The Third Age of Antimicrobial Therapy

Arturo Casadevall

Division of Infectious Diseases, Departments of Medicine and of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York

(See the article by Pachl et al. on pages 1404–13)

In this issue, Pachl et al. [1] report that administration of an antibody fragment to a fungal heat shock protein in combination with lipid-associated amphotericin B to patients with invasive candidiasis reduced *Candida*-attributable mortality by >4-fold, markedly improved the overall response, and increased the rate of culture-confirmed clearance of *Candida* species, compared with the administration of amphotericin B alone. This remarkable result, if confirmed by subsequent studies, could hasten the arrival of the third age of antimicrobial therapy.

The first age of antimicrobial therapy began in 1890, when von Behring and Kitasato [2] discovered that administration of immune serum could protect an immunologically naive animal against tetanus and diphtheria. That observation led to the rapid development of serum therapy for a wide variety of conditions, including tetanus, diphtheria, pneumococcal pneumonia, meningococcal meningitis, and erysipelas (reviewed in [3–5]). Serum therapy provided physicians with the first effective means to intervene in an ongoing infectious disease. Although serum therapy was effective, it was difficult to administer, and the use of animal serum was associated with significant adverse effects, including allergic reactions and serum sickness. The active ingredient in serum therapy was specific antibody, and the use of serum therapy required a specific diagnosis. Thus, to treat pneumococcal pneumonia, a physician would both have to accurately determine that the problem was caused by *Streptococcus pneumoniae* and to establish the serotype. Consequently, the development of serum therapy was a major catalyst for immunological research, as investigators tried to understand the nature of effective antibodies and develop rapid diagnostic methods. By the 1930s, the art of diagnosis was so advanced that it was possible to diagnose pneumococcal pneumonia within several hours by injecting sputum into mice, recovering the organism, and typing with serological reagents.

The first age of antimicrobial therapy came to a relatively abrupt end in the late 1930s with the introduction of effective chemotherapy in the form of sulfonamide. Serum therapy could not compete with chemotherapy, because serum therapy was more expensive, was difficult to use, had significantly more adverse effects, and was pathogen specific. In contrast, antibiotics were active against many types of microbes and, consequently, could be given empirically without a diagnosis of microbial infection. The introduction of antibiotics into clinical medicine heralded the second age of antimicrobial therapy and is unquestionably one of the greatest medical triumphs of the 20th century. Numerous classes of antimicrobial drugs were introduced within a short time, and by the 1950s, physicians were able to treat most bacterial diseases successfully [6]. Unfortunately, drug resistance inevitably developed; fortunately, the introduction of newer drugs maintained the arsenal of effective drugs for a long time. However, by the last decades of the 20th century, the cycle of antibiotic development—followed by drug resistance, followed by the development of new agents to overcome drug resistance—began to fail, because drug discovery could not keep up with the proliferation of drug-resistant microbes. The unchecked emergence of antimicrobial resistance, combined with economic considerations that limited the ability to keep up with the need for new agents, led to a decline in the development of new antimicrobial drugs [7]. In fact, one could argue that the subspecialty of infectious diseases is the only branch of medicine in which the therapeutic options were better in the mid-20th century than at the beginning of the 21st century. For example, some diseases that were treatable with a single drug in 1960, such as tuberculosis, became essentially untreatable when they were caused by multidrug-resistant strains. The increasing prevalence of drug-resistant organisms, combined with the emergence of many unsuspected microbes as human pathogens in epidemics among

Received 5 February 2006; accepted 6 February 2006; electronically published 12 April 2006.

Reprints or correspondence: Dr. Arturo Casadevall, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461 (casadeva@aecom.yu.edu).

Clinical Infectious Diseases 2006; 42:1414–6

1058-4838/2006/4210-0010$15.00

immunocompromised hosts, for whom antimicrobial therapy was significantly less effective, created a sense of crisis in the field [8].

In 1975, Kohler and Milstein [9] described the generation of monoclonal antibodies by hybridomas. That technology was capable of delivering an unlimited supply of an immunoglobulin of a defined class and specificity. The advent of monoclonal antibodies (mAb) catalyzed a revolution in diagnostics and therapy for certain diseases. Today, there are >1 dozen licensed mAb therapies for such diverse conditions as cancer, rheumatoid arthritis, and asthma and for the prevention of organ rejection, and the market has exploded with numerous products in development [10]. However, only 1 mAb is licensed for use against an infectious disease: palivizumab is available for the prevention of respiratory syncytial virus–related diseases.

