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Review

Monoclonal antibody-based therapies for microbial diseases

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ABSTRACT

The monoclonal antibody (mAb) revolution that currently provides many new options for the treatment of neoplastic and inflammatory diseases has largely bypassed the field of infectious diseases. Only one mAb is licensed for use against an infectious disease, although there are many in various stages of development. This situation is peculiar given that serum therapy was one of the first effective treatments for microbial diseases and that specific antibodies have numerous antimicrobial properties. The underdevelopment and underutilization of mAb therapies for microbial diseases has various complex explanations that include the current availability of antimicrobial drugs, small markets, high costs and microbial antigenic variation. However, there are signs that the climate for mAb therapeutics in infectious diseases is changing given increasing antibiotic drug resistance, the emergence of new pathogenic microbes for which no therapy is available, and development of mAb cocktail formulations. Currently, the major hurdle for the widespread introduction of mAb therapies for microbial diseases is economic, given the high costs of immunoglobulin preparations and relatively small markets. Despite these obstacles there are numerous opportunities for mAb development against microbial diseases and the development of radioimmunotherapy provides new options for enhancing the magic bullet. Hence, there is cautious optimism that the years ahead will see more mAbs in clinical use against microbial diseases.

Contents

The field of infectious diseases has largely missed the monoclonal antibody (mAb) therapeutic revolution of the past decade. In contrast to such fields as oncology and rheumatology where mAbs have provided new effective therapies, only one mAb has been licensed for the treatment of an infectious disease [1]. This omission in the anti-infective armamentarium is particularly distressing given that the therapy of infectious disease is in crisis, since it is arguably the only field of medicine where effective intervention options have declined [2]. The crisis in infectious disease therapeutics is a consequence of four simultaneous developments, that in combination have significantly reduced treatment options for certain microbial diseases: (1) widespread antimicrobial drug resistance; (2) an epidemic of immunocompromised hosts in whom antimicrobial therapy is not as effective as in hosts with intact immunity; (3) the emergence of new pathogenic microbes for which no therapy exists; (4) the re-emergence of older

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pathogenic microbes, often in drug-resistant form, as exemplified by multidrug-resistant (MDR) *Mycobacterium tuberculosis*.

The reticence for adopting mAb therapies against infectious diseases is intriguing given that antibody therapies were the first effective antimicrobials. In the early 20th century serum therapy was used against a diverse range of infectious diseases, including pneumococcal pneumonia, meningococcal meningitis, erysipelas, anthrax and others [3,4]. These successes established antibody therapy as a powerful tool against infectious disease. Unfortunately, the immunological complications associated with the use of heterologous sera in humans, such as serum sickness and immediate hypersensitivity, significantly limited its usefulness [4]. Importantly, the problems of serum therapy do not necessarily apply to mAb therapy. Technological developments, such as improved purification techniques and the ability to engineer humanized mAbs, have greatly reduced these complications, allowed for increased specificity and expanded the range of possible targets. However, for many infectious diseases the availability of antimicrobial therapy has proved to be too much competition, and that combined with the complexity of introducing mAbs to clinical practice has hindered the pace of mAb-based therapeutic advancements.

Despite its current underdevelopment, the potential of antibody therapy in the form of mAbs is vast, especially for combating microbes that are resistant to antibiotic therapy, for emerging viral diseases or for the organisms or toxins responsible for bioterrorist threats. We believe that mAbs are well poised to be important reagents in a new age of antimicrobial therapy [2,5]. In this review, we focus on mAbs for infectious diseases and note that several recent reviews have addressed the topic of antimicrobial immunoglobulin therapy [6–8]. Our goal is to review the state of the field and to identify areas where the development of mAb-based therapies may be particularly valuable.

