Perspectives in targeted therapy

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Abstract

Targeted therapeutic agents have changed the landscape of therapy in rheumatoid arthritis (RA). They have also provided valuable insights into the utility of animal models for development of targeted therapies, clinical trial design, pharmacodynamics, immunobiology and key pathogenic elements of disease. Studies of chimeric anti-CD4 monoclonal antibodies in RA demonstrated the need for pre-clinical studies to more closely approximate the human therapeutic paradigm as well as the importance of synovium as an appropriate pharmacodynamic window to predict efficacy and adverse side effects of the agents. Targeted therapies have been instructive in discerning the importance of TNF, IL-1, IL-6, IL-15 and RANKL in the pathological process themselves, such as the uncoupling of inflammation and structural damage. Current trends in the use of targeted therapeutics include aggressive earlier use, combination with methotrexate, use in moderate rather than severe disease, tight control as well as induration and maintenance regimes. Despite therapeutic advances with target therapies a number of unmet needs exist, including a low remission rate, cost and inadequate access as well as the lack of biomarkers to predict response and safety concerns. Despite this, target therapies have revolutionized the treatment of RA. In addition to having a substantial effect on clinical outcomes, a number of valuable lessons have been learned.

Introduction

An improved understanding of the pathogenesis of rheumatoid arthritis (RA) coupled with recent advances in biotechnology has led to selective targeting of the pathogenic elements of disease utilizing biological agents. As a consequence of the development of targeted agents there has been an explosion in the number of disease modifying agents (DMARDS) approved for the treatment of RA. Prior to 15 years ago, a new DMARD was introduced about every 15 years. Over the last 15 years 8 DMARDS have reached the marketplace – 6 of which are biological targeted therapies. Studies of these biological agents have provided extremely valuable insights into the utility of animal models for development of targeted therapies, clinical trial study design, pharmacodynamics human immunobiology, and key pathogenic elements of disease.
Proof of efficacy of therapeutic agents in animal models of RA is used to predict efficacy in human disease. Despite this, there are numerous instances in RA where pre-clinical data were not reflective of the human situation. Agents demonstrating benefit in rodent models of RA, but not in RA, include anti-ICAM-1 and anti-IL-8 monoclonal antibodies (mAbs), as well as immunomodulators IL-4, IL-10 and IL-11 (reviewed in [1]). One notable example of the discord between pre-clinical studies and results in humans was the anti-CD4 T cell-depleting mAb. Despite efficacy in several pre-clinical models of RA, anti-CD4 mAbs were shown not to be beneficial in RA [2–5]. However, a number of valuable insights were gained into the pharmacodynamics of immune cell depletion with anti-CD4 mAbs that were not predicted by the animal models. Thus, although profound depletion of circulating CD4\(^+\) T cells was observed, synovial T cells were still detected, suggesting that the pharmacodynamic window correlating with therapeutic effect was the synovium and not the circulation [6]. This concept was supported by the positive correlation between anti-CD4 mAb coating of synovial fluid cells, but not circulating CD4\(^+\) T cells, with therapeutic benefit [7].

T cell-depletion studies appeared to demonstrate substantial differences in T cell biology in mouse and humans. Thus, despite short-term depletion of CD4\(^+\) T cells in rodent models, profound long-term depletion of circulating CD4\(^+\) T cells was observed in humans [8]. Of significance, the prolonged T cell depletion observed with anti-CD4 mAbs was actually predicted by pre-clinical data. Thus, whereas short-term CD4\(^+\) T cell depletion was demonstrated with an anti-CD4 mAb in young mice, prolonged depletion of CD4\(^+\) T cells was observed in older mice with an age comparable to that of mAb-treated RA patients. In addition, pre-clinical models showed more T cell cytotoxicity with a chimeric mAb than with a heterologous counterpart. Thus, chimeric anti-CD4 mAb studies in animal models of RA appeared to reflect the human situation and may have predicted the prolonged T cell depletion in RA. The results provide an important insight into the need for pre-clinical studies to more closely approximate the human therapeutic paradigm.

The importance of an appropriate pharmacodynamic window was emphasized by the failure to observe an increase in infection or malignancy in RA patients despite a profound long-term depletion of circulating CD4\(^+\) T cells well below the levels observed in HIV. Nowhere was the failure of pre-clinical studies predictive of an effect on humans more evident than in the multi-organ failure that resulted from infusion of an anti-CD28 mAb in a recent Phase I study [9].

As a consequence of the therapeutic failure of depleting anti-CD4 mAb in RA, non-depleting anti-CD4 mAbs were evaluated. Initial studies were carried out with a primatized IgG4 mAb in which the first generation mAb demonstrated good clinical benefit [10]. A second trial with the same mAb generated by a different manufacturing process yielded significantly reduced efficiency and caused CD4 T cell depletion.