Letters to the editor

Effects of rituximab therapy on elastic properties of vascular wall in patients with progressive systemic sclerosis

Sirs,

Progressive systemic sclerosis (PSS) is a systemic autoimmune connective tissue disease, predominantly characterised by generalised microvascular involvement of large and small vessels of limbs and internal organs (8).

Therapeutic approaches to PSS are so far limited to the available immunosuppressive drugs. If standard immunosuppressive treatments fail, several experts recommend rituximab, a biologic drug that induces B-cell depletion. Although rituximab is not approved for treatment of PSS, its potential efficacy in treatment of this disease was demonstrated in two small open-label trials. (4, 9). Assuming the importance of vascular damage in the pathogenesis of PSS, the aim of the present study was to investigate the influence of combined treatment with rituximab and cyclophosphamide on arterial stiffness in patients with refractory PSS. Therefore, novel methods of noninvasive assessment of elastic properties of large vessel walls measuring arterial stiffness were used to provide insight into changes of characteristics of the wall defined by its composition and morphological structure after immunosuppressive treatment.

We investigated 5 patients with diffuse cutaneous PSS confirmed according to ACR (ARA) criteria 1980. All patients were refractory to standard treatment with cyclophosphamide pulse-therapy in combination with low-dose steroids showing progression of interstitial pulmonary fibrosis and skin involvement persistent over the past 6 months despite ongoing therapy.

Treatment regimen consisted of 2 infusions of rituximab in a dose of 1000 mg at day 1 and day 14 after standard premedication. At day 1 and day 14 all patients received 500 mg of cyclophosphamide. In order to exclude the effect of concomitant vasoactive therapy, treatment with vasoactive drugs was started at least one year before the study and continued unchanged during observation.

Follow-up evaluation was performed 6 months after anti-B-cell therapy. Measurement of vascular stiffness was performed with applanation tonometry with SphygmoCor system (AtCorMedical, Australia).

After a 6-month follow-up, a partial improvement of symptoms or stabilisation of organ involvement was noted in 4 out of 5 PSS patients. Dynamics of main clinical manifestations and changes in instrumental assessment are shown in Table I. Subjective reduction in complains of skin constriction and induration as well as an objective decrease of Rodnan score were noted in all patients.

After 6 months, unidirectional decrease of pulse wave velocity and augmentation index (AI) was documented. Mean pulse wave velocity decreased significantly from 7.5±1.9 (5.6–9.8) m/sec to 6.6±1.3 (5.4–8.2) m/sec (p=0.04), mean AI decreased markedly from 30.2±11.4 (13–42) to 13.2±7.7 (4–24) (p=0.02).

As a result, we were able to achieve a stabilisation of disease status in four out of five patients. Unidirectional decrease in main parameters of vascular stiffness including pulse wave velocity and AI was evident.

In PSS, several studies published so far have demonstrated an increase in arterial stiffness (5, 8, 10). In these analyses, high arterial stiffness was associated with more severe PSS (6).

Another study in 24 patients with PSS showed a positive relationship between arterial stiffness and soluble markers for inflammation and endothelial cell activation like sE-selectin and sVCAM-1 (1). These data suggests that in PSS arterial stiffness reflects vascular wall remodelling, but not the magnitude of atherosclerosis *per se*.

A decrease of arterial stiffness was also shown by several studies in RA patients under treatment with infliximab. Of note, traditional cardiovascular risk factors also remained unchanged under therapy with TNF-inhibitors (2, 3, 7).

In summary, we were able to show a significant improvement of arterial wall stiffness in patients with PSS after initiation of a combination therapy with rituximab and cyclophosphamide. According to these findings, the observed improvement of elastic properties of the vascular wall indicates a possible involvement of B cells into the pathogenesis of vasculopathy in PSS.

Table I. Clinical characteristics of patients with PSS and outcome of treatment with Rituximab.

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender, M/F	M	F	F	F	F
Age, years	49	27	34	37	49
Disease duration, years	5	2	6	1.8	10
Interstitial lung disease, CT scan	diffuse	diffuse	diffuse	diffuse	diffuse
Pulmonary artery pressure mm.Hg	55	30	18	38	30
Glomerular filtration rate (MDRD), mL/min/1.73 m^2	130	123	89	113	135
Vasoactive and cardiovascular treatment	Selective beta-blocker	Calcium antagonist	Calcium antagonist	Calcium antagonist	Calcium antagonist with diuretic
Skin involvement (modified Rodnan score, points) at initial examination / after a 6-month follow-up	33/24	11/13	27/10	20/17	24/10
Pulse wave velocity, m/s, at initial examination / after a 6-month follow-up	9.5/8.2	6.3/5.8	9.8/7.8	5.6/5.4	6.5/5.8
Pulse wave augmentation index, at initial examination / after a 6-month follow-up	38/15	13/4	26/24	32/15	42/8

A.L. MASLYANSKIY[1], *MD, PhD*
S.V. LAPIN[2], *MD, PhD*
E.P. KOLESOVA[3], *MD*
I.N. PENIN[1], *MD*
M.D. CHESHUINA[1],
E. FEIST[4], *PD, Dr. med*.
A.O. KONRADI[5], *MD, PhD, Prof*.

[1]*Dept. of Rheumatology, Federal Almazov Heart, Blood and Endocrinology Centre, St. Petersburg;*
[2]*Centre for Molecular Medicine, St. Petersburg Pavlov State Medical University;*
[3]*Dept. of Cardiology, Federal Almazov Heart, Blood and Endocrinology Centre, St. Petersburg;*
[4]*Dept. of Rheumatology and Clinical Immunology, Charité Universitätsmedizin, Berlin, Germany;*
[5]*Federal Almazov Heart, Blood and Endocrinology Centre, St. Petersburg, Russian Federation.*

Address correspondence and reprint requests to: Alexey L. Maslyanskiy, MD, PhD, Dept. of Rheumatology, Federal Almazov Heart, Blood and Endocrinology Centre, Akkuratova str. 2, 97341 St. Petersburg, Russian Federation.
E-mail: esc_4@mail.ru

Competing interests: none declared.

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