

Etanercept and Other Anti-TNF Therapies

The decision to start Methotrexate as treatment for arthritis or other inflammatory disease can be difficult, but agreeing upon anti-TNF therapy (eg etanercept also known as Enbrel[®]) may be even more so. Although there is good evidence that anti-TNF therapy works very well and generally without complications many parents and patients find it difficult to agree to its use. Here at the Oxford Paediatric and Adolescent Rheumatology Centre (OxPARC) concerns raised by parents include it is a new class of drug with insufficient data to judge its long term safety and therefore there is a lot of concern expressed on the internet. While these points are true, they do not provide the whole story and unfortunately cloud the value of the drug at a time when patients and parents are coping with the failure of other medication including methotrexate. This article will discuss these points to provide sufficient information to allow parents and patients to help in deciding the way forward.

What is anti-TNF therapy and how does it work?

Anti-TNF therapy is one of a new class of drugs (biologic agents) that target specific proteins in the immune system known to increase arthritis and other inflammatory diseases such as inflammatory bowel disease, vasculitis, juvenile dermatomyositis. By blocking these proteins these drugs reduce inflammation but without causing side effects by blocking other important processes.

The immune system is a complex network of cells and proteins which protect the body from invading micro-organisms (germs such as bacteria and viruses) that cause infection. In juvenile idiopathic arthritis (JIA) inflammation is caused by over-action of the immune system which thinks that some cells or tissue in joints are alien and attacks them. Why this should occur in some people is not known. However, what is known is some proteins play a very important role in making the immune system work harder and so can be targeted. In arthritis these proteins, which include TNF, cause more inflammation, swelling and pain.

TNF, which stands for tumour necrosis factor, an old fashioned name from when it was discovered, has high concentrations in inflamed arthritic joints. In the 1980's researchers proposed that cancelling the effect of TNF would be helpful to control arthritis without reducing the body's defences. Trials of the drug and follow-up data on the many hundreds of thousands of patients have shown that in general this remains the case.

What forms of anti-TNF therapy are there?

There are currently three forms of anti-TNF therapy: etanercept (Enbrel[®]), infliximab (Remicade[®]) and adalimumab (Humira[®]). Etanercept is the most widely used by rheumatologists. It has a licence for use in children with arthritis and in 2002 was given approval by the National Institute of Clinical Excellence (NICE), a governing body in the NHS. Although infliximab and adalimumab do not have such a licence (up to a third of all drugs used in children do not have this licence) these drugs have also been used effectively and safely in children.

Etanercept is given twice a week as an injection just under the skin (subcutaneous) similar to methotrexate and insulin for diabetes. Using needles and syringes may initially cause anxiety in both the patient and parent, but plenty of support is available to ensure that the medication is given safely and with minimum discomfort. There are hospital and community based children's nurses, the nurse specialist and other members of the paediatric rheumatology team and even dedicated nurses who work with the company supplying the medication. All of these professionals are able to provide advice and to teach parents and patients how to give the medication. If necessary it can be arranged for a nurse to give the injections until parental

confidence has increased, but most parents prefer the convenience of giving the medication themselves. In addition, by giving the injection to themselves many of our teenagers feel they have greater control of the disease. Sharps boxes and other equipment are provided for safe needle disposal.

Infliximab was introduced in the early nineties and was the first of the anti-TNF drugs used to treat inflammatory disease. Since it is different in structure to etanercept, it has a different form of action and is given in hospital as an infusion over 4 hours every 4-8 weeks. This provides a choice for patients, especially those with severe needle phobia, although attending the hospital may be less convenient. Infliximab may also be considered if etanercept has not worked or as treatment for other inflammatory diseases including arthritis of Crohn's disease, vasculitis and uveitis where it has been shown to be most effective.

Adalimumab has a structure and action more closely related to infliximab than etanercept. It is given by subcutaneous injection once every fortnight. It has only recently been introduced but studies are very encouraging.

What are the benefits of anti-TNF therapy?

Laboratory experiments and patient-based (i.e. clinical) studies have shown that blocking TNF reduces inflammation in arthritis. This results in less swelling, pain and stiffness and unique to anti-TNF therapy is evidence that joints damaged by persistent inflammation may repair. Anti-TNF therapy has also been shown to reduce inflammation in eyes, muscles and blood vessels.

Important clinical studies in children include a trial showing benefit of etanercept in JIA over a four year period. Patients were cared for at centres throughout the United States and had not responded to conventional treatment such as Methotrexate. During the first 3 months of treatment three-quarters of patients benefited from etanercept and over a third had an excellent response. Similar results were found by researchers in Europe. There is no evidence that one form of anti-TNF therapy is better than another.

If improvement occurs it can be felt after just two weeks (4 doses), but it may take 3 months and may be enhanced by the simultaneous use of methotrexate. If after 3-6 months there has not been a satisfactory response the medication will be stopped and an alternative found. Since patients may feel better able to do things without the swelling necessarily disappearing, doctors use several measures to assess response. An adequate response is shown when there is improvement in at least three of the following: sense of well-being; number of joints with pain, swelling or restriction; a health questionnaire; and blood tests. Although some adult patients have received the drug for over 10 years generally if patients have received benefit they should expect to receive treatment for at least two years and until they have been free from signs and symptoms of arthritis for 6 months to a year.

How do I know this is not going to cause more harm than benefit?

