Immunomodulatory Drugs and Monoclonal Antibodies

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7.1 Immunity: Recognition of Nonself

The traditional classification of the human immune system divides the host response to external pathogens and transformed cells into innate immunity and adaptive immunity (Parkin and Cohen 2001). The innate immune system is comprised of neutrophils, monocytes, macrophages, dendritic cells, NK lymphocytes, and the plasma complement proteins. More recent definitions have expanded the innate immune system to include platelets, endothelium, and the coagulation cascade (Parkin and Cohen 2001; Blumberg et al. 2009; Mantovani et al. 1997; Loof et al. 2011). The innate immune system represents the first line of host defense against foreign pathogens. Innate immunity performs its immune surveillance function via Toll-like receptors which recognize conserved pathogen-associated molecular patterns (PAMPS) but also pattern-recognition receptors (PRRs) and NK receptors (Kawai and Akira 2011). The initial response of the innate immune systems feeds into and directs the subsequent responses of adaptive immunity by antigen processing and cytokine production (Parkin and Cohen 2001).

Adaptive immunity involves the expression of a targeted lymphoid response against foreign pathogens involving thymic (T) lymphocytes and antibody-producing B lymphocytes. The targeted responses of the adaptive immune system can further recruit and amplify the cellular responses of the innate immune system (Parkin and Cohen 2001). This is performed in large part by antibody-mediated pathogen clearance. Antibodies can also mediate complement lysis of pathogens in

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addition to Fc-receptor phagocytosis of pathogens by neutrophils, monocytes, macrophages, and hepatic Kupffer cells. Also cytokines and immune-modulatory molecules produced by lymphocytes can activate and upregulate innate immune responses by activation of subtypes of monocytes and macrophages (Gordon and Taylor 2005). Cellular immune responses of the cytotoxic (CD8+) T lymphocytes can clear viral infected and transformed cells. Both antibody and cellular immune responses are regulated by antigen-specific helper/inducer (CD4+) T lymphocytes. The CD4 lymphocyte can also function as an effector cell, enhancing the intracellular macrophage killing of pathogens by the production of interferon-γ (Gordon and Taylor 2005).

7.2 Autoimmunity: Loss of Self-Tolerance

During the development of mature B and T cells, lymphoid precursors highly attracted to self-antigens are eliminated. Lymphocytes in the bone marrow will become B cells and those that enter the thymus will become T cells. As they are maturing, those cells that are self-reactive will undergo apoptosis, in a process that is called central tolerance. Most of the deletion of strongly self-reactive T lymphocytes occurs in the thymus (Palmer 2003; Sakaguchi 2004).

Most of the lymphocytes that recognize nonself (foreign) antigens will, therefore, enter the peripheral circulation occupying lymph nodes, spleen, and bone marrow where they will expand when they meet antigen. A few self-recognizing lymphocytes with low reactivity to self will also enter the peripheral circulation, where they will either remain inactive or be deleted when activated in order to prevent disease. This is called peripheral tolerance (Sakaguchi 2004; Takahashi and Nomura 2003). Peripheral tolerance is mediated in large part by natural and inducible T regulatory cells (T_{reg}) (Gordon and Taylor 2005; Palmer 2003; Sakaguchi 2004; Takahashi and Nomura 2003).

The existence of families with multiple individuals with autoimmune disorders, an increased risk of autoimmune disorders in siblings, and the pronounced increased risk of such disorders in identical twins strongly speaks to a genetic propensity for autoimmune diseases (Kuchroo et al. 2012; Gregersen and Behrens 2006). Murine and human genome-wide studies have found a number of genes associated with an increased risk of autoimmunity. While some genes are well known to be associated with immune regulation, genes in the major histocompatibility complex (MHC) region account for the greatest number of genetic associations with autoimmune disease (Rioux et al. 2009). Such changes in the MHC genes may account for the failure to delete some lower affinity self-reacting lymphocytes which can escape central deletion.

Environmental factors undoubtedly contribute to the development of autoimmunity. Even in identical twins, the incidence of autoimmune disorders is only 40–50% of the monozygotic sibling (Selmi et al. 2004). There are a number of environmental factors that have been shown capable of inducing autoimmune responses in genetically susceptible individuals. Epidemiologic studies have

found associations between acute and chronic viral or bacterial infections, immunizations, environmental toxins, certain drugs, smoking, vitamin D deficiency, and even changes in the intestinal microbiome to potentially induce autoimmune disorders (Kuchroo et al. 2012; Gregersen and Behrens 2006; Kosiewicz et al. 2014).

