Commentary

Where is biological therapy going?

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Abstract

The substantial progress in our understanding of molecular and cellular biology has allowed us to design biological therapeutics ('biologicals') with defined targets and effector functions. These biologicals have greatly contributed to our current knowledge of pathogenetic mechanisms in autoimmune diseases. However, although some of the biologicals have been extremely successful in treating the symptoms of chronic inflammation, biological therapy has not yet met the expectations of permanently silencing the chonic immune response. In this commentary we discuss current concepts and future directions of biological therapy, and the potential usefulness of biologicals as a treatment of human autoimmune diseases in appropriate critical applications with the use of suitably designed agents.

Keywords: biologicals, cytokines, monoclonal antibodies, rheumatoid arthritis, treatment

Biological therapy refers to treatment strategies of human diseases employing compounds as therapeutic modalities that have been generated by living cells, in contrast to conventional pharmacologicals which are generally synthesized chemically. The substantial progress in our understanding of molecular and cellular biology in recent years has allowed us to use different cellular sources for the production of a variety of potential biological therapeutics ('biologicals') such as monoclonal antibodies (mAbs) and recombinant cytokines in highest qualities and substantial quantities. Furthermore, genetic engineering has opened the road to the specific modification of existing proteins and thus the design of new ones, for example by engrafting the complementarity-determining regions of murine mAbs on the variable regions of a human immunoglobulin or by creating fusion proteins between receptor molecules and immunoglobulins.

The use of biological therapy in human autoimmune diseases is motivated by the desire to interfere specifically with pathogenetic mechanisms of the respective diseases and thereby modulate the course of, and ultimately stop, the chronic inflammatory processes without imposing unbearable toxicity. Because autoimmune diseases result from specific immune responses against self-antigens, immunosuppressive drugs have long been employed with

ICAM-1 = intercellular adhesion molecule-1; mAb = monoclonal antibody; RA = rheumatoid arthritis; Th cell = T helper cell; TNF = tumor necrosis factor.

some clinical benefit. However, because they are associated with a number of side effects related to general immunosuppression, they cannot be considered optimal therapy. An ideal form of therapy would be one that exclusively targeted those cells perpetuating the chronic inflammation with minimal effects on other aspects of the immune or inflammatory systems. Although the present understanding of the pathogenesis of human autoimmune diseases is still incomplete, it has become clear in recent years that the mechanisms resulting in the destruction of tissue and the loss of organ function during the course of an autoimmune disease are essentially the same as those in protective immunity against invasive microorganisms.

Of fundamental importance in initiating, controlling and driving these specific immune responses are $CD4^+$ T cells. $CD4^+$ T cells are activated by an antigen (a peptide) recognized specifically by their T cell receptor if presented in the context of a specific MHC (major histocompatibility complex) class II molecule on the surface of an antigen-presenting cell. Once activated, $CD4^+$ T cells become the central regulators of specific immune responses and determine to a large extent the outcome of immune reactions by activating different effector functions of the immune system. It is therefore no surprise that activated $CD4^+$ T cells can be found in inflammatory infiltrates in many human autoimmune diseases and it is generally agreed that $CD4^+$ T cells have a pivotal role in initiating and maintaining autoimmunity. The induction of tissue-damaging autoimmunity in some animal models of autoimmune diseases by the transfer of $CD4^+$ T cells from sick animals into healthy syngeneic recipients can be regarded as further evidence of the importance of $CD4^+$ T cells in autoimmunity.

Consequently, on the basis of the concept that activated $CD4^+$ T cells are the key mediators of chronic autoimmune inflammation, patients with autoimmune diseases have been given biologicals that interfere with the activation of T cells, and in particular $CD4^+$ T cells, such as mAbs against CD4, CD5, CD7, CD25 and CD52. The data from those trials have been reported in detail [1–3], and an extensive review of the clinical experience is beyond the scope of this commentary. It became apparent from those initial studies that biologicals can safely be given to patients with relatively few and minor side effects and that the application of mAbs to T cell surface receptors might be associated with a clinical benefit. However, those studies have also raised several issues that will need to be addressed before mAb therapy to T cell surface receptors can be considered for wider use as a treatment principle.

First, so far neither the specific autoantigen(s) eliciting human autoimmune diseases nor the specific disease initiating or perpetuating T cells are known. Thus, as outlined above, targeting activated T cells or T cell subsets is so far the most rational approach to combating T cell-mediated autoimmunity in humans feasible. However, this approach does not meet the expectations of exclusively affecting only those cells involved in the pathogenesis of the disease. Therefore, although they were not seen in the initial trials, one still has to be observant for possible unwanted side effects of a sustained depression of T cell function by the prolonged application of T cell-directed biologicals, for example increased prevalences of opportunistic infections and/or malignancies.

Second, with very few exceptions, the mAbs employed have generally failed to induce a sustained clinical improvement. In animals, mAbs against CD4 have been used successfully not only to prevent the induction of the disease in a variety of experimental autoimmune diseases but also to inhibit further disease progression when given after the initial inflammation has already become manifest [4–6]. However, the hope that mAbs might 'reprogram' the immune response in humans and permanently silence those $CD4^+$ T cells that were activated, for example, under the 'umbrella' of an anti-CD4 mAb [7,8] has so far been completely unfulfilled.