No medication is absolutely safe in all children and it is the role of the doctor together with the family to work out whether the benefit of treatment out-weighs the potential and severity of side effects before any drug is started. All drugs have minor or temporary side effects if given for long periods of time and on very rare occasions more serious side effects may occur. However, this does not mean that a child put onto the treatment is likely to have side effects. Far from it. Most children have no side effects at all and in those who do experience a problem it often quickly resolves. This section describes what may happen in a few children to help you with decide whether to start the medication and to know what to look out for and report when it is used.

Most of our understanding of side effects from anti-TNF therapy has been taken from studies and databases of hundreds of thousands adults worldwide in whom it has been found to be well tolerated with only a very small risk of serious side effects. Although far fewer children

have received the medication, probably nearing five hundred children in this country, there is no evidence that this is any different in children. In particular the on-going collection of data on children by registries in the UK, Germany and the US shows the medication to be safe in children. The UK biologic registry, situated at the Children's Hospital in Birmingham, plans to collect continuous data on all children who receive etanercept and if you or your child receives anti-TNF therapy you will be asked for your permission to send data. This registry respects privacy, but allows for constant surveillance on large populations to detect particular concerns that individual treatment centres would not be able to identify.

The majority of side effects are minor and include injection site reactions and minor headaches, rashes and tummy pains that typically respond to simple pain relief and reassurance. Allergic reactions following the use of infliximab may be more severe but quick and effective treatments are available. Adalimumab injections may be a little more painful than etanercept. Unlike methotrexate, there is little problem with nausea. Nor is there the same concern for effects on blood cells and the liver which means less blood tests are required.

Because anti-TNF therapy affects the immune system one of our main concerns is the risk of infection, although by targeting one protein it is assumed the ability to fight infection is not greatly compromised. On the whole this appears to be true and the numbers of infections are not high. If they do occur most are mild and typically viral infections such as a sore throat and cough. More serious infections may be treated with antibiotics. For early detection we recommend that patients see a doctor and inform the paediatric rheumatology centre if they are taking anti-TNF therapy and:-

- have a high fever
- come into contact with chickenpox when not immune to this infection
- come into contact with tuberculosis (TB)
- there is any other major concern for an infection

It may be recommended that the patient stop receiving anti-TNF therapy during treatment of a serious infection and your paediatric rheumatologist should advise on this. Because of the risk of infection we also screen patients about this before starting the medication. In particular we will ask about contact with TB and may arrange a skin test and chest X-ray.

The chance of developing serious side effects is very low. Serious side effects are those that require admission to hospital or specific additional treatment to avoid damage to another part of the body. They include a flare of inflammation of the eye (uveitis) and the development of a mild and transient form of lupus. Reports have also identified a risk of multiple sclerosis, although very rare and in adults at an age when MS may have occurred despite treatment with anti-TNF therapy. Young patients with normal hearts (or minor abnormalities) are not at risk from heart failure whilst on anti-TNF therapy. Obviously all patients and parents will be concerned about these serious side effects and a full discussion with your doctor will help to ease any worries.

What precautions can be taken?

We recommend simple precautions including avoiding smoking and avoiding the risk of pregnancy because of possible effects on the lungs and an unborn baby. Live vaccines such as the MMR, BCG (for TB) and chicken-pox vaccines should not be given to patients. Inactivated polio vaccination is recommended for patients and all household contacts. And since patients are more susceptible to food-borne infections such as salmonella and listeria we recommend avoiding raw eggs, under-cooked meats and poultry and unpasteurised dairy products.

Who is entitled to anti-TNF therapy?

Anti-TNF therapy is considered in any young person with a serious rheumatic condition that is not responsive to conventional therapy. Because these medications are expensive, up to

£10000 per patient per year, it has been necessary for NICE to provide guidelines on its use. It has stated that for arthritis in children or young people a patient is entitled to anti-TNF therapy if there is persistent swelling, pain and stiffness of 5 or more joints despite the use of Methotrexate at an appropriate dose. Anti-TNF therapy should also be given if methotrexate cannot be taken because of the side effects it causes. If you think your child should have Etanercept your doctor will be happy to discuss this with you and will explain specific circumstances when it cannot or should not be prescribed.

What next?

Once it has been agreed with your doctor to use anti-TNF therapy, funding of the drug will have to be approved by your local Primary Care Trust, of which your GP practice is part. There may already be formal arrangements for this, but in some cases this may cause a delay. If infliximab is prescribed arrangements will be made for it to be given via a drip in hospital as a day case. The order for etanercept and adalimumab is placed through a subsidiary company who will supply batches of the drug to be kept in the fridge at your home and equipment for the safe disposal of the needles and syringes. Initially a nurse from the company will also visit you at home to give further advice and to support the giving of the injection. Thereafter further information and support is always available from the hospital nurse specialists, via the helpline. Subsequent hospital follow-up appointments and occasional blood tests are to check the benefit of this medication and for any side effects and decisions about continuing or stopping the medication is made in accordance with the guidelines identified above (see *What are the benefits of anti-TNF therapy*).

For more information

Please check the websites of:

- arthritis and rheumatism council – www.arc.org.uk
- paediatric Rheumatology international trials organisation – www.printo.org.it
- British Society of Paediatric and Adolescent Rheumatology (BSPAR) – www.bspar.org.uk
- your paediatric rheumatologist
- Oxford Paediatric and Adolescent Rheumatology Centre (OxPARC) – www.noc.nhs.uk

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