The innate immune system also plays an important role in maintaining self-tolerance. However, an aberrant innate immune response to pathogens, drugs, toxins, or commensal microbiota can induce a severe inflammatory state presenting the adaptive immune system with autoantigens derived from damaged tissues and inducing an adaptive T- and B-lymphocyte autoimmune reaction. Under such circumstances the presence of inflammatory-induced co-stimulatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) further drives the adaptive immune response by inhibiting T_{reg} suppressor function leading to a chronic autoimmune state (Kuchroo et al. 2012; Gregersen and Behrens 2006; Dissanayake et al. 2011).

In susceptible individuals, the induction of autoimmunity pushes the T-lymphocyte repertoire toward a pro-inflammatory state defined by a pattern of cytokines expressed by the subsets of thymic lymphocytes (Kuchroo et al. 2012; Gregersen and Behrens 2006). The inflammatory T_H1 CD4+ helper lymphocyte repertoire is defined by the production of interferon-γ, interleukin 2 (IL-2), and TNF. The T_H17 lymphocyte repertoire is defined by the secretion of IL-17 and IL-22. A third pro-inflammatory repertoire termed T_{FH} lymphocytes expresses the CD4+ inducible T-cell co-stimulator receptor and the C-X-C chemokine 5 receptor and secretes IL-21. T_{FH} lymphocytes support the expansion of autoantibody production. A T_H2 repertoire expresses the anti-inflammatory cytokine Il-10, along with IL-4, IL-5, IL-6, IL-9, and IL-13, which can invoke strong antibody responses and inhibit some neutrophil and macrophage effector functions (Del Prete 1998). Suppression of the pro-inflammatory lymphocyte repertoires requires reconstitution of T_{reg} suppressor function (Kuchroo et al. 2012; Gregersen and Behrens 2006; Sakaguchi et al. 2006).

The challenge for the clinician is to modulate the immune system in patients with autoimmune disease resulting in a therapeutic induced self-tolerance without inducing significant immune suppression, therefore, diminishing the patient's immune response to foreign pathogens and transformed cells. The heterogeneity of the underlying pathophysiology may account for the variable responses to many treatment regimens. In addition, the process of immunomodulation can in and of itself result in further disruption of immune tolerance resulting in the emergence on new autoimmune disorders. This can occur with immune suppression in patients with bone marrow or solid organ transplants (Minchinton and Waters 1985; Taylor et al. 2006). The recent use of the cytotoxic anti-CD52 monoclonal antibody, alemtuzumab, in multiple sclerosis has resulted in a surprisingly high incidence of autoimmune disorders suggesting that imbalance in T-lymphocyte recovery after significant lymphocyte depletion can lead to a loss of self-tolerance (Cuker et al. 2011; Daniels et al. 2014; Von Kutzleben et al. 2016; Jones et al. 2013).

7.3 Therapeutic Approaches to Immune Modulation

The development of immune-modulating therapies for induction of self-tolerance with transplantation and treatment of autoimmune disorders has progressed rapidly since the first reports by Schwartz and Dameshek on the induction of immune tolerance in rabbits with 6-mercaptopurine (Schwartz and Dameshek 1959, 1960). Only 4 years after their initial reports, they subsequently reported on the use of the drug for treatment of patients with autoimmune hemolytic anemia (Schwartz and Dameshek 1962). Most often designated as immunosuppress drugs, subsequent therapeutic agents have been developed that target one or more components of the immune system. They can be broadly defined as inhibitors of T-lymphocyte activation and proliferation, inhibitors of B-lymphocyte activation and proliferation, inhibitors of the innate immunity, inhibitors of immune cell trafficking, cytokine inhibitors, and drugs that deplete T or B lymphocytes or both (Table 7.1). In addition they can also be classified as cytotoxic drugs used to deplete broad or specific

