

Antibody-directed therapy: Past, present, and future

Erwin W. Gelfand, MD *Denver, Colo*

Antibody-based therapy, which is the administration of polyclonal, hyperimmune, or monoclonal antibodies, has emerged as an important therapeutic approach in a wide variety of diseases. Polyclonal intravenous immunoglobulin became available in the early 1980s and supplanted intramuscular IgG in the treatment of antibody-deficiency diseases. During the last 2 decades, intravenous immunoglobulin has shown potent immunomodulatory and anti-inflammatory effects in many diseases. Whether these effects are mediated through specific antibody or Fc-receptor interactions is unclear. This review examines some of the current and future prospects for antibody-based therapy. (*J Allergy Clin Immunol* 2001;108:S111-6.)

Key words: Anti-inflammatory, autoimmunity, monoclonal antibody, polyclonal antibody, hyperimmune Igs, immunomodulation

Administration of IgG prepared from plasma pooled from hundreds to thousands of donors has been used to treat antibody-deficiency disorders for more than 4 decades. In the last several decades, preparations suitable for intravenous use provided opportunities to easily administer larger quantities of passive antibody. As a result, pooled polyclonal intravenous IgG (IVIG) (containing very small amounts of IgA and IgM) has become standard therapy for patients receiving replacement therapy for antibody deficiency. Polyclonal IVIG was first demonstrated to be effective in autoimmune disorders about 20 years ago in the treatment of idiopathic thrombocytopenia (ITP), which presented in patients with immunodeficiency.¹ Since that time, IVIG has been used to treat a wide variety of disorders, many of them seemingly unrelated. The presumption has been that such an extensive or broad range of activities in these diseases reflects the functions of circulating immunoglobulins in maintaining a balance in immune function.² However, whether specific antibodies play a major role in the benefits seen is unclear. Nevertheless, antibody therapy, specific or polyclonal, has emerged as an effective treatment in many conditions. Here, the wide usage of antibody therapy is reviewed.

USE OF ANTIBODY-BASED THERAPY

In addition to pooled polyclonal antibodies (IVIG), preparations of specific antibodies (hyperimmune IgG)

Abbreviations used

FcεRI: High-affinity IgE receptor
ITP: Idiopathic thrombocytopenia purpura
IVIG: Intravenous immunoglobulin
RSV: Respiratory syncytial virus

or monoclonal antibodies (mAbs) have been used in different clinical settings. Antibody-based therapy has 3 major uses: detection of disease, specific treatment, and replacement therapy. The indications for antibody-based therapy are quite diverse, as shown in Table I.

Antibodies for detection of disease

Antibodies, generally monoclonal, have been used for the detection of cells, particularly malignant cells, and to identify metastatic disease. For example, in prostate cancer, no standard noninvasive diagnostic test reliably differentiates patients with organ-confined prostate cancer from those with lymph node metastases. An mAb to prostate cancer cells (capromab) radiolabeled with indium-111 (111In-capromab pentetide) was investigated for its ability to identify sites of metastatic disease in patients at moderate to high risk of nodal involvement.³ The results indicated that immunoscintigraphy with the radiolabeled mAb outperformed standard diagnostic imaging techniques for detection of prostate cancer-lymph node metastases. It also provided additional prognostic information that complemented prostate specific antigen levels and clinical staging.

A second approach in the area of detection has been the use of mAb as a prognostic indicator. For example, MIB-1, mAb to the Ki-67 antigen, was used in patients with endometrial cancer to determine its effectiveness as a prognostic indicator of recurrent disease or survival. In a series of 147 patients with endometrial cancer, the extent of mAb staining was shown to be a good prognostic indicator of 5-year survival.⁴

Monoclonal antibody-based therapeutics

Monoclonal antibody-based therapeutics are beginning to achieve the predictions made more than 20 years ago when the core technology was first established. This area, known as serotherapy, has advanced considerably in generating specific mAbs or constructs that react with targeted antigens. The excitement in serotherapy is based on 3 factors: the potential for optimal targeting of a multitude of antigens, the rapid increase of available targets, and the successful application of molecular engineering and affinity-maturation techniques to mAb optimization.

The general principle in creating most mAbs is to use

From the Division of Cell Biology, Department of Pediatrics, National Jewish Medical and Research Center, Denver, Colo.

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Reprint requests: Erwin W. Gelfand, MD, National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206.