Third, controlled clinical studies have largely failed to confirm the initial encouraging clinical observations (reviewed in [1–3]). A number of reasons, such as differences in study design, the use of diverse biological agents directed against the same target molecule with unexpected variances in biological activity and different definitions of a clinical response, might have contributed to the unfavorable results of the placebo-controlled trials. Moreover, in animal studies it has been demonstrated that, for example, concentrations of an anti-CD4 mAb above a specific threshold were necessary for anti-CD4 mAb-induced tolerance which, in addition, takes many weeks of treatment to become complete. However, those requirements were rarely met by the human studies. One notable exception to the disappointing controlled clinical trials was a study in which a non-depleting mAb against CD4, OKTcdr4a, was employed in patients with severe refractory rheumatoid arthritis (RA) [9]. The results from this placebo-controlled double-blind multicenter study suggest that clinical improvement in patients with refractory RA can be achieved by a non-depleting mAb against CD4. Repeated administration of the anti-CD4 mAb resulted in increased clinical benefit. Most interestingly, a profound impact on T cell functions was induced by the mAb, leading to a marked diminution in the capacity of peripheral blood mononuclear cells to produce pro-inflammatory cytokines [9]. Carefully designed future studies that take the concerns and arguments outlined above into consideration will have to show whether biologicals directed against T cell receptors are not only safe, but also powerful immunomodulatory agents capable of permanently terminating unwanted and pathogenic autoimmune reactivity, if employed under appropriate critical conditions with suitably designed mAbs.

Because of the central role of T cells in initiating and perpetuating the chronic immune reactions characteristic of autoimmune diseases, it was natural to employ biologicals first that directly interfered with T cell function by targeting the T cells themselves. However, T cell effector functions at sites of inflammation might also be regulated by controlling the recruitment of the lymphocytes into the tissue by targeting adhesion receptors. Several lines of evidence suggest that interactions between the endothelial cells of post-capillary venules and mononuclear cells in the circulation, mediated by a variety of adhesion molecules, govern the entry of inflammatory cells into the tissues [10].

Thus, one possible target for adhesion receptor-directed therapy is the adhesion receptor–counter-receptor pair leukocyte-function-associated antigen-1 (LFA-1, CD11α/CD18) and intercellular adhesion molecule-1 (ICAM-1, CD54). The interaction of these receptors is critical for the transendothelial migration of T cells and for their subsequent activation [11,12]. In one clinical study, the hypothesis was tested that the application of a mAb against ICAM-1 was able to ameliorate the signs and symptoms of RA by blocking the migration of T cells into the synovium and their subsequent stimulation by locally expressed antigenic peptides *in vivo* [13]. Although the study was not especially designed to test clinical efficacy, the data are consistent with the conclusion that ICAM-1 has a central role in rheumatoid inflammation and might therefore be an important target in the treatment of RA. With our increasing knowledge of the adhesion receptors involved in controlling the transendothelial migration of T cells and, more specifically, T cell subsets, treatment principles targeting adhesion receptors, including chemokine receptors, should be of major interest for study in the future. However, because the mAb against ICAM-1 was of murine origin, it was of considerable immunogenicity. When patients were treated again with this agent, immune-complex-mediated side effects, including urticaria, angioedema, and serum complement protein consumption, were noted [14]. Therefore, if this type of treatment is to be of any beneficial effect in autoimmune diseases, it has to be substantiated with further trials in double-blind placebo-controlled studies with agents of lower immunogenicity.

Whereas the cellular basis of the immunopathogenesis of human autoimmune diseases has not been completely resolved, it has become clear that the excessive production of cytokines contributes to the pathogenesis of most of the diseases [15,16]. For example, many pro-inflammatory cytokines, in particular tumor necrosis factor (TNF)-α and IL-1, were demonstrated to be present in inflamed rheumatoid joints in high concentrations and also to be expressed in high copy numbers in synovial tissue, where they seem to account for many of the pathological and clinical manifestations of the disease [15]. TNF-α and IL-1 both contribute to leukocyte migration into the inflamed tissue by activating endothelial cells, and, probably more importantly, promote cartilage and bone resorption and destruction by suppressing the synthesis of matrix components and by the stimulation of metalloproteinase production in fibroblasts [17]. Thus, the idea of blocking the biological activity of TNF-α or IL-1 became an attractive treatment principle. Neutralization of these cytokines can be achieved by a variety of different methods such as mAbs directed against the cytokines themselves, by mAbs blocking the interaction of the cytokines with their receptor, by applying cytokine receptor antagonists that bind to the cytokine receptors without expressing an intrinsic activity on the target cells, or by soluble cytokine receptors. During the past decade, all of those reagents have been explored as therapeutic means for treating autoimmune diseases. Some of the cytokine-directed biologicals have entered the clinic, where they have contributed substantially to the immense progress that has been made in recent years in the management of patients with autoimmune diseases. Currently, biologicals that neutralize TNF-α have established themselves as a most valuable treatment alternative for an increasing number of autoimmune diseases.

