Biomarkers in connective tissue diseases

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Activity Objectives:

1. To understand the utility of autoantibodies in managing connective tissue disease.
2. To identify statistical measures of commonly ordered autoantibody tests.
3. To recognize important associations between particular biomarkers and clinical manifestations of disease.

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Autoimmune connective tissue diseases are clinically variable, making biomarkers desirable for assessing future disease risk, supporting early and accurate diagnosis, monitoring disease activity and progression, selecting therapeutics, and assessing treatment response. Because of their correlations with specific clinical characteristics and often with disease progression, autoantibodies and other soluble mediators are considered potential biomarkers. Additional biomarkers might reflect downstream pathologic processes or appear because of ongoing inflammation and damage. Because of overlap between diseases, some biomarkers have limited specificity for a single autoimmune connective tissue disease. This review describes select current biomarkers that aid in the diagnosis and treatment of several major systemic autoimmune connective tissue disorders: systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and anti-neutrophil cytoplasmic antibody–associated vasculitides. Newly proposed biomarkers that target various stages in disease onset or progression are also discussed. Newer approaches to overcome the diversity observed in patients with these diseases and to facilitate personalized disease monitoring and treatment are also addressed. (J Allergy Clin Immunol 2017;140:1473-83.)

Key words: *Connective tissue diseases, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, vasculitis, biomarkers*

Autoimmune connective tissue disorders are a heterogeneous group of diseases that affect connective tissue in various organs resulting from poorly controlled autoimmune responses, complement activation, interferon dysregulation, and associated inflammation. Although their clinical presentations vary, these diseases share significant genetic risk factors, as demonstrated by cross-analysis of genome-wide association studies[1] and common regulatory mechanisms of autoimmune diseases.[2] Environmental and female-associated factors also play critical roles in development of autoimmune diseases.[3-7] In nearly all systemic

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Abbreviations used

AAV: ANCA-associated vasculitides
ACA: Anti-centromere antibody
ACPA: Anti-citrullinated protein antibody
ACR: American College of Rheumatology
ANA: Anti-nuclear autoantibody
ANCA: Anti-neutrophil cytoplasmic antibody
Anti-CarP: Antibodies against carbamylated proteins
BLyS: B-lymphocyte stimulator
CCP: Cyclic citrullinated peptide
CRP: C-reactive protein
DAS28: Disease Activity Score-28 joints
dcSSc: Diffuse cutaneous systemic sclerosis
DLCO: Diffusing capacity of the lungs for carbon monoxide
dsDNA: Double-stranded DNA
EGPA: Eosinophilic granulomatosis with polyangiitis
ESR: Erythrocyte sedimentation rate
GDF-15: Growth differentiation factor 15
GPA: Granulomatosis with polyangiitis
HES: Hypereosinophilic syndrome
ILD: Interstitial lung disease
lcSSc: Limited cutaneous systemic sclerosis
LN: Lupus nephritis
MPA: Microscopic polyangiitis
MPO: Myeloperoxidase
NT-proBNP: N-terminal prohormone of brain natriuretic peptide
PAH: Pulmonary arterial hypertension
PR3: Proteinase-3
RA: Rheumatoid arthritis
RF: Rheumatoid factor
RNAP III: RNA polymerase III
SLE: Systemic lupus erythematosus
SSA: Sjögren syndrome type A antigen
SSc: Systemic sclerosis

autoimmune rheumatic diseases evaluated to date, autoantibody production and immune dysregulation precede clinical onset,[8-15] although a significant amount of this information is not yet integrated to standard clinical care. Ongoing research is focused on improving biomarkers for diagnosis, prognosis, treatment selection, and optimized therapy. This review describes current and new emerging biomarkers for major connective tissue diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides.

