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Preface xiii

Nancy Misri Khardori

Biologic Response Modifiers: Relevance & Repercussions 719

Romesh Khardori and Nancy Misri Khardori

Biologic response modifiers (BRMs) are substances that occur naturally in the body. They can also be manufactured in the laboratory and then administered as targeted therapy. Undoubtedly BRMs will find expanded role in terminal illness like cancer where other therapies have failed. However, great caution must be exercised in prescribing these agents in chronic indolent diseases where potential for ultimate harm might outweigh short-term benefits.

Overview of Biologic Response Modifiers in Infectious Disease 723

K. Noel Masihi and Hubert Schäfer

The conventional treatment of infectious agents is increasingly encountering antimicrobial resistance. This resistance has led to an intense search for novel treatment modalities for infectious diseases. Elucidation of the mechanisms underlying the inhibitory activity of chemokines has been instrumental in the rational design of anti–human immunodeficiency virus chemokine drugs. The immune-based therapies, in combination with antimicrobial drugs, for viral hepatitis have attracted much attention. Recognition of toll-like receptors by synthetic immunomodulators is used for certain viral infections. New methodologies have the potential to identify novel targets and foster the development of individually tailored immunomodulatory drug treatments.

Role of Endogenous Biological Response Modifiers in Pathogenesis of Infectious Diseases 733

Praveen K. Mullangi, Lokesh Shahani, and Janak Koirala

Biologic response modifiers (BRMs) interact with the host immune system and modify the immune response. BRMs can be therapeutically used to restore, augment, or dampen the host immune response. Although they have been used for decades, their clinical applications have been expanded in the past decade for diagnosis and treatment of many diseases including cancers, immunologic disorders, and infections. This article discusses endogenous biological response modifiers (ie, naturally occurring immunomodulators as a part of the host immune system), which play vital roles as regulators of both innate and adaptive immune responses.

Vaccines and Vaccine Adjuvants as Biological Response Modifiers 755

Cristian Speil and Robert Rzepka

Vaccines have been used successfully for many years to prevent death and morbidity from infectious diseases. In the last two decades major
advances in the fields of genetics and immunology have allowed a significant increase in the use of immunomodulatory drugs in a broad range of pathologic conditions. This article reviews several uses of immunomodulating properties of vaccines, both old and new, with a focus on cancer and autoimmune diseases. Special emphasis is placed on the historical aspects and current applications of the bacillus Calmette-Guérin vaccine, the first vaccine to be used in cancer immunotherapy.

**Polyclonal Immunoglobulins and Hyperimmune Globulins in Prevention and Management of Infectious Diseases**

Jennifer L. Hsu and Nasia Safdar

Immunoglobulin therapy has a rich history of use in preventing and treating infectious diseases; however, clinical data on the efficacy of immunoglobulin is lacking for many infectious diseases. Immunoglobulin therapy is routinely used in postexposure prophylaxis for bacterial infections, including tetanus, botulism, and diphtheria, and viral infections, including hepatitis A and B and varicella. Immunoglobulin therapy has also been used in many severe and life-threatening infections where treatments are limited, including toxic shock syndrome, respiratory syncytial virus infection, and cytomegalovirus infection. The authors review the evidence for the use of immunoglobulin therapy in common adult infectious diseases.

**Monoclonal Antibodies in Infectious Diseases: Clinical Pipeline in 2011**

Jan ter Meulen

Of the more than 20 monoclonal antibodies (mAbs) generated to combat infectious diseases (ID) that are in clinical development in 2011, most are in phase 1 or 2 and are directed against either viruses or bacterial toxins. Several high-profile anti-ID mAbs have recently failed in clinical trials. Despite the advancement in recombinant engineering technologies, anti-ID mAbs have yet to deliver on their promise as “magic bullets,” especially against nosocomial infections. A paradigm shift in favor of developing mAb combinations, which act synergistically with each other or with small molecule drugs, may be required to move the field forward.

