When rheumatology and infectious disease come together

George E Fragoulis and Nikolaos V Sipsas

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Correspondence to:
George E Fragoulis
Institute of Infection, Immunity and Inflammation, University of Glasgow, 120 University Place, Glasgow G12 8TA, UK
geofragoul@yahoo.gr

First Department of Propaedeutic Internal Medicine, "Laiko" General Hospital, National and Kapodistrian University of Athens, Athens, Greece

Nikolaos V Sipsas
Department of Pathophysiology, General Hospital of Athens "Laiko", and Medical School, National and Kapodistrian University of Athens, Greece

Infectious and autoimmune rheumatic diseases (ARDs) are closely linked. Apart from the challenging, sometimes differential, diagnosis between these conditions, it is recognized that microbes play an important role in the pathogenesis of the latter.

Many infective agents have been implicated in the pathophysiology of autoimmune conditions. To mention some of the paradigms, the association of infectious disease in the pathogenesis and exacerbation of anti-neutrophil cytoplasmic autoantibodies-mediated vasculitis[1] is well known as it is the relationship between hepatitis B virus (HBV) infection and necrotizing vasculitis, which possibly represents a subset of polyarteritis nodosa.[2] Also, several data support the notion that primary Sjögren's syndrome is linked with infection from retroviruses[3] such as human T-lymphotropic virus 1[4] as well as the association of the Epstein–Barr virus (EBV) with autoimmune diseases like systemic lupus erythematosus (SLE) and multiple sclerosis (MS).[5] In addition, reactive arthritis can occur after infections, usually of the gastrointestinal or genitourinary system.[6]

Many mechanisms have been proposed to explain the role of infectious agents in the pathogenesis of ARDs. These include epigenetic modifications induced by microorganisms, epitope spreading, toll-like receptor (TLR) activation, complementary peptides[1] and molecular mimicry, with the association between rheumatic fever and group A *Streptococcus* being a classical paradigm of the latter.[7] Furthermore, the role of alterations in the microbiome (also knowns as dysbiosis), has been increasingly appreciated over recent years[8] in several ARDs such as seronegative spondyloarthropathies,[9] rheumatoid arthritis[10] and inflammatory bowel diseases.[11] Also, some pathogenetic pathways seem to be shared between autoimmune and infectious diseases. Several genetic defects leading to immune system dysregulations are found to predispose to both ARDs and recurrent infections in the context of immunodeficiencies.[12] Besides, a considerable number of patients with primary immunodeficiencies have autoimmune manifestations.[12] That said, aberrancies in the innate immune system (e.g. deficient phagocytosis of the apoptotic cells) have been described as contributing to the pathogenesis of ARDs like SLE and Sjögren's syndrome.[13]

On the other hand, it has been described that infections might offer some protection from autoimmune diseases. For example, it has been found that *Helicobacter pylori* is negatively associated with MS and inflammatory bowel disease[8] and a possible protective role has been suggested for HBV infection and SLE.[8] Studies on animal models also support this notion. There is a wealth of data showing that non-obese diabetic mice, which are used as a model for type 1 diabetes, are protected from disease development upon infection with various microbes.[14] To explain the observed negative correlation between frequencies of infectious and autoimmune diseases,[14] the 'hygiene hypothesis' has been formulated. The main underlying mechanisms of this theory are regulation of specific immune cells and their mediators by pathogens or commensals, antigen competition, and desensitization of TLR *via* repeated low-dose stimulation.[14] One should note however that this hypothesis does not apply for all ARDs.[14] In addition, it is of interest that several genes associating with ARDs have been found to offer protection from infectious diseases, therefore leading to positive selection over the years.[15]

On clinical grounds, infections, especially chronic infections, can cause a plethora of autoimmune phenomena, thus mimicking ARDs. Therefore, the differential diagnosis between ARDs and infectious diseases is sometimes challenging as they often display similar clinical manifestations. Several viruses like parvovirus

B19, cytomegalovirus, EBV and HIV as well as bacteria like *Borrelia burgdorferi, Mycobacterium tuberculosis* and other microbes like *Leishmania* spp. can mimic the clinical picture of SLE.[16] Similarly, HBV, hepatitis C virus (HCV), HIV, endocarditis, *Staphylococcus aureus, Coxiella burnetii*[17] and other bacteria can resemble the clinical picture of vasculitis.[18,19] Also, in the differential diagnosis of aortitis, apart from autoimmune and other diseases (e.g. Takayasu arteritis, giant-cell arteritis, IgG4-related disease), *Treponema pallidum, Streptococcus pneumoniae, S. aureus, Salmonella* and tuberculosis (TB) are included.[20] Finally, viruses like HCV and HIV can produce sicca symptomatology (i.e. dry eyes and mouth) mimicking Sjögren's syndrome, as well as cryoglobulinaemia and autoimmune anaemia through molecular mimicry.[21,22]

Another facet of the close link between infectious and autoimmune diseases is the infections that arise during treatment with immunosuppressive drugs. Glucocorticoids and conventional or biologic disease-modifying antirheumatic drugs (DMARDs) have been associated with opportunistic infections, the most well recognized of which is *Pneumocystis jirovecii*. Although the beneficial effects of treatment with trimethoprim-sulfamethoxazole are recognized, it is still debatable for which immunosuppressive drugs and for which doses, chemoprophylaxis should be given,[20] especially considering the possible side effects of the antibiotics.[23] Other opportunistic pathogens, such as endemic fungi in the USA[24] and *Leishmania* in Mediterranean countries,[25] cause serious infections in patients with ARDs receiving biologics, suggesting that local epidemiology should be taken into account when considering prophylaxis. Future guidelines from rheumatology associations need to address this issue, either in a disease-specific manner or by producing generic recommendations for immunosuppressives used in rheumatology.

TB in the context of ARDs is often expressed with extrapulmonary manifestations[26] leading to delayed diagnosis and treatment. Screening for TB is *sine qua non* for patients commencing treatment with biologic drugs, however some questions remain unanswered. For example: are there any differences between biologics and what is the risk for newer synthetic DMARDs like Janus kinase inhibitors? are the biologics the only culprits or do conventional DMARDs and glucocorticoids also predispose to TB development?[27] A more intensive screening for TB might be needed, given the socioeconomic changes that have occurred during the last few years together with population ageing.

Similarly, some answers are needed for chronic viral infections like HBV. Should all patients be screened for HBV? If so, which of them have to be treated? Also, what policy should be followed for patients with past HBV infection?[28]

Furthermore, among the several issues discussed between the rheumatologists and infectious disease doctors is the effect of immunosuppressive drugs on the immunogenicity of vaccines.[29] Having said that, it should be highlighted that vaccinations in patients with ARDs are of paramount importance. However, there are still issues for which adequate evidence is still lacking. For example, in the European League Against Rheumatism 2011 recommendations it is suggested that vaccination should ideally be administered in patients with stable disease due to the theoretical risk of a disease flare after vaccination. It is worth mentioning that the strength of this recommendation was graded with 'D' as this was largely based on expert opinion[30] and there are not many studies supporting this statement.

In this Special Collection of *Therapeutic Advances of Musculoskeletal Diseases*, the above-mentioned and other questions are discussed. It is highlighted that the immune system can be our friend or our foe considering that its function and dysregulation are the common denominators in autoimmune and infectious diseases. In the era of new drugs and new therapeutic strategies, safety of the patients should always be our first concern.

ORCID iD

George E Fragoulis https://orcid.org/0000-0003-4932-7023

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