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Commentary

The role of autoantibody markers in predicting interstitial lung disease in patients with systemic sclerosis: the Larissa experience in Thessaly, Greece

Running title: Autoantibody markers of ILD in systemic sclerosis

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Abstract

This commentary underlines the need for continuous research on interstitial lung disease related to autoimmune rheumatic diseases. Amongst the numerous unmet needs, there is the urgent demand for better stratification of patients in terms of prognosis or response to treatment. Disease-related or disease-specific autoantibodies have been proven useful diagnostic tools but their clinical significance in stratifying patients who are gone have a poor prognosis is still a matter of debate. Autoantibody testing relates to the underlying cause of the disease, which in our case can vary amongst a plethora of autoimmune rheumatic diseases, such as systemic sclerosis, rheumatoid arthritis, mixed connective tissue disease or anti-synthetase syndrome. Better stratification of the patients using prompt biomarkers may assist efforts for very early intervention and better outcome.

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I. INTRODUCTION

Interstitial lung disease (ILD) is used as an umbrella term for a large group of diffuse parenchymal lung diseases characterized by fibrosis and/or inflammation of the lungs(1, 2). The common denominator of those diseases is that they affect the interstitium. The most common form of ILD is idiopathic pulmonary fibrosis, which has unknown cause, despite extensive investigations, hence the term idiopathic (2). Such investigations can include hematological tests, imaging (X-rays, CT scan including high-resolution CT scan, pulmonary function tests, and lung biopsy(1, 2).

Amongst the various causes of ILD, pathogens including several bacteria, viruses and fungi have been identified, which can cause interstitial lung pneumonia (3). Exposure to environmental factors such as asbestos, coal, silica or grain dust, talc etc. have been considered likely causes of ILD. Drug-induced or drug-related ILD due to antibiotics (such as nitrofurantoin), immunomodulators (such as rituximab), chemotherapy agents (such as bleomycin) or even anti-arrhythmic medications (such as amiodarone) have heavily been described in the literature over the years. In addition, one of the most common causes of ILD is autoimmune rheumatic diseases (ARDs) such as systemic sclerosis (SSc), rheumatoid arthritis (RA), anti-synthetase syndrome (ASS), idiopathic inflammatory myopathies, mixed connective tissue disorders, Sjögren's syndrome and systemic lupus erythematosus. All those been identified as major causes of ILD and pulmonary fibrosis. This explains why ILD patients without a profound causal link must be screened for underlying autoimmune causes.

Despite being extremely complex, a vigorous diagnosis of a specific form of ILD now days is more robust. This is due to practice guidelines for the diagnosis, management and treatment, which are issued by authorative thoracic societies such as the American Thoracic Society and the European Respiratory Society. Those guidelines are based on the rigorous assessment of evidence-based literature but as per other guidelines for other medical conditions cannot be applied to a broad scale i.e in patients all over the word. The epidemiology of ILD differs

throughout the globe, and exposure to a heterogenous group of environmental and occupational triggers prevents from a universal applicability of such clinical practice guidelines. Moreover, there is a huge variation of the diagnostic criteria applied. Also, in several countries there is a limited access to medical care, which is readily available in other countries. Finally, most guidelines and consensus statements have been issued on idiopathic interstitial pneumonias (IIPs), and in particular IPF, which offer no assistance or little help to non-IIPs such as those of relevant to ILD related to ARDs. In recent years, rheumatological societies such as ACR and EULAR with participants from respiratory society bodies have issued guidelines centered on ILD related to ARDs, including treatment recommendations for RA-ILD and SSc-ILD.

