

Therapy of autoimmune diseases: clinical trials and new biologics

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Successful clinical efficacy trials have been recently completed for a growing array of new biologics. Prospects are improving for rational therapeutic interventions that potently interrupt adaptive immune response pathways. By contrast, disappointing results with antigen-based therapeutics highlight the difficulties of achieving tolerance in the context of active autoimmunity. Combination immunotherapy is probably necessary to sequentially or simultaneously inhibit inflammation, uncouple innate immune pathways, interrupt or ablate the adaptive memory response and promote antigen-specific tolerance in a suitable immunological context.

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Abbreviations

IL interleukin
TNF tumor necrosis factor

Introduction

There has been a dramatic change in the immunotherapy of autoimmune diseases in which biological agents, such as monoclonal antibodies, soluble receptors and molecular mimetics, offer the potential to enhance or replace conventional immunosuppressive therapies. Over the last year, successful clinical trials have been reported for several promising immunologics that target defined pathways in the adaptive immune response. Thoughtful design of trials utilizing these agents offers the prospect for significantly expanding options for the treatment of many autoimmune diseases.

The impetus to test new biologic agents in clinical trials comes on the heels of several years of clinical success for tumor necrosis factor (TNF) blockade in patients with rheumatoid arthritis or Crohn's disease. These anti-TNF biologics (etanercept, infliximab and onercept) have recently been found to be efficacious also in ankylosing spondylitis, psoriatic arthritis and psoriasis [1–3]. Clinical efficacy is notable, even in patients refractory to conventional therapies [4,5]; however, the frequent return of disease after termination of therapy, and the failure of TNF blockade to show clinical benefit in multiple sclerosis [6], indicate the need for therapies that will interrupt additional key pathways of the autoimmune response.

In sharp contrast with therapeutic blockade of TNF function, alternative approaches to immunotherapy have been developed using administration of antigens or antigen

analogues. To date, however, these approaches have been extremely disappointing, as promising results from early pilot trials have not been confirmed, for example, oral collagen administration as a therapy for rheumatoid arthritis [7,8], parenteral insulin trials for type 1 diabetes [9,10] and the use of an altered myelin basic protein peptide in multiple sclerosis [11,12]. Some of the limitations of these studies have recently been discussed [13,14], emphasizing the importance of such variables as the route of antigen administration, the choice of adjuvants, the dose dependence of immune effects, and the human leukocyte antigen genotype of the patients, as well as the precise choice of antigen being administered. Of even greater concern, however, is the growing realization that such antigen-specific immunomodulation is a fairly subtle stimulus for immune deviation and that the rampant activated immune response in a patient with clinical disease is, by contrast, a very unsubtle environment. Indeed, the only convincing example of oral tolerance in humans utilized keyhole limpet hemacyanin, a foreign antigen, in immunologically naïve volunteers [15]. For antigen immunomodulation and immune deviation to succeed in the context of an active autoimmune environment it may well require a more sophisticated clinical approach, in which key pathogenic immunologic pathways are interrupted as an integral part of therapy.

Key pathways define new targets

Fortunately, a large and growing number of targeted therapeutics are available for this purpose. Table 1 lists several of these compounds and their molecular targets, which have been reported to show clinical efficacy in recent trials. Most of these new biologics target specific signaling molecules or target molecules associated with the adaptive immune response; however, there have been a few recent trials that, like the TNF studies mentioned above, selectively interrupt effector cytokine pathways. For example, the cytokine interleukin (IL)-10 has recently been shown to prolong clinical remission in patients with psoriasis: a T cell-dependent autoimmune disease associated with high levels of γ -interferon and TNF in skin lesions [16,17]. IL-2 blockade continues to show promising clinical efficacy, with recent studies showing efficacy of anti-CD25 antibodies as monotherapy for epidermolysis bullosa acquisita [18,19]. Importantly, treatment with the monoclonal antibody to the IL-2 receptor CD25 led to downregulation of the receptor but did not deplete the T cells. In view of recent studies in murine models, in which naïve CD25⁺CD4⁺ T cells perform important regulatory functions, even when CD25 is downregulated [20], this may be another important consideration for human autoimmune disease.

Monoclonal antibodies to three other T cell surface molecules (CD3, CD4 and CD52) have all been successfully

used in clinical efficacy trials for autoimmune diseases, although all are associated with transient depression of circulating T lymphocytes. Results of a recent clinical trial using alemtuzumab (CAMPATH-1H, anti-CD52) documented profound lymphopenia, with recovery of B cells and CD8⁺ T cells and a longer lasting CD4 cytopenia [21]. As has previously been reported for treatment of rheumatoid arthritis patients using this antibody [22,23], the recent study documented sustained clinical responses in patients with autoimmune haematological diseases, including idiopathic thrombocytopenic purpura, haemolytic anaemia and autoimmune neutropenia [21].

Concern about long-term CD4⁺ T cell depletion has led to trials with other potential anti-T cell therapeutics, including a non-depleting anti-CD4 monoclonal antibody with efficacy in rheumatoid arthritis [24] and, more recently, a modified anti-CD3 antibody known as hOKT3 γ 1(Ala-Ala). In a pioneering study in new onset type 1 diabetes mellitus, patients were treated with this anti-CD3 monoclonal antibody for 12 days — soon after the diagnosis of autoimmune diabetes. In the majority of patients, clinical benefit, measured as maintenance of insulin production and improved metabolic control, was observed [25**]. T cell depletion with this therapeutic antibody was transient, and modifications to the monoclonal antibody structure prevented complications of T cell activation previously associated with anti-CD3 therapies.

