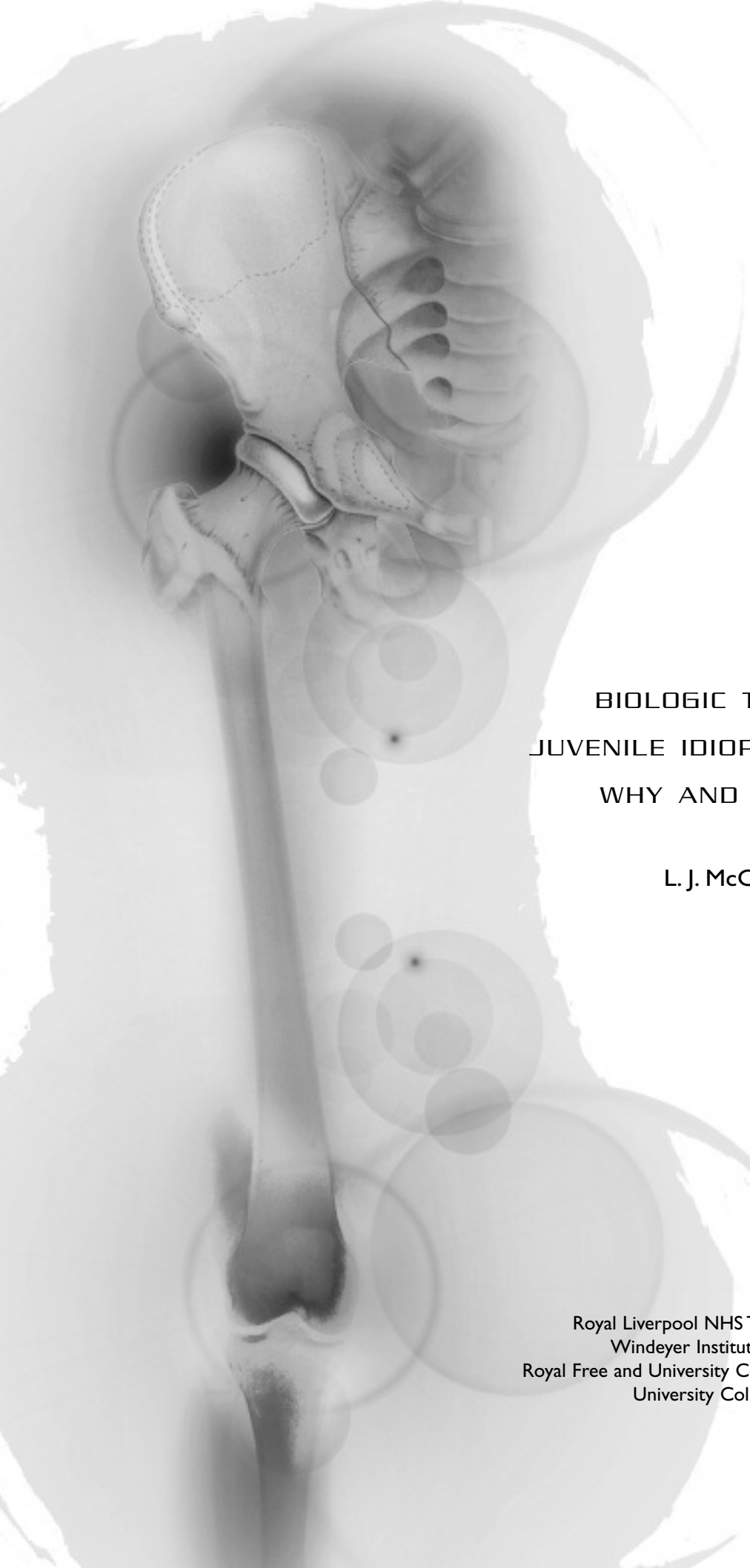

BIOLOGIC THERAPIES IN JUVENILE IDIOPATHIC ARTHRITIS: WHY AND FOR WHOM?

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ABSTRACT

With greater understanding of pathophysiological, genetic and environmental influences on juvenile arthritis, there is an opportunity to develop new targets for therapy and greater control of disease. Early, aggressive control of arthritis is essential in order to prevent long-term disability. For those children that are resistant to standard therapy, new and exciting alternative medications are emerging. However, continued research is needed to gain a greater understanding of immunological and genetic profiles of the disease. Pharmaco-vigilance is essential to establish efficacy and side effect profiles. Physiotherapy, occupational therapy, nursing issues, and psychology remain integral to the management of JIA, along with liaison with ophthalmology, orthopaedic and dental colleagues. This article reviews the current biologic treatment options available for children with arthritis and the evidence base that supports their use.

