**Paediatric rheumatology in 2017 [Au: All our Year in Review articles require a strapline, OK?]**

**Child-centred research is the key to progress [Au: The original title was too long (we have a limit of 60 characters including spaces). Edited title OK?]**

Michael W Beresford and Athimalaipet V. Ramanan **[Au: We don’t include titles in our author lists, OK?]**

**Standfirst**

The rarity, severity and complexity of paediatric rheumatic diseases make progress in treating these diseases a challenge. In 2017, a new series of recommendations for treatment, studies that unravel the complexity of juvenile idiopathic arthritis and clinical trials that tackle sight-threatening uveitis have helped to improve paediatric care. **[Au: Standfirst edited to fit the 50 word limit, OK?]**

**Main Text**

Paediatric rheumatic diseases prove challenging to clinicians and scientists seeking to improve standards of care and to ultimately cure these potentially devastating childhood disorders. **[Au: Sentences edited to avoid similarity to the standfirst, OK?]** The key to advances in understanding and treating these diseases has been to keep the child as the focal point of collaborative, multi-disciplinary initiatives (Figure 1). **[Au: Added figure citation OK?]** Indeed, despite paediatric rheumatology being one of the last paediatric sub-specialities to develop, the rapid progress that has been made in translational research, clinical science and patient engagement is proving exemplar across paediatric specialties. In 2017, advances have been made in improving the health and wellbeing of children and young people with any of a spectrum of systemic autoimmune and autoinflammatory diseases (1), in understanding the complexity of juvenile idiopathic arthritis (JIA) (6) and in treating co-morbidities associated with JIA, including uveitis (9). **[Au: Sentence moved up so that the 3 advances being discussed are mentioned in the opening paragraph, OK?]**

All children have a right to take part in clinical research to improve our knowledge and understanding of paediatric diseases. The Single Hub and Access Point for Paediatric Rheumatology in Europe (SHARE) initiative was launched in 2012 and aims to optimise and disseminate diagnostic and management regimens for children and adolescents with rheumatic diseases. In 2017, SHARE’s key recommendations for collaborative paediatric research, including recommendations for biobanking, set a robust international framework for the implementation of research across and beyond international borders (1).

**[Au: I’ve removed the paragraph about the UN charter. At the moment, the article is too long (the whole article needs to be less than 1,200 words, and although this paragraph was very interesting, it was a little tangential to the main discussion. I hope that’s OK?]**

This international framework is the first of its kind, is underpinned by a structured and comprehensive evidence-based review process and importantly, integrates the perspectives of the families of children and young people living with paediatric rheumatic diseases. **[Au: Edited sentence OK?]** Although formulated within a given geographic region and being specific for paediatric rheumatic disorders, the approach of the SHARE initiative is transferrable to other collaborative research projects in rare paediatric diseases. **[Au: Sentence removed as it just restates information already provided, OK?]** In 2017, four evidence-based or consensus-based sets of SHARE recommendations were published. These set important minimal ‘standards of care’ for the diagnosis and treatment of juvenile dermatomyositis (2), paediatric antiphospholipid syndrome (3), childhood-onset systemic lupus erythematosus (4) and childhood lupus nephritis (5). Together, these recommendations help to harmonize and optimize care and research to produce the best outcomes for all patients.

Systemic-onset JIA (sJIA) has long been recognized to be different from other types of JIA in its clinical manifestations and the response of patients to medications such as methotrexate and anti-TNF therapies. Of all the JIA subtypes, sJIA is associated with the greatest degree of disease-related morbidity. **[Au: Edited sentence OK?]** Although deaths from JIA are rare, most are caused by macrophage activation syndrome, a complication seen mainly in children with sJIA, and in general, sJIA is considered to be an autoinflammatory condition that is driven by the innate immune system.

In 2017, Ombrello *et al.* provided further evidence supporting this hypothesis (6). The International Childhood Arthritis Genetics (INCHARGE) consortium gathered data on 982 children from nine countries in three continents (6), exemplifying the great spirit of international collaboration within paediatric rheumatology. Ombrello *et al.* performed a genome wide association study on 770 children with sJIA and identified two loci that exceeded the threshold for genome wide significance (*P*<2.5x10-8). One of these, the MHC locus, had previously been noted (7); however, the authors also identified a novel locus on the short arm of chromosome 1 that includes 14 sJIA-associated single nucleotide polymorphisms (SNPs) that span 20.6kb (6). A further 23 novel loci were also putatively associated with sJIA (*P*<5x10-8). Most importantly, none of the key loci identified intersected with susceptibility loci for other types of JIA (8). These findings add weight to the feeling held among clinicians **[Au: OK?]** that sJIA is both clinically and genetically distinct from other types of JIA. The priority now will be to explore the functional significance of these loci and to identify therapeutic novel targets to specifically treat children with sJIA, which despite recent advances is still associated with a substantial degree of morbidity and mortality. **[Au: Edited sentence OK?]**

Children with JIA, particularly young children with mild forms of arthritis (such as oligoarthritis), are at a high risk of developing uveitis. JIA-associated uveitis is associated with a large degree of morbidity. **[Au: OK?]** Almost half **[Au: half of all childrean with JIA or half of children with JIA and uveitis?]** develop visual impairment that leads to cataracts, glaucoma and loss of vision. Although there have been many clinical trials of novel biological agents in JIA over the past few years, **[Au: OK?]** they have all specifically excluded children with active uveitis.

