Does angiotensin and endothelin receptor blockade have an impact on lung function? An analysis from the EUSTAR database

Sirs,

Antibodies against the angiotensin II type-1 receptor (AT1R) and endothelin-1 type A receptor (ETAR) are simultaneously present in the majority of patients with systemic sclerosis (SSc). Higher levels of these receptors are associated with severe SSc vascular manifestations such as pulmonary arterial hypertension (PAH) (1). Anti-AT1R and anti-ETAR antibodies are more frequent in PAH associated to SSc compared with other forms of pulmonary hypertension. They may serve as prognostic biomarkers of cardiovascular complications and mortality (2). Animal models have demonstrated that passive transfer of anti-AT1R and anti-ETAR IgG antibodies from SSc patients into mice triggers similar pathological features to those observed in SSc patients (2, 3). Human AT1R-immunised mice have developed functional autoantibodies against AT1R and induced SSc-like disease with consequent interstitial inflammation in the lung and skin fibrosis (4). It is suggested that these antibodies may contribute to lung involvement by stimulating their receptors. In SSc patients levels of anti-AT1R and anti-ETAR antibodies strongly correlate with each other and show cross-reactivity for both receptors (5). Thus, angiotensin receptor blockers (ATRB) and/or endothelin receptor blockers (ETRB) may exhibit beneficial effects on lung function. The objective of our study was to evaluate possible benefit of simultaneous ATRB and ETRB blockade, analysing the EUSTAR database, described previously (6). Patients fulfilling the American College of Rheumatology (ACR) classification criteria for SSc were divided into clinical subgroups defined according to LeRoy *et al*. (7). SSc patients with lung fibrosis prospectively followed and treated with ETRB and/or ATRB were analysed in regard to the evolution of forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO) and compared to patients without receptor blockade. Pulmonary fibrosis was defined by evidence of fibrosis such as bibasilar fibrosis on chest x-rays or HR-CT scans or both. Patients receiving immunosuppressive therapy were excluded.

In total, 9862 patients were analysed: 764 patients took ETRB and 674 ATRB, of whom only 410 patients had at least one annual follow-up (mean period 13.12 months, SD ±3.25). Due to concomitant immunosuppressive therapy, 239 were excluded from further analyses. Finally, 31 patients with simultaneous ATRB/ETRB, 31 patients with ATRB, 31 patients with ETRB and 31 patients not receiving any blockade were matched and compared (Table I). Patients with simultaneous ATRB/ETRB and ETRB blockade had a higher prevalence of lung fibrosis (as suggested by chest x-rays or HR-CT scans) in comparison to the group with the other two groups: only ATRB blockade and without any blockade. As expected, patients receiving ETRB had a higher prevalence of PAH (as suggested by echocardiography) compared to patients without blocker therapy. In contrast, the prevalence of these complications in patients receiving ATRB did not differ in comparison to the group without any blockade.

Table I. Clinical and laboratory characteristics of the matched SSc patients [data expressed as absolute number (%), unless otherwise indicated].

	ETRB-/ATRB- (n=31)	ETRB-/ATRB+ (n=31)	ETRB+/ATRB- (n=31)	ETRB+/ATRB+ (n=31)
Age[a]	55.25 ± 13.40	62.66 ± 8.29	57.77 ± 14.42	61.31 ± 13.28
Disease duration[b]	9 (1-13)	9 (5-13)	8 (3-17)	6 (1-37)
Disease subset (lcSSc/dcSSc)	18/9	14/12	19/7	16/10
DLCO[a]	67.78 ± 13.19	67.19 ± 15.42	66.14 ± 20.16	61.42 ± 18.27
FVC[a]	94.52 ± 15.89	101.30 ± 23.82	88.66 ± 18.90	93.92 ± 19.72
Lung fibrosis	4 (14.81)	4 (15.3)	13 (37.1)	8 (30.7)
Anti topo I	11 (40.7)	10 (38.4)	22 (62.8)	8 (30.7)
ACA	12 (44.4)	8 (30.7)	7 (20.0)	9 (34.6)
ANA	27 (100.0)	24 (92.3)	35 (100.0)	26 (100.0)
PAH	2 (7.4)	3 (11.5)	13 (37.1)	15 (57.7)
DU	10 (37.0)	5 (19.2)	20 (57.1)	14 (53.8)

[a]Values expressed as mean±SD.
[b]Values expressed as median (minimum–maximum range).
SSc: systemic sclerosis; ETRB-/ATRB-: SSc patients without endothelin antagonist (bosentan) and angiotensin receptor blockers; ETRB-/ATRB+: SSc patients with only AT receptor blockers; ETRB+/ATRB-: SSc patients with only endothelin antagonist (bosentan); ETRB+/ATRB+: SSc patients with endothelin antagonist (bosentan) and angiotensin receptor blockers; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; DLCO: carbon monoxide diffusing capacity; FVC: forced vital capacities; ACA: anticentromere antibodies; ANA: antinuclear antibodies; PAH: pulmonary arterial hypertension; DU: digital ulcers; SD: standard deviation.

Table II. Change in DLCO (% predicted) and FVC (% predicted). Data are expressed as mean±SD.

	ETRB-/ATRB-	ETRB-/ATRB+	ETRB+/ATRB-	ETRB+/ATRB+
Change in DLCO (% predicted)[a]	2.9 ± 15.3	3 ± 14.3	4 ±8.6	-7.0 ±16.0
Follow-up time (months)[a]	24.2 ± 12.8	15.6 ± 7.9	13.6 ±6.4	15.5 ±6.7
Change in FVC (% predicted)[b]	-0.2 ± 11.6	-0.9 ± 13.4	0.7 ±15.9	-3.4 ±11.9
Follow-up time (months)[b]	20.0 ± 15.2	16.8 ± 13.2	13.6 ±6.4	15.5 ±6.7

[a]Data available for 31 patients in each group for change in DLCO.
[b]Data available for 29 patients in each group for change in FVC.

