17 DECREASED INTERLEUKIN-6 RECEPTOR (IL-6R α) AND INCREASED SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3) PHOSPHORYLATION IN RHEUMATOID ARTHRITIS (RA) ARE REVERSED BY IL-6R α BLOCKADE

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10.1136/annrheumdis-2011-201230.17

Background and objectives Increased IL-6 would be expected to decrease IL-6R α and the phosphorylated form of Stat3 (pStat3). The anti-IL6R α antibody tocilizumab is effective in RA and blocks inflammation. The authors therefore analysed the situation in RA, and the effects of tocilizumab in rheumatoid arthritis (RA) patients.

Materials and methods Lymphocytes of 33 RA patients were compared to those of 25 healthy individuals (HC). Ten RA patients were subsequently treated with tocilizumab with follow up samples under this therapy. Serum CRP was determined in clinical routine. PBMC were immediately prepared from peripheral venous blood. For determining the percentage of IL-6R α (CD126) positive cells, PBMC were stained with PE-labelled anti-CD126 or control antibodies. For the determination of pStat3, cells were analysed unstimulated or stimulated with IL-6 (0.5 mg/ml) for 10 and 15 min, fixed with formaldehyde (2%), permeabilised with methanol (80%), and stained with PE-labelled anti-pStat3 or control antibodies. Cells were analysed on a Becton Dickinson FACSCalibur fluorocytometer, gating for lymphocytes. Mean fluorescence intensity (mfi) was used as a semiquantitative measure for pStat3 contents.

Results At baseline, the percentage of CD126+ RA lymphocytes was decreased (mean $\pm$ SD 46.3 $\pm$ 18.2% vs 55.0 $\pm$ 9.9% in HC, $p=0.02$) and negatively correlated with CRP (Pearson $r=-0.72$, $p=0.002$), but not disease activity (Spearman $r=0.23$, $p=0.44$ for CDAI). Baseline pStat3 was increased in RA lymphocytes (median (range) mfi 16.56 (8.82–60.49) vs. 13.84 (8.82–27.77) in HC, $p=0.02$). While IL-6 stimulation of HC lymphocytes led to a maximum mean increase in pStat3 of mfi 16.11 $\pm$ 7.60, this was much less pronounced in RA lymphocytes, with an increase of 5.61 $\pm$ 5.51, $p<0.0001$. Under IL-6R α blockade with tocilizumab, CD 126+ lymphocytes increased, and baseline pStat3 decreased, to normal levels (57.2 $\pm$ 17.7% and mfi 14.26 (8.88–36.27), respectively). The pStat3 increase upon IL-6 stimulation was almost completely abolished (mfi 16.29 (11.91–38.17) at 10 min, 17.64 (9.70–39.05) at 15 min).

Conclusions IL-6-dependent changes of IL-6R α on and pStat3 in RA lymphocytes are present, which correlate with CRP, but not clinical disease activity. These changes are reversed by therapeutic IL6R α blockade, which also renders lymphocytes hyporesponsive to in vitro IL-6 stimulation.