Methods Patients with symptomatic gout and elevated sUA (≥6 mg/dL) were treated with fixed doses of pegsiticase (0.2 mg/kg or 0.4 mg/kg) alone or co-administered with SVP-R (0.05, 0.08, or 0.1 mg/kg). SEL-212 was infused in 28 day cycles x3 doses followed by challenge with pegsiticase alone on 28 day cycles x2 doses. Safety, tolerability, sUA, and ADAs were monitored

Results In the SEL-212 Phase 1b study, 70% of patients administered 0.4 mg/kg pegsiticase with a mid-dose of 0.1 mg/kg SVP-R showed low or no ADA formation correlating with sustained low sUA levels for at least 30 days after a single dose, compared to 20% for patients treated with pegsiticase alone. In the ongoing Phase 2 study, the majority of patients receiving 0.1 mg/kg SVP-R administered with either 0.2 or 0.4 mg/kg pegsiticase also showed low or no ADAs and maintained low sUA levels after 3 monthly doses of SEL-212, indicating sustained activity with repeated doses of SEL-212. However after 2 subsequent doses of pegsiticase alone, a drop in activity was noted. These data suggest that either a higher dose of SVP-R or the addition of SVP-R at the 4th and 5th dose may be required to sustain activity through 5 months. Currently patients are being dosed with 0.15 mg/kg SVP-R, a dose level which enabled sustained control of sUA levels in all patients in Phase 1b. SEL-212 was generally well tolerated and associated with a low rate of gout flare rates compared to those treated with pegsiticase alone.

Conclusions SVP-R showed a dose-dependent reduction in ADAs and enabled sustained control of sUA with repeated dosing of SEL-212. SVP-R is a promising approach to prevent the formation of ADAs against immunogenic biologic therapies.

REFERENCE

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Disclosure of interest None declared.

Introduction Patients with rheumatoid arthritis (RA) are exposed to an increased risk of lymphoma and the impact of treatments is difficult to assess. Tofacitinib, an oral Janus Kinase (Jak) 3 and 1 inhibitor that has shown positive results in treating RA patients, may impair NK-cell function due to its inhibitory action on IL2 and IL15 signalling.

Objectives Given the fact that NK cells have been recently shown to participate to anti-lymphoma immunosurveillance, we aimed to assess if tofacitinib might impact NK-cell function and anti-lymphoma activity in vitro and in vivo in BAFF transgenic mice (a model of B cell autoimmunity associated with an increased risk of lymphoma).

Methods We have studied the consequences of in vitro exposure of NK to tofacitinib (10, 50 and 100 nM) or to DMSO (vehicle) during 6 days in presence of IL-2 (200 UI/ml): phenotype has been studied and cytotoxicity against 2 non-Hodgkin B-cell lymphoma cell lines [Farage (EBV+) and SU-DHL4 (EBV-)] was assessed. In addition, BAFF transgenic mice were treated for 6 months with tofacitinib (2.25 mg/kg/d n=11; 4.5 mg/kg/d n=10) or vehicle (PEG: DMSO, n=6). Incidence of lymphoma was assessed by histologic examination using a composite score.

Results Firstly, we did not observe difference concerning the survival of NK cells in presence of tofacitinib or vehicle after 6 day culture. Secondly, we observed that culture in presence of tofacitinib was associated with a decreased level of activation with a dose effect. In addition, we observed a decreased expression of activating receptors such as Nkp30, Nkp44 and Nkg2D. Last, we found that tofacitinib blocked NK cell maturation as observed with the significant decreased expression of CD57 on NK cells exposed to tofacitinib at 50 and 100 nM. These phenotypic abnormalities were associated with an impaired function of NK as assessed by co-culture: degranulation and cytotoxicity were significantly decreased after exposure to tofacitinib. In BAFF transgenic mice, the crude mortality and incidence of lymphoma did not differ between the 3 groups of treatment.

Conclusions This study demonstrates that tofacitinib treatment negatively impact the state of activation, maturation and functions of NK cells. These defects were not associated with a higher incidence of lymphoma in BAFF Tg mice after 6 months of exposure. However, this negative impact of tofacitinib on NK cells might participate to the increased risk of herpes zoster infection in patients treated with tofacitinib and suggest to remains cautious about a possible increased risk of lymphoma.

Disclosure of interest None declared.
Methods Human adipose-derived stem cells (hASCs) were encapsulated via a micromolding method. We first manufactured polydimethylsiloxane chips containing 1600 micromolds with a circular shape, 150 μm in diameter and 100 μm in depth. For cell encapsulation, a solution of 2% alginate (w/v) containing 3 million of hASCs per ml polymer was deposited onto the chips, loaded in the moulds either by sedimentation or centrifugation and crosslinked using an agarose gel charged with CaCl2. The number of encapsulated cells was evaluated by a CyQUANT assay immediately and 24 hour after encapsulation. The impact of encapsulation on metabolic activity was determined by a presto blue assay 24 hours after encapsulation and 24 hour after their injection through a 26G needle.

Results We successfully obtained cylindrical alginate microparticles presenting a diameter of 103±0.7 μm. Using cell quantification, we determined that the centrifugation method allowed the encapsulation of 30 333 (±5552) cells within one chip versus 6056 (±2862) by sedimentation. Cell number and metabolic activity remained stable for 24 hours after encapsulation. We also demonstrated that injection through a 26G needle had no impact on the viability of encapsulated cells.

Conclusions Our results show that micromolding allows hASCs encapsulation into alginate particles injectable through a 26G needle without impacting cell viability. Future work will focus on evaluating in vitro long-term encapsulated cell survival and functionality. In case of success, we will then consider intra-articular injection in an animal model of osteoarthritis.

Disclosure of interest None declared

P113 ARGINASE I AND THE METABOLIC CONTROL OF OSTEOCLASTOGENESIS

Introduction Osteoclasts are giant, multi-nucleated cells that derive from the monocyte-macrophage lineage and are regulators of bone turnover. Availability and catabolism of L-Arginine have been implicated with immune cell biology, skewing inflammatory responses within myeloid cells in a pro- or anti-inflammatory manner.

Objectives While the role of L-Arginine within certain myeloid lineages such as macrophages is well appreciated, its role within osteoclasts is relatively unknown. We therefore aim to investigate L-Arginine metabolism in the context of osteoclastogenesis.

Methods We analysed osteoclastogenesis of C57BL/6J wildtype bone marrow cells in vitro in the presence and absence of recombinant Arginase 1 (recArg1). This approach was complemented via qPCR analysis of relevant osteoclast marker genes and an extracellular flux assay. We further investigated the