Immunotherapy for Autoimmune Diseases

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Abstract

Various pathologies caused by a dysregulated immune system characterized by chronic inflammation leading to pain or permanent damage to tissue are grouped under an umbrella term "autoimmune disorders." Immunotherapy is a field of immunology that facilitates discovery of therapies for diseases by means of stimulation, augmentation, or suppression of an immunoresponse. Several emerging and promising next-generation immunotherapy modalities for autoimmune diseases such as checkpoint based immunotherapy, antigen-specific immunotherapies, anti-cytokine therapy, anti-T-cell therapy, anti-B-cell therapy and biologics and their combination therapy, etc., have evolved and initiated the new era of immunotherapy for autoimmune diseases in the recent past. We discuss these modalities in detail along with comprehensive tables that elucidate the specific therapies. Further, we delineate current immunotherapeutics in clinical trials for autoimmune diseases and discuss the "financial toxicity" of current immunotherapies in autoimmune diseases.

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4.1 The Immune System: An Overview

The human immune system is a complicated set of cellular and molecular mechanisms involving different proteins and biochemicals, which protects the human body against infectious pathogens, cancer cells, and alien substances without attacking the endogenous molecules. The protection of the host body against all types of infections by specifically recognizing and eliminating foreign agents is the prime function of the immune system (Viswanath 2013). In general, the immune system has two lines of defense: innate immunity and adaptive immunity. The first immunological, antigen-independent (non-specific) mechanism for combating an intruding pathogen is innate immunity. It is a rapid immune response which occurs within minutes or hours after attack. The innate immune response has no immunologic memory and, therefore, is unable to recognize or "memorize" the same pathogen when the body gets exposed to it in the future. Various cells are employed in the innate immune response such as phagocytes (macrophages and neutrophils), dendritic cells, mast cells, basophils, eosinophils, natural killer (NK) cells, and lymphocytes (T-cells) as well as complement system (Warrington et al. 2011). Both types of phagocytes act by a similar mechanism of engulfing the microbes. Besides this similar function, neutrophils release their specific granules which assist in the elimination of pathogenic microbes and macrophages also play an important role in antigen presentation to T-cells. Dendritic cells act as important messengers between innate and adaptive immunity by their ability to phagocytose and function as antigen-presenting cells (APCs). Both mast cells (which reside in the connective tissue surrounding blood vessels) and basophils (which reside in the circulation) are involved in the initiation of acute inflammatory responses, such as those seen in allergy and asthma. Eosinophils are granulocytes that possess phagocytic properties and play an important role in the destruction of large parasites which are difficult to phagocytose. NK cells also known as large granular lymphocytes (LGLs) play a major role in the rejection of tumors and the destruction of cells infected by viruses which is achieved through the release of perforins and granzymes from NK-cell granules which induce apoptosis (programmed cell death) (Stone et al. 2010). On the other hand, adaptive immunity is antigen-dependent and antigen-specific due to which it involves a lag time between exposure to the antigen and maximal response. When infection is established due to the inability of innate immunity to effectively eliminate infectious agents, adaptive immunity develops. The main characteristic feature of adaptive immunity is its ability to memorize the initial immunologic response which endows the host to generate a more rapid and efficient immune response upon subsequent exposure to the antigen. The most important functions of

the adaptive immune response are the detection of specific "non-self" antigens in the presence of "self" antigens; the activation of pathogen-specific immunologic effector pathways that eradicate specific pathogens or pathogen-infected cells; and the development of an immunologic memory that can promptly eliminate a specific pathogen when subsequent infections occur in future (Warrington et al. 2011). Adaptive responses are of two types: cell-mediated immunity, conducted by T-cells and facilitated by APCs; and humoral immunity (antibody-mediated immunity), mediated by antibodies produced by B-cells. The T lymphocytes account for 60–80% of total lymphocytes and have a very high lifetime. They primarily eradicate the intracellular pathogens by activating macrophages and kill virally infected cells by recognizing the primary structure of an antigen. T helper (Th) lymphocytes represent 2/3 of total lymphocytes and secrete interleukins (messenger molecules that assist the communications between immune system cells). Depending on the type of cytokines secreted, two types of Th cells are distinguished: Th1 cells which produce interleukin-2, IFN-γ, and TNF-α and trigger inflammatory reactions; and Th2 cells which produce interleukins 3, 4, and 5. In humoral immunity, activation of B lymphocytes results into the synthesis of antigen-specific immunoglobulins (antibodies) by plasma cells and development of immunological memory by memory B-cells (Grigore and Inform 2017). In conclusion, the tightly regulated interplay between T-cells, B-cells, and APCs play a significant role(s) in the development of adaptive immunity in concurrence with innate immunity to eradicate infectious agents. Thus, defects in either system can lead to immune pathological disorders such as hypersensitivity reactions, autoimmune diseases, and immunodeficiencies (Warrington et al. 2011).

4.2 Autoimmunity and Immune Tolerance

In simple words, the defect in the host's immune system that results in loss of normal immune homeostasis and produces an abnormal response to its own tissues is referred to as autoimmunity. The presence of self-reactive T-cells, auto-antibodies, and inflammation are the hallmarks of the autoimmunity (Warrington et al. 2011). The Nobel Prize-winning hypothesis of the "forbidden clone" by Macfarlane Burnet led to a better understanding of not only autoimmunity but also of lymphoid cell development, thymic education, apoptosis, and deletion of autoreactive cells and mechanisms of autoimmunity that led to clinical disease (Wang et al. 2015). Thus, autoimmunity is considered to be an interruption in the process of antigenic detection and elimination. Body's cells may undergo antigenic variation as a result of physical, chemical, or biological influences. Such "neo-antigens" (altered antigens) may elicit an immune response that destroys body's own cells (Ganapathy et al. 2017). Thus, autoimmunity may also be defined as the genesis of immune system reactivity via autoantibodies or T-cell responses to self-structures (Viswanath 2013).

The concept of immune tolerance was defined as an ability of the immune system to prevent itself from targeting self-molecules, cells, or tissues (Wang et al. 2014). During maturation of the immune system, it becomes "tolerant" to self by

eliminating the immune cells that react against self-tissues. To understand immune tolerance, it is important to realize the key concepts such as central tolerance, peripheral anergy, T regulatory cells (Tregs), and the homeostasis produced by cytokines and chemokines and their cognate receptors. During central tolerance in the thymus, developing lymphocytes go through positive selection in the cortex prior to maturing and entering the circulation while lymphocytes with impending reactivity against self-peptides are negatively selected and deleted in the thymic medulla. After leaving the thymus, mature T-cells undergo secondary selection (peripheral tolerance) by which the majority of self-reactive T-cells are deleted or rendered anergic. Further in the process of clonal deletion or clonal anergy, immature B-cells expressing surface immunoglobulin M (IgM) capable of recognizing ubiquitous self cell surface antigens are eliminated. Even though mature B-cells are under the control of peripheral tolerance, with the help of process known as clonal deletion or clonal anergy, autoreactive B-cells can escape deletion (Wang et al. 2015; Salinas et al. 2013). It is important to note that, in normal individuals also, potentially self-reacting lymphocytes can still "leak out" in small numbers into the periphery, even under the strict surveillance of central and peripheral tolerance. Thus, depending upon the existence of self-reactive T and B lymphocytes and their abilities to produce autoantibodies, autoimmunity can be classified as "physiological" and "pathological" autoimmunity (Avrameas and Selmi 2013). Physiological autoimmunity is generally staged without evidence of clinical disease where natural autoantibodies help to maintain normal immune homeostasis by eliminating self and foreign antigens. On the other hand, pathological autoimmunity is a stage that develops when immune tolerance is broken and autoantibodies and self-reactive lymphocytes become involved in inflammation which further lead to development of autoimmune diseases (Wang et al. 2015).

4.3 Autoimmune Diseases

The breach of immune tolerance, i.e. the failure to differentiate self from non-self, leading to the development of autoimmunity is the basis for autoimmune diseases. Various pathologies caused by a dysregulated immune system characterized by chronic inflammation leading to pain or permanent damage to tissue are grouped under an umbrella term "autoimmune disorders." In simple words, autoimmune diseases are the variety of diseases arising due to the irregular functioning of the immune system, that leads to the generation of immune system reactivity (Viswanath 2013). Indeed, autoimmune diseases are multi-etiological entities that develop due to disturbed immunoregulatory processes, as well as environmental and genetic abnormalities. Heredity accounts for about 30% of the risk of developing an autoimmune disease, while non-inherited, environmental factors account for the remaining 70% risk (Viswanath 2013; Nagy et al. 2015). There is a permanent failure of one or several tolerance mechanisms in autoimmune diseases due to the cumulative effect of various specific human leukocyte antigen (HLA), non-HLA genes, and environmental factors and/or derailed immune regulatory processes. This

leads to the development of self-reactive B- and T-cell clones, which cause damage to tissues or organs (Ermann and Fathman 2001). There are nearly 100 distinct autoimmune diseases, some of which are organ-specific such as primary biliary cirrhosis (PBC) and some of which reflect a variety of immunological dysfunction involving multiple organs such as systemic lupus erythematosus (SLE) (Wang et al. 2015; Yu et al. 2014). Thus, clinically autoimmune diseases can be classified as organ-specific (e.g., Type 1 diabetes mellitus) or systemic (e.g., systemic lupus erythematosus). The common types of autoimmune diseases such as Addison's disease, autoimmune hepatitis, celiac disease, Type 1 diabetes, Grave's disease (overactive thyroid), Guillain–Barre syndrome, Hashimoto's disease, hemolytic anemia, inflammatory myopathies, idiopathic thrombocytopenic purpura, multiple sclerosis, myasthenia gravis, psoriasis, primary biliary cirrhosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and vitiligo with their pathogenesis aspects are described elsewhere (Viswanath 2013; Wang et al. 2015).

