Tocilizumab Demonstrates Superior Inhibition of MMP-Mediated Basement Membrane Collagen Degradation Compared to Methotrexate or Placebo

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BACKGROUND

Rheumatoid arthritis (RA) pathogenesis involves a range of immune cells, for instance **T-cells, neutrophils and macrophages**. They produce proinflammatory factors, such as proteolytic enzymes, which interact with tissue components such as collagens, leading to a release of unique tissue fragments into the circulation.

Type IV collagen is a basement membrane supporting endothelium and epithelium. From previous studies, we know that T-cell activity may be quantified by measuring C4G, a metabolite of Granzyme B (a cytotoxic granule enzyme) mediated degradation of type IV collagen, while C4M is a marker of MMP activity.

Quantifying these unique metabolites reflecting the **interaction between immune cell and type IV collagen** may provide a deeper understanding of the tissues affected by RA and be more relevant to disease activity and progression than simply quantifying the immune cell number or cytokines.

The objective was to investigate the association between the unique immune cell activity metabolites C4G and C4M, and clinical outcomes in RA before and after intervention with tocilizumab, methotrexate (MTX) and placebo.

METHODS

This is an explorative post-hoc analysis of left-over samples from the AMBITION trial (NCT00109408). The two biomarkers were measured pre- and post-treatment serum samples (8 weeks) in **169 biological naïve RA patients treated with either tocilizumab (TCZ, 8 mg/kg), placebo** or methotrexate (MTX) monotherapy (7.5-20 mg/kg).

Biomarker levels were correlated to clinical outcomes by Spearman's correlation. Comparison between treatment and treatment groups were done by ANCOVA, adjusted for baseline biomarker levels, age, sex, BMI, and disease duration.

Table 1.
Patient overview

Variable	Mean (IQR) or %
Age (years)	50 (42-59)
Sex	79 % females
BMI (kg/m2)	26.0 (22.9-30.0)
RA duration (years)	3.1 (0.6-10.0)
Sera pos.	100 %
DAS28	6.9 (6.3-7.4)
CRP (mg/dL)	2.24 (0.85-4.3)
SJC	17 (12-24)
TJC	31 (22-39)
VAS Pain	62 (49-79)

RESULTS

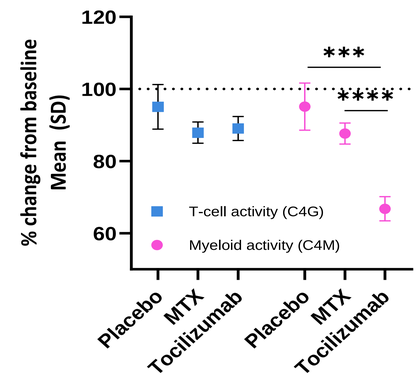
Table 2
Correlation (r, p values) of C4G and C4M with baseline variables .

Baseline variable	C4G	C4M
CRP	0.089 Ns	**0.681** **<0.0001**
AGE	**-0.241** **0.0016**	-0.058 Ns
BMI	-0.08 Ns	0.085 Ns
RA duration	-0.042 Ns	-0.11 Ns
SJC	**0.164** **0.033**	**0.185** **0.016**
TJC	0.133 Ns	0.057 Ns
VAS PAIN	-0.044 Ns	0.064 ns
DAS28	0.024 Ns	**0.29** **0.0001**
ESR	-0.125	**0.428** **<0.0001**
HAQ	0.036	**0.304** **0.0001**
C4M	0.097	-

This study investigated type IV collagen degradation

- Patient had high activity at baseline (table 1)
- Serum C4G and C4M was not correlated (table 2).
- Tocilizumab had a great effect on myeloid activity, but not on T-cell activity

Table 3
C4M, but not C4G, was reduced in response to tocilizumab.



CONCLUSION

Type IV collagen is a basement membrane protein important for tissue integrity. It is degraded during RA leading to a destabilized tissue. The two biomarkers C4G and C4M were differentially associated with clinical outcome measures. Importantly, only C4M, MMP-derived tissue destruction, could be inhibited by tocilizumab. None of the markers were modulated by MTX.

Contact: Dr Anne Bay-Jensen, Disclosures: SFM is a former employee of Nordic Bioscience, ACBJ, DS, MB, PD and MAK are share Holders of Nordic Bioscience