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Controversies in in rheumatology and autoimmunity: Is CORA meeting a good educational tool to increase the scientific knowledge?

Mariangela Salvato, Andrea Doria *

Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy

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ABSTRACT

Rheumatology and Autoimmunity are closely related fields and are among the most exciting areas in Medicine. Many conditions once regarded as mysterious and incurable are better understood and managed nowadays. Part of the great interest in these subjects derives from the fact that many controversial issues have arisen due to the rapid progression of knowledge, which means they are debatable. Over the years, the Controversies in Rheumatology and Autoimmunity (CORA) meetings promoted critical discussions not as an end but as a tool to increase the scientific knowledge of Rheumatologists and Clinical Immunologists. Beyond pursuing knowledge, being critical means questioning our inveterate beliefs and evaluating new conjectures and hypotheses. Thus, the approach to the debates in Medicine should be done with an open mind and free from all prejudices. Freedom of thought and speech are the fundamental values of our University, as exemplified by the motto "*Universa Universis Patavine Libertas*" which means "Padua freedom is universal for everyone". *Patavine libertas* initially referred to freedom from political and religious power but also freedom in research and teaching. For these reasons, Galileo Galilei moved to Padua in 1592, where he spent the most prosperous years of his life before being accused of heresy by the catholic church.

We aim for the CORA congress to be an open-minded forum where active participation and exchange of ideas are promoted without prejudice.

This special Issue of Autoimmunity Reviews is devoted to some controversies debated during the 7th CORA conference held in Turin, Italy, on March 16-18, 2023. Here we will discuss controversial entities, the use of old and new drugs, and insights into the classification, assessment of disease activity, and management of rheumatic diseases.

Fibromyalgia (FM) is a clinical condition commonly seen in Rheumatological clinical practice, which includes widespread pain and stiffness and several other somatic, emotional, and neuropsychic manifestations. The pathophysiology of FM remains controversial. During the CORA Congress, two leading experts in this field debated whether FM is an autoimmune disease; the debate is summarized in a review article published in this journal issue [1]. We know that FM belongs to nociplastic pain, which means that the central nervous system is deeply involved in the pain mechanism. Interestingly, anti-G protein-coupled receptor antibodies (GPCR), autoantibodies, directed against the autonomic nervous system receptors, have been detected in the serum of patients with FM, and their titers correlated with clinical symptoms. However, classic inflammatory indices are unremarkable in FM, there are no inflammatory signs on examination (e.g., synovitis) and no identifiable tissue damage; thus, FM has none of the classic signs of an autoimmune disease.

Another intriguing condition is the Breast Implant Illness BII/ASIA Syndrome (Shoenfeld's Syndrome: Autoimmunity/autoinflammatory syndrome induced by adjuvants), whose existence itself has been questioned by some authors. The syndrome was first described in 2011 and occurs after exposure to many adjuvant molecules, including silicone. ASIA syndrome belongs to the spectrum of autoinflammatory syndromes [2,3]. Silicone breast implants can induce a chronic inflammatory response that results in various pathologic manifestations, including capsular contraction and, more rarely, cancer and autoimmune diseases. Although the underlying pathophysiology is not yet fully understood, BII/ASIA syndrome meets Bradford Hill's criteria for causation [4]. However, the condition's rarity and the risk of biased interpretation must be considered [4].

Seronegative autoimmune diseases are a challenge for

* Corresponding author at: Rheumatology Unit, University of Padova, Via Giustiniani, 2, 35128 Padova, Italy.
E-mail address: adoria@unipd.it (A. Doria).

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rheumatologists, as serum biomarkers can aid in diagnosis and prognostic stratification of rheumatic diseases [5]. Up to 30% of Sjogren's disease (SjD) patients are seronegative for specific autoantibodies (ANA, antiRo/SSA, antiLa/SSB). The characteristics of this subset of patients are under evaluation, and "new" autoantibodies have been described [6]. Minor salivary gland biopsy so far is not mandatory in SjD; however, the characterization of the inflammatory infiltrate provides additional prognostic information. On the other hand, ultrasound and new biomarkers may replace its role in the future [6].

Infections and autoimmune diseases have multifaceted and multidirectional relationships [7,8]. Infections may trigger autoimmunity in predisposed individuals and are a frequent complication of AIRD (Autoimmune Inflammatory Rheumatic Diseases), resulting in increased morbidity and mortality. Therefore, vaccination is a crucial preventive strategy. The COVID-19 pandemic brought this topic under the spotlight [9,10]. The timing of vaccination and its relationship with concomitant immunosuppressive therapy has been debated here [11]. Disease activity and background immunosuppression must be considered when performing vaccination since both impact vaccine efficacy. For this reason, vaccination should preferably be administered before starting immunosuppressive therapy and preferentially during quiescent AIIRD.