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TABLE I. Antibody-directed therapy

Elimination of an organism (eg, CMV hyperimmune)
Prevention of infection (eg, RSV hyperimmune, RSV mAb)
Neutralization of a toxin (eg, staph toxin [IVIG])
Inhibition of a function (eg, preventing clotting [mAb anti-gp IIb/IIIa])
Removal of a cell (eg, anti-CD20 [mAb anti-CD20])
Targeting a therapy (eg, radionucleotides [mAb to cell-surface receptors])

CMV, Cytomegalovirus

TABLE II. Targets

Cytokines and their receptors
Surface receptors
Graft vs host disease
Malignancy
Immune suppression
Inflammation
Platelet aggregation

TABLE III. Antibodies targeted for human asthma

Polyclonal (eg, IVIG)
Anti-cytokine (eg, anti-IL-4, anti-IL-5, anti-IL-4 receptor, anti-IL-5 receptor, anti-TNF- α , anti-TNF- α receptor, anti-IL-6, anti-IL-9, anti-IL-13 receptor)
Anti-IgE (eg, anti-IgE, anti-CD154)
Anti-adhesion (eg, anti-ICAM-1, anti-VLA-4, anti-selectin)
Anti-T cell (eg, anti-CD3)
Anti-CD23
Anti-chemokines (eg, anti-CCR3)

TABLE IV. Hyperimmune IgS

Tetanus
Rabies
Hepatitis B
Rh
CMV
RSV
Varicella/zoster

CMV, Cytomegalovirus.

a genetically engineered derivative of a parental murine mAb that can be used in humans. In this process, complementarity-determining regions are grafted within a human IgG1 mAb, and the heavy chain region is altered by site-directed mutagenesis to alter Fc-receptor-binding activity and complement activation. Many mAbs are now in clinical use. The targets include cytokines and their receptors, surface molecules, and tumor antigens (Table II). These mAbs have been used as anti-inflammatory reagents, for immunosuppression, in tumor debulking, and in graft versus host disease, as well as for interference with platelet function. In some cases, the mAbs have been labeled with radiochemicals to deliver a significant but targeted radiation dose.^{5,6}

Some of the antibodies are in advanced study or have received Federal Drug Administration approval. Anti-TNF- α mAb has shown important benefits in the treatment of rheumatoid arthritis and inflammatory bowel disease.⁷⁻⁹ There are a number of antibody-based strategies to treat human malignancy.¹⁰ Anti-CD20 mAb has shown significant clinical activity in patients with bulky, relapsed, or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma.¹¹ This mAb may also be effective in Epstein-Barr virus-associated lymphoproliferative disorder.¹² Since normal B cells also express CD20, use of this mAb may result in normal B-cell depletion and secondary hypogammaglobulinemia for periods, necessitating replacement therapy.

A number of antibody strategies that target human asthma are at various stages of development (Table III). Polyclonal IVIG has shown efficacy in severe steroid-dependent asthma.¹³⁻¹⁶ Other strategies that use mAbs target cytokines and their receptors, adhesion molecules, chemokines and their receptors, T cells, or other receptors.

Since IgE is believed to be a central-effector antibody in asthmatic patients' response to allergen, targeting IgE may be beneficial. An mAb to IgE was developed for use in humans that recognizes the specific Fc ϵ 3 portion of circulating IgE that binds to the high-affinity IgE receptor, Fc ϵ RI. Clinical trials with subcutaneous or intravenous administration of this antibody have shown rapid and significant decreases in circulating IgE, attenuation of the early and late-phase asthmatic responses, and improvement in asthmatic symptoms.^{17,18}

Hyperimmune antibody preparations

Hyperimmune antibody preparations are obtained from the plasma of donors with particularly elevated titers of specific IgG antibody. These titers may be elevated as a consequence of natural infection or exposure or after purposeful vaccination or immunization. A number of preparations are available (Table IV). Most are available as intramuscular preparations, although some may be administered intravenously. There has been limited experience with mAbs to infectious agents. One exception has been the prophylaxis of respiratory syncytial virus (RSV) infection. Both RSV IgG and anti-RSV mAb appear to significantly affect the incidence of RSV-related hospitalizations, severity of illness, and the cost of RSV-related care of infants at risk for significant RSV disease.¹⁹⁻²¹