1. Historical perspective: from the origins of serum therapy to antibody use today

The prophylactic and therapeutic potential of immune serum was discovered by Behring and Kitasato, who showed that passive transfer of antibody from the blood of infected animals could provide immunity to diphtheria [9]. Their work led to the first instance of industrial production of protective serum from sheep for human therapy in 1893 [10] and to the first Nobel Prize in Medicine for Behring. Immune animal sera from horses, sheep, and chickens were used to treat diseases where a protective immune response could be induced in the animal host by vaccination. In cases where humans were the only hosts, such as viral diseases, human convalescent sera were successfully used. For example, in the early 1900s, serum from individuals who recovered from measles was used to treat and prevent infection. Until the 1930s, serum from animals or people was collected and pooled to treat a number of infections, from streptococcal infection to toxin-mediated diseases like diphtheria [11]. Overall, serum was effective, and for some diseases like pneumococcal pneumonia and meningococcal meningitis, the prompt administration of serum was associated with significantly improved survival [3].

However, despite these successes, the discovery of antibiotics in the 1930s and 1940s rapidly replaced serum therapy. Antibiotics were easier to manufacture, had less toxicity in patients and produced more consistent results. In contrast to serum therapy, which depended on animal sources that exhibited great lot-to-lot variation, antibiotics were the products of industrial processes and could be formulated in preparations with consistent activity. Furthermore, serum therapy was generally effective only early in the course of infection while antibiotic therapy maintained efficacy even when given late in the course of a microbial disease. Another advantage of antibiotic therapy was that it could be used without a specific diagnosis while the use of antibody therapy required knowledge of the pathogen responsible for disease. Consequently, serum therapy was unable to compete with antibiotics, and the development of new broad-spectrum antibiotic therapy displaced antibody-based therapies (Table 1).

Despite the general abandonment of serum therapy for bacterial diseases, certain niches developed where it continued to be used, such as the prophylaxis and treatment of a small number of viral and toxin-mediated diseases for which there were no alternative therapeutic options. This point is important because it illustrated that antibody therapy can thrive in certain situations where it lacked competition, such as in the treatment of diseases which have no other effective therapies. For example, antibody preparations continue to be used to prevent rabies and toxicity from snakebite venoms. In developed countries serum therapy was often replaced by hyperimmune serum from pooled human donors. Today, hyperimmune human sera immunoglobulin is used to treat many diseases including those caused by cytomegalovirus (CMV), respiratory syncytial virus (RSV), hepatitis A virus (HAV), hepatitis B virus (HBV), rabies, vaccinia, vesicular stomatitis virus (VZV), and measles, underscoring the fact that antibody therapy remains an effective means of treatment [6,12].

Compared to hyperimmune sera, or even to modern antibiotics, mAb therapy has many advantages and some disadvantages (Table 1). mAbs inherently have a high specificity for their target and, since microbes are generally antigenically distinct from humans, the cross-reactivity with host tissues is minimal. In contrast to antibiotics, which target both harmful microbes and the host flora, mAbs will only target a specific microbe and their systemic administration should not affect other resident beneficial microbes. This could prove to be a significant advantage given increasing reports associating certain chronic diseases such as asthma, atopy, and even certain forms of cancer with antimicrobial drug use [13,14]. Microbial specificity means that mAbs are unlikely to select for drug-resistant microbes among non-targeted microbes. The ability to specifically target disease-causing microbial populations without selecting for resistance makes mAb therapy potentially superior to current broad-spectrum antibiotics that are generally used in therapy, at least for microbial diseases caused by single microbes. The increasing prevalence and rising cost of treating methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and other resistant infections in both nosocomial and community settings emphasizes the need to develop new strategies for controlling infections.

2. mAbs as therapeutics

Serum therapy by definition uses immune sera-derived immunoglobulins that are polyclonal preparations consisting of many types of antibodies of which only a minute fraction is specific for the intended microbe. In contrast, mAb preparations consist of one type of immunoglobulin with a defined specificity and a single isotype. This represents both an advantage and a disadvantage when mAbs are compared to polyclonal preparations. One advantage is that mAbs, by virtue of the fact that they are chemically defined reagents, exhibit relatively low lot-to-lot variability in contrast to polyclonal preparations, which can differ over time and by source of origin since different hosts mount different antibody responses. Another advantage for mAb preparations is a much greater activity per mass of protein since all the immunoglobulin molecules are specific for the desired target. This phenomenon is illustrated by the report that two 0.7 mg doses of two mAbs provided the same protection against tetanus