Over the years, screening tools for autoimmune rheumatic diseases such as disease-specific or disease-related ARDs autoantibodies assisted efforts to identify causes of ILD, which cannot be attributed anywhere else. This is based on the consensus argument, which is now widely accepted, that the diagnosis of idiopathic ILD must incorporate practices, which are based on the exclusion of ARDs or other causes. This is not always feasible, because at times, ILD precedes long-before the development of overt ARDs. Attempts to document serological evidence of ARDs may assist efforts for prompt diagnosis of the underlying disease of the existing ILD, especially is the evidence in the blood relates to immunological parameters with high sensitivity and specific for ARDs. For example, the presence of autoantibodies which are directed against Scl-70, an autoantibody which at high-titre and in the absence of infections or other causes which can account for its presence is closely linked with SSc, may indeed indicate the development of very very early SSc (VVESSc), even if there are no other clinical features related to the disease itself. This is of paramount importance foe the prompt identification of the underlying cause and the proper management of the disease.

Recently, an international consensus statement introduced the concept of “interstitial pneumonia with autoimmune features (IPAF)”, which has been proposed and widely accepted by the European Respiratory Society/American Thoracic Society Task force. This term is widely used currently to describe all those causes of ILD which can be attributed to or related with systemic autoimmune disorders, without meeting criteria for a define ARD. Amongst the three domains included in the classification criteria for IPAF, one is related to serology, one to clinical features and one to morphological features. At least one feature from at least two of the three domains is required for the classification The serological domain incorporates anti-nuclear antibody (ANA) ⩾1:320 with diffuse, speckled, and/or homogeneous patterns or any titer in case of nucleolar or centromere pattern; Rheumatoid factor⩾2 × upper limit of normal; and disease-specific autoantibodies such as anti-synthetase, anti-MDA5, anti-topo I antibodies and anti-centromere antibodies. The clinical domain includes Raynaud phenomenon, unexplained digital edema, Gottron sign, digital ulcers, mechanic hands, palmar telangiectasias, inflammatory arthritis or prolonged polyarticular morning stiffness. The morphological domain consists of chest imaging, histopathological patterns, or other pulmonary physiological features in addition to interstitial pneumonia.

Given that the presence of early stage ILD is difficult to be documented in ARDs, despite vigorous monitoring and thorough assessment, and taking into account that its presence is associated with major morbidity and mortality, as it can be the major cause of death in those patients, it is of paramount importance to identify serological prognosticators of future development of ILD in patients with ARD, with no apparent evidence of existing ILD.

To this end our group has assessed several autoantibody markers, which are potentially linked with the development of ILD in patients with SSc. Others have also done the same in a single center of multi center studies. In our cohort of SSc, which originates from Thessaly in central Greece, we have found interesting features, which are worthy to mention. Our results attracted the attention of several investigators and several investigators now cite our studies over the globe. Before discussing further our findings, we must provide some information regarding the geographic origin of our cohorts. Thessaly (approx. 732,000 inhabitants) is one of the 13 official administrative regions of Greece. It is located in the Centre of the mainland country and is sub-divided into four regional units. Larissa is the most populated and its capital city (281,000 inhabitants) with the same name has two hospitals, one of which is the only university hospital of the region. Magnesia (including the Sporades islands), Karditsa, Trikala are the remaining three regions, each of which has a district hospital. The General University Hospital of Larissa is the only one of those, which has a dedicated in-patient Clinic for the case of patients with rheumatic diseases (Department of Rheumatology and Clinical Immunology). In recent years, the district hospital of Larissa and Karditsa have developed

out-patient clinics for the management of patients with rheumatic diseases. Our department is one of the biggest of its kind in Greece and is the only referral center for rheumatic diseases in Central Greece, over exceeding 9.000 visits per year.

The university hospital is also a tertiary hospital and referral Centre for patients with lung diseases, as it operated a dedicated department for respiratory medicine with in - patient and out-patient clinics overseeing patients from Central Greece. The Department of Respiratory Medicine runs a dedicated out-patient clinic for patient with ILD and a joint out-patient clinic (for the care of patients with ILD-ARDs and patients with IPAF) was established in 2018, to deal with the increasing demands for personalized care. Moreover, the Department of Rheumatology and Clinical Immunology runs specialized out-patient clinics for specific diseases (RA, SSc, SLE etc.), which allows meticulous assessment, and specialized diagnostic and therapeutic management approaches, which cannot be offered in district hospitals. It has also assisted efforts to initiate a plethora of translational studies (4-67).

