ANTI-TNF DRUGS FOR CHRONIC NON-INFECTIONOUS UVEITIS IN ADULTS – A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Inês Leal1, Filipe B Rodrigues2, David Cordeiro Sousa3, Gonçalo Duarte2, Vasco C Romão6, Carlos Marques-Neves3, Manuel Monteiro-Grillo3, João Costa5, João Eurico Fonseca4

1Centro Hospitalar Lisboa Norte; Centro de Estudos das Ciências da Visão, Faculdade de Medicina, Universidade de Lisboa, 2Laboratory of Clinical Pharmacology and Therapeutics, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa; Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa; Centro Hospitalar Lisboa Norte; Centro de Estudos Ciências da Visão, Faculdade de Medicina, Universidade de Lisboa; 3Department of Rheumatology, Centro Hospitalar Lisboa Norte; Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa; 4Laboratory of Clinical Pharmacology and Therapeutics, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa; 5Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa; Evidence Base

Background: Non-infectious uveitis (NIU) comprises a group of inflammatory diseases of the uvea that results from an immune-mediated response to ocular antigens. Current treatment of this sight-threatening disease includes corticosteroids and immunomodulatory therapy. Although only formally approved in Europe since June 2016, anti-tumor necrosis factor (TNF) agents have been extensively used off-label in NIU.

Objectives: To assess the efficacy and safety of anti-TNF drugs for chronic NIU in adults.

Methods: DATA SOURCES: We searched CENTRAL, MEDLINE and EMBASE, from inception to September 2016. Clinical trial registries were also pursued, as were grey literature and reference lists from included studies. STUDY ELIGIBILITY CRITERIA: parallel-designed randomised controlled trials (RCTs) of any duration, assessing efficacy and safety of any anti-TNF versus control interventions in adults with chronic NIU. The control arm comprised patients not receiving anti-TNF, including placebo interventions. PARTICIPANTS: adults with a clinical diagnosis of chronic NIU, irrespective of the aetiology. STUDY APPRAISAL AND SYNTHESIS METHODS: risk of bias of individual studies was assessed using the Cochrane risk of bias tool. Two additional domains were added: for-profit bias, and prospective trial registration. Rate ratios and risk ratios were pooled from raw data through random effects model meta-analysis. When appropriate, a generic inverse variance model was used to meta-analyze rate ratios and a Mantel-Haenszel model for risk ratios. Overall quality of the evidence was assessed according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) standards. Statistical heterogeneity was calculated via I² statistic. PROSPERO registration number: CRD42016039068.

Results: After de-duplication, a total of 1157 references were considered. Twenty references were examined in full-text, and three studies were included in the final analysis. Etanercept was compared to methotrexate in one small RCT enrolling 20 patients with active NIU. The remaining two studies compared adalimumab versus placebo for active and inactive NIU, respectively. The overall risk of bias was moderate. In patients with active NIU, the adalimumab group showed an increased likelihood of visual acuity (VA) preservation (risk ratio 1.75, 95% CI 1.32 to 2.32, n=217), whereas the etanercept group showed a decreased likelihood of VA preservation (risk ratio 0.81, 95% CI 0.57 to 1.14, n=20). In patients with inactive NIU, adalimumab group was also associated with increased likelihood of VA preservation (risk ratio 1.31, 95% CI 1.12 to 1.53, n=226). The rate of adverse events did not differ between the anti-TNF drugs and control arms (rate ratio 1.03, 95% CI 0.94 to 1.13, n=410, I²=37%), nor of serious adverse events (rate ratio 1.48, 95% CI 0.84 to 2.63, n=410, I²=17%). LIMITATIONS: We included one trial at high risk for reporting bias for which prospective clinical trial registration was unavailable. All trials were industry-funded.

Conclusions and implications of key findings: There is moderate quality evidence that adalimumab is associated with a lower risk of VA worsening in both active and inactive NIU patients comparing with placebo. Anti-TNF drugs do not seem to increase the rate of adverse events and serious adverse events. Since published evidence is scarce, long-term RCTs will help to clarify the efficacy and safety of anti-TNF drugs in NIU patients.