A simple hypothesis for autoimmune diseases is that polymorphisms in various genes result in imperfect regulation or reduced threshold for lymphocyte activation, and environmental factors commence or enhance activation of self-reactive lymphocytes that have escaped control and are composed to react against self-constituents (Rosenblum et al. 2015). Autoimmune disorders are a group of diseases wherein structural/functional damage to cells/tissues/organs/organ systems is caused by the action of immunologically competent cells/antibodies against normal body constituents. To initiate autoimmunity several endocrine, genetic, and environmental factors interact together on immune system by the following mechanisms (Ganapathy et al. 2017; Wucherpfennig 2001):

1. *Cytolysis of the target cells*: Due to the release of tissue-specific autoantibodies via complement;
2. *Immune complex deposition*: Due to the binding of auto-antibody to soluble mediators;
3. *Phagocytosis, cytotoxicity, and antibody-mediated cellular immunity*: Due to the auto-antibody-mediated attack on immune system;
4. *Molecular Mimicry*: Auto-antibody against foreign antigen and auto-antigen epitopes which mimic foreign antigen (cross reactive antigen) leading to tissue damage;
5. *Stimulation/obstruction of the target structure*: Due to the action on cell surface structures by autoantibodies.

Thus, the stimulation and maintenance of immune tolerance signify major therapeutic goals in autoimmunity-caused autoimmune diseases (Janikashvili et al. 2016).

4.4 Immunotherapy for Autoimmune Diseases: General Considerations

Immunotherapy is a field of immunology that facilitates discovery of therapies for diseases by means of stimulation, augmentation, or suppression of an immunoresponse. Simply, immunotherapy is a type of therapy which uses substances made by a body or in a laboratory to stimulate or suppress the immune system in order to improve or restore normal functions of the immune system, so that the body can effectively fight against cancer, infection, and other diseases. Immunotherapies capable of initiating or boosting the immune response are referred to as "activating immunotherapies," while those capable of repressing the immune response are referred to as "suppressive immunotherapies" (Wraith 2017). More recently, the potential of immunotherapy to enhance or repress immune responses has been globally recognized and appreciated particularly in two areas of immunotherapy, i.e. suppressing immunotherapies for autoimmune diseases and activating immunotherapies for cancer. In the twenty-first century, the "immunotherapy revolution" started, with the approval of ipilimumab for melanoma. These cancer treatment approaches were based on activating immunotherapies which inhibit the inhibitors of the immune system releasing the brakes on the immune system. Subsequently, different immune checkpoint inhibitors, vaccines, and co-stimulatory agonists have been discovered and commercialized for a number of cancer types (Wraith 2017; De Miguel-Luken et al. 2017; Chen and Mellman 2013). On the other hand, the increased understanding of mechanisms of autoimmunity in recent years has paved the way to new promising therapeutic strategies for treating autoimmune diseases. This leads to the development of new types of immunotherapeutics that are capable of effectively and selectively targeting the self-reacting immune cells, cytokines, and other mediators of the immune response and are now available as cutting-edge therapies for autoimmune disease patients (Ostrov 2015).

The foremost challenge in the treatment of autoimmune diseases is to selectively suppress the autoimmune disease without affecting the control of rest of the functional immune system over cancers and infectious diseases. Hence, development of novel treatments with increasing specificity for the particular autoimmune disease is important with no or decreased risk of potential side effects (Wraith 2017). Historically in the 1980s, intra-venous immunoglobulin (IVIG) became a standard approach in managing autoimmune disorders, after the serendipitous discovery of polyclonal IgG immunoglobulin for the treatment of autoimmune thrombocytopenia (Imbach et al. 1981). After subsequent trials on many autoimmune disorders, greater than 70% of the IVIG prescribed in the United States by 2014 was for autoimmune and inflammatory diseases rather than for immunodeficiency (Ballow 2014). In recent years, further advancements in the research with various kinds of innovative work identifying new receptors, signaling pathways, monoclonal antibodies (MABs) and with the development of hybridomas and molecular cloning led to the discovery of new biologic agents directing the new treatments for autoimmune diseases (Ostrov 2015).

The current treatment strategies of autoimmune diseases include two major approaches, first is a "conservative approach" where a symptomatic or replacement therapy is given and second is an "aggressive approach" where immunosuppressive or immune modulation therapy is preferred. For instance, autoimmune thyroid disease is mainly managed either by reducing the production of thyroxin at the stage of hyper functioning of the thyroid gland or by hormone replacement therapy when the gland is damaged. On the other hand, in systemic diseases like SLE which targets vital organs like kidney, the primary treatment is immunosuppressive therapy in order to prevent more organ damage. Generally in autoimmune disease, 60–70% response is observed for immunosuppression with gradual decrease in the response to the drug used. Although in few cases there is a long-lasting remission of autoimmune diseases, some of the autoimmune diseases go for clinical remission to relapse after sometime (Chandrashekara 2012). It is important to note that currently available steroid and non-steroid immunosuppressive medicines for autoimmune diseases also have limited efficacy and we have been dependent on non-specific immunosuppressive therapies for quite some time (Wraith 2017). Hence, there is an immense need to develop new approaches and ways to modulate the immune system for developing new therapeutic strategies of immunotherapy for different autoimmune diseases. In the last few decades, significant advancements have occurred in the approaches of immunosuppressive therapy for autoimmune diseases. Compared to the initial immunosuppressive drugs which were non-specific and interfering with larger pathways and cells, current immunosuppressive drugs are more target-specific with profound immunosuppression effect, increased remission rate, and reduced toxicity on other collateral systems (Feldmann and Steinman 2005; Böhm et al. 2006). In recent years, several new types and therapeutic strategies of immunotherapy for autoimmune diseases have evolved. James P. Allison and Tasuku Honjo were awarded the 2018 Nobel Prize in Physiology or Medicine for the discovery of cancer therapy by inhibition of negative immunoregulation of CTLA4 and PD1 immune checkpoints. Immune checkpoint therapy has led to tremendous progress in clinical development and revolutionized cancer treatment. This seminal discovery has fundamentally improved the outcomes for many people with advanced cancer (Smyth and Teng 2018). Similarly, several emerging and promising next-generation immunotherapy modalities for autoimmune diseases such as checkpoint based immunotherapy, antigen-specific immunotherapies, anti-cytokine therapy, anti-T-cell therapy, anti-B-cell therapy and biologics and their combination therapy, etc., have evolved and initiated the new era of immunotherapy for autoimmune diseases over a past few decades. These modalities are being discussed in upcoming sections of this chapter.

4.5 Checkpoint-Based Immunotherapy for Autoimmune Diseases

As mentioned earlier, the important characteristic of an autoimmune disease is the induction of B-cell and T-cell autoreactivity directed against self proteins, i.e. autoantigens. In other words, self-tolerance is the unresponsiveness of the immune system to self-antigens, and dysregulation of immune homeostasis along with self-tolerance leads to autoimmunity, resulting in harmful inflammation in and destruction of autoantibodies generated by B-cells and self-tissues mediated by autoreactive T-cells (Zhang and Vignali 2016). During the T-cell development process, the majority of T-cells which are specific for self-antigens are erased or deleted in a process of thymic elimination to set up a focal tolerance prior to the entry of T-cells into the periphery (Hogquist et al. 2005). However, it is a known fact that, potentially self-reacting lymphocytes can still "leak out" in small numbers into the periphery, even under the strict surveillance of central and peripheral tolerance due to the incomplete thymic deletion process. Thus, in order to circumvent the attack on normal host cells by remaining self-specific T-cells, additional mechanisms are required. These mechanisms include inhibition of proliferation of self-antigen specific T-cells by development of regulatory T-cells (Tregs) and regulation of T-cell activation and their functions by development of checkpoint pathways. The peripheral tolerance mechanisms play a significant role in checking autoimmune diseases (He et al. 2017). According to the two-signal model, activation of native T-cells requires two signaling processes: stimulation by major histocompatibility complex (MHC)–peptide molecules of T-cell receptor (TCR), and co-stimulation on antigen-presenting cells (APCs) via co-stimulatory receptors and their corresponding ligands (Zhang and Vignali 2016). APCs express B7–1 (CD80) or B7–2 (CD86), the co-stimulatory molecules, which initiate the subsequent signals. T-cell co-stimulatory receptor CD28 recognizes these co-stimulating molecules and thus an engagement of both TCR and CD28 on same T-cells triggers their multiplication by prompting an initiating signal to the T-cells, leading to a T-cell response to a self-antigen (in autoimmunity) or a foreign antigen (He et al. 2017). On the other hand, the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) which is a T-cell receptor inhibitor, has a more prominent affinity for CD86 and CD80 ligands than the stimulatory receptor CD28. Consequently, CTLA-4 competes with CD28 for CD80 and CD86 (co-stimulating molecules) thereby serving as a checkpoint for T-cell response further leading to hyporesponsiveness or T-cell anergy (Linsley et al. 1994). Similarly, programmed death-1 (PD-1) has also been recognized as an immune checkpoint on T-cells or other immune cells. Along with its cognate ligands PD-L1 or PD-L2, PD-1 plays an important role in the process of peripheral tolerance to protect normal host tissue against self-reactive or specific T-cells by two mechanisms: blocking the escape of self-reactive T-cells into the periphery and promoting Treg development and function (Francisco et al. 2010; Fife and Pauken 2011). Thus, the immune checkpoint pathways play a crucial role in maintaining health by modulating harmony between protective T-cell response and T-cell tolerance.

