Background: Patients with active rheumatoid arthritis (RA) have increased cardiovascular mortality, paradoxically associated with reduced circulating lipid levels (1-3). Several disease-modifying antirheumatic drugs (DMARDs), such as the JAK inhibitor tofacitinib, ameliorate disease activity along with an increase in serum lipids (4, 5). We previously demonstrated in vitro that tocilizumab favored cholesterol efflux from macrophages through an ABCA1-dependent mechanism (6). Furthermore, tofacitinib-treated chronic arthritic rabbits showed increased circulating lipids and decreased lipid accumulation within the synovium (6).

Objectives: Our aim was to explore in vivo whether inflammation impedes cholesterol efflux from macrophages, and whether tofacitinib restores macrophage cholesterol release during chronic arthritis. For that purpose, we assessed the ability of intraperitoneally injected 3H-cholesterol labelled macrophages to efflux cholesterol to circulating lipoproteins in collagen-induced arthritis (CIA) mice treated with tofacitinib or placebo, as compared to healthy controls.

Methods: DBA/1J mice were randomly assigned to healthy controls (Control, n = 9), CIA (CIA, n = 6) and CIA mice receiving 50 mg/kg/day tofacitinib, orally, for three consecutive days, starting on day 39 after CIA induction and coinciding with disease peak (CIA+TOFA, n = 6). The day after, 3H-cholesterol labeled RAW264.7 macrophages were intraperitoneally injected into mice and tracer appearance was monitored in plasma lipoprotein subfractions, synovium, liver, bile and feces.

Results: The CIA group showed higher C-Reactive protein levels (CRP, g/ml; Control: 10.9±0.49, CIA: 13.86±1.05, p=0.03 vs. Control) and lower circulating 3H-cholesterol levels (% of injected disintegrations per minute (dpm)/ml; Control: 1.29±0.11, CIA: 0.92±0.11, p=0.04 vs. Control). Both serum CRP and 3H-cholesterol –particularly the HDL fraction– were restored to baseline after the treatment with the JAK inhibitor (CIA+TOFA: 10.97±0.67 g/ml and 1.37±0.20 % of injected dpm/ml, respectively, p=0.05 vs. CIA). Concomitantly, we observed an upward trend in 3H-cholesterol accumulation within the synovium of CIA animals as compared to controls, which tended to normalize with the treatment.

Conclusion: Systemic inflammation induces cholesterol sequestering within macrophages in vivo by acting on cholesterol efflux transporters (6). Tofacitinib favors cholesterol release to plasma lipoproteins, hence increasing circulating cholesterol. This is not only due to a decrease in inflammation –an effect very likely shared with some other biologic DMARDs–, but also to a direct mechanism on ABCA1 transporters that favors cholesterol efflux. To our knowledge, this is the first report suggesting that cholesterol dynamics in the macrophage may contribute to the overall circulating cholesterol levels by considering that this phenomenon may occur in other cell types, such as adipocytes.

REFERENCES

Disclosure of Interests: None declared