Combination biologic therapy

J.D. Isaacs[1], A.W. Morgan[1], V. Strand[2]

[1]Department of Rheumatology, University of Leeds, UK; [2]Division of Immunology, Stanford University, Palo Alto, California, USA.

John D. Isaacs, PhD, FRCP, Senior Lecturer; Ann W. Morgan, BSc, MRCP, Medical Research Council Clinical Training Fellow; V. Strand MD, Clinical Associate Professor.

Please address correspondence and reprint requests to: John D. Isaacs, PhD, FRCP, Molecular Medicine Unit, Clinical Sciences Building, St James's University Hospital, Leeds LS9 7TF, UK.
E-mail: rrrjdi@leeds.ac.uk

ABSTRACT

Biologic therapies refer to genetically engineered treatments such as monoclonal antibodies and receptor-immunoglobulin fusion proteins. Following many disappointments, the introduction of anti-tumor necrosis factor (anti-TNFα) therapies into the clinic has clearly demonstrated the exciting potential of biologic agents. Many of these have been designed to modulate a specific aspect of the underlying autoimmune process, thus avoiding generalized immunosuppression. They include products which interfere with the trimolecular complex of major histocompatibility complex II-Antigen-T cell receptor interaction; others designed to block the secondary signals for T cell activation and T cell interaction with antigen-presenting cells; and cytokine agonists as well as antagonists.

Whilst reducing the degree of global immunosuppression associated with therapy, this targeted specificity may reduce the likelihood that a single therapeutic agent will provide long-term disease control. On the other hand, animal models have demonstrated synergy of combination biologic therapy, particularly for the re-induction of self-tolerance. As our knowledge of immune physiology and, particularly, immune regulation improves, it can be expected that many combination biologic therapies will be tested in the clinic. Pilot studies of combined anti-CD4 and TNFα blockade are underway; combination use of TNFα and interleukin-1β inhibitors are expected. This article reviews the potential for combination biologic therapy, including likely adverse effects, for the treatment of rheumatoid arthritis and other autoimmune diseases.

Introduction

If combination therapy is designed to achieve additive or synergistic effects by targeting different effector mechanisms or cell activation pathways, then the logic behind combining biologic therapies is overwhelming. In general, biologic therapies offer more precise specificity than conventional disease-modifying antirheumatic drugs (DMARDs), and targeting discrete aspects of the underlying disease pathology may avoid generalized immunosuppression. By the same argument, it is unlikely that a single biologic agent will provide long-term disease modification. Alternatively, targeting two or more critical pathways could have far-reaching effects, and a number of scenarios can be envisioned:

- Antagonising two or more proinflammatory cytokines, such as tumor necrosis factor (TNFα) and interleukin 1 (IL-1β), or stimulating one or more antiinflammatory cytokines such as IL-4 and IL-10.
- Targeting two facets of T cell activation, such as anti-CD4 monoclonal antibodies (mAb) plus anti-CD40L mAb.
- Targeting T cells on the one hand and antigen-presenting cells (APC) on the other, to reduce T cell interactions with, and the T cell regulation of B cells and dendritic cells. For example, the combination of anti-CD40L mAb plus CTLA4-Ig.
- Antagonising proinflammatory cytokines while simultaneously targeting T cell activation using, for example, TNFα blockade plus anti-CD4 mAb.

To these may be added therapies that target synoviocytes and/or matrix-degrading enzymes. The advantages of using biologic agents include their rapid onset and reversibility of effect, as well as potential synergy with currently used second-line therapies. Disadvantages include a frequent necessity for parenteral administration, infusion-related toxicities, increased cost, brief duration of clinical responses, and tachyphylaxis upon re-treatment, possibly related to immunogenicity. Delayed effects such as infections, autoimmune manifestations, and lymphoproliferative disorders may be treatment-associated or may reflect the underlying disease process.

An additional, important advantage provided by biologic therapies has been the insights into underlying disease processes provided by their use. The efficacy of TNF blockade provides convincing evidence for the major role of this pro-inflammatory cytokine in the rheumatoid arthritis (RA) disease process. Nonetheless, a proportion of patients respond incompletely to this treatment, implying that at least one other mechanism is also important in this subgroup. A combination of biologic therapies shown to be effective in these patients would not only provide a major therapeutic advance but would also offer further insights into the underlying pathogenesis of RA.

