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SHORT ANALYTICAL REVIEW

Passive Antibody Therapies: Progress and Continuing Challenges

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In recent years antibody-based therapies have returned as first-line therapy for a variety of diverse conditions that include viral infections, inflammatory disorders, and certain malignancies. Renewed interest in antibody-based therapies is a consequence of major advances in the technology of antibody production and the need for new therapeutic agents. Dozens of antibody preparations are in clinical use. Several monoclonal antibodies are now licensed for clinical use and many are in advanced clinical development. Antibody-based therapies have both significant advantages and disadvantages relative to conventional chemotherapy. Advantages include versatility, specificity, and biological functions not replicated by available chemotherapeutic drugs. Disadvantages include high cost and small markets that hinder commercial development. The available experience suggests that antibody-based therapies can be successfully developed for use in clinical situations where no effective therapy is available. Continued success in the development of antibody-based therapies will require extensive clinical research to learn how to use these compounds optimally and basic immunological research to define the basic mechanisms of antibody action.

Key Words: **monoclonal antibody; immunotherapy; serum therapy.**

INTRODUCTION

Passive antibody therapies were first used in the 1890s following the discovery that administration of immune sera could be used to prevent or treat certain infections in experimental animals. The heyday of passive antibody therapy was in the late 1920s and early 1930s when a variety of sera were available for the treatment of pneumococcal pneumonia, meningococcal meningitis, diphtheria, scarlet fever, measles, etc. (reviewed in (1, 2)). Passive antibody therapy was called "serum therapy" because most antibody preparations were derived from rabbit and horse immune serum (1). Excepting certain viral illnesses like measles, animal sera were routinely used because obtaining sufficient human convalescent sera for therapeutic purposes was impractical. The efficacy of serum varied for the type of infection. Highly effective sera were available for the treatment of pneumococcal pneumonia (1) but the efficacy of serum therapy for tuberculosis was variable (3). Although serum therapy was clinically effective, the administration of heterologous sera was associated with significant toxicity including a high risk of immediate and delayed allergic reactions (1, 2). Other problems that plagued serum therapy were lot to lot variation, efficacy only during early infection, a need for intravenous (iv) administration, uncertain dosing, and high expense. The introduction of antimicrobial chemotherapy into clinical use in the form of sulfomamide in 1935 followed by penicillin in 1942 led to the rapid abandonment of most types of serum therapies against bacterial infections.

The arrival of antibiotics did not cause the complete demise of serum therapy because certain antibody preparations were useful for conditions where no drugs were available. Antibody preparations continued to be used against toxin-mediated diseases such as tetanus, botulism, and diphtheria, albeit in decreasing frequency as these infections were controlled by better sanitation and widespread vaccination. Antitoxins remained first-line therapy for the treatment of venomous bites (4). Given the paucity of effective antiviral drugs, antibody-based therapies were used against several viral pathogens for postexposure prophylaxis including rabies and hepatitis (Table 1). A Fab preparation with high specificity for digitoxin was developed and used for the treatment of digitalis overdoses (5). However, in the second half of the 20th century, antibody-based therapies were largely marginalized relative to their predominant position earlier in the century.

From 1940 to 1980 significant improvements were made to the technology for antibody generation and purification. In the 1940s Cohn developed a cold-ethanol purification method to separate immunoglobulins from other serum proteins (6). However, such prepara-

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TABLE 1

Diverse Use of Antibody-Based Therapies (Not a Complete List)