In 2017, making use of a profile line immunoassay for the detection of autoantibodies, we reported our experience on the presence of SSc-specific or SSc-related autoantibodies in a consecutive cohort of 131 patients with SSc, followed up in our Department (11). Amongst those 111 were females including 49 with diffuse cutaneous SSc and 82 with limited cutaneous SSc. All patients fulfilled the 2013 American College of Rheumatology criteria for SSc. Autoantibody testing was performed by conventional indirect immunofluorescence assay (IIF) using HEp-2 as antigenic substrate and a line immunoassay (Euroline SSc profile IgG assay) which enables testing of 13 autoantigens, namely Topo I (known also as Scl-70), centromere proteins A (CENP-A) and B (CENPB), RNA polymerase III subunits 11 (RP11) and 155 (RP155), fibrillarin, NOR-90, Th/To, PM-Scl100, PM-Scl75, Ku, PDGFR, and Ro52 (from SS-A) (11). Over the 131 SSc patients, 97% had positive ANA by IIF. One hundred twenty-one patients (92.4%) had at least one of the 13 autoantibodies. Excluding anti-Ro52 antibodies (which were present in 22.1% of the patients and are not highly specific for SSc), 89.3% of the patients had detectable autoantibodies against at least one of the remaining 12 autoantigens (11). The most common autoantibodies were those against anti-Topo I (41.2% in undivided SSc, 26.8% in lcSSc and 71.4% in dcSSc), followed by anti-CENP (28.2% in total, 39% in lcSSc and 4.1% in dcSSc), and anti-RP in 14.5% total SSc. In regard to the observed clinical associations of detectable autoantibodies, as it is described previously, anti-Topo I was associated with dcSSc and anti-CENP antibodies with lcSSc. We have also found in that cohort that anti-Topo I antibodies were more frequent in patients with ILD, while anti-CENP were negatively correlated (11).

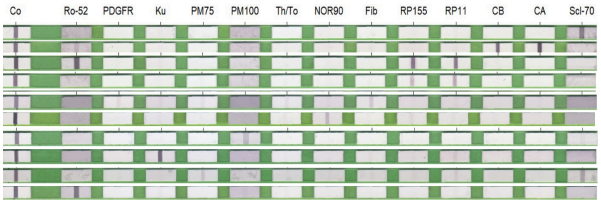

Fig.1. *Multiparametric antibody testing associated with systemic sclerosis using line immunoassay*

In a subsequent study in an extended cohort of 158 SSc patients, we confirmed the observed frequencies of the tested autoantibodies and the association of anti-Topo I antibody positivity with ILD and its negative association with anti-CENP (12). Once again, we have failed to report an association with anti-Ro52 antibodies with ILD (12), contrasting such a finding reported by other studies not only finding that anti-Ro52 is more prevalent in ILD-SSc but is also a marker of poor prognosis. There is no doubt that multiparametric profiling of SSc-specific and SSc-related autoantibodies is of paramount importance for diagnostic and likely prognostic purposes and needs to be advised in case of urgent need of patients' stratification (12). We intend to report similar data on profiling assays in a larger cohort over exceeding 250 patients from our Department and assess whether clinically meaningful association may arise. Currently, we assess all patients with suspected SSc, using this approach (ANA by IIF and subsequent multiparametric test in ANA positive and ANA negative individuals with strong suspicion of SSc). We prefer such testing than that limited to IIF alone or that including ANA by IIF and anti-centromere and/or anti-Topo I alone, without testing other disease related specificities. In our cohort, approximately 13% of the patients had anti-RNA pol III antibodies and anti-Ro52 antibodies were the third most common autoantibodies in SSc(12). One third of the anti-Ro52 antibody positive SSc patients did not have detectable anti-Topo I, anti-CENP or anti-RNA poly III antibodies. In accordance with previous studies, the concurrent presence of anti-Topo I, anti-CENP or anti-RNA poly III antibodies was not found(12). Equally importantly, approximately 20% of our patients had detectable autoantibody reactivity other than anti-Topo I, anti-CENP-A and -B and anti-RNA pol III (11 and 155) making reasonable to assume that testing of other autoantibody specificities could be of diagnostic value, especially if a diagnostic dilemma exists(12). The fact that anti-Topo I is strongly associated with ILD precludes that

