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Table 1. Association between clinical and therapeutic factors with mortality in SLE patients.

Factors associated with mortality	Univariado	Multivariado
	β (95 % IC)	β (95 % IC)□
Age	0.93 (0.96-1.02)	0.98 (0.96-1.02)
Use of mechanical ventilation	3.83 (1.07-13.4)*	3.07 (0.59-16.04)
Previous use of steroids	3.92 (1.51-10.15)*	2.04 (0.58-7.35)
Previous use of immunosupression	4.04 (1.42-11.45)*	2.85 (0.71-11.48)
Infection	3.57 (1.41-9.01)*	3.25 (1.19-8.86)*

p <0.05 *

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AB0282 SAFETY, TOLERABILITY AND SELECTIVE EXPANSION OF REGULATORY T CELLS BY A SINGLE DOSE OF THE NOVEL IL-2 MUTEIN PT101 IN A PHASE 1 STUDY IN HEALTHY VOLUNTEERS

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Background: Activation and expansion of regulatory T cells (Tregs) has been proposed as a strategy to treat autoimmunity. When administered in low doses, IL-2 expands and activates Tregs leading to clinical response in several autoimmune diseases. However, the narrow therapeutic window of IL-2 results in loss of selectivity for Tregs and concurrent activation of conventional T cells (Tconv) and NK cells, limiting its clinical utility. This loss of selectivity may negate the clinical benefit of Treg activation and lead to dose-limiting side effects. PT101 is a novel engineered variant of IL-2 fused to an Fc protein backbone which in preclinical studies selectively activates Tregs without expanding Tconv or NK cells. PT101 is in clinical development for the treatment of patients with autoimmune diseases.
Objectives: To assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of PT101 after a single dose in healthy human volunteers.
Methods: We conducted a randomized, double-blind, single-ascending dose trial of PT101 or placebo (3:1 allocation). Five dose levels from 1 mg to 10 mg were administered by subcutaneous injection. Adverse events, physical examination findings, and clinical laboratory results were assessed for 29 days. Serum PT101 levels and antidrug antibody were assessed. Changes in mononuclear cell populations were measured in peripheral blood by flow cytometry.
Results: 56 subjects were administered PT101 or placebo. All subjects completed the study. There were no deaths, serious adverse events, dose limiting toxicities, or clinically significant changes in vital sign, ECG, or laboratory results. All adverse events were Grade 1 or 2 and self-limited. Injection site reactions were the most common adverse event. Transient increases in eosinophil counts were observed in some subjects, consistent with the known class effect of IL-2. Peak levels of PT101 occurred 11.0 to 14.6 hours after administration, and declined with a mean half-life of 20.4 to 28.3 hours, demonstrating linear exposure through the dose range. No anti-drug antibodies were induced. PT101 caused dose-related expansion of Tregs that plateaued at doses between 3.5 and 10 mg. Mean maximum expansion above baseline was 3.6-fold for total Tregs and 72.5-fold for the CD25bright subset of Tregs. Maximal expansion was observed by Day 8-10 with a return toward baseline by Day 29. Over 80% of subjects achieved a 2-fold or greater expansion of total Tregs (Table 1). No significant expansion of Tconv or NK cells was observed at any dose level.

Table 1. Percent Total Treg Responders

	Placebo	1 mg	3.5 mg	5 mg	7.5 mg	10 mg
Fold Change Total Tregs	(n=14)	(n=6)	(n=12)	(n=12)	(n=6)	(n=6)
≥ 2X	7%	33%	83%	83%	100%	100%
≥ 3X	0%	0%	58%	75%	33%	50%
≥ 4X	0%	0%	24%	42%	33%	17%

Conclusion: PT101 was safe and well tolerated after a single dose in healthy volunteers. Marked expansion of both total Treg and CD25bright Treg cells was observed. High selectivity for Tregs was observed with no significant expansion of pro-inflammatory Tconv and NK cells even at the highest dose studied. These results support the therapeutic potential of PT101 in planned multiple dose studies in systemic lupus erythematosus, ulcerative colitis, and other autoimmune diseases.
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AB0283 CHOREOATHETHOSIS AND LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS AS RARE AND SEVERE MANIFESTATIONS OF NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS AND PRIMARY SJÖGREN'S SYNDROME – A TWO-CENTER EXPERIENCE

