

Different corticosteroid induction regimens in children and young people with juvenile idiopathic arthritis: the SIRJIA mixed-methods feasibility study

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Scientific summary

The SIRJIA mixed-methods feasibility study

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Scientific summary

Background

In the UK, juvenile idiopathic arthritis is the most common inflammatory disorder in childhood, affecting 10 : 100,000 children and young people each year, with a population prevalence of around 1 : 1000. Juvenile idiopathic arthritis is a set of related disorders, but all include chronic arthritis, with or without other extra-articular features, with no other associated diagnoses, such as infection or other autoimmune multisystem disorders. It is difficult to quantify arthritis in juvenile idiopathic arthritis, as the different types of active disease cause different symptoms or clinical signs in different patients and even in different active joints in the same patient. Pain in the joint is not always present and can also be caused by many non-inflammatory conditions. Signs of arthritis can include some or all of joint swelling, tenderness, warmth and restriction of movement, and can be seen in varying degrees and combinations. However, some joints, such as spinal joints and the hips, are enclosed in bone or deeply hidden from direct touch, making it impossible to feel tenderness and swelling in these joints. Similarly, restriction of movement can be due to both acute inflammation and later joint damage, and it is not always possible to distinguish these causes on clinical examination, which makes this an unreliable measure of disease activity if used alone.

The natural untreated outcomes of juvenile idiopathic arthritis are serious and disabling, but with modern treatment regimens, including biologic drugs, the prognosis has improved dramatically. However, there is no sustainably effective treatment or cure, and some cases, or some individual joints, are still relatively resistant to treatment with available drugs. In addition, the ability to withdraw treatment fully without subsequent disease flare is possible in about only one-third of cases. Most people with juvenile idiopathic arthritis still have a clinical need for corticosteroids at some point.

Aims and objectives

Given the lack of an evidence base and of consensus as to which corticosteroid induction regimen should be used in children with different disease subtypes and severities of juvenile idiopathic arthritis, we aimed to establish the feasibility and acceptability of a randomised controlled trial to evaluate the safety and efficacy of different corticosteroid regimens in children and young people with juvenile idiopathic arthritis. We carried out a mixed-methods study, with engagement in each phase of the process of appropriate stakeholders such as health-care professionals, patients and parents.

This aim was addressed through six research objectives, which were to:

1. establish current practice
2. determine the acceptability of treatment arms
3. identify the primary outcome
4. carry out a structured survey and discussion group with stakeholder consensus
5. conduct an observational feasibility study to test the study design
6. hold a discussion and consensus meeting and establish the final protocol.

Methods

This was a mixed-methods study and included several work packages that would enable the study research objectives to be met. The work packages included:

- A literature review – a review of the literature, the latest revision of the European Medicines Agency guideline on juvenile idiopathic arthritis trial design [European Medicines Agency (EMA). *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis*. London: EMA; 2015.] and the outcomes of the Single Hub Access for Rheumatology in Europe conclusions [Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, *et al*. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis* 2018 Aug;**77**:1107–17. Kuemmerle-Deschner JB, Hansmann S, Wulffraat NM, Vastert SJ, Hens K, Anton J, *et al*. Recommendations for collaborative paediatric research including biobanking in Europe: a Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative. *Ann Rheum Dis* 2018 Mar;**77**:319–27.].
- A national e-survey. UK health-care professionals in both specialist children’s centres and district general hospitals with paediatric rheumatology clinics, identified through the British Society of Paediatric and Adolescent Rheumatology, were surveyed on current practice, their reasons for treatment choices, the capability/acceptability of undertaking a trial, and the numbers of patients and the type of juvenile idiopathic arthritis and corticosteroid used.
- A national screening log – UK Paediatric Rheumatology Centres recorded basic anonymised demographic information and treatment details of children and young people with juvenile idiopathic arthritis who were receiving corticosteroid treatments over a 6-week period.
- A qualitative study of patients and parents – qualitative interviews with patients and parents with a specific focus on the acceptability of a randomised controlled trial of corticosteroid regimens, with in-depth discussion of their experiences of treatment, the influences on their choice of administration route and their willingness to be randomised and to provide consent.
- A national survey and consensus process – defining the primary and secondary outcome measures of induction of response for a proposed randomised controlled trial. UK-wide health-care professionals and parents/patients were invited to participate in a process to achieve consensus on the primary outcome measure.
- An initial consensus meeting – with health-care professionals, children, young people and their families, with equal voting rights, to finalise the agreement on key aspects of a proposed randomised controlled trial, including patient groups, primary outcome, control and treatment arms.
- An observational prospective feasibility study – identifying patients nationally, with agreed eligibility criteria, receiving current/proposed treatments with observational data on the consensus agreed primary outcome collected at baseline and 6 weeks after corticosteroid treatment and at 12 weeks, to inform an estimate of sample size for a future randomised controlled trial.
- A final consensus meeting – health-care professionals from throughout the UK, with children and young people with juvenile idiopathic arthritis and their families, voted on the final key parameters including inclusion/exclusion criteria, the primary outcome, minimally important clinical difference and treatment arms.
- A report on the feasibility of the proposed randomised controlled trial – preparation of the final study report detailing the feasibility of any future randomised controlled trial.

