

Immunotherapy in Autoimmune Diseases

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Abstract

Immunotherapy has the potential to modify or re-balance the immune system and hence useful in the management of autoimmune conditions. This article aims to review clinically useful immunotherapies available for treatment of autoimmune conditions, with particular emphasis on Type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus. A Medline search for the period 1992 to 2002 (10 years) using the unrestricted keywords “immunotherapy AND autoimmune” was done. Full-length articles were selected for reviews based on the contents of their published abstracts. Additional Medline searches were focussed on the keywords “immunotherapy AND diabetes mellitus”, “immunotherapy AND multiple sclerosis”, “immunotherapy AND rheumatoid arthritis”, and “immunotherapy AND systemic lupus erythematosus”. Relevant publications referenced in the reviewed literature were further included for review, if not present in the original Medline search. Immunotherapy in Type I diabetes mellitus has focussed on the induction of tolerance to β cell antigens, and in multiple sclerosis trials of anti- α 4 integrins and altered peptide ligand of myelin basic protein (MBP 83-99) showed initial promising results. The use of anti-cytokine therapy (anti-TNF α and IL-1Ra) in rheumatoid arthritis has improved the quality of life of patients with refractory disease. The use of anti-CD20 monoclonal antibody for in vivo B cells depletion and early trials of autologous peripheral stem cell transplants represent additional immunomodulatory treatment modalities for systemic lupus erythematosus patients. Better understanding of autoimmune conditions and advances in the production of humanised monoclonal antibodies, promises better immunotherapy in the near future.

Ann Acad Med Singapore 2002; 31:702-6

Key words: Monoclonal antibody, Multiple sclerosis, Rheumatoid arthritis, Systemic lupus erythematosus, Type I diabetes mellitus

Introduction

In the early 1700s, Lady Mary Wortley Montagu, wife of the British ambassador to Turkey, introduced the practice of variolation against smallpox into Western Europe. This act of immunisation had since been better understood. Experimental findings of pioneer scientists like Edward Jenner, Louis Pasteur, Eli Metchnikoff, George Nuttall, Emil von Boehringer, Shibasaburo Kitasato, Almroth Wright and many others allow us to understand the biological basis of immune responses. They laid the foundations for modern immunology.¹ We are now aware of how cellular and humoral responses play key roles in the immune response, how central and peripheral tolerance develops, and how cytokine and chemokine mediators affect the inflammatory process. The immune system is indeed a wonderful creation and its workings ensure swift and specific protection against microbial agents and mutant cells. However, its dysfunction can also cause multifold problems, chief of which are the development of autoimmunity and malignancy. Hence, the attractive idea of using biologic agents e.g. monoclonal antibodies to restore balanced immune responses. In the 1980s, therapeutic monoclonal

antibodies are murine based and they had serious drawbacks. Apart from having a short half-life, usually less than 24 hours instead of weeks for human antibodies,² they also elicit an anti-murine antibody response in the vast majority of treated patients.³ These drawbacks preclude their use as long-term therapeutic agents. Technological progress in the generation of monoclonal antibodies – from murine to chimeric, to humanised, and then to phage-displayed human antibodies⁴⁻⁶ – rekindles the interest in immunotherapy for immune-mediated diseases. In the 10-year period between 1986 and 1996, 2 antibodies (muromonab-CD3 against CD3 and abciximab against gpIIb/IIIa) were approved by the Food and Drug Administration (FDA) for therapeutic use, but between 1997 and 2001, another 11 antibodies preparations were approved for clinical use in immune-mediated conditions.⁷ They are used for the clinical treatment of oncological, infectious and autoimmune conditions. This review focuses on the clinically useful immunotherapeutic agents in autoimmune diseases. Autoimmune diseases are defined as “a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause”.⁸ A Medline

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search for the period 1992 to 2002 (10 years) using the unrestricted keywords “immunotherapy AND autoimmune” yielded more than 300 articles for review. Full-length articles, pertaining to immunotherapy in autoimmune conditions, were selected for reviews based on their published abstracts. Relevant publications referenced in the reviewed literature were further included for review, if not present in the original Medline search. Four autoimmune conditions, Type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, were selected to highlight the use of immunotherapy in autoimmune conditions.