this autoantibody testing is a necessary tool for the assessment of ILD(12). More recently, we reported in our cohort an association between anti-C1q antibodies and the presence of ILD in patients with SSc. This finding requires further assessment and external validation(13).

Others have found that anti-Ro52 may indeed have prognostic value for the future development of ILD with poor prognosis, thorough consideration for the assessment of anti-Ro52 testing as a routine in those patients may indeed offer an additional diagnostic and potentially clinical value(68, 69). A multi-national multi-center study including 1,574 patients with SSc has found that anti-Ro52 antibody monospecificity is associated with ILD and poor survival rates(69). A long-term observational Norwegian study has reported that anti-Ro52 (in the absence of arthritis) is one of the strongest predictors of ILD progression in patients with ARDs. Others have failed to corroborate such findings (70). In the absence of well-standardized techniques to test for anti-Ro52 antibodies by molecular-based assays it is difficult to predict the extent of the clinical significance of those (as well as other SSc-related) autoantibodies (9-12, 27, 36, 68-71).

II. CONCLUSION

In conclusion, studies on this topic gained a continuum over the years and will shed a light resolving conclusively this issue.

AUTHORS CONTRIBUTIONS

DPB and LIS had had the original idea and scripted the original draft and subsequent drafts; CL, EP and TS scripted parts of the manuscript and reviewed the literature. EP prepared the artwork All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. 2016;352:h6819.
2. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020;383(10):958-68.
3. Wells AU, Cottin V. Nonspecific interstitial pneumonia: time to be more specific? Curr Opin Pulm Med. 2016;22(5):450-5.
4. Efthymiou G, Dardiotis E, Liaskos C, Marou E, Scheper T, Meyer W, et al. A comprehensive analysis of antigen-specific antibody responses against human cytomegalovirus in patients with systemic sclerosis. Clin Immunol. 2019;207:87-96.
5. Efthymiou G, Liaskos C, Simopoulou T, Marou E, Patrikiou E, Scheper T, et al. Antigen-specific humoral responses against Helicobacter pylori in patients with systemic sclerosis. Immunol Res. 2020;68(1):39-47.
6. Gkiouras K, Grammatikopoulou MG, Bogdanos DP. On the efficacy and safety of rituximab therapy in patients with systemic sclerosis disease: missing points, bottlenecks, over-exaggeration, and discrepancies-comments on the article by Moradzadeh et al. Clin Rheumatol. 2021;40(10):4365-6.
