90% of ACPA-IgGs harbour N-linked glycans in the antibody variable (V) domain. The corresponding N-glycosylation sites in the amino acid backbone of ACPA V-regions result in somatic hypermutation, a T cell-dependent process. Notably, both genetic evidence and data obtained from the analysis of serum ACPA indicate that T-cells drive the maturation of the ACPA-response prior to the onset of arthritis.

**Objectives:** We investigated whether ACPA-IgG carry V-domain N-glycans prior to the development of arthritis and whether the occurrence of such glycans predicts the transition from pre-disease autoimmunity to overt RA.

**Methods:** Two independent sets of serum samples were obtained from RA patients and from ACPA-positive first-degree relatives (FDR) of RA-patients (n=126) of an Indigenous North American (INA) population with high incidence rates of ACPA-positive RA. These samples comprised cross-sectional and longitudinal samples of individuals who did or did not transition to inflammatory arthritis. Serum ACPA-IgG were affinity-purified and subjected to enzymatic glycan release and UHPLC-based glycan analysis.

**Results:** ACPA-IgG V-domain glycosylation could be detected in RA patients and in FDR of RA patients. In both datasets, FDR-derived ACPA-IgG displayed markedly lower levels of V-domain glycans (<50%) compared to ACPA-IgG from RA-patients. Notably, FDRs that later developed RA showed extensive V-domain glycosylation before the onset of arthritis. Moreover, the degree of ACPA-IgG V-domain glycosylation in FDRs was strongly associated with future development of RA (HR: 6.07 [95% CI: 1.46-25.2]; p=0.013).

**Conclusion:** Glycosylation of the ACPA-IgG V-domain can be detected prior to the onset of disease. Extensive glycosylation is present in a subset of predisposed FDRs of INA RA patients. The presence of this feature substantially increases the risk of RA development. This finding provides a novel cell-division marker with a pivotal role for T cells in the selection and expansion of ACPA-expressing B cells, possibly by facilitating the introduction of N-glycosylation sites in ACPA-IgG V-domains. Moreover, glycosylation of the ACPA-IgG V-domain represents a predictive marker for RA development in ACPA-positive individuals and may serve to better time and target preventive therapeutic interventions.

**Disclosure of Interests:** Lise Halkenscheid: None declared, Emma C. de Moel: None declared, Irene Smolik: None declared, Stacy Tanner: None declared, Bas C. Jansen: None declared, Albert Bondt: None declared, Manfred Wurher: None declared, Thomas Huizinga Consultant for: Merck, UCB, Bristol Myers Squibb, Biostat AG, Pfizer, NSK, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience Inc., Nycomed, Boehringer, Takis, Euphos, Eli Lilly, Rene Toes Grant/research support from: Sanofi, Han El-Gabalawy: None declared, Hans Ulrich Scherer Grant/research support from: Sanofi, EU DOI: 10.1136/annrheumdis-2019-eular.7067

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**ABERRANT ADENOSINE TO INOSINE RNA EDITING IN ACTIVE RHEUMATOID ARTHRITIS**

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**Background:** Adenosine to inosine (A-to-I) RNA editing is a widespread post-transcriptional RNA modification mainly located in repetitive Alu elements and mediated by the enzyme adenosine deaminase acting on RNA-1 (ADAR1). A-to-I RNA editing controls various aspects of RNA metabolism, which may affect tissue-specific gene expression. Although deregulation of RNA editing has been previously reported in various human diseases including cardiovascular disease and cancer (Stellos et al., Nat Med, 2017; Liu et al., Nat Med, 2019 and Ishizuaka et al., Nature, 2019), its role in autoimmune diseases and especially in rheumatoid arthritis (RA) remains unknown.

**Objectives:** To study whether A-to-I RNA editing is involved in the pathogenesis of RA and to determine the impact of anti-rheumatic treatment on RNA editing.

**Methods:** We first analysed the expression of ADAR1 in 185 RA synovial tissues versus 76 healthy/osteoarthritic synovia derived from 4 independent RNA-sequencing and microarray datasets. We validated the findings in peripheral blood mononuclear cells (PBMCs) derived from 19 patients with active RA vs 14 controls and performed an additional ADAR1 isoform analysis (ADAR1p110/ADAR1p150) by RT-qPCR. Further, we studied in single nucleotide level the A-to-I RNA editing levels of the pro-inflammatory gene cathepsin S (CTSS) 3' untranslated region (3' UTR), a matrix degradation enzyme which is a well-established target of ADAR1, by Alu Sanger sequencing and RNA editing analysis. Last, we examined the effect of anti-rheumatic treatment on RNA editing.

**Results:** Expression of the RNA editor ADAR1 was significantly increased in RA synovium compared to healthy or osteoarthritic synovia. Similarly, a significant increase of ADAR1, mainly due to an increase of the interferon-inducible ADAR1p150 isoform, was observed in PBMCs from active RA. Next, we studied the RNA editing levels in PBMCs from active RA patients before and after 12-week treatment versus controls. RNA editing of CTSS 3' UTR AluSx was increased in active RA (6.47% increase in editing rate of 8 individual adenines, all P<0.05). Increased CTSS mRNA expression in RA PBMCs was associated with both ADAR1p150 expression (r=0.623, P=0.004) and RNA editing rate of 12 individual adenines (r=range 0.45-0.72, P<0.05 for all) located within the CTSS 3' UTR AluSx. The correlation between CTSS and ADAR1 was also observed in synovial tissue. Notably, 3'UTR expression and RNA editing rate reached control levels after 12-week treatment with methotrexate ± corticosteroids and/or biologics in patients with good clinical response (EULAR responders) but remained unchanged in the EULAR moderate/non-responders.