking of the Fc-receptors of phagocytic cells such as monocytes/macrophages and neutrophils (11). This hypothesis is supported by the finding that the F(ab')<sub>2</sub> fraction of natural immunoglobulin preparation did not exert this effect at all whereas the Fc preparation did reveal this effect (10, 11, 12). The finding that the non-specific platelet activation in ITP patients was inhibited by anti-FcR<sub>II</sub> antibody also supports this hypothesis (26). Blocking the Fc-receptors impairs undesirable phagocytosis by Fc-receptor-expressing cells. It is quite likely that a relatively high concentration of natural immunoglobulin is necessary for the large increase in platelet number, since the blocking of Fc-receptors is generated by nonspecific binding to the Fc-receptor. In the related thrombocytopenias such as adult type ITP, heparin-associated thrombocytopenia (26), and Onyalaï, a special form of immune thrombocytopenia in Africa (27), the immunoglobulin preparation also shows this effect. For septic thrombocytopenia, this preparation caused an elevation of platelet number and improvement of clinical symptoms via the anti-systemic inflammatory effect of the natural immunoglobulin (28).

### 4.3. Autoimmune Diseases

Autoimmune diseases is one of the most typical conditions for the use of human natural immunoglobulin preparation (29, 30, 31). The clinical improvement by HunIg may be related to blocking the Fc-receptors with the anti-cytokine activity of this preparation also playing a role (13). ITP is an autoimmune disease where anti-platelet autoantibodies play a critical role in platelet damage. However, the clinical effect of the immunoglobulin preparation in this condition is thought to depend exclusively on the Fc-blocking by the HunIg. There are several other autoimmune diseases where this preparation has been used. Among them, Kawasaki disease is a classic indication for the use of HunIg (32, 33). Kawasaki disease is believed to be a viral infection where autoimmune processes contribute to its symptomatology. HunIg should be effective in the systemic inflammation that is seen in Kawasaki disease. Prevention of coronary lesions has been observed when this preparation has been used during the acute phase of the disease (34). Although several modes of usage exist for the treatment of this disease, administration of a single large dose (1 to 2 g/kg) of HunIg along with antipyretics is typically recommended (34, 32). This method of administration of the HunIg is also most cost effective.

Use of HunIg has also been used in Guillain-Barre syndrome (35, 36, 37). The pathophysiology of this

disease is an acute demyelinating polyneuropathy caused by an autoimmune process. Along with the use of steroid hormone, administration of 400 mg/kg/day of natural immunoglobulin preparation for several days has been recommended (35). Plasma exchange therapy is another mode of therapy with HunIg (36).

Systemic vasculitis of autoimmune origin is another indication for the clinical use of HunIg preparation (38, 39). With the use of HunIg, patients with vasculitis with positive anti-neutrophil cytoplasmic antibody show improvement in their clinical symptoms (40).

HunIg has also been used in other autoimmune diseases such as myositis and myopathies (41). Granulomatous disorders such as Wegener's granulomatosis, lupus erythematosus-related symptoms and juvenile arthritis, autoimmune-mediated chronic active hepatitis, chronic glomerulonephritis with autoimmune etiology, Graves' ophthalmopathy and pretibial myxedema, multiple sclerosis and neurologic autoimmune diseases have also been targets for the treatment with HunIg (42-44). There are many reports of other autoimmune diseases treated by this preparation; however, the clinical effectiveness of HunIg against these disorders has not been clearly established.

### 4.4. Asthma

Allergic disorders including asthma is one indication for the use of human immunoglobulin preparation (45, 46). The mechanism of action of HunIg in these disorders is most likely related to both the Fc-blocking and anti-cytokine attributes of HunIg. Improvements of symptoms and reduction in the dosage of steroid hormones have been reported during and after 4 months of intravenous immunoglobulin therapy (47). However, the effect of HunIg appears to be variable from patient to patient, and its repeated use requires careful monitoring of the symptoms of the patients.

