Article

Research and drug trials

Research helps us to understand all aspects of JIA better, whether it's through getting more and potentially better treatments for the condition or having a better understanding of the causes and risk factors for JIA.

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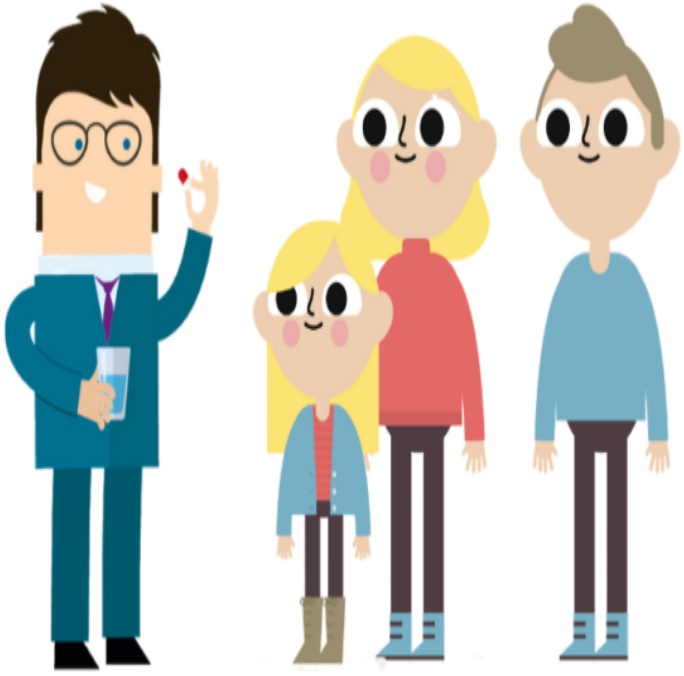

Treating children | Some of the issues

Juvenile Idiopathic Arthritis (JIA) refers to a group of seven different conditions with chronic ongoing arthritis as a common factor. Symptoms can range between mild to severe and the different types of JIA may require different types of management and treatment. Traditionally, treatments (medicines,

injections, physiotherapy) and investigations to understand the extent of the problem for children, including those with JIA, have relied on evidence gained from adult clinical drug studies. However, this approach has disadvantaged children in the past because the diseases are not the same and a simple scaled-down drug treatment dose regime is not scientifically correct.

This means there can be some issues for the doctors in making treatment decisions due to the lack of research evidence specifically relating to the management of JIA. Overall, there is a lack of: 'head to head' comparative trials in children (this is where the gold standard treatment is compared with the newer drug); research into discontinuing treatment when remission is achieved; insufficient trials into specific JIA subgroups and up to now, a need to refine more personalised treatment plans.

Getting the dose right

The way the drugs work in the body, for instance, the distribution and the uptake of the active ingredient, is different in children of different ages and sizes and unless these factors are studied specifically children can be under or over-dosed relative to adult doses. A good example of this is the dosing of Tocilizumab in children. Children weighing less than 30kg require a dose of 10mg for every kilogram body weight (10mg/kg); larger children require the lower dose of 8mg/kg to achieve the same drug benefit. Children under 2 years old may require even higher doses and the apparent poor response to treatment which can sometimes happen, may be because the dose of the medication is too low. Interestingly, the paediatric dosing system of a dose per kilogram body weight is now being used in some adult treatments. This is because clinicians have started to realise that individual doses are really important and it is apparent that individualised treatment plans are needed.

Window of opportunity

Results from adult rheumatoid arthritis (RA) studies have found there is a "Window of opportunity" which shows that if a patient receives treatment within a specific period after they first show symptoms they have better long term control of their RA. This is increasingly shown to be true in children with JIA. Research has also found that the cumulative effect of having inflammatory disease from an early age (ie. from childhood) causes greater damage to the joints, the growth plates, muscle and bone development and growth in height. For this reason, the approach of waiting for adult experience before researching into potentially important treatments in childhood is no longer seen to be equitable or ethical.

Tight control

Early active treatment to gain tight control of the inflammatory process is increasingly implemented to achieve remission of JIA as soon as possible. A variety of treatments are used and the child's response to these is frequently reviewed so that any changes in the dosing, such as increasing or reducing the dose, can be done in a timely way. The sooner the inflammatory system is brought under control the better, because control drastically improves the long term prospects in terms of joint damage, flare-ups and the immune system's response to the prescribed drugs.