In 2017, the paediatric rheumatology community worked closely with parents and patients to develop a trial that sought to definitively answer the crucial question of whether anti-TNF therapy in children with methotrexate-refractory JIA-associated uveitis is effective (9). **[Au: Edited sentence OK?]** In developing the SYCAMORE trial (9), the randomized placebo phase withdrawal design adopted by the majority of JIA trials was deemed to be unsatisfactory by both patients and clinicians. Working closely with patients’ families, a pragmatic but robust 2:1 randomization placebo controlled trial was designed. This design ensured rigorous trial methodology and ensured appropriate safeguards and ‘escape routes’ for children with active, uncontrolled disease. The SYCAMORE trial was stopped early after recruitment of 90 patients (rather than the desired 114) by the Independent Data and Safety Monitoring Committee and demonstrated highly significant results (*P*<0.0001) in favour of treating uveitis with adalimumab and methotrexate compared with treating with methotrexate alone (9). **[Au: Edited sentence OK?]**

The SYCAMORE trial excluded children with idiopathic uveitis; however it is now widely acknowledged that children with idiopathic chronic anterior uveitis have essentially the same disease as children with JIA-associated uveitis (10). The use of placebo meant that children intolerant to methotrexate (~30-40%) **[Au: 30-40% of the children in the trial?]** were not included in the SYCAMORE trial (9), making any conclusions about the role of adalimumab as a monotherapy in the management of JIA-associated uveitis difficult. However, this trial demonstrated that proactive engagement with patients and parents can successfully lead to clinical trials of novel agents that use methodologically robust designs and that can actually answer clinically important questions.

The success of the SYCAMORE trial confronts the position accepted by many that it is not feasible or possible to carry out placebo controlled studies in children. The SYCAMORE trial is a paradigm for partnership between clinicians, the families of children and yound people affected by rheumatic diseases, government agencies and charities in studying rare diseases. Clinicians need to be able to directly address questions raised by children and parents such as ‘Which drug best works for me?’. To achieve this goal, researchers need to step away from conventional study designs and to include adaptive designs or head-to-head studies of new agents versus existing approved biologics (11). **[Au: You can have a maximum of 10 references in this article. I suggest removing this reference]** The clinical community, children, families, industry and regulators need to work together to put the child at the centre of paediatric research and to ensure that trials are not just meeting regulatory requirements but are answering life-changing questions.

The advances discussed above build on two decades of progress in our understanding of the mechanisms that underlie rheumatic diseases, an explosion of new therapies underpinned by paediatric clinical trials and the introduction of new biological agents to the routine armoury of medications used by clinicians. But progress requires continued commitment. The international community is encouraged **[Au: OK?]** to gather around and seek constructive ways to overcome the national, international, institutional, clinical and academic barriers that can limit progress. **[Au: This paragraph was moved down from the start of the text because it provides a nice conclusion, OK?]**

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**[Au: Editing your article has changed the reference order. At the end of your revisions, please ensure that references are listed in the correct order in both the reference list and the text, OK?]**

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**[Au: This is an OPTIONAL section. Space is available to note any acknowledgements you would like to be included with the article, such as grant support or external editorial assistance]**

**Competing interests statement**

The authors declare no competing interests. **[Au: I realise that you stated your involvement in the featured studies on our online tracking system, but that is the nature of the majority of our year in review articles, so we do not usually list this as a competing interest, OK? Please confirm that this statement is correct]**

**Key advances**

**[Au: Please provide a list of 3 bullet points listing the key advances for this year. Each bullet point should reference on of the 3 key papers mentioned in the article.]**

**Example:**

* **Myositis-specific autoantibodies, such as anti-FHL1 antibodies, can be used to stratify patients into distinct clinical phenotypes with clearly defined histopathology5**

**Figure 1. Keeping the child at the centre of paediatric research.** **[Au: Edited title OK?]**

To make progress in tackling rare and complex disorders that affect children and young people, we need to foster partnerships between multi-disciplinary teams and collaborations with healthcare and research funding bodies, industry and regulators to improve clinical trials, bench-to-bedside translation and standards of care. **[Au: Edited figure legend OK?]**

**Online only**

**Competing interests statement**

The authors declare no competing interests. **[Au: This statement needs to match the one in the main text]**

**Subject ontology terms**

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Health sciences / Pathogenesis / Clinical genetics / Disease genetics

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