7. Gkiouras K, Grammatikopoulou MG, Simopoulou T, Daniil Z, Bogdanos DP. Comparative effectiveness of mycophenolate mofetil versus cyclophosphamide in systemic sclerosis-related interstitial lung disease. Clin Rheumatol. 2021;40(8):3379-80.
8. Gkoutzourelas A, Barmakoudi M, Bogdanos DP. A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis. Mediterr J Rheumatol. 2020;31(1):50-70.
9. Gkoutzourelas A, Liaskos C, Mytilinaiou MG, Simopoulou T, Katsiari C, Tsirogianni A, et al. Anti-Ro60 Seropositivity Determines Anti-Ro52 Epitope Mapping in Patients With Systemic Sclerosis. Front Immunol. 2018;9:2835.
10. Gkoutzourelas A, Liaskos C, Simopoulou T, Katsiari C, Efthymiou G, Scheper T, et al. A study of antigen-specific anti-cytomegalovirus antibody reactivity in patients with systemic sclerosis and concomitant anti-Ro52 antibodies. Rheumatol Int. 2020;40(10):1689-99.
11. Liaskos C, Marou E, Simopoulou T, Barmakoudi M, Efthymiou G, Scheper T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity. 2017;50(7):414-21.
12. Liaskos C, Marou E, Simopoulou T, Gkoutzourelas A, Barmakoudi M, Efthymiou G, et al. Multiparametric autoantibody profiling of patients with systemic sclerosis in Greece. Mediterr J Rheumatol. 2018;29(3):120-6.
13. Liaskos C, Rentouli S, Simopoulou T, Gkoutzourelas A, Norman GL, Brotis A, et al. Anti-C1q autoantibodies are frequently detected in patients with systemic sclerosis associated with pulmonary fibrosis. Br J Dermatol. 2019;181(1):138-46.
14. Marou E, Liaskos C, Efthymiou G, Dardiotis E, Daponte A, Scheper T, et al. Increased immunoreactivity against human cytomegalovirus UL83 in systemic sclerosis. Clin Exp Rheumatol. 2017;35 Suppl 106(4):31-4.
15. Marou E, Liaskos C, Simopoulou T, Efthymiou G, Dardiotis E, Katsiari C, et al. Human cytomegalovirus (HCMV) UL44 and UL57 specific antibody responses in anti-HCMV-positive patients with systemic sclerosis. Clin Rheumatol. 2017;36(4):863-9.
16. Mavropoulos A, Liaskos C, Simopoulou T, Bogdanos DP, Sakkas LI. IL-10-producing regulatory B cells (B10 cells), IL-17+ T cells and autoantibodies in systemic sclerosis. Clin Immunol. 2017;184:26-32.
17. Mavropoulos A, Simopoulou T, Varna A, Liaskos C, Katsiari CG, Bogdanos DP, et al. Breg Cells Are Numerically Decreased and Functionally Impaired in Patients With Systemic Sclerosis. Arthritis Rheumatol. 2016;68(2):494-504.
18. Melissaropoulos K, Kraniotis P, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Targeting very early systemic sclerosis: a case-based review. Rheumatol Int. 2019;39(11):1961-70.
19. Ntelis K, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Platelets in Systemic Sclerosis: the Missing Link Connecting Vasculopathy, Autoimmunity, and Fibrosis? Curr Rheumatol Rep. 2019;21(5):15.

