Factors associated with disease progression in early-diagnosed pulmonary arterial hypertension associated with systemic sclerosis: longitudinal data from the DETECT cohort

Carina Mihai[1], Milos Antic[2], Rucsandra Dobrota[1,2], Diana Bonderman[3], Harbajan Chadha-Boreham[4], J Gerry Coghlan[5], Christopher P Denton[6], Martin Doelberg[4], Ekkehard Grünig[7], Dinesh Khanna[8], Vallerie V McLaughlin[9], Ulf Müller-Ladner[10], Janet E Pope[11], Daniel M Rosenberg[4], James R Seibold[12], Madelon C Vonk[13], Oliver Distler[2]

[1]Department of Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

[2]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

[3]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria

[4]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland.

[5]Cardiology Department, Royal Free Hospital, London, UK.

[6]Centre for Rheumatology, Royal Free Hospital, London, UK

[7]Centre for Pulmonary Hypertension, Thoraxclinic at the University Hospital Heidelberg, Heidelberg, Germany.

[8]Division of Rheumatology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

[9]Division of Cardiology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA.

[10]Department of Rheumatology and Clinical Immunology, Justus-Liebig University, Giessen, Germany.

[11]Department of Medicine, Division of Rheumatology, Western University of Canada, London, ON, Canada.

[12]Scleroderma Research Consultants LLC, Litchfield, CT, USA, and Medical College of Georgia, Augusta, GA, USA.

[13]Department of Rheumatology, Radboud University Medical Centre, Nijmegen, The Netherlands

Keywords: systemic sclerosis, pulmonary arterial hypertension, disease progression, risk factors

Word count: 1500

Corresponding author:

Oliver Distler, MD, Department of Rheumatology, University Hospital Zurich, Gloriastr. 25, 8091 Zürich, Switzerland, Email: Oliver.Distler@usz.ch, Tel: +41-44-255-2977

Abstract

Objective: Pulmonary arterial hypertension (PAH) is a severe complication of systemic sclerosis (SSc). In this longitudinal study, we aimed to identify factors associated with an unfavourable outcome in SSc patients with early PAH (SSc-PAH) from the DETECT cohort.

Methods: Patients with SSc-PAH enrolled in DETECT were observed for up to 3 years. Associations between cross-sectional variables and disease progression (defined as the occurrence of any of the following events: World Health Organization Functional Class worsening, combination therapy for PAH, hospitalisation, or death) were analysed by univariable logistic regression.

Results: Of 57 patients with PAH (median observation time 12.6 months), 25 (43.9%) had disease progression. The following factors [odds ratio, (95% confidence interval)] were associated with disease progression: male gender [4.1 (1.2-14.1)], high Forced Vital Capacity (FVC) % predicted/ DLCO % predicted ratio [3.6 (1.2-10.7)], high Borg dyspnoea index [1.7 (1.1-2.6)], and DLCO % predicted (non-linear relationship).

Conclusion: More than 40% of early-diagnosed SSc-PAH patients had disease progression during a short follow-up time, with male gender, functional capacity, and pulmonary function tests at PAH diagnosis being associated with progression. This suggests that even mild PAH should be considered a high-risk complication of SSc.

Abstract word count: 192

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe complication of systemic sclerosis (SSc), with high mortality if not promptly diagnosed and treated.[1,2] Correct diagnosis of PAH requires invasive investigation by right-sided heart catheterisation (RHC).[3]

The DETECT study was the first multicentre, real-life study systematically using RHC in patients with SSc at increased risk to develop PAH.[4] In its cross-sectional stage, DETECT developed an algorithm able to select patients with SSc and a high suspicion of PAH for referral to RHC, minimizing missed diagnoses in addition to identifying patients with milder PAH, in whom prompt

institution of treatment might improve the disease course.

However, the prognosis of these patients with early detection of PAH has not been established to date. As part of the DETECT study, patients have been observed longitudinally for up to 3 years. This study reports on the longitudinal phase of the DETECT study, aiming to describe factors associated with an unfavourable outcome in patients with an early diagnosis of SSc-PAH.

