Selected Summaries

Lymphotoxin-alpha: Another (and better?) therapeutic target in autoimmune disease?

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SUMMARY

This study describes a novel antibody that targets lymphotoxin-a (LT-a) and inhibits disease in several animal models of Th_1-mediated autoimmune disease. Since T helper type 1 (Th_1) and Th_{17} cells are believed to play a major role in the pathogenesis of autoimmune disease, the authors identified a surface LT-a common to Th_0, Th_1 and Th_{17} cells by doing a genomewide search using an immune response *in-silico* database (a microarray database that contains the expression level of immune molecules in different immune cells). They then confirmed that LT-a was indeed expressed by activated Th_1 and Th_{17} cells, both in humans and mice. They generated a depleting monoclonal antibody (mAb) against LT-a that specifically bound to surface LT-a and killed the cells, as also bound soluble trimeric LT-a_3 and prevented its binding to tumour necrosis factor (TNF) receptor II.

The authors tested this LT-a-specific mAb in a KLH-induced delayed hypersensitivity model and found that it significantly inhibited disease as well as antigen-specific T cell proliferation. In an experimental allergic encephalomyelitis (EAE) model of multiple sclerosis, administration of LT-a-specific mAb led to reduced disease severity. In the collagen-induced arthritis (CIA) model for rheumatoid arthritis, LT-a-specific mAb prevented disease if given before its onset, and reduced the disease intensity, if given later. In this model, treated mice showed a preservation of cortical bone, as well as a reduction in inflammation with only minimal histological changes. Even before clinical efficacy was evident, there was reduction in pro-inflammatory cytokine production; thus suggesting an early beneficial effect.

To study the mechanism of T cell depletion, they generated another antibody with a mutation in the Fc receptor (FcR). This mutant antibody, which did not bind to FcR, was incapable of inhibiting disease in the various animal models studied. It also did not deplete T cells, suggesting that the cell kill is mediated via antibody-dependent cell cytotoxicity.

Another important aspect of LT-a-specific mAb was that it did not affect the splenic T cell number, and had no effect on regulatory and follicular T helper cells, which are natural regulators in T-cell-mediated autoimmune diseases.

To further prove that LT-a-specific mAb is effective only in Th_1- and Th_{17}-mediated diseases, they showed that it was ineffective in an asthma model, a Th_2-mediated disease. These data indicate that depleting LT-a-expressing lymphocytes with LT-a-specific mAb may be beneficial in the treatment of autoimmune disease.

COMMENT

Naïve T (Th_0) cells, which come out of the thymus, can differentiate into pro-inflammatory T cells (Th_1 that produce interferon [IFN] and Th_{17} that produce interleukin [IL]-17) or anti-inflammatory T cells (Th_2 cells that produce IL-4 and T regulatory cells [Tregs] that produce IL-10) depending on the signals received on exposure to an antigen. Th_1 and Th_{17} cells and their products such as IFN-g, TNF-a, IL-17 and IL-21 are the major players in the immunopathogenesis of autoimmune disease.[1] In contrast, administration of Tregs reduces the disease severity in the colitis model.[2]

LT-a belongs to the TNF superfamily and can exist either in a membrane-bound form coupled with LT-b2 (LTa1b2) or in a soluble trimeric form (LT-a3). The soluble form, LT-a3, binds to both TNF receptors I and II and induces an inflammatory response. However, its levels are low and its actual contribution to immuno-inflammation is not known. The membrane-bound LTa1b2 binds to LTb2 receptors, present predominantly on follicular dendritic cells, B cells, etc. and helps in the development of germinal centres and tertiary lymphoid follicles in chronically inflammed tissues.[3]

Currently, a vast array of biologicals is available in the market for the treatment of autoimmune diseases. Some of these such as TNF-blockers have shown excellent efficacy in many autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, Crohn disease and ankylosing spondylitis.[4] Antibodies to different T cell molecules such as CD3 and CD52 are also being used in post-transplant situations as well as in autoimmune diseases. Even the lymphotoxin pathway has been explored in the past as a potential target.[5] An LTb receptor decoy fusion protein (LTbR-Ig), which binds to membrane-bound LTa1b2 preventing its ligation to its natural receptor, has shown a beneficial effect in the EAE model. However, in the collagen-induced arthritis model, it provided contradictory results, varying from good efficacy[6] to deterioration.[7] In a recent phase IIb trial in patients with rheumatoid arthritis, LTbR-Ig (Baminercept) demonstrated only a modest efficacy and the primary end-point was not achieved.

