6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MMP). These metabolites, rather than the absolute dose of AZA, are associated with clinical efficacy and toxicity. An idiosyncratic skewed metabolism towards 6-MMP in some patients ("shunters") increases the risk of hepatotoxicity and treatment failure. Allopurinol can correct such shunts[1]. Therapeutic protocols using metabolite concentrations have been shown to be cost effective, improve efficacy, and decrease treatment morbidity in IBD[1]. Only one small study estimated a therapeutic 6-TGN level for SLE patients[2]. There are scant data on AZA shunters in connective tissue disease[3].

Objectives: Explore the proportion of AZA therapeutic failure, toxicity, and shunters in CTD patients.

Methods: Retrospective, multicentre audit of AZA metabolite levels in CTD patients from 2012–2016. Patient demographics, treatments, disease activity and drug toxicity were also extracted.

Results: 61 testing episodes occurred in 34 patients whose mean age was 55 (32–79) years; predominantly female (N=26, 77%), with SLE (N=19, 56%). Active disease was present in 15/61 (25%) episodes. 20/34 (60%) patients were on HCQ + AZA. 25/34 (76%) of patients were either on no or <10mg/day of prednisone. 22/61 (36%) episodes had bone marrow suppression, and 8/61 (13%) had moderate liver function derangement. 12/35 (34%) patients were AZA shunters.

Based on AZA metabolite levels, patients were classified into four categories:

Classification[3]	6-TGN	6-MMP	Prevalence in Study (N)
Underdosed/ noncompliant	Low	≤ Normal	9
Appropriately dosed	Therapeutic	≥ Normal	23
Overdosed	High	≥ Normal	16
6-MMP Shunter	Low	> Normal	13

SLE patients were over-represented in the underdosed/non-compliant category (7/9). Patients in underdosed and 6-MMP shunter categories had more active disease (44% & 31%), compared with appropriate and overdosed (17% and 19% p=0.24). Surprisingly, patients who were overdosed by 6TGN levels had the lowest mean AZA dose. 6-MMP shunters had significantly lower median 6TGN levels (147pmol/8x10^8 RBC), yet toxic MMP levels (9630pmol/8x10^8 RBC) that was associated with worst LFT derangement prevalence (4/13, 31% vs <13%, p=0.16).

Conclusions: AZA dose is poorly predictive of 6-TGN and 6-MMP levels. Overall, one third of CTD patients were shunters, with lower 6-TGN levels and more hepatotoxicity. Only 40% of test episodes were appropriately dosed. Patients with low disease activity are more likely to have adequate 6TGN levels, however, 40% of patients with CTD won't have adequate disease control despite therapeutic 6-TGN levels. AZA metabolites can identify the multiple causes for therapeutic failure (under dosing, shunter, or true non-response), and enable early detection of shunters to avoid liver toxicity.

References:

[1] Croyle, L., & Morand, E. F. (2015). Optimizing the use of existing therapies in lupus. Int J Rheum Dis 18(2), 129–37.
[2] Askanase, AD et al (2009). Use of pharmacogenetics, enzymatic phenotyping, and metabolite monitoring to guide treatment with azathioprine in patients with systemic lupus erythematosus. J Rheum, 36(1), 89–95.
[3] Haines, ML et al (2011). Clinical usefulness of therapeutic drug monitoring of thiopurines in patients with inadequately controlled inflammatory bowel disease. Inflam Bowel Dis, 17(6), 1301–7.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.2405

AB0465 ASSOCIATION BETWEEN SAFETY, EFFICACY AND HYDROXYCHLOROQUINE DOSAGE IN THE TREATMENT OF CUTANEOUS LUPUS ERYTHEMATOSUS AND SYSTEMIC LUPUS ERYTHEMATOSUS

R. Wakiya, T. Kameda, M. Izumikawa, S. Nakashima, H. Shimada, H. Ozaki, A. Kondo, N. Kadowaki, H. Dobashi. *Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Kagawa University, Kagawa, Japan*

Background: Hydroxychloroquine (HCQ) are considered to be effective against cutaneous lupus erythematosus (CLE) and symptoms associated with systemic lupus erythematosus (SLE) such as rashes, joint pain, and fatigue. In a randomized controlled trial in stable active patients with SLE on HCQ treatment, those who achieved blood HCQ levels greater than or equal to 1000ng/ml had a tendency for reduced SLE flares during a 7 month period [1]. To prevent ocular toxicity, HCQ should be maintained at a dose of 6.5mg/kg or less for ideal body weight [2], however, optimal HCQ dosage is unclear.