PATIENTS AND METHODS

Data collection during the longitudinal stage of DETECT

The cross-sectional part of the DETECT study has been published.[4] Eighteen of the 62 centres involved in DETECT continued to follow up patients diagnosed with SSc-PAH at baseline on a yearly basis. The following data were recorded: survival status, reason for end of follow-up or death, WHO Functional Class (FC), PAH-related hospitalization (>1 day) since last visit, 6-Minute walk distance (6MWD), current or past treatment with PAH specific therapies, including duration of therapy, and combination therapy. At the time of longitudinal data collection, combination therapy for PAH was used for more severe PAH, as the advantages of upfront combination therapy for PAH have emerged later.[5] Patients in WHO-FC I and II are further referred to as having mild, or early, PAH.

Statistical methods

Disease progression was defined by expert consensus as a composite outcome, based on the presence of at least one of the following events during follow-up: worsening in WHO FC from enrolment; presence of combination therapy for PAH; PAH-related hospitalization; and death from any cause.

The main analysis set comprises all SSc-PAH patients who were included in the longitudinal stage of the DETECT study and who had available follow-up data. The complementary set of SSc-PAH patients, who could not be included in the longitudinal stage, was used only for examining any potential selection bias that may have occurred. Two subgroups of the SSc-PAH analysis set were defined by the binary disease progression outcome i.e., "With disease progression" (progressive PAH) or "Without disease progression" (stable PAH).

Twenty-one of 121 baseline (cross-sectional) variables considered to be potential predictors of disease progression were selected for further analysis, based on input from the authors on feasibility of the variables and on their clinical relevance to PAH. Univariable Logistic Regression (ULR) analysis was performed using the binary disease progression outcome as dependent variable and the selected baseline variables as independent variables. ULR included the determination of odds ratio (OR) and its 95% confidence interval (95% CI), and area under the receiver-operating characteristic curve (ROC-AUC) and its 95% CI. Accuracy of a predictor was considered fair if its AUC was <0.70. For each continuous baseline variable analysed by ULR, a quadratic term in the regression model was also included, in order to examine a non-linear functional relationship with the outcome. A sensitivity analysis, excluding patients with missing outcome data, was also performed. The statistical analysis plan was developed and analyses were carried out by qualified statisticians using the SAS software (version 9.4.).

RESULTS

Study cohort

Of the 145 patients with SSc-PH identified in the DETECT study, 87 (60%) had PAH, of whom 57 patients had follow-up visits and the remaining 30 patients did not have follow-up visits (Figure 1). Median time of

follow-up was 12.6 months (range 2.4-35.8, interquartile range 10.7-21.7).

Demographic and clinical characteristics

Using the composite definition of disease progression, 25/57 (43.9%) of the PAH patients with longitudinal data had progressive PAH and 32/57 (56.1%) had stable PAH. Demographics and clinical characteristics at enrolment of all, stable and progressive PAH patients respectively are displayed in Table 1. Baseline mean mPAP was 32.5 (standard deviation 8.3) mmHg and 33/57 (57.9%) of patients were in WHO-FC I or II. Stable PAH patients had a slightly longer follow-up, when compared to progressive PAH patients ([months, mean, (Q1, Q3)]: 13.0 (11.0, 21.6) vs. 11.7 (10.2, 21.9)) but this difference was not significant (as shown by the overlapping 95% Hall-Wellner Bands of the Kaplan-Meier estimates, Figure S1 in the online supplement). Twenty-four of the 25 patients with progressive PAH and 28/32 patients with stable PAH received PAH treatment during follow-up. Four patients had missing data among the outcomes defining disease progression; they were included in the subgroup without disease progression (see Table 1), but were excluded in the sensitivity analysis.

Disease progression events

Among the 25 patients with disease progression, 4 died, 11 were hospitalized for PAH, 14 had at least one occurrence of worsening in WHO-FC, and 8 received PAH-specific combination treatment. Among the 4 patients who died, 3 were died from a PAH-related cause (all in WHO-FC III at enrolment), while the fourth died from severe pneumonia complicating surgery on the leg. Time to death in all cases was <12 months from baseline (range 2.4 - 10.5 months). Although the 1-year survival rate in this cohort was high (93%), there is some uncertainty as shown by the wide 95% Hall-Wellner Bands (online supplement, Figure S1).