Results

Literature review

We found that there was good evidence to support the use of intra-articular corticosteroid injections in children and young people with juvenile idiopathic arthritis. However, no standardised dosing regimens for either induction or maintenance therapy, or for tapering doses for corticosteroids administered by other routes, were available in the literature. There is very little evidence regarding

the corticosteroid treatment regimens and, in particular, there is no good evidence of differential efficacy and tolerability of oral and intravenous modes of administration.

Qualitative study of patients and parents

Families engaged with the logic of the proposed juvenile idiopathic arthritis trial and provided valuable input into the trial design before further investment of resources. The study identified potential barriers to recruitment for a CS induction regimen trial in juvenile idiopathic arthritis, including preferences regarding corticosteroid treatments, divergent views between the children and young people and their parents, and identified areas for further exploration, including clinician treatment preferences.

National e-survey and screening log

The results from the national survey of clinical practice showed that the management of new patients with juvenile idiopathic arthritis, as well as those who are experiencing flares, varies between centres and between clinicians. Data from the screening log exercise (reporting on 250 patients) confirmed health-care professionals' direct reports of their practice and showed that in all subtypes of juvenile idiopathic arthritis the most commonly used route of corticosteroid was intra-articular corticosteroid injection. It was noted, however, that there was also evidence of the use of intramuscular injections in paediatric patients.

The majority of health-care professionals who completed this survey indicated that they would be prepared to consider entering patients into a trial that randomised to the various modes of administration of corticosteroid, and approximately half of the health-care professionals replied that they would be happy to randomise patients to any of the four delivery methods.

National survey and consensus process

The primary outcome measures for inclusion in a prospective feasibility study of corticosteroid regimens in children and young people with juvenile idiopathic arthritis were co-prioritised by all key stakeholders, with children, young people, their families and health-care professionals all playing a role in the ultimate selection of the Juvenile Arthritis Disease Activity Score, as an appropriate composite outcome measure by consensus agreement.

Observational prospective feasibility study

The findings from this study show that there is an eligible population of patients in the UK that is potentially willing to take part in a future randomised controlled trial. Ninety-five patients (of 224 evaluated patients) were recruited from 15 centres. Twenty-eight (29.5%) had a new diagnosis of juvenile idiopathic arthritis and 67 (70.5%) were experiencing a flare; data were missing for one patient. These patients covered all subtypes of juvenile idiopathic arthritis: persistent oligoarticular arthritis (34/95; 35.8%), extended oligoarticular arthritis (20/95; 21.1%), rheumatoid factor-negative polyarticular arthritis (25/95; 26.3%), rheumatoid factor-positive polyarticular arthritis (3/95; 3.2%), systemic juvenile idiopathic arthritis (5/95; 5.3%), enthesitis-related arthritis (3/95; 3.2%), psoriatic juvenile idiopathic arthritis (4/95; 4.2%) and undifferentiated arthritis (1/95; 1.1%).

