Are antibodies against La (SSB) no longer useful for the diagnosis of Sjögren's syndrome?

Sirs,

The 2016 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) classification criteria for primary Sjögren's syndrome (SS) do not take into account the presence of anti-La (SSB) antibodies (1). The decision to exclude anti-La (SSB) was based on group discussions, data showing that anti-La (SSB) antibodies seldom exist without anti-Ro (SSA) (2), and on a study showing no significant association with SS features of anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients, relative to anti-Ro(SSA)$^-$/anti-La(SSB)$^-$ participants of the SICCA cohort (3). The present study (Swissethics; study no. 2018-00088) retrospectively assessed the value of anti-La (SSB) determination for the diagnosis of SS between 2010 and 2016.

2011 anti-Ro (SSA) and 1970 anti-La (SSB) antibody determinations were performed for 807 patients. Thirty-six (4.5%) patients resulted anti-Ro (SSA)$^-$/anti-La(SSB)$^+$. For these patients, mean anti-La (SSB) value was 50U (95%CI:37U–63U). Positivity was confirmed by dot blot testing in 83% of cases. None had a previous diagnosis of SS. During follow-up throughout June 2018, two patients were diagnosed with primary SS, two with SS secondary to systemic lupus erythematosus. One of them fulfilled the 2002 American-European Consensus Group classification criteria for primary SS (4), but none fulfilled the 2012 ACR (5) or ACR-EULAR criteria (1). Eleven developed other connective tissue diseases (CDT) (Table I). Among seventeen retested, two (11.8%) showed negative anti-La (SSB). None developed anti-Ro (SSA).

In order to assess the impact of positive anti-La(SSB), the prevalence of SS among anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients was compared to a anti-Ro(SSA)$^-$/anti-La(SSB)$^-$ control group, matched 1:4 according to gender and age. The analysis was aborted after finding four patients with newly diagnosed SS among 105 patients in the control group, according to pre-established criteria for rejecting the null-hypothesis (two-tailed Fisher's test; 5% significance level). The prevalence of SS was 11% (95%CI:0.85%–21.38%) in anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients and 4% (95%CI:0.15%–7.47%) in anti-Ro(SSA)$^-$/anti-La(SSB)$^-$ patients.

In order to investigate the role of anti-La(SSB) as a marker of an underlying autoimmune disease, ANA positivity by indirect immunofluorescence on human epithelial (Hep2) cell line was compared among different serological subgroups. A significant difference was found between anti-La(SSB)$^-$ and anti-La(SSB)+ patients, irrespective of anti-Ro(SSA) antibody status (positivity in 59% and 89% respectively, $p<0.0001$), and between anti-Ro(SSA)$^+$/anti-La(SSB)$^-$ and anti-Ro(SSA)$^+$/anti-La(SSB)$^+$ patients (67% and 96% respectively, $p<0.0001$). No difference was found comparing anti-Ro (SSA)$^-$/anti-La (SSB)$^-$ and anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients (55% and 58% respectively, $p=.86$). The impact of the different expression of anti-Ro (SSA) and anti-La (SSB) in Hep2 cells has not been further investigated.

In summary, probably due to the low number of anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients, our study did not show a significant difference in the prevalence of SS compared to anti-Ro(SSA)$^-$/anti-La(SSB)$^-$ patients. Only 4 anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients have been diagnosed for SS during follow-up. Whether this is worth performing approximately 2000 anti-La(SSB) analysis, is debatable and supports previous studies indicating the low value of anti-La(SSB) testing. However, it has to be reminded that the study showing no SS phenotypic differences of anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients compared to anti-Ro(SSA)$^-$/anti-La(SSB)$^-$ patients, was performed studying patients of the SICCA cohort with symptoms or signs indicative of possible to well-established SS (3). Identifying SS phenotypic differences in this cohort might be more difficult than in a broader population as investigated in our study, in which anti-La(SSB) analysis has been performed to investigate various causes of dryness or for suspected CDT. As indicated by the various CTD that developed during follow-up in anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients, our study shows that anti-La(SSB) positivity might indicate a higher risk of an underlying auto-immune disease and might be helpful in the real-life situation where SS diagnosis is based on the physician's appreciation and not on classification criteria. Further, our study shows that only a minority of anti-Ro(SSA)$^-$/anti-La(SSB)$^+$ patients loose anti-La(SSB) positivity and that development of anti-Ro(SSA) during follow-up is rare.