Activity	Condition or target	Formulation	Development (trade name)	Ref.
Antitoxin	Diphtheria	Equine polyclonal	In use	(57)
	Tetanus	Human polyclonal	In use (Baytet)	(58)
	C. difficile colitis	Bovine polyclonal	Clinical trials	(25,59)
	Botulism	Equine polyclonal and $F(ab')_2$	In use	(22,60)
	Toxic shock syndrome	Human polyclonal	Case reports	(61)
Antiviral	Hepatitis B	Human polyclonal	In use (Bayhep, H-BIG)	(40)
	Cytomegalovirus	Human polyclonal	In use (Cytogam)	(57)
	Cytomegalovirus	Human IgG mAb	Clinical trials	(62)
	Varicella zoster virus	Human polyclonal	In use	(57)
	Respiratory syncitial virus	Human polyclonal and humanized IgG	In use (Respigam)	(31)
	HIV	Several mAbs	Clinical trials	(63,64)
	Rabies	Human and horse polyclonal	In use (Bayrab)	(57)
	Parvovirus B6	IVIG	In use	(28)
	Llasa fever	Human polyclonal	Case reports	(65)
Immune suppression	Anti-TNFα	Mouse–human chimeric, IgG1	In use (Infliximab, Remicade)	(34)
	Anti-CD3	Murine IgG2a	In use (Orthoclone OKT3)	(19)
	Anti-IL2 receptor	Humanized IgG1	In use (Daclizumab, Zenapax, Basiliximab, Simulet)	(32,66)
Drug neutralization	Digoxin toxicity	Sheep Fab fragments	In use (Digibind)	(5)
Antibacterial	Pneumococcus	Horse, rabbit	Discontinued 1940s	(1)
	Meningococcus	Horse	Discontinued 1940s	(1)
	Group A streptococcus	Horse	Discontinued 1940s	(2)
Antiparasite	Cryptosporidium parvum	Human polyclonal, bovine colostrum	Case reports	(67,68)
Antiisoimmunization	Rh_0(D) immunization	Human polyclonal	In use (Bayrho-D)	(69)
Antilymphoma	Lymphoma	IgG1 mouse-human chimeric	In use (Rituximab, Rituxan)	(70)
Antivenom	Poisonous bites	Equine polyclonal	In use	(71)
Platelet inhibition	Arterial thrombosis	Mouse–human chimeric Fab	In use (Abciximab, ReoPro)	(38)
Antitumor	Breast cancer	Humanized murine mAb (IgG1)	In use (Trastuzumab)	(72)

tions contained a significant amount of antibody aggregates that could produce severe anaphylactic-like reactions when infused iv (6). Later, improvements to the method for antibody purification resulted in antibody preparations suitable for the iv administration of immunoglobulins (IVIG) (6). Human immunoglobulin preparations proved effective in reducing infections in children with agammablobulinemia (7). The description of hybridoma technology in 1975 provided the means to generate unlimited amounts of monoclonal antibody (mAb) preparations with one specificity and one isotype (8). In the 1980s advances in molecular biology led to a proliferation of strategies to modify murine mAbs and generate mouse–human chimeric and humanized mAbs (9, 10). These molecules have reduced immunogenicity and a longer half-life than the murine counterpart and provide significant advantages in clinical use (Fig. 1). Other technological advances included phage display of combinatorial antibody libraries (11), domain and chain shuffling to generate antibodies with new functional properties (12), the construction of mice that expressed human antibodies (13), and expression of antibodies in edible plants (14). These technologies provided the means to generate antibody preparations that lacked the toxicity and lot to lot variation of the heterologous antibody preparations used in the preantibiotic era.

Early efforts to exploit mAbs for clinical use focused primarily in developing new therapies for cancer. The first use of a mAb for cancer therapy was reported in 1980 when a murine mAb purified from ascites was administered to a patient with refractory lymphoma resulting in a transient decrease in the number of circulating tumor cells without significant toxicity (15). Other early case reports suggested that antibody therapy could be effective against B and T cell tumors (16–18). Unfortunately, responses to mAb therapy were often short lived, and for B cell lymphomas alterations in idiotype recognized by the mAb resulted in the emergence of clones that escaped antibody therapy (17, 18). In the field of organ transplantation a murine mAb to the CD3 antigen in T cells was developed for the treatment and prevention of organ rejection (reviewed in (19)). In the field of antiinfective therapy, a considerable effort was undertaken to develop mAbs that neutralized bacterial endotoxin for the treatment of septic shock. Two mAbs to endotoxin underwent clinical evaluation but neither were successful, possibly because an incomplete understanding of the physiological complexity of the sepsis syndrome precluded

