FRI0215

SIROLIMUS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS RELATED THROMBOCYTOPENIA (SLE-TP): A SINGLE-ARM, OPEN-LABEL CLINICAL TRIAL

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Background: Autoimmune thrombocytopenia (AITP) is common in systemic lupus erythematosus (SLE) patients and may be refractory to conventional therapies. SLE related thrombocytopenia (SLE-TP) patients have T-cell dysfunction that was reported to be associated with the activation of the mammalian target of rapamycin (mTOR). Rapamycin (RAPA) inhibits antigen-induced T-cell proliferation and has been developed as a medication named sirolimus.

Objectives: We assessed safety, tolerance, and efficacy of sirolimus in a prospective, open-label clinical trial.

Methods: We did a single-arm, open-label study of sirolimus in patients with refractory SLE-TP unresponsive to, or intolerant of, conventional medications at Peking Union Medical College Hospital (PUMCH, Beijing, China). We enrolled refractory TP patients (aged ≥ 18 years) with systemic lupus erythematosus (SLE) who visited our referral center since September 2017. We excluded patients with allergy or intolerance to sirolimus, patients with life-threatening manifestations of lupus, such as RPGN, NPLE or PAH and patients with uncured infection. All eligible participants had signed informed consents. Patients received oral sirolimus at a starting dose of 2 mg per day for 3 days and a sequential dose of 1mg per day, with dose adjusted according to tolerance and to maintain a therapeutic range of 6–15 ng/mL. Patients were treated with sirolimus for 6 months. Safety outcomes included tolerance as assessed by the occurrence of common side-effects. The primary efficacy endpoint was complete remission rate and partial remission rate at the sixth month. The secondary efficacy endpoint was the remission rates at the third month. The efficacy endpoints were assessed in all patients who completed 3 or more months of treatment, and all patients who received at least one dose of treatment were included in the safety analyses.

Results: Between September 2017 and November 2018, 12 lupus patients (1 male and 11 female) were enrolled with an average age of 33.3y, average disease duration of 8.4 years. All patients haven't achieved remission with front-line therapy, including corticosteroids, intravenous immunoglobulin, and immunomodulatory agents, such as azathioprine, FK506, mycophenolate mofetil, and cyclosporine. After sirolimus therapy (2 weeks to 6 months), 5 of 12 patients achieved CRR. 11 patients have finished 4 months' assessment, and 9 of them achieved remission. One patient had mild oral ulcers and no other complications were noted. The study is still in regular follow-up. There will be more results and conclusions in the later period.

Table 1. Demographics and Characteristics for Patients With SLE-TP

Patient No.	Age (y)	Gender	Prior Therapies	Time to Sirolimus (y)	Duration of Sirolimus (m)	Therapy Outcome
1	36	F	GCs, MMF, AZA	15	12	CR
2	44	F	GCs, FK506	13	11	CR
3	48	F	GCs, MMF	7	11	CR
4	35	F	GCS, MMF	2	9	CR
5	31	F	GCs, FK506	7	9	CR
6	39	F	GCs, CTX	8	6	NR
7	30	F	GCs, MMF, CsA, CH	15	5	PR
8	29	F	GCs, FK506	7	6	NR
9	18	M	GCs, MMF, FK506, CsA	3	4	PR
10	20	F	GCs, CTX, FK506, CsA, MMF, IVIg	14	4	PR
11	31	F	GCs, FK506	6	4	PR
12	38	F	GCs, CsA	4	2	NR

AZA, azathioprine; CH, Chinese herbs; CR, complete response; CsA, cyclosporine; CTX, cyclophosphamide; FK506, tacrolimus; GCs, glucocorticoid; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; NR, no response; PR, partial response.

Conclusion: Sirolimus is effective for the treatment of refractory SLE-TP and can be a choice of the second-line treatment. Further prospective studies are needed to evaluate sirolimus as a therapeutic option for SLE-TP and to monitor for potential long-term side effects.

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Acknowledgement: None

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7068

FRI0216

IGURATIMOD MIGHT BE AN ALTERNATIVE OPTION FOR REFRACTORY LUPUS NEPHRITIS: A PRELIMINARY OBSERVATIONAL STUDY

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Background: Despite significant advances in the management of patients with lupus nephritis (LN), a significant proportion of patients either do not respond to first-line immunosuppressive drugs, or relapse after initial remission. Iguratimod is a novel disease modifying anti-rheumatic drug that has been approved for treating rheumatoid arthritis in East Asia and has shown benefits in lupus animal model in our previous research.(1)

Objectives: The aim of the present study was to make a preliminary observation on the efficacy and safety of iguratimod in treating refractory LN patients.