Table 7.1 Targets of immune-modulating agents

T lymphocyte	B lymphocyte	Monocyte, macrophage	Inhibitors of cell trafficking	Cytokine and cytokine receptor inhibitors
Corticosteroids	Corticosteroids	Corticosteroids	Corticosteroids	Corticosteroids
6-Mercaptopurine	IVIG	IVIG	IVIG	IVIG
Azathioprine	6-Mercaptopurine	6-Mercaptopurine	Natalizumab	*TNF inhibitors*
Mycophenolate	Azathioprine	Azathioprine	Crizanlizumab[a]	Infliximab
Cyclophosphamide	Mycophenolate	Mycophenolate	GMI1070[b]	Adalimumab
Alemtuzumab	Cyclophosphamide	Cyclophosphamide		Golimumab
Cyclosporine	Alemtuzumab	Fostamatinib[c]		Certolizumab
Tacrolimus	Rituxumab			*IL-1 inhibitors*
Sirolimus	Ofatumumab			Anakinra
Everolimus	Veltuzumab			Canakinumab
BI655064[d]	Ocrelizumab			Rilonacept
BMS98004[d]				*IL-12/23 inhibitors*
				Ustekinumab
				IL-6 inhibitors
				Tocilizumab
				IL-17 inhibitors
				Secukinumab
				Ixekizumab
				Brodalumab
				BAFF inhibitors
				Belimumab

[a]Crizanlizumab is a P selectin inhibitor in trial
[b]GMI 1070 is an E-selectin inhibitor in trial
[c]Fostamatinib is a Syk inhibitor in clinical trial
[d]BI655064 and BMS986004 are CD40 ligand inhibitors in clinical trial

cellular populations or agents that inhibit signaling pathways which can mediate their effect by blocking extracellular or intracellular targets. The contemporary repertoire of immune-modulating agents has expanded from such cytotoxic chemotherapeutic agents as cyclophosphamide, methotrexate, and 6-mercaptopurine to now include humanized monoclonal antibodies that either are lymphocyte cytotoxic, cytokine inhibitory, and cytokine receptor inhibitory or block important trafficking molecules for neutrophils, monocytes, or lymphocytes. In addition, there are an expanding number of small molecules that inhibit important intracellular signaling pathways in lymphocytes. These can be cytotoxic for selected lymphocyte cellular populations or downregulate lymphocyte cellular responses to activating signals.

7.4 Glucocorticosteroids

Glucocorticosteroids (GC) were the first (Hench et al. 1949) and remain one of the most important agents for the treatment of autoimmune disorders with the broadest spectrum of immune-modulatory effects (Van der Goes et al. 2014). The spectrum of their biologic effects can change with increasing doses. At low doses they affect immune cell trafficking, downregulate FcR expression on macrophages and neutrophils, and modulate cell signaling. With higher doses they can induce apoptosis of eosinophils and mast cells, inhibit dendritic cell differentiation, and suppress cytokine production from T lymphocytes, macrophages, endothelial cells, and smooth muscle cells. At very high doses, they can induce apoptosis of plasma cells and T and B lymphocytes. Corticosteroids can inhibit B-lymphocyte differentiation into plasma cells (Yan et al. 2015). Long-lived T-lymphocyte memory cells appear to be resistant to the cytotoxic effect of corticosteroids. A recently described subset of T lymphocytes termed IL-17 producing CD4/CD8 double-negative T lymphocytes were described in patients with Sjogren's syndrome. When studied this subpopulation of thymic lymphocytes was resistant to dexamethasone treatment when compared to CD4+ and CD8+ thymic lymphocytes (Alunno et al. 2013). This and other studies show that different subsets of T lymphocytes may have significant differences in their sensitivity to corticosteroids.

Compared to other immune-modulating agents, the onset of action by glucocorticoids can be very rapid. Upon binding to the glucocorticoid receptor (GR), the complex of the receptor with the glucocorticoid (GR/GC) is rapidly transported to the nucleus where it binds to the glucocorticoid binding sites for transcription of specific genes. Among such gene products are other transcription factors which work with the GR to induce transcription of additional gene products in what is termed a feed-forward gene regulatory loop (Meijsing et al. 2009; Psarra and Sekeris 2009; Sasse et al. 2013). In addition to its role in gene transcription, the GR/GC complex has direct and indirect effects on mitochondrial function and as yet unexplained cytoplasmic cellular effects.