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Background: Systemic lupus erythematosus (SLE) can affect almost any organ system. Nevertheless, Lupus nephritis and neuropsychiatric manifestations (NPSLE) are associated with increased mortality (1). Therapeutic options include glucocorticoids, often pulse methylprednisolone (MP), and other immunosuppressive therapies. In refractory cases, therapeutic plasma exchange, rituximab, or intravenous immunoglobulins are often used (2). However, an optimal therapeutic strategy has not been established because NPSLE is an exclusion criterion in most clinical trials. In addition, NPSLE can present with a broad spectrum of manifestations ranging from cognitive dysfunction to severe and life-threatening disease with choreoathetosis or transverse myelitis (TM). In primary Sjögren's syndrome (pSS), neurological manifestations most often include peripheral neuropathies, but TM has also been reported.
Objectives: To analyze the clinical presentation and outcomes after treatment in severe, life-threatening NPSLE.
Methods: We retrospectively analyzed clinical, laboratory, and imaging features in severe NPSLE manifestations in SLE and pSS patients at two tertiary academic centers (University Medical Center Göttingen, Germany, and ASST Spedali Civili Brescia, Italy) with a high volume of SLE patients. Severe NPSLE was defined as either severe movement disorder or extensive tetra- or paraplegia secondary to (longitudinally extensive) transverse myelitis.
Results: Our retrospective chart review resulted in seven patients fulfilling the inclusion criteria (six with SLE and 1 with pSS). Of these, five were females (71.4%). Median age was 26 (16-55) years. Three were of Asian origin, four were of European descent. Median disease duration was 15 (2-228) months. Three patients presented with severe choreoathetosis, all had positive ANA, anti-dsDNA antibodies (abs), and complement consumption. Of note, all three had at least one positive antiphospholipid antibody (APLA). All patients received IV MP 1g x 3 and mycophenolate mofetil and achieved complete remission. Of the four patients with longitudinally extensive TM, all were ANA positive, only two had anti-dsDNA abs. None of them had APLA, and only one tested positive for anti-aquaporine-4 abs. Of all patients, only one had positive ribosomal P-abs. Patients with TM received IV MP 1g x 5 and either RTX (4 cycles with 375 mg/m^2 or IVIg 0.4 g/kg/d x 5). All four TM patients improved; two improved markedly, two only moderately with residual deficits as assessed by EDMUS-grading scale and functional independence measure.
Conclusion: Severe NPSLE, defined as choreoathetosis or TM require intensive treatment. While the former patients achieved complete remission, two of four patients with TM only achieved partial remission. Our data support the use of early

and aggressive immunosuppressive therapy. Nevertheless, therapy for TM in the context remains insufficient and should be assessed in a controlled clinical trial setting.

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AB0284 COMBINATION THERAPY WITH RITUXIMAB AND BELIMUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Objectives: To assess the efficacy of combined therapy with rituximab (RTM) and belimumab (BLM) in patients with active systemic lupus erythematosus (SLE).

Methods: The study included 12 SLE pts (1M/11F) with severe (SLEDAI2K≥10 – 8pts.) and moderate (SLEDAI2K<10- 4pts.) disease activity; out of them 5 patients had lupus nephritis, vasculitis and 7 had predominantly mucocutaneous and articular manifestations of SLE. The dose of oral GC was: 60 mg in one patient with vasculitis, LN, cerebrovasculitis; in 9 patients from 10 to 5 mg; in 2 patients without oral glucocorticoids. All patients with SLE with kidney damage, CNS, and vasculitis received cytostatics. All patients with vasculitis, LN, etc. received mycophenolate mofetil or cyclophosphamide. Rituximab (RTM) was administered at 500-2000 mg, with subsequent adding of Belimumab (BLM) 1-6 months later at a standard dosing regimen 10 mg/kg once a month a total of 7 infusions. The following parameters were evaluated: the effectiveness of therapy, the concentration of autoantibodies, the dose of oral corticosteroids initially at the time of RTM administration and then every 3 months after the initiation of BLM therapy.

Results: 8 pts demonstrated the decrease in clinical and laboratory SLE activity, starting from 3mo of follow-up. After the start of BLM infusions, a decrease in SLE activity was observed in all patients. Among them, 9 had SLEDAI-2K activity of less than 4 points (SLEDAI-2k Me 12 [9,5;17], after treatment of RTM and BLM 4[2;4]). Only one patient (№4) had a relapse of SLE, due to the omission of the BLM infusion. He was receiving standard GC doses. In dynamics, a decrease anti-double DNA titres (Me 101 [39;250]U/ml vs 19 [9;70] U/ml), C3 (0,44 [0,39;0,59]g/l vs 0,81 [0,72;0,87] g/l), C4 (0,06 [0,031;0,1] g/l vs 0,14 [0,13;0,14] g/l) was registered. The GC dose was reduced in most patients (tab. 1), but the previously prescribed immunosuppressive therapy continued. There were no cases of severe infection.