Objectives: To extract the problem of the dosage based on ideal body weight and identify safer and more effective HCQ dosage.

Methods: We enrolled patients who took HCQ for SLE or CLE more than 3 months in our institute and 2 related facilities from September 2015. We used Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI) to evaluate cutaneous symptoms and evaluated effect at start of administration and 3 months of that. The attending doctors assessed the adverse events (AEs). We investigated the change of serum biomarker, such as the value of serum complement and anti-ds-DNA body, the number of white blood cells, lymphocytes and platelets.

Results: We enrolled the 30 patients with administration of HCQ more than 3 months and in CLE were 2 cases, in SLE were 28 cases. In 21 cases HCQ dosage were based on ideal weight. The AEs were in 13/30 cases (43.3%). The AEs were the new cutaneous symptoms in 5 cases, eye manifestation in 3 cases (abnormal visual field in 2 cases, color anomaly in 1 case), diarrhea in 2 cases, fever in 2 cases, feeling of fatigue in 2 cases, renal dysfunction in 1 case, muscular pain in 1 case, and pericarditis in 1 case. The eye manifestation in the 3 cases disappeared for a few days by stopping or reducing HCQ dosage. Although we needed glucocorticoid treatment for pericarditis, the other AEs improved by reducing HCQ dosage or stopping. The AEs of taking HCQ 200mg/day were in 6 cases, 200mg and 400mg alternatively on every other day in 6 cases, and 400mg/day in 1 case. The AEs of taking HCQ dosage based on ideal body weight were in 10/21 cases (47.6%) and by minimal dosage in 3/9 cases (33.3%). 22/28 cases (78.6%) significant improved cutaneous symptoms (amount of mean change of CLASI -4.57, p=0.024). There is no difference in the efficacy of cutaneous symptoms between group received HCQ based on ideal body weight (80.0%) and the others (92.3%). 5/21 cases of HCQ based on ideal body weight were made to reduce HCQ dosage due to AEs, but all 5 cases improved cutaneous symptoms. 53.3% (16/30) cases increased complement, but other biomarkers didn't change.

Conclusions: HCQ was effective for the treatment of CLE even when HCQ dosage was reduced due to AEs. These findings suggest that low-dose HCQ is also effective and safe, and HCQ initial dosage wasn't the need to adjust for ideal body weight.

References:

[1] Costedoat-Chalumeau N, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2013;72(11):1786–92.
[2] Ronald B. Melles, Michael F.Marmor. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol. 2014;132(12): 1453–60.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3928

AB0466 THE EFFECT OF OMEGA-3 FATTY ACIDS ON DISEASE ACTIVITY, ENDOTHELIAL FUNCTION, INFLAMMATORY MARKERS, AND LIPID PROFILE IN SYSTEMIC LUPUS ERYTHEMATOSUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

R. Castillo[1], P.P. Uy[1], D.M. Francisco[1], S. Lakshminarayanan[2]. *[1]Internal Medicine; [2]Rheumatology, University of Connecticut, Farmington, United States*

Background: Omega-3 fatty acids have been shown to have potentially beneficial immunomodulatory activity in autoimmune conditions such as rheumatoid arthritis and Sjogren's syndrome. Whether this extends to systemic lupus erythematosus (SLE) remains unclear.

Objectives: We undertook this study to summarize the body of evidence available from published clinical trials on the effectiveness of omega-3 fatty acids on clinical and laboratory outcomes in SLE.

Methods: Two independent reviewers systematically searched PubMed, MEDLINE, Scopus, and the reference lists of related articles for studies published from inception to November 2016 using relevant keywords. Randomized, controlled trials (RCTs) on SLE patients comparing omega-3 fatty acids with placebo were included in the analysis. The quality of the included RCTs was assessed in accordance with the Cochrane Handbook. A random effects model was used to pool extracted data. Heterogeneity was evaluated with Chi^2 test and I^2, with *p*-values <0.05 considered significant. Data presented in median and interquartile range were converted to mean and standard deviation using the method described by Wan et al.

