The use of biologicals in paediatric onset inflammatory bowel disease

D Devadason
K Jones
A Rodrigues

Abstract

The treatment of inflammatory bowel disease (IBD) in childhood has undergone a quiet revolution over the last 15 years as newer agents, biologics, have been developed and then studied in children. These have, in combination with other immunomodulatory agents, transformed the care of children with inflammatory bowel disease. Importantly, they have very significantly decreased the reliance upon steroid-based therapies with their predictable undesirable effects upon growth and development. However, biologics are costly and have the potential for serious toxicity and longer term risks including that of malignancy. This article recounts the clinical experience with the available biological therapies, discusses the known risks and aims to offer the reader an overview of their utility in the management of paediatric IBD.

Keywords biologics; biosimilars; Crohn's disease; inflammatory bowel disease; steroid-sparing; ulcerative colitis

Introduction

The immunomodulators (6-mercaptopurine, azathioprine and methotrexate) and biologics are the mainstay of medications used in the management of paediatric inflammatory bowel disease (IBD). If properly utilized, these medications can control active disease, reduce corticosteroid exposure, induce remission, and promote normal growth and development. However, these medications also have significant toxicity and increase the risk of infections and lymphoma.

What is a biologic?

A biologic is usually made within a living system such as a bacterial, plant or animal cell. Most biologics are large, complex molecules or mixtures of molecules. Many biologics are produced using recombinant DNA technology. Two common types exist, monoclonal antibodies (these end with the suffix *−mab*) and fusion proteins (these end with the suffix *−cept*).

The use of biologics in the management of paediatric IBD is now firmly established in contemporary paediatric gastroenterology practice. The first biologic for the treatment of CD, infliximab, came into widespread use around 2001, on the basis of studies demonstrating its efficacy both as induction and as maintenance therapy in adults. Most UK paediatric gastroenterology centres are now using biologics early in the course of the disease to help achieve remission. Their use in paediatric IBD is proportionately greater in comparison to adults with IBD. This should not be too surprising as IBD in children often tends to be more extensive and aggressive than adult onset disease. With the early use of biologics more patients are being maintained in steroid-free remission, the need for surgery has diminished, and IBD-specific quality of life (QoL) scores have improved.

The biological agent mainly used in paediatric IBD is anti-tumor necrosis factor (anti-TNF) therapy (infliximab given intravenously/adalimumab given subcutaneously). This works by blocking the cytokine TNF disrupting the inflammatory cascade, and is recommended for inducing and maintaining remission in children with chronically active IBD despite prior optimised therapy. It is also used in children with active perianal fistulising Crohn's disease in combination with appropriate medical/surgical intervention although this is an unlicensed indication (Table 1).

Although it is usual to adopt a step-up approach to biological therapies, there may be justification for its early use in selected children with high risk for poor outcomes (e.g. severe disease at presentation) and in those presenting with severe extra-intestinal manifestations (e.g. severe arthritis, pyoderma gangrenosum).

Types of biologic agents

Anti-TNFα agents

Infliximab is a chimeric monoclonal antibody against TNF alpha that was developed originally from mice as a mouse antibody. Because humans have immune reactions to mouse proteins, the mouse common domains were replaced with similar human antibody domains. Infliximab is then manufactured in an immortalized cell line. Infliximab was originally marketed as Remicade® and was first used in the treatment of rheumatoid arthritis. It was the first biologic agent to be used in the treatment of inflammatory bowel disease (IBD) and is given intravenously. It has a serum half-life of 9−10 days and can be detected in serum 8 weeks after infusion treatment.

Adalimumab is a fully human monoclonal antibody that was discovered via phage display, a technique that allows facilitates positive selection of high-affinity antibody fragments from a library. Adalimumab is marketed as Humira®. Its half-life is similar to infliximab at around 10 days and it is generally administered subcutaneously every 2 weeks for maintenance therapy in IBD.

Golimumab is another fully human anti-TNFα monoclonal antibody, newer to the market than adalimumab and marketed as Simponi®. It may be possible to have longer dosing intervals

D Devadason *MB BS MRCPCH Consultant Paediatric Gastroenterologist, Nottingham Children's Hospital, Queen's Medical Centre, Nottingham, UK. Conflict of interest: none declared.*

K Jones *MB BS MRCPCH Specialist Registrar, John Radcliffe Hospital, Oxford, UK. Conflict of interest: none declared.*

A Rodrigues *MB BS MRCPCH Consultant Paediatric Gastroenterologist, John Radcliffe Hospital, Oxford, UK. Conflict of interest: none declared.*

Biologicals with FDA approval for Crohn's disease

	Original	Mechanism	Trade name
1	Adalimumab	Anti tumour necrosis factor	Humira
2	Certolizumab pegol	Anti tumour necrosis factor	Cimzia
3	Infliximab	Anti tumour necrosis factor	Remicade
4	Golimumab	Anti tumour necrosis factor	Simponi
5	Natalizumab	Integrin receptor antagonist	Tysabri
6	Vedolizumab	Integrin receptor antagonist	Entyvio

Table 1

than with adalimumab and in some individuals has a half-life of up to 20 days.