20. Sakkas LI, Bogdanos DP. The Role of B Cells in the Pathogenesis of Systemic Sclerosis. Isr Med Assoc J. 2016;18(9):516-9.
21. Sakkas LI, Bogdanos DP. Infections as a cause of autoimmune rheumatic diseases. Auto Immun Highlights. 2016;7(1):13.
22. Sakkas LI, Bogdanos DP. Systemic sclerosis: New evidence re-enforces the role of B cells. Autoimmun Rev. 2016;15(2):155-61.
23. Sakkas LI, Daoussis D, Mavropoulos A, Liossis SN, Bogdanos DP. Regulatory B cells: New players in inflammatory and autoimmune rheumatic diseases. Semin Arthritis Rheum. 2019;48(6):1133-41.
24. Sakkas LI, Mavropoulos A, Bogdanos DP. Phosphodiesterase 4 Inhibitors in Immune-mediated Diseases: Mode of Action, Clinical Applications, Current and Future Perspectives. Curr Med Chem. 2017;24(28):3054-67.
25. Sakkas LI, Mavropoulos A, Perricone C, Bogdanos DP. IL-35: a new immunomodulator in autoimmune rheumatic diseases. Immunol Res. 2018;66(3):305-12.
26. Sakkas LI, Simopoulou T, Katsiari C, Bogdanos D, Chikanza IC. Early systemic sclerosis-opportunities for treatment. Clin Rheumatol. 2015;34(8):1327-31.
27. Scholz J, Grossmann K, Knutter I, Hiemann R, Sowa M, Rober N, et al. Second generation analysis of antinuclear antibody (ANA) by combination of screening and confirmatory testing. Clin Chem Lab Med. 2015;53(12):1991-2002.
28. Simopoulou T, Grammatikopoulou MG, Gkiouras K, Bogdanos DP. On the diagnostic test accuracy of N-terminal pro-brain natriuretic peptide (NT-proBNP) for pulmonary arterial hypertension in patients with systemic sclerosis. Comment on : "Diagnostic value of cardiac natriuretic peptide on pulmonary hypertension in systemic sclerosis: a systematic review and meta-analysis" by Zhang et al. Joint Bone Spine 2021:105287. Joint Bone Spine. 2021:105317.
29. Bogdanos DP, Daniil Z, Zakynthinos E, Gourgoulianis K, Sakkas LI. When there is a pandemic there is no time to waste: should we have hydroxychloroquine in our armoury against COVID-19 infected patients? Mediterr J Rheumatol. 2020;31(1):94-7.
30. Kourkouni E, Mitsogiannis G, Simopoulou T, Liaskos C, Katsiari CG, Daniil Z, et al. Interstitial Lung Disease in Anti-Synthetase Syndrome. Mediterr J Rheumatol. 2019;30(3):186-9.
31. Gkoutzourelas A, Bogdanos DP, Sakkas LI. Kawasaki Disease and COVID-19. Mediterr J Rheumatol. 2020;31(Suppl 2):268-74.
32. Patrikiou E, Liaskos C, Mavropoulos A, Ntavari N, Gkoutzourelas A, Simopoulou T, et al. Autoantibodies against specific nuclear antigens are present in psoriatic disease and are diminished by secukinumab. Clin Chim Acta. 2020;510:400-7.
33. Angelopoulou F, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Immune checkpoint inhibitor-induced musculoskeletal manifestations. Rheumatol Int. 2021;41(1):33-42.
34. Asteriou E, Gkoutzourelas A, Mavropoulos A, Katsiari C, Sakkas LI, Bogdanos DP. Curcumin for the Management of Periodontitis and Early ACPA-Positive Rheumatoid Arthritis: Killing Two Birds with One Stone. Nutrients. 2018;10(7).
35. Bogdanos DP. Mediterranean Journal of Rheumatology September 2018 Highlights. Mediterr J Rheumatol. 2018;29(3):118-9.
36. Bogdanos DP, Gkoutzourelas A, Papadopoulos V, Liaskos C, Patrikiou E, Tsigalou C, et al. Anti-Ro52 antibody is highly prevalent and a marker of better prognosis in patients with ovarian cancer. Clin Chim Acta. 2021;521:199-205.
37. Bogdanos DP, Sakkas LI. Enterococcus gallinarum as a component of the Autoinfectome: the gut-liver-autoimmune rheumatic disease axis is alive and kicking. Mediterr J Rheumatol. 2018;29(4):187-9.