USE OF POLYCLONAL Ig IN THE TREATMENT OF AUTOIMMUNE, ALLERGIC, AND INFLAMMATORY DISORDERS

A role for polyclonal antibody (IVIG) in the treatment of a number of diseases emerged from the experience with replacement therapy (intramuscular and IVIG) in patients with antibody deficiency (Table V). After intramuscular IgG or IVIG, resolution of ITP, neutropenia, alopecia, skin lesions, arthritis, reactive airway disease, and diarrhea have been observed. These effects often rapidly followed Ig replacement, and the benefits

TABLE V. Conditions in which antibody replacement has shown benefit

Skin lesions
Infiltrative lesions
Alopecia totalis
Eczema-like lesions
Arthritis
Neutropenia, thrombocytopenia
Reactive airway disease
Diarrhea
Linear growth

TABLE VI. Diseases that respond to IVIG therapy

	Reference
Diseases responding in controlled trials	
Antibody-deficiency diseases*	
Idiopathic thrombocytopenia purpura*	
Pediatric HIV disease*	35
Kawasaki syndrome*	36
Dermatomyositis	37
Guillain-Barré syndrome	38-40
Chronic inflammatory demyelinating polyneuropathy	41, 42
Multifocal motor neuropathy	43, 44
Diseases appearing to respond in clinical trials, but which need further verification	
Steroid-dependent asthma	13-16
ANCA-positive vasculitis	45, 46
Multiple sclerosis	47-49
Myasthenia gravis	50
Lambert-Eaton syndrome	51
Toxic shock syndrome	52-55

ANCA, Antineutrophil cytoplasm antibody.

*FDA approved.

appeared to wane as trough levels of IgG were re-established. The benefits reappeared after the next injection. Treatment with IVIG has been initiated in many diseases, and demonstrable benefit in controlled trials has been established for some diseases (Table VI).

The mechanism of action of IVIG in these diseases remains elusive. It is unclear whether a similar or single mechanism of action is responsible or whether different mechanisms play a role. A number of mechanisms have been proposed, with some supportive experimental evidence in each case (Table VII). One of the best demonstrated effects of IVIG is anti-inflammatory activity, perhaps best exemplified in the treatment of Kawasaki syndrome (Table VIII). The anti-inflammatory action of IVIG is potentially multifold. Importantly, IVIG contains antibodies to a number of cytokines, receptors, and membrane molecules potentially important in immune regulation (Table IX), and IVIG administration triggers changes in cytokine levels (Table X).²²⁻²⁹ Analysis of the immunoregulatory and anti-inflammatory effects of IVIG reveals the significant therapeutic potential of this treatment approach. However, until the mechanism(s) of action is more clearly identified in responding disease states, our approach remains inefficient and costly, with potential overuse of an important, but limited, resource.

TABLE VII. Potential mechanisms of action of IVIG

Fc-receptor blockade
Idiotypic-anti-idiotypic interactions
Downregulation of autoantibody formation
Neutralization of superantigens or toxins
Immunologic changes in T-cell subsets
Administration of soluble products (eg, CD4, CD8, HLA classes I and II)
Prevention of formation of complement-membrane-attack complex
Decrease in cytokine production

HLA, Histocompatibility locus antigen.

TABLE VIII. Anti-inflammatory effects of IVIG in Kawasaki syndrome

Decreased temperature
Decreased white blood cell count
Decreased serum levels of acute phase reactants
α -1-antitrypsin
Fibrinogen
C-reactive protein
Decreased serum soluble IL-2 receptors

TABLE IX. Proteins for which antibodies are detected in IVIG

	Reference
Immunoglobulin idiotypes	25
CD4	27
CD5	25
T-cell receptor: variable region, constant region β chain	22
MHC class I	26
MHC class II	25
Fas (CD95)	28, 29
CD40	25
Heat-shock proteins	25
IL-1 α	24
IFN- α	24
TNF- α	24
IL-6	24
GM-CSF	23
IL-4 receptor	25

What also remains unclear is whether the benefits reflect activities of specific antibodies or are mediated by other means (eg, Fc-receptor interactions).

ANTIBODY REPLACEMENT THERAPY IN PATIENTS WITH ANTIBODY DEFICIENCY

Antibody replacement has been the primary prophylactic therapy in patients with documented abnormalities in antibody response to specific challenge. Protective effects have been shown to be dose-dependent; when pulmonary function and frequency of infection were monitored, trough levels of IgG greater than 500 mg/dL were associated with better outcomes.^{30,31} An upper limit for protection has not been established.