Keywords: Juvenile Arthritis; Biologic Therapy; Etanercept; Infliximab.

RESUMO

Com o maior conhecimento dos mecanismos fisiopatológicos, da influência genética e ambiental na artite idiopática juvenil (AIJ), abrem-se oportunidades para novos alvos terapêuticos e para um melhor controlo da doença. O controlo precoce e agressivo da artrite é essencial para prevenir a incapacidade futura. Para as crianças resistentes ao tratamento convencional, estão a surgir novas alternativas terapêuticas. Contudo é necessário que a investigação prossiga com vista a uma melhor compreensão dos aspectos imunológicos e genéticos da doença. A farmacovigilância é essencial para estabelecer o perfil de eficácia e de efeitos adversos dos fármacos. A fisioterapia, a terapia ocupacional, o apoio de enfermagem e psicológico permanecem parte integrante da abordagem da AIJ, juntamente com a ligação à oftalmologia, ortopedia e estomatologia. Este artigo faz uma revisão das terapêuticas biológicas actualmente disponíveis para as crianças com artrite e da evidência em que se baseia a sua utilização.

Palavras-Chave: Artrite Juvenil; Terapêutica Biológica; Etanercept; Infliximab.

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Introduction

The majority of children with Juvenile Idiopathic Arthritis (JIA) respond to traditional treatment with non-steroidal anti-inflammatory drugs, steroids (intra-articular, intravenous or oral as needed) and disease modifying anti-rheumatic drugs such as methotrexate.[1] Traditionally, the overall prognosis has been thought to be good, with up to 60% of cases entering remission before adulthood[2] although recent studies suggest that the risk of relapse or extension into adulthood is significant.[3] The approach to treatment depends on assessment of individual needs and sub-type of disease. Patients with oligoarthritis may respond adequately to intermittent intra-articular steroid injections whereas those with systemic onset disease, polyarticular or extended oligoarthritis will require more intensive therapy, usually starting with a combination of steroids and methotrexate. Other co-morbidity, such as the presence of uveitis, may influence treatment decisions. For those children with refractory disease who are resistant to traditional treatment regimes, further medical intervention is required. It is this group of children, who, up until recently, suffered the greatest disability from their arthritis and experienced adverse effects of medications that were unable to control their disease. Anti-Tumour Necrosis Factor (TNF) therapy now provides a promising outlook.

Why use anti-TNF therapy for JIA?

The concept of JIA entering remission before adulthood has been challenged in the last decade and it has become clear that JIA is not as benign as previously thought. Many long-term studies reflect historical treatment, but one multi-centre retrospective cohort study of 392 patients, including patients with recent disease treated aggressively with disease modifying drugs and intra-articular steroid injections, suggests that disease often extends into adulthood.[3] Although functional outcome improved, the probabilities of remission at 10 years after onset were 37% for systemic onset, 47% for oligo-JIA, 23% for Rheumatoid Factor (RF) negative polyarticular JIA and only 6% for RF positive polyarticular JIA. Looking specifically at children aged 16 or over (n=205), remission was only achieved in one third of patients with systemic arthritis, a quarter of those with RF negative polyarticular JIA and half of those with oligo JIA by their 16th birthday. None of the 35 patients with RF positive JIA entered remission by the age of 16.[3]

Another long-term study of 246 patients, of whom 74.4% had received a disease-modifying drug, including 40.7% on methotrexate, demonstrated that approximately 50% of adults with JIA suffer from persistent inflammation and significant disability secondary to prolonged periods of disease activity.[2] Problems include joint deformity and destruction, growth abnormalities, osteoporosis, pain, impaired psychological health and difficulty with daily living. Active synovitis was found in 43.3% of adults with JIA and 54.4% had evidence of disease activity on laboratory markers. Many (between 30-56%) had severe functional limitation, particularly in systemic onset and polyarticular groups.[2] Fewer patients were in stable relationships compared to their siblings, with the majority feeling that JIA had a negative effect on body image.[4] JIA sufferers had a higher level of anxiety than the general population and pain intensity was higher in adults with JIA than reported pain intensity in children with JIA.[5] Rate of unemployment for patients was found to be three-fold higher than local controls despite excellent educational results.[6]