Table I. Characteristics of the 36 patients with positive anti-La(SSB) and negative anti-Ro(SSA) at the time of testing and their final diagnosis. Numbers of patients for which data were available are given in brackets.

Gender (n=36) [%]		
male	8	[22.2]
female	28	[77.8]
Mean age (n=36) [range]	48	[16-85]
Symptoms leading to anti-La(SSB) analysis (n=30) [%]		
sicca	9	[30.0]
arthralgia	10	[33.3]
neuropathy	3	[10.0]
cutaneous disorder or photosensitivity	9	[30.0]
CNS manifestation	6	[20.0]
fetal loss	1	[3.3]
other	17	[56.7]
Sicca present at the moment of analysis (n=26 [%]		
oral	5	[19.2]
ocular	3	[11.6]
oral and ocular	9	[34.6]
genital	0	[0]
no	9	[34.6]
Schirmer test or BUT abnormal (n=26) [%]		
ND	18	[69.2]
yes	4	[15.4]
no	4	[15.4]
Sialometry abnormal (n=26) [%]		
ND	17	[65.4]
yes	1	[3.9]
no	8	[30.8]
Associated conditions (previous) (n=31) [%]		
RA	2	[6.5]
SLE	2	[6.5]
ITP	1	[3.2]
chronic HBV infection	1	[3.2]
chronic HCV infection	3	[9.7]
IgA RF positivity (n=18) [%]	2	[11.1]
IgM RF positivity (n=21) [%]	7	[33.3]
Hypergammaglobulinaemia (n=23) [%]	4	[17.4]
Anti-U1RNP positivity (n=34) [%]	3	[8.8]
Anti-Scl70 positivity (n=34) [%]	2	[5.9]
Anti-Jo1 positivity (n=34) [%]	1	[2.9]
Low C3 (n=19) [%]	2	[10.6]
Low C4 (n=19) [%]	1	[5.3]
Cryoglobulins positivity (n=11) [%]	0	[0]
Anti-b2GP1 positivity (n=16) [%]	0	[0]
Lupus anticoagulans positivity (n=16) [%]	0	[0]
Anti-cardiolipins positivity (n=13) [%]	1	[7.7]
ANA titre by IIF ≥ 1:160 (n=36) [%]	21	[58.3]
Speckled pattern	11	[30.6]
Homogeneous pattern	6	[16.7]
Homogeneous/Speckled pattern	3	[8.3]
Centromere pattern	1	[2.8]
Anti-DNA positivity (n=19) [%]	0	[0]
Anti-nucleosomes positivity (n=28) [%]	4	[14.3]
Final physician's diagnosis after follow-up (n=31) [%]		
Primary Sjögren Syndrome	2	[6.5]
Secondary Sjögren Syndrome (SLE)	2	[6.5]
RA	5	[16.1]
SLE	2	[6.5]
Ankylosing spondylitis	1	[3.2]
UCTD	3	[9.7]
Cutaneous lupus	1	[3.2]
Fibromyalgia	1	[3.2]
Small fibre neuropathy	1	[3.2]
Stroke	2	[6.5]
Telogen effluvium	1	[3.2]
Bronchiectasia	1	[3.2]
Osteoarthritis	1	[3.2]
Hypertensive kidney disease	1	[3.2]
Migraine	1	[3.2]
Toxic polyneuropathy	1	[3.2]
Physiological livedo	1	[3.2]
Vertigo	1	[3.2]
Obesity	1	[3.2]
Atopic dermatitis	2	[6.5]

ND: not done; BUT: break up time; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ITP: idiopathic thrombocytopenic purpura; HBV: hepatitis B virus; HCV: hepatitis C virus; UCTD: undifferentiated connective tissue disease; RF: rheumatoid factor; b2GP1: β2-glycoprotein-I; ANA: Anti-nuclear antibody; IIF: indirect immunofluorescence.

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