Results: A total of seven clinical trials consisting of 303 subjects with a duration of treatment ranging from 12 to 52 weeks were included. In studies using SLAM-R as the measurement of disease activity (n=82), there was a statistically significant mean score reduction in the omega-3 fatty acid group vs. the placebo group at 24 weeks. However, in studies that used mean change in SELENA-SLEDAI (n=117, WMD: -0.87, 95% CI: -3.9, 2.17, I^2=0%, p=0.58) and PGA (n=117, WMD -0.46, 95% CI: -1.16, 0.24, I^2=85%, p=0.20) scores, there was no significant effect (Figure 1). Mean brachial artery diameter after 12 weeks likewise did not reveal

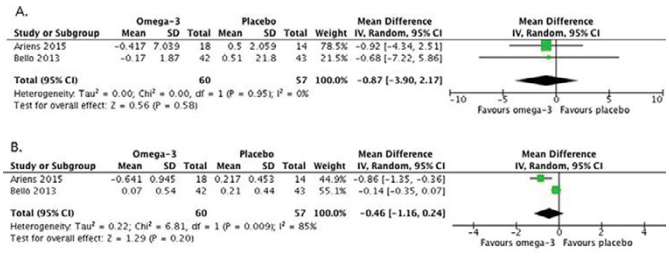

Figure 1. Effect of omega-3 fatty acids on SLE disease activity as measured by mean change in SELENA-SLEDAI (A) and PGA (B) scores.

any difference between the two groups (n=141, WMD: -0.01, 95% CI: -0.03, 0.01, I^2=0%, p=0.26). The data on percent increase in flow-mediated dilation was conflicting. In terms of inflammatory markers, there were likewise no clear associations, with some studies reporting significant changes in ESR, CRP, IL-12, and IL-13 levels which were not observed in others. With regards to lipid profile, treatment with omega-3 fatty acids was associated with a non-significant trend toward increase in all lipid profile parameters at 12 weeks including HDL (WMD 6.83, 95% CI: -4.37, 18.02, I^2=12, p=0.23), LDL (WMD 5.41, 95% CI: -1.27, 12.10, I^2=0%, p=0.11), and total cholesterol (WMD 8.48, 95% CI: -0.38, 17.33, I^2=0, p=0.06).

Conclusions: The limited data on the use of omega-3 fatty acids has not shown clear benefit in improving disease activity, endothelial function, inflammatory markers, or lipid profile in patients with SLE. Larger studies for longer durations using standardized scales for measuring outcomes are needed.

References:

[1] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135–148.

Acknowledgements: Dr. Chia-Ling Kuo.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2666

AB0467 EFFICACY AND SAFETY OF ASSISTED REPRODUCTIVE TECHNOLOGIES (ART) IN RHEUMATIC PATIENTS: A MULTICENTER STUDY

R. Reggia[1], H. Sebbar[1], L. Andreoli[1], A. Hoxha[2], M. Larosa[3], F. Ceccarelli[4], V. Canti[5], V. Ramoni[6], A. Inversetti[7], A. Ruffatti[2], A. Doria[3], F. Conti[4], G. Valesini[4], P. Rovere Querini[5], C. Montecucco[6], A. Lojacono[8], L. Fallo[8], A. Tincani[1]. *[1]Rheumatology and Clinical Immunology, ASST Spedali Civili di Brescia, BRESCIA; [2]Rheumatology Unit, Department of Medicine - DIMED; [3]Rheumatology Unit, Hospital and University of Padua, Padua; [4]Internal Medicine and Medical Specialties Department, Policlinico Umberto I, "La Sapienza" University of Rome, Rome; [5]Allergology and Clinical Immunology, U.O. Internal medicine, Ospedale San Raffaele, Milan; [6]Rheumatology Unit, IRCCS Policlinico San Matteo and University of Pavia, Pavia; [7]Department of Obstetrics and Gynaecology, Ospedale San Raffaele, Milan; [8]Maternal-Fetal Medicine, ASST Spedali Civili di Brescia, BRESCIA, Italy*

Background: Always more frequently rheumatic patients (pts) ask for Assisted Reproductive Technologies (ART) for infertility problems. The main concern is determined by the ovarian stimulation, associated with an increased risk of disease flare and thrombosis.

