Mini Review
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Autoimmune diseases: the new frontiers

Abstract

Immunosuppressive drugs have long been used in the treatment of autoimmune diseases (AD). These drugs such as corticosteroids, methotrexate and cyclophosphamide cause the suppression of the immune system particularly on the T cell activation and inhibition of inflammatory cytokines production. However, patients prescribed with these drugs suffer from reduced immunity. They have increased susceptibility to serious infections and risk of malignancies. Therefore, more specific approaches against AD were developed to reduce the negative effects resulting from the blanket immunosuppression of AD-related drugs. These approaches; antigen based immunotherapy, checkpoint-based immunotherapy, targeted inflammatory cytokines and stem cell therapy, although not refined has shown great promises in animal models and were at various stages of clinical trials.

Keywords: autoimmune diseases, antigen-based immunotherapy, checkpoint-based immunotherapy, targeted inflammatory cytokines, stem cell therapy

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Abbreviations: AD, autoimmune diseases; TCR, t cell receptor; MHC, major histocompatibility complex; TREG, regulatory t cell; CD, cluster of differentiation; IL, interleukin; USFDA, united states food and drug administration; PD-1, programmed death 1; TGF, transforming growth factor; IFN, interferon; TNF, tumour necrosis factor; CTLA-4, cytotoxic T lymphocyte associated antigen 4

Introduction

Autoimmune diseases (AD) are a group of chronic condition resulting from the impairment in the regulation of the immune system. These diseases occur as a result of immune reactivity against self-antigens termed autoimmunity. To date, no specific cure of AD has been reported. Current treatment regimes target the symptoms of AD with the aim to improve the quality of life and delaying organ damages.[1] The usage of immunosuppressive drugs in conventional therapy targeted critical parts of the immune systems which in turn increases patients' susceptibility to infection. Although immunosuppressive drugs improved the survival rate of patients with AD, these drugs increase the incidences of organ failures and secondary malignancies.[2,3] Therefore, researches are now actively carried out to find a better solution for AD. Ideally, the best strategy is to target the impaired immune cells leaving the healthy cells intact. The new frontiers of these targeted therapies which are antigen-based chemotherapy, targeted inflammatory cytokines, checkpoint-based immunotherapy and stem cell therapy are the focus of this mini review.

Antigen-based immunotherapy

In normal immune system, lymphoid progenitor cells in the bone marrow will migrate to the thyme where broad repertoires of T cells that can respond to various pathogens are generated. A subset of T cells, the destructive T cells that recognise self-antigens are deleted through the negative thymic selection Figure 1. However, some destructive T cells escape the selection process and migrate to the periphery. These destructive T cells recognize self-antigens and if activated, they have the potential to cause autoimmunity. T cell requires two signals to be fully activated. Signal 1 occurs through the engagement of T cell-antigen specific receptor (TCR) with the major histocompatibility complex (MHC) leading to semi-activated T cell or T cell tolerance. The second co-stimulatory signal which up regulate the inflammatory environments is delivered by different receptor-lig and interactions such as CD40-CD40L and PD-1-PDL1 interactions. This co-stimulatory signal causes T cell activation which then differentiates into effectors cells.

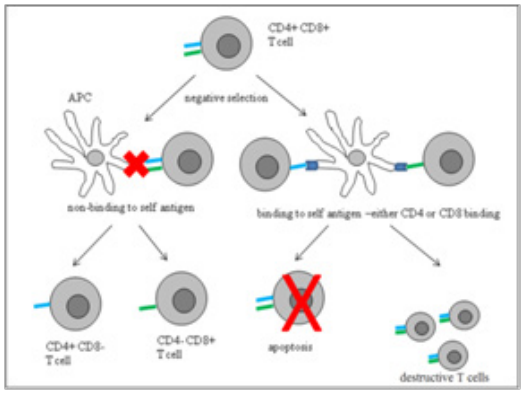

Figure 1 Negative selection of T cells in the thymus. Antigen presenting cells (APC) present self antigens to the double positive T cell. T cells that do not bind to the APC will become helper T cells (CD4+ CD8-T) and cytotoxic T cells (CD4- CD8+). Cells that bind to self antigen will undergo destruction and apoptosis (negative selection). However, some cells escape the negative selection process and migrate to the circulation where they potentially became destructive T cells.