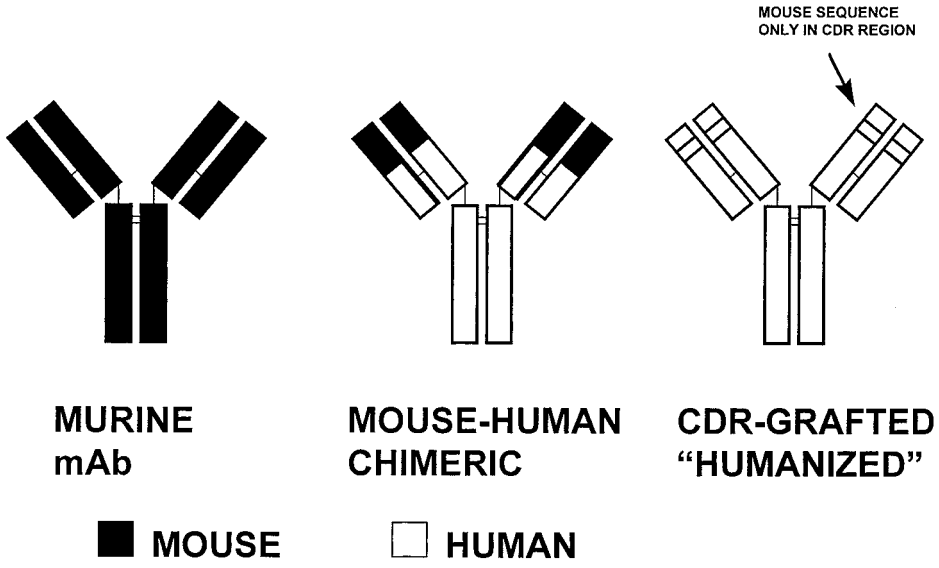

FIG. 1. Schematic diagram of murine mAb, mouse–human chimeric antibody, and CDR-grafted or humanized antibody. Mouse–human chimeric antibodies have a human constant region and mouse variable regions. CDR-grafted or humanized antibodies are composed of mostly human sequences except for those areas in contact with antigen, which are derived from mouse sequences.

the identification of patient subsets that would benefit from antibody therapy (20). Despite the failure of the antiendotoxin mAbs and the discouraging early efforts against cancer, steady progress was made such that by 1999 dozens of mAbs are in clinical trials (Table 2) and several are in routine clinical use (Table 1). Hence, interest in antibody therapies went full circle in the 20th century from high in the early years, to virtual abandonment in midcentury, to a renaissance in the past 2 decades.

THE VERSATILITY OF ANTIBODY-BASED THERAPIES

Antibodies have physiological properties and activities that have not been duplicated by small-molecule drugs and these include toxin neutralization, microbial opsonization, complement activation, and antibody-directed cellular cytotoxicity (ADCC). The versatility of antibodies as therapeutic agents is illustrated by the fact that they can be used to enhance or reduce immune function depending on the specificity of the antibody preparation. Enhancement of immune function is usually desirable for antibody therapies against infectious agents and tumors where antibody administration can help host defenses eradicate an infection or damage malignant cells, respectively. In contrast, the same properties of antibodies that mediate tissue damage can be exploited to reduce the number of immune cells, neutralize cytokines, or block receptors to interfere with immune function and produce immune suppression. Reduction in immune function is desirable for antibody use in rheumatic diseases, prevention of transplant rejection, or clinical syndromes where host damage results from immune activation.

Since antibody preparations can theoretically be generated with specificity for virtually any antigen, antibodies are a remarkably versatile class of therapeutic. This versatility is enhanced by the availability of various isotypes that confer different biological properties to the antibody molecule. Furthermore, it is possible to link radionucleotides, enzymes, drugs, toxins, and cytokines to the antibody molecule to enhance its biological efficacy and/or take advantage of its specificity to deliver a second pharmacologically active molecule to the targeted tissue. A comprehensive discussion of all possible uses of antibody-based therapies is outside the scope of this review and the main focus will be in the use of unmodified (naked) antibodies as therapeutics.

Toxin neutralization. The ability of specific antibodies to bind and neutralize bacterial and animal toxin is a classical property of humoral immunity used for the treatment of many toxin-mediated diseases for more than 100 years. Antimicrobial agents can kill or inhibit toxin-producing bacteria but are ineffective against toxins released into tissues. Antibody preparations continue to be used for treatment of diphtheria, tetanus, botulism, and venomous bites (21–24). The efficacy of antibody therapy varies with the type of toxin and the timing of antibody administration relative to the onset of symptoms. For some conditions such as botulism, late administration of antibody therapy is not very effective because the antibody does not neu-

TABLE 2

Examples of mAbs in Clinical Development (Not a Complete List)