38. Cantarini L, Rigante D, Vitale A, Napodano S, Sakkas LI, Bogdanos DP, et al. Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenging yet promising future. Immunol Res. 2015;61(3):326-37.
39. Dardiotis E, Bogdanos DP. Searching for Possible Links between Alzheimer's Disease and Systemic Sclerosis. Mediterr J Rheumatol. 2020;31(4):378-81.
40. Florou DT, Mavropoulos A, Dardiotis E, Tsimourtou V, Siokas V, Aloizou AM, et al. Tetracyclines Diminish In Vitro IFN-gamma and IL-17-Producing Adaptive and Innate Immune Cells in Multiple Sclerosis. Front Immunol. 2021;12:739186.
41. Grammatikopoulou MG, Gkiouras K, Dardiotis E, Zafiriou E, Tsigalou C, Bogdanos DP. Peeking into the future: Transdermal patches for the delivery of micronutrient supplements. Metabol Open. 2021;11:100109.
42. Grammatikopoulou MG, Gkiouras K, Nigdelis MP, Bogdanos DP, Goulis DG. Efficacy of Vitamin D3 Buccal Spray Supplementation Compared to Other Delivery Methods: A Systematic Review of Superiority Randomized Controlled Trials. Nutrients. 2020;12(3).
43. Grammatikopoulou MG, Gkiouras K, Theodoridis X, Asteriou E, Forbes A, Bogdanos DP. Oral Adjuvant Curcumin Therapy for Attaining Clinical Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2018;10(11).
44. Grammatikopoulou MG, Nigdelis MP, Theodoridis X, Gkiouras K, Tranidou A, Papamitsou T, et al. How fragile are Mediterranean diet interventions? A research-on-research study of randomised controlled trials. BMJ Nutr Prev Health. 2021;4(1):115-31.
45. Kelepouri D, Mavropoulos A, Bogdanos DP, Sakkas LI. The Role of Flavonoids in Inhibiting Th17 Responses in Inflammatory Arthritis. J Immunol Res. 2018;2018:9324357.
46. Maslyanskiy A, Lazareva N, Olinek P, Schierack P, Hentschel C, Cuccato J, et al. Anti-hnRNP B1 (RA33) autoantibodies are associated with the clinical phenotype in Russian patients with rheumatoid arthritis and systemic sclerosis. J Immunol Res. 2014;2014:516593.
47. Mavropoulos A, Varna A, Zafiriou E, Liaskos C, Alexiou I, Roussaki-Schulze A, et al. IL-10 producing Bregs are impaired in psoriatic arthritis and psoriasis and inversely correlate with IL-17- and IFNgamma-producing T cells. Clin Immunol. 2017;184:33-41.
48. Mavropoulos A, Zafiriou E, Simopoulou T, Brotis AG, Liaskos C, Roussaki-Schulze A, et al. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology (Oxford). 2019;58(12):2240-50.
49. Mytilinaiou MG, Bogdanos DP. Primary biliary cirrhosis-specific autoantibodies in patients with systemic sclerosis. Dig Liver Dis. 2009;41(12):916; author reply -7.
50. Pagkopoulou E, Simopoulou T, Maragkouli E, Perifanou-Sotiri S, Kotsakis A, Bogdanos DP. Arthritis and Myositis in a Patient Treated with Programmed Cell Death-1 (PD-1) Inhibitor Pembrolizumab for Lung Cancer. Mediterr J Rheumatol. 2020;31(3):355-7.
51. Rigamonti C, Bogdanos DP, Mytilinaiou MG, Smyk DS, Rigopoulou EI, Burroughs AK. Primary biliary cirrhosis associated with systemic sclerosis: diagnostic and clinical challenges. Int J Rheumatol. 2011;2011:976427.
52. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmun Rev. 2017;16(1):10-5.
53. Sakkas LI, Bogdanos DP. Multiple hit infection and autoimmunity: the dysbiotic microbiota-ACPA connection in rheumatoid arthritis. Curr Opin Rheumatol. 2018;30(4):403-9.
54. Sakkas LI, Bogdanos DP, Kousvelari EE. Loss of C9orf72 function leads to autoimmunity. Ann Transl Med. 2017;5(3):60.