Antigen-based immunotherapy aims to target the first T cell activation signal by delivery of modified self-derived peptide in the absence of inflammatory signal.[4] The idea is to silence the destructive T cells into tolerant T cells while leaving the immune system intact. This is carried out by prescribing AD patients with altered self-derived in the hope to alter the T cell activation signal. However, targeting the specific T cells that cause AD is a complex process coupled with the difficulty to identify specific antigens of AD.[5] Nevertheless, excellence progress has been made to resolve these issues in animal models with a number of clinical trials ongoing.[6,7]

In animal models of rheumatoid arthritis and type 1 diabetes, rats that were given altered heat shock protein deviate the immune response from self-antigens.[8,9] Heat shock protein is an intracellular

chaperone that regulates the innate immunity and act as important auto-antigen in these AD. Rats administered with altered heat shock protein shown increased production of anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β.[10] Mouse model of type 1 diabetes which is caused by autoimmune destruction of pancreatic β cells showed similar profile; the changes of pro-inflammatory cytokines production to anti-inflammatory cytokines upon intake of altered peptides.[11] Animal models of other ADs also showed promising results in term of antigen-based immunotherapy which induced T cells tolerance following altered peptide induction.[12] However, most of these studies focussed on naive T cells rather than memory T cells that are critical in the pathogenesis of AD.

In clinical trials involving antigen-based immunotherapy, hypersensitivity reactions became one of the major concerns. The T cell activation signal was altered following peptides induction leading to quantitative changes in T cell responses. Human trials on multiple sclerosis have been unsuccessful as the altered peptide of myelin basic protein failed to induce T cell tolerance and the incidence of anaphylaxis increased significantly among these AD patients.[13] In rheumatoid arthritis, phase I clinical trial using an altered peptide of dnaJP1 has succeeded in inducing T cell tolerance. In that trial, IL-4 and IL-10 production increased significantly while IL-2 and IFN-γ levels were reported to be significantly decreased.[14] A good indicator of this therapy was also recorded in the phase II of clinical trial; however the endpoints for clinical efficacy were not met. So far, significant progress on antigen-based immunotherapy was made on systemic lupus erythematosus where phase III clinical trial is currently in progress after a success in phase I and phase II trials.[15]

Antigen-based immunotherapy is a current modality for treating AD. While the animal models of this therapy were a success, translation into clinical practise has not been smooth. The factors causing unsuccessful replication of antigen-based immunotherapy in human studies remain unclear. Further studies and trials need to be conducted before this therapy is ready to be used clinically.

Checkpoint-based immunotherapy

As mentioned, T cells activation requires a second signal which is provided by co-stimulants expressed by the antigen presenting cells. CD80 or CD86 on the antigen presenting cell will engage to the T cell receptor and CD28 on the T cell and initiate T cell response to foreign antigen. In the case of auto-immunity, this response is towards self-antigen. In normal condition, the activation pathway is controlled by inhibitory molecules for normal immune function. Cell cycle checkpoints are critical in maintaining normal immune function, failure of which will result in immune-related disorders. Checkpoint-based therapy in AD aims to block T cell activation and restore T cell tolerance via regulatory T cell (Treg) activations. Checkpoint-based immunotherapy has made tremendous progress in AD with the translation into clinical trials and the usage of checkpoint-based drug in clinical settings.

Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) is an inhibitory receptor on T cells. This receptor has higher binding capacity to CD80 or CD86 on the antigen presenting cell compared to CD28.[16] Engagement of CTLA-4 with the ligands transmit inhibitory signal to T cell and this engagement has been the focus in autoimmune-related researches. Figure 2 shows the interaction of CTLA-4 receptor with CD80/CD86 ligand which will disrupt the co-stimulatory signals on T cells, reducing the activation of self-antigenic T cells in AD. In fact, CTLA-4 checkpoint has been extensively studied in cancer. Ipilimumab, a monoclonal antibody targeting CTLA-4 has been approved by the US FDA in 2011 for the treatment of metastatic melanoma. Clinical trials are being conducted on Ipilimumab effectiveness on other cancer. However, the progress of check-point based therapy in AD is slower compared to cancer.