In order to prevent continuing disability and damage, with significant health care costs and implications for employment, early aggressive therapy is needed. This aggressive treatment regime has been

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shown to be effective in a study that demonstrates that children with erosions and disability due to JIA had received treatment later than those who were well.[7] Trials in rheumatoid arthritis suggest a 1-2 year therapeutic window to limit joint damage, with optimal control of disease achieved with the use of disease modifying drugs during the first 3 months of onset.[8]

Long-term studies reflect historical regimes and one would hope that with better treatment of disease, that the long-term outlook of today's children with JIA will be improved. However, studies that include children diagnosed more recently and managed with aggressive treatment strategies (excluding biologic agents), still show a poor overall outcome.[3,9] Early treatment with disease modifying agents has been found to have important advantages in suppressing disease activity (measured by disability and pain, joint count and erythrocyte sedimentation rate) over a therapeutic regime where disease-modifying agents are postponed, such as the traditional pyramid model.[10] Within paediatrics, there has been a shift towards early aggressive treatment of JIA to limit inflammation and achieve a normal lifestyle, particularly in those with poor prognostic indicators (Table I).[11,12,13] This includes moving quickly to use anti-TNF therapy if control is not achieved with a combination of steroids and methotrexate, now established as the first line anti--rheumatic drug.[1]

A significant number of children do not respond to traditional treatment regimes and are troubled by chronic pain and stiffness, disability, growth retardation, risk of irreversible joint damage in addition to the emotional and psychosocial implications of having a chronic disease. In many cases, methotrexate or alternative disease modifying drugs, are useful in controlling disease, but do not lead to remission, and may have unacceptable adverse effects. Instead of using broad spectrum immunosuppression, it seems sensible to chose a particular molecular target thought to be important in causing or provoking inflammation, and create a antibody or molecule that blocks the action of that target alone (immuno-modulation). In this way, it is hoped that the molecule will work directly at the site of action, with increased efficacy and specificity and fewer adverse effects. However, the target molecules are involved in many important pathways, particularly in host defence, which can potentially lead to adverse effects.

Table I. Poor prognostic indicators in JIA[11-13]

- Active systemic disease at 6 months in systemic onset JIA (fever, need for corticosteroid, and thrombocytosis)
- Polyarticular onset and polyarticular disease course
- Extended oligo JIA
- Female
- Rheumatoid Factor positive
- ANA positive
- Persistent Early Morning Stiffness
- Tenosynovitis
- Subcutaneous Nodules
- Rapid involvement of the small joints of the hands and feet with erosions
- Hip involvement
- Higher mean ESR
- Generalised lymphadenopathy

Immuno-modulation: a novel approach

Inflammation in JIA is complex and involves cellular components of the innate and adaptive immune response, activation of endothelial cells and fibroblasts, and soluble mediators (cytokines, chemokines, complement pathways and coagulation or fibrinolytic pathways). Although cells of the adaptive immune system (T cells and B cells) participate in the disease process, many aspects of arthritis can be attributed to inflammatory mediators. Monocyte derived cytokines appear to be the major mediators of joint damage in children. Cytokines are a large group of polypeptides and small proteins that interact with each other to maintain a dynamic equilibrium in immune and inflammatory responses. An imbalance in pro- and anti-inflammatory cytokines and T helper cells is considered to be important in arthritis and other autoimmune diseases.[14] In patients with systemic onset JIA, serum concentrations of interleukin 1 (IL-1), tumour necrosis factor-α (TNF- α), IL-6, IL--8, and IL-12 have all been found to be consistently raised.[15-18] Serum concentrations of IL-6 are also raised in children with active polyarticular JIA.[18] IL-12 has been found to be raised in active oligoarticular JIA and decreases quickly on remission of oligo and poly JIA.[18] On synovial fluid analysis, elevated levels of IL-6, TNF- α, IL-1, and IL-8 are found in children with different sub-types of JIA.[15,19-22]

An increasing understanding of pathophysiology of childhood and adult arthritis, and the realisation that cytokines play a key role, has provided a wide array of targets for therapeutic intervention. In recent years, specific inhibitors of various cytokines have been developed for treatment with promising results. TNF-α and IL-1 are potent inducers of inflammation and act synergistically in inducing joint damage. Thus, if it is possible to block one of these agents, the activity of the cytokine at its site of action can be reduced, with the hope of decreasing joint damage and minimising adverse effects elsewhere.