Despite the fact that advancements in checkpoint-based immunotherapies for autoimmune diseases are relatively slow compared to that for cancer, this field has attracted a great deal of research interest. In both cases the aims for checkpoint-based immunotherapies are different where activation of T-cells is the prime aim in treating the cancer and chronic infections, whereas blocking the activation of self-specific or self-reactive T-cells is the prime goal in the treatment of autoimmune diseases (He et al. 2017). CTLA4-Ig (Abatacept) is an FDA-approved drug used to treat diseases like juvenile idiopathic arthritis and rheumatoid arthritis, and is currently being tested for other autoimmune diseases in several clinical studies. Abatacept is a soluble recombinant human fusion protein that is characterized by an extracellular domain of human CTLA-4 which is linked to a modified Fc domain of human IgG1. This agent binds to the co-stimulatory molecules B7–1/B7–2 present on APCs and mimics the action of the native CTLA-4. This results in the downregulation of autoreactive effector T-cell responses due to competitive inhibition of the crucial CD28:B7–1/B7–2 co-stimulatory signaling pathway(s) required for T-cell activation (Ruperto et al. 2008). The use of an Fc-chimeric version of PD-L1 in an in vitro model has demonstrated collapse of self-reactive T-cells on administration of a PD-1 agonist (McKinney et al. 2015). It is also demonstrated that the de novo generation of Tregs from naïve CD4 T-cells is amplified by PD-L1 (Francisco et al. 2009). These discoveries imply that it is possible to achieve dual benefits by utilizing the therapeutic capability of Tregs and concurrently reducing the augmentation proliferation and the role of activated self-reactive T-cells. Thus, it is important to understand and study the different molecular mechanisms of checkpoint-based immunotherapeutic agents particularly on Tregs and autoreactive activated T-cells in order to overcome the several autoimmune diseases by this novel approach. However, it is also critical to understand the fact that immunotherapies that repress activation or induce collapse of autoreactive T-cells can possibly trigger global immunosuppression. This may cause damaged immune function against infected or newly mutated cells or decreased immune control of malignancy and chronic infections. Hence, the use of checkpoint-based immunotherapies for autoimmune diseases remains challenging, where there is a strong need to improve specificity of these agents in order to minimize the immune-related adverse effects (irAE) (He et al. 2017).

4.6 Auto-Antigen Specific Immunotherapies for Autoimmune Diseases

Antigen specificity is considered as a fundamental mechanism of adaptive immunity. An alternate appealing approach to avoid global immune-suppression that can affect overall control of the immune system during the treatment of autoimmune diseases by immunotherapy is believed to be auto-antigen specific immunotherapies (ASIs). Hypothetically, minimal damage would be caused to the overall defensive immunity against foreign antigens acquired from microbial pathogens and cancer cells by restricting the induction of T-cell exhaustion only to the activated autoreactive

(autoantigen-specific) T-cells that have escaped thymic deletion (He et al. 2017; Bluestone and Bour-Jordan 2012). It is a known fact that T-cell remains anergic (unresponsive) to the resultant antigenic challenges if it receives only antigen-specific stimulation through its TCR without the subsequent stimulation signal via its co-stimulating receptor (Chen and Flies 2013) .In concurrence with this idea, ASI has been investigated in mouse models and has been reported to reverse or prevent autoimmune diseases, thus demonstrating that inducing tolerance to a finite number of autoantigens or epitopes is adequate to elicit therapeutic benefits (Macleod and Anderton 2015). Thus, the goal of ongoing research in immune tolerance is the development of autoantigen-specific immunotherapeutic treatments such as ASI that allow for the specific blockade of the harmful effects of self-reactive immune-cell function while retaining the ability of the immune system to clear non-self antigens (Miller et al. 2007).

Antigen-specific tolerance can be induced by introducing an antigen under tolerogenic conditions rather than immunogenic conditions. In reality, antigen introduced orally or in soluble form appears to decrease, and not potentiate, subsequent immune response to the antigen. Thus, antigen-specific tolerance forms the basis for the use of allergen extract-based immunotherapy to treat allergies, and has been suggested as a potential means to treat autoimmune diseases (Smilek et al. 2014). Although ASI for autoimmune disease has the potential to control the disease much like allergen-specific immunotherapy, there are basic differences between both, including that allergic diseases consist of helper T-cell; Th2 dominant responses, whereas autoimmune diseases consist of Th1and Th17 dominant responses. If we understand the pathophysiology and identify the autoantigens involved in particular autoimmune diseases, it is possible to manipulate autoantigen-related pathways to induce immune tolerance against self-antigens. Based on this concept, several considerable efforts have been made to use ASI approach to modify the immune response in autoimmune diseases. Several studies in animal models that stimulate chronic inflammatory conditions have found that controlled administration of autoantigens can provide protection from autoimmune disease (Hirsch and Ponda 2014). Table 4.1 summarizes several ASI studies reported for the treatment of different autoimmune diseases.

From Table 4.1, it is clear that T1D is one of the most researched autoimmune diseases due to the availability of well-defined autoantigens and NOD mouse models. Although ASI for T1D has shown promising results in animal models and Phase I trials, few have shown efficacy in Phase II studies, raising concern that ASI for T1D therapy may not be a viable option. In the case of MS, some animal studies of EAE reported limited efficacy of oral/nasal administration of soluble myelin peptides in prevention of EAE but not in treatment of EAE after onset. Unfortunately, human clinical trials with oral bovine MBP have not been successful, and the oral route appears limited in inducing tolerance in ongoing disease. ASIs for RA have been limited by the lack of systematic knowledge of the pathogenesis of autoimmunity; whereas more studies are necessary to study the putative role of ASI for celiac disease, SLE, and other autoimmune diseases (Hirsch and Ponda 2014).

Table 4.1 Reported ASI studies in the treatment of autoimmune diseases

Autoimmune disease	Auto-antigen targeted	Type of study	ASI treatment approach	Findings	Ref
Type 1 diabetes (T1D)	Insulin, proinsulin, insulin peptides	Animal study in NOD mice model	Administration of insulin, proinsulin, and insulin peptides by IV, SC, IN, and oral routes	Protection/suppression of T1D in NOD mice	Chatenoud (2010)
	Insulin	A multicenter RCT	Oral insulin (2.5 mg or 7.5 mg daily)	No difference observed between placebo and treatment groups	Chaillous et al. (2000)
	Insulin	DPT-1: Double-blind trial	Oral insulin (5 mg daily)	No difference observed between placebo and treatment groups	Pozzilli et al. (2000)
	Insulin	A double-blind crossover study	Intranasal insulin (1.6 mg)	Intranasal insulin was safe and caused immune changes that were consistent with insulin mucosal tolerance	Harrison et al. (2004)
	Insulin	A RCT, non-blinded	SC insulin (0.25 unit/kg daily)	In persons at high risk for diabetes, insulin does not delay or prevent type 1 diabetes	Diabetes Prevention Trial--Type 1 Diabetes Study Group (2002)
	Insulin	A double-blind, RCT	Intranasal insulin (1 unit/kg daily)	No difference observed between placebo and treatment groups	Näntö-Salonen et al. (2008)
	Insulin peptide	A randomized, four-arm, placebo-controlled, dose-ranging phase 2 trial	SC injections of the altered peptide ligand, NBI-6024 at 1, 0.5, or 0.1 mg repeated doses	No effects	Walter et al. (2009)
	GAD65	Animal study in NOD mice model	IP injection of 100 μg GAD65 in 50% IFA	Prevents and inhibits autoimmune damage of β-cells	Tian et al. (1996)
	GAD65	Animal study in NOD mice model	IV administration	Suppression of the diabetogenic response is by	Tisch et al. (1998)

(continued)

Table 4.1 (continued)

Autoimmune disease	Auto-antigen targeted	Type of study	ASI treatment approach	Findings	Ref
				induction of GAD65-specific CD4+ regulatory T-cells	
	GAD65	Animal study in NOD mice model	IN administration using CTB as a vaccine carrier	Using CTB as a vaccine carrier, tandem GAD65 peptides can prevent T1D in NOD mice at the late stage of disease	Wang et al. (2009)
	GAD65	Animal study in NOD mice model	Oral administration of GAD65 CTB	Significant decrease in inflammation of pancreatic islets and diabetes	Gong et al. (2010)
	GAD65	Randomized, double-blind, placebo-controlled phase II study	SC injections of 20 μg of recombinant human GAD65 (Diamyd®)	Significant efficacy was reported in preservation of β-cell function	Ludvigsson et al. (2008)
	GAD65	A randomized double-blind trial, phase II	SC injections of 20 μg GAD-alum (Diamyd®)	No difference in loss of insulin secretion	Wherrett et al. (2011)
	GAD65	Phase III study	SC injections of 20 μg GAD-alum (Diamyd®)	There was no significant difference in β-cell function (assessed by C-peptide levels) between treatment and placebo after follow-up of 15 months	Ludvigsson et al. (2012)
	HSP60	Animal study in NOD mice model	IN vaccination of DiaPep277, a synthetic peptide derived from human HSP60	Prevents T1D development	Fierabracci (2011)
	HSP60	A phase III, double-blind, randomized, parallel group, placebo-controlled, study	SC injections of DiaPep277 or placebo	DiaPep277 safely contributes to preservation of β-cell function and to improved glycemic control in patients with type 1 diabetes	Raz et al. (2014)