MAb	Type	Specificity	Isotype	Investigational use	Ref.
2A11	Murine	Gastrin releasing peptide	Not stated	Treatment of small cell lung cancer	(73)
42/6	Murine	Transferrin	IgA	Antitumor	(74)
Anti-CD3	Murine	CD3	IgG1	Antitumor therapy	(50)
BRAD-3 and BRAD-5	Human	Rh D	IgG3 and IgG1	Prevention of RhD hemolytic disease	(75)
BTI-322	Rat	CD2	IgG2b	Treatment of steroid resistant acute graft-versus-host disease	(76)
CAMPATH-1H	Humanized	CD52	IgG1	Leukemia	(77)
CAMPATH-1G	Rat	CD52	IgG2b	Prevention of graft-versus-host disease and graft rejection	(78)
CGP-51901	Chimeric	IgE	IgG1	Seasonal allergic rhinitis	(79)
Enlimomab	Mouse	ICAM-1	IgG2a	Prevention of renal transplant rejection	(80)
F105	Human	HIV gp120	IgG1k	Anti-HIV1	(63)
Hu23F2G	Humanized murine	CD11/CD18	IgG4	Multiple sclerosis	(81)
IDEC-CE9.1, keliximab	Primatized IgG1	CD4	IgG1	Rheumatoid arthritis, asthma	(82,83)
OKTcdr4a	Humanized	CD4	IgG4	Refractory rheumatoid arthritis	(84)

tralize tissue-bound toxin. Recently, there has been interest in developing antibody-based therapies against toxins produced by other pathogens. *Clostridium difficile* causes diarrhea in hospitalized patients treated with antimicrobial agents and the symptoms are caused by bacterial toxins. A bovine immunoglobulin concentrate with neutralizing IgG to *C. difficile* toxins was shown to retain activity after passage in the human gastrointestinal tract suggesting that passive oral immunotherapy may be feasible (25). Antibody therapy also is being developed for treatment of infections with *Escherichia coli* strains producing enterotoxins (26).

Viral neutralization. Antibody preparations are first-line therapies for postexposure prophylaxis and the treatment of many viral infections. Specific antibodies can be active against viruses through mechanisms that include virion neutralization, interference with attachment, promotion of ADCC, and complement mediated damage. The efficacy of human convalescent therapy against viral illness was demonstrated in the preantibiotic era when human immune serum to measles and mumps was shown to prevent infection in children (27). Human polyclonal antibody preparations prepared from immune donors are available against several viruses including hepatitis B, varicella-zoster virus, cytomegalovirus, and rabies (Table 1). These preparations are usually employed for postexposure prophylaxis. Human antibody preparations in the form of IVIG often contain sufficient antibodies to common human viral pathogens to make them useful for therapy of certain diseases. In this regard, chronic cell aplasia due to persistent parvovirus B19 infection has been successfully treated with IVIG (28). There have been several efforts to develop antibody therapy against HIV (reviewed in (29)) but this task has been difficult because of antigenic variation of HIV isolates and intracellular persistence of infection. One advantage of antibody-based therapies is that they can be developed rapidly against new or reemergent infectious agents. For example, recent Ebola virus outbreaks have led to consideration of antibody preparations for therapy. A horse serum preparation with high neutralizing activity to Ebola virus has been described but its therapeutic efficacy is unknown (30). Polyclonal and humanized monoclonal (palivizumab, Synagis) antibody preparations are now available for prevention of respiratory syncytial virus infection in high-risk infants (reviewed in (31)).

Reversal of drug toxicity. In a variation of their classical antitoxin activity, specific antibody preparations can be use to treat drug toxicity. One example is the use of digoxin-binding Fab fragments to treat life-threatening digitalis intoxication (5).