Table 1. Description of demographic and clinical characteristics at enrolment (cross-sectional stage) by group

	PAH-L (PAH patients with longitudinal data)			PAH patients without longitudinal data (N = 30)
	All Overall PAH-L group (N = 57)	Progressive PAH (PAH-L patients with disease progression) (N = 25)	Stable PAH (PAH-L patients without progression) (N = 32)	
Demographics				
Age (years): Median (Q1,Q3)	61.0 (55.0, 66.0)	61.0 (54.0, 66.0)	62.5 (55.5, 68.0)	64.0 (58.0, 70.0)
Males: n (%)	16 (28.6 %)	11 (44.0 %)	5 (16.1 %)	6 (20.0 %)
Body mass index (kg/m2): Median (Q1,Q3)	25.81 (23.8, 28.4)	24.89 (22.5, 28.6)	26.26 (24.4, 28.0)	24.19 (21.1, 28.3)
Disease characteristics				
SSc duration* (months): Median (Q1,Q3)	129.51 (62.6, 201.9)	129.64 (59.7, 214.7)	120.46 (83.9, 190.1)	133.5 (64.7, 185.6)
dcSSc: n (%)	15 (26.3 %)	6 (24.0 %)	9 (28.1 %)	3 (10.3 %)
Functional capacity				
WHO functional class, n (%)				
I	11 (19.3 %)	6 (24.0 %)	5 (15.6 %)	5 (16.7 %)
II	22 (38.6 %)	7 (28.0 %)	15 (46.9 %)	18 (60.0 %)
III	24 (42.1 %)	12 (48.0 %)	12 (37.5 %)	7 (23.3 %)
6-min walk test (m): Median (Q1,Q3)	387.5 (326.5, 479.0)	373.75 (312.5, 411.1)	419.37 (333.0, 524.5)	403.15 (290.0, 452.0)
Borg dyspnoea index: Median (Q1,Q3)	3 (2, 4)	2 (2, 4)	2 (1, 3)	2 (1, 6)
Pulmonary function tests				
DLCO % predicted: Median (Q1,Q3)	45.0 (35.0, 53.0)	39.0 (32.0, 45.0)	51.0 (43.1, 55.8)	43.0 (37.0, 48.0)
FVC % predicted/ DLCO % predicted: Median (Q1,Q3)	2.07 (1.7, 2.4)	2.25 (1.9, 2.9)	1.87 (1.6, 2.2)	2.22 (1.8, 2.5)

Laboratory tests				
ACA positive: n (%)	27 (49.1 %)	11 (44.0 %)	16 (53.3 %)	13 (52.0 %)
NT-proBNP (pg/ml): Median (Q1,Q3)	204 (99, 710)	363 (150, 809)	160.5 (95, 471)	192 (106, 462)
Serum urate, mg: Median (Q1,Q3)	6.0 (5.0, 6.9)	6.0 (5.7, 7.1)	5.6 (5.0, 6.7)	5.2 (4.6, 6.4)
ECG parameters				
Right axis deviation: n (%)	9 (16.4 %)	4 (16.0 %)	5 (16.7 %)	2 (7.1 %)
Right ventricular strain: n (%)	9 (16.4 %)	4 (16.0 %)	5 (16.7 %)	3 (10.7 %)
Echocardiography parameters				
Right atrium area, cm^2 Median (Q1,Q3)	16.3 (14.1, 20.5)	16.8 (15.0, 20.8)	15.5 (13.9, 20.0)	14.0 (12.0, 17.0)
Right ventricle area, cm^2 Median (Q1,Q3)	19.0 (16.1, 22.7)	19.4 (17.6, 22.7)	18.4 (13.5, 22.7)	16.0 (13.1, 21.0)
TR velocity m/s Median (Q1,Q3)	3.0 (2.6, 3.5)	3.1 (2.6, 3.6)	2.9 (2.6, 3.4)	3.20 (2.7, 3.5)
RHC parameters				
mPAP, mmHg Median (Q1,Q3)	29 (27, 36)	29 (27, 38)	28.5 (26, 35)	30.5 (26, 37)
PCWP, mmHg Median (Q1,Q3)	12.0 (9.9, 13.0)	10.0 (7.0, 13.0)	12.0 (10.0, 13.0)	10.0 (6.0, 12.0)
PVR ($dyn \cdot s/cm^5$) Median (Q1,Q3)	270.97 (231.9, 400.0)	312.64 (231.9, 409.8)	263.95 (229.6, 366.7)	316.66 (231.1, 480.0)
Cardiac Index (l/min/m2) Median (Q1,Q3)	2.84 (2.5, 3.3)	2.83 (2.4, 3.3)	2.89 (2.6, 3.3)	2.87 (2.6, 3.6)