Unexpectedly, patients without any blockade did not show reduction in mean DLCO levels during follow-up period (Table II). DLCO reduction was prevented in patients receiving ATRB with DLCO worsening ≥10% (% predicted) in only 3 patients (9.7%), and most patients receiving ATRB/ETRB had stable DLCO values compared to baseline (74.2%). There was no statistically significant improvement of predicted DLCO values according to treatment. There was no significant effect of ATRB or ETRB on FVC levels (Table II), although a higher proportion of patients receiving ATRB (27.6%) showed improved FVC levels ≥ 10% predicted, compared to 17.2% in the control group without blockers.

Contrary to animal models' suggestions, our data do not indicate a potentially beneficial effect of ATRB or ETRB on lung function parameters. Study was limited by its size, observational design and differences in disease activity/severity between groups. Higher prevalence of lung fibrosis in groups of patients with ETRB and simultaneous ETRB/ATRB blockade could also account for the fact that beneficial effect of simultaneous ETRB/ATRB and only ETRB blockade was not demonstrated in this study. Current EULAR recommendations for the treatment of SSc-PAH or lung disease have not considered the possibility of simultaneous ATRB and ETRB therapy (8, 9). Agents blocking ETAR or AT1R, approved for treatment of various autoimmune diseases, have been successfully used to treat clinical complications, however the effect on inflammatory cell recruitment to the lungs still remains to be determined (10, 11). Further larger prospective studies are warranted to elucidate the role of angiotensin and endothelin receptor blockade in possible prevention of lung function deterioration.

M. Radic[1,2], *MD, PhD*
M.O. Becker[2,3], *MD, MSc*
O. Distler[3], *MD*
D. Huscher[4], *PhD*
E. Siegert[2], *MD, BA*
G. Riemekasten[2,5], *MD, PhD*
on behalf of the EUSTAR group

[1]University Hospital Split, Rheumatology and Clinical Immunology, Split, Croatia;
[2]University Hospital Charité, Rheumatology and Clinical Immunology, Berlin, Germany;
[3]Rheumatology, University Hospital Zurich, Switzerland;
[4]German Rheumatism Research Centre Berlin, Epidemiology, Berlin, Germany;
[5]University Hospital Schleswig-Holstein, Rheumatology, Lübeck, Germany.

Please address correspondence to:
Dr Mislav Radić,
Šižgorićeva 20/II,
21 000 Split, Croatia.
E-mail: mislavradic@gmail.com

Competing interests: O. Distler had a consultancy relationship and/or has received research funding from Actelion, Acceleron Pharma, Amgen, AnaMar, Baecon Discovery, Blade Therapeutics, Bayer, Boehringer Ingelheim, Catenion, CSL Behring, ChemomAb, Curzion Pharmaceuticals, Ergonex, Glenmark Pharmaceuticals, GSK, Inventiva, Italfarmaco, iQone, iQvia, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Target Bio Science and UCB in the area of potential treatment of scleroderma and its complications. In addition, he has a patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143). D. Huscher has received travel recompensation for study meetings from Actelion, Switzerland, and Boehringer Ingelheim, Germany. E. Siegert has received grants and travel bursaries from Actelion. The other co-authors have declared no competing interests.

References

1. RIEMEKASTEN G, PHILIPPE A, NÄTHER M *et al*.: Involvement of functional autoantibodies against vascular receptors in systemic sclerosis. *Ann Rheum Dis* 2011; 70: 530-6.
2. BECKER MO, KILL A, KUTSCHE M *et al*.: Vascular receptor autoantibodies in pulmonary arterial hypertension associated with systemic sclerosis. *Am J Respir Crit Care Med* 2014; 190: 808-17.
3. KILL A, TABELING C, UNDEUTSCH R *et al*.: Autoantibodies to angiotensin and endothelin receptors in systemic sclerosis induce cellular and systemic events associated with disease pathogenesis. *Arthritis Res Ther* 2014; 16: R29.
4. YU X: Anti-AT1R ab and as cause or contributor to skin fibrosis and interstitial lung disease. rab. 23 Sep.2018 [cited 10Dec.2018];1(1):Advances in RAB Research, Vol 1, No 1, 2018 -. Available from: https://journals.infinite-science.de/index.php/RAB/article/view/26
5. MORONCINI G, SVEGLIATI BARONI S, GABRIELLI A: Agonistic antibodies in systemic sclerosis. *Immunol Lett* 2018; 195: 83-7.
6. WALKER UA, TYNDALL A, CZIRJÁK L *et al*.: Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007; 66: 754-63.
7. LEROY EC, MEDSGER TA JR.: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-6.
8. KOWAL-BIELECKA O, FRANSEN J, AVOUAC J *et al*. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327-39.
9. DENTON CP, KHANNA D: Systemic sclerosis. *Lancet* 2017; 390: 1685-99.
10. CABRAL-MARQUES O, RIEMEKASTEN G: Functional autoantibodies targeting G protein-coupled receptors in rheumatic diseases. *Nat Rev Rheumatol* 2017; 13: 648-56.
11. ORLANDI M, BARSOTTI S, LEPRI G *et al*.: One year in review 2018: systemic sclerosis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S3-23.