Multiple sclerosis (MS)	MBP	EAE animal model for MS	IN administration of encephalitogenic peptide	IN dose of peptide profoundly inhibited EAE when administered prior to disease induction	Metzler and Wraith (1993)
	MBP	Novel DA rat system	IN administration of MBP	Prevented induced EAE	Bai et al. (1998)
	PLP	EAE animal model for MS	Treatment of oligomerized T-cell epitope of myelin proteolipid protein (PLP139–151)	Disease protection was shown to be antigen-specific and effective in both prevention and treatment of ongoing EAE	Puentes et al. (2013)
	MBP	Double-blind human clinical trial	Daily capsules of bovine myelin or a control protein	Reduction in T-cells that are reactive with myelin basic protein	Weiner et al. (1993)
	MBP	Phase I clinical trial	IV administration of synthetic peptides containing epitope P85 VVHFFKNIVTP96	IV administration of this peptide induced tolerance	Warren et al. (1997)
	APL of MBP	Phase II clinical trial	SC administration of 50 mg to 5 mg CGP77116 (APL) weekly	APL resulted in disease exacerbation	Bielekova et al. (2000)
	APL of MBP	Double-blind, randomized, placebo-controlled phase II trial	SC administration of 50 mg to 5 mg NBI 5788 (APL) weekly	Hypersensitivity reactions (9% incidence)	Kappos et al. (2000)
	MBP MOG PLP	1 year, placebo-controlled cohort study	TD treatment with a mixture of 3 myelin peptides: MBP85–99, PLP139–151, and MOG35–55	TD treatment caused immunologic tolerance to myelin antigens	Juryńczyk et al. (2010)
	MBP MOG PLP	1 year double-blind, placebo-controlled cohort study	Skin patch comprising a mixture of three myelin peptides: MOG35–55, MBP85–99, PLP139–155	The patch was safe and well tolerated and significantly reduced the measures of disease activity	Walczak et al. (2013)

(continued)

Table 4.1 (continued)

Autoimmune disease	Auto-antigen targeted	Type of study	ASI treatment approach	Findings	Ref
Rheumatoid arthritis (RA)	CII	Animal study in polyarthritis model (mice)	ID injection of 300 ug of CII in emulsified form	Decreased incidence of collagen-induced arthritis	Nagler-Anderson et al. (1986)
	CII	Animal study in WA/KIR rats	Oral administration of CII by gavage, before disease onset	Reduced (IgG)-collagen specific antibodies; developed a T-cell population that could transfer tolerance to naïve mice	Thompson et al. (1993)
	CII	Animal study in inbred female Lewis rats	Oral administration of 20 mg mBSA/ml of distilled water	No therapeutic effect after oral administration	Yoshino (1995)
	CII	Animal study in male DBA/1 mice	Single oral administration of PLGA-CII (nanoparticles)	PLGA may serve as a powerful vehicle to promote the tolerance effect of oral CII	Kim et al. (2002)
	CII	A double-blind, randomized clinical trial	A daily oral dose of 0.5 mg triple helical CII	A significant increase in disease activity	Hauselmann (1998)
	dnaJP1	A pilot clinical trial	Oral administration of dnaJP1 for 6 months	Upregulated T-cell production of IL-4/IL-10 and downregulated production of IL-2, IFNγ, TNFα	Prakken et al. (2004)
	dnaJP1	A double-blind, placebo-controlled, pilot phase II trial	Oral doses of 25 mg of dnaJP1 or placebo daily for 6 months	Induced IL-10 production and inhibited TNFα	Koffeman et al. (2009)
	Hsp60	Animal study in female inbred Lewis rats and BALB/c and BALB/c Thy1.1 mice	ID, SC treatment by APL-1 designed from a novel epitope of Hsp60	Enhanced Tregs and inhibited disease progression	Dominguez et al. (2011)
	Hsp60	Clinical study	APL-1 treatment to PBMCs derived from RA patients	APL-1 upregulated Tregs and caused apoptosis of activated CD4+ cells, thus regulating inflammatory immune responses	Barberá et al. (2013)

Systemic lupus erythematosus (SLE)	Nucleosomal histones	Animal study in (SWR x NZB)F1 mouse model of lupus	IV administration of peptides from histone region	Treatment delayed the onset of severe lupus nephritis, prolonged survival, and even halted the progression of renal disease	Kaliyaperumal et al. (1999)
	snRNP	Animal study in lupus-prone MRL/lpr mice	IV administration of phosphorylated peptide, P140 in saline	Decreased proteinuria and anti-DNA antibody production, and significantly prolonged survival of treated mice	Monneaux et al. (2003)
	snRNP	An open-label, dose-escalation phase II clinical study	SC administrations of a clinical batch of P140 (IPP-201101) peptide at 2-week intervals	Safe and tolerable; primary endpoint of reduction in anti-dsDNA antibody titers achieved	Muller et al. (2008)

NOD non-obese diabetic, IV intra-venous, SC subcutaneous, IN intranasal, RCT randomized controlled trial, DPT-1 diabetes prevention trial of type I diabetes, GAD65 glutamic acid decarboxylase 65-kilodalton isoform, CTB cholera toxin B subunit, IP intraperitoneal, HSP60 heat-shock protein 60, MBP myelin basic protein, MOG myelin oligodendrocyte glycoprotein, PLP proteolipid protein, APL altered peptide ligands, TD transdermal, CII type II collagen, ID intradermal, IgG immunoglobulin G, mBSA methylated bovine albumin, Hsp60 heat-shock protein 60, PBMCs peripheral blood mononuclear cells, snRNP ribonucleoproteins

4.7 Anti-Cytokine (Anti-IL-1, Anti-IL-6, Anti-TNF Agents) Therapy for Autoimmune Diseases

During the development of the normal immune response, cytokines not only regulate a broad range of physiological processes but are also involved in the pathogenesis of autoimmune diseases. Autoimmune pathogenesis can be triggered when immune system cells recognize self tissue as foreign and the balance between pro- and anti-inflammatory cytokines is disturbed. Thus, anti-cytokine treatment alone and/or in combination with varied classes of immune suppressive molecules is highly effective, where some cytokines have been successfully identified as potential targets for the therapy of inflammatory/autoimmune diseases. Many anti-cytokine therapeutics are currently being used clinically, and many biologicals are in the pipeline (Astrakhantseva et al. 2014). There are three main categories of anti-cytokine agents which are popular for the treatment of autoimmune diseases: anti-interleukin 1 (IL-1), anti-interleukin 6 (IL-6), and anti-tumor necrosis factor (TNF) agents.

In 1975, TNF-α was found to be a specific product of macrophages and lymphocytes that induced breakdown of specific types of cells which also include tumor cells (Carswell et al. 1975). TNF-α is present on cell surfaces of lymphocytes and macrophages as a transmembrane protein. Cleavage of this protein leads to release of soluble TNFα. There are two TNF receptors that regulate the function of this mediator—TNFR1 and TNFR2. The TNFR1 receptor is membrane bound and upon stimulation by TNF-α releases other cytokines such as IL-2 and interferon (IFN), while the soluble TNFR2 receptor is present in the extracellular milieu where it serves to deactivate soluble TNF and blunts its inflammatory activity (Ostrov 2015). Various clinical trials of TNF inhibitors have revealed that it is possible to abrogate immune system activation, control inflammation, mitigate damage to joints, and sometimes cause stable remission in patients after discontinuing anti-TNF therapy merely by inhibiting a single cytokine (Huang et al. 2012; Verazza et al. 2013; Regueiro et al. 2014). Infliximab is the first TNF inhibitor that was found to be effective for patients with RA and Crohn's disease (unresponsive to conventional therapy). Later, it was also demonstrated to be efficacious in the treatment of psoriasis and ankylosing spondyloarthritis. Currently, various autoimmune diseases are effectively being treated with the use of TNF inhibitors, and five TNF inhibitors are approved in the majority of developed countries (Astrakhantseva et al. 2014).

IL-1, the first identified cytokine, was called the "endogenous pyrogen" because of its main action of inducing fever. IL-1α and IL-1β are the active products of this cytokine. Inactive IL-1β is cleaved to the active form by the inflammasome complex leading to the signs of inflammation (Ostrov 2015). IL-1 cytokines are a key factor in regulating the immune response and developing inflammation by controlling the expression of numerous effector proteins like chemokines, cytoplasmic metalloproteinases, cytokines, etc. (Dinarello 1996). Dysregulated IL-1α/β synthesis/secretion may result in grave pathologies. Upregulated IL-1α/β due to activation of its synthesis/secretion by triggering inflammasomes is generally responsible for many "classic" chronic inflammatory diseases. Several chronic inflammatory diseases including cryopyrin-associated periodic syndromes (CAPS), gout, multiple

sclerosis, hypertension, type-2 diabetes, etc., are associated particularly with the increased level or production of IL-1β. These chronic inflammatory diseases are actively treated by IL-1 inhibitors like anakinra, rilonacept, and canakinumab which inhibit signal transduction pathways via IL-1/IL-1receptor (IL-1R) and thus crosstalk with the cycle of inflammation (Astrakhantseva et al. 2014).