The clinical efficacy of neutralizing TNF-α as demonstrated in the various trials seems to be obvious [18–22]; however, the optimal treatment regimens with respect to dosage and duration and interval of application still need to be defined. Moreover, it should be kept in mind that in applying anti-inflammatory cytokines or pro-inflammatory cytokine inhibitors one has to be aware of our lack of knowledge of side effects that might appear during a longer course of treatment. For example, 7% of RA patients who were treated with one mAb against TNF-α developed antibodies against nuclei and against double-stranded DNA of the IgM and IgG subclasses [23]. Although these antibodies disappeared with the cessation of therapy, possible long-term effects of these autoantibodies have not been documented. Finally, it has not been shown in greater detail whether long-term neutralization of TNF-α might be associated with the induction of any form of malignancy.

The success of the biologicals, in particular their clinical efficacy combined with their currently documented high degree of safety, has shown that a complex disease such as RA can be safely modulated by new therapeutic strategies that are directed to modulate a specific aspect of the underlying autoimmune process, thus avoiding general immunosuppression. However, it is becoming clear that decreasing the degree of global immunosuppression associated with therapy by employing targeted specificity might decrease the likelihood that a single therapeutic agent will provide long-term disease control. Consequently, biologicals are currently combined with conventional anti-rheumatic drugs in an attempt to achieve a

synergistic clinical efficacy without increased toxicity. For example, the combination of methotrexate with TNF-α inhibitors has already provided some encouraging results [24]. In animal models, a synergy of combination biological therapy has also been demonstrated and it is to be expected that many of those combinations will also be tested clinically. Pilot studies of a combination treatment with mAbs against CD4 and against TNF-α are already under way and the simultaneous use of TNF-α and IL-1 inhibitors will also be tested shortly.

Apart from the treatment principles described here in more detail, other innovative therapeutic strategies have been defined, some of which have already entered clinical trials. It will be interesting to observe the effect of those biologicals, such as inhibitors of CD28-mediated T cell co-stimulation, or recombinant cytokines that might modulate T cell effector function (IL-4, IL-10). An exciting approach to the treatment of autoimmune diseases, based on the increasing knowledge of different T helper (Th)-cell-mediated effector functions, has been discussed recently [25]. As evidence emerges that immune responses driven preferentially by activated Th1 cells seem to have a central role in the pathogenesis of several organ-specific autoimmune diseases in animals [26–28], recent data suggest that RA might reflect ongoing inflammation largely mediated by Th0 or Th1 cells without sufficient differentiation of Th2 cells to downmodulate inflammation [29]. Thus, the idea of switching the apparently detrimental Th1-dominated chronic immune response in RA into Th2-mediated immunity is intriguing. This treatment principle has been applied successfully to various animal models of human autoimmune diseases [30]. However, clinical trials in humans have not yet been conducted but will certainly be performed as soon as appropriate biologicals become available. In this regard, it is of interest to note that a defect in Th2 cell differentiation is characteristic of early stages of RA [31]. As molecular mechanisms involved in directing Th1 or Th2 cell differentiation are defined, they might serve as new targets for therapeutic immunomodulation, by either inhibitory or activatory biologicals, respectively.

Of all biologicals employed in the clinic so far, none has been specific for the cells or mechanisms involved in the pathogenesis of the respective diseases. Rather, although the tools were generally more specific than conventional immunosuppressants, they were still aimed at a broad range of targets throughout the body. If the eliciting autoantigen(s) of the diseases were known, one could target explicitly those T cells mediating the inflammation. It has been demonstrated that the replacement of single amino acids in immunogenic peptides might alter the differentiation of T cells to perform certain effector functions [32]. Thus, altering the T cell receptor ligand with a peptide analogue on functional antigen-presenting cells might deliver a signal to a T cell that confers differentiation of immunomodulatory rather than pro-inflammatory effector cells ('immune deviation'). In animal models, altered peptide ligands have been used successfully to prevent the onset and even inhibit the progress of experimental autoimmune diseases [33]. It is to be expected that treatment principles based on the concept of immune deviation will be tested in the clinic in the future.

In conclusion, on the basis of our expanding knowledge of the immune system, various biologicals have been designed, produced and employed in the clinic over the past decade. Although some biologicals have proved to be extremely successful in treating the symptoms of chronic inflammation and also seem to be able to slow disease progression, biological therapy has not yet met the expectations of permanently silencing chronic (auto)immune inflammation. However, it can be expected that an increasing understanding of the basic mechanism of immunity will define new possible target structures for therapeutic intervention. Therefore, exciting biological tools will enter the clinic and be tested for their efficacy in treating autoimmune diseases. It remains to be shown whether they will be able to terminate unwanted and pathogenic autoimmune reactions. Nevertheless, with the progress of recent years in mind, it is fair to keep our expectations high.

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