Rheumatology and Autoimmunity in *The Israel Medical Association Journal* (*IMAJ*): 2017

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KEY WORDS: intravenous immunoglobulins (IVIg), rheumatoid arthritis, vitamin D, biomarkers, immune-mediated diseases

IMAJ 2017; 19: 781–783

The *Israel Medical Association Journal* (*IMAJ*) maintains its tradition in hosting updates and publishing advances in the field of rheumatology and autoimmunity. Rapid developments in understanding pathogenic aspects of immune-mediated diseases and the continuous introduction of new therapeutic strategies were widely addressed in *IMAJ* in 2017.

In this editorial, I summarize pathogenic mechanisms, biomarkers, and new treatments aspects. This editorial focuses particularly on research and advances in rheumatoid arthritis, intravenous immunoglobulins in immune-mediated diseases, vitamin D and autoimmune diseases, uveitis treatment and quality of life, and vaccination and autoimmunity.

RHEUMATOID ARTHRITIS

The progression of disease activity and the development of systemic complications, including organ damage, in rheumatoid arthritis (RA) is irreversible when not treated early and aggressively enough; therefore, early diagnosis is one of the most important goals. The discovery of specific serological or genetic biomarkers in RA is continuously reported, focusing on their usefulness in guiding disease activity and the management of different phases of disease [1,2]. In a comprehensive review, Atzeni and colleagues [3] pointed to the potential of good biomarkers in providing prognostic information, which enables clinicians to choose proper treatments and monitor a sufficient response and outcome. Biomarkers such as rheumatoid factor (RF) and anti-citrullinated protein antibodies are thought to be reliable in identifying individuals with pre-clinical RA many years before the onset of disease. They can be correlated with a risk of developing rheumatoid arthritis and can predict the risk of tissue damage such as bone erosions and severe disease progression. Erythrocyte sedimentation rate and C-reactive protein (CRP) levels are considered prognostic biomarkers, providing information about disease activity. Using such biomarkers should improve patient care and reduce medical costs [3].

Biomarkers were used to establish predictive factors of remission and improve disease activity in 308 RA patients who received first line tumor necrosis factor-inhibitors (TNF-i) for 2 years. Positive predictors of remission included male gender, ≤ 54 years of age at the time of therapy initiation, and negative baseline CRP. The documentation of any co-morbidity was considered as a negative predictor of remission. This study concluded that demographic and clinical features are reliable predictor for achieving remission [4].

The initiation of biological therapies was an important advance in improving the prognosis of RA and in increasing disease remission. Abatacept is a co-stimulation modulator, which effectively prevents T-cell activation. Aiming to assess its effects on adaptive immune responses, Conigliaro and colleagues [5] analyzed immune cell functions in 48 RA patients treated with abatacept, based on a clinical practice setting. They noticed a significant decrease of serum immunoglobulin levels in a positive correlation with disease activity. In addition, a significant reduction of RF was also reported after 3 months of abatacept treatment. The absolute number and percentage of cytotoxic (CD8+) T cells was also reduced, but mainly in patients who responded well to abatacept therapy. This result suggests that the beneficial effect of abatacept is mediated by the reduction of both polyclonal B-cell activation and CD8+ T cells [5].

INTRAVENOUS IMMUNOGLOBULINS IN IMMUNE-MEDIATED DISEASES

High-dose intravenous immunoglobulins (IVIg) have been used for many years due to their beneficial effect in many autoimmune diseases such as systemic lupus erythematosus (SLE), anti-phospholipid syndrome (APS), dermatomyositis, and Kawasaki disease. Some of the most important effector mechanisms relevant in the treatment of these diseases are based on the fragment crystallizable (Fc) region of IgG, and include the blockade and modulation of IgG receptors (Fc gamma receptor or the neonatal Fc) [6,7]. When classical therapeutic modalities for severe APS fail, mainly in obstetric complications or in patients with catastrophic APS, IVIg is considered a good option. Tenti and colleagues [8] analyzed 35 studies and found that IVIg was highly beneficial. IVIg was also reported to be a useful component of the complex therapy in CAPS, especially in reducing the rate of mortality.

Many immune mediated diseases are candidates for high-dose IVIg therapy when they are refractory to classical therapies. Behçet's disease is an example, especially when it involves articular, neurological, and vascular systems. When systemic involve-

ment in Behçet's disease is severe and requires continuous steroid and immune-suppressive therapies, IVIg may become a beneficial option for treatment. In a recent study, four patients with severe Behçet's disease (refractory to classical therapies) were given IVIg. In all patients, a beneficial response was sustained over a long period of time and without any side effects [9]. High dose IVIg are also highly beneficial in refractory juvenile dermatomyositis (JDM). However, due to possible side effects such as nausea and vomiting, which may affect compliance to therapy, high-dose recombinant human hyaluronidase facilitated subcutaneous immunoglobulins (fSCIg) was seen as an alternative option. This mode of therapy allows the administration of lower doses and yet is highly beneficial. In one study, 1g/kg fSCIg was administered every 14 days to five refractory JDM patients in whom side effects from IVIg did not allow maintenance of therapy. Following the initiation of fSCIg for 6 months, the therapy was found to be safe and median IgG peak levels were comparable to those achieved following IVIg [10].