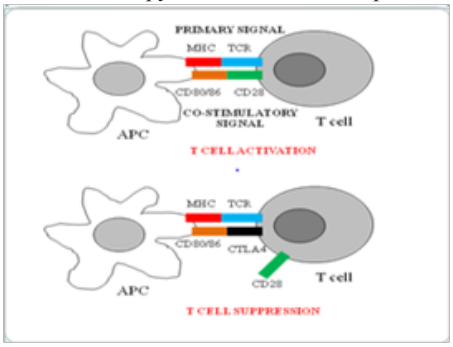

Figure 2 Checkpoint-based immunotherapy in AD. T cell activation requires two signals. The primary signal occurs between major histocompatibility complex (MHC) and T cell receptor (TCR). Upon inflammation, the APC will deliver the second co-stimulatory signal to the T cells via CD80/86 and CD28 interaction. CTLA4 is a inhibitory receptor that bind to CD80/86 causing T cell suppression and reducing the occurance of AD.

Abatacept is a CTLA-4-Ig fusion protein which is used as a new therapeutic approach in rheumatoid arthritis.[17] This drug inhibits CD80/86 and CD28 interaction thus blocking the secondary signal of T cell activation to effectors cell. In animal model of arthritis, abatacept reduced the antibody production against type II collagen and inhibit the germinal centres generation in the spleen and lymph nodes. Seven phase II and III clinical trials conducted on the clinical efficacy of abatacept concluded that abatacept is effective in rheumatoid arthritis patients when they failed to response to other drugs such as methotrexate.[18–20] However, the long term effects of abatacept in causing malignancies, serious infections and organ damages remain to be evaluated. Besides rheumatoid arthritis, abatacept is currently tested in multiple phase of clinical trials for type I diabetes mellitus, multiple sclerosis, myasthenia gravis, antiphospholipid syndrome and primary biliary cirrhosis.[21,22]

PD-1 or programmed death 1 is another cell cycle checkpoint in terminating immune responses. PD-1 promotes regulatory T cell (Treg) development and causing direct inhibition of self-reactive T cells. PD-1$^{-/-}$mice model was shown to develop spontaneous AD and this finding showed the importance of PD-1 membrane protein in normal immune function.[23] The function and activation of PD-1 have been extensively studied in antitumor and antiviral immunity but less is known about PD-1 in autoimmunity. Therefore, it is worth to include PD-1 as the next target of checkpoint-based immunotherapy in curing AD.

Regulations of inflammatory cytokines

Persistent production of inflammatory cytokines is one of the underlying mechanisms of AD. TNF-α and IL-1 stimulate macrophages, keratinocytes and dendritic cells to produce inflammatory cytokines and chemokines in the immediate environment which in the case of AD, is uncontrolled. Given the importance of inflammatory cytokines in the pathogenesis of AD, researches are focussing on targeted inflammatory cytokines to treat AD. This treatment is highly effective as neutralizing agents or act as antagonist against their receptors.

TNF-α, a pro-inflammatory cytokine is elevated in many AD. This cytokine exhibits an immune-regulatory role that lead to acute immunological response. TNF-α directs the production of key interleukins such as IL-1 and IL-6 which in turn stimulate the production of enzymes that destroy cartilage and bone.[24] Therefore, targeting TNF-α is very important as this will also reduce the production of other pro-inflammatory cytokines, shifting the balance towards homeostasis in AD patients. TNF-α inhibitors such as infliximab and adalimumab have been used as neutralizing antibodies in various immune mediated diseases such as inflammatory bowel disease, psoriasis and rheumatoid arthritis.[25] The first trial of anti-TNF inhibitor was carried out in 1992. It was reported that combined methotrexate-anti TNF therapy was proven to be more effective than using either agent alone.[26] However, a subpopulation of patients did not response well to this therapy and actual mechanism of immune-regulatory role of anti-TNF therapy remains to be studied. Certain patients also developed malignancies, fungal infections and tuberculosis as after-effects of anti-TNF therapy. Therefore, work is ongoing to develop a more effective anti-inflammatory blocker for AD.