* from the first non-Raynaud symptom

Q1,Q3 = interquartile range; dcSSc – diffuse cutaneous SSc; WHO – World Health Organization; DLCO – carbon monoxide lung diffusion capacity; FVC – forced vital capacity; ACA – anti-centromere antibodies; NT-proBNP – N-terminal pro-(Brain Natriuretic Peptide); ECG – electrocardiogram; TR – tricuspid regurgitation; RHC – right-sided heart catheterization; mPAP – mean pulmonary artery pressure on RHC; PCPW – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance.

Factors associated with disease progression

Baseline factors potentially associated with PAH disease progressionwere analysed by ULR (table 2). Male gender, high FVC%/DLCO%, low DLCO%, and high Borg dyspnoea index at enrolment were found to be significantly associated with disease progression. However, the first two had an AUC<0.70, denoting a relatively poor performance as single predictors. The results of the sensitivity analysis were similar and are reported in the online supplement.

Table 2. Univariable logistic regression analysis for baseline parameter associations with disease progression

Variable	Progressive PAH (with disease progression) (N=25) n	Stable PAH (without disease progression) (N = 32) n	Univariable logistic regression OR [95% CI]	Wald Chi-square p-value*	ROC-AUC [95% CI]
Demographics					
Age	25	32	0.985 (0.929-1.045)	0.623	0.539 (0.38- 0.695)
Male sex	**25**	**31**	**4.085 (1.181-14.128)**	**0.026**	**0.639 (0.520-0.758)**
Disease characteristics					
Disease duration (months)	25	32	0.999 (0.994-1.003)	0.548	0.514 (0.357-0.672)
SSc subtype (dcSSc vs. lcSSc)	25	32	0.978 (0.288-3.325)	0.971	0.566 (0.436-0.697)
Functional capacity					
WHO functional class					
I+II vs. III+IV	25	32	0.650 (0.225-1.880)	0.427	0.553 (0.421-0.684)
6-min walk test	20	24	0.996 (0.990-1.001)	0.141	0.621 (0.450-0.791)
Borg dyspnoea index	**21**	**24**	**1.685 (1.092-2.598)**	**0.018**	**0.711 (0.560-0.863)**
Pulmonary function tests					
DLCO %	**25**	**32**	**-§**	**0.008**	**0.753 (0.626-0.881)**
FVC%/DLCO%	**25**	**32**	**3.608 (1.223-10.647)**	**0.020**	**0.693 (0.553-0.832)**
Laboratory tests					
ACA positive	25	30	0.688 (0.237-1.998)	0.491	0.547 (0.412-0.681)
NT-proBNP	25	30	1.668 (0.595-4.673)	0.330	0.599 (0.446-0.753)

Serum uric acid	25	30	1.224 (0.853-1.756)	0.272	0.601 (0.448-0.755)
ECG parameters					
Right axis deviation	25	30	0.952 (0.226-4.008)	0.947	0.503 (0.403-0.603)
Right ventricular strain	25	30	0.952 (0.226-4.008)	0.947	0.503 (0.403-0.603)
Echocardiography parameters					
US right atrium area	22	31	1.019 (0.923-1.126)	0.704	0.609 (0.456-0.761)
US right ventricle area	21	32	1.034 (0.952-1.124)	0.424	0.601 (0.448-0.755)
TR velocity	22	29	1.204 (0.503-2.881)	0.677	0.522 (0.355-0.689)
RHC parameters					
Cardiac index	25	31	1.129 (0.492- 2.586)	0.775	0.492 (0.333-0.650)
mPAP	25	32	1.018 (0.951-1.090)	0.607	0.561 (0.411-0.712)
Mean PCWP	25	32	0.864 (0.720-1.037)	0.117	0.616 (0.463-0.768)
PVR	25	32	1.001 (0.998-1.003)	0.651	0.547 (0.390-0.703)

[§] The odds ratio is not given, because the quadratic functional relationship in the ULR model showed statistical significance. The p-value and ROC-AUC are from the ULR model with the quadratic functional form. A sensitivity analysis excluding 4 patients with missing data on disease progression did not change the conclusions.

