9. SUCCESSFUL USE OF IL-6 PATHWAY BLOCKADE TO TREAT AUTOINFLAMMATION OCCURRING IN THE CONTEXT OF A NOVEL TNFRS1A GENE MUTATION

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Introduction: Autoinflammatory fever syndromes are rare and present significant diagnostic and treatment challenges. We present a case which illustrates some key concepts regarding the diagnosis and treatment of a patient with an autoinflammatory disorder, and also touches on the management of active autoinflammation in pregnancy.
Case description: A 29-year-old woman with a recently identified autoinflammatory disorder was referred to the local rheumatology service in September 2018. She reported having been symptomatic of fever, rashes and arthralgia since the age of 10, and TNF receptor 1 associated periodic syndrome (TRAPS) was suspected on the basis of an N71 deletion on axon 2 of the TNFRS1A gene when tested by a national reference centre 9 months previously.
At the time of presentation she was 25 weeks into her sixth pregnancy, the first with a new partner. She reported significant pregnancy morbidity having given birth to a daughter with multiple congenital abnormalities who unfortunately died two days after birth. She suffered 4 subsequent miscarriages at 5-7 weeks gestation with the same partner and underwent extensive genetic testing. At her initial review in the obstetric clinic, she was already receiving low-molecular-weight heparin with aspirin. Colchicine 1 mg tds, did not confer significant symptomatic benefit.
One month later, with careful counselling about pregnancy exposure to this biological treatment, IL-1 receptor antagonist (anakinra) therapy was instituted but discontinued after three weeks for generalised rash, as well as lack of efficacy manifesting in raised inflammatory markers. Infection was excluded during a subsequent hospital admission, and prednisolone treatment resulted in significant improvement in clinical course and acute phase response. The patient gave birth to a healthy infant at 37 weeks' gestation.
In the postpartum period, a recurrence of symptoms was observed. IL-6 receptor antagonist (tocilizumab) treatment was commenced at 12 weeks postpartum but discontinued owing to reports of sore throat, cough, headache and fever on the day of the injection. The patient had also discontinued prednisolone on the day of the injection and tocilizumab was rechallenged with good symptomatic response, normalisation of inflammatory markers, and successful reduction in prednisolone dose.
Discussion: This case highlights some interesting points with relation to the treatment of autoinflammatory disorders refractory to IL-1 pathway blockade, and also, of the management of flares of autoinflammation during pregnancy.
Firstly, this lady failed to respond to IL-1 receptor antagonist anakinra which has been associated with efficacy in several reports for individuals with TRAPS, and has supplanted TNF blockade with agents such as etanercept for this condition. Only a handful of case reports describe successful IL-6 inhibitor administration for this condition, and this merits further study. This patient's flare of autoinflammation was treated in the post-partum period, but the demographic characteristics of the autoinflammatory diseases are such that people of child-bearing age may be required to receive treatment in order to prevent pregnancy morbidity as a result of uncontrolled inflammation. IL-6 blockade has not to date been associated with adverse pregnancy outcomes, although this data requires extension and validation. 2 cases of renal agenesis have been reported in children born to mothers with anakinra, but the very small numbers of exposed parents warrants further examination of this observation and the careful study of ongoing pharmacovigilance data to explore this observation.
Secondly, success with IL-6 inhibition has been reported in a series of patients with familial Mediterranean fever, the most common autoinflammatory disorder, but this treatment does not feature in the most recent European guidelines for this condition. IL-6 inhibition is well-established in the treatment of adult-onset Still's disease (AoSD) however, and this lady's presentation shares important features with that condition. The existence of TNF-receptor 1 mutations has been reported in patients with AoSD, and it may be that this patient's presentation is more akin to adult-onset Still's disease and that her TNF receptor mutation is an incidental finding.
Key learning points: This report adds to the handful cases in which IL-6 blockade has been used successfully to treat the autoinflammatory manifestations of suspected TNF receptor 1 associated periodic syndrome (TRAPS) after the failure of IL-1 receptor blockade with anakinra.
Careful history and examination are required to differentiate between potentially overlapping symptoms of drug reaction, autoinflammation, and infection in patients with systemic autoinflammatory disorders (SAIDs). Once a history consistent with autoinflammatory flare was established, cautiously rechallenging with an IL-6 pathway inhibitor ensured this effective treatment was not discounted due to concerns over a drug reaction.
With a degree of commonality between the more common conditions in the SAID family, a detailed examination of the clinical phenotype is essential to the interpretation of genetic tests used for the diagnosis of TRAPS and related disorders.
Uncontrolled inflammatory disease is associated with pregnancy morbidity and very limited information is available about the short and long-term safety of treatments for autoinflammatory diseases in general. Current guidelines do not recommend the use of IL-6 inhibitor therapy in pregnancy.
Conflict of interest: The authors declare no conflicts of interest.