One such cytokine is IL-17. IL-17 confers protective immunity against extracellular and intracellular pathogenic agents. IL-17 is produced by Th17 cell subset derived from $CD4^+$ T cell. In AD, relatively higher amount of IL-17 was produced due to excess stimulation by IL-1β and IL-6 secreted by macrophages and tissue cells. IL-17 was isolated from T cell of rat-mouse hybridoma and to date, six homologous molecules are found, IL-17A through IL-17F. IL-17A and IL-17RA was extensively studied as they are predominantly expressed by Th17. Th17 have been established as the inducer of chronic inflammatory AD such as multiple sclerosis and psoriasis.[27] In addition, genome-wide association study and experimental works using animal models have concluded that IL-23 and IL-12 stimulation, the key mediators of inflammation confers higher pathogencity on Th17 cells in AD.[28]

Clinical trial is in progress regarding humanized anti-IL-23 antibodies, humanized anti-IL-17 antibodies and humanized IL-17R antibodies. These clinical trials focus on rheumatoid arthritis, chronic inflammatory intestinal diseases, psoriasis and multiple sclerosis. In these trials, favourable developments were observed on the safety and efficacy use of ustekinumab, a human anti-IL-23 and anti-IL-12 monoclonal antibody in patients with psoriasis.[29] In this phase III double blind placebo-controlled study, treatment of ustekinumab for every 12 weeks is effective in patients with moderate to severe psoriasis. Another phase III trial on secukinumab which is a human anti-IL-17A monoclonal antibody also showed that this antibody is effective against psoriasis with its ability in neutralizing IL-17A.[30] Both of these studies showed that the presence of neutralizing antibodies against pro-inflammatory cytokines was not associated with adverse events.

Stem cell therapy

In the current years, stem cell therapy has become one of the hottest debates in the field of regenerative medicine and immune therapies. Stem cell therapy is clinically relevance for treatment of AD, a pathophysiological conditions resulting from the failure of normal immune-regulatory processes. Despite extensive research in the animal models, the clinical applications of haematopoietic stem cell and mesenchymal stem cell to treat AD are still vague. Studies are now focusing on the mechanisms of action, route and dosage of administration and the safety and efficacy of stem cell treatment of AD.

Hematopoietic stem cells are stem cells that derived from the mesoderm that give rise to other myeloid and lymphoid lineage of blood cells. Hematopoietic stem cells are found in the bone marrow of adults especially in femur, pelvis and sternum and also in the umbilical cord blood. Autologous hematopoietic stem cell transplantation started as a concept to cure AD in the early 1990s.[29] Theoretically, person with overt autoimmune disease can be cured with bone marrow transplantation from allogeneic normal donor. The idea behind hematopoietic stem cells transplantation is to reset the host immune system leading to the generation of self-tolerant lymphocytes. However, during phase I clinical trial on systemic lupus erythematosus patients, the morbidity and mortality associated with this procedure was high, preventing its application in clinics.[31] On the other hand, a contradict result was reported in a study of 53 SLE patients in Europe.[32] In that study, remission was achieved in two-third of systemic lupus erythematosus patients, however, one-third of the patients relapsed after 6 months. This is in accordance with another study showing that two-thirds of patients receiving haematopoietic stem cell therapy will eventually relapse.[33] High expression of CD3 and CD4 combined with the higher concentration of C-reactive proteins in serum of relapse patients were suggested as the determining factors.