Soluble TNF receptors (TNFr), which mop up circulating TNF-a and LT-a3, have shown excellent results in patients with rheumatoid arthritis. It has become a standard treatment in patients with rheumatoid arthritis who do not respond to conventional drugs. However, soluble TNFr has a short half-life and thus needs twice-weekly administration. In addition, it lacks specificity and is associated with an increase in the risk of systemic infections.[4]

Other anti-T cell-depleting antibodies such as anti-CD3, anti-CD25 and anti-CD45 do not have selectivity for activated Th_1 and Th_{17} cells. Thus, these cause depletion of both pro- and anti-inflammatory cells, and also cause profound immuno-suppression leading to an increased risk of infection and malignancy. Anti-CD3 antibodies as well as regulatory T cells are now being used to induce tolerance in autoimmune diseases.[8,9]

Since it was not possible to target Th_{17} cells selectively, antibodies to IL-17 and IL-7r have been tried in pre-clinical studies and have shown efficacy. Anti-IL-17 antibody (AIN457) is undergoing phase II studies in rheumatoid arthritis, psoriasis and Crohn disease.[10] However, this antibody will not block Th_1 cells.

How does this new antibody (LT-a-specific mAb) then improve upon the previous biomolecules developed to block these immune pathways? First, it targets a molecule that is selectively expressed on activated T cells, and hence should selectively kill only the pathogenic T cells. Thus, it is unlikely to cause generalized immunosuppression and is expected to be associated with lower toxicity. Second, it does not interfere with the development of germinal centres; thus, it should preserve the development of affinity maturation and class switching of antibodies in response to infection.

However, we must exercise caution in reading too much into these results. Humans can behave differently from mice and have very different and unexpected results, as occurred with anti-CD28 antibody (TGN1412).[11]

Overall, the new anti-LT-a antibody that inhibits the lymphotoxin pathway appears to be a promising addition to the rapidly growing range of biological compounds that are being developed to control T cell-mediated autoimmune diseases such as insulin-dependent diabetes mellitus, multiple sclerosis and rheumatoid arthritis.

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Acutely ill patients: Rapid sequence intubation with etomidate or ketamine

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SUMMARY

This prospective, randomized, multicentre, controlled, single-blind trial was aimed at comparing early and 28-day morbidity after a single dose of etomidate or ketamine for emergency endotracheal intubation in critically ill adult patients. Over a period of 10 months, 655 patients requiring sedation for emergency tracheal intubation were randomized to receive an intravenous bolus of etomidate (0.3 mg/kg) or ketamine (2 mg/kg). Succinlycholine (1 mg/kg) was administered after the sedative to facilitate tracheal intubation. After confirmation of optimal placement of the endotracheal tube, sedation was provided by midazolam and fentanyl/sufentanil infusions. Those patients who were discharged alive from the intensive care unit (ICU) within 3 days or died before reaching the hospital were excluded from the study so that the outcome of those with the most severe illness was studied. Laboratory variables (haematological and biochemistry), arterial blood gases, results of short adrenocorticotropin hormone test when recommended by the physician, incidence of serious adverse events, intubation difficulty scores and any major interventions done were noted. The primary end-point was the maximum score of the sequential organ failure assessment (SOFA) during the first 3 days of stay in the ICU. The secondary end-points were maximum SOFA score during the stay minus the admission SOFA score, duration of weaning from ventilator, organ support-free days (mechanical ventilation and vasopressors), 28 days all-cause mortality and length of stay in the ICU during the 28-day follow up period.

The results of 469 patients (234 in the etomidate and 235 in the ketamine group) were analysed. Adrenal function was assessed in