Clinical trials have been completed for several new biologics that target specific functional pathways of T lymphocytes associated with co-stimulation or with trafficking between blood and tissues. Alefacept, a soluble LFA3/IgG1 fusion protein that binds CD2 on T cells as well as binding Fc receptors, was recently found to be efficacious in treatment of chronic psoriasis [26,27]. The therapeutic effect correlated with lower numbers of circulating memory (CD45RO⁺) T cells, which is consistent with the proposed mechanism of inducing apoptosis through CD2 interactions [28]. Significant improvement in psoriasis was also reported for efalizumab: an anti-LFA1 monoclonal antibody thought to interfere with lymphocyte trafficking and co-stimulation without decreasing T cell numbers [29,30].

New therapeutics directly targeted at the T cell-trafficking pathway include natalizumab, an antibody to α -4 integrin (very late antigen-4; VLA-4). Clinical efficacy was observed both in ulcerative colitis [31] and in active Crohn's disease [32], consistent with clinical benefit previously reported in multiple sclerosis [33]. By contrast, a recent trial of anti-E selectin in psoriasis showed no benefit compared to placebo [34].

The relative contributions of T cells and B cells to clinical autoimmunity are controversial and their functions may well be intertwined; thus, several recent clinical trials have focused on B cell depletion as a potential therapeutic strategy. Rituximab (anti-CD20) and epratuzumab (anti-CD22)

Table 1

Lexicon of recent biologics with efficacy in clinical autoimmunity.

Compounds	Target
Infliximab, etanercept, onercept	TNF α
Daclizumab, basiliximab	CD25 (IL-2 receptor)
Alemtuzumab	CD52
Alefacept	CD2
Efalizumab	CD11a (LFA-1)
Natalizumab	VLA-4
Rituximab	CD20
Epratuzumab	CD22
hOKT3 γ 1 ala-ala	CD3
OKTcdr4a	CD4
Glutiramer acetate	TCR-MHC interaction

MHC, major histocompatibility complex; TCR, T cell receptor.

administration leads to profound B cell depletion associated with clinical improvement for autoimmune haemolytic anaemia in patients who had failed conventional therapies [35–37]. Extension of these studies to autoimmune diseases in which both B cells and T cells participate, such as systemic lupus erythematosus and rheumatoid arthritis, are likely to be forthcoming.

One of the most intriguing therapeutic advances over the last year has been the use of glutiramer acetate (Copaxone, Copolymer-1) in patients with multiple sclerosis [38–42]. Glutiramer acetate is a synthetic polypeptide with a random mixture of alanine, glutamate, lysine and tyrosine. Effects appear to be dependent on major histocompatibility complex binding and on T cell-receptor recognition; therefore, it has been proposed that this peptide acts as an altered peptide ligand with antagonist or immune deviation properties. Consistent with this hypothesis, clinical outcome appears to be positively correlated with the DRB1•1501 human leukocyte antigen genotype in patients [38].

Several conclusions can be drawn from these recent clinical trials with new biologics. First, it is evident that potent therapeutics for T and B cell depletion, which were previously studied in the context of lymphoid malignancy, such as anti-CD52 and anti-CD20, can have profound therapeutic effects in autoimmunity as well. Indeed, there may be some parallels between the spontaneous immune reconstitution after induction of cytopenia using these agents with other therapeutic attempts at immune reconstitution, such as autologous stem cell transplantation following irradiation or cytoreduction therapy. Second, there is encouraging clinical benefit from several of the biologics that target likely effector populations and functions in T cell autoimmunity, such as interference with the CD2, VLA-4 or CD25 pathways. It remains to be seen, however, how these therapeutics will relate to disease specificity; that is, different clinical settings, different disease stages and different types of autoimmune diseases may respond distinctly to

Figure 1

Therapy 1	Therapy 2	Therapy 3
Un-couple innate immune activation	Interrupt adaptive immune memory	Establish tolerance
e.g. TNF blockade	e.g. selective T and/or B cell biologics (see Table 1)	e.g. antigen or altered peptide administration

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A classification scheme for combination immunotherapy, in which potent anti-inflammatory biologics, such as TNF inhibitors, set the stage for anti-T and B cell therapeutics, which target both effector and memory populations. Antigen-specific therapeutics can then be introduced in an immunological context more suitable for the generation of tolerance.

these types of compounds. Third, attempts to modify signaling through the T cell receptor are a very intriguing approach, encouraged by both the anti-CD3 trial in autoimmune diabetes and the glutiramer acetate studies in multiple sclerosis. Ultimately, these approaches may prove to be minimally toxic strategies for redirecting T cell outcomes.

Conclusions

The successful clinical trial results with biologics, targeting the adaptive immune response, represented by the T and B cell compartments, is in sharp contrast with the lack of efficacy for the antigen-specific therapeutics so far tested. Hopes for truly efficacious antigen-specific immunomodulation may need to be revised to take advantage of these clinical realities. Figure 1 illustrates a road map for combination immunotherapy, which takes advantage of the strengths of each of the major biologic modalities in use. The rationale for this approach is based on the notion that patients with clinically active autoimmune disease pose at least three distinct challenges for immunotherapy: first, the need to arrest ongoing inflammatory responses that drive innate immune activation, promulgate autoimmune pathways and provide a significant barrier to potential tolerogenic therapy; the second is the need to interrupt the adaptive memory response, potentially in both the T and B cell compartments, which is based on the notion that tolerogenic therapies in animal models are much more efficacious directed to the naïve response; and third, antigen-specific immunomodulation. With the recent evidence that the adaptive memory response can be ablated with potent biologics, with minimal complications, it is possible to envision an induction form of immunotherapy in which uncoupling of the innate response, with a therapeutic such as anti-TNF, along with interruption of the

adaptive memory response, with monoclonals to T and B cell effector pathways, would set the stage for subsequent antigen-specific tolerance.

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