Another key cytokine which along with IL-1 and TNF contributes to inflammation in autoimmune diseases is IL-6. It stimulates B-cell antibody production, elevates inflammatory serum markers (especially C-reactive protein), and promotes Th17 cell maturation (Ostrov 2015). Dimerization of gp130 is initiated by the receptor binding of IL-6 which leads to the activation of JAK tyrosine kinases. Activated JAKs further phosphorylate and activate STAT transcription factors, e.g. STAT3 for IL-6 receptor; hence, dysregulation of this cytokine network may result in autoimmune diseases, chronic and acute inflammations, and neoplastic disorders (Astrakhantseva et al. 2014; Heinrich et al. 1998). The uncontrolled production of IL-6 may cause various chronic inflammatory and autoimmune diseases by shifting the balance to the side of Th17/Th1 side with Treg reduction (Kimura and Kishimoto 2010). Tocilizumab, an inhibitor of IL-6, was the initial molecule clinically approved in its class. It alters common IL-6-receptor (IL-6R) complex functioning, and inhibits downstream activation of adhesion molecules, osteoclasts, and maturation of both B- and T-cells (Rosman et al. 2013). This agent is approved by the FDA to treat RA, adult-onset Still's disease (AOSD), systemic juvenile idiopathic arthritis (JIA), and polyarticular JIA. Tocilizumab has also undergone recent promising trials in SLE and Crohn's Disease (CrD) (Ostrov 2015). The clinical success of tocilizumab led to the development of other inhibitors of IL-6 such as sirukumab, sarilumab, olokizumab, and clazakizumab, which are now in the second phase of clinical trial (Tanaka and Mola 2014). Table 4.2 summarizes the recent anti-cytokine immunotherapeutics with their characteristic features and therapeutic applications. In summary, besides the few limitations of anti-cytokine immunotherapy due to its ability to affect basic protective bodily functions through specific cytokines, its use in the clinical setting for autoimmune diseases and chronic inflammatory diseases is, indeed, revolutionary. Based on enhanced understanding of the molecular mechanisms of cytokine-associated pathologies, it is already being actively used in several countries and will most certainly become a trail-blazing trend in clinical medicine in the future (Astrakhantseva et al. 2014).

4.8 Anti-T-Cell Therapy for Autoimmune Diseases

Emerging knowledge from the current developments in the field of immunotherapy has revealed that peripheral tolerance mechanisms that fail in autoimmunity are implicated in progressive malignancies and chronic infections. Thus, pathways targeted for therapeutic intervention in autoimmune diseases can be modulated in the opposite sense in malignancy and infectious disease (Bucktrout et al. 2018). Major therapeutic strategies of anti-T-cell therapy for autoimmune diseases are

Table 4.2 List of recent anti-cytokine immunotherapeutics used for various autoimmune diseases

Cytokine target	Drug	Structure	Half life (approx.)	Therapeutic applications
Soluble and membrane bound TNF-α	Infliximab	Mouse/human chimeric IgG1 mAb	14 days	CrD, UC, RA, AS, PsA, Ps
	Etanercept	TNFR2 dimer bound to fc-fragment of human IgG1	70 hours	RA, JIA, PsA, AS, Ps
	Adalimumab	Human IgG1 mAb	14 days	RA, JIA, PsA, CrD, AS
	Golimumab	Human IgG1 mAb	14 days	RA, PsA, AS
	Certolizumab pegol	PEGylated fab-fragment of human IgG1 mAb	14 days	CrD, RA, PsA, AS
IL-1α/β	Anakinra	Recombinant human IL-1 receptor antagonist	4–6 hours	RA, CAPS
	Rilonacept	Dimer of IL-1R1 and IL-1RAcP bound to fc-fragment of IgG1	7.5 days	CAPS, Muckle−Wells syndrome
	Canakinumab	Human IgG1 mAb	26 days	CAPS, Muckle−Wells syndrome
IL-6R	Tocilizumab	Human IgG1 mAb	11–13 days	RA, Castleman disease, JIA clinical
	Sarilumab	Human IgG1 mAb	8–10 days	RA, AS
	Sirukumab	Human IgG1 mAb	15–19 days	RA, SLE
sIL-6R	Sgp130Fc	Human gp130 extracellular domain bound to IgG1Fc-fragment	72 hours	RA
IL-6	Olokizumab	Human IgG1 mAb	31.5 days (SD 12.4 days)	CrD, RA
	Clazakizumab	Human IgG1 mAb	30 days	RA

AS ankylosing spondyloarthritis, CAPS cryopyrin-associated periodic syndromes, CrD Crohn's disease, IL-6R IL-6 receptor, JIA juvenile idiopathic arthritis, mAb monoclonal antibody, PsA psoriatic arthritis, Ps psoriasis, RA rheumatoid arthritis, sIL-6R soluble IL-6 receptor, UC ulcerative colitis

immunomodulation of T-cell co-stimulation, migration, and inflammation. The rationale behind the development of such therapies is that such immunotherapeutics could selectively target pathogenic T-cells during autoimmune conditions. It has been observed that CD28, a co-stimulatory molecule, expresses on T-cells; and that interaction of CD28 with B7–1 or B7–2 is necessary for T-cell activation as well as effector function. Thus, inhibiting CD28/B7 interactions in the TCR signaling axis may lead to tolerance resulting from deletion of T-cells and/or anergy, which is important to re-establish tolerance in autoimmune diseases (Bluestone and

Bour-Jordan 2019). In vivo studies showed that abrogation of CD28 signaling by means of a fusion protein of CTLA4Ig was efficacious in ameliorating many autoimmune diseases such as MS or SLE (Scalapino and Daikh 2008). Two fusion proteins (CTLA4Ig) composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4, viz., Abatacept and Belatacept (the higher-affinity Belatacept which is a second-generation variant) demonstrated more than 50% response rate in patients with psoriasis and RA who were refractory to anti-TNF-α therapy; these are approved by FDA for RA/JIA (Genovese et al. 2005). However, abatacept could not reduce disease flares during Phase II studies on SLE patients treated with oral corticosteroids, and was found ineffective in a Phase III trial of CrD (Merrill et al. 2010). The lack of response to abatacept in patients with CrD may be due to limited co-stimulatory activity by intestinal T-cells which do not express CD28 (Mayer et al. 2012). In a recent multi-center trial in newly diagnosed T1D patients, treatment with abatacept for 2 years was well tolerated and delayed the reduction in B-cell function compared with placebo (Orban et al. 2011). Many clinical studies of abatacept or belatacept are currently ongoing in SLE, MS, or T1D. Current therapy with CTLA4Ig was not found to lead to extensive immunosuppression or augmented infection rates, which is clearly beneficial in the therapy of autoimmune disease (Bluestone and Bour-Jordan 2019). Alefacept is a fusion protein of LFA-3-Ig that inhibits the interaction of lymphocyte function-associated antigen 3 (LFA-3/CD58) on the APCs with CD2, a co-stimulatory molecule on T-cells. It was reported to be efficacious in decreasing lesions in a psoriasis Phase III trial and is currently FDA-approved for psoriasis (Sugiyama et al. 2008). It has been reported that interactions between CD154 and CD40, the former on T-cells and the latter on APCs, are critical for stimulating autoreactive T-cells, activating APCs and producing autoantibodies; hence therapeutic abrogation of this pathway appeared promising in the 1990s. Unfortunately, clinical studies of anti-CD154 monoclonal antibodies were initiated in many autoimmune diseases such as SLE, CrD, MS, and psoriasis, but had to be discontinued due to occurrence of many thromboembolic events (Bluestone and Bour-Jordan 2019).

It is a well-known fact that key factors for the inducing or maintaining tolerance include T-cell trafficking and lymph node occupancy. Hence, immunotherapies which target T-cell migration in autoimmune disease may be used in combination therapy during immunosuppression to enable homing to lymph nodes of autoreactive T-cells and their tolerization (Bluestone and Bour-Jordan 2019; Ochando et al. 2005). Based on this theory, two most successful drugs developed for cell trafficking blockade are anti-integrin mAbsnatalizumab and efalizumab. These drugs are indicated in relapsing-remitting multiple sclerosis (RRMS), CrD, and psoriasis (Dubertret et al. 2006; Derfuss et al. 2013). Natalizumab, an FDA-approved mAb for CrDor RRMS, for patients suffering from severe disease or disease which is non-responsive to other standard-of-care, needs to carry an additional label warning. Further, efalizumab has been voluntarily withdrawn by the manufacturer due to the association of progressive multifocal leukoencephalopathy (PML) cases with the treatment (Hartung 2009). Another drug fingolimod capable of regulating T-cell trafficking by crosstalk with members

of the sphingosine pathway was also found to improve the rate of relapse and progression to disability within 1–2 years in a Phase III clinical trial of RRMS patients and thereby turned out to become the first oral therapeutic approved by the FDA for MS (Kappos et al. 2010; Cohen et al. 2010). Due to the adverse effects associated with fingolimod therapy, second-generation molecules targeting the sphingosine signaling pathway are in development with potentially decreased side effects, and clinical trials are in progress for many autoimmune diseases (Bluestone and Bour-Jordan 2019). Along with these T-cell immunomodulation strategies, immunotherapies targeting proinflammatory cytokines (discussed in the previous section) or other inflammatory mediators in autoimmune diseases are also found to be useful, not just for improvement in clinical parameters but also for their ability to restore tolerance.