Methods: We have enrolled adult refractory LN patients who were eligible if they experienced at least two times of failure or relapse before enrollment. Failure was defined as no response to one certain immunosuppressive drug for at least six months. After enrollment, we simply switched their previous immunosuppressant to daily iguratimod (25 mg twice per day), while keeping all other medications. Complete/partial remission (PR/CR) was used as the primary outcome. 24h urine protein, blood cell counts, liver and kidney function were routinely monitored.

Results: A total of 20 refractory LN patients had been enrolled (18 female and 2 male patients) since 2015. At enrollment, the median proteinuria was 2.588g/24h (range: 0.98–13.79g/24h). None of them had overt extra-renal involvement. All of them had biopsy-proven LN (class III/IV/V) and two patients agreed repeated biopsy before switching to iguratimod. The median prednisone dosage was 10mg/d (range: 5–35mg/d). One patient was lost to follow-up and one withdrew from the study. Of the remaining 18 patients, 16 patients achieved PR/CR and 2 did not respond to iguratimod. Of the 16 patients who achieved remission, 3 had renal relapse after initial PR and 1 had extra-renal flare after initial CR. One PR patient withdrew from the study due to severe anemia and another due to noncompliance. For the remaining 10 patients who were still in follow-up, the median follow-up was 84 weeks (range: 28–144

weeks), with 4 having CR and 6 PR. The median response duration (MRD) was 12 weeks.

Conclusion: Our study provided preliminary but promising clinical evidence for iguratimod in treating refractory LN patients. A large randomized clinical trial is needed to establish its safety and efficacy for refractory LN.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.875

FRI0216B SELECTIVE IRAK4 INHIBITOR DAMPENS MYD88 SIGNALING AND AMELIORATES INFLAMMATION AND FIBROSIS IN A MOUSE MODEL OF LUPUS NEPHRITIS

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Background: IRAK4 is an important signaling mediator of the innate immune system. IRAK4 initiates MyD88-dependent signaling from most TLRs and from IL-1Rs, resulting in downstream production of pro-inflammatory cytokines¹.

Objectives: Inhibition of IRAK4 kinase activity is a promising therapeutic approach for the treatment of autoimmune diseases, such as lupus. To this end, we identified a potent and highly selective inhibitor of IRAK4 kinase activity, BIIB-IRAK4i.

Methods: Recombinant kinase assays and DiscoverX kinomeScan were used to measure BIIB-IRAK4i kinase inhibition and selectivity, respectively. BIIB-IRAK4i-mediated proximal and distal pharmacodynamics effects (PD) were measured in both cell lines and whole blood assays. The ability of BIIB-IRAK4i to inhibit cytokine production induced by TLR ligands was measured *in vitro* and *in vivo*. Acute antibody-mediated lupus nephritis mouse model, which is a TLR-7 dependent and characterized by severe glomerular proliferative lesions with crescent formation, was used to determine the efficacy of BIIB-IRAK4i.

Results: BIIB-IRAK4i displayed equipotent proximal inhibition of MYD88 signaling and distal inhibition of cytokine production *in vitro*. BIIB-IRAK4i led to potent inhibition of cytokine production in whole blood assays stimulated with various synthetic TLR ligands as well as more physiological stimuli such as immune complexes, a hallmark of lupus pathogenesis. BIIB-IRAK4i inhibited TLR9-mediated cytokine production with same potency *in vitro* and *in vivo*. In addition, BIIB-IRAK4i decreased both inflammation and fibrosis in an acute antibody-mediated lupus nephritis mouse model. BIIB-IRAK4i inhibited crescent formation as well as markers of tubulointerstitial fibrosis, which are both associated with decreased survival and adverse outcomes in human lupus nephritis.

Conclusion: Our study highlights that pharmacological inhibition of IRAK4 can reverse two key components of lupus nephritis; the inflammatory and the fibrotic response.