It is for this indication and in these patients that the question may be asked: Is replacement therapy simply the provision of missing antibodies or are other mecha-

TABLE X. Serum cytokine and cytokine-receptor levels that increase after IVIG infusion

	Reference
Soluble-TNF- α receptor	56
TNF- α	56
IL-6	56
IL-4 receptor	56
IL-10	56
IL-1 receptor antagonist	56

TABLE XII. Pneumococcal antibody levels in IVIG

Serotype											
(antibody nitrogen administered/mL blood volume)											
1	3	4	6B	7F	8	9N	12F	14	18C	19F	23F
1144	212	492	1188	1438	72	652	714	453	554	898	927

Protective levels: > 200 antibody nitrogen/mL blood

nisms of protection operative? Also, how important are specific antibodies and antibody diversity? One assumption has been that pooling plasma from thousands of donors provides the broad spectrum of antibody diversity required for protection in patients with antibody deficiency. On the other hand, single-donor plasma appears to provide similar protection when administered at 10 to 20 mL/kg of body weight.

Beyond passive antibody protection, antibody administration may work via other mechanisms that are in many ways similar to the activities in other immune and inflammatory conditions (Table XI). Nonspecific antibody-mediated protection could include the anti-inflammatory properties of IVIG, Fc-receptor immunomodulation, or properties that have not been defined. Several pieces of information support these alternatives. First, examination of antibody titers to some common pathogenic organisms reveals that they are relatively low. Table XII illustrates the mean anti-pneumococcal antibody titers in 3 separate batches of IVIG for several of the common serotypes, calculated in terms of antibody nitrogen per milliliter of blood volume (70-kg adult). This does not account for any equilibration between intravascular and extravascular spaces after administration or natural catabolism. For most of the serotypes, only nonprotective antibody levels (< 200 antibody nitrogen/mL) would be achieved.

The second piece of evidence is in the context of the unique susceptibility of patients with antibody deficiency to infection with mycoplasma and, in particular, *Ureaplasma urealyticum*. We and others have documented mycoplasma infection in both acute and chronic infections in isolates from the lung, skin, lymph nodes, urine, and joints.^{32,33} These mycoplasmas necessitate specific antimicrobial therapy (eg, doxycycline) that is different from conventional antibiotics used for treatment of *Streptococcus pneumoniae* and *Haemophilus influenzae*. As a result, chronic infection in patients with antibody deficiency may represent a major clinical issue. Pertinent to this discussion is that the number of mycoplasma isolates is significantly higher when trough IgG levels are less

TABLE XI. Potential mechanisms of action of replacement therapy in patients with antibody deficiency

Passive antibody protection
Anti-inflammatory properties
Toxin neutralization
Fc γ -receptor-mediated immunomodulation
Undefined properties providing benefit

than 500 mg/dL than when levels are greater than 500 mg/dL.³⁴ The reasons for this relationship are unclear since antibodies to a number of mycoplasmas and to several serotypes of *U. urealyticum* are not detectable in IVIG. Thus, the protection provided by IVIG may not simply reside in the provision of passive antibody.

SUMMARY

In its broadest context, antibody-based therapy encompassing polyclonal, hyperimmune, and mAb preparations is increasingly being used for diagnosis, detection, and treatment of many different diseases. Molecular engineering has evolved to provide an array of important, therapeutic agents for immunosuppression, reduction of inflammation, and treatment of many malignancies. Future prospects for this form of therapy seem endless. Hyperimmune IgGs afford protection against a number of infectious agents and their toxins or diseases, such as Rh disease. As demonstrated with RSV, mAbs may supplant hyperimmune IgGs, despite the much narrower epitope specificity of an mAb. Development of mAbs against other infectious organisms may also provide protection beyond that achieved with polyclonal IgG.

Finally, polyclonal IgG used at doses of 2 g/kg of body weight has offered an alternative treatment to plasmapheresis or the use of high-dose steroids or cytotoxic drugs in a number of diseases, including Guillain-Barré syndrome, chronic demyelinating inflammatory polyneuropathy, ITP, severe asthma, and dermatomyositis. In diseases such as Kawasaki syndrome, polyclonal IgG represents the only effective therapy available. Although apparently at opposite ends of the disease spectrum, both antibody-deficiency disorders and autoimmune and inflammatory diseases appear to benefit from similar polyclonal IgG therapy. In both cases, this may be a result of normalization of immunoregulatory pathways. As information accumulates and mechanisms unfold, we may be able to more rationally and effectively apply specific antibody or polyclonal-antibody therapy in these different diseases.

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