4.9 Anti-B-Cell Therapy for Autoimmune Diseases

The B-cell humoral response leading to production of autoantibodies and immune complexes contributes to manifestations of autoimmune diseases such as SLE and Sjogren's syndrome. The B-cell dysfunction contributes to the development of autoimmune phenomena via anomalies in B-cell's mechanisms such as antigen presentation, cytokine release, and T-cell activation (Ostrov 2015). From the last 10–15 years, B-cells are the recognized therapeutic targets for the treatment of autoimmune diseases. Presently, several promising and very efficient drugs specifically targeting plasma cells or B-cells are either in clinical use or under development for the treatment of several autoimmune diseases. These B-cell-directed therapies have proven to be therapeutically effective not only in classic B-cell/autoantibody-driven disorders, such as antibody/immune-complex-mediated SLE, autoimmune blistering skin diseases, or myasthenia gravis, but also in diseases that are believed to be mainly driven by T-cells, most importantly MS or RA (Hofmann et al. 2018). B-cells were recognized for their function as immune response enhancers in autoimmunity, as a result of their ability to generate autoantibody-producing plasma cells, and elicit $CD4^{+}$T-cell responses by antigen presentation. Such B-cells are typically classified as effector B-cells. Recently, studies indicated a potential role(s) of B-cells as negative sensors of immune response in autoimmunity, implicating interleukin 10 (IL-10) regulatory B-cell compartment (Breg). Thus, the abrogation of autoreactive effector B-cells in consonance with enhancement of autoantigen-driven Bregs, with immune surveillance maintenance, may be a key strategy to target B-cells. Anti-B-cell immunotherapies employ drugs directed against B-cell surface markers such as CD20/CD22, activating factors such as BAFF/TACI, and cytokines such as IL-6/TNFα/IFNα to target these B-cells (Musette and Bouaziz 2018). Table 4.3 summarizes the recent strategies to target B-cells with their drugs and implications in autoimmune diseases.

From the literature, it is clear that a great advancement has been made in decreasing resident and circulating B-cells in inflamed tissues or secondary lymphoid organs. The future of immunotherapy may require specific targeting,

Table 4.3 Recent anti-B-cell immunotherapy strategies with respective drugs and their implications

Anti-B-cell immunotherapy strategy	Specific target	Structure	Drugs under development	Implications in autoimmune diseases	Ref.
Drugs directed against B-cell surface markers	CD20	Type I anti-CD20 humanized/human mAbs	Rituximab,	RA, pemphigus, GPA, and MPA	Guillevin et al. (2014) and Joly et al. (2017)
			Ofatumumab	RA, MS	Pers and Jorgensen (2016)
			Ocrelizumab	RRMS	Hauser et al. (2017)
		Type II anti-CD20 humanized mAb	Obinutuzumab	–	Musette and Bouaziz (2018)
	CD19	A human IgG1 anti-CD19 mAb	Inebilizumab	MS	Agius et al. (2015)
	CD19 & CD3	A recombinant mouse derived bispecific mAb	Blinatumomab	–	Velasquez et al. (2018)
	CD22	Humanized mAb	Epratuzumab	SLE	Wallace et al. (2013)
Drugs directed against B-cell activating factors	BAFF	Human anti-BAFF mAb	Belimumab	SLE	Blair and Duggan (2018)
	BAFF	Human IgG4 mAb	Tabalumab	SLE	Hofmann et al. (2018)
	APRIL	Recombinant fusion protein combined with the extracellular ligand binding portion of TACI	Atacicept	RA, SLE	Hofmann et al. (2018)
Direct targeting of plasma cells	Plasma cells	Small molecule proteasome inhibitor	Bortezomib	Sjögren's syndrome, refractory SLE, TTP	Hofmann et al. (2018)
Inhibition of B-cell receptor signaling	BTK	Pharmacological BTK inhibitor	Ibrutinib	SLE, GVHD	Kil et al. (2012) and Miklos et al. (2017)

mAbs monoclonal antibodies, RA rheumatoid arthritis, GPA granulomatosis with polyangiitis, MPA microscopic polyangiitis, RRMS relapsing-remitting multiple sclerosis, SLE systemic lupus erythematosus, APRIL a proliferation-inducing ligand, TACI transmembrane activator and calcium-modulating cyclophilin ligand interactor, TTP thrombotic thrombocytopenic purpura, BTK Bruton's tyrosine kinase, GVHD graft versus host disease

particularly of B-cell pathogenic effector functions, and augmentation of their regulatory role(s) without altering B-cell-dependent immune surveillance. Indeed, better patient management will be possible with better targeted therapeutics against specific B-cell populations and their functions (Musette and Bouaziz 2018).

4.10 Current Immunotherapeutics in Clinical Trials for Autoimmune Diseases

Several clinical trials are being performed on immunotherapeutics for autoimmune diseases as seen in Table 4.4. The majority of these molecules are being tested for safety and efficacy in psoriasis and rheumatoid arthritis. In both these diseases, one notes a larger proportion of immunotherapeutics in advanced clinical testing including Phases II and III. There is also considerable work that is ongoing with several immunotherapeutics in clinical trials for SLE, many of which are in Phase I or II. Interestingly, there are fewer immunotherapeutics in clinical trials for IBD, Crohn's disease, and MS; however, the few that are being investigated are mostly in Phase III. As seen in Table 4.4, there are a huge number of immunotherapeutics in clinical trials for various autoimmune diseases, and the number is likely to increase in the near future given the promise of immunotherapy in these diseases.

4.11 Financial Toxicity of Immunotherapies in Autoimmune Diseases

In recent years, the cost of immunotherapies in general and indeed for autoimmune diseases is reaching great proportions which brings into picture the financial burden which the patients and their families suffer from in different parts of the world despite having access to health insurance (Nipp et al. 2018; Zaprutko et al. 2017). The spectrum from diagnosis to treatment and post treatment care involves huge investments, financial as well as emotional, by the patients and their families who are afflicted by autoimmune diseases like CrD, inflammatory bowel syndrome (IBD), Grave's disease, MS, psoriasis, RA, Sjogren's syndrome, SLE, etc. (Lerner et al. 2015).

Inflammatory Bowel Syndrome, Crohn's Disease

Zheng et al. and Ylisaukko-Oja et al. discussed in their studies how along with cost of biologics, the secondary costs for outpatient visits, hospitalization, telephone consultation, laboratory visit, surgery, imaging, endoscopy added to the total cost of the treatments of inflammatory bowel syndrome (IBD) (Zheng et al. 2017; Ylisaukko-Oja et al. 2019). According to Berns et al., in previous years a patient with CrD was burdened with surgical intervention and hospitalization charges only but with modern anti-TNF-α biologic era the treatment itself accounted for 64% of the total cost, which was around $22,663 for infliximab in the United States. However such burden can be brought under control in future by the use of

Table 4.4 Current immunotherapeutics in clinical trials for autoimmune diseases

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
1	Crohn's disease	Guselkumab, Ustekinumab	2000	Recruiting	NCT03466411	II/III	Clinicaltrials.gov. A Study of the Efficacy and Safety of Guselkumab in Participants With Moderately to Severely Active Crohn's Disease (GALAXI). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03466411
2	Crohn's disease	Risankizumab	940	Recruiting	NCT03105128	III	Clinicaltrials.gov. A Study of the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Crohn's Disease. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03105128
3	Crohn's disease	Ustekinumab	600	Recruiting	NCT03942120	IV	Clinicaltrials.gov. Post-Marketing Surveillance for Crohn's Disease Participants Treated With Stelara (Ustekinumab) (STELARA CD PMS). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03942120

(continued)

Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
4	Crohn's disease	Ustekinumab, Adalimumab	350	Recruiting	NCT03464136	III	Clinicaltrials.gov. Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year (SEAVUE). - Stuy Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03464136
5	Inflammatory bowel disease	Infliximab	60	Recruiting	NCT03445624		Clinicaltrials.gov. Abdominal Ultrasound With Doppler and Peripheral Hemogram in Assesment Inflammatory Bowel Disease. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03445624
6	Inflammatory bowel disease	Infliximab	194	Recruiting	NCT02994836	IV	Clinicaltrials.gov. GIS-SUSANTI-TNF-2015 (Anti-TNF Discontinuation). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02994836
7	Inflammatory bowel disease	Vedolizumab	2500	Recruiting	NCT03375424	III	Clinicaltrials.gov. Vedolizumab Study With Inflammatory Bowel Disease Patients in Germany (VEDOibdI). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03375424

8	Grave's ophthalmopathy	RVT-1401	8	Recruiting	NCT03922321	II	Clinicaltrials.gov. Study of RVT-1401 for the Treatment of Patients With Moderate to Severe Active Graves' Ophthalmopathy (GO). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03922321
9	Grave's orbitopathy	Teprotumumab	83	Active, not recruiting	NCT03298867	III	Clinicaltrials.gov. Treatment of Graves' Orbitopathy (Thyroid Eye Disease) to Reduce Proptosis With Teprotumumab Infusions in a Randomized, Placebo-Controlled, Clinical Study (OPTIC). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03298867
10	Multiple sclerosis	ATA188	60	Recruiting	NCT03283826	I	Clinicaltrials.gov. Phase 1 Study to Evaluate the Safety of ATA188 in Subjects With Progressive and Relapsing-Remitting Multiple Sclerosis. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03283826

(continued)

Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
11	Multiple sclerosis	Elezanumab	165	Recruiting	NCT03737851	II	Clinicaltrials.gov. A Study to Assess the Safety and Efficacy of Elezanumab When Added to Standard of Care in Relapsing Forms of Multiple Sclerosis. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03737851
12	Multiple sclerosis	Ocrelizumab	1500	Recruiting	NCT03599245	III	Clinicaltrials.gov. This is an Extension Study of the Roche P-trial to Investigate Safety and Effectiveness of a Single Ocrelizumab Dose in Participants With Multiple Sclerosis (MS). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03599245
13	Multiple sclerosis	Ofatumumab	929	Active, not recruiting	NCT02792218	III	Clinicaltrials.gov. Efficacy and Safety of Ofatumumab Compared to Teriflunomide in Patients With Relapsing Multiple Sclerosis (ASCLEPIOS I). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02792218

