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Editorial

Ro52, Myositis, and Interstitial Lung Disease

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Ro52 is a member of the tripartite motif-containing (TRIM) family and, hence, is also known as TRIM21. Ro52 is distinct, with no structural homology to Ro60 (also known as TROVE2),[1] although both are major targets of autoantibody responses in several autoimmune connective tissue diseases (CTDs). Indeed, early studies describing anti-Ro (SSA) do not make a distinction between the separate autoantibody specificities, although they frequently coexist in conditions such as systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) and are often accompanied by anti-La (SSB). However, there is compelling evidence that the separate measurement of anti-Ro52 adds important information concerning patient management and outcomes, not least in idiopathic inflammatory myopathy (IIM) and interstitial lung disease (ILD).

In the context of IIM, anti-Ro52 is regarded as a myositis-associated autoantibody (MAA) and can be found in other CTDs including SLE, SS, systemic sclerosis (SSc), and mixed CTD (MCTD). In contrast, myositis-specific autoantibodies (MSAs) are uncommonly encountered in other conditions apart from IIM and rarely coexist in the same patient.[2] An important point to note is that MSAs may occur in some manifestations of the IIM spectrum, such as in ILD or in clinically amyopathic dermatomyositis (CADM) without any apparent muscle involvement, and arguably should be redesignated as myositis spectrum autoantibodies. For instance, some of the rarer anti-tRNA synthetase autoantibodies (anti-PL7 and anti-PL12) may be found in patients with ILD alone, or where ILD is the major disease manifestation.[3] The other important example is anti–melanoma differentiation-associated gene 5 (anti-MDA5), previously called anti-CADM140, that typically occurs in patients with CADM and is a major marker for patients at risk of rapidly progressive ILD (RP-ILD).

The ability of MSAs to identify important subphenotypes of IIM is now well established. Their value in determining future disease course, and ideally acting as biomarkers to inform precision medicine, is less well developed and requires prospective studies with stratified treatment approaches. Further, it is becoming apparent that the additional presence of an MAA such as anti-Ro52 needs to be taken into consideration. In a study published in this issue of *The Journal of Rheumatology*, Lv et al report retrospectively on a large regional cohort of 246 patients with myositis-associated ILD and positive for anti-MDA5 gathered from 10 centers.[4] Anti-Ro52 was present in 158 of the 246 anti-MDA5 patients (64%) and was significantly associated with a higher rate of development of RP-ILD and about twice the mortality rate (29% compared to 16% in anti-Ro52–negative patients). There are major limitations in such a retrospective study, including selection bias, treatment effects, and the lack of adjustment for person-years at risk. Also, anti-Ro52 and anti-MDA5 were measured by line blot, which, at best, is a semiquantitative method for measuring autoantibody levels, and the actual level of autoantibody may be an additional important factor. Nonetheless, the findings (and parallel analyses reported separately on the same cohort[5,6]) are reasonably convincing and lead to the conclusion that there is a degree of heterogeneity in anti-MDA5–positive patients that can be dissected by measuring anti-Ro52.

There is also accumulating evidence from other studies in the myositis field that the measurement of anti-Ro52 in addition to other MSAs adds important information, especially in association with either anti-Jo1 or anti-MDA5. One of the earliest studies comes from a Hungarian cohort[7] reported in 2009, although in this study, an ELISA for anti-SSA was used that is not specific for anti-Ro52. A summary of relevant studies, including the current report from Lv et al, is given in the Table.[3,4,7-15] All but 1 study[3] found that the presence of anti-Ro52 with anti-Jo1 was associated with more severe ILD and poorer outcomes. Notably similar findings were reported in a large cohort of children with juvenile myositis in the United States, where ILD is far less common.[10] Further, in recent studies of 3 separate large Chinese cohorts, the combination of anti-Ro52 with anti-MDA5 was associated with either more frequent RP-ILD, poorer outcome, and/or higher mortality.[13-15] Also of interest is a Japanese prospective study of interstitial pneumonia, where patients with CTD were excluded and those with anti-Ro52 alone had worse survival.[11] So, despite the variability between studies in the patient populations, and

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Table. Summary of studies investigating anti-Ro52 and outcomes in myositis and ILD.

