NHS England Specialised Services

Clinical panel report

Date: 15 May 2024

Intervention: Etanercept and adalimumab

Indication: deficiency of adenosine deaminase type 2 (aged 5 years and older)

URN: 2319

Gateway: 2, Round 1

Programme: Blood and Infection

CRG: Specialised Immunology and Allergy Services

Information provided to the Panel

Policy Proposition

Two Evidence Reviews completed by Solutions for Public Health

Two Clinical Priorities Advisory Group (CPAG) Summary Reports

Evidence to Decision (EtD) Summary

Equalities and Health Inequalities (EHIA) Assessment

Patient Impact Assessment (PIA)

Four Blueteq® Forms – initiation and continuation for adults and Medicines for Children policy access.

Policy Working Group (PWG) Appendix

This Policy Proposition recommends the off-label use of etanercept and adalimumab as treatment options for people aged 5 years and older with a confirmed diagnosis of deficiency of adenosine deaminase type 2 (DADA2).

DADA2 is a rare, inherited disorder caused by autosomal recessive mutations in the ADA2 gene which results in inflammation in the blood vessels (vasculopathy/vasculitis), dysregulated immune function, and/or abnormalities in blood counts due to an excess secretion of proteins that cause inflammation such as tumour necrosis factor (TNF). Vasculitis is a predominant feature which can lead to early-onset strokes and peripheral vascular disease. Without adequate treatment, patients continue to have vasculitic events that can lead to progressive organ damage and death. Mortality is estimated to be approximately 8% for patients under 30 years of age.

Etanercept and adalimumab are both TNF inhibitors that block the action of the protein TNF. Both medicines are given subcutaneously. There is currently no commissioned treatment for DADA2 in England. Panel members were informed that the care of patients is decided locally and this can lead to inconsistency between centres.

The estimated prevalence in England is approximately 250 cases and estimated incidence is 23 new cases/year, although this will likely increase by an uncertain amount as DADA2 has been added to the Generation Study gene list.

The two evidence reviews were presented to Panel members.

For both reviews, the critical outcomes for clinical effectiveness were number of ischaemic events, disease activity/response and symptom alleviation. Important outcomes were steroid use reduction, quality of life, hospitalisation and change in acute phase reactants. No evidence relating to quality of life, hospitalisation, treatment effects in subgroups or cost effectiveness were identified for either review. The evidence presented for all critical and important outcomes for both reviews was reported as very low using modified GRADE.

The first evidence review of etanercept consisted of nine papers, from which retrospective case series data was presented for in scope study participants. Evidence of patient benefit compared to baseline was noted across studies for most measures of critical outcomes, although not for haematologic parameters of disease activity, and also for steroid use reduction. Improvements in acute phase reactant measurements were noted as well. The limited evidence on safety outcomes did not identify harms associated with etanercept treatment. Similar clinical effectiveness and safety results were noted for the second review of adalimumab which consisted of six papers from which retrospective case series data was presented for in scope study participants.

Limitations of the studies presented were discussed including the lack of comparison with standard care, narrative presentation of results, lack of statistical analyses and very small numbers of study participants.

The proposition and supporting documents were considered and questions for clarification raised. A query was raised regarding the sequencing of diagnostic testing prior to treatment as stated in the inclusion criteria. An explanation was given, and no amendments required.

EHIA – no amendments requested.

PIA – no amendments requested.

Blueteq® Forms - The Policy Proposition has been drafted on the available evidence which is in those aged 5 years and over. However, because the Children’s British National Formulary notes children aged 2 years and over can receive etanercept and adalimumab treatment, children between ages 2-5 years will have access these treatments through the Medicines for Children Policy and so corresponding Blueteq® Forms have been drafted.

Recommendation

Clinical Panel agreed with the proposition and recommended this proceeds as a routine commissioning proposition.

Why the panel made these recommendations

The evidence and reported outcomes were considered carefully. Panel members discussed the very low certainty of the evidence but agreed that clinical benefit can be seen particularly in relation to ischaemic events and other critical outcomes.

Documentation amendments required

None

Declarations of Interest of Panel Members: One received relating to the interests of a partner.

Panel Chair: Anthony Kessel, Deputy National Medical Director, Specialised Services