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Acknowledgements: We thank Jean-Jacques Dubost medical rheumatologist France for sharing the questionnaire that we used in this research.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.7095

AB0484

MONOTHERAPY WITH FILGOTINIB, A JAK1-SELECTIVE INHIBITOR, REDUCES DISEASE SEVERITY AND ALTERS IMMUNE CELL SUBSETS IN THE NZB/W F1 MURINE MODEL OF LUPUS

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Background: Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterised by immune system hyperactivation leading to the production of autoantibodies and immune attack on multiple organs including the skin and kidneys. High levels of type I interferons (IFN α /b) alter the activation state of immune cell populations and have been identified as a risk factor for SLE. Antibody blockade of the interferon alpha receptor (IFNAR) has demonstrated clinical efficacy in a Phase 2b study in SLE, and validates targeting this pathway in SLE¹. Janus kinase 1 (JAK1) is critical for mediating downstream signalling of type I IFNs. Inhibition of JAK1, therefore, is anticipated to reduce IFN signalling, activation of immune cell subsets, and SLE disease activity. The JAK1 selective inhibitor filgotinib (FIL) is currently being evaluated in three proof-of-concept Phase 2 studies in SLE-like diseases.

Objectives: To characterise the efficacy and mechanism-of-action of FIL in the NZB/W F1 spontaneous mouse model of lupus in a therapeutic setting.

Methods: FIL was tested in the NZB/W F1 model of lupus at two concentrations (0.05% and 0.1%) formulated in chow and administered *ad libitum* from weeks 28–40. Cyclophosphamide (CP) was used as a positive control at 5 mg/kg, once daily, i.p. Efficacy was determined by changes in proteinuria, renal histopathology, and survival. Splenic cell populations were analysed by flow cytometry at study termination at week 40 to measure changes in immune cell subsets in diseased versus non-diseased mice and following FIL treatment. An *in vitro* murine whole blood pSTAT1 assay and PK exposure data were used to assess target coverage in the model.

Results: In the NZB/W model, FIL showed a dose-dependent decrease in proteinuria with a concomitant reduction in BUN levels, renal inflammation, improved glomerular morphology, and increased survival (table 1). Diseased mouse spleens had decreased frequencies of naive T cells, increased frequencies of CD11⁺dendritic cells (DCs), and an increased ratio of memory:naive T cells versus non-diseased mice. FIL treatment showed a dose-responsive reversal of these populations toward non-diseased levels. FIL inhibited *in vitro* IFN α -stimulated pSTAT1 signalling in T cells. Calculated JAK target coverage of pSTAT1 inhibition was similar to that observed in human studies at clinical doses.

Abstract AB0484 – Table 1. Efficacy scores in the NZB/W F1 model

	Placebo	FIL (0.05%)	FIL (0.1%)	CP (5 mg/kg)
Proteinuria ^a	30.72	29.03 (-5%)	23.40 (-24%)*	17.47* (-43%)
Survival	55%	73%	93%*	100%*
Glomerular diameter	3.66	2.10 (-43%)	0.83 (-77%)*	0.75*
Summed renal histology ^b	14.71	6.81 (-54%)	3.20 (-78%)*	0.37 (-90%)*
Glomerular myeloperoxidase	3%	2% (-52%)	1.1% (-101%)*	1.6% (-73%)*

^aUrine score AUC (week 28–40)

^bIncludes: glomerular diameter, protein casts, interstitial inflammation, and vasculitis p-values comparing % changes between treatment and placebo groups:

*p<0.05

Conclusions: FIL demonstrated efficacy in the NZB/W F1 murine model of lupus with an alteration of splenic immune cell subsets affected by type I IFNs toward non-diseased levels. This data provides the basis for the evaluation of FIL as monotherapy in the currently ongoing Phase 2 studies in lupus-related diseases.

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Disclosure of Interest: C. Pohlmeier Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, Z.-H. Cui Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, P. Han Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, A. Clarke Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, R. Jones Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, N. Mollova Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, I. Mikaelian Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, S. Zaboli Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, A. Shauf Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc, J. Di Paolo Shareholder of: Gilead Sciences, Inc, Employee of: Gilead Sciences, Inc

DOI: 10.1136/annrheumdis-2018-eular.3367

AB0485

COMPARATIVE EFFICACY OF TOFACITINIB AND BIOLOGIC DMARDS IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH INSUFFICIENT RESPONSE TO SUBCUTANEOUS METHOTREXATE IN CLINICAL PRACTICE

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Background: Tofacitinib (TOFA) – the first registered member of the group of Janus-kinase inhibitors – actively entered into practice. Some clinical trials show efficacy similar to biological DMARDs, but we still do not have enough data from the practice of post-marketing use.

Objectives: To evaluate the comparative effectiveness of TOFA and biological DMARDs in clinical practice.

Methods: Patients with RA (according to the ACR/EULAR 2010 criteria) having active disease despite treatment by subcutaneous (SC) methotrexate (MTX) were included in post-marketing observational study (REMARCA trial). The patients received a combination of MTX and biologics or TOFA. The follow-up period was 12 months. Patients received biologics in clinical practice according to national standards of care. We used SDAI as a main parameter of disease activity.

Results: In total 163 patients were included (81,6% females, 80,4% anti-CCP positive, 79,8 RF-positive, 74,9% with erosive disease, mean age 50,65±12,54, disease duration 30,45±41,9, BMI 27,1±5,78). All patients received SC MTX in the mean dose 22,17±3,92 mg per week, but the most of them had high activity at baseline (SDAI=32,42±14,59). After switching to a combination treatment regimen 88 patients received TNF inhibitors (70 patients – adalimumab, 18 patients – certolizumab pegol), 34 patients – abatacept (ABA), 41 patients – TOFA. Patients in the groups were comparable according to age and the main characteristics of disease severity. We found significant decrease of disease activity in every group (see table 1). In the group receiving TOFA results at 12 months were comparable with patients on anti-TNFs and significantly better than in patients on ABA. Remission (SDAI <3,3) has been achieved in 35,7% of patients on TOFA, in 28,4% – on anti-TNFs and in 14,7% on ABA (p=0055 in comparison with TOFA). No significant differences in safety parameters were found.

Abstract AB0485 – Table 1. Changes in disease activity in RA patients during follow-up period.

Group	SDAI at baseline	SDAI at 12 months
Biologics (total), n=122	33,22±15,18	11,05±9,94
Anti-TNFs, n=88	33,98±14,49	9,79±9,22
Abatacept, n=34	31,11±17,05	14,32±11,09*
Tofacitinib, n=41	30,20±12,24	7,59±8,37*

*) p<0,05 between the groups

Conclusions: Tofacitinib demonstrated similar efficacy in comparison to TNF inhibitors and was slightly better than abatacept in clinical practice in RA patients who did not respond to SC methotrexate.

Disclosure of Interest: E. Luchikhina Grant/research support from: Biocad, Speakers bureau: Abbvie, Pfizer, Biocad, D. Karateev Consultant for: Pfizer, Biocad, Egis, Novartis, Speakers bureau: Abbvie, Bristol Myers Squibb, Pfizer, Roche, Biocad, Novartis, Egis, MSD, UCB, G. Loukina: None declared, M. Borisova: None declared, N. Demidova: None declared, E. Nasonov: None declared

DOI: 10.1136/annrheumdis-2018-eular.7306