Depletion of immune effector cells and molecules. The involvement of the immune system in many pathologic processes had led to the development of antibody therapies that target specific immune molecules and cells (Tables 1 and 2). Muronab CD3 (Orthoclone OKT3) and Daclizumab (Zenapax) have been licensed for use in the prevention of organ rejection. The OKT3 targets the CD3 antigen in T cells and has been in clinical use since the 1980s for the prevention of renal and hepatic allograph rejection (19). Daclizumab targets the high-affinity IL-2 receptor expressed in acti-

vated T cells and interferes with clonal expansion and viability of activated T cells (32). A chimeric IgG1 mAb to TNFα (Infliximab, Remicade) was recently approved for use in the treatment of Crohn's disease, providing the first specific therapy for this condition. Infliximab binds to soluble and membrane TNFα and neutralizes its activity. Patients with Crohn's disease treated with Infliximab had significant reduction of gastrointestinal inflammation (33, 34). Infliximab has also shown promise for the treatment of rheumatoid arthritis in combination with methotrexate (35). The experience with Infliximab illustrates how mAbs that target immune effector molecules can be used to treat diseases where host damage is mediated by the immune system. Several mAbs with specificity to immune components are in various stages of clinical development (Table 2). For example, the observation that serum IgE level correlates with the severity of symptoms in asthma and some atopic diseases has led to interest in antibody therapy directed toward neutralizing IgE activity. Two mouse–human chimeric antibodies in clinical development are CGP591 with specificity for serum IgE (36) and Rhu-MAb-E25 with specificity for the human IgE high affinity receptor (reviewed in (37)). Both CGP-581 and Rhu-MAb-E25 have proven safe during initial clinical testing suggesting that the binding of mAb to IgE or its receptor is well tolerated even in atopic individuals. From a commercial consideration, antibody therapy directed toward components of the immune system is attractive because it has the potential for further clinical development against other medical conditions.

Inhibition of host cell function. Antibodies to cellular antigens can be used to interfere with cell function and achieve a therapeutic effect. A Fab fragment preparation (Abciximab, ReoPro) of the mouse–human chimeric antibody c7E3 with specificity for glycoprotein IIb/IIIa in human platelets has been approved for prevention of arterial closure during angioplasty (reviewed in (38)). The Fab fragments are cleared rapidly from the circulation but those bound to platelets persist for several days. The main complication of therapy is a higher risk for bleeding resulting from platelet dysfunction. Abciximab is being evaluated for efficacy in a variety of cardiac-related conditions and indications for its use may increase in the future.

Anticancer therapy. The ability of certain antibodies to bind host tissues and mediate tissue damage through ADCC and/or activation of the complement system suggests that they can be useful for therapy of cancer provided they bind to antigens preferentially expressed in neoplastic cells. However, the application of hybridoma technology for cancer therapy has proved difficult because of the paucity of suitable tumor-specific antigens, antigenic variation in tumors, poor tissue penetration, and development of human immune responses to therapeutic antibodies (reviewed in (39)). Evidence for hard-won successes in this area is demonstrated by the recent approval of two mAbs, rituximab (Rituxan) and trastuzumab (Herceptin), for the treatment of malignancies. Rituximab is a chimeric antibody to CD20 antigen approved for the treatment of lymphoma. Herceptin is a humanized murine IgG1 antibody that binds the human epidermal growth factor receptor 2 protein (HER2) protein antigen found in approximately 30% of human breast tumors. Monoclonal antibody therapy has also shown encouraging results in the treatment of colon cancer (reviewed in (40)). Interestingly, the therapeutic effect of mAb therapy for colon cancer may be mediated by antiidiotypic responses suggesting that for some tumors antibody therapy may function by eliciting new immune responses (40). Many other mAbs are in clinical testing and one can anticipate that additional antibody-based therapies against cancer will be available in the future.

NICHES FOR ANTIBODY-BASED THERAPIES

Antibody-based therapies are expensive and their high specificity often translates into smaller potential markets. Since, the economics of antibody-based therapies are generally unfavorable relative to traditional small-molecule drugs, antibody-based therapies must fill special niches in the pharmacological arsenal to be economically successful. A compelling rationale can be made for the development of antibody-based therapies for conditions where no drugs exist or where existing therapy is not very effective, such as cancer, chronic inflammatory conditions, and certain infections. Another area where antibodies may be potentially very useful is as adjuncts to antimicrobial therapy for the treatment of emergent infections and infectious diseases in immunocompromised hosts (29, 41). The economics for the development and utilization of antibody-based therapies may improve as advances are made in technology of antibody production. Furthermore, advances in immunological knowledge may significantly reduce the empiricism currently associated with the current development of antibody therapies and consequently reduce the costs associated with development and production.

