FRI0323

APREMILAST THERAPY IN REFRACTORY SKIN LUPUS LESIONS

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Background: Skin lesions of lupus may be refractory to standard therapy. Apremilast is an orally small molecule which inhibits phosphodiesterase-4 (PDE-4) that modulates some inflammatory pathways.

Objectives: Our aim was to assess the efficacy of apremilast in lupus rashes refractory to conventional treatment.

Methods: Retrospective study on 5 lupus patients treated with apremilast at standard dose of 30 mg twice daily. The outcome was improvement of lupus rashes.

Results: We described 5 patients (4 women and 1 male) with a mean age of 44.2 ±8.5 years with extensive skin lesions due to lupus. Three patients had a discoid lupus and 2 patients had systemic lupus erythematosus (SLE) (one with panniculitis and the other with polycyclic ring lupus). The cutaneous lupus was confirmed in all patients by skin biopsy. Prior to apremilast all patients had received conventional treatment: topical corticosteroids (n=5), antimalarials (n=5), topical tacrolimus (n=2), oral corticosteroids (n=2), thalidomide (n=1), belimumab (n=1) and rituximab (n=1). After a mean follow-up of 6.2±2.9 months, all the patients experienced improvement of the skin lesions (in two patients was complete). In one patient it was necessary to reduce the dose of apremilast to 30 mg/day because of digestive symptoms.

Conclusions: Apremilast can be useful in the treatment of refractory skin lesions of lupus.

Disclosure of Interest: None declared

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FRI0324

IMMUNOSUPPRESSION FOR PRIMARY SJOGREN'S SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: The current focus of treatment in primary Sjögren's Syndrome (pSS) is mainly symptom management. Since pSS is an autoimmune disease with multi-system involvement, there may be a role for systemic immunosuppression and/or biologic therapy. A wide variety of immune response targets have been examined in existing randomised controlled trials including inhibiting purine synthesis, blocking TNF-alpha, and depleting B lymphocytes. There is conflicting evidence as to whether immunomodulation alters disease progression.

Objectives: To assess the efficacy and safety of immunosuppressive therapy on pSS from clinical trials.

Methods: Five electronic databases (MEDLINE, EMBASE, CENTRAL, CLINICALTRIALS.GOV, WHO ICTRP) were searched to include randomised controlled trials of systemic immunosuppressive therapies in adults with pSS published in English prior to Oct 1, 2017. Efficacy measures included ocular dryness, oral dryness, fatigue, tear production, unstimulated and stimulated salivary flow, quality of life (QOL), ESSPRI, ESSDAI, ESR/CRP; Safety measures included serious adverse events (AEs) and withdrawals due to AEs.

Results: The searched yielded 32 trials evaluating 19 different medications. Studies enrolled anywhere between 7 to 133 patients, with the exception of 1 study with 497 patients. Mean age was in the fifth decade, with an average duration of diagnosis up to 9.2 years.

Twenty-two trials examined ocular and oral dryness, of which 2 and 3 revealed statistically significant improvements respectively (table 1). Only 1/14 trials found benefit for fatigue, none for tear production; 3/16 trials and 2/14 trials found increases in unstimulated and stimulated salivary flow respectively. Reductions in ESR were seen in 3/14 trials. Few studies examined QOL, ESSPRI, ESSDAI, and CRP. Trials often noted non-statistically significant trends toward improvement, but no particular drug or drug class consistently showed discrete benefit in subjective or objective efficacy measures possibly due to low statistical power.

