We discussed two papers published in the 20 December edition of the New Engladn Journal of Medicine. Both were Phase II trials assessing the efficacy and safety of 2 monoclonal antibody therapies for Juvenile Idiopathic Arthritis (JIA). There is some evidence that IL-6 might be an important mediator of JIA/RA and has a role in skeletal development and so far Anakinra, another IL-1R antagonist has been used in JIA but seems to only be efficacious in a subset of patients.

The first was an anti-IL-6R antibody called Tocilizimab currently already in clinical use for a number of autoimmune disorders. The trial had a 12-week randomised, double-blind, placebo-controlled phase followed by an open label extension phase when all participants were allowed to take the drug. The drug overall seemed efficacious with 85% of 122 participants reaching a JIA ACR 30 response defined as at least a 30% improvement in 3 or more of the ACR variables and without the worsening by more than 30% of more than one of the variables. Fever being a prominent systemic feature of the disease people with a fever despite a JIA ACR 30 response were not deemed to have had a JIA ACR 30 response. There were significant improvements in JIA ACR score as well as other hallmarks of the disease and after the open label extension, 48% of participants had no active joints, 28% of the patients met the criteria for clinically inactive disease and 52% of patients had successfully discontinued glucocorticoids. There were, however, significant adverse effects with 25% risk of having a *serious adverse event* (including a number of infections as well as fractures, dislocations, macrophage activation syndrome, etc.) and 11.1% risk of having a serious infection if on **Tocilizumab**. The authors propose that the drug might be useful for very severe, so far unresponsive systemic JIA.

The second paper was about a trial of **Canakinumab** a specific anti-IL-1-beta antibody that interferes with IL-1 signalling. This trial had a slightly less straight-forward design with only a single-dose double-bind, randomised, placebo-controlled phase of 29 days followed by and 12-32 week (3-8-dose) open-label extension phase. This in turn was followed by a withdrawal phase where patients were randomised again until a total of 37 flare events had occurred. Eligibility for the second trial was complex. Patients with persistent fever beyond day 3 in trial 1 could be unblinded and, if on placebo, were permitted to enrol in trial 2. **Canakinumab** responders in trial 1 rolled over to trial 2 on day 29. Patients who tapered glucocorticoid and achieved adapted JIA ACR 30 responses were then randomised for the withdrawal phase of trial 2. During this withdrawal phase patients who demonstrated a predefined disease flare definition were re-treated with canakinumab in a long-term open-label fashion as were all patients who were unable to taper glucocorticoids, lost response in the open-label phase, or flared in the withdrawal phase. Adverse events were reported in particular during the open-label and withdrawal pauses of trial 2 but the very short exposure to placebo needs to be taken into account when interpreting those data. Overall the drug seemed efficacious with a large proportion of participants achieving JIA ACR 30 or more. 56% of patients underwent glucocorticoid tapering during the open-label phase of trial 2 and median time to flare-up was 236 days in the placebo arm of the trial but not measurable in the treatment-arm.

We talked about how the use of monoclonal antibodies has been pushed following the success of anti-TNF treatment in Crohn's, UC and RA. The exact mechanism of action of many of the targets of theses therapies are still unclear as demonstrated by the failure, relatively speaking, of anti-IL-17 therapy for a number of autoimmune disorders, anti-IL-13 in asthma to name but a few examples. These drugs are also still very toxic as many of their targets have other effects, on haematopoiesis and T cell differentiation in addition to their apparent role in the pathogenesis of autoimmunity.

In addition we talk about the validity and merit of open-label extensions of new drugs. There was little added value to the relatively convoluted design of the 2 trials in the second paper - what were the authors trying to show that they would not have been able to show using either a simple double-blind randomised placebo-controlled trial with a subsequent cross-over or withdrawal phase? Another issue with these open-label phase extensions is an ethical consent related one and it is that patients who know of the open-label extension phase of the trial may in fact be *more likely* to consent to taking part if there is an open-label extension phase. Often also other than any standard safety reviews the evidence from the original double-blind trial may not be published/analysed yet and so the treatment

may or may not be better than existing treatments. Finally, although these trials may be able to generate longer-term safety and tolerability of the drug a proportion of the participants eligible for the study will have already taken the study drug. Those who *did not tolerate the drug at that stage* are unlikely to take part in the extension study introducing a bias in the study population.

Further reading for those interested and keen:

Chan, A. C. & Carter, P. J. Therapeutic antibodies for autoimmunity and inflammation. *Nat Rev Immunol* **10**, 301–316 (2010). **This entire issue of Nature Reviews Immunology is worth perusing...**

Parren, P. W. & van de Winkel, J. G. An integrated science-based approach to drug development. *Current Opinion in Immunology* **20**, 426–430 (2008).

Taylor, G. J. & Wainwright, P. Open label extension studies: research or marketing? *BMJ* **331**, 572–574 (2005).