Innate immunity in rheumatic diseases

POS0364 EFFECT OF BIOLOGIC DMARDS TREATMENT ON GENE EXPRESSION AND ACTIVITY OF NATURAL KILLER CELLS IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is the most common inflammatory type of arthritis, with various immune players implicated in its pathogenesis. Natural killer (NK) cells are innate lymphocytes that showed controversial roles in RA, whether pathogenic or protective (Shegarfi, H. et al. 2012, Yap, H.-Y. et al. 2018). Previously, we were able to identify a gene signature in NK cells of RA patients that can aid in understanding the state of NK cells in RA disease and identify RA patients from healthy controls (Elemam, N.M. et al. 2019, Elemam, N.M. et al. 2020). Furthermore, this signature might facilitate the selection of biomarkers that can be used for early detection of RA and prediction of effectiveness of RA treatment.

Objectives: In this study we aimed at exploring the effect of several RA therapeutic agents such as tocilizumab, rituximab and anti-TNFα (adalimumab, etanercept and golimumab) on the previously identified gene signature in NK cells of RA patients.

Methods: Whole blood transcriptomic data from publicly available dataset (GSE93272) was used to predict the percentage of activated NK cells in the blood of RA patients using the software CIBERSORT. Then, a correlation analysis was done between the percentage of NK cells and number of days of receiving tocilizumab treatment. Whole blood samples were collected from the recruited 17 RA patients (satisfying the 2010 ACR/EULAR classification criteria for RA). NK cells were isolated using RosetteSep negative selection method and RNA was extracted and gene expression was assessed using qRT-PCR. RA patients taking tocilizumab, rituximab, or anti-TNFα (adalimumab, etanercept or golimumab but none of the patients received infliximab) were compared to those not receiving any biological DMARDs. Statistical analysis was done using Student's t-test.

Results: In silico analysis has shown that the percentage of activated NK cells is positively correlated with the number of days of tocilizumab therapy in RA patients, suggesting a direct enhancing effect of tocilizumab on NK cell activity. Then, it was crucial to investigate the effect of different biological DMARDs on NK gene expression in RA patients. All the investigated chemokines (CCL2, CXCL10, CXCL16, CXCR1, CXCR2, CXCR6 and CCR4) in the identified gene signature showed a significant change in RA patients receiving tocilizumab, rituximab, or anti-TNFα therapies. Furthermore, the other genes including RELA, ICAM, IL1RN, TLR3 and TLR10 were significantly changed in NK cells of RA patients receiving biological DMARDs in comparison to patients not receiving the treatments. However, some of the genes including CD56, BTK, IBTK, ITGB7, IL1B, PECAM-1, IL12RB2, IFNG and CKLF did not show a significant change upon receipt of biological DMARDs.

Conclusion: In conclusion, NK cell activity and gene expression could be affected by the type of biological DMARDs received by RA patients. Therefore, this identified gene signature of NK cells could be used as a diagnostic tool to identify RA patients and a target for biological DMARDs in RA.

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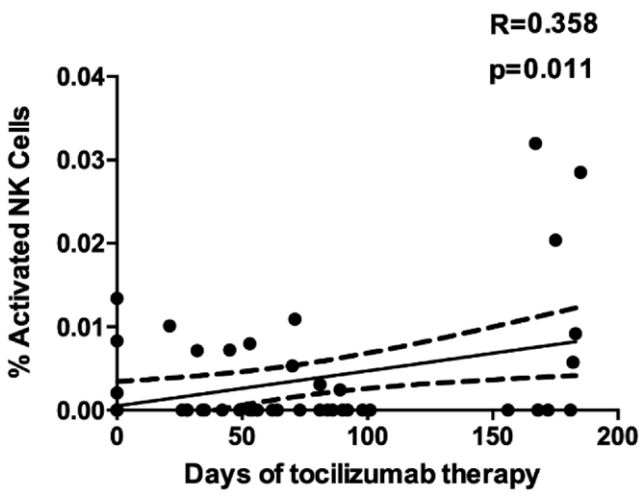

Figure 1. In silico analysis and correlation of NK cell activity with the number of days of Tocilizumab therapy in RA patients.

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POS0365 ANTI-TNF GLUCOCORTICOID RECEPTOR MODULATOR ANTIBODY DRUG CONJUGATE FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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Background: Glucocorticoids (GC) are potent drugs used for treating many inflammatory diseases. While GCs are effective in many immune diseases, dose and duration of administration is limited due to significant side effects. Resting immune cells have very little TNF expression on the cell surface and it is only in an activated state that TNF expression is upregulated. Upon immune cell stimulation, TNF is upregulated and although a significant amount of TNF is cleaved from an activated cell, a portion remains on the cell surface. We have observed that anti-TNF antibodies bind to transmembrane TNF (tmTNF) and undergo endocytosis to the lysosome (1). We have developed a stable antibody drug conjugate (ADC), ABBV-3373, that has a proprietary, highly potent, glucocorticoid receptor modulator (GRM) payload linked to an anti-TNF monoclonal antibody (mAb) that is able to deliver the GC payload to activated immune cells.

Objectives: We hypothesized that a TNF ADC with a GRM payload would be able to deliver increased efficacy through both TNF inhibition and targeted GRM payload delivery to activated immune cells while sparing systemic glucocorticoid side effects.

Methods: A mouse surrogate TNF GRM ADC was characterized in an acute *in vivo* contact hypersensitivity model of inflammation (CHS) and in a mouse model of collagen induced arthritis (mCIA). Additionally, the human anti-TNF GRM ADC, ABBV-3373 has been characterized in healthy volunteers.

Results: In the CHS model the anti-TNF GRM ADC significantly inhibited the inflammatory response with minimal effect on systemic GC biomarkers. In mCIA a single dose of an anti-TNF GRM ADC, administered at disease onset, was able to completely inhibit arthritis for greater than 30 days while an anti-TNF mAb only partially inhibited disease. ABBV-3373, a human anti-TNF GRM ADC with a GC payload, was evaluated in a Phase 1 study in healthy volunteers. ABBV-3373 demonstrated antibody-like PK profile and ABBV-3373 did not impact cortisol levels at predicted efficacious doses while control subjects that received a single oral dose of 10 mg prednisone demonstrated expected decreases in cortisol levels.

Conclusion: These data suggest that an anti-TNF ADC delivering a GRM payload into activated immune cells may provide improved efficacy in immune mediated diseases, while minimizing systemic side effects associated with standard GC treatment.

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