Response to: 'Anti-Ku syndrome with elevated CK: association with myocardial involvement in systemic sclerosis' by Campochiaro *et al*

We thank Campochiaro *et al* for their interesting comment[1] on our work in which we used hierarchical clustering on principal components to define clinically meaningful subgroups of patients with anti-Ku antibodies.[2]

Among a bi-centric cohort of patients with systemic sclerosis (SSc), Campochiaro *et al* identified four patients with anti-Ku and retrospectively reviewed these cases.

All patients had increased creatine kinase (CK), three (75%) of whom had interstitial lung disease (ILD). These findings support our observations according to which anti-Ku patients with elevated CK are at risk of ILD.

Of particular interest, Campochiaro *et al* proposed that myocarditis could further represent a specific feature of anti-Ku patients with elevated CK given that all of their four anti-Ku SSc patients had cardiac magnetic resonance (CMR) imaging established myocarditis according to Lake Louise criteria. Two (50%) had heart failure while the remaining two had subclinical presentation. By contrast, in our cohort, one anti-Ku patient had heart failure with positive CMR (2% of all anti-Ku patients and 7% of anti-Ku patients with elevated CK).

Comparability between the Campochiaro *et al*'s study and our study is limited however since: (1) Campochiaro *et al* studied patients with SSc and all of their anti-Ku patients were diagnosed with myositis. The association of these two conditions has been associated with a high risk of myocarditis per se.[3 4] By contrast, only two (5%) of our anti-Ku patients fulfilled the ACR/EULAR criteria for SSc and only one also fulfilled the EULAR/ACR criteria for myositis; (2) Campochiaro *et al* performed CMR in all patients with increased serum troponin T levels, an enzyme whose serum level is increased in myositis patients irrespectively of the presence of myocarditis.[5] By opposition, our patients underwent CMR only when clinical signs of myocarditis were present.

To further address the interesting point raised by Campochiaro *et al*, we conducted an extensive review of the literature. The inclusion criteria were original articles in English pertaining to anti-Ku in which cardiac manifestations were defined and prevalence was directly mentioned or easily calculated from the available data. Pubmed and Web of Science were searched using 'anti-Ku', 'auto-antibodies', 'myositis', 'systemic sclerosis' and 'myocarditis'. Reference lists of relevant papers were also reviewed. Results and ensuing meta-analysis are shown in table 1.

Nine articles were included, reporting the prevalence of cardiac involvement in a total of 198 anti-Ku patients with huge variations (0% to 100%). The meta-analysed prevalence of cardiac involvement in anti-Ku patients was 23% (95% CI 9% to 46%). A significant heterogeneity was also found (p<0.001), likely resulting from the heterogeneous screening and definition

Table 1 Prevalence of cardiac involvement in patients with anti-Ku autoantibodies and controls

First author, year of publication	Studied population	Patients assessed for heart involvement, n	Definition for heart involvement	Prevalence of heart involvement, n/total (%(95% CI))		Risk of heart involvement, OR (95% CI)
				Anti-Ku patients	Control patients	
Parodi, 1989[7]	Any CTD	3	Abnormal ECG, echocardiogram, chest X-ray film, (depending on the patients)	1/3 (33)	No control group	–
Hausmanova, 1997[8]	Myositis	50	Palpitation	3/7 (43)	18/43 (42)	1.04 (0.21 to 5.24)
Rozman, 2007[9]	SSc	52	Palpitation or conduction block or abnormal diastolic function or reduced ventricular ejection fraction*	3/14 (21)	8/38 (21)	1.02 (0.23 to 4.57)
Rodriguez-Reyna, 2011[10]	SSc	60	LVEF <45% or pericarditis by echocardiogram or CMR, or arrhythmia requiring treatment, or conduction defect	3/6† (50)	4/54‡ (7)	12.50 (1.88 to 83.3)
Lakota, 2012[11]	Any CTD	73	Palpitations, conduction blocks, abnormal diastolic function	14/73 (19)	No control group	–
Cruellas, 2013[12]	Myositis	222	Myocarditis or heart failure, as revealed by myocardial scintigraphy and echocardiogram examination	0/9 (0)	0/213	1.00 (0.00 to 21163)
Kaji, 2014[13]	SSc	127	Clinical evidence of symptomatic pericardial effusion, congestive heart failure, or an arrhythmia considered to be due to SSc requiring treatment	8/40 (20)	16/87 (18)	1.11 (0.43 to 2.86)
Spielmann, 2019[2]	Any CTD	42	Clinical congestive heart failure and positive CMR	1/42 (2)	No control group	
Campochiaro, 2019[1]	SSc	Not reported	New onset cardiac signs and/or symptoms, raised troponin T and/or NTproBNP and positive CMR	4/4 (100)	No control group	–
Meta-analysis§ -All studies, test of heterogeneity: p<0.001 (I^2=81.8%, τ^2=1.91, H=2.34) Controlled studies, OR test of heterogeneity: p=0.226 (I^2=29.3%, τ^2=0.29, H=1.19)	–	–	–	**22.7 (9.2 to 46.0)** **22.4 (14.4 to 33.1)**	– **8.5 (1.4 to 37.6)**	– **1.60 (0.66 to 3.87)**

Result of meta-analysis are in bold.
*For each definition, the highest prevalence reported was taken into account.
†Sample numbers are derived from the 10% prevalence in the whole cohort.
‡Sample numbers are derived from the 90% prevalence in the whole cohort).
§Result of the random effect (with a constant continuity correction of 0.5 for analysis of proportions and "treatment arm" continuity correction for pooling ORs).
CMR, cardiac magnetic resonance; CTD, connective tissue disoders; LVEF, left ventricular ejection fraction ;SSc, systemic sclerosis .

used for cardiac involvement; and/or from the heterogeneity of the studied populations.

Five studies were controlled (representing a total of 76 anti-Ku patients vs 435 anti-Ku negative patients). The meta-analysed risk of cardiac involvement was not significantly increased in anti-Ku patients vs anti-Ku negative patients (OR 1.60 (95% CI 0.66 to 3.87)).

The important comments of the Campochiaro *et al* study together with the above data highlight several crucial unmet needs for myocarditis in connective tissue diseases patients, namely:

- There is no widely accepted definition of cardiac involvement. Notably, the authors of the Lake Louise criteria warned that CMR criteria for myocarditis are based on expert consensus in light of the limited evidence of its performance compared with endomyocardial biopsy.[6]
- The screening strategies as well as definition for cardiac involvement are heterogeneous among centres.
- There is a need for identifying biomarker(s) of cardiac involvement of which auto-antibodies could be useful toward this aim.
- The prognosis of patients with subclinical CMR myocarditis is currently unknown and whether such patients benefit from increased immunomodulation (vs its potential risks for the patient) is unanswered.

Future research agendas should address these points.

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