Background: Etanercept is the only tumour necrosis factor (TNF) inhibitor that is approved by the National Institute for Health and Clinical Excellence (NICE) for JIA. Its use has revolutionized the treatment of childhood arthritis and efficacy has been proven in randomized controlled trials. TNF is a key cytokine in the pathogenesis of inflammatory arthritis. Several studies have demonstrated high levels in serum of children with JIA and this may correlate with disease activity. TNF is expressed by many cells inducing responses in the innate and adaptive immune systems by binding two receptors (the p55 TNF receptor and p75 TNF receptor). Etanercept is a soluble p75 receptor and neutralizes TNF by binding it as a monomer. The mechanism of action is different from that of infliximab and adalimumab which are monoclonal antibodies and are capable of binding TNF via two antigen-binding sites. In addition, transmembranous TNF may also be bound by these molecules inducing intra-cellular signalling pathways. The aim of our study was to look for an association between serum levels of TNF and disease activity in our cohort of patients with JIA.

Methods: Serum was collected from patients with JIA attending the adolescent clinic at University College London Hospital at the time of routine blood tests. Samples were stored at −80°C until needed. TNF levels were measured by enzyme linked immunosorbent assay (ELISA) (ebioscences) according to the manufacturer’s protocol. Samples were tested in duplicate and Etanercept was added to a negative control at therapeutic serum concentration (2.5 mg/l) to ensure there was no cross-reactivity with the assay.

Results: 160 patient samples were analysed. 32.9% had polyarticular JIA, 23.8% had oligoarticular JIA, 32.5% had enthesitis related arthritis, 7.3% had systemic onset JIA and 3.7% had PsA. 31.9% were on etanercept at the time of blood sampling. Interestingly, there was no correlation with clinical or serological markers of disease activity, including CRP and ESR. However, patients on etanercept were noted to have significantly elevated TNF levels [mean 138.2 pg/ml (range 0–531.0 pg/ml)] compared with those on DMARDS and other anti-TNF agents [mean 7.62 pg/ml (range 0–162.0 pg/ml)] P = 0.0001.

Conclusion: Finding significantly elevated TNF levels in patients treated with a TNF antagonist was an unexpected result. As the vast majority of patients with elevated TNF on etanercept were in remission, it is unlikely that this circulating TNF is biologically active and further studies are now on-going to confirm this and dissect out the mechanisms involved. The association is so strong, that we postulate measuring TNF levels, a relatively simple assay, could be used to monitor adherence in this cohort of patients, where adherence to medication can be a major issue. This will require validation in larger cohorts of patients.

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