### 4.5. Systemic Inflammation Associated Disorders

Systemic inflammation in neonates, especially those in the high-risk group is an indication for the use of HunIg (48, 49, 50). When used in the early phase of bacterial infections in conjunction with antibiotics, natural immunoglobulin preparation reduced the mortality rate of neonates (48). Along with the use neutrophil transfusion, HunIg has also been used as a supplemental therapy (22). The possible mechanisms of action of HunIg are the anti-cytokine activity of HunIg along with inactivation of complements. Improvements of immunologic and hematologic parameters were reported when HunIg was included in the treatment of premature infants with group B streptococcal infections (49, 51). In such patients, administration of 500 to 750 mg/kg is generally recommended (49, 50). Children with acute intestinal infections, neonatal neutropenia, neonatal bacterial sepsis or refractory infections are distinct clinical conditions for the use of HunIg (53, 54, 55). 200

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to 500 mg/kg of HunIg may be most effective when used for prevention of infection in preterm infants who are at high risk for developing infection (52). The prophylactic use of HunIg in the late phase of infection in low-birth weight neonates has also been strongly recommended (48). However, no clear benefits were reported when HunIg was used in these conditions (50). Randomized studies should be carefully carried out in the use of HunIg in these disorders, and clear guidelines for of this preparation should be established (56).

Although HunIg has been extensively used in shock, sepsis and multiple organ failures, some have failed to observe to demonstrate a significant improvements upon its use in these conditions (1, 28, 57, 57, 58). Administration of HunIg has also been advocated for severe infections in the field of surgery (59) as well as in trauma and burned patients (60, 61).

### 4.6. Spasms

HunIg has been used in spastic disorders (62, 63, 64) such as West (62, 64), and Lennox-Gestaut (62) syndromes. However, particularly in these syndromes, the clinical improvements have been disappointing (62, 64). The use of HunIg has been suggested as an alternative treatment strategy when other treatments such as ACTH have failed (64). HunIg has also been used in the treatment of epilepsy that has an immunogenetic basis (64).

### 4.7. Neuropathy

Patients with multifocal motor neuropathy and polyneuropathy associated with monoclonal gammopathy (65, 66) as well as patients with chronic demyelinating neuropathy (67) were reported to exhibit clinical improvement by the use of HunIg.

### 4.8. Renal Failure

The therapeutic effect of HunIg in acute renal failure has been controversial (68, 69). While a significant reduction in mortality rate has been observed when HunIg has been administered to these patients (68), no beneficial effect was reported for major complications of the disorder (68). The therapeutic effectiveness of HunIg has been shown in acute renal failure associated with rhesus hemolysis (70). Given that this disorder is immune-complex mediated, it is not hard to realize why HunIg has been found useful in this condition.

### 4.9. Other Diseases

HunIg has been used for the treatment of many other diseases. These conditions include chronic lymphocytic leukemia, multiple myeloma, lymphoma, chronic fatigue syndrome, recurrent acute otitis media, chronic relapsing colitis, (20, 21, 56, 71), and AIDS (56, 72, 73). The effectiveness of combination of HunIg-zidovuzine has been tested in the treatment of AIDS (72). However, the effect by this combination treatment was not prominent.

## 5. SPECIAL PREPARATIONS AND TRIALS

Special preparations have been developed from the HunIg for specific treatment protocols. Anti-cytomegalovirus immunoglobulin is quite useful prophylactically in patients who receive an organ transplant (56, 75). Cytomegalovirus infections are common in these patients, particularly, when they receive immunosuppressive agents such as FK506 and cyclosporin A. Recently, human monoclonal antibody to cytomegalovirus was developed and has been tried clinically for prophylaxis (74). In group B streptococcal infections in neonates, hyperimmune globulin is more beneficial than the HunIg (50, 51). Anti-LPS preparation has been used for reduction of risk of septic shock (76). However, since many types of LPS exist, effective neutralization of LPS is not a simple task. Special antibodies have recently been prepared, and some are being used in various clinical trials. These include monoclonal antibodies against TNF, interleukin-1, interleukin-8, and CD16 (77, 78, 79, 80). The utility of monoclonal antibody against CD20 for treatment of recurrent B-cell lymphoma has been tested (81). A bispecific antibody reactive to both tumor and immune cells has been developed and used in the treatment of malignant tumors (82). Recombinant immunoglobulins are being developed for treatment that their hyper-variable regions have been genetically altered (82). Along with Zidovudine, anti-CD4 monoclonal antibody is being used in the treatment of AIDS patients (83).

## 6. IATROGENIC INFECTIONS BY IMMUNOGLOBULIN PREPARATION

In patients with hemophilia, the use of HunIg has been associated with iatrogenic infections such as infection by retroviruses. The most effective way for prevention of transmission of infectious microorganisms, by plasma preparations including natural immunoglobulin is heat-treatment of these preparations (84).

## 7. CONCLUSION

Natural human immunoglobulin for intravenous administration has been proven to be effective for treatment of some disorders. Although in view of its limited side effects, this preparation is being widely used, the cost and benefit of its use should be carefully examined and specific guidelines for its use should be established.

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