7.5 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) was first shown to have immunomodulatory effects in the treatment of immune thrombocytopenia (Imbach et al. 1981; Newland et al. 1983). While most responses as a single agent are of short duration, longer duration responses were reported in an early trial on the treatment of ITP with repeated infusions for patients not candidates for splenectomy (Bussel et al. 1988). A number of possible mechanisms for the immune-modulatory effects of IVIG have been proposed using murine experimental models and translational studies of treated patients (Imbach et al. 2010). It is reasonable to assume that there are several different immune-modulatory mechanisms mediated by this complex mixture of antibodies, inclusive of immune complexes, anti-idiotypic antibodies, cytokines, and cellular receptors that can affect the underlying immunopathology for a variety of autoimmune disorders (Seite et al. 2008; Blasczyk et al. 1993). Its toxicities have been well characterized and maybe related to the patients' age, comorbidities, the rate of IVIG infusion, and the dose of IVIG used (Hamrock 2006). However, the lack of uniformity in most IVIG preparations could also explain the variability in therapeutic response. It is notable that when given in a 24-h continuous infusion combined with platelet transfusions, it induced sustained increases in platelet counts for refractory patients who previously failed to respond to IVIG (Chandramouli and Rodgers 2000; Olson et al. 2016). Other chapters in this volume will cover, in greater detail, the biologic and immune-modulatory effects of IVIG. However, it could be generalized that IVIG, after corticosteroids, is the broadest immunomodulatory agent affecting both the innate and adaptive immune system (Imbach et al. 2010).

IVIG has often been combined with other immunomodulatory agents. Not cytotoxic, IVIG immune-modulatory effects spare bone marrow function. It is often combined with corticosteroids in regimens for refractory ITP and autoimmune hemolytic anemia (Bussel et al. 1988; Boruchov et al. 2007; Barcellini et al. 2014). When combined with corticosteroids, the combination also appears to reduce the incidence and severity of unwanted IVIG toxicities such as infusion-associated reactions and aseptic meningitis. In the treatment of chronic ataxic neuropathy, IVIG has also been combined with rituximab (Loscher et al. 2013). Combination therapy for refractory ITP patients has also incorporated vincristine and azathioprine (Boruchov et al. 2007).

7.6 Cytotoxic Chemotherapeutic Agents

Cytotoxic agents such as cyclophosphamide (CTX), methotrexate (MTX), azathioprine (AZA), 6-mercaptopurine (6-MP), and mycophenolate mofetil (MMF) all demonstrate a broad spectrum of cellular cytotoxicity that can deplete T and B lymphocytes along with general bone marrow suppression. They also, in a dose-dependent manner, inhibit bone marrow production of important effectors of the innate immune system, neutrophils, and macrophages.

7.6.1 Cyclophosphamide

The immunologic effects of cyclophosphamide have been most extensively studied and have documented significant dose-related immune-modulating effects. Low doses of CTX can transiently suppress $CD4^+FOXP3^+$ T regulatory cells, shifting the CD4 T-lymphocyte repertoire toward a T_H1 inflammatory pattern (Ghiringhelli et al. 2007). Higher doses have a broader depletion of T and B lymphocytes. With higher doses the $FOXP3^+$regulatory T lymphocytes and hematopoietic stem cells are much more resistant to cyclophosphamide due to their increased expression of aldehyde dehydrogenase (Kanakry et al. 2013). Clinically, the superiority of high-dose intravenous CTX versus low-dose oral CTX for the treatment of autoimmune disorders has been clearly demonstrated in clinical trials on its use for the treatment of vasculitic disorders (de Groot et al. 2009). Complete remission was obtained with low doses of CTX when given as intravenous pulses (de Groot et al. 2009).

7.6.2 Methotrexate

Methotrexate, a dihydrofolate reductase inhibitor, was initially developed as an antineoplastic agent but is often used today as an immune modulator in rheumatoid arthritis and other autoimmune disorders. It rapidly induces apoptosis of activated lymphocytes. Lymphocytes in G0 or G1 phase of the cell cycle are resistant to the drugs cytotoxic effect (Genestier et al. 1998). This selective deletion of activated T lymphocytes may partially explain how MTX therapy in juvenile rheumatoid arthritis predominantly suppresses T effector cell activity but spares T regulatory cells (Calasan et al. 2015). Methotrexate is now most often used in combination therapy of rheumatoid arthritis but contributes to higher response which is associated with suppression of Th1/Th2 and Th17 phenotype with increase in T_{reg} number and function (Lina et al. 2011).