Disease progression was defined as presence of one of the following events: clinical worsening, combination PAH therapy, hospitalization, or death. All variables except gender, disease subset and ACA-positivity have been analysed as linear terms. Results in bold characters are statistically significant.

OR – odds ratio; 95% CI – 95% confidence interval; AUC – area under the curve; dcSSc – diffuse cutaneous SSc; lcSSc – limited cutaneous SSc; ACA – anti-centromere antibodies; WHO – World Health Organization; DLCO – carbon monoxide lung diffusion capacity; FVC – forced vital capacity; NT-proBNP – N-terminal pro-(Brain Natriuretic Peptide); ECG – electrocardiogram; US – ultrasonography; TR – tricuspid regurgitation; RHC – right-sided heart catheterization; mPAP – mean pulmonary artery pressure on RHC; PCPW – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance.

Discussion

This study is the first longitudinal observation of a cohort of patients with SSc-PAH diagnosed by systematic RHC.[4] Most patients had mild or no PAH symptoms. None of these patients had been diagnosed with PH by RHC before study enrolment and the majority were in WHO FC I and II (33/57, 57.9%).

We observed that 25/57 patients (43.9%) had disease progression during a median follow-up of 12.6 months; 13/25 were in WHO-FC I or II and 4/25 died during the first 12 months since PAH diagnosis (1-year survival rate 93%). This demonstrates that even mild PAH should be regarded as a high-risk complication of SSc.

The factors found to be associated with disease progression were male gender, lower DLCO%, higher FVC%/DLCO% ratio, and higher Borg dyspnoea index. These factors are similar to risk factors identified for more advanced PAH patients.[7-11] Low DLCO and male gender are independent, major risk factors for death in all SSc patients, as shown in several large cohorts.[12-14] Higher FVC%/DLCO% ratio is not only a risk factor for PAH in patients with SSc [4], but also suggests the absence of significant interstitial lung disease. Of note, patients in the DETECT cohort had, by enrolment criteria, DLCO<60% predicted and FVC>40% predicted; this has certainly influenced the FVC%/DLCO% ratio, which was rather high in the entire DETECT cohort.

The risk factors identified by our exploratory analysis are highly feasible to use in clinical practice. Particular attention should be given to DLCO monitoring, both for PAH screening and prognostic purposes in patients with SSc.

One of the main strengths of this study is the uniqueness of the DETECT cohort, in which every patient underwent RHC at enrolment and had not been diagnosed with PAH before. High data quality was ensured

by standardised echocardiographic and RHC protocols in all centres, with centralised laboratory testing and data management, and strict data quality monitoring.[4] The composite definition of disease worsening includes strong outcomes like death and hospitalization due to PAH, adjudicated as per investigators' judgement.

One of the study limitations is the lack of longitudinal data in 30 patients with SSc-PAH from the original DETECT cohort. However, the baseline data displayed in Table 1 show that these patients without follow-up data were in most aspects similar to PAH patients having longitudinal data. Another potential limitation is the preselected nature of this cohort, limiting generalisation of our results. Although 4 patients in the PAH cohort had missing data on disease progression and were classified as having stable PAH, obtaining similar results in the sensitivity analysis which excluded these patients proved the validity of our results. Further potential limitations include the relatively short follow-up, the variability in PAH treatment due to the international, multicentre character of the study and the impossibility to perform multivariable analysis or to adjust the analysis for PAH treatment, due to the small number of cases.

In conclusion, the results of our study have practical implications, as they show that patients with early SSc-PAH have a meaningful rate of disease progression over a relatively short time, requiring close follow-up. Male patients with lower DLCO%, high FVC%/DLCO%, and high Borg dyspnoea index might need particular attention.