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune condition triggered by a number of environmental factors [12]. The assessment of SLE disease activity remains challenging [13–15]. The most popular disease activity index, SLEDAI-2 K, has several limitations. Several groups have recently worked on developing new tools or improving existing ones. The SLE-DAS shows better sensitivity to clinically meaningful changes in disease activity and predicting damage accrual than SLEDAI-2 K [16–20]. The Easy-BILAG represents a clear evolution compared to the BILAG-2004 format ensuring high accuracy and less variability. The burning debate is still unsolved, as to date, the sensitivity to change of SLE-DAS has not been tested against the Easy-BILAG. The face-to-face discussion between Professor Inês and Professor Edward was one of the highlights of the congress [21].

Lupus nephritis (LN) is one of the most severe manifestations of SLE since it significantly affects patients' prognosis and quality of life. Thus, the management of LN is a real challenge both in terms of patient prognosis and economic burden [22–24].

Baseline kidney biopsy is recommended in LN for classification, therapy assessment, and prognostication [25]. Repeat kidney biopsy is a valuable tool to guide therapeutic decisions in complex cases and to distinguish between active and chronic lesions [26]. Based on the recently demonstrated discordance between clinical and histological response, some physicians recommend per-protocol biopsies performed at fixed time points, regardless of clinical response. The per-protocol biopsy can inform treatment efficacy and guide maintenance therapy's duration. The prognostic value of histological activity in patients in clinical remission is debated, but an activity index >3 in patients in clinical remission may portend renal flare [27].

The prognosis of LN has improved in recent decades, but 5–20% of patients still progress to kidney failure. Belimumab and voclosporin have been recently approved for LN. In Randomized Controlled Trials (RCTs), a higher proportion of patients treated with Belimumab or Voclosporin plus the standard of care (combination regimen) achieved renal response, which is known to be protective from nephron loss and the risk of kidney failure. Given these encouraging results, it is legitimate to wonder whether the new drugs should be used early in the disease course [28]. The main reasons supporting the early use are based on the RCTs that demonstrated benefits when a combinatory regimen was initiated early in incident and relapsing patients. However, many patients achieved renal response without add-on medications. Thus, reserving these medications for relapsing/refractory patients might be more cost-effective. Since good predictors of renal response are lacking, it remains difficult to identify who will benefit from combination therapy [29].

Despite the advent of new drugs, glucocorticoids (GCs) remain a cornerstone of the treatment of SLE. Long-term low-dose GC use is a divisive issue in rheumatology [30,31].

European Alliance of Associations for Rheumatology (EULAR) recommendations support GCs withdrawal, when possible, due to the acknowledged risk of damage accrual in SLE patients treated with GCs. Several observational studies showed that discontinuation of GCs is associated with lower damage accrual. While most studies assumed a cut-off of 7.5 mg/day of prednisone equivalent, the effect of a lower dose of GCs on damage accrual is contentious. The main concern with GCs withdrawal is the risk of flares, which are strongly associated with organ damage, mortality, healthcare costs, and decreased quality of life. A recent randomized trial has shown that a daily dose of 5 mg of prednisone in SLE patients in short-term remission can prevent up to 50–75% of flares, with an acceptable safety profile. We do not have a reliable method to identify patients who may require long-term low-dose GC. Therefore, further research is needed to identify a subgroup at high risk of relapse who would benefit from continuing prednisone.

Similarly, a lively discussion was about long-term GC use in rheumatoid arthritis (RA) [31]. Seventy-five years ago, GCs were first used by Hence and Kendall to treat severe RA [32]. The discovery of glucocorticoids marked a significant breakthrough in rheumatology; however, the characteristic side effect profile and the disease's relapse after GCs withdrawal were soon noticed. GCs exert a kaleidoscopic effect on the immune system and are widely used to treat many rheumatic conditions [33]. GCs can rapidly suppress synovial inflammation and provide symptomatic relief to patients [34]. Nevertheless, their use does not lead to permanent resolution of synovitis.

During the last decades, thanks to the increased knowledge of disease pathogenesis, the therapeutic landscape of RA rapidly evolved but GCs are still widely prescribed [35]. Real-world data show that up to 50% of RA patients continue to take GCs during the disease course. At the same time, the American College of Rheumatology (ACR) and EULAR recommendations for the management of RA strongly advise against chronic use and suggest limiting their role as bridging therapy due to safety concerns. One of the main arguments supporting the long-term use of GCs is the effect on radiographic progression in early RA [31]. However, adverse events of GCs usually occur after long-term use, limiting the generalizability of RCTs proving no or minimal harm. Observational studies show conflicting results regarding the safety of GSs and are subjected to a high risk of bias, including indication bias. Moreover, GCs use is widespread among difficult to treat (D2T) RA populations [36]. It is crucial to distinguish those with multiple therapy-resistant refractory RA from those with persistently high disease activity indexes in the absence of inflammation since the latter group would benefit from different management strategies [37,38].