How can it be that the field that pioneered antibody therapy has failed to reembrace this option, when advances in technology have eliminated many of the problems of serum therapy? The answer to this question is complex. On one hand, mAb therapy found willing enthusiasts in the fields of oncology and transplantation medicine, where there was a dearth of effective treatment options. In contrast, antimicrobial therapy continues to be available, despite widespread resistance, and the reintroduction of antibody therapy would necessarily have to compete with an established treatment modality that is renowned for efficacy, ease of administration, low toxicity, and low cost. The reintroduction of antibody therapy also ran against the culture of infectious disease specialists, who had grown comfortable with treating many infectious diseases without making a microbiological diagnosis. The availability of low-cost broad-spectrum drugs with low toxicity had led to the withering of diagnostic microbiology, such that rapid diagnostic tests were not available to support the reintroduction of antibody therapies. There was also the high-profile failure of several antisepsis antibodies, which soured the pharmaceutical industry's enthusiasm for taking on infectious diseases problems. Perhaps one of the greatest problems of reintroducing antibody therapies for infectious diseases was the exquisite specificity of antibody reagents. This property meant that antibodies could only be used for diseases caused by the responsible microbe, making them commercially unattractive, given the dictum that market size is proportional to the breadth of antimicrobial activity. Therefore, development of hybridoma technology and the advances in immunology that brought us human antibody reagents did not lead to traction for the wide scale reintroduction of antibody therapy, despite determined efforts to develop mAb therapy for anthrax [11], cytomegalovirus [12], and cryptococcal diseases [13].

The finding that an antibody fragment to fungal heat shock protein is effective in the treatment of human candidiasis is the culmination of tireless efforts by Drs. Matthews and Burnie to develop a new therapy based on their observation in the 1980s that patients who recovered from invasive candidiasis had an antibody response to this antigen [14]. The new therapeutic is called Mycograb (*Neu*Tec Pharma) and consists of a recombinant antibody fragment that includes the antigen-combining site. This agent has undergone a long development process that showed efficacy in vitro and in animal models against *Candida albicans* [15, 16]. Mycograb has direct antifungal activity against *C. albicans* in vitro by a mechanism that is not understood. Interestingly, Mycograb is also effective against *Cryptococcus neoformans.* The broad activity of this immunoglobulin fragment is a result of the fact that heat shock protein 90 is a highly conserved protein across fungal species. Thus, Mycograb may represent a broad-spectrum antibody-derived therapy. Pachl et al. [1] report that the rate of *Candida*-attributable mortality was 4% among patients who received combination therapy with Mycograb and lipid-associated amphotericin B, compared with 18% among those receiving lipid-associated amphotericin B alone. These are dramatic results, with the caveat that, for critically ill patients with systemic candidiasis, it can be difficult to establish the cause of death. Nevertheless, if the reduction in the *Candida*-attributable mortality rate is validated by subsequent studies, one can anticipate that Mycograb will be a significant new therapeutic agent. Like most immunoglobulin-derived therapies, Mycograb was well tolerated. Nevertheless, the study revealed the peculiar finding that Mycograb administration was associated with transient hypertension in a minority of patients. The mechanism for this effect is unknown and warrants further study.

Given that the overall therapeutic options in antifungal therapy have dramatically improved in recent years with the introduction of echinocandins and later-generation azoles, one might question the need for developing antibody therapy against candidiasis. However, candidiasis is associated with an unacceptably high mortality rate, even when it is treated with antifungal agents to which the fungus is susceptible. Furthermore, the development of alternative therapies is a wise decision, given that the prevalence of antifungal drug resistance is increasing. In this regard, the suggestion that Mycograb improved outcome introduces a new dimension in assessing therapeutic needs. Fungal infections are notoriously difficult to treat with antifungal therapy, because they often occur in individuals who are immunocompromised. For these fungal diseases, the immune system often makes a critical contribution to antifungal therapy. Consequently, there has been great interest in combining immunotherapy and antifungal therapy [5, 17]. There is overwhelming evidence from animal studies and limited evidence from human studies that immunotherapy can significantly augment the efficacy of standard antimicrobial therapy. Recently, there have been studies of

adjunctive IFN and antibody therapy for cryptococcal meningitis [18]. The widespread introduction of immunotherapy in the form of antibodies, cytokines, and growth factors, in combination with conventional antibiotic therapy, would constitute the third age of antimicrobial therapy. However, the development of adjunctive immunotherapy faces the significant hurdle of demonstrating superiority over standard antimicrobial therapy, which greatly complicates clinical trial design. In this regard, it is noteworthy that the clinical evaluation of Mycograb required combination with and comparison with amphotericin B, which has been the "gold standard" for antifungal therapy for 4 decades. Therefore, we do not know whether Mycograb is effective as a single agent for treatment of human candidiasis.