Abstract FRI0324 – Table 1. Efficacy Outcome Measures

Outcome	# Trials Total	# Trials showing statistical improvement
Ocular dryness	22	1 of 1 Prednisone 1 of 2 Rituximab
Oral dryness	22	1 of 3 Prednisone 1 of 3 Rituximab 1 of 3 DHEA
Fatigue	14	1 of 4 Rituximab
Tear production	19	0
Unstimulated saliva production	16	2 of 3 Rituximab 1 of 3 Interferon alpha

Stimulated saliva production	14	2 of 4 Interferon alpha
Quality of life (mental component)	8	0
Quality of life (physical component)	8	0
ESSPRI	7	1 of 1 Iguratimod
ESSDAI	6	1 of 1 Bimnercept 1 of 1 Iguratimod
ESR	14	1 of 1 Nandrolone 1 of 1 Prednisone
		1 of 3 Hydroxychloroquine
CRP	3	1 of 1 Hydroxychloroquine

Meta-analyses of the above outcomes were performed at 6 months (figure 1). With pooled estimates, significant improvements were seen in unstimulated salivary flow (p=0.003), stimulated salivary flow (p=0.02), and ESR (p<0.001). There was a trend towards increased serious AEs in the intervention groups, and a significant increase in withdrawals from AEs (RR 2.33, 95% CI 1.38 to 3.96).

Abstract FRI0324 – Figure 1. Meta-analyses at 6 months

Conclusions: Reducing immune activity and inflammation potentially improves salivary gland function. Subjective measures may be less helpful as sicca symptoms likely have subtle progression if trials span less than 1 year. Given that most trials were small, beneficial treatment effects could be missed. Standardisation of objective, reliable, clinically meaningful outcome measures that are sensitive to change may allow for positive treatments in the future.

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FRI0325

RITUXIMAB IN PRIMARY SJÖGREN'S SYNDROME: A SYSTEMATIC REVIEW ON ITS EFFICACY

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Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that produces a lymphoplasmocytic infiltrate of the exocrine glands. Considering the primary role attributed to B-lymphocytes in pSS pathophysiology, it has been suggested that Rituximab (RTX) may have certain role in controlling the disease.

Objectives: To evaluate RTX efficacy in the treatment of xerostomia, xerophthalmia and systemic manifestations (including fatigue) in patients with pSS.

Methods: In the framework of the preparation of a recommendations document of the Spanish Society of Rheumatology on the use of biologics in pSS, a systematic search of the literature was carried out (until May 2017). Were included adults older than 18 years who met the 2002 American European Consensus Criteria, treated with RTX, with desired comparison to groups treated with other drugs or

Abstract FRI0325. Table 1.. * Analysed in MA of Souza 2016

Author/year	Souza 2016	Devauchelle 2014*	Meijer 2010*	Dass 2008*	Carubbi 2013	Pipje 2005	Gottenberg 2013	Mekinian 2012	Seror 2007
Study type (LOE)	SR and MA (1+)	RCT (1+)	RCT (1+)	RCT (1-)	Not randomised (1-)	Not controlled ³	Retrospective ³	Retrospective ³	Retrospective ³
Groups and N	RTX 145/Pbo 131	RTX 63/Pbo 59	RTX 20/Pbo 10	RTX 8/Pbo 9	RTX 19/ DMARDs22	RTX 7	RTX 86	RTX 17	RTX 16
Dryness:									
VAS (oral, ocular, global).	-	-	-	-	+				
Salivary flow	+	-	-	-	+	+			
Schirmer	-	-	-	-	+	-			
Lissamine green			+						
Rose Bengal						+			
TBUT			-			+			
General and systemic manifestations:									
ESSDAI	-	-			+		+	+	
SF-36	-	-	-	-		+			
Fatigue VAS.	-	-	-	-	+	+			
Global VAS: patient/physician.		-/-			+/+				
Lab (IgG/A/M, beta2-microglobulin, RF, B cells).		+	+	+		+			+
Systemic:			+		+		+	+	

with placebo and a follow-up time of 6 months. The quality of the studies was assessed through the levels of evidence (LOE) of SIGN scale.