Other biologic agents in IBD

Vedolizumab

Lymphocyte migration from the circulation into tissues depends on interaction between proteins expressed on their surface (integrins), and endothelial cellular adhesion molecules. The α4β7 integrin expressed by lymphocytes preferentially interacts with MAdCAM-1, which is an adhesion molecule whose expression is restricted to the endothelium of blood vessels supplying the gut. Vedolizumab specifically binds (and blocks) the α4β7 integrin, and therefore prevents lymphocyte accumulation in the gut wall. To date there is more experience of its use in ulcerative colitis than Crohn's disease.

Ustekinumab

Ustekinumab is a monoclonal antibody that binds to IL-12p40, a subunit of IL-12 and IL-23, and inhibits both of these cytokines' activity. IL-12 and IL-23 are important pro-inflammatory cytokines that influence the development of Th1 and Th2 phenotypes in T cells.

It is important to recognize that although TNFα-blockade is currently the mainstay of biologic treatment of IBD, TNFα is but one of a complex network of cytokines and other mediators. It is possible in the future that detailed immunophenotyping at the individual patient level will be able to guide tailored biologic therapy. This is particularly the case in paediatric IBD, where concomitant primary immune dysfunction may be more common.

Biosimilars

Biosimilars are to biologic therapies what generics are to drugs. They become available once a manufacturer's patent on their originator product expires. Biosimilar products have the same amino acid sequence to the originator, but because the proteins are produced in different expression systems and may theoretically be subject to different post-translational modifications, manufacturers have to demonstrate 'bioequivalence' via an array of physicochemical and functional tests.

Biosimilars undergo a licensing process to show that the molecule acts and is safe as the original biologic. The infliximab biosimilar CT-P13 (Remsima or Inflectra) received marketing authorisation in June 2013 & biosimilar preparations of infliximab came onto the market in the UK in 2015. Remsima or Inflectra are both widely used in the treatment of inflammatory bowel disease. Controlled trial evidence of biosimilar infliximab's safety and efficacy equivalence to Remicade® is limited to two studies in rheumatoid arthritis and ankylosing spondylitis, though recent reports have suggested that the biosimilar product behave as expected in IBD.

Side effects of anti-TNFα agents

The most important side effects of biologic agents relate to their immunosuppressive qualities, which can increase risks of serious and opportunistic infections, and certain types of malignancies via an impact on tumour surveillance. It is helpful to subdivide these into short, medium and longer term risks.

Short-term risks (infusion-related)

Mild symptomatic reactions during infliximab infusion are relatively common. These probably occur in at least 5% of prescribed infusions. The most frequently reported side effects are pruritus, flushing, dyspnoea, chest discomfort, myalgia, nausea and rash. The risk of an immediate reaction is highest for treatment-naïve individuals, for those re-starting after a break in treatment, and for those with proven anti-infliximab antibodies. The presence of these antibodies has been associated with infusion reactions in patients and shortens the duration of effect. The detection of anti-TNF antibodies also guides management decisions on dose escalation, frequency, switching and concomitant immunosuppression.

Co-administration of immunomodulators may reduce the risk of immediate reactions (and almost certainly reduces the risk of developing anti-infliximab antibodies), and should be considered in all cases. The value of premedication with corticosteroids and antihistamines is uncertain. Severe immediate reactions have been reported, which should be managed with usual supportive treatment and intramuscular adrenaline if required.

Medium-term risks

Rarely, patients can develop a serum-sickness-type reaction 1 to 3 weeks after their infliximab infusion. This is probably caused by immune-complex deposition associated with anti-infliximab antibodies. Symptoms include fever, malaise, polyarthralgia, and rash. Symptoms usually settle with conservative management. High levels of antibodies and resumption of treatment after an interruption are key risk factors. Adalimumab can be associated with local injection-site reactions but may be less immunogenic than infliximab.

A recent systematic review found that the risk of serious infection among children being treated with anti-TNFα agents for IBD was 352 per 10,000 patient years follow-up, or one serious infection for each 28 years treatment. Patients are susceptible to a very broad spectrum of infectious diseases, and maintaining a high index of suspicion for both opportunistic and conventional pathogens is essential. Pooled paediatric data indicate adverse effects of infliximab include acute infusion reactions (15%), delayed hypersensitivity reactions (8%), serious infection (sepsis, pneumonia, meningitis, abscesses, herpes zoster, opportunistic fungal infections) risk (3.3%), and skin (eczema and psoriasis) eruptions (8%). While significant, it is important that these risks are put in their proper clinical context: most fatal