In the first age of antimicrobial therapy, physicians tried to kill pathogenic microbes by helping the host immune response eradicate the infection with passive antibody therapy. In the second age of antimicrobial therapy, physicians tried to kill microbes directly using small molecules that interfered with microbial metabolism. Third-age antimicrobial therapies will combine microbe-killing and host-enhancing strategies to improve the outcome of infectious diseases. By this categorization, Mycograb fits better within second-age medicines, because it directly targets the microbe, with the caveat that it is a large protein molecule derived from an immunoglobulin. Mycograb is neither an antibiotic nor an antibody molecule but combines features of both. Thus, the third age of antimicrobial therapy is not quite here. Nevertheless, Mycograb constitutes an important advance that could hasten the day when third-age therapeutics become available.

Acknowledgments

Financial support. National Institutes of Health (AI033142-11, AI033774-11, AI052733-04 and HL059842-08).

Potential conflicts of interest. A.C.: no conflicts.

References

1. Pachl J, Svoboda P, Jacobs F, et al. A randomized, blinded, multicenter trial of lipid-associated amphotericin B alone versus in combination with an antibody-based inhibitor of heat shock protein 90 in patients with invasive candidiasis. Clin Infect Dis **2006**; 42:1404–13 (in this issue).
2. von Behring EA, Kitasato S. Ueber das Zustandekommen der Diptherie-Immunität und der Tetanus-Immunität bei Thieren. Deutch Med Woch **1890**; 49:1113–4.
3. Casadevall A, Scharff MD. Serum therapy revisited: animal models of infection and the development of passive antibody therapy. Antimicrob Agents Chemother **1994**; 38:1695–702.
4. Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. Clin Infect Dis **1995**; 21:150–61.
5. Buchwald UK, Pirofski L. Immune therapy for infectious diseases at the dawn of the 21st century: the past, present and future role of antibody therapy, therapeutic vaccination and biological response modifiers. Curr Pharm Des **2003**; 9:945–68.
6. Jawetz E. Antimicrobial therapy. Ann Rev Microbiol **1956**; 10:85–114.
7. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis **2004**; 38:1279–86.
8. Casadevall A. Crisis in infectious diseases: time for a new paradigm? Clin Infect Dis **1996**; 23: 790–4.
9. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature **1975**; 256:495–7.
10. Reichert JM, Dewitz MC. Anti-infective monoclonal antibodies: perils and promise of development Nat Rev Drug Discov **2006**; 5:191–5.
11. Subramanian GM, Cronin PW, Poley G, et al. A phase 1 study of PAmAb, a fully human monoclonal antibody against *Bacillus anthracis* protective antigen, in healthy volunteers. Clin Infect Dis **2005**; 41:12–20.
12. Aulitzky WE, Schulz TF, Niederwieser D, et al. Human monoclonal antibodies neutralizing cytomegalovirus (CMV) for prophylaxis of CMV disease: report of a phase I trial in bone marrow transplant patients. J Infect Dis **1991**; 163:1344–7.
13. Larsen RA, Pappas PG, Perfect JR, et al. A phase I evaluation of the safety and pharmacodynamic activity of a murine-derived monoclonal antibody 18B7 in subjects with treated cryptococcal meningitis. Antimicrob Agents Chemother **2005**; 49:952–8.
14. Matthews RC, Burnie JP, Tabaqchali S. Isolation of immunodominant antigens from sera of patients with systemic candidiasis and characterization of serological response to *Candida albicans*. J Clin Microbiol **1987**; 25: 230–7.
15. Matthews R, Hodgetts S, Burnie J. Preliminary assessment of a human recombinant antibody fragment to hsp90 in murine invasive candidiasis. J Infect Dis **1995**; 171:1668–771.
16. Matthews RC, Rigg G, Hodgetts S, et al. Preclinical assessment of the efficacy of mycograb, a human recombinant antibody against fungal HSP90. Antimicrob Agents Chemother **2003**; 47:2208–16.
17. Casadevall A, Pirofski L. Adjunctive immune therapy for fungal infections. Clin Infect Dis **2001**; 33:1048–56.
18. Pappas PG, Bustamante B, Ticona E, et al. Recombinant interferon-γ 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. J Infect Dis **2004**; 189:2185–91.