The term biologics has arisen to describe therapies with biologic properties, including monoclonal antibodies, soluble cytokine receptors and recombinant receptor antagonists. Biologic agents that decrease activity of TNF- α (etanercept, infliximab and adalimumab) or antagonise the IL-1 receptor (anakinra), are currently in use. Other targeted therapies look promising in clinical trials, such as blocking IL-6 with tocilizumab.[23,24] A more recent approach has looked at the construction of fusion proteins that prevent engagement of co-stimulatory molecules required for T cell activation, thereby immunomodulating by targeting early in the immune cascade. Early trials of CTLA4-Ig (abatacept), a selective co-stimulator molecule that binds to CD80 / CD86 ligands on antigen presenting cells, thereby blocking interaction with CD28, are underway in juvenile arthritis, having shown promise in adult rheumatoid arthritis.[25]

Who needs anti-TNF therapy?

It has become common practice to move directly to anti-TNF therapy for the treatment of arthritis in children who have failed to respond adequately to methotrexate or have been unable to tolerate methotrexate due to adverse effects. Currently, only etanercept is licensed for use in children in the USA, Canada and Europe. In the UK, the National Institute of Clinical Excellence (NICE) guidelines recommend it for children aged 4-17 years, with active JIA in at least 5 joints, whose condition has not responded adequately to methotrexate, or who have been unable to tolerate methotrexate.[26]

In addition to its use in JIA, etanercept is approved for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Increasingly, anti-TNF therapy is being used in the treatment of resistant uveitis secondary to either JIA[27-30] or Behçet's disease when children have failed to respond to standard therapies. However, Infliximab appears to be more effective than etanercept for this indication and there have been reports of uveitis arising during treatment with etanercept.[31,32]

Infliximab is approved as a treatment option in Crohn's disease[33,34] as well as rheumatoid arthritis[35] but not licensed for use in JIA. Anti-TNF therapy appears to be a therapeutic option in children with TRAPS (tumour necrosis factor receptor-associated periodic syndrome) and HIDS (hyper immunoglobulin D with periodic fever syndrome)[36-38] although it is not currently licensed for use in this context and further trials are needed. Use of anti-TNF medication is described in granulomatous disease such as sarcoidosis[39,40] as well as in vasculitis.[41,42] In children it has been used with success in Kawasaki disease[41] as well as systemic vasculitis[42] and in adults, in neuro-Behçet's disease,[43,44] Takayasu arteritis[45] and ANCA positive vasculitis.[46] Other reports have described successful use in pyoderma gangrenosum[47] and polymyositis or dermatomyositis[48,49] resistant to standard therapy.

Which anti-TNF?

There are three anti-TNF preparations currently available, namely etanercept, infliximab and adalimumab. Etanercept is a chimeric fusion molecule of two human soluble p75 TNF receptor molecules fused to an Fc fragment of human IgG, given by subcutaneous injection twice weekly. Infliximab is a chimeric antibody genetically engineered to combine the variable region of murine antibody to TNFα with human IgG1. It is given by infusion every 4-12 weeks, but should be used with concomitant low dose methotrexate in order to minimise antibody formation. Adalimumab is engineered to be indistinguishable in structure and function from naturally occurring human immunoglubulin G1. It is given by subcutaneous injection every alternate week. The low immunogenicity of adalimumab avoids the need for concomitant methotrexate administration.

Differences in efficacy of etanercept, infliximab and adalimumab may be explained by different drug characteristics, binding properties, pharmacokinetic profiles, dosing patterns, or pathophysiology of disease type. Etanercept has proven efficacy in inflammatory arthritis in adults and chil-

dren, but has limited efficacy in Crohn's disease, sarcoid, and Wegener's vasculitis. Because etanercept, but not infliximab, binds α–lymphotoxin, which has an important role in JIA, immune defence and immune system development, etanercept would theoretically be more effective in this subgroup of patients. In practice, however, infliximab has been found to have similar efficacy to etanercept in adult rheumatoid arthritis, in addition to being beneficial in granulomatous disease. The bolus administration of infliximab leads to greater variability of drug concentration over time, but possibly better tissue penetration at higher peaks.[50] Adalimumab has demonstrated efficacy in rheumatoid arthritis[35] and psoriatic arthritis[51] but full results of randomised trials of its use in other conditions are awaited.