CONSIDERATIONS IN THE DEVELOPMENT OF ANTIBODY-BASED THERAPIES

Polyclonal versus monoclonal. Antibody therapeutic preparations can be either polyclonal or monoclonal. Polyclonal preparations usually originate from immune donors but could be designed in theory by mixing mAbs of various isotypes and specificity. Polyclonal preparations have the advantage over mAb preparations of including antibodies of various specificities and

isotype that provides diversity in biological function. A disadvantage of polyclonal preparations is that the desired antibody activity may be found in only a small fraction of the total immunoglobulin protein and this can require the administration of large amounts of antibody protein to obtain the desired effect. For example, the dosage of RSV-enriched human immune globulin (RSV-IVIG) required for treatment is 750 mg/kg and it has been estimated that the cost of treating a 3-kg infant with five infusions of RSV-IVIG is $4340 per season (31). In contrast, mAb preparations have higher specific activity per protein content that can translate into lower dosing and less expense. Treating the same child with a humanized mAb (palivizumab) to RSV requires smaller amounts of protein that reduces the cost of treatment to $2378 (31). Another example is provided by antibodies to tetanus toxin where a 0.7-mg mixture of two neutralizing of mAbs to tetanus toxin had comparable activity to 100–170 mg of tetanus immune globulin (42). MAb preparations generated *in vitro* are theoretically less likely to transmit infectious agents. However, mAb preparations are at significant disadvantage relative to polyclonal sera for venomous bites where the toxicity is caused by a complex and poorly understood combination of toxins and enzymes (43). One lingering concern in the use of polyclonal preparations derived from human or animal sources is the possibility of inadvertent transmission of infectious agents. In this regard some cases of hepatitis C have been linked to IVIG administration (44).

Heterologous vs homologous. Given equal potency, homologous (e.g., human derived) antibody preparations are always preferable to heterologous (e.g., animal derived) antibody preparations because the latter are associated with hypersensitivity reactions and the possibility of serum sickness. However, there are certain circumstances where the use of heterologous antibody preparations is practical and necessary. Heterologous antibody preparations are usually cheaper than human immune globulin or mAb preparations. In Thailand human tetanus immune globulin costs $155 and the equine preparation $7 (43). For antidiphtheria immune globulin the costs for the human and equine preparations are $1290 and $10, respectively (43). Homologous antibody preparations are often scarce and simply not available in many third-world countries where there is great need for these reagents (43). For some antigens such as venomous toxins heterologous antibody sources must be used because generating human immune globulin is impractical. However, the use of heterologous preparations can sensitize a patient and preclude repeat therapy with the same product.

Intact antibody versus Fab fragments. For conditions where constant region function is not required, such as toxin neutralization, receptor blocking, drug chelation, or some types of viral neutralization, Fab preparations are adequate for therapy. Advantages of Fab preparations include lower immunogenicity when derived from heterologous antibodies (reviewed in (45)). For example, the percentage of patients developing human antimouse antibodies (HAMA) after administration of intact murine mAb, $F(ab')_2$, and Fab, was 53, 83, and 2%, respectively (45). Fab preparations have much a shorter half-life than intact preparations. Nonetheless, an equine Fab specific for rabies virus has a clinically useful serum $t_{1/2}$ ranging from 50 to 70 h after intramuscular injection (46). However, for conditions where constant region function is required, such as therapies where the activity results form increased opsonization, complement activation, or ADCC, intact antibody molecules are necessary.

Antibody molecules can be used “naked” or conjugated to toxins, drugs, radionucleotides, or immune molecules such as cytokines. For such preparations the antibody specificity provides a means to deliver the conjugate to the target tissue. Conjugation can increase the therapeutic efficacy of antibody molecules. Bispecific antibodies are another modification that involves the synthesis of molecules with different specificities such that two antigens can be targeted.

Antibody specificity. The great attraction of antibody-based therapies is that they provide the potential to design therapies with great specificity for infectious agents, individual cells, or certain types of tissues. However, specificity can be both an advantage and a disadvantage for antibody-based therapies. High specificity for the antibody target is a desirable quality in therapeutic antibodies intended for malignant cells but can be a drawback in design of some antiinfective therapies. Specificity is a disadvantage when developing antibody therapies for infectious agents that are antigenically diverse such as *Streptococcus pneumoniae.* In the preantibiotic era, the success of serum therapy for pneumococcal pneumonia was dependent on the use of type specific serum that required precise knowledge of the serotype responsible for infection plus the availability of sera to multiple serotypes (1). This made serum therapy cumbersome and undoubtedly contributed to its abandonment when effective chemotherapy became available. All mAbs developed for human use should be tested on panels of human tissues to determine their reactivity with normal tissue since cross-reactivity could in theory translate into enhanced toxicity (47).

