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Foreword

Immunotherapeutic agents for SLE

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Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease whose pathogenesis is multifactorial relying on genetic and environmental factors and on abnormalities of both the innate and the adaptive immune system. The induction, maintenance and progression of the disease are a multistep process that may take a long time, eventually leading to tissue injury. The resulting tissue damage is influenced by the presence of local factors responsible for the final lesions and the clinical manifestations [1].

In spite of such a variety of pathogenic mechanisms, the control of the disease activity and the progression to end-stage organ damage has improved in a substantial manner in the last decade. Accordingly, the morbidity and mortality of lupus patients changed dramatically with a definitely better prognosis [2].

However, the battery of therapeutic tools has been limited and most of the drugs commonly used in SLE have been the same for a long time, even if with new combinations and dosages. The only exception was represented by the use of mycophenolate mofetil in the induction and maintenance treatment of lupus nephritis [3].

This situation is rather in contrast to the revolution of the immunosuppressive armamentarium in other systemic autoimmune diseases and in transplantation. This is particularly true for autoimmune inflammatory

arthritis where a number of biological agents are now available. Most of them are monoclonal antibodies or soluble receptors able to antagonize proinflammatory mediators (i.e., proinflammatory cytokines) or synthetic compounds interfering with costimulatory molecules on effector immune cells.

Not surprisingly, this scenario is moving also for lupus, since innovative therapeutic tools are now available or about to be available soon. In line with the rationale behind the development of the new drugs for inflammatory arthritis, most of the new molecules for lupus are monoclonal antibodies targeting the B-cell compartment. Such an approach fits well with the widely accepted hypothesis that lupus is mainly an autoantibody-mediated disease.

The authors of this book have addressed a variety of innovative relevant management issues for the treatment of SLE, which are already available or under active validation.

The first chapter by Kaul and Hughes sets the scene, summarizing the recent pathogenic steps for the lupus disease. The immune system deregulation in SLE is characterized by several abnormalities affecting the cellular and humoral compartment and involving both adaptive and innate immunity. The heterogeneity of SLE pathogenesis may also explain the clinical variety in line with the identification of patient subgroups with distinct clinical and serological features. Defects or altered functions have been reported in the T-cell compartment, including the role of Tregs, as well as in dendritic cells and in the B-cell compartment. All these cells can be candidate targets for treatment either directly and indirectly through the blocking of the secreted soluble mediators. Additional therapeutic tools are represented by molecules able to block complement activation or by the stem cell therapy.

Although the T-cell compartment is also actively involved, SLE has been traditionally considered a prototype of an autoantibody-mediated autoimmune disease. In this regards, particular attention has been paid on drugs targeting B cells.

Díaz-Lagares, Ramos-Casals and Khamashta cover the topic of the use of rituximab for lupus patients in Chapter 2. Rituximab is a chimeric anti-human CD20 monoclonal antibody designed to deplete CD20-positive immature, naive, memory and germinal-center B cells, but not early pre-B cells or plasma cells. Despite negative results in controlled trials, substantial clinical experience has been accumulated in the off-label use of rituximab, mainly in refractory lupus patients.

Another B-cell-targeted monoclonal antibody is epratuzumab: a humanized monoclonal anti-CD22 IgG_{1κ} that binds to the third Ig-like domain of CD22. CD22 modulates signaling via the B-cell receptor complex playing a role in B-cell activation and survival. Goldenberg and Wallace (Chapter 3) review its development in treating lupus patients. Epratuzumab appears to be safe and ameliorative in patients with moderate to severe SLE in preliminary studies.

The survival and maturation of B cells are regulated by several molecules that bind to specific cell membrane receptors and trigger intracellular signaling. Interfering with such an interaction may downregulate B-cell survival/activation and represents the rationale behind the development of antagonists against B lymphocyte stimulator (BLyS) or a proliferation-inducing ligand (APRIL).

Belimumab is a fully human monoclonal antibody that binds soluble BLyS, thus preventing its activity as a key factor in the selection and survival of B cells. Its use in SLE is reviewed by Cervera and Espinosa (Chapter 4). Two Phase III trials have demonstrated that belimumab, in combination with standard-of-care therapy, significantly reduced disease activity and flare rates in patients with active SLE. The drug has been approved by the European and American medicine regulatory agencies, becoming the first biological therapy available for SLE.

Bertoli and Alarcon discuss the role of other antagonists targeting BAFF and APRIL (Chapter 6). Atacicept (TACI-Ig) is a soluble, fully human, recombinant fusion protein of IgG₁ Fc and the extracellular domain of the TACI receptor that binds BAFF and APRIL, and inhibits their action on B cells. LY2127399 is a fully human IgG₄ monoclonal antibody that neutralizes membrane-bound and soluble BAFF. Both molecules appear promising in modulating the B-cell compartment in SLE.

The use of intravenous immunoglobulins (IVIgs) in lupus patients is not new, but it is becoming more and more common for treating a variety of clinical manifestations. Rozman and Zandman-Goddard review IVIg use in Chapter 5. Although large clinical trials are still lacking because of the huge costs and the difficulties in their planning, there is strong evidence that IVIGs are effective as an adjunct therapy for refractory patients or for those that refuse conventional steroid and immunosuppressive treatment. The mechanism(s) of action is (are) not unique and is (are) still matter of investigation.

Finally, the potential role of TNF- α -blocking agents in SLE is discussed in Chapter 6 as a further therapeutic approach. The balance between the possible benefit of infliximab in active SLE and the potential ability of

TNF- α -blocking agents to trigger antinuclear autoantibody production and or a true drug-induced lupus is a hot point. The finding in favor of a therapeutic effect is still limited to few studies that enrolled a small number of patients and the safety was demonstrated only for short periods of treatment.

The approach to SLE has rapidly evolved over the last few years. Our diagnostic power has dramatically improved as well as our skill in treating the major complications of the disease. This is particularly true for the kidney involvement. On the other hand, physicians taking care of lupus are aware of the potential cardiovascular comorbidity and are ready to start aggressive primary prophylaxis. The availability of new (and innovative) drugs raises the concrete possibility to hypothesize different therapeutic strategies tailored to individuals depending on the clinical subtypes.

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