14	Multiple sclerosis	Rituximab	200	Recruting	NCT03979456	III	Clinicaltrials.gov. RItuximab Long-Term DOSE Trial in Multiple Sclerosis - RIDOSE-MS (RIDOSE-MS). - Study Results - Clin [online] Available https//clinicaltrials.gov/ct2/show/NCT03979456
15	Multiple sclerosis	Ublituximab	48	Active, not recruiting	NCT02738775	II	Clinicaltrials.gov. Phase 2 Study of Ublituximab in Patients With Relapsing Forms of Multiple Sclerosis. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02738775
16	Plaque Psoriasis	Adalimumab	400	Recruiting	NCT03849404	III	Clinicaltrials.gov. Efficacy, Safety, and Immunogenicity of AVT02 With Moderate-to-Severe Chronic Plaque Psoriasis. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03849404
17	Psoriasis	Adalimumab	56	Completed	NCT03217734	II	Clinicaltrials.gov. MAP Study: Methotrexate and Adalimumab in Psoriasis (MAP). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03217734

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
18	Generalized Pustular Psoriasis (GPP)	ANB019	10	Recruiting	NCT03619902	II	Clinicaltrials.gov. A Study to Evaluate the Efficacy and Safety of ANB019 in Subjects With Generalized Pustular Psoriasis (GPP). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03619902
19	Chronic Plaque Psoriasis	Bimekizumab	43	Completed	NCT03230292	II	Clinicaltrials.gov. This is a Study to Evaluate the Long-term Safety, Tolerability and Efficacy of Bimekizumab in Adult Patients With Chronic Plaque Psoriasis. - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03230292
20	Moderate to Severe Chronic Plaque Psoriasis	Bimekizumab	1355	Recruiting	NCT03598790	III	Clinicaltrials.gov. A Study to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects With Moderate to Severe Chronic Plaque Psoriasis (BE BRIGHT). - Study Results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03598790

21	Moderate to Severe Plaque Psoriasis	Bimekizumab, Adalimumab	480	Active, not recruiting	NCT03412747	III	Clinicaltrials.gov. A study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis (BE SURE). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03412747
22	Moderate to Severe Chronic Plaque Psoriasis	Bimekizumab, Secukinumab	743	Active, not recruiting	NCT03536884	III	Clinicaltrials.gov. A study to evaluate the efficacy and safety of bimekizumab compared to an active comparator in adult subjects with moderate to severe chronic plaque psoriasis (BE RADIANT). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03536884
23	Moderate to Severe Plaque Psoriasis	Brodalumab	39	Completed	NCT03403036	IV	Clinicaltrials.gov. Brodalumab in subjects with moderate to severe plaque psoriasis who have failed IL-17A therapies. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03403036

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
24	Psoriasis Vulgaris	Brodalumab	210	Completed	NCT03331835	IV	Clinicaltrials.gov. A trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of fumaric acid esters in adults with moderate to severe plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03331835
25	Plaque Psoriasis	Etanercept, Ixekizumab	201	Active, not recruiting	NCT03073200	III	Clinicaltrials.gov. Study of ixekizumab (ly2439821) in children 6 to less than 18 years with moderate-to-severe plaque psoriasis (Ixora-peds). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03073200
26	Psoriasis	Guselkumab	888	Recruiting	NCT03818035	III	Clinicaltrials.gov. A study to evaluate further therapeutic strategies with guselkumab in participants with moderate-to-severe plaque-type psoriasis (GUIDE). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03818035

27	Chronic Plaque Psoriasis	Guselkumab, Etanercept	125	Recruiting	NCT03451851	III	Clinicaltrials.gov. No a study to evaluate the efficacy, safety, and pharmacokinetics of subcutaneously administered guselkumab for the treatment of chronic plaque psoriasis in pediatric participants (PROTOSTAR). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03451851
28	Plaque Psoriasis	HLX03, Adalimumab	216	Recruiting	NCT03316781	III	Clinicaltrials.gov. Study of efficacy and safety of HLX03 in subjects with moderate to severe plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03316781
29	Psoriasis	Humira®, BI 695501	259	Recruiting	NCT03210259	III	Clinicaltrials.gov. The VOLTAIRE-X trial looks at the effect of switching between Humira® and BI 695501 in patients with plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03210259

(continued)

Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
30	Generalized Pustular Psoriasis and Erythrodermic Psoriasis	Ixekizumab	12	Recruiting	NCT03942042	IV	Clinicaltrials.gov. A study of ixekizumab (LY2439821) in participants in Japan With generalized pustular psoriasis and erythrodermic psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03942042
31	Psoriasis	Mirikizumab	1816	Recruting	NCT03556202	III	Clinicaltrials.gov. A Long-term Study to Evaluate Safety and Maintenance of Treatment Effect of LY3074828 in Participants With Moderate-to-Severe Plaque Psoriasis (OASIS-3). - Study Results - Clin [online] Available https//clinicaltrials.gov/ct2/show/NCT03556202
32	Psoriasis	Mirikizumab	530	Active, not recruiting	NCT03482011	III	Clinicaltrials.gov. A study to evaluate the efficacy and safety of mirikizumab (LY3074828) in participants with moderate-to-severe plaque psoriasis (OASIS-1). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03482011

33	Psoriasis	Mirikizumab	26	Recruiting	NCT03718884	I	Clinicaltrials.gov. A study of mirikizumab in participants with plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03718884
34	Psoriatic Arthritis	Risankizumab	964	Recruiting	NCT03675308	III	Clinicaltrials.gov. A study comparing risankizumab to placebo in subjects with active psoriatic arthritis (PsA) who have a history of inadequate response to or intolerance to at least one disease modifying anti-rheumatic drug (DMARD) therapy. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03675308
35	Psoriatic Arthritis (PsA)	Risankizumab	444	Recruiting	NCT03671148	III	Clinicaltrials.gov. A study comparing risankizumab to placebo in subjects with active psoriatic arthritis including those who have a history of inadequate response or intolerance to biologic therapy (IES). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03671148

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
36	Psoriasis	Risankizumab	50	Active, not recruiting	NCT03518047	III	Clinicaltrials.gov. Risankizumab therapy versus placebo for subjects with psoriasis in the Russian Federation (IMMPRESS). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03518047
37	Psoriasis	Risankizumab	2171	Active, not recruiting	NCT03047395	III	Clinicaltrials.gov. A Study to Assess the Safety and Efficacy of Risankizumab for Maintenance in Moderate to Severe Plaque Type Psoriasis (LIMMITLESS). - Study Results - Clin [online] Available https//clinicaltrials.gov/ct2/show/NCT03047395
38	Psoriasis	Risankizumab, Secukinumab	327	Active, not recruiting	NCT03478787	III	Clinicaltrials.gov. Risankizumab versus secukinumab for subjects with moderate to severe plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03478787

39	Psoriasis	Secukinumab	24	Recruiting	NCT03131570	II	Clinicaltrials.gov. Safety and efficacy of secukinumab in mild psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03131570
40	Plaque Psoriasis	Secukinumab	122	Recruiting	NCT03589885	III	Clinicaltrials.gov. Study of efficacy and safety of secukinumab 2 mL auto-injector (300 mg) in subjects with moderate to severe plaque psoriasis (MATURE). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03589885
41	Plaque Psoriasis	Secukinumab	196	Recruiting	NCT03020199	IV	Clinicaltrials.gov. Study of the efficacy of early intervention with secukinumab 300 mg s.c. compared to narrow-band UVB in patients with new-onset moderate to severe plaque psoriasis (STEPin). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03020199

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
42	Generalized Pustular Psoriasis	Spesolimab	171	Recruiting	NCT03886246	III	Clinicaltrials.gov. A 5-year study to test BI 655130 in patients with generalized pustular psoriasis who took part in previous studies with BI 655130. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03886246
43	Psoriasis	Ustekinumab	75	Recruiting	NCT03218488	I	Clinicaltrials.gov. A safety study of ustekinumab in the treatment of pediatric participants aged 12 years and older with moderate to severe plaque psoriasis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03218488
44	Rheumatoid arthritis	Abatacept	25	Recruiting	NCT03652961	IV	Clinicaltrials.gov. Rheumatoid arthritis memory B cells and abatacept (RAMBA) (RAMBA). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03652961

45	Rheumatoid Arthritis	ABBV-3373, Adalimumab	48	Recruiting	NCT03823391	II	Clinicaltrials.gov. A study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ABBV-3373 in participants with moderate to severe rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03823391
46	Rheumatoid Arthritis	AMG 570	34	Active, not recruiting	NCT03156023	I	Clinicaltrials.gov. Multiple ascending doses of AMG 570 in subjects with rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03156023
47	Rheumatoid Arthritis	BAT1806, Actemra	621	Recruiting	NCT03830203	III	Clinicaltrials.gov. Comparative study of BAT1806 to RoActemra® in rheumatoid arthritis patients with inadequate response to methotrexate. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03830203

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
48	Rheumatoid Arthritis	CT-P17, Humira	564	Active, not recruiting	NCT03789292	III	Clinicaltrials.gov. A study to compare efficacy and safety of CT-P17 with humira in patients with active rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03789292
49	Rheumatoid Arthritis	Etanercept	50	Completed	NCT03193957	II	Clinicaltrials.gov. An multicentre clinical study to evaluate the usability and safety of the autoinjector and pre-filled syringe of SB4 in subjects with rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03193957
50	Rheumatoid Arthritis	Infliximab	300	Recruiting	NCT03885037	III	Clinicaltrials.gov. Infliximab biosimilar for intravenous drip infusion 100 mg "Pfizer" drug use investigation (rheumatoid arthritis). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03885037