7.6.3 Azathioprine, 6-Mercaptopurine, and Mycophenolate

Less is known about the dose-related immunologic effects of 6-MP, AZA, and MMF on T-lymphocyte subsets. AZA, 6-MP, and MMF influence purine synthesis by inhibiting the proliferative response of lymphocytes to activating stimuli. AZA and 6-MP inhibit the first step of de novo purine synthesis suppressing both T and B lymphocytes. The antiproliferative effect is nonselective and can result in significant neutropenia from bone marrow suppression at higher doses (Maltzman and Koretzky 2003). MMF is more selective for lymphocyte suppression by both inhibiting purine synthesis and by competitive inhibition of inosine monophosphate dehydrogenase (IMPDH). Activated lymphocytes are highly dependent on the IMPDH salvage pathway for purine synthesis (Allison and Eugui 1996). Therefore, there is less direct bone morrow suppression and greater lymphocyte selectivity (Sollinger 1995).

In randomized trials to evaluate the efficacy of AZA and MMF in prevention of acute graft rejection after kidney transplantation, MMF has shown higher efficacy (Merion et al. 2000). However, there is no comparative data on the use of these agents in the treatment of autoimmune disease. Using these agents, response to treatment may require several months of therapy. A study on the treatment of immune thrombocytopenia (ITP) with AZA, response in some patients took up to 4 months (Quiquandon et al. 1990).

7.7 Monoclonal Antibodies

Monoclonal antibodies, targeting specific antigens on lymphocyte subsets, have proven to be important therapeutic agents for the treatment of various autoimmune disorders. The contemporary repertoire of therapeutic immune-modulating humanized monoclonal antibodies can be classified as either cytotoxic for subsets of lymphocytes or inhibitory of important cytokines or chemokines, their receptors, and important cellular trafficking molecules.

7.7.1 Cytotoxic Monoclonal Antibodies

The B-lymphocyte antigen, CD20, was the first target for the development of a humanized monoclonal antibody. This was antigen originally selected as a potential target for treatment of B-cell lymphomas. Rituximab, the first of these humanized monoclonal antibodies to target the CD20 antigen on B lymphocytes, has been successfully utilized in the treatment of a number of autoimmune disorders. There are case reports and Phase II clinical trials on its use in patients with autoimmune hemolytic anemia, immune thrombocytopenia, coagulation factor VIII inhibitors, thrombotic thrombocytopenic purpura, rheumatoid arthritis, vasculitis, cryoglobulinemia, multiple sclerosis, and neuromyelitis optica (Dierickx et al. 2015; Patel et al. 2012; Franchini and Lippi 2008; Coca and Sanz 2012; Cacoub et al. 2012; Rubenstein et al. 2006). However, in the United States, rituximab is only FDA approved for the treatment of rheumatoid arthritis in combination with methotrexate. It is frequently combined with corticosteroids and other immune-modulating agents when used to treat autoimmune disorders (Bussel et al. 2014; Gupta et al. 2002). What is notable in regard to these antibody-mediated disorders is that the pathogenic antibodies are IgG immunoglobulins, produced primarily by plasma cells which show minimal CD20 expression. Despite this, treatment responses, depending upon the specific immunopathic disorder, range from 20 to 80%. In ITP, studies by Stasi and colleagues found that specific changes in the T-lymphocyte repertoire best define those patients who obtain a complete response to rituximab treatment compared to patients who failed to respond (Stasi et al. 2007, 2008). Increases in $CD4^{+}FOXP3^{+}$ T regulatory cells number and function are seen in the patients who obtain long-term complete remissions (Stasi et al. 2007, 2008). This effect may be due to modulation or B- and T-lymphocyte cross talk or depletion of

B lymphocytes as antigen-presenting cells. The later mechanism may be favored since anti-CD20 therapy given to adult ITP patients in the first year after diagnosis appears to be associated with a higher rate of complete response. This was further supported by a Phase II trial of a subcutaneous anti-CD20 humanized monoclonal antibody, veltuzumab, which showed a higher response to patients treated in the first year (Liebman et al. 2013). The anti-CD20 humanized monoclonal antibody, ocrelizumab, has recently been FDA approved for the treatment of primary progressive multiple sclerosis, becoming only the second humanized B-cell-depleting monoclonal to be FDA approved to treat nonmalignant autoimmune disorders (Montalban et al. 2017).