During the data collection period, 55 (57.9%) patients were treated with intra-articular corticosteroids only, 16 (16.8%) with oral corticosteroids only and two with intravenous corticosteroids only. Twenty-two patients (23.2%) received corticosteroids by more than one route, with the majority of patients receiving intra-articular and oral (9/95; 9.5%) or intravenous and oral corticosteroids (8/95; 8.4%). No patients received intramuscular corticosteroids.

Blood samples were collected for determination of the proposed primary outcome, the full Juvenile Arthritis Disease Activity Score, 71-joint count, which incorporates most of the joints in the body (to a total of 71) as well as the erythrocyte sedimentation rate. However, a large number of data were missing, showing that it would not be feasible to use this as a primary outcome at 6 weeks; there were fewer missing data for the clinical Juvenile Arthritis Disease Activity Score, which does not require a

blood test. This has been shown to correlate well with the Juvenile Arthritis Disease Activity Score and, therefore, could be used instead.

Overall, the mean (standard deviation) Juvenile Arthritis Disease Activity Score, 71-joint count, score at baseline was 12.5 (10.1). By 6 weeks this had fallen by 5.9 (8.7), and by 12 weeks it had fallen slightly more, by 5.4 (7.0). A considerable number of Juvenile Arthritis Disease Activity Score, 71-joint count, data were missing at 6 weeks (75%) and at 12 weeks (75%).

Using the clinical Juvenile Arthritis Disease Activity Score, 71-joint count, the proportion of missing data was lower both at 6 weeks (26%) and at 12 weeks (22%). The mean change in score at both time points was slightly lower than the change in the Juvenile Arthritis Disease Activity Score, 71-joint count: 5.3 at 6 weeks and almost the same, 5.4, at 12 weeks.

At 6 weeks, 34 (35.8%) patients achieved American College of Rheumatology Pediatric (ACR Pedi) 30, 32 (33.7%) achieved ACR Pedi 50, 24 (25.3%) achieved ACR Pedi 70, 15 (15.8%) achieved ACR Pedi 90 and 11 (11.6%) achieved ACR Pedi 100. There were similar findings at 12 weeks for each of the outcomes.

Final consensus meeting

In both of the proposed protocols that were discussed in the final consensus meeting, intra-articular corticosteroid injection was defined and agreed as the control arm by virtue of being by far the most commonly used route of corticosteroid administration. There was unanimous agreement among health-care professionals that the age range for recruitment to all treatment arms should have no lower age limit, with this being left to physician and family discretion. However, there was a clear feeling that the upper age limit should be extended to at least 18 years, to avoid disadvantaging young adults with juvenile idiopathic arthritis. The clinical Juvenile Arthritis Disease Activity Score measured at 6 weeks was still supported as the primary outcome measure of choice. A protocol enabling a direct comparison of all routes of administration was clearly favoured, with randomisation felt to be appropriate. Two possible protocols were equally favoured, with all other options ruled out because of a lack of support.

Conclusions

This mixed-methods study has confirmed the lack of a published evidence base for a corticosteroid regimen of choice for use in new or flaring juvenile idiopathic arthritis.

We have shown that this issue is important to children and young people with juvenile idiopathic arthritis, their families and health-care professionals alike, as corticosteroids are a long-established part of treatment in juvenile idiopathic arthritis, although decisions about route and dose are usually based on clinician opinion and experience coupled with patient choice.

We have demonstrated excellent agreement and 'buy-in' to a multicentre study and have developed two different possible study protocols, which have been worked up in a truly open and consensus-derived manner. A total of 511 patients (and their families) were considered for this complete study, and 373 eventually took part: 250 in the screening log, 95 in the observational feasibility study and 28 in the qualitative interviews. This represents the size of the population involved in finding the answers to the study questions.

Trial registration

Current Controlled Trials ISRCTN16649996.

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This report

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