Therapeutic Strategies

Different therapeutic approaches have been used to target different components of the immune system. They range from the blockade or antagonism approach to induction of tolerance and immune system reconstitution. One of the challenges in the therapeutic tolerance approach is that tolerising treatments are given only after diagnosis is made clinically. Hence data culled from prophylactic tolerance in experimental animals, which can demonstrate elegantly that an agent is efficacious in preventing the development of a specific autoimmune condition, usually cannot be extrapolated to humans. Clinically overt disease means that T cells have been exposed to and primed by many tissue antigens. Immune system reconstitution can potentially mean a “cure”, though morbidity and mortality risks are high. However, proper selection of patients, and adequate expertise and infrastructure, are necessary to ensure good outcome.

Type I Diabetes Mellitus

Type I or insulin-dependent diabetes mellitus (IDDM) develops gradually over many years before they have clinically overt disease.⁹ IDDM is an autoimmune condition arising from the destruction of pancreatic β cells. The cellular and molecular pathogenic mechanisms are reviewed recently by Yoon and Jun.¹⁰ Macrophages, dendritic cells, B and T cells, as well as β cell autoantigens i.e. glutamic acid decarboxylase (GAD),¹¹ insulin, 38-kD antigen,¹² IA-2 Autoantigen-37/40kD Tryptic Fragment,¹³ have been reported to be involved in the pathogenetic process. Studies involving immunisation of non-obese diabetic (NOD) mice with purified GAD results in the tolerization of GAD-reactive T cells. This then blocks the development of T-cell responses to other β cell antigens, thus preventing insulinitis and diabetes.^{14,15} The role that insulin plays as an autoantigen in IDDM have been demonstrated in studies in NOD mice. Oral intake of insulin retards disease progression in the NOD mouse, probably through induction of immunoregulatory T cells.¹⁶ Prevention of diabetes in NOD mice was noted when the insulin B chain was administered either by intrathymic or subcutaneous injection, or by

intranasal administration.¹⁷ A diabetogenic CD8+ T cell clone, which causes diabetes in neonatal NOD mice, was also found to recognize insulin B chain amino acids 15-23.¹⁸ The exact roles of the latter 2 antigens await further studies. The challenge of using immunotherapy in IDDM is that in clinically overt disease, there may be only a limited number of β cells left, hence raising doubts as to whether treatment would be useful. Observations in the NOD mice, however, indicate that β cell destruction seems to be preceded by reversible T cell inflammation¹⁹ and recent evidence suggest that β cells regeneration may be possible from ductular stem cells.²⁰ The approach of inducing tolerance to β cell autoantigens, though attractive, has not yielded much success at the human level. Two clinical trials using oral insulin as tolerogens, one involving 82 patients²¹ and the other involving 131 patients²² demonstrated no beneficial effect. We have to await results of further trials of subcutaneous administration of insulin in persons at risk. Other approaches include cytokine-based therapy e.g. administration of IL-4²³ or antagonism of IL-12.²⁴ In a study by Fujihira and co-workers,²⁵ they demonstrated that the timing of anti-IL-12 antibody is critical as it can either prevent or enhance the disease onset in NOD mice. An anti-T cell strategy may work through direct effect on pathogenic T cells and/or through induction of regulatory cells. The use of anti-T cell monoclonal antibodies has shown promising results in a clinical study involving 24 patients with Type 1 diabetes mellitus.²⁶ A single 14-day course of a non-activating humanised monoclonal antibody against CD3-hOKT3 γ 1(Ala-Ala), given within 6 weeks of diagnosis, maintained or improved insulin production in 9 of 12 treated patients when assessed at 1 year post-treatment. The control group showed only 2 of 12 patients sustain or improve their insulin production after 1 year. No severe adverse reactions were reported and additional studies may further refine this form of immunotherapy.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system, characterised by the presence of areas of demyelination and perivascular inflammation in the brain white matter. Symptoms may vary dramatically in their expression and severity over many years. Currently, 3 types of medications are approved for treatment of multiple sclerosis – β interferons (IFNs), glatiramer acetate, and mitoxantrone. Two recent clinical trials – CHAMPS²⁷ and ETOMS²⁸ – reported that β interferons are effective in MS. In CHAMPS, a randomised, double-blind trial of 383 patients, interferon β -1a was administered to those who had a first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or brain-stem or cerebellar syndrome) and evidence of prior subclinical demyelination

