Potential anti-TNF response biomarker identified

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DNA methylation has been identified as a potential biomarker of response to etanercept and adalimumab in patients with rheumatoid arthritis (RA) according to preliminary results from one of the largest methylome-wide investigations of treatment response to anti-TNF therapies.[1] These data, presented today at the European League Against Rheumatism Annual Congress (EULAR 2014), bring clinicians a step closer to being able to personalise a patient's treatment pathway.

Anti-TNF therapies have proved a huge advance for the treatment of rheumatoid arthritis and have transformed the treatment of inflammatory arthritis for millions of people around the world. However, only 20-40% of patients achieve a good response according to EULAR criteria.[2]

"It can take several years to identify the most effective treatment for an RA patient. This is not only costly in terms of the financial burden, but also in terms of patient outcomes and the irreversible joint damage that is being done," said Amy Webster, University of Manchester, United Kingdom. "Because of this, the identification of biomarkers that can predict a patient's response to a treatment is an important area of research which will allow the most effective treatment for each patient to be identified early in the course of the disease."

She continued, "Based on recent studies showing a role for epigenetics in RA and other autoimmune disorders, we hypothesised that epigenetic changes, such as DNA methylation, may provide potential biomarkers of

response to anti-TNFs."

RA is a chronic systemic disease that affects the joints, connective tissues, muscle, tendons, and fibrous tissue. A disabling condition that often causes pain and deformity, symptoms of RA tend to appear between the ages of 20 and 40. The prevalence of RA globally varies between 0.3% and 1% and is more common in women and in developed countries. Within 10 years of onset, at least 50% of patients in developed countries are unable to maintain a full-time job.[3] In this study, patients were selected from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) longitudinal cohort based on having an extreme response phenotype after three months of treatment with etanercept or adalimumab. Of the patients in the study, 36 patients were good responders to etanercept and 45 to adalimumab as defined by having an endpoint of DAS28 0.01 were removed. Differentially methylated positions between responders and non-responders were identified using the F-test following quantile normalisation.

In the etanercept study, four CpG* sites showed differential DNA methylation that passed a false discovery rate of 0.05, while in the adalimumab study less significant results were observed. The most differentially methylated position in etanercept patients mapped to the LRPAP1 gene ($p=1.46x10^{-8}$). This gene encodes a chaperone of low density lipoprotein receptor-related protein 1 (LRP1) which is known to influence TGF-β activity. Technical validation of methylation at this site by pyrosequencing showed very good correlation (Spearmans r=0.8). In the adalimumab patients, the most differentially methylated position maps to the PDZD8 gene. Joint analysis of the two drugs together identified a differentially methylated region overlapping the CRYZ and TYW3 genes, which have previously been associated with inflammation and Type 2 diabetes.[4]

More information: Abstract Number: OP0257

1 Webster A, Plant D, Eyre S et al. Differential DNA methylation related to response to adalimumab and etanercept in patients with rheumatoid arthritis. EULAR 2014; Paris: Abstract OP0257
2 Hetland ML, Christensen J, Tarp U et al. Direct Comparison of Treatment Responses, Remission Rates, and Drug Adherence in Patients With Rheumatoid Arthritis Treated With Adalimumab, Etanercept, or Infliximab. Arthritis Rheum 2010; 62(1): 22
3 Chronic diseases and Health Promotion: Chronic Rheumatic Conditions, World Health Organisation. www.who.int/chp/topics/rheumatic/en/. [Accessed 06/06/2014] 4 Qi Q, Menzaghi C, Smith S et al. Genome-wide association analysis identifies TYW3/CRYZ and NDST4 loci associated with circulating resistin levels. Hum Mol Genet 2012; 21(21):4774-80

* CpG sites – regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases along its length

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