55. Sakkas LI, Daoussis D, Liossis SN, Bogdanos DP. The Infectious Basis of ACPA-Positive Rheumatoid Arthritis. Front Microbiol. 2017;8:1853.
56. Sakkas LI, Mavropoulos A, Zafiriou E, Roussaki-Schulze A, Bogdanos DP. The effect of Apremilast on signal transduction and IL-10 production in CD39high regulatory B cells in patients with psoriatic arthritis. Mediterr J Rheumatol. 2018;29(1):59-61.
57. Skyvalidas D, Mavropoulos A, Tsiogkas S, Dardiotis E, Liaskos C, Mamuris Z, et al. Curcumin mediates attenuation of pro-inflammatory interferon gamma and interleukin 17 cytokine responses in psoriatic disease, strengthening its role as a dietary immunosuppressant. Nutr Res. 2020;75:95-108.
58. Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. Helicobacter pylori and autoimmune disease: cause or bystander. World J Gastroenterol. 2014;20(3):613-29.
59. Smyk DS, Mytilinaiou MG, Milkiewicz P, Rigopoulou EI, Invernizzi P, Bogdanos DP. Towards systemic sclerosis and away from primary biliary cirrhosis: the case of PTPN22. Auto Immun Highlights. 2012;3(1):1-9.
60. Stamatis P, Bogdanos DP, Sakkas LI. Upadacitinib tartrate in rheumatoid arthritis. Drugs Today (Barc). 2020;56(11):723-32.
61. Stamostergiou J, Theodoridis X, Ganochoriti V, Bogdanos DP, Sakkas LI. The role of the Mediterranean diet in hyperuricemia and gout. Mediterr J Rheumatol. 2018;29(1):21-5.
62. Theodoridis X, Grammatikopoulou MG, Stamouli EM, Talimtzi P, Pagkalidou E, Zafiriou E, et al. Effectiveness of oral vitamin D supplementation in lessening disease severity among patients with psoriasis: A systematic review and meta-analysis of randomized controlled trials. Nutrition. 2021;82:111024.
63. Theodoridis X, Pittas S, Bogdanos DP, Grammatikopoulou MG. Social Media as Tools to Study Dietary Habits of Patients with Rheumatic Diseases: Learning from Relevant Work on Inflammatory Bowel Diseases. Mediterr J Rheumatol. 2020;31(4):382-3.
64. Tsiogkas SG, Mavropoulos A, Skyvalidas DN, Patrikiou E, Ntavari N, Daponte AI, et al. Delphinidin diminishes in vitro interferon-gamma and interleukin-17 producing cells in patients with psoriatic disease. Immunol Res. 2021.
65. Tsouris Z, Liaskos C, Dardiotis E, Scheper T, Tsimourtou V, Meyer W, et al. A comprehensive analysis of antigen-specific autoimmune liver disease related autoantibodies in patients with multiple sclerosis. Auto Immun Highlights. 2020;11(1):7.
66. Vranou P, Gkoutzourelas A, Athanatou D, Zafiriou E, Grammatikopoulou MG, Bogdanos DP. Let Food Be Thy Medicine: The Case of The Mediterranean Diet in Rheumatoid Arthritis. Mediterr J Rheumatol. 2020;31(3):325-9.
67. Zafiriou E, Daponte AI, Siokas V, Tsigalou C, Dardiotis E, Bogdanos DP. Depression and Obesity in Patients With Psoriasis and Psoriatic Arthritis: Is IL-17-Mediated Immune Dysregulation the Connecting Link? Front Immunol. 2021;12:699848.
68. Reiseter S, Gunnarsson R, Mogens Aalokken T, Lund MB, Mynarek G, Corander J, et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. Rheumatology (Oxford). 2018;57(2):255-62.
69. Wodkowski M, Hudson M, Proudman S, Walker J, Stevens W, Nikpour M, et al. Monospecific anti-Ro52/TRIM21 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects: evidence of an association with interstitial lung disease and worse survival. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S131-5.
70. Lee A, Patterson KA, Tan DJ, Wilson ME, Proudman SM, Stevens W, et al. Anti-Ro52/TRIM21 is independently associated with pulmonary arterial hypertension and mortality in a cohort of systemic sclerosis patients. Scand J Rheumatol. 2021;50(6):469-74.
71. Liu C, Hou Y, Yang Y, Xu D, Li L, Li J, et al. Evaluation of a commercial immunoassay for autoantibodies in Chinese Han systemic sclerosis population. Clin Chim Acta. 2019;491:121-5.