Alemtuzumab is a humanized monoclonal antibody that binds to the CD52 antigen present on most mature lymphocytes. It rapidly depletes both T and B lymphocytes and was originally approved in the United States for the treatment of refractory chronic lymphocytic leukemia. A number of case reports and small clinical trials have documented its use in several autoimmune disorders (Ru and Liebman 2003; Gomez-Almaguer et al. 2010). Recently, alemtuzumab was approved in the United States and Europe for the treatment of relapsing-remitting multiple sclerosis with significant clinical superiority over β-interferon 1a (Cohen et al. 2012). However, an unexpected late complication of this highly effective therapy has been the development of a variety of autoimmune disorders. Over a third of patients develop immune thyroid disease, most often Grave's disease, which is distinctly different from the pattern of thyroid disease that develops in the general population (Daniels et al. 2014; Weetman 2014). Also cases of immunopathic renal disease have been observed which include membranous glomerulonephritis and anti-GBM antibody disease (Goodpasture's disease) (Clatworthy et al. 2008). In 2% of patients treated in the clinical trials, acute decreases in platelet counts consistent with ITP were observed, beginning 14–36 months after the last injection of alemtuzumab (Cuker et al. 2011). These ITP cases all responded to standard ITP first-line therapies and all appeared to develop unmaintained remissions similar to pediatric ITP patients. The occurrence of the late development of other autoimmune disorders, despite effective control of the patients' multiple sclerosis, suggests that the potent lymphoid depletion by alemtuzumab results in a prolonged and significant defect in peripheral immune tolerance that can persist for years after treatment.

7.7.2 Noncytotoxic Immune-Modulating Monoclonal Antibodies

A number of humanized monoclonal antibodies have been developed to bind to and inhibit inflammatory cytokines or their receptors. The first initial therapeutic target was tumor necrosis factor-alpha (TNF-α). TNF is a broad family of potent cytokines central to systemic inflammation (Aggarwal 2003). It is produced by activated cells of the innate immune system including macrophages, neutrophils, eosinophils, NK cells, and mast cells. Inappropriate expression has been linked to a number of inflammatory autoimmune disorders such as rheumatoid arthritis, Crohn's disease,

ulcerative colitis, and psoriasis (Rutgeerts et al. 2005). The first of these antibodies, infliximab, which targets TNFα, has documented efficacy in inflammatory bowel disease, rheumatoid arthritis, psoriasis, and ankylosing spondylitis (Aggarwal 2003; Rutgeerts et al. 2005; Sands et al. 2004; Maini et al. 1999; Fong et al. 2016). Golimumab, adalimumab, and certolizumab are the second, third, and fourth anti-TNF-α inhibitory antibodies with the same general clinical indications as infliximab (Hibi et al. 2017; Colombel et al. 2007; Weinblatt et al. 2017). Adalimumab was the first totally humanized monoclonal therapeutic antibody, but except for this structural difference, there appear to be no significant therapeutic advantages to this antibody over the other two approved TNF-α inhibitory antibodies. A TNF receptor fusion protein, etanercept, acts as a competitive inhibitor of TNF binding to its receptor and is a therapeutic alternative to direct TNF inhibition.

The next generation of inhibitory antibodies targeted interleukin 1 (IL-1). IL-1 is produced by cells of the innate immune system, macrophages, monocytes, fibroblasts, and dendritic cells. It may also be produced by endothelial cells, NK cells, and B lymphocytes. There are 11 members of the IL-1 cytokine family, with IL-1 alpha and IL-1 beta being the most often studied (Garlanda et al. 2013). IL-1 is a central mediator of the inflammatory response of the body against infection. It induces expression of adhesion molecules on endothelial cells which results in neutrophil and monocyte adhesion to the vessel wall, rolling, and diapedesis into tissues. It is also the major inducer of TNF and the febrile response to infection. Canakinumab was the first FDA-approved humanized monoclonal directed against IL-1 beta to treat auto-inflammatory syndromes such as cryopyrin-associated periodic syndromes and more recently to treat juvenile rheumatoid arthritis (Kuemmerle-Deschner et al. 2016; Orrock and Ilowite 2016). The antibody also has documented efficacy in familial Mediterranean fever and other rare inflammatory syndrome (Kucuksahin et al. 2017; Gattorno et al. 2017). Similar to the TNF receptor competitive inhibitor, etanercept, interleukin 1 receptor competitive inhibitors, anakinra and rilonacept, have also demonstrated activity in the treatment of rheumatoid arthritis and other inflammatory disorders.