The need for combination biologic therapy

It is likely that it will soon be possible to provide significant symptomatic relief for patients using combinations of cytokine antagonists. Disadvantages of this approach may be, at worst, a requirement for long-term therapy and, at best, a requirement for long-term surveillance. An efficient and chronic blockade of TNF production, for example, may increase the risk for severe and/or life-threatening infections, impair tumour surveillance, or increase the likelihood of a second autoimmune disease (1). Targeting additional cytokines may well provide additive or synergistic therapeutic as well as deleterious effects. In animal models of RA, TNF appears to be responsible predominantly for systemic inflammation, and IL-1 for bone and cartilage destruction (2-4). Both cytokines mediate the weight loss and decreased lean body mass in "RA cachexia" (5,6). Antagonists of IL-1 plus TNF are synergistic in streptococcal cell wall and collagen II models of arthritis, but clinical data with this combination are lacking (7-10). Although animal models have suggested relatively specific effects for these proinflammatory cytokines in mediating the signs and symptoms of inflammatory arthritis, it is likely that human disease will be more heterogeneous.

It is also unclear at present whether therapies targeted to cytokines or T cell activation will halt the bone and cartilage destruction characteristic of RA. Although arguments often favor mechanisms centred on either the T-cell and/or cytokine-driven secretion of degradative enzymes by synoviocytes (11, 12), additional stimuli and mechanisms to explain the perpetuation of the inflammatory response abound. Therefore approaches which additionally target tissue-degrading enzymes such as metalloproteinases specifically should provide significant therapeutic advantages (13).

The holy grail of RA therapy is to discover a treatment that provides long-term amelioration of symptoms following a short course of therapy. How and whether this is achievable in RA remains to be seen. If the primary inciting event in chronic RA leads to a defect within the fibroblastic synoviocyte, then this cell must be targeted to halt disease progression. Abnormalities within this cell population are slowly being unravelled (14, 15) and should offer therapeutic possibilities. On the other hand, it can be argued that we already have many of the tools necessary to "reprogram" the immune system in autoimmune disease, implying an ability to convert an autoreactive immune system into a self-tolerant one (16).

Initial attempts to reprogram the immune system employed anti-CD4 mAb in animal models of transplant rejection. Although these agents enabled subsequent transplantation of histo-incompatible skin, therapy was not effective across major histocompatibility complex (MHC) barriers, nor in a primed immune system. More importantly, monotherapy could not prevent ongoing rejection. Subsequent combinations of anti-CD4 and anti-CD8 mAb therapy, again in animal models, achieved transplantation tolerance in these more complex scenarios. Furthermore, treatment led to the emergence of regulatory T cells which "policed" the tolerant state and provided robust, long-term therapeutic effects despite only a short course of therapy (17). Increasingly, a role for regulatory T cells has been implicated in the induction and maintenance of both experimental and natural tolerant states (18). Although not yet fully characterised (and they may comprise multiple cellular subsets), overwhelming evidence for their existence offers us further incentive to attempt immune reprogramming (19).

The molecular mechanisms underlying immune reprogramming also remain unclear. There are numerous possibilities: anti-T cell mAb may transmit "negative" signals, thereby inducing tolerance in autoreactive T cells; alternatively, they may interfere with antigen presentation, resulting in tolerance as a default state; or, antigen presentation may occur, but the signals are subverted, resulting in anergy. Data from animal models suggest that T cell mAb may simply act as "blindfolds," preventing autoreactive lymphocytes from recognising self-antigen. Under such circumstances, the default state seems to be one of self-tolerance with the emergence of regulatory cells (20).

On the other hand, our view of the immune system is evolving from a T cell-centric one to an APC-centric one. Whereas T cells determine the effector phase of the immune response, it is now clear that APC determine the T cell phenotype upstream (21). Therapeutic combinations designed to target both the T cell and APC may therefore provide advantages, notwithstanding the fact that exact criteria to guide their clinical application have not yet been identified. Similarly, the administration of antiinflammatory cytokines such as IL-10 may down-regulate immune responses (22) and provide synergistic effects in combination with anti-T cell or anti-APC therapies.

Regardless of their relevance to the "spontaneous" occurrence of autoimmune disease in animals or human experimental data using combination biologic therapies lead us to a number of important hypotheses. Even with inbred animal strains, tolerance is easier to achieve with combination therapy: antiCD4 and CD8 mAb act synergistically; robust tolerance has also been achieved following combination CTLA4-Ig and anti-CD40L therapy (23), as well as anti-intercellular adhesion molecule 1 (anti-ICAM-1) and anti-lymphocyte function-associated antigen 1 (anti-LFA-1) treatment (24). Because we do not fully understand the mechanisms underlying immune reprogramming, we must also take care with co-administered therapies, however.