Drug management

For JIA this involves a mix of treatments. Clinical trials have shown that early use of steroid joint injections alone, or in combination with other treatments, can have a long-lasting benefit. Nearly all

children will need joint injections as part of their care, to control the actively inflamed joints. A non-biologic disease-modifying anti-inflammatory drug (DMARD) is often required and there is strong supporting evidence for the use of methotrexate as the first-line drug. Sulfasalazine may be used in enthesitis-related arthritis (one form of JIA) and dependant on the advice and assessment by the consultant, leflunomide may also be used in JIA. As soon as it is clear that these measures are insufficient, biologic drugs will be started. Increasing, numbers of biologic drugs are now licensed and gaining regulatory approval as well as clinical experience. Newer treatment options are also available including stem cell transplantation.

What's happening in drug research for JIA?

It is important to be aware that young people now are clear and definite in stating that it is their right to be involved in clinical trials. They want to know that they have access to the newest treatments with reliable and accurate evidence base for their effectiveness and safety.

The very best research evidence is from randomised placebo controlled trials (this means the participants are randomly allocated to receive the active drug or to receive the 'dummy' drug without being told which group they are in). This enables statistical comparisons to be made between the groups and ultimately adds to the knowledge base for informed decisions on treatment.

However, because of parent's understandable concerns that their child may be disadvantaged whilst on the dummy treatment, creative trial designs have been developed that minimise the chance and

duration of placebo treatments with safe opportunities to “escape” to active drug treatment.

Research into drug treatments for JIA not only give a scientific evidence base to its management but also show us what effect individual inflammatory cells have on the disease process. Research into the effects of biologic drugs for the subtype, systemic onset JIA, for example, has been extensive.

Drugs such as etanercept, infliximab, adalimumab, golimumab and certolizumab have been shown to be very effective in blocking the cytokine protein known as tumour necrosis factor (TNF), that are overproduced by the body and cause inflammation and damage to bones, cartilage and tissue. These drugs, known as anti-TNF drugs block the action of these proteins thereby inhibiting inflammation and reducing joint damage.

The very first controlled trial for JIA-related uveitis commenced in October 2011. This trial, called the Sycamore Trial, looked at the outcomes of the anti-TNF biologic drug, adalimumab compared with other known drugs. This is a landmark study because it is one of the very first randomised controlled trials in uveitis and the results of the study are awaited with great anticipation.

Children and young people in the UK who are taking biologic drugs are registered onto the appropriate research database. These look at the longer-term outcomes and safety of the drugs in treating the disease and their effects on the body. The British Society for Paediatric and Adolescent Rheumatology (BSPAR) set up the BSPAR Etanercept Biologics Register which registers children and young people taking etanercept and, the Biologics for Children with Rheumatic Diseases (BCRD) database includes all children and young people with JIA on any other biologic drug apart from etanercept.

Summary

Treatment issues in children

- Evidence for treatment in children has relied on adult clinical drug studies
- This ‘scaled down’ approach to drug treatment is not scientifically correct
- There is a lack of research evidence specifically into treatment for children with JIA

Getting the dose right

- Treatment in children can be found to be under- or over-dosed when information is available on the distribution and the active ingredient of the drugs in relation to the age and the weight of the child
- The paediatric dosing system of mg/kg bodyweight is now being used in some adult treatments

Window of Opportunity

- Evidence from adult rheumatoid arthritis studies shows a ‘window of opportunity’ for optimum control and future prognosis
- Early treatment is increasingly seen to be important in children
- Inflammatory disease from an early age can cause greater damage to the joints and overall growth
- Waiting for research evidence from adults is no longer equitable or ethical

Tight control

- Early active treatment to achieve remission is increasingly implemented
- Control as soon as possible improves long term prospects

Drug management

- A better understanding and knowledge of the effects of drugs and drug combinations means treatments are tailored to each child’s needs, using a step-by-step approach

Drug research in JIA

- Young people are clear in their right to be involved in clinical trials
- Young people want accurate evidence for effectiveness and safety of their treatments
- Parents have concerns around their children participating in clinical research
- The Sycamore trial is the first randomised controlled trial into uveitis
- All children and young people on biologic medication are registered onto the appropriate data base so that long term studies on the evidence from each drug can be collected and evaluated

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