Conclusion: In the tofacitinib RA clinical programme, MACE were largely associated with BL CV risk in the overall cohort, consistent with results of ORAL Surveillance, although caution should be interpreted due to low pt-yrs of exposure in some pt groups. Noting this limitation, these findings emphasise the importance of assessing and addressing BL CV risk when treating pts with RA.

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COMPARISON OF THE EFFECT OF DIFFERENT JANUS KINASE INHIBITORS ON ACTIVATION, FUNCTION AND PROPERTY OF NK CELLS TO CONTROL CANCER CELL LINES PROLIFERATION: AN EX VIVO AND IN VITRO STUDY.

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Background: Janus kinase inhibitors (JAKi) are effective targeted synthetic DMARDs licensed in rheumatoid arthritis (RA) and other immune-mediated diseases. Among the adverse events described, the increased risk of herpes zoster is specific of this therapeutic class but variable depending on the drugs, especially lower with filgotinib (FILG0). Recently, the ORAL Surveillance study highlighted an increased risk of lymphoma and lung cancer with tofacitinib (TOFA) in RA patients older than 50 years with cardio-vascular risk factors. Because of their antitumor and antiviral role, especially against herpes viruses, effect of JAKi on NK cells may play a causal role in these adverse events. Our working hypothesis is that the different JAKi could have a differential impact on the activation and function of NK cells leading to the variability of the tolerance profiles observed between the molecules.

Objectives: To evaluate the phenotypic and functional impact of JAKi on NK cells.

Methods: We first performed ex vivo phenotypic analyses of NK cells in RA patients treated with TOFA or baricitinib (BARI) in comparison with patients treated with metothexate (MTX). To go deeper, we phenotyped sorted NK cells from healthy donors after 6 days of culture with 4 JAKi (TOFA, BARI, upadacitinib (UPA) and FILG0) or control (DMSO). We used 3 different doses carefully chosen to mimic in vivo exposure (therapeutic concentration (therap) defined as mean concentration in patients at the licensed dose, infra therapeutic (infra, mean -2SD) and supra therapeutic concentration (supra, mean +2SD)). Thirdly, we stimulated sorted NK cells from healthy donors exposed to TOFA or BARI at therapeut and supra concentrations with anti-NKp30 crosslinking to assess NK cells function: intra-cellular IFNγ/TNF production and degranulation (CD107a). Finally, we challenged sorted NK cells from healthy donors exposed in vitro to TOFA or BARI at therapeut and supra doses with 2 different tumor cells line to assess degranulation and cytotoxicity: a lung cancer line A549 and a lymphoma cell line SU-DHL-4.

Results: Twenty-eight RA patients were included in the ex vivo assay (12 MTX, 6 TOFA, and 10 BARI). Patients under TOFA and not under BARI had a significant reduced CD69 (an activation marker) expression on NK cells (p<0.05) compared to MTX. After in vitro culture of NK cells with JAKi, we confirmed the negative impact of JAKi on NK cells activation (CD69), maturation markers (CD57, Tim3) and activating receptor (NKp30), more pronounced with TOFA and UPA (Figure 1A). After crosslinking with anti-NKp30, NK cells exposed to TOFA produced significantly less IFNγ/TNF and expressed less CD107a compared to DMSO (p<0.005). There was a non-significant trend for a dose-effect (Figure 1B). BARI did not induce any significant effect. Lastly, when NK cells were co-cultured with the cancer cell lines, previous exposure to TOFA but not to BARI led to a significant reduction of CD107a expression on NK cells (p<0.005) and to reduced cytotoxicity (p<0.05) of NK cells versus A549 at therapeut dose. Studies regarding SU-DHL-4 are still in progress.

Figure 1. Impact of in vitro exposure to JAKi at therapeut and supra dose on NK cells regarding phenotype (A) and function after co-culturing (B).

Conclusion: JAKi have a phenotypic and functional dose-effect impact on NK cells activation, both in ex vivo and in vitro experiments. TOFA has more impact than other JAKi on NK cells phenotype and function and has the property to impair the control of proliferation of lung cancer and lymphoma cell lines by NK cells. The question remains open if this mechanism could explain the increased risk of lung cancer and lymphoma observed with TOFA in the ORAL surveillance trial.

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Disclosure of Interests: None declared


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