Antibody dosing. Dose selection is a critical factor in the success of antibody therapies in clinical trials.

Unfortunately, the selection of antibody dose for clinical use is a complicated task that is dependent on the type of antibody preparation, the amount of antigen present, the pharmacokinetics of the antibody, and the intended use. Unlike conventional drugs for which initial dosing estimates can be inferred from their *in vitro* activity, therapeutic antibodies often mediate their effects through other components of the immune system (e.g., complement activation, ADCC, etc.) and this greatly complicates dose selection. For pneumococcal pneumonia, the potency of therapeutic sera was standardized based on its ability to protect mice against a lethal challenge (1). However, this provided only a gross estimate of activity and dosing was based on clinical response. Today antibody dosing remains largely an empiric science that is also a major determinant of the cost of therapy.

Antibody pharmacokinetics. The serum half-life ($t_{1/2}$) for a homologous antibody that does not react with host tissues is a dependent on the isotype (reviewed in (48)). IgG isotypes have much longer $t_{1/2}$ than either IgM or IgA. For heterologous antibodies the serum $t_{1/2}$ varies with both isotype and antigenicity of the antibody in the host. Administration of murine mAbs to humans elicits HAMA, which form antigen antibody complexes and limit the duration of therapy. As a result several strategies have been developed to engineer murine antibodies such that specificity is preserved while reducing antigenicity and these include the synthesis of mouse–human chimeric antibodies and complementarity-determining region (CDR)-grafting. Chimeric and humanized antibodies have longer serum $t_{1/2}$ in humans that their parent murine mAbs. For example, the serum $t_{1/2}$ of daclizumab, a humanized IgG1, is 20 days, which matches that of normal IgG (32).

Combination therapy. For an antibody-based therapy to succeed clinically it must have superior efficacy and/or lower toxicity than existing therapy when used alone or in combination with existing therapy. Since some form of therapy already exists for most medical conditions one must anticipate that the candidate antibody therapy will be tested against and in combination with existing therapy. Hence, preclinical development should consider the possible beneficial and adverse effects of adjunctive antibody therapy on the condition being treated.

TOXICITY

Antibody-based therapies are generally well tolerated. However, antibody therapies can be associated with significant toxicity that may depend on either the antibody preparation or the activity of the therapeutic antibody. Historically, most toxicities associated with antibody therapy were a result of the use of polyclonal heterologous preparations that could elicit allergic reactions or serum sickness. Administration of murine antibodies in patients with HAMA responses can result in immune complexes that have the potential to induce serum sickness or renal toxicity (49). HAMA responses can also interfere with the therapeutic efficacy of murine antibodies by promoting clearance through formation of immune complexes or inhibiting binding to the intended target (49). HAMA responses vary with the antibody used and the patient population and can occur by 1 week after the initiation of therapy (49). In one study HAMAs developed in 14 of 26 patients given one dose of murine antibody to CD3 (50). HAMAs are primarily of IgG and the majority have specificity for the Fc portion of the murine antibody molecule (49). The rapidity of HAMA response and the predominance of IgG isotype suggests a secondary response (49). Interestingly, human responses to some antibody therapies may contribute to the therapeutic effect. It has been suggested that the therapeutic effect of some antitumor mAbs is the result of antiidiotypic responses given that for some murine mAbs there has been a correlation between the intensity of the HAMA response and the clinical response (reviewed in (40, 45)).