on magnetic resonance imaging (MRI) of the brain. Another 308 patients were studied in ETOMS with early treatment. Both demonstrated beneficial effects in the treatment group when compared to placebo. Recently, a study (INCOMIN) comparing high-dose interferon β -1b administered every other day and interferon β -1a given once a week showed that the former is more effective.²⁹ Experimental evidence suggest that the IFNs bind to cell surface-specific receptors, initiating a cascade of signalling pathways that end with the secretion of antiviral, antiproliferative, and immunomodulatory gene products.³⁰ Glatiramer acetate, a random copolymer of 4 amino acids, had been compared to interferon β -1b in an open label study of 58 MS patients. After 2 years of follow-up, their efficacy and safety profiles are found to be similar.³¹ Glatiramer acetate, a non-specific inhibitor of T cells³² and inducer of immune deviation from Th1 to Th2 helper T cells,³³ was shown to have a beneficial and sustained clinical effect in a randomised placebo-controlled study of 251 MS patients.³⁴ Mitoxantrone, a cytotoxic agent and potent immunosuppressive agent, is useful in the treatment of frequent, disabling exacerbations. Its long term use is, however, limited by potential cardiotoxicity.³⁵ In a randomised, double-blind, placebo-controlled trial of 72 patients with active relapsing-remitting and secondary progressive MS, short-term treatment with monoclonal antibody against α 4 integrin results in a significant reduction in the number of new active lesions on MRI.³⁶ The study was, however, not designed to look at treatment effect on relapse rate. Two recent studies using the altered peptide ligand approach produced conflicting results. Kappos³⁷ reported beneficial effect in a double-blind placebo-controlled study of 142 patients, while Bielekova reported exacerbations in 3 of 9 patients in an open-label study.³⁸ Kappos' trial was, however, suspended due to the presence of hypersensitivity reactions in 9% of study patients. TNF- α blockade has been tried as an option for immunotherapy. However, in a double-blind, placebo-controlled phase II study comprising 168 patients, most with relapsing-remitting MS, administration of a recombinant TNF receptor p55 immunoglobulin fusion protein (sTNFR-IgG p55; Lenercept) worsens the disease.³⁹

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that can lead to severe joint deformities. Advances in the understanding of its pathogenesis had yielded molecular targets for therapeutic intervention. A recent review by Choy and Panayi⁴⁰ identified Interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF- α as the key cytokines that drive inflammation in rheumatoid arthritis. Transgenic mice carrying 3'-modified hTNF transgenes show deregulated patterns of expression and develop chronic inflammatory polyarthritis. Administration of a monoclonal