**Colony-Stimulating Factors in the Prevention and Management of Infectious Diseases**

Andrea V. Page and W. Conrad Liles

Colony-stimulating factors (CSFs) are attractive adjunctive anti-infective therapies. Used to enhance innate host defenses against microbial pathogens, the myeloid CSFs increase absolute numbers of circulating innate immune effector cells by accelerating bone marrow production and maturation, or augment the function of those cells through diverse effects on chemotaxis, phagocytosis, and microbicidal functions. This article summarizes the evidence supporting the accepted clinical uses of the myeloid CSFs in patients with congenital or chemotherapy-induced neutropenia, and presents an overview of proposed and emerging uses of the CSFs for the prevention and treatment of infectious diseases in other immunosuppressed and immunocompetent patient populations.
Interferons as Therapeutic Agents for Infectious Diseases

Scott J. Bergman, McKenzie C. Ferguson, and Cathy Santanello

This article explains the rationale for development of interferons as therapeutic agents, and describes commercial products available today. It also provides a summary of studies that have been performed with interferons for use as exogenous biological response modifiers in viral infections. Overall, the best data exist for treatment of viral hepatitis B and C, for which interferons are a cornerstone of therapy. Although infections with human papillomavirus and common cold viruses sometimes respond favorably to interferons, their outcomes are far from ideal. Finally, the role of interferons as vaccine adjuvants is still being explored but could be promising.

Mediators of Systemic Inflammatory Response Syndrome and the Role of Recombinant Activated Protein C in Sepsis Syndrome

Vivek Kak

The systemic inflammatory response syndrome, the host’s response to infection involves a series of cascading events that mobilize a series of mediators involving the immune system, complement, and the coagulation cascade. Although the initial focus of mediators is to limit infection, this cascade may run amok and cause the development of hypotension, vascular instability, and disseminated intravascular coagulation, leading to morbidity and mortality in the host. Several therapeutic trials have focused on the modulation of these mediators, but use of recombinant human activated protein C in patients with severe sepsis is the only one that has shown a benefit in clinical trials.

The Common Immunogenic Etiology of Chronic Fatigue Syndrome: From Infections to Vaccines via Adjuvants to the ASIA Syndrome

Hemda Rosenblum, Yehuda Shoenfeld, and Howard Amital

Chronic fatigue syndrome (CFS) is characterized by unexplained fatigue that lasts for at least 6 months with a constellation of other symptoms. Most cases start suddenly, and are usually accompanied by a flu-like illness. It is a symptom-based diagnosis of exclusion, the pathogenesis of which is unknown. Studies have examined and hypothesized about the possible biomedical and epidemiologic characteristics of the disease, including genetic predisposition, infections, endocrine abnormalities, and immune dysfunction and psychological and psychosocial factors. Recently, the AISA (autoimmune/inflammatory syndrome induced by adjuvants) syndrome was recognized, indicating the possible contribution of adjuvants and vaccines to the development of autoimmunity.

Mycobacteria and Biological Response Modifiers: Two Sides of the Relationship

Vidya Sundareshan, Jignesh Modi, and Nancy Misri Khardori

With increasing use of biological response modifiers (BRMs) for various systemic inflammatory diseases there is a need to be vigilant about complications with the use of these therapies. It is important to have appropriate
screening for the infections in patients requiring BRMs. However, many studies have reported benefits of certain BRMs in the treatment of infections such as tuberculosis as adjuncts. Continued research and technical advances in immunogenetics helps understand complex mechanisms in the usage of the BRMs. This article summarizes the different aspects of the relationship between mycobacterial infections and the use of various BRMs for inflammatory conditions.

Biologics and Infections: Lessons from Tumor Necrosis Factor Blocking Agents 895

Robert S. Wallis

In the decade since tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)) antagonists were first approved for clinical use, they have proven invaluable for the treatment of specific types of chronic inflammation. Currently licensed TNF blockers fall into two classes, monoclonal antibody (or antibody fragments) and soluble receptor. Although they are equally effective in rheumatoid arthritis and psoriasis, important differences have emerged with regard to efficacy in granulomatous inflammation and risks of granulomatous infections, particularly tuberculosis. This article focuses on recent studies that inform prevention and management of infections in this susceptible patient population.