In children with JIA, etanercept is usually the first anti-TNF medication to be given in view of it's proven efficacy and the fact it is licensed for children at a dose of 0.4 mg/kg twice weekly in the FDA of the USA and EMEA of the EU. A once weekly regime of etanercept at a dose of 0.8mg/kg is an alternative, approved by the FDA. This regime has been shown in a clinical trial simulation to yield overlapping steady state time concentration profiles as 0.4mg twice weekly, thereby suggesting similar clinical outcomes.[52] High dose etanercept at 0.8mg/kg per dose (up to a maximum of 25mg) has been evaluated in children who had inadequate response to standard dose etanercept. Given at this higher dose, etanercept was found to be safe and well tolerated in polyarticular JIA, but efficacy was limited.[53]

Infliximab is given by an intravenous infusion and may be useful for poor compliance with etanercept or injection site reactions. In JIA, infliximab tends to be used for children that have failed to respond to etanercept or have not been able to tolerate etanercept. Efficacy is probably comparable to etanercept in polyarticular JIA[54] but unfortunately a recent multicentre placebo controlled phase II study has failed to demonstrate a statistically significant difference between infliximab and placebo groups because the number of subjects who could be evaluated was underpowered for the analysis.[55] Other attractive features of infliximab include infrequent administration under the direct supervision of a healthcare professional. Patients, who fail to respond or show a poor response to etanercept, may respond to infliximab, or vice versa in adult rheumatoid arthritis,[56] but this is not proven in JIA.

Preliminary data of adalimumab in polyarticular JIA suggests a similar efficacy to etanercept and infliximab.[57] Its once-fortnightly injections may make it attractive, particularly in adolescents when drug adherence is an issue. At present, adalimumab is indicated for JIA when patients fail to respond to etanercept or are unable to tolerate etanercept. It may be chosen in preference to infliximab when there is concern over antibody formation with infliximab infusions (particularly if patients refuse to take methotrexate in combination), or co-existing uveitis, which may not be controlled by infliximab. For some patients, the choice of subcutaneous injections rather than hospital visits for intravenous infusions may make adalimumab more favourable than infliximab when etanercept fails to control disease. All anti-TNF preparations induce immunogenicity to a greater or lesser extent and all three preparations are more efficacious when used in combination with methotrexate. However, the need for concomitant methotrexate is most important with infliximab. In practice, a significant number of children on anti-TNF medication will refuse methotrexate due to previous adverse effects. This makes the more humanised potential of adalimumab attractive, and use of this third anti-TNF medication may increase with time and greater experience.

Anti-TNF therapy – evidence of efficacy:

Etanercept (Enbrel®)

Studies in adult RA have shown evidence of true disease suppression with prevention of erosions and joint destruction, particularly when used in combination with methotrexate.[58] Paediatric trials have demonstrated impressive short-term efficacy with minimal side effects.[59-61] A combination of etanercept and methotrexate is well tolerated and may enhance efficacy in polyarticular JIA.[62]

In a two-part study, etanercept was tested on 69 patients with active polyarticular JIA, refractory or intolerant of methotrexate. Initially all patients received etanercept at 0.4mg/kg twice weekly for 90 days. 51 patients (74%) achieved the JRA30 definition of improvement. The second part of the study was a randomised, double blind, placebo-controlled trial of etanercept responders. Significantly fewer etanercept patients experienced a disease flare (28%) compared with placebo patients (81%) and the median time to disease flare was signifi-

cantly longer in the etanercept group.[59] Subsequent studies have demonstrated safety and efficacy over a 2-year[60] and 4 year period.[61]

Children with systemic onset JIA can be more challenging to treat and the response to etanercept may not be as good, perhaps due to a unique cytokine profile. One study looked at response to etanercept in 82 children with systemic onset JIA by a retrospective survey of objective data (such as medication dose, presence of joint pain or systemic symptoms, blood test results, active joint count and physician global assessment) at baseline and last visit. With a follow up period of between 3 and 70 months, 46% of children had a good or excellent response to etanercept, with the majority being able to discontinue steroid treatment.[63] Although a proportion of children with SOJIA respond well to anti-TNF therapy, other cytokines, particularly IL-6 and IL-18, have been found to be important in the articular disease and systemic manifestations.[64-69] In view of this, targeted therapy directed against these cytokines may be more beneficial in this sub-group.

