Proceedings Paper:
Ouboussad, L, Wong, C, Hunt, L et al. (4 more authors) (2017) Effect of tocilizumab therapy on il-6 signalling pathway in early rheumatoid arthritis patients. In: Annals of the Rheumatic Diseases. EWRR, 02-04 Mar 2017, Athens. BMJ Publishing Group , A40-A40.

https://doi.org/10.1136/annrheumdis-2016-211049.24

EFFECT OF TOCILIZUMAB THERAPY ON IL-6 SIGNALLING PATHWAY IN EARLY RHEUMATOID ARTHRITIS PATIENTS

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Background and objectives

We previously reported increased constitutive but unchanged induced CD4+ p-STAT3 in established RA versus healthy control (HC) (1).

This study aims to evaluate in early RA (ERA) (i) cell-subset constitutive and Cis (IL-6) and Trans (IL-6/sIL6R)-induced IL-6 signalling (ii) effect of tocilizumab (TCZ; +/-MTX) (iii) for an association between baseline phosphorylation intensities and TCZ (+/- MTX) response.

Materials and methods

Multiparameter phosphoflow cytometry was performed on 20 treatment-naïve, ERA patients randomised to TCZ monotherapy or TCZ-MTX to determine STAT3, Akt and Erk phosphorylation intensities. PBMCs were isolated and cryopreserved at baseline, and weeks 24 and 48 post-TCZ. HC samples (n=10) were also obtained. PBMCs were unmodulated, stimulated with IL-6 or soluble IL-6 receptor (sIL-6R) and median fluorescence intensities (MFI) were measured.

Results

Baseline data, HC & ERA

Constitutive CD4+ p-STAT3 was numerically higher in ERA compared to HC, with non-significant increase following stimulation in both groups.

There was no significant difference in constitutive monocyte p-STAT3 in HC vs ERA. Stimulation did not induce further increase in monocyte p-STAT3 in ERA.

Constitutive CD4+ p-Akt was significantly higher in ERA versus HC (p=0.01), with no change post-stimulation.

Pre/Post TCZ in ERA

Constitutive CD4+ pSTAT3 expression did not alter following TCZ exposure.

Statistically significant decreases in IL-6 stimulated CD4+ pSTAT3 expression from baseline to weeks 24 and 48 were observed (p=0.005 and 0.01 respectively); and similarly using IL-6/sIL-6R at week 48 (p=0.01).

Constitutive monocyte p-STAT3 expression appeared to increase at week 24 compared to baseline (p=0.03); similar observation following stimulation with IL-6/sIL-6R at both weeks 24 and 48 was observed (p=0.01)

TCZ led to non-significant decrease in constitutive and IL6-stimulated CD4+ p-Akt expression weeks 24 and 48. TCZ otherwise had no significant effect on p-Akt and p-Erk in other studied cell subsets.

Conclusions

TCZ reduced induced IL-6 signalling via CD4+ STAT3. This preliminary analysis also suggests importance of monocyte subset and relevance of Akt in IL-6 signalling. Complete analysis of these data will clarify the relative roles and impact of IL-6R targeting further.

References

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