SLE

SLE is a systemic autoimmune disease characterized by production of anti-nuclear autoantibodies (ANAs). Early and accurate diagnosis and disease monitoring are hindered by its heterogeneous presentation and clinical course. Serologic and urinary biomarkers are either in use or are emerging as potential biomarkers for SLE. These autoantibodies (Table I), complement products, and cytokines/chemokines/soluble mediators have the potential to facilitate diagnosis, identify subjects at greater risk for SLE, and monitor disease activity or specific organ involvement (Fig 1).

Autoantibodies

ANAs are a hallmark of SLE. Nearly all patients with SLE exhibit ANAs at diagnosis, with a 1:80 immunofluorescent titer showing up to 98% sensitivity but 75% specificity for SLE classification.[16] ANAs are also found in patients with many other autoimmune diseases, malignancies, or hepatic diseases; unaffected family members of patients with lupus; and even up to 14% of healthy subjects,[17] especially with increasing age. Therefore a positive ANA value serves as a necessary but insufficient criterion for SLE classification or diagnosis but not as a definitive test.[18] Patients with a negative ANA test result are extremely unlikely to have any lupus-specific autoantibodies. Therefore through the Choosing Wisely campaign, the American College of Rheumatology (ACR) recommends testing for specific autoantibodies only when a positive ANA level and clinical suspicion are present.[19] Repeat testing is not indicated in subjects with positive ANA results because changes in ANA titers alone show no clinical correlation with increased disease activity or worsening prognosis. Testing of ANAs and other autoantibodies in preclinical disease states or to identify subjects for potential preventive interventions will require additional studies and guidelines.[20]

Anti–double-stranded DNA (anti-dsDNA) antibody responses have high specificity (92% to 96%) and moderate sensitivity (57% to 67%) for SLE.[21] They constitute a criterion for SLE classification by ACR criteria (requiring 4/11 criteria for classification) and by the Systemic Lupus International Collaborating Clinics criteria (requiring 4/17 criteria or dsDNA plus biopsy-proven lupus nephritis [LN]).[22-24] Anti-dsDNA forms immune complexes with nucleosomes observed in patients with SLE, leading to immune complex deposition in the kidney.[25] Furthermore, anti-dsDNA antibodies show cross-reactivity to α-actinin and can bind to mesangial cells in the kidney.[26] Immune complexes formed by anti-dsDNA antibodies in the kidney can activate the complement cascade, leading to damage in patients with glomerulonephritis.[27] Patients with proliferative LN have increased anti-dsDNA as early as 4 years before diagnosis, and an increase of greater than 1 IU/mL/y was specific for LN.[28] Anti-dsDNA with low complement levels also associates with mucocutaneous, renal, and hematologic flare within 1 year.[29] In patients with clinically stable SLE and increasing levels of anti-dsDNA (≥25%) and C3a (≥50%), the free released product of complement activation, treatment with moderate prednisone can avert severe clinical flares.[30]

Although less common (sensitivity, 26% to 31%) antibodies against the Sm antigen are highly specific (95% to 99%) for SLE and can associate with early mortality.[31] About 30% to 70% of patients with SLE have anti-Ro/Sjögren syndrome type A antigen (SSA), and Ro/SSA is associated with subacute lupus erythematosus, sicca symptoms, and secondary Sjögren syndrome. Anti-Ro/SSA antibodies can bind to either of 2 antigenic proteins: 52-kDa and 60-kDa Ro. Antibodies to 60-kDa Ro/SSA are more frequently observed in patients with SLE and correlate with photosensitivity, cutaneous vasculitis, and hematologic disorders.[32] Antibodies to a related antigen, La/SSB, are present in approximately 10% of patients with SLE and associated with lower prevalence of renal disease.[32] Anti-ribosomal P antibodies, similar to anti-Sm antibodies, are very specific for SLE but occur in only approximately 20% of white patients with SLE. Anti-ribosomal P is enriched in neuropsychiatric[33] and pediatric-onset disease.[34] A number of other autoreactivities have been reported in patients with SLE.[21] Of interest are anti-nucleosome responses, which correlate with disease activity in clinically quiescent patients,[35] and anti-cardiolipin responses, which are implicated in