“Kwik-Fiximab” — how a monoclonal antibody transformed care of Crohn’s

In this month’s article on landmark drugs, Jenny Bryan takes a look at how monoclonal antibodies transformed the lives of millions of people with autoimmune disorders

Hailed as the magic bullets of modern medicine when they were first produced in 1975, monoclonal antibodies (MAbs) did not find their way beyond nice-but-dull diagnostic kits until the mid-1990s. Among the first to show promising therapeutic potential was infliximab (Remicade) — a product of collaborative research between scientists at New York University and biotechnology company, Centocor, now a subsidiary of Johnson & Johnson. Licensed first for the treatment of Crohn’s disease and then for rheumatoid arthritis, infliximab finally started to show what MAbs were capable of: transforming the lives of millions of people with autoimmune disorders.

“Before infliximab, we really struggled with Crohn’s disease that had become unresponsive to steroids and to immunosuppressant treatment with azathioprine or methotrexate. Surgery was the only option left to us,” explains Jeremy Sanderson, consultant gastroenterologist at Guy’s and St Thomas’ Hospitals, London, and medical spokesman for Crohn’s and Colitis UK.

“Not only did infliximab turn people’s lives around, it helped to change our goals for Crohn’s disease. We went from improving symptoms to aiming to modify the disease process and promote mucosal healing in order to reduce complications and need for surgery,” he adds.

Monoclonal discovery

The ability to produce endless quantities of predefined, identical antibodies for medicinal uses was a major goal for scientists working in the rapidly developing field of biotechnology in the early 1970s. In 1975, Cesar Milstein and Georges Kohler reported that they had fused antibody-producing spleen cells with longevity-promoting myeloma cells to produce hybrid cell lines (hybridomas) capable of yielding a potentially unlimited supply of antibodies against sheep red blood cells. The technique was rapidly taken up but, realising that the mouse hybridomas used to generate the antibodies were likely to trigger allergic reactions if the MAbs were used to treat human patients, researchers set about generating cell lines that would produce human MAbs — something that was not achieved for a further five years.

Watching progress with MAb technology was Czech-born microbiologist Jan Vileček, who was studying the cytotoxic effects of gamma interferon from mononuclear cells at New York University. Recognising that other cytokines, notably tumour necrosis factor alpha (TNFα), were involved in the cytotoxic response and that TNFα antibodies had potential for treating autoimmune and other diseases, Vileček and co-worker Junming Le approached Centocor to help them develop MAbs against TNFα. The result was a mouse-human chimeric antibody, with mouse DNA responsible for the antigen-binding part of the antibody and human DNA for the neutralising part. With specificity for recombinant and natural human TNF, the chimeric MAb was designed to have lower immunogenicity and better human pharmacokinetics than earlier mouse anti-TNF MAbs.

Preclinical research confirmed that the antibody (which became infliximab) effectively blocked a range of TNF-mediated biological activities both in vitro and in vivo. Receptor-binding studies suggested that infliximab blocked TNF binding at two receptor sites on cells.

Infliximab goes into humans

Clinical studies got off to a good start. Eight out of 10 patients with active Crohn’s disease unresponsive to conventional therapy who were given a single infusion of infliximab had normal Crohn’s disease activity index scores and ulcer healing within four weeks after treatment. The average duration of response was four months and no adverse reactions to
infliximab should be used within its licensed indications to treat patients with severe active Crohn’s disease who have failed to respond to step-wise treatment with steroids and/or immunosuppressive therapy, or who are intolerant to or have contraindications to conventional therapy. Treatment is recommended for those with fistulising disease that has failed to respond to antibiotics, drainage and immunosuppressive therapy.

However, Dr Sanderson explains that a strong case can be made for “hit hard and step down” treatment with infliximab in patients at high risk of complications: “Patients with a penetrating type of disease are more likely to have abscesses and fistulae, which are markers of progression, and probable need for surgery. So it makes sense to start them on infliximab at an earlier stage and, once you’ve got their disease under control, step down to azathioprine.”

In contrast, patients with severe inflammatory disease without signs of penetrating disease are probably better suited to the “step-up” approach of steroids and azathioprine, keeping infliximab for a “rainy day”.

As Dr Sanderson points out, it is important to strike a balance between using the most effective treatment and not running through all the options too quickly: “The downside of infliximab is that it stops working so well with time. We’re getting better at using it and we know, for example, that combining it with azathioprine, at least for the first six months, can protect against formation of antibodies that can reduce its efficacy. But patients may only get about four years of benefit from infliximab, so we need to time their treatment to match their needs as carefully as possible.”

Optimising anti-TNF treatment

Recent research has shown that combination therapy with infliximab and azathioprine is more effective in immunosuppression-naive patients with moderate to severe Crohn’s disease than either drug alone, and infliximab has also shown beneficial, although lesser, effects in ulcerative colitis.

Following the success of infliximab, other anti-TNF treatments have been introduced for Crohn’s disease. Adalimumab is available as a subcutaneous alternative to infliximab infusion and, in some countries (not the UK), certolizumab is also marketed.

A third MAb, natalizumab, targets the cellular adhesion molecule 4 integrin rather than TNF, and efficacy has been demonstrated in Crohn’s disease and multiple sclerosis. But safety issues have limited its availability worldwide and it is not licensed in the UK.

“If patients stop responding to infliximab, you can transfer them to adalimumab and get a reasonable response, and there are data to show that it’s possible to go on to a third agent, but the response is less good,” says Dr Sanderson.

Immunosuppressive therapy is not without risk for Crohn’s patients, and there is an approximately four-fold increased risk of infection and a four- to six-fold increased risk of lymphoma. Although the absolute risk of lymphoma is low, it is higher in the over-65s, so particular caution is needed with this group.

Dr Sanderson concludes: “Infliximab isn’t a magic bullet or a cure for Crohn’s. You have to know what you’re doing and we’re still learning the best way to combine it with other treatments. But when you talk to patients who previously couldn’t work because of their Crohn’s and whose lives were ruled by their symptoms, there’s no doubt that infliximab has revolutionised their treatment.”

References