Mouse–human chimeric antibodies are less immunogenic than murine antibodies but still elicit significant human antichimeric antibodies (HACA) in a significant percentage of treated patients (reviewed in (45)). The probability of inducing a HACA response is related to the dose used and the type of antibody used. In a double-blind placebo control study of a chimeric antibody to TNFα (Infliximab) with methotrexate for the treatment of rheumatoid arthritis the percentage of patients with serum HACA at the completion of a 12-week course was inversely proportional to the dose used, and was 53, 21, and 7% in the groups receiving 1, 3, and 10 mg/kg (35). Although the mechanism by which higher dose resulted in lower immunogenicity is not understood, it is possible that the effect resulted from induction of tolerance or concomitant immune suppression resulting from methotrexate administration (35). Humanized or CDR-grafted antibodies are less immunogenic than mouse–human chimeric antibodies. Humanization of a mouse mAb to CD4 resulted in a molecule that was not immunogenic in humans (51). Human antibodies are much less immunogenic that murine or murine-derived mAbs but even fully human mAbs can sometimes elicit antibody responses (45). When comparing the relative immunogenicity of antibody preparations in different studies it is important to use caution when drawing conclusions because the methodology for measuring HAMA and HACA is not well standardized (45).

Infusion reactions are common adverse events during mAb administration and can range from minor to

life-threatening. The likelihood of infusion-related adverse effects depends on the type of antibody used, the dose administered, and the underlying condition of the patient population being treated. Severe infusion-related reactions commonly follow the administration of the OKT3 mAb and this phenomenon has been attributed to the systemic release of several cytokines including TNFα (19, 52). In one study, infusion-associated hypotensive events (one requiring blood pressure support) were observed in 8 of 40 (20%) courses of iv administration of a murine antibody to CD3 given with IL-2 for cancer therapy (50). The OKT3-related infusion reactions have been called a "cytokine release syndrome" which is characterized by fever (81%), chills (31%), headache (19%), nausea (22%), vomiting (19%), hypotension (19%), and dyspnea (9%) (53). The cytokine release syndrome is the result of Fc receptor binding but this antibody function is not essential for anti-CD3-mediated immune suppression (52, 54). Infusion-related reactions have been described with many other mAbs but this phenomenon may not always be caused by the antibody preparation. The incidence of adverse effects in a double-blind study of patients receiving anti-TNFα therapy for Crohn's disease was approximately the same in antibody-treated patients and those receiving a placebo solution composed of 0.1% human serum albumin (34). Infusion-related adverse reactions may be reduced by administration of steroids and antihistamines.

For some therapeutic antibodies the toxicities result from the specificity and activity of the antibody molecule. Several melanoma patients treated with an IgG2a murine antibody to the GM-2 ganglioside have developed polyneurapathy and endocrine complications that have been attributed to binding of the antibody to peripheral nerve myelin and pituitary cells (55). The pathogenesis of the toxic effect is presumed to be the result of antibody binding to nerve and pituitary cells triggered ADCC and complement mediated lysis resulting in demyelinating neuropathy and loss of neuroendocrine cells (55). Anti-TNFα therapy with Infliximab can result in the appearance of serum antibodies to double-stranded DNA (35). Antibodies that target components of the immune system and mediate their effects by producing immune suppression can be associated with an increased risk of infection. For example, antirejection therapy with the OKT3 mAb is associated with severe infections (19, 56). The use of OKT3 mAb for treatment or prophylaxis of organ rejection in transplant patients has also been associated with a significantly increased risk of lymphoproliferative malignancies (19).

In summary, toxicity depends on the type of Ab preparation used, the Ab specificity of the antibody, and the effector function of the Ab constant region. Like conventional drugs, each antibody preparation is likely to have a unique toxicity profile that must be established empirically in clinical trials.

FUTURE PROSPECTS

Dozens of mAbs are now in advanced clinical and preclinical development and one can anticipate that additional mAbs will be licensed for routine clinical use in the future. The development of antibody therapies remains an empiric science because our knowledge of antibody function is insufficient to design therapeutic antibodies from basic principles. In this regard there is a great need for additional basic immunological studies of antibody constant region function, isotype interaction with Fc receptors, physiology of immune complexes, and the interactions of antibodies with immune effector cells. Given that each mAb is different, the development of each antibody therapy must be individualized. As a result, the introduction of antibody-based therapies into clinical practice is likely to be an evolutionary process. Hence, it is unrealistic to expect that antibody therapies will perform as "magic bullets" for most medical conditions for which such therapies are being developed. Instead, a more likely scenario is that antibody-based therapies will be introduced into clinical practice incrementally and produce a quiet revolution from the aggregate effects of steady progress against many intractable clinical conditions. The future prospects for antibody therapies are very bright.

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