7 CHANGES IN IGG-FC N-GLYCAN SIALYLATION, GALACTOSYLATION AND FUCOSYLATION INFLUENCE DISEASE ACTIVITY DURING AND AFTER PREGNANCY IN RHEUMATOID ARTHRITIS

Albert Bondt,[1,2] Maurice H J Selman,[2] Johanna M W Hazes,[1] André M Deelder,[2] Manfred Wuhrer,[2] Radboud J E M Dolhain[1] *[1]Department of Rheumatology, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Biomolecular Mass Spectrometry Unit, Department of Parasitology, Leiden University Medical Center, The Netherlands*

10.1136/annrheumdis-2011-201234.7

Background and objectives Pregnancy is known to be a naturally occurring tolerisation in rheumatoid arthritis (RA). RA improves during pregnancy but flares after delivery.[1] Recent publications suggest a role for N-glycosylation of the Fc-fragment of IgG herein.[2] Previous studies mainly focused on changes in galactosylation (Gal). However, animal studies suggest a more important role for sialylation (SA) in the process of immune suppression.[3] Fucosylation is also reported as an immunomodulatory feature by affecting binding to the Fcγ-receptor III via a carbohydrate-carbohydrate interaction.[4] This study describes how changes in glycosylation of IgG are associated with decreased disease activity in RA during pregnancy and the flare after delivery.

Materials and methods Sera were obtained before pregnancy, three times during pregnancy and three times after delivery from RA-patients (n=251) and healthy controls (n=32) participating in a prospective cohort study on RA and pregnancy (PARA study). At all timepoints the Disease Activity Score incorporating 28 joints (DAS28-3 (CRP)) was assessed and medication was recorded.

The glycosylation states of tryptic Fc-glycopeptides of Protein G captured IgGs were analysed subclass specific (IgG1, 2/3 and 4) using a newly developed, fast and robust mass-spectrometric method.[5]

Results In patients and controls it was found that during pregnancy Gal (in patients for IgG1 from 59.8±1.1% to 65.3±1.0%; mean±SEM) and SA (in patients for IgG1 from 19.1±0.5% to 21.8±0.5) increase, while fucosylation (in patients for IgG1 from 94.1±0.4% to 93.7±0.4%) decreases. These changes were all associated with improvement of RA. The relative increase in sialylation was more pronounced than the increase in galactosylation ($p<0.01$) on all IgG subclasses. Linear regression analysis showed that both changes in Gal as well as SA were independently associated with improvement of RA. After delivery

levels of Gal and SA decrease, while fucosylation increases. This was associated with a relapse of disease activity.

Conclusions and discussion Galactosylation, sialylation and fucosylation change during pregnancy and are correlated with disease activity. In contrast to animal studies the results of this study show that in humans not only sialylation, but also galactosylation might be involved in improving disease activity of RA during pregnancy. The molecular mechanism still has to be unravelled. Whether the immunomodulatory properties resulting from changes in glycosylation of IgG are due to influencing the interaction with Fcγ-receptors will be the subject of future research.

Funding This research project is financed by the Dutch Arthritis Association.

REFERENCES

1. **de Man YA**, Dolhain RJ, van de Geijn FE, *et al.* Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008;**59**:1241–8.
2. **Van de Geijn** FE, Wuhrer M, Selman MHJ, *et al*. Immunoglobulin G galactosylation and sialylation are associated with pregnancy-induced improvement of rheumatoid arthritis and the postpartum flare: results from a large prospective cohort study. *Arthritis Res Ther* 2009;**11**(6):p R193.
3. **Kaneko Y**, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. *Science* 2006;**313**:670–3.
4. **Ferrara C**, Grau S, Jäger C, *et al.* Unique carbohydrate-carbohydrate interactions are required for high affinity binding between FcgammaRIII and antibodies lacking core fucose. *Proc Natl Acad Sci USA* 2011;**108**:12669–74.
5. **Selman MHJ,** Derks RJE, Bondt A, *et al.* Fc specific IgG glycosylation profiling by robust nano-reverse phase HPLC-MS using a sheath-flow ESI sprayer interface. *Journal of Proteomics*;2011.(In Press).