Etanercept has demonstrated efficacy in psoriatic arthritis in adults. A placebo controlled trial of 60 patients showed that 87% of patients in the etanercept group met the Psoriatic Arthritis Response Criteria compared to 23% in the placebo group.[70] A further phase III trial of 205 adults with psoriatic arthritis showed an ACR 20 in 59% of patients in the etanercept group compared to 15% in the placebo group.[71] Trials in children with psoriatic JIA are lacking, although there is no reason to suggest that results would not be comparable.

Etanercept has been assessed in several randomised controlled trials in adult alkylosing spondylitis with good effect.[72-74] In particular, the inflammation of the axial skeleton is controlled effectively for the first time by anti-TNF therapy. The paediatric experience of use of anti-TNF therapy for juvenile enthesitis related arthritis (ERA) is mostly limited to case reports and case series, but from these observations, treatment seems to be as effective as it is in adults. One open label pilot trial of etanercept use in 8 children with active ERA, refractory to treatment with non-steroidal anti-inflammatory drugs, methotrexate and other disease modifying drugs, demonstrated significant improvement in joint count, laboratory indices and well-being, sustained over a 2 year period.[75] Radiological remission, sustained over a 2-year period, has been demonstrated in a case report using contrast-enhanced magnetic resonance imaging (MRI).[76]

Adverse effects of etanercept include injection-site reactions, headaches, minor upper respiratory tract infections, rhinitis, urticarial reactions, abdominal pain, nausea, and vomiting.[59] There is loss of efficacy from 9 months to 1 year in some children when etanercept is used at a dose of 0.4mg /kg. With more long-term use of anti-TNF agents in adults, concerns regarding other possible adverse effects are emerging.[77] Anti-TNF preparations can precipitate ANA and anti-dsDNA antibody formation causing a lupus-like syndrome that disappears on cessation of therapy.[78] There have been reports of increased serious infections, lymphoma and demyelinating disorders in adults after anti--TNF therapy[79-82] Further long-term surveillance studies are needed in JIA and a Biologics Registry has been established in the UK (http://www.bspar.org.uk), Sweden, Germany [31], France and other European counties for this purpose.

Despite these concerns, anti-TNF treatment appears to be effective in children with resistant JIA with few adverse-effects in practice. Treatment is usually stopped once a child has a 2-year disease free period, but there is a 30% risk of relapse (www.nice.org.uk).[26]

Infliximab (Remicade®)

A non-randomised, open label study of 24 JIA patients showed that infliximab had equivalent efficacy to etanercept but adverse effects were more common.[54] A more recent international, phase III, multicentre, randomised double blind placebo controlled trial in 122 children with polyarticular JIA demonstrated efficacy of infliximab, but unfortunately, without statistical significance.[55] The drug was used for 14 weeks, followed by a double blind treatment extension for 44 weeks in patients with polyarticular JIA receiving concomitant methotrexate. Two groups of patients received either placebo followed by infliximab at a dose of 6mg/kg with methotrexate, or infliximab at 3mg/kg and methotrexate followed by placebo. Infliximab was generally well tolerated, with a better safety profile at a dose of 6mg/kg rather than 3mg/kg. At lower does (3mg/kg), infliximab had a 3-fold higher incidence of infusion reactions, as well as a higher occurrence of antibody formation to infliximab and antinuclear antibodies.

Infliximab has been used successfully in adult ankylosing spondylitis in several trials, especially for inflammation of the spine and sacro-iliac jo-

ints.[83-85] It has also been shown to be effective in psoriatic arthritis in adults in randomised controlled trials.[86] In childhood, infliximab has been shown to be efficacious in a case report of 2 children with juvenile ERA[87] and 8 children in another study over a 1-year period[88]

Infliximab may also be a useful adjunct to the management of refractory uveitis associated with JIA, and has shown efficacy in several case reports and case series.[27-29] Infliximab appears to have better efficacy than etanercept for JIA associated uveitis.[32]

Adalimumab (Humira®)