51	Rheumatoid Arthritis	Olokizumab	1880	Recruiting	NCT03120949	III	Clinicaltrials.gov. Evaluation of the long term safety, tolerability and efficacy of two dosing regimens of olokizumab (OKZ), in subjects with rheumatoid arthritis (RA) who previously completed 24 weeks of blinded treatment in one of the core studies - CREDO 1, 2 or 3. (CRED. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03120949
52	Rheumatoid Arthritis	Sarilumab	84	Active, not recruiting	NCT03449758	IV	Clinicaltrials.gov. Effect of sarilumab on patient-reported outcomes in patients with active rheumatoid arthritis (SariPRO). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03449758
53	Rheumatoid Arthritis	Tocilizumab, Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab pegol	208	Recruiting	NCT03100253	IV	Clinicaltrials.gov. Rheumatoid arthritis treatment after first anti-TNF investigation (RAFTING). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03100253

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
54	Rheumatoid Arthritis	VAY736	50	Recruiting	NCT03574545	I	Clinicaltrials.gov. Study comparing two VAY736 drug products in patients with rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03574545
55	Sjogren's syndrome	RSLV-132	28	Completed	NCT03247686	II	Clinicaltrials.gov. A study of RSLV-132 in subjects with primary Sjogren's syndrome (RSLV-132). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03247686
56	Primary Sjogren Syndrome	VAY736	195	Recruiting	NCT02962895	II	Clinicaltrials.gov. Safety and efficacy of VAY736 in patients with primary Sjogren's syndrome (pSS). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02962895
57	Systemic lupus erythematosus	Aldesleukin	16	Recruiting	NCT03312335	II	Clinicaltrials.gov. Low-dose interleukin-2 for treatment of systemic lupus erythematosus (Charact-IL-2). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03312335

58	Systemic Lupus Erythematosus	AMG 592	29	Recruiting	NCT03451422	I	Clinicaltrials.gov. Safety and efficacy of AMG 592 in subjects with active systemic lupus erythematosus. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03451422
59	Systemic Lupus Erythematosus	Anifrolumab	36	Completed	NCT02962960	II	Clinicaltrials.gov. A study to characterize the pharmacokinetics, pharmacodynamics, and safety of anifrolumab in adult type I interferon test high systemic lupus erythematosus subject with active skin manifestations. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02962960
60	Systemic Lupus Erythematosus	Belimumab + Rituximab	292	Active, not recruiting	NCT03312907	III	Clinicaltrials.gov. A study to evaluate the efficacy and safety of belimumab administered in combination with rituximab to adult subjects with systemic lupus erythematosus (SLE) - BLISS-BELIEVE. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03312907

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
61	Systemic Lupus Erythematosus	Belimumab	20	Completed	NCT02880852	I	Clinicaltrials.gov. Belimumab phase i study in Chinese subjects with systemic lupus erythematosus. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02880852
62	Systemic Lupus Erythematosus	Belimumab	30	Recruiting	NCT03747159	II	Clinicaltrials.gov. Synergetic B-cell immunomodulation in SLE - 2nd study. (SynBioSe-2). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03747159
63	Systemic Lupus Erythematosus	Benlysta	600	Recruiting	NCT03370263	III	Clinicaltrials.gov. BENLYSTA® special drug use investigation. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03370263
64	Systemic Lupus Erythematosus	BOS161721	143	Recruiting	NCT03371251	I, II	Clinicaltrials.gov. Study of BOS161721 in systemic lupus erythematosus (sle) patients on a background of limited standard of care. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03371251

65	Systemic Lupus Erythematosus	ILT-101	100	Completed	NCT02955615	II	Clinicaltrials.gov. ILT-101 in patients with active moderate to severe systemic lupus erythematosus (SLE) (LUPIL-2). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT02955615
66	Systemic Lupus Erythematosus	NKTR-358	48	Recruiting	NCT03556007	I	Clinicaltrials.gov. A study of NKTR-358 in participants with systemic lupus erythematosis (SLE). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03556007
67	Systemic Lupus Erythematosus Arthritis	Rituximab	30	Recruiting	NCT03054259	II	Clinicaltrials.gov. Rituximab objective outcome measures trial in SLE (ROOTS). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03054259

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Table 4.4 (continued)

Sr no.	Autoimmune disease	Intervention	Number of patients	Recruitment status	Clinical trial registry identifier	Phase	Ref.
68	Systemic Lupus Erythematosus	TAK-079	24	Recruiting	NCT03724916	I	Clinicaltrials.gov. A study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of TAK-079 in combination with standard background therapy in participants with moderate to severe systemic lupus erythematosus (SLE). - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03724916
69	Systemic Lupus Erythematosus	Ustekinumab	516	Recruiting	NCT03517722	III	Clinicaltrials.gov. A study of ustekinumab in participants with active systemic lupus erythematosus. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03517722
70	Systemic Lupus Erythematosus	VAY736, CFZ533	120	Recruiting	NCT03656562	II	Clinicaltrials.gov. Study the efficacy and safety of VAY736 and CFZ533 in SLE patients. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03656562

Multiple diseases							
71	Crohn's disease, Inflammatory bowel disease, Multiple sclerosis, Rheumatoid arthritis, Sjogren's syndrome, Systemic lupus erythematosus	Nivolumab	264	Recruiting	NCT03816345	I	Clinicaltrials.gov. Nivolumab in treating patients with autoimmune disorders or advanced, metastatic, or unresectable cancer. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03816345
72	Systemic lupus erythematosus, Rheumatoid arthritis	PF-06835375	112	Recruiting	NCT03334851	I	Clinicaltrials.gov. Safety and tolerability study Of PF-06835375 in subjects with seropositive systemic lupus erythematosus or rheumatoid arthritis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03334851
73	Systemic lupus erythematosus, Sjogren's syndrome	VIB7734	32	Recruiting	NCT03817424	I	Clinicaltrials.gov. A study to evaluate VIB7734 in participants with systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), Sjogren's syndrome, systemic sclerosis, polymyositis, and dermatomyositis. - Study results - Clin [online] Available https://clinicaltrials.gov/ct2/show/NCT03817424

biosimilars which have equivalent efficacy and safety profile as soon as the patent for branded biologics expire, which will no doubt have a positive economic impact with immense cost savings for the patients (Berns and Hommes 2016). When Severs et al. through COIN study compared the cost burden of biologic drugs and biosimilars it was found that in a Dutch IBD population of 85,400 patients [equaling 507 patients per 100,000 inhabitants, 55% UC and 45% CD patients], there was a cost saving of €493 million with biosimilars which is almost a reduction of 28% in the total healthcare costs which also covered the costs of IBD-specific hospitalizations, outpatient clinic visits, and surgeries of the inhabitants (Severs et al. 2016).

Multiple Sclerosis

Hartung et al. reported that the first generation of disease modifying therapies (DMTs) for MS in 1993 costs the patient $8000 to $11,000, but with the entry of new DMTs the prices increased up to $60,000 in the year 2013 because they are prescription drugs which were affected by medical inflation in the United States (Hartung et al. 2015). Hartung et al. and Chen et al. found out that this amount went up to $70,000 in the United states in the year 2017, which was due to an increase in the costs of patient care facilities (Chen et al. 2017; Hartung 2017). Similarly, the annual costs for MS in European countries like Spain and France were around €30,050 and €38,100, respectively, on a per patient basis in the year 2017 (Fernández et al. 2017; Kobelt et al. 2017).

Psoriasis

The economic burden associated with psoriasis is significant and it increases even further as the disease progresses from moderate to severe (Al Sawah et al. 2017; Augustin et al. 2017). The United States in the year 2013 estimated an overall expense of $11,498 was paid by an individual patient of psoriasis throughout his treatment (Brezinski et al. 2015; Vanderpuye-Orgle et al. 2015). Meanwhile in European countries like the United Kingdom, France, Germany, Spain, and Italy, the cost of the treatment was in the range of US$2077–13,132 (Augustin et al. 2017; Burgos-Pol et al. 2016).

Rheumatoid Arthritis

RA, a systemic autoimmune disorder accounts for economic burden in the range of €2.0 billion per year in European nations which included direct costs of the biologics and indirect costs of the various services and maintenance for the early rapidly progressing RA (ERPRA) patients (Mennini et al. 2017; Cross et al. 2014). A similar approach of using biosimilars of these biologics will result in decreased economic burden in the future (Gulácsi et al. 2015).

Systemic Lupus Erythematosus

SLE is a multisystem autoimmune disease that could potentially lead to serious organ complications and even death with its incidence being as low as 0.3–31.5 cases per 100,000 individuals every year (Carter et al. 2016; Sebastiani et al. 2016). The annual cost for hospitalization was US$51,808.41 per patient in Rochester city

of New York state for an approximate stay of 8.5 days in the hospital (Anandarajah et al. 2017). Meacock et al. concluded that in a randomized population in the United States, the mean annual treatment cost was in the range of US$2239–$35,540 until the year 2010 (Meacock et al. 2013).

4.12 Conclusion and Future Perspectives

There has been great progress and renewed interest in immunotherapies for autoimmune diseases. As discussed, various modalities ranging from immune checkpoint blockade to anti-T-cell therapy or anti-B-cell therapy, amongst others are in current use. This has seen the emergence of very many novel immunotherapies which we have delineated earlier. Of interest, there are a sizeable number of immunotherapies for autoimmune diseases in early and advanced stages of clinical trials and recent trends indicate that their number is only going to increase. Although this is laudable to provide access to better care to suffering patients, one needs to also balance the financial toxicity of these immunotherapies which can oftentimes defeat the very purpose of providing healthcare to those who need it most. It is recommended that all stakeholders from discovery scientists to clinicians to health management organizations and insurance providers as also lay members of the public be brought on the same page to appreciate all these "facets" of immunotherapies to make it a successful and go-to healthcare therapy for autoimmune diseases in the future that will benefit a greater proportion of patients.

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