antibody against human TNF completely prevents development of this disease.⁴¹ Genetically modified mice, deficient in IL-1Ra, were found to develop chronic erosive polyarthritis, thus providing an insight into the role of IL-1Ra in regulation of IL-1.⁴² These and other studies raise the possibilities of targeting IL-1 and TNF- α in RA patients to halt, or at least attenuate, the inflammatory process. Clinical trials with etanercept (a recombinant tumour necrosis factor receptor:Fc fusion protein) and infliximab (monoclonal antibody against TNF- α) demonstrated rapid and sustained improvement in rheumatoid disease activity. The etanercept trial treated 89 patients over a 24-week period and showed significant improvement in those treated with etanercept and methotrexate versus those treated with placebo and methotrexate (71% versus 27% for ACR 20 and 39% versus 3% for ACR 50 assessment).⁴³ In the ATTRACT trial, 428 patients were studied and assessed after 30 weeks. Treatment with infliximab with methotrexate was found to be more efficacious than methotrexate alone, and improved the patients' quality of life as well as halted the progression of joint damage.^{44,45} There is, however, a concern of infliximab inducing anti-dsDNA antibodies in treated patients. In a study of multiple pre- and post-infliximab sera from 156 patients, 1 patient developed high titres of anti-dsDNA antibodies of IgG, IgM, and IgA class, peaking at 22 weeks and resolving by 54 weeks.⁴⁶ A recombinant human interleukin-1 receptor antagonist, used singly to treat 472 patients in a 24-week, double-blind, randomised, placebo-controlled, multicentre study showed efficacy, safety and retardation of radiographic joint erosions.⁴⁷ A recent 419-patient study demonstrated the safety and tolerability of anakinra and methotrexate combination. Assessment at 12 and 24 weeks showed significant benefits on 1 mg/kg and 2 mg/kg doses when compared to placebo (ACR 20: 46% and 38% versus 19% respectively).⁴⁸ Theoretically, IL-6 blockade should also provide similar benefit in RA patients; however, no large trials have been reported since Wendling demonstrated in a small (5 patients) pilot study that intravenous anti-IL-6 Mab provided short-term improvement.⁴⁹ IL-18, a member of the IL-1 cytokine family, has been postulated to have a proinflammatory role in RA,⁵⁰ particularly in chronic inflammation;⁵¹ and in IL-18 deficient mice, the incidence of collagen-induced arthritis is reduced.⁵² Hence, it is another potential target for RA therapy.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease characterised by the presence of multiple autoantibodies. Though intravenous immunoglobulins have been used to treat immune-mediated thrombocytopenia associated with SLE, there has been a paucity of data for treatment of SLE *per se*. In a study of 14 patients with lupus

nephritis, it was shown to be comparable to monthly pulsed cyclophosphamide over an 18-month period,⁵³ and in an open-label trial of 20 unselected patients, it demonstrated beneficial clinical response.⁵⁴ LJP 394, a molecule consisting of 4 double-stranded oligonucleotides attached to a non-immunogenic polyethylene glycol platform, was designed to induce tolerance in B cells directed against double-stranded DNA (dsDNA). It cross-links their surface antibodies in the absence of a second signal from T cells.⁵⁵ A phase I trial in 4 patients showed immediate reduction of anti-dsDNA titre following an infusion of LJP 394⁵⁶ and a more recent trial in 58 patients confirmed the findings and its safety profile.⁵⁷ Results from larger trials are yet to be published. Anti-CD20 monoclonal antibody (Rituximab) has been used in SLE with life-threatening autoimmune haemolytic anaemia.⁵⁸ However, its therapeutic usefulness as an *in vivo* B cell depletor in unselected SLE patients is not yet known. Immune reconstitution by autologous haematopoietic stem cell transplant following intense immune suppression has been used for treatment of patients with severe lupus erythematosus⁵⁹ and represents a potential for “cure”. Randomised trials with long-term follow-up data will be necessary to establish its role in the treatment of severe lupus.

Conclusion

Vaccinology, 300 years after Lady Mary Wortley Montagu's efforts, has come a long way. The development of DNA vaccine has opened up new therapeutic potentials in areas of infectious diseases, oncology, neurology and immunology. Wildbaum et al⁶⁰ found that pre-immunisation with a plasmid encoding TNF- α protected against adjuvant induced arthritis. In this RA model, the beneficial anti-TNF- α response ameliorates the arthritis even after its onset, a potential clinically useful finding. In the years ahead, immunotherapy will definitely play key roles in the treatment of autoimmune conditions and technological advances will continue to improve its efficacy and safety profiles.

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