ANTI-TNF-ALPHA THERAPY FOR CROHN’S DISEASE

Michael A Kamm
Professor of Gastroenterology, St Mark’s Hospital, UK

Previous therapies in Crohn’s disease, such as steroids and 5-aminosalicylic acid, achieved their therapeutic response by the modulation of multiple inflammatory pathways and mechanisms. Anti-TNF alpha therapy was the first successful strategy designed to block a single mediator central to the inflammatory cascade. The fact that it has been so dramatically successful is a testament to the practical application of the science of mucosal immunology and rational drug design.

Infliximab, a chimeric IgG1 antibody to TNF-alpha, is the only licensed anti-TNF compound. It is about 25% murine. CDPS71, an IgG4 humanised antibody, is about 5% murine; it is not yet licensed. Other anti-TNF approaches include the use of recombinant soluble TNF receptors, vaccination against TNF, and inhibition of TNF production by oral agents such as pentoxifylline and thalidomide. Antibody therapy is of proven marked efficacy; soluble TNF receptor treatment has provided mixed results, while there is only uncontrolled evidence for moderate benefit from oral TNF inhibitors.

TNF alpha antibody therapy has been demonstrated to cause a substantial clinical improvement in two thirds of patients with active Crohn’s disease, and to induce remission in one third of patients. These responses are all the more impressive when demonstrated in patients previously unresponsive to other therapies. This drug therapy is the first to demonstrate rapid mucosal healing. Half the patients in whom remission is induced can be maintained in remission over a year. Anti TNF antibody treatment heals perianal fistulae in more than 50% of patients, although MRI and ultrasound studies suggest that the track of subcutaneous fistulas may persist; the length of treatment required to fully heal fistulae is not known. In 4 percent of patients mucosal healing can lead to stricture formation; treatment in patients with a known stricture is therefore contraindicated.

The major concerns with potent antibody treatments are immunogenicity, infections and enhancement of cancer risk. Acute infusions can be associated with an allergic reaction. Development of human anti-chimaeric antibodies (HACA) is associated with acute infusion reactions, delayed type hypersensitivity reactions, and altered drug pharmacokinetics with a consequent diminution in clinical efficacy. The development of (HACA) may be reduced by pre-treatment of infusions with intravenous steroids, or the long term use of concomitant immunosuppressives such as azathioprine. The antibody CDP-571, still in development, is less immunogenic. Further refinement can be expected which will result in pure human antibodies which elicit minimal immunological response.

Infliximab increases the risk of infection. The risk of tuberculosis has been estimated as approximately 3 per 10,000, and has led to some deaths. Crohn’s disease is associated with an increased cancer risk; any increased risk from treatment remains controversial.

Current anti-TNF therapies are part of an evolutionary strategy. Newer compounds that have low immunogenicity and can be given subcutaneously are likely to replace those requiring intravenous infusion. The goal of a traditional non-immunogenic orally absorbed simple molecule that inhibits TNF production is currently being actively pursued.

One only has to see a dramatic response in a small number of patients with disabling disease, unresponsive to other drug therapies, and on the verge of a major resection such as a proctocolectomy, to appreciate that these therapies are a major step forward in the treatment of Crohn’s disease. Despite issues of cost and side effects, their impact clinically, and on quality of life, should not be underestimated.

REFERENCES


Farrell et al. A randomised, double-blind, placebo-controlled trial of intravenous hydrocortisone in reducing human anti-chimeric antibody following infliximab therapy. Gastroenterology 2001; 120 (suppl 1):A618.


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