Author, Year	Country, Study Population	N	Study Design	Method of Detection	Findings
Vansca, 2009[7]	Hungary, IIM	315 (27 anti-Jo1; 12 anti-SSA, of whom 8 had anti-Jo1 and anti-SSA)	Prospective	ELISA (anti-SSA)	A combination of anti-Jo1 and anti-SSA was associated with more severe course of ILD.
Marie, 2012[8]	France, consecutive patients with AS	89 anti-Jo1 (36 anti-Ro52)	Retrospective record review	ELISA (Ro-SSA)	Anti-Ro52 was associated with more frequent symptomatic ILD and poorer survival.
Shi, 2017[9]	China, rheumatology department, consecutive patients with AS	124 (36 anti-Ro52)	Retrospective	Line blot (moderate or strong positive)	Anti-Ro52 was associated with higher frequency of RP-ILD.
Pinal-Fernandez, 2017[3]	USA, myositis center cohort testing positive for ASA	169 (111 anti-Ro52)	Prospective	ELISA/line blot/IP	Anti-Ro52 was seen more frequently with anti-Jo1 but was not associated with more severe ILD.
Sabbagh, 2019[10]	US multicenter cohort, juvenile myositis	371 (53 anti-Ro52)	Cross-sectional with prospective arm	ELISA	Anti-Ro52 was associated with ASA (64%), anti-MDA5 (31%), ILD, and poorer outcome.
Temmoku, 2019[11]	Japan, DM/PM with stable disease	84 (39 anti-Ro52)	Retrospective	ELISA	Anti-Ro52 with anti-MDA5 was associated with poorer survival.
Morita, 2020[12]	Japan, interstitial pneumonia excluding patients with CTD	285 (29 anti-Ro52)	Prospective with 2-yr follow-up	Line blot (≥ 2 positive)	Anti-Ro 52 mono-positive had worse survival than anti-Ro52 negative.
Yang, 2021[13]	China, DM/PM or CADM with anti-MDA5	90 (64 anti-Ro52)	Retrospective	Line blot	Anti-Ro52 was associated with poorer survival.
Wen, 2022[14]	China, hospitalized with IIM	515 (124 anti-MDA5, 285 anti-Ro52; 72 had both)	Retrospective	Line blot	Anti-MDA5 with anti-Ro52 was associated with poorer outcome.
Lv, 2022[4]	China, multicenter, myositis-associated ILD cohort with anti-MDA5	246 anti-MDA5 (158 anti-Ro52)	Retrospective	Line blot	Anti-Ro52 was associated with higher rate of RP-ILD and mortality.
Gui, 2022[15]	China, IIM-associated ILD	267 (148 anti-Ro52 and 87 anti-MDA5)	Retrospective, hospital-based (respiratory admissions)	Line blot	Anti-Ro was predictive of RP-ILD and mortality, and more so when present with anti-MDA5.

AS: antisynthetase syndrome; ASA: antisynthetase antibody; CADM: clinically amyopathic dermatomyositis; CTD: connective tissue disease; DM/PM: dermatomyositis/polymyositis; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; IP: immunoprecipitation; MDA5: melanoma differentiation-associated gene 5; RP-ILD: rapidly progressive interstitial lung disease.

the potential for bias already alluded to in what are mostly retrospective studies, there does seem to be solid evidence that the presence of anti-Ro52 is a poor prognostic indicator in IIM.

The case for measurement of anti-Ro52 and its importance in the management of CTDs becomes even stronger when looking at outcome in ILD associated with CTDs other than IIM; the case has been the subject of recent comprehensive reviews.[16,17] In conditions where ILD is relatively frequent, such as SS, SSc, and MCTD, the presence of anti-Ro52 is most often associated with an increase in frequency of ILD that tends to be more severe and generally confers poorer outcome and survival.

Ro52 has several key properties and functions that may help explain why it is a common target for an autoimmune response in connective tissue disease and how that response is linked to the propensity for severe ILD. First, it is known to be highly antigenic[18] and is highly expressed in lungs compared to other tissues.[17] Second, Ro52 is likely to play an important role in host responses to viral infections postulated to be initiators of conditions such as in IIM and SS. It has another important role as an Ig-binding protein and in the innate clearance of intracellular IgG-bound complex. Ro52 acts as a cytosolic receptor binding to the Fc region of IgG antibodies and, hence, acts to neutralize and degrade pathogens that antibodies have carried into the cell.[16] Ro52 is also an interferon (IFN)-inducible E3 ligase that acts to downregulate IFN transcription factors and by so doing puts a check on proinflammatory cytokine responses. In this regard, it is worth noting as well that MDA5 is an IFN-inducible protein and acts as a cytosolic viral dsRNA sensor. Together, Ro52 and MDA5 are involved in effective responses to viral infection through IFN signaling and by virtue of protein-protein interactions, may become potential targets for a common autoimmune response.

It is also conceivable that anti-Ro52 antibodies may have a direct pathogenic role rather than simply be an imprint of an aberrant autoimmune response, although the evidence for such stems mainly from studies of neonatal SLE.[16] For instance, anti-Ro52 may block the regulatory activity of Ro52 protein as described above and directly amplify proinflammatory signals mediated through type 1 IFN. It is known that autoantibodies to Ro52 directly inhibit its E3 ligase activity.[19] Ro52 knockout mice develop severe dermatitis and manifestations of SLE as well as enhanced production of proinflammatory cytokines.[20] However, regardless of whether anti-Ro52 may have a direct effect, the takeaway measure for clinicians involved in the management of CTD, and even more so in patients at risk of ILD, is that anti-Ro52 is certainly worth measuring.

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