Results: The search resulted in a total of 749 articles and only 9 of them were selected (**figure 1**). The best available evidence for each variable studied is summarised in **chart 1** ("+" significant improvement; "-" no significant improvement). The most relevant results obtained in the studies with **LOE 1+**, showed significant differences comparing RTX with placebo ($p < 0.05$) in: 1) Souza 2016: Salivary flow rate at 24 w (weeks) (0.09; 95% CI 0.02 to 0.16). 2) Meijer 2010: Ocular dryness VAS score at 24 (-27.00, 95% CI -46.28 to -7.72), 36 and 48 w. Lissamine green test at 24 w (-2.00, 95% CI -3.52 to -0.48). Absolute number of B cells from 5 to 48 w (-0.23; IC 95% -0.31 to -0.15). Rheumatoid Factor at 12, 24 and 36 w. Tendomyalgia at 12 and 36 w. Vasculitis at 24 w. 3) Devauchelle-Pensec 2014: Immunoglobulin's G (1.2 g/L; 95% CI 0.4 to 2 g/L), A, M and beta2-microglobulin (1.6 g/L; 95% CI 0.5 to 2 g/L) at 24 w. The studies with **LOE 3** also report improvement in a percentage of patients in other systemic manifestations, but without demonstrating statistical significance.

Abstract FRI0325 – Figure 1. Flow chart.

Conclusions: The studies of high methodological quality that evaluate the efficacy of RTX in pSS do not find significant improvement in the primary outcome variables, such as ESSDAI, glandular involvement and other objective parameters of dryness. However, open and retrospective studies find significant improvement in activity parameters, systemic manifestations, glandular involvement and improvement of certain objective tests of dryness.

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FRI0326

IMMUNE CELLULAR PROFILE ASSOCIATED WITH DIFFERENT TREATMENT OUTCOME IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ON CYCLOPHOSPHAMIDE

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Background: Cyclophosphamide (CFA) is an effective immunosuppressive drug used for treatment of severe manifestations of systemic lupus erythematosus (SLE). The knowledge about modulatory effect of CFA on circulating immune cells and its changes associated with treatment response is limited.

Objectives: To determine the effect of a cumulative dose of CFA on circulating immune cells in SLE patients and to assess its association with treatment outcome.

Methods: Using 6-colour flow cytometry (BD FACSCanto II) we analysed T and B lymphocytes, NK cells, neutrophils, and monocytes in peripheral blood from 11 SLE female patients. SLE patients were investigated before and after cumulative 1000 mg and 3000 mg of CFA dose. Patients subgroups were assessed according to the treatment response (n=5, good responders; n=6, poor responders); SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) was used to assess the disease activity. Healthy age-matched females (n=12) were included in the study. Statistics was done by GraphPad Prism and R statistical software package.

Results: Cumulative dose of 1000 mg of CFA resulted in decreased percentage of B lymphocytes ($p=0.0004$) and CD4 +T lymphocytes ($p=0.02$) and increased the percentage of total and CD8 +T lymphocytes ($p=0.03$; $p=0.0003$ respectively). After 3000 mg CFA, the percentage of B lymphocytes ($p=0.002$), naïve B lymphocytes ($p=0.005$), memory B lymphocytes ($p=0.02$) and CD4+/CD8 +ratio ($p=0.01$) decreased while the percentage of CD8 +T lymphocytes ($p=0.0003$), Tregs ($p=0.01$) and CD69 +NK cells ($p=0.02$) increased. CFA treatment in our patients resulted in reduction of B lymphocyte percentage reaching the values of healthy controls. In good responders, decreased percentage of B lymphocytes ($p=0.04$), CD4 +T lymphocytes ($p=0.04$), CD4+/CD8 +ratio ($p=0.007$) and increased percentage of CD8 +T lymphocytes ($p=0.004$), CD69 +NK cells ($p=0.04$) and non-classical monocytes ($p=0.04$). In poorly responding patients percentage of CD8 +T lymphocytes ($p=0.01$), activation marker HLA-DR on both CD4 +and CD8+T lymphocytes ($p=0.01$; $p=0.02$ respectively), Tregs ($p=0.02$), memory B lymphocytes ($p=0.03$) were increased and percentage of total B lymphocytes was decreased ($p=0.02$). The analysis using advanced data mining methods for identification of treatment outcome related profiles are ongoing

Conclusions: Administration of CFA modulates several cell populations in SLE patients, whereas changes in B and T lymphocytes were associated with different treatment outcome. Whether the immune profile may predict the treatment response deserves further investigation.

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