Conclusion: Combination therapy allows to gain control over disease activity in short time, due to the effect of RTM, while added BLM provides further prolongation of the effect achieved, minimizing the risk of flare. The use of such therapy contributes to a rapid and effective reduction in the activity of the disease, normalization of laboratory markers of SLE (at to ds-DNA, C3, C4), the use of lower doses of oral GCs. This combination may be used as a method of choice in pts with severe SLE involving vital organs, and in persistent cutaneous-articular disease and high immunological activity.

Table 1. Dose of oral glucocorticoids (prednisone), mg

№ patient	Before the introduction of RTM, mg	1st 7th injection of of BLM, mg	7th injection of BLM, mg	
1	20	20	15	↓
2	7,5	5	5	↓
3	5	5	5	=
4	10	10	10	↓
5	5	5	5	=
6	60	7,5	2,5	↓↓↓
7	10	2,5	0	↓↓↓
8	10	10	5	↓
9	2,5	2,5	2,5	=
10	10	10	5	↓
11	0	0	0	=
12	0	0	0	=

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AB0285 EFFECTIVENESS OF IMMUNOSUPPRESSIVE THERAPY FOR CONNECTIVE TISSUE DISEASE–ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

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Background: Connective tissue disease (CTD) associated pulmonary arterial hypertension (PAH) is considered to be an indication for immunosuppressive therapy (IT) except scleroderma associated PAH. However, the response rate defined by improvement of WHO functional class and hemodynamic parameters is reported to be around 50% [1]. Since CTDs are systemic diseases, it may be difficult to evaluate the efficacy of IT by subjective symptoms. Although there are previous studies reporting that the combined use of IT and pulmonary vasodilators significantly improved hemodynamics [2], response to IT without titration of pulmonary vasodilators remains to be elucidated.

Objectives: To examine whether IT is effective for CTD-PAH.

Methods: We retrospectively examined the medical records of consecutive 13 patients with CTD-PAH (female 13, mean age 47 ± 15 years) treated with methylprednisolone (1 mg/kg/day, oral) and intravenous bolus cyclophosphamide (IVCY) (500 mg/m^2) every four weeks for six times. Patient characteristics are described in Table 1. Right heart catheterization (RHC) was done at prior to IT, before adding PAH specific agents, and at the fifth or sixth course of IVCY. In treated cases, the previous vasodilators remained unchanged during the first term of IT.

Results: At the first follow up RHC, decrease of mean pulmonary arterial pressure over 5 mmHg was observed in all patients, and decrease of pulmonary vascular resistance (PVR) was observed in twelve out of 13 patients (Figure 1). Over 20% of PVR reduction was observed more in the patients of pulmonary vasodilator naïve and started IT within one year from symptoms than others (6/7 vs 1/6, p=0.03). Although six-minutes walk distance (6MWD) tended to be prolonged between first and second RHC (298 ± 70 m vs 382 ± 81 m; p=0.054; n = 9), 6MWD was shortened in some cases with good hemodynamic improvement (2/5). All patients were prescribed oral PAH specific agents finally, but no one needed parenteral prostanoids. Two patients (15%) died during maintenance therapy for causes other than PAH. Three-year and five-year survival rates were 91.7% and 81.5%, respectively.

Conclusion: IT without titration of pulmonary vasodilators significantly improved hemodynamic parameters despite of less improvement in 6MWD in CTD-PAH patients. Considering that CTDs itself might affect the exercise tolerance regardless of PAH, these hemodynamic changes may contribute to better prognosis and IT might be considered especially for patients early in clinical courses and treatment naïve.

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Table 1. Characteristics of patients

Patient	Age, yr	Connective Tissue Disease	Years from symptom to immunosuppressive therapy	Previous vasodilators	vasodilators at final visit
1	47	SS	1.5	PGI2	ERA
2	62	SS, RA	2	none	PDE5
3	32	SS	1	none	ERA
4	57	SS, SSc	0.5	none	PDE5
5	26	SS,MCTD, SLE,SSc	0.5	none	PDE5
6	70	SSc, SS s/o	13	sGC, ERA	sGC, ERA
7	32	SS s/o, SLE	0.1	none	PDE5
8	31	MCTD	3	ERA,PDE5, PGI2	ERA,PDE5, PGI2
9	43	SSc, SLE	0.6	ERA, PDE5	ERA,PDE5, PGI2
10	67	MCTD,PM	0	none	sGC
11	41	SS	0.1	none	ERA, PDE5
12	69	SS	0.3	none	PDE5
13	44	SS, MCTD s/o, SLE s/o	0.1	none	ERA, sGC

N.A, not acquired; s/o, suspect of; SS, Sjögren's syndrome; RA, rheumatoid arthritis; SSc systemic sclerosis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; PM, Polymyositis; PGI2, prostacyclin derivative; sGC, soluble guanylate cyclase stimulator; ERA, endothelin receptor antagonist; PDE5, phosphodiesterase type 5 inhibitor.