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Disclosure of Interests: Dania Rabah Shareholder of: Employee and shareholder of Biogen, Employee of: Biogen, Ramon Bonegio Grant/research support from: Merck, Chugai Pharmaceuticals, Astra Zeneca, Aurinia Pharmaceuticals, Consultant for: Merck, Chugai Pharmaceuticals, Agnes Gardet Shareholder of: Biogen, Employee of: Biogen, Holly Legault Shareholder of: Biogen, Employee of: Biogen, Ian Rifkin Grant/research support from: Chugai, Merck, Biogen, Kyowa Kirin, Consultant for: Eisai, Ti Wang Shareholder of: Biogen, Employee of: Biogen, Chris Roberts Shareholder of: Biogen, Employee of: Biogen, Jeffery Vessels Shareholder of: Biogen, Employee of: Biogen, Norm Allaire Shareholder of: Biogen, Employee of: Biogen, Andrea Bertolotti-Ciarlet Shareholder of: Biogen, Takeda, Employee of: Biogen, Takeda, Kevin Guckian Shareholder of: Biogen, Employee of: Biogen

DOI: 10.1136/annrheumdis-2019-eular.3385

SLE, Sjögren's and APS – clinical aspects (other than treatment)

FRI0217 PREGNANCY OUTCOME IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IN TERTIARY UNIVERSITY HOSPITAL IN EGYPT

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Background: Pregnant systemic lupus erythematosus (SLE) patients have various risks to their fetus and themselves because a severe disease flare may be life-threatening, and some of the medications that are used to treat SLE adversely affect fetus.⁽¹⁾

Objectives: To evaluate the pregnancy outcome in SLE patients and to determine the predictive factors for adverse fetal and maternal outcomes.

Methods: The study was conducted on the pregnant SLE patients attending Rheumatology department, Zagazig University hospitals in the period from January 2013 to January 2018. The data was collected retrospectively; demographic, laboratory and serological data on all patients, age at the onset of SLE, disease duration, systems affected, their disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), treatment received immunosuppressive regimen (dose and duration) before and during pregnancy, SLE flare during pregnancy, the fetal and the maternal outcomes.

Results: Fifty-two pregnancies were observed in 49 SLE patients with mean age of (27.5±5.6), mean SLE disease duration (3.7±2.2) and mean SLEDAI (5.4±6.1). 39 (75%) pregnancies with successful live births and 13(25%) fetal losses were observed. 36 of the live births (92.3%) were full-term and 3 (7.7%) were preterm births. Fetal losses included six spontaneous abortions, 3 stillbirths and 4 therapeutic abortions; 2 of them due to observed fetal anomalies and one due to life threatening lupus flare. We found SLEDAI significantly higher in patients with lost pregnancies ($p<0.0001$) than successful pregnancies. Proteinuria during pregnancy was a predictive factor for adverse fetal outcomes (odds ratio [OR] 19.7; $P<0.0001$), also the presence of antiphospholipid antibodies (OR 15.3; $P<0.0001$), low C3 and C4 (OR 15.3; $P<0.0001$), anti-RO antibodies (OR 11.1; $P=0.02$), anti-LA (OR 4.7; $P=0.03$), chronic hypertension (OR 54.8; $p<0.0001$) and SLE flares (OR 32; $p=0.003$). SLE flares occurred in 10 pregnancies (19.2%), mostly during the second trimester (60%). Renal involvement (70%) was the most common SLE flare during pregnancy. SLE flares during pregnancy were highly associated by nephritis prior to pregnancy (adjusted OR 9; $P=0.04$) and the presence of antiphospholipid antibodies (adjusted OR 12; $p=0.01$).

Conclusion: Favorable pregnancy outcome was observed in Egyptian SLE patients; particularly in those with longer period of remission. Planned pregnancy is very important to reduce undesirable fetal and maternal outcomes in SLE patients. The presence of lupus nephritis, chronic hypertension, antiphospholipid syndrome, active disease at the onset of pregnancy, and proteinuria were highly associated with bad outcome.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8173

FRI0218 IMMUNOPHENOTYPIC SUBGROUPS OF SLE DEFINED BY AUTOANTIBODIES, GENE EXPRESSION AND FLOW CYTOMETRIC ANALYSIS

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Background: SLE may be stratified according to a range of different immune assessments but the relationships between these are less well defined. MASTERPLANS is an MRC-funded consortium that seeks to identify immunophenotypic subgroups of patients that predict response to therapy.