Janus Kinase inhibitors (JAKis) are very efficacious drugs and showed superiority to methotrexate and TNF inhibitors in RCTs [39]. Recently, concern over their safety was raised by the results of the Oral Surveillance trial. Since then, regulatory authorities have added warnings labels to JAKis. Should Rheumatologists then use JAKis as first-line advanced treatment? The review article published in this journal's issue addresses this critical question [40]. Some rheumatologists have argued that biologics should be the first line treatment since extensive effectiveness and safety data exist. In addition, with the advent of biosimilars, they are the most cost-effective treatment. On the other hand, when TNF inhibitors are contraindicated and/or an oral drug is preferred JAKis can be used as first-line treatment, providing patients are informed of the risk and are involved in the decision-making process.

Another interesting discussion was about revising the immunological item of the ACR/EULAR classification criteria for RA [41]. The presence of positive rheumatoid factor (RF) and/or anti-cyclic citrullinated protein/peptide antibodies (ACPA) eases the recognition of RA. Yet the debate is open on whether this scoring system ought to be optimized by hierarchizing ACPA or the combination of ACPA and RF over single positivity, prioritizing specificity over sensitivity. The risk of misdiagnosis and misclassification are often entangled, yet they are not the same

[42]. The perspective published in this journal's issue presents two conflicting views on the topic, discussing the performance of available criteria and the potentiality and pitfalls of their refinement according to novel data on ACPA and RF contribution and the emergence of newly discovered specificities [41].

Residual chronic pain is a major unmet need in RA, as it erroneously overinflates disease activity measures, potentially resulting in over-treatment [43]. Pain in RA can be secondary to inflammation but can also generate neuroendocrine responses that initiate neurogenic inflammation and enhance cytokine release, leading to persistent hyperalgesia. However, fibromyalgia is prevalent in RA patients and may significantly contribute to the D2T status, especially among patients without objective signs of inflammation [37]. Thus, it is essential to compare subjective and objective measures of disease activity to distinguish central sensitization. In addition, ultrasound is a precious tool for assessing the presence of subclinical synovitis. Finally, IL-6 and JAK inhibitors effectively reduce residual pain in RA patients, suggesting pain-reducing effects independent of their anti-inflammatory properties.

Spondyloarthritides (SpA) are a heterogeneous group of inflammatory disorders characterized by axial (axSpA) and or peripheral inflammatory joint diseases and variable extra-articular manifestations, such as inflammatory bowel disease, uveitis and psoriasis [44,45]. A considerable number of AxSpA patients do not reach remission despite targeted therapies. Although the concept of refractory axSpA is not clearly defined yet, two possible scenarios could underpin a refractory state: treatment failure or misdiagnosis [46]. The diagnosis of an active axSpA relies upon the clinician's ability to interpret the patients' symptoms and MRI signs without overlooking structural damage, fibromyalgia, comorbidities, and psychosocial issues [47].

A debate on whether anticoagulants and/or antiplatelet drugs should be prescribed in antiphospholipid syndrome (APS) patients and carriers of antiphospholipid antibodies (aPL) with thrombocytopenia is reviewed here [48]. Among the new criteria recently included in the 2023 ACR/EULAR classification criteria for APS, thrombocytopenia is one of the most frequent. Patients with aPL have an increased risk of thrombocytopenia due to peripheral platelet consumption and destruction subsequently to their activation by aPL, regardless of the presence of an underlying autoimmune disease. Although severe thrombocythemia is uncommon in APS, bleeding risk may be a concern in some circumstances [49]. The main argument supporting the use of antiplatelet drugs is the association between thrombocytopenia and APS-related events (a 3-fold increased risk for thrombotic events or obstetrical morbidity or all-cause deaths) [48].

Finally, the role of cyclophosphamide (CYC) in severe, rapidly progressive Systemic Sclerosis is discussed in a review article in this issue of the Journal [50]. CYC is considered the gold standard for severe progressive Systemic Sclerosis (SSc), especially in patients with concomitant interstitial lung disease (ILD). Several observational studies and RCTs support the use of cyclophosphamide in SSc-ILD. The use of CYC is time-limited (induction treatment) due to acute and cumulative adverse events. However, other immunosuppressive and biological agents showed efficacy but better safety profile in patients with SSc and SSc-ILD. Recently the results of the first head-to-head RCT comparing Rituximab and Cyclophosphamide in patients with severe, rapidly progressing CTD-ILD have been published [51]. According to the available data, experts' opinion has changed the attitude toward CYC as an anchor drug in the management of severe SSc. Indeed, CYC has been pushed to the second or even third treatment option after mycophenolate mofetil, tocilizumab, or rituximab. Comprehensive patient stratification according to a molecular, cellular, and phenotypic pattern may help in the choice of personalized treatment should be the future direction.

We hope that tackling these complex and contentious subjects in this special issue of Autoimmunity Reviews will help clinicians to approach controversial areas in the treatment of difficult patients while also improving our knowledge in Rheumatology and Immunology.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The Authors have no competing interest regarding this article.

Data availability

No data was used for the research described in the article.

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