Objectives: To describe a case series of ART cycles in pts affected by rheumatic diseases, analyzing pregnacy rate and outcome, fetal-maternal complications and disease flares.

Methods: We included all the consecutive pts evaluated in the Pregnancy Clinic of 5 Italian Rheumatology Units after having performed ≥1 ART cycle from 1997 to 2016.

Results: We included 60 pts: infertility was primary (no previous spontaneous conception) in 68% of cases, idiopathic in 76.5%, of male origin in 8.3%, of female origin in 15%, mixed in 0.2%. One hundred and eleven ART cycles were performed: 13IUI, 44FIVET (3eterologous), 53ICSI (14eterologous), 1embryodonation. Antiphospholipid antibodies were positive in 23 (38.3%) pts and in 45 (40.5%) cycles. Procedures were unstimulated in 14 (12.6%) stimulated in 97 (59.5%) cases: with GnRH-Antagonist in 26 (26.8%), GnRH-agonist in 60 (61.8%), gonadotropins only in 7 (7.3%) and with clomiphene in 4 (4.1%) cases. We registered 3 (3%) cases of Ovarian Hyperstimulation Syndrome, all after Agonist protocol. Overall we observed 46 pregnancies, with a *pregnancy rate* of 38.7% for omologous procedures and of 55.5% for eterologous. No miscarriages were reported. Pregnancies ended with 35 single and 5 twin birth, 6 are still ongoing: we recorded 4 (8.9%) perinatal deaths: 1 baby died at birth for multiple malformations and 3 died in the first days of life for extreme prematurity. One or more fetal complications were reported in 11 (27.5%) pregnancies: 3PROM, 3IUGR, 3oligohydramnios, 4fetal malformation (2 severe, 1multiple and fatal). The mean age of the women suffering from fetal complications was significantly lower (p:0.03). One or more maternal complications were reported in 13 (32.5%) pregnancies: 4gestational diabetis, 2thrombocytopenia, 2pre-eclampsia, 2placenta previa, 1hypothyroidism, 1gestational hypertension, 1cholestasis of pregnancy. Disease Flares were reported in 5 (12.5%) pregnancies: 4 articular (2 in RA patients, 2 in SLE patients), 1haematological (in SLE patient, after spontaneous therapy discontinuation). No cases of thrombosis were reported.During puerperium: 1 (2.5%) post-partum hemorrage (no LMWH ongoing), 1 articular flare (2.5%). Additional informations are available in Table 1.

Mean age at procedure; [median]; range	36.4; [37]; 19-45	
Diagnosis	22 SLE (2+APS), 12 UCTD, 5 PAPS, 8 RA, 5 AS, 2 SjS, 1 DM, 1PA, 1 Takayasu Arteritis, 1 Churg-Strauss Vasculitis, 1 Behcet Disease, 1SSc.	
Mean disease duration at procedure; [median]; range	6.9 years; [6]; 1-22	
Prophylactic therapy during ovarian stimulation (data available in 109 cycles) Mean n' of embryos transferred in utero; [median]; range	yes in 71 (65.1%)	LDA only n:23 (32.4%)
		LMWH only n:25 (35.2%) Prophylactic dose in 25(100%)
		LDA+LMWH n:23 (32.4%)
	no in 38 (34.9%)	
	1.6; [2];1-4	
Single embyo-transfer vs Multiple embryo-transfer	n:32 (31.2%), *pregnancy rate*: 50% n:48 (68.8%), *pregnancy rate: 39.6%* (p:0.37)	
Prophylactic therapy during pregnancy (administered in 35 pregnancies)	-LDA only n:9 (25.7%); -LMWH prophyilactic only n:4 (11.4%); -LDA+LMWH prophyilactic n:20 (57.1%); -LDA+LMWH therapeutic n:1 (2.9%); -UH therapeutic n:1 (2.9%).	
Deliveries	vaginal n:17 (42.5%), cesarean section n:23 (57.3%); at term n:33 (82.5%), pre-term n:7 (17.5%).	
Mean age at delivery; [median]; range	37 weeks; [38]; 24-41.	
Mean weight and lenght at delivery; [median], range	2780.8g; [3005g]; 420-3900g. 47.6cm; [49]; 28-53.	