Therapeutic inhibitory humanized monoclonal antibodies inhibitory of interleukin 6 (IL-6), tocilizumab; inhibitory of interleukin 17 (IL-17), secukinumab, ixekizumab, and brodalumab; inhibitory of the interleukin 12/23 complex (IL12/23), ustekinumab; and inhibitory of B-cell-activating factor (BAFF), belimumab, are now approved for various immunopathic disorders.

Tocilizumab has demonstrated therapeutic efficacy in rheumatoid arthritis (Teitsma et al. 2016) and giant cell arteritis (Ostrowsk et al. 2014). Secukinumab, ixekizumab, and brodalumab have FDA approval and efficacy in the treatment of refractory psoriasis and psoriatic arthritis (Mease 2015; Mease et al. 2016, 2017). Ustekinumab by inhibition of IL12/23 downregulates the production of IL17 (Mease 2015). Therefore, it is not surprising that it has similar efficacy in the treatment of psoriasis and psoriatic arthritis (Kavanaugh et al. 2016). Belimumab is the first immune-modulating therapy approved for the treatment of systemic lupus erythematosus (Lutalo and D'Cruz 2014). The antibody also shows promise in the treatment of primary Sjogren's disease (Mariette et al. 2015).

7.8 Inhibitory Drugs of T-Lymphocyte Function

Calcineurin inhibitors, cyclosporine and tacrolimus, inhibit the calcineurin-mediated dephosphorylation the transcription factor nuclear factor of activated T cells (NF-AT), which is necessary for interleukin (IL)-2 transcription and T-cell activation. The potent T-lymphocyte suppression has made these drugs the primary therapeutic agents for preventing graft rejection for solid organ and bone marrow transplants (Wiederrecht et al. 1993). They have been used in a number of small studies for the treatment of autoimmune disorders, but their toxicities and inability to induce long-term remissions in most patients have limited their use. In refractory ITP low-dose cyclosporine (2–3 mg/kg) in several small case series could induce remissions in 40–50% of patients treated (Gesundheit et al. 2001; Kappers-Klunne and van't Veer 2001; Choi et al. 2015). However, approximately 70% of patients relapse after drug withdrawal. The addition of cyclosporine to combination regimens appears to enhance responsiveness in patients with refractory ITP (Choi et al. 2015).

Sirolimus and everolimus are inhibitors of the mTOR pathway through which a number of cytokines induce cell proliferation. Sirolimus blocks the T-lymphocyte proliferative stimulus of Il-2. However, the drug has a differential effect on T-lymphocyte subsets and appears to have little suppressive effects on the in $CD4^{+}FOXP3^{+}$ T regulatory cells (Shan et al. 2014). This may be an important role of the drug in its use for the treatment of graft versus host disease following allogeneic bone marrow transplant. Only a few case reports and case series have been published on the use of sirolimus for autoimmune disorders, the majority in pediatric disorders (Miano et al. 2014; Chatrath et al. 2014). However, a recent report has suggested an important role for the mTOR pathway in the pathophysiology of the antiphospholipid antibody syndrome (Canaud et al. 2014).

7.9 Summary

The increasing number of therapeutic agents for autoimmune disorders has significantly improved the outcomes for many patients but has resulted in only a small number of sustained unmaintained remissions. The variability of treatment outcomes to individual agents has clearly heterogeneous. As suggested by Cines and colleagues, many autoimmune disorders, like immune thrombocytopenia, should best be termed a syndrome and not a disease (Cines et al. 2009). Unraveling the heterogeneity of the various autoimmune disorders should result in better selection of therapeutic agents for the treatment of such patients.

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