Being indistinguishable from naturally occurring IgG, the low immunogenicity of adalimumab avoids the need for concomitant methotrexate administration. It is approved for use in Rheumatoid Arthritis, and trials in JIA are underway. A phase III randomised, double blind placebo controlled trial in adult RA with open label extension has shown good efficacy and safety[89,90] particularly when used in combination with methotrexate.[91] In children, preliminary data from a phase III multicentre randomised placebo controlled trial of 171 patients with polyarticular JIA (aged 4-17 years) demonstrates a rapid beneficial response to treatment, with a reassuring safety profile over a one--year period.[57] At the end of a 16-week open label phase, 83% of patients showed a 30% improvement in disease activity (ACR Ped 30 response), 74% showed a 50% improvement (ACR Ped 50) and 52% showed a 70% improvement (ACR Ped 70). 133 patients entered the double blind phase of the trial. 4% of patients withdrew, but of the remainder, patients receiving adalimumab had significantly fewer disease flares than patients receiving placebo, when used with methotrexate (36.8% vs. 64.9%, p=0.015) and without methotrexate (43.3% vs. 71.4%, p=0.031, primary endpoint). ACR 30, 50 and 70 responses at the end of 48 weeks were significantly better in the adalimumab group compared to placebo. Adalimumab was generally well tolerated with few patients experiencing serious adverse events. Most adverse effects were infections (mostly mild upper respiratory tract infections).[57]

What happens when anti-TNF fails? Future options with other biologics:

Anakinra (Kineret®)

Anakinra is a recombinant IL-1 receptor antagonist that has efficacy and safety in rheumatoid arthritis.[92] Further trials are required in JIA, but its short half-life with a need for daily subcutaneous injections may limit use. However, for children with systemic onset JIA who have not responded to standard therapy, anakinra may provide a welcome therapy. Deregulated IL-1 production plays a critical role in systemic onset JIA, and early studies show that children with resistant systemic onset JIA can respond to anakinra.[93] Seven out of nine (77%) patients in one small study showed a good response to IL-1 blockade.[93] However, a recent French report suggests that less than 50% of systemic JIA responded well to anakinra in their cohort[94]. Results in polyarticular JIA may not be particularly favourable, with preliminary results from an open label portion of a trial showing 58% of children demonstrating clinical improvement based on JIA 30% core set criteria.[95]

Tocilizumab (MRA, Actemra®, anti-IL6 monoclonal antibody)

Use of Recombinant IL-6 monoclonal receptor antibody (MRA / tocilizimab) shows promise in adult RA with significant improvement in clinical and laboratory features.[96] High levels of IL-6 seem to play an important part in the pathogenesis and maintenance of systemic onset JIA[23] and early use of tocilizumab has shown great promise in resistant cases. An open label single-dose Phase 2 trial in the UK and France in 18 children with severe, refractory systemic onset JIA showed a 30% improvement in 11 out of 18 (61%) patients, observed for up to 8 weeks.[24] An open label ascending dose study in Japan of 11 children with refractory systemic onset JIA evaluated fortnightly doses of Tocilizumab. Disease activity (febrile episodes, active arthritis, functional assessment scores and acute phase reactants) rapidly reduced in 10/11 (91%) patients.[97] A more recent Japanese Phase III double blind study demonstrates a rapid and substantial improvement in children with JIA, with 51out of 56 (91%) achieving a JIA core set of 30% improvement by 6 weeks, and consistent improvement during a randomised double-blind period. The drug was well tolerated by most children, with the most common adverse event experienced being infection.[98] A multicentre Phase III double-blind placebo controlled study is being planned.

Rituximab (Mabthera®, anti-CD20)

Arthritis is considered to be predominantly a T cell

mediated disease, but removal of autoreactive B cells may suppress antigen presentation to T cells and modify the immune response. Rituximab is an anti-CD20 antibody that has been found to be effective in adult rheumatoid arthritis when used in combination with cyclophosphamide or with methotrexate in randomised placebo controlled trials.[99,100] Trials in JIA are awaited.

Conclusions

Over time, with continued research, a greater understanding of the role of cytokines and cytokine genotypes in sub-groups of JIA will allow for improved targeting according to disease type or genetic make up. At present, biologic therapies are indicated when conventional therapies (such as methotrexate) have failed to control disease or cannot be tolerated. The high cost of biologic therapies remains a barrier, but needs to be viewed within the context of minimising or preventing long-term disability with significant life-long cost savings. Meanwhile, work continues with the concept of moving from laboratory bench to clinical practice and back to bench for continued laboratory development and refinement. The management of JIA has changed enormously in the last 10 years, and with continued work, the prognosis for children with JIA looks favourable.

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