Acknowledgements

The authors would like to thank all investigators and patients involved in the DETECT study.

Contributors:

All authors participated in study design. OD, MA, DK, JGC, CPD, EG, DB, UML, JEP, MCV, JRS and

VVM recruited patients to the DETECT study and collected data. HCB and DR conducted the statistical analyses. CM, RD and OD drafted the manuscript, which was critically reviewed, edited and approved for submission by all authors.

Funding

Actelion Pharmaceuticals Ltd. funded the DETECT study including is longitudinal phase presented in this manuscript.

Competing interests

Carina Mihai has/had consultancy relationship and/or has received honoraria from Actelion Pharmaceuticals Ltd, Abbvie, Roche, and Geneva Romfarm in the area of systemic sclerosis and its complications.

MA- no disclosures.

Rucsandra Dobrota has received research funding from Actelion Pharmaceuticals Ltd and Pfizer (Articulum fellowship).

Diana Bonderman has/had consultancy relationship and/or has received research funding from Actelion Pharmaceuticals Ltd, GlaxoSmithKline, Merck Sharp & Dohme, Bayer, Pfizer, AOP Orphan, United Therapeutics.

J Gerry Coghlan has/had consultancy relationship and/or has received research funding from Actelion Pharmaceuticals Ltd, GlaxoSmithKline, United Therapeutics, Bayer and Endotronics.

Christopher P Denton has/had consultancy relationships, received lecture honoraria and/or has received research funding from Actelion Pharmaceuticals Ltd, Pfizer, GlaxoSmithKline, Sanofi-Aventis and Novartis.

Ekkehard Grünig received speaker honoraria/advisory board fees and has taken part in clinical trials from Actelion Pharmaceuticals Ltd, GlaxoSmithKline, Merck Sharp & Dohme, Bayer, United Therapeutics, Pfizer, OMT, AOP Orphan, Novartis.

Dinesh Khanna has/had consultancy relationship and/or has received research funding from Actelion Pharmaceuticals Ltd, Bayer, Bristol-Myers Squibb, Covis, Cytori, EMD Serono, Genentech/Roche, Gilead, GSK, Sanofi-Aventis, NIH K24AR063120

Vallerie V McLaughlin VVM has acted as a consultant and/or received honoraria/lecture fees from Actelion Pharmaceuticals Ltd, Bayer, Gilead and United Therapeutics. She has received research funding (to the University of Michigan) from Actelion Pharmaceuticals Ltd, Bayer, Novartis and United Therapeutics.

Ulf Müller-Ladner has acted as a consultant and lecturer for Actelion Pharmaceuticals Ltd, Pfizer and GlaxoSmithKline.

Janet E Pope consults for Actelion Pharmaceuticals Ltd, Bayer, Bristol-Myers Squibb, Merck, Roche with respect to potential SSc treatment.

James R Seibold has/had consultancy relationships with Acer, Anthera, arGen-X, aTyr, Bayer, Blade, Boehringer-Ingelheim, Bristol Myers Squibb, Biogen Idec, Covis, Eiger, EMD Serono, Genkyotex, Gilead, Ironwood, Medac, MedImmune, Mitsubishi, Octapharma, Roche-Genentech, Sanofi, Teva and United Therapeutics.

Madelon C Vonk has/had consultancy relationship and/or has received research funding from Actelion Pharmaceuticals Ltd, Therabel and United Therapeutics.

Harbajan Chadha-Boreham, Martin Doelberg and Daniel M Rosenberg are employees of Actelion Pharmaceuticals Ltd.

Oliver Distler has/had consultancy relationship and/or has received research funding from 4 D Science, Actelion Pharmaceuticals Ltd, Active Biotec, Bayer, Biogen Idec, Boehringer Ingelheim Pharma, Bristol-

Myers Squibb, ChemomAb, EpiPharm, Ergonex, espeRare foundation, GlaxoSmithKline, Roche-Genentech, Inventiva, Lilly, Medac, MedImmune, Mitsubishi Tanabe, Pharmacyclics, Pfizer, Sanofi, Serodapharm and Sinoxa in the area of potential treatments of scleroderma and its complications. He has a patent on mir-29 for the treatment of systemic sclerosis licensed.

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