Tab.1 Main features of patients, procedures and newborns

SLE: Systemic Lupus Erythematosus; PAPS: Primary Antiphospholipid Syndrome; UCTD: Undifferentiated Connective Tissue Disease; SjS: Sjögren Syndrome; SSc: Systemic Sclerosis; PA: Psoriasic Arthritis; AS: Ankylosing Spondylitis.

Conclusions: We didn't found any good reasons to discourage ART performance in rheumatic pts: the safety seems to be high and the *complications rate* is in line with that reported in general population. An adequate prophylaxis during stimulation, pregnancy and puerperium seems to provide a good protection from thrombotic complications.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2351

AB0468 POSSIBLE EFFECTS OF BELIMUMAB THERAPY ON T- AND B-CELL PHENOTYPE IN A COHORT OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

S. Piantoni[1], F. Regola[1], M. Scarsi[2], F. Dall'Ara[1], L. Andreoli[1], A. Tincani[1], P. Airò[1]. *[1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia; [2]Internal Medicine Unit, Esine-Vallecamonica Hospital, Esine, Italy*

Background: B- and T-cell activation are one of the pathogenic mechanisms of systemic lupus erythematosus (SLE). After repeated antigenic stimulation, T-cells undergo different modifications, leading to the differentiation into effector memory T-cells (CCR7-CD45RA-) and highly experienced memory T-cells (CCR7-CD45RA+). Similarly, down-modulation of CD28 may lead to the expansion of the CD28neg T-cells, a subpopulation with peculiar effector activities (1).

Recent studies showed that memory CD4+ T-cells are increased in the peripheral blood of SLE patients, whereas contradictory data are reported on CD28 neg T-cells (2).

Peripheral transitional B-cells (38high24high) are immature B-cells transiting to secondary lymphoid organs, where their maturation into follicular or marginal zone B-cells is driven by a stimulating factor called BLyS. This population is expanded in patients with SLE (3). The anti-BLyS therapy agent belimumab is approved for treatment of SLE.

Objectives: The aims of this study were to characterize B- and T-cell phenotype in a cohort of patients with SLE, according with disease activity, and to analyse their modifications therapy with belimumab.

Methods: Phenotypic analysis of peripheral blood B and T lymphocytes was made by flow-cytometry. First, a cross-sectional study on 51 consecutive SLE patients (F/M: 48/51; median age: 35 years; anti-dsDNA: 16 UI/ml; C3: 79 mg/dl; C4: 10 mg/dl) was performed.

Second, 18 patients treated with belimumab were longitudinally followed.

Disease activity was evaluated by SLEDAI-2K score.

Results: SLE patients were divided in two groups according disease activity: patients with SLEDAI-2K ≥6 (n:13) had a higher percentage of circulating CD4+T-cells with CD28neg phenotype: median value (25th-75th percentile)=13 (5–19) vs 3 (1–5) % of CD4+ T-cells, p<0.01), as well as of those with an effector memory (37 (29–40) vs 18 (12–27) % of CD4+ T-cells, p<0.01), highly experienced memory phenotype (9 (7–12) vs 1 (1–3) % of CD4+ T-cells, p<0.01), and of B-cells with a transitional phenotype (3 (0.5–5) vs 0.2 (0–0.4) % of CD19+ cells, p=0.02), in comparison with patients with low disease activity (n:38).

After 6 months of treatment with belimumab, no significant variation in the T-cell subset was observed, but there was a reduction in the number of circulating naïve B-cells (from 49 (30–71) to 21 (11–36) % of CD19+ cells; p<0.01). Among these patients, the proportion of transitional B-cells, was raised (as compared with normal controls) at baseline in 3/11 patients with SLEDAI-2K ≥6, and 0/7 with low disease activity. After 6 month of therapy, their number normalized in 2 of these 3 patients.

Conclusions: CD4+ T-cells subpopulations displaying phenotype characteristics of effector lymphocytes, and transitional B-cells are expanded in peripheral blood of patients with active SLE. Therapy with belimumab may inhibit the production of transitional and naïve B-cells.

References:

[1] Strioga M, et al. Immunology 2011.
[2] Ugarte-Gil M, et al. Lupus 2016.
[3] Jacobi AM, et al. Arthritis Rheum 2008.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.5976