Editorial: Autoimmune and Inflammatory Rheumatic Diseases: Identifying Biomarkers of Response to Therapy with Biologics: Volume II.

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Abnormal immune responses against tissues and organs of the body including cell death dysregulation, uncontrolled complement cascade activation, inflammation, recruitment of self-reactive immune cells leading to uncontrolled release of cytokines and autoantibodies represent the basis of a wide variety of systemic autoimmune diseases (SADs), rheumatic diseases included. In most cases, the mechanisms underlying these diseases are not clearly identified and a great number of studies is aimed at their elucidation (1-4).

The identification of markers, such as specific cytokines or growth factors, or characteristic antibodies, represent an urgent need for disease classification and severity prediction (5). In line with that, a study from Zhou J et al on patients affected by Idiopathic Inflammatory Myopathies (IIMs), found increased levels of various cytokines (Eotaxin, IL-7, IL-18, IP10, MCP1, MCSF, MIG, and SCGFβ), and correlation of levels of some of these cytokines with clinical indices. Additionally, groups of patients expressing different myositis specific antibodies (MSA), namely anti-ARS, anti-MDA-5, and anti-TIF1γ, which are used for diagnosis and classification of IIMs, presented unique cytokine expression patterns (Front Pharmacol. 2022 Apr 20;13:852055).

During the last few years, the pharmacological treatments of these diseases have included an increasing number of various biological drugs ranging from monoclonal antibodies and small inhibitory molecules directed against cytokines or their cell receptors, to therapies targeted to key elements and regulators of cellular responses (e.g., jak-inhibitors) (6-10).

In contrast to traditional immunosuppressive strategies, these drugs show selectivity of action towards specific targets and are currently employed to induce remission or treat specific organ involvements. One of the main treatments based on biological drugs is represented by the subcutaneous administration of tumour necrosis factor inhibitors (SC-TNFis) that has turned out to be of great relevance in the treatment of chronic progressive immune mediated rheumatic diseases (IMRDs) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Altogether IMRDs are responsible of joint deformation and progressive disability that can impact in healthcare resource utilization (HCRU) costs. In their work, Carballo N et al have evaluated the impact on HCRU costs of persistent and non-persistent SC-TNFis therapy comparing costs between 12 months before and 12 months after the beginning of treatment. The results show that long-term persistent treatment of IMRD naïve patients with SC-TNFis may indeed be associated with savings in HCRU costs (Front Pharmacol. 2021 Nov 29;12:752879), indicating that targeted, and possibly personalized therapies, may have economic significance, besides being undoubtedly relevant to patients' well-being.

Among SADs, systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and antiphospholipid syndrome (APS) are important mimickers of multiple sclerosis (MS) since invariably affecting the CNS with various MS-like manifestations. A consistent differentiation between MS and CNS involvement in the setting of SADs is not fully achievable neither by brain MRI, cerebrospinal fluid (CSF) analysis, nor by autoantibodies (i.e., ANA or antiphospholipid antibodies) detection. The study from Karathanasis DK et al. showed that some distinct clinical, imaging, and laboratory characteristics may be helpful in early differentiation between MS and CNS-involving SADs, and that peripheral blood type I IFN activity was a strong predictor for SADs presenting with CNS involvement. These results allow for optimal therapeutic strategies, particularly considering the potentially significant therapeutic role of type I IFN receptor blockade in SAD patients with evidence of CNS involvement as a cardinal manifestation (Front Pharmacol. 2022 Aug 12;13:898049).

In some cases, these innovative drugs have unfortunately failed to meet their primary endpoints in randomized-controlled trials, especially in complex diseases such as SLE and systemic sclerosis (SSc). This has led to changes to therapies currently used as well as to the development of new approaches in some cases based on the use of natural ingredients whose mechanisms of action have become more known (11).

Osteoarthritis (OA) is one of the most common joint degenerative diseases in the world (12, 13). In the treatment of OA novel reagents such as IL-1 antagonists and nerve growth factor inhibitors have entered clinical trials. Additionally, increasing evidence demonstrated that active ingredients of natural plants have great potential for treating this disease. Among these ingredients, in their review (Front Pharmacol. 2022, Nov 17;13:945876) Shentu et al. explored the pharmacological effects of bioactive alkaloids obtained from traditional Chinese medicines, such as Matrine and Sinomenine, and some other products of plant extracts such as Osthole, and Curcumin, Loganin and Morroniside, which are significant iridoid glycosides, the yellow flavonoid Quercitrin, Resveratrol, Ligustilide, Icariin, Baicalein, and modin. Moreover, the authors suggest that use of novel drug delivery strategies may overcome the shortcomings of conventional preparations and enhance the bioavailability of drugs, as well as decrease significantly the side effects (Front Pharmacol 2022, Nov 17;13:945876). As regard resveratrol, it has long been regarded as a potential antioxidant drug for RA treatment. The review from Sheng et al (Front Pharmacol. 2022 Aug 22;13:829677) treats of how resveratrol is currently considered to exert therapeutic effects on RA by activating silent information regulator 1 (SIRT1) and its downstream pathways. There is notable crosstalk between the SIRT1 and NF-κB pathways, and these pathways, which play an essential role in the development of RA, are unexpectedly linked to the influence of resveratrol.

In conclusion, in this research topic some new relevant aspects regarding pathogenetic mechanisms, new treatment strategies and identification of biomarkers in systemic autoimmune or degenerative diseases have been explored.

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