Thus, it may seem logical to combine anti-CD4 therapy with methotrexate, leflunomide, glucocorticoids, or even non-steroidal antiinflammatory drugs (NSAIDs), but it is possible that these drugs could interfere with the induction of tolerance. For example, cyclooxygen-ase-2 (COX-2) has recently been shown to be important in the induction of mucosal tolerance (25), and its blockade could have adverse effects on therapeutic attempts at tolerance induction.

Combination biologic therapy - The reality

To date, there have been few attempts to test the theoretical arguments outlined above. We (JDI and AWM) have recently completed pilot studies of the first biologic combination to be examined in RA patients. We employed the following rationale: to control inflammation first with an anti-cytokine agent designed to block TNF effects, and to follow this with an anti-T cell therapeutic (anti-CD4 mAb) once inflammation was controlled. We used a fully humanised anti-CD4 mAb and a p55 TNF receptor-human-IgG1 fusion protein (26, 27). Both agents were prepared in the Oxford Therapeutic Antibody Centre, an academic facility. We chose not to use conventional anti-inflammatory drugs such as glucocorticoids or NSAID because of their pleio-tropic cellular effects and their potential effects on immune regulation.

Patients selected for therapy were multi-DMARD resistant and within 5 years of diagnosis. Nine patients underwent combination therapy in iterative open studies, in which the level and duration of TNF and CD4 blockade was slowly increased. In short-term, one to six-week regimes, there was some evidence for synergy with the two agents. Subsequently, in our final cohort of three patients, therapy was continued for 3 months, but disease activity remains reduced one year later. Thus one patient is not taking DMARD a year after the cessation of therapy, and the other two now have minimal disease activity while taking conventional DMARD therapy (26, 27, and manuscript in preparation).

Adverse effects

Potential downsides to chronic cytokine blockade have been alluded to above. If it were possible to re-induce self-tolerance in autoimmune disease, however, in the longterm there should be no ill effects on the immune system. This is particularly true now that it is possible to design reagents which do not deplete target cells (28). There is no evidence that transient therapy with anti-T cell mAb has any other lasting effects on the immune system. In particular, tolerance appears only to be induced to antigens that are being presented at the time of therapy, and persists only as long as the antigen persists (however, for a self-antigen, presumably a lifetime). Theoretically, a pathogen present at the time of therapy may lead to the induction of lifetime tolerance to this antigen, but careful patient screening and existing clinical data suggest this will not occur (29).

Other adverse effects attributed to biologic therapies include neutralising antiglobulin reactions (30) and first-dose reactions (31). Antiglobulin reactions may not pose a problem for short-term therapies, and recent data suggest that co-administration with immuno-modulatory agents may abrogate the host-immune response in the longer term (32-34). First-dose reactions are associated with certain biologic therapies and are more severe with treatments that target cells rather than soluble mediators. Common manifestations are fever and chills, but hypotension and chest tightness may occur. As with immunosuppression, these are less likely with Fc-mutated biologics (35). Furthermore, although these reactions may on occasion be frightening to the patient, they are not life threatening and can be treated symptomatically. Whereas pre-medication with, for example, glucocorticoids may prevent such reactions (36), we do not routinely use such drugs and prefer careful prior counselling of the patient.

Large biologics versus small molecules

To date, specific cytokine blockade and T cell or APC targeting have been achieved with mAb, soluble receptors, or recombinant versions of natural products, such as the IL-1 receptor antagonist (37). Apart from the inconvenience of parenteral administration, a major downside of such therapies remains the cost associated with their clinical use, which is related to the development and production costs leading to their approval and marketing. Inevitably, products currently under development will act as proofs of principle and, once their potential is proven, they will lead to small-molecule analogues. Although the equivalent clinical specificity for such analogs must await *in vitro* and *in vivo* testing, the ultimate savings in production and administration costs provide a significant inducement to their development.

Summary

We are in an exciting era, when the use of biologically based therapies for the treatment of autoimmune disease is rapidly being realised (38, 39). Within the next 10 years, it seems likely that we will effectively modulate not only the symptoms of diseases such as RA but also their long-term course. The most likely route to the latter will be by iterative experimentation using biologic therapies in relatively short courses. Although the desired effects may be achievable using monotherapy, animal models suggest that combinations are more likely to be effective. Ultimately, we can look forward to a time when small-molecule drugs replace cumbersome mAb and soluble receptor molecules and achieve a similar effect.

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