Apart from hematopoietic stem cell therapy, mesenchymal stem cell transplantation was also suggested as a potential cure for AD. Mesenchymal stem cells are multipotent stromal cells that can differentiate into bone, cartilage, muscle cells and connective tissue. Mesenchymal stem cell was shown as immune-modulator and regulates the proliferation and activation of B lymphocytes, T lymphocytes, dendritic cells and neutrophils.[34] This stem cell modulates immune responses through the activation and synthesis of Tregs. In animal model of multiple sclerosis, intravenous administration of mesenchymal stem cells managed to improve this AD through the release of anti-inflammatory and neuroprotective molecules.[35] In addition, mesenchymal stem cell based therapy was also carried out on systemic lupus mouse model. Results showed marked improvement in serum level of immunoglobulins at both early and matured stage of this AD.[31] Currently, pilot clinical trials are being carried out in subjects of advanced multiple sclerosis and lupus based on this stem cell-based therapy.[36–40]

Conclusion

Remarkable progress has been made in understanding the pathway of AD and the targeted treatments.[41–45] In some personalized therapy of AD, although the results from animal models look promising, the translation to the clinical settings proved to be more challenging. However, some immunomodulatory therapy discussed in this article showed excellence results during the clinical trial Table 1. These show that translation into clinical practise is possible to develop the AD therapy that will ultimately repair the immune imbalances with minimal adverse effects.[46–48]

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None.

Table 1 Summary of the developments associated with the targeted therapies (antigen based immunotherapy, checkpoint-based immunotherapy, targeted inflammatory cytokines and stem cell therapy) in AD

Targeted therapies	Autoimmune diseases	Current stage
Antigen-based chemotherapy		
Altered heat shock protein (dnaJP1)	Rheumatoid arthritis, idiopathic arthritis	Successful in phase I clinical trial, which induced T cell tolerance. Currently in phase II clinical trial.[36]
Altered heat shock protein (APL-1)	Rheumatoid arthritis	In animal models, this APL was found to increase Tregs and inhibit progression of the disease; Translational research is underway.[37]
Altered peptide ligands (APL) of insulin (NBI-6024)	Type 1 diabetes	Phase I was a success. Phase II revealed that NBI-6024 did not improve islet cell function.[37]
Recombinant human GAD65	Type 1 diabetes	Phase II clinical trial reported that significant long term efficacy was demonstrated in preserving β-cell function.[38]
Myelin basic protein (MBP)	Multiple sclerosis	Animal studies demonstrated efficary in the prevention of AD. However, phase I clinical trial have been unsuccessful.[13]
P140 peptide	Systemic Lupus Erythematosus	Phase II clinical trial was a success and resulted in significant decrease in the SLE Disease Activity Index (SLEDAI) score. Phase III clinical trial is under way.[15]
Checkpoint-based immunotherapy		
CTLA-4-Ig fusion protein (Abatacept)	Rheumatoid arthritis, multiple sclerosis	Successful phase III clinical trial. Currently; the epidemiology study on the long term effect of Abatacept.[18,21,22]
PD-1 or CD279	Rheumatoid arthritis, Type 1 diabetes, Systemic lupus erythematosus	Animal studies show very promising results in understanding the PD-1 pathway as key regulator of T-cell activation.[39–41]
Targeted inflammatory cytokines		
Human anti-IL-23 and anti-IL-12 monoclonal antibody	Rheumatoid arthritis, Psoriasis, multiple sclerosis, inflammatory bowel disease	Phase I and II trials showed significant improvement of AD. Phase III clinical trial is underway.[42,43]
human anti-IL-17A monoclonal antibody (Secukinumab)	Psoriasis, multiple sclerosis	Phase I and II clinical trials completed with efficacy data supported. Currently in phase III trial.[44]
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Arthritis, Psoriasus. Myasthenia gravis, Type 1 diabetes, Collitis	Phase I clinical trials completed with promising results. Phase II trial is underway.[45,46]
Stem cell therapy		
Hematopoietic stem cell transplantation	Systemic lupus erythematosus, Rheumatoid arthritis	Phase I and II clinical trial were carried out. However, the mortality associated with HSC transplant was high.[47,48]
Mesenchymal stem cell transplantation	Multiple sclerosis	Excellent results reported in animal model. In phase ½ a study, no severe adverse events reported. Now ongoing is phase 1 clinical study.[48]

Conflicts of interest

Author declares that there is no conflicts of interest.

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