The beneficial usage of fSCIg in autoimmune cytopenias was evaluated in common variable immunodeficiency (CVID). CVID is the most common primary immune deficiency in adults and is frequently associated with autoimmune disorders such as hemolytic anemia and thrombocytopenia. The efficacy and safety of fSCIg were studied in four women with CVID associated with idiopathic thrombocytopenic purpura (ITP; n=3) and autoimmune hemolytic anemia (AIHA; n=1). During a median follow-up of 22 months, remission from cytopenias was maintained in all patients. In addition, the dosage of prednisone was significantly reduced. This treatment is a safe mode of therapy and effective in improving cytopenias, with a steroid sparing effect. Future studies should examine the exact immunomodulatory mechanisms of fSCIg [11].

VITAMIN D AND AUTOIMMUNE DISEASES

Vitamin D deficiency is frequent in Western countries where sun exposure is limited, in contrast to sunny countries such as Israel where the rate of this deficiency is different [12]. Vitamin D deficiency has been proven by many epidemiological studies to be associated with multiple autoimmune diseases such as SLE, RA, and inflammatory bowel diseases. This association was also shown to be with allergic diseases such as bronchial asthma [13-15]. In many experimental in vitro studies, vitamin D was shown to enhance regulatory functions such as those of regulatory T cells (Tregs) and macrophages, which are maintained by regulatory enhancement of self-mechanisms [16]. Women with recurrent pregnancy loss (RPL) are reported to have humoral and cellular immune disorders. Therefore, the possibility of vitamin D deficiency in such cases was suggested. In this respect, vitamin D deficiency was found to be prevalent in women with RPL and in association with increased immune disorders including T cell, B cell and natural killer (NK) cell defects [17].

In a study from Italy, vitamin D deficiency was analyzed among patients suffering from ITP, autoimmune hemolytic anemia, and chronic idiopathic neutropenia. In this patient sample, vitamin levels were found to be significantly lower in all patients than in controls. In ITP, very low vitamin D levels were found to correlate with reduced platelet counts. Interleukin (IL)-6, IL-17, and IFN-γ levels were much higher in these patients than in controls, suggesting a correlation between vitamin D deficiency and autoimmune cytopenias and with disease severity. In another review from Italy, the biological active form of vitamin D–1,25(OH)2D–and the status of vitamin D receptors including its polymorphisms were found to be associated with increased incidence of autoimmune diseases and other biological processes such as bone health. In this review the authors mentioned that it was not always clear whether vitamin D deficiency was the cause or rather a consequence of all studied disorders. Aiming to evaluate the status of vitamin D and its active form in other diseases such as pulmonary tuberculosis and sarcoidosis, levels of 25(OH)D were found significantly lower in all patients. In addition, the induced production of IFN-γ, IL-2, and IL-17 by peripheral blood mononuclear cells was significantly increased in these patients [18-20]. Results from long-term supplementation of vitamin D may prove to be a real therapeutic outcome due to its ability to restore immune mediated inflammation.

UVEITIS, TREATMENT, AND QUALITY OF LIFE

Uveitis is a primary intraocular inflammation, frequently of immune-mediated origin and in association with systemic diseases. As such, it is identified as non-infectious uveitis (NIU). When not treated sufficiently, it leads to irreversible visual impairment and adversely affects health-related quality of life (QoL). When QoL was assessed in these patients, a significant decrease in the physical and social functioning was found [21]; therefore, early and efficient therapies are required to prevent visual impairment. These therapies include the usage of corticosteroids and conventional immune suppressants. When these methods fail, biological drugs are introduced. The beneficial effects of up-regulating the function of Tregs in autoimmune diseases led to the development of specific or polyclonal Tregs aimed at improving regulatory functions and decreasing immune-mediated inflammation [22]. In a recent study, the efficacy of dexamethasone implants in treating Behçet's disease-related uveitis was evaluated. Following a single intravitreal dexamethasone injection, best correlated visual activity (BCVA) and central macular thickness (CMT) were assessed. After 6 months of follow-up, none of the eyes showed macular edema. BCVA was significantly increased and the mean CMT was significantly decreased. Treatment with a dexamethasone implant in Behçet's disease-uveitis is safe and of value when combined to other systemic therapies. The efficacy of long used immunosuppressive therapies was reviewed in 13 studies. Researchers found that methotrexate, cyclosporine-A, azathioprine, and adalimumab are efficient in controlling autoimmune uveitis flares, in reducing ocular inflammation, and in

acting as steroid sparing drugs. In another recent study, autoimmune uveitis was successfully treated with tocilizumab, namely when macular damage was refractory to other classical therapies [23-25].

VACCINATION AND AUTOIMMUNITY

Vaccination was one of the most important achievements in the history of medicine and in the battle against infectious diseases. The improvement of public health included a significant reduction in morbidity and hospitalization days among the adult population. However, even more impressive was the significant reduction of the pediatric mortality rate following the routine initiation of viral vaccines. Ensuring that the benefits from vaccination outweigh the possible adverse effects is important in establishing their importance when this issue is discussed. Post-vaccination adverse effects are mostly related to the immunogenicity of some vaccination components, including some of the adjuvants such as aluminum salts and oil-in-water emulsions, which have been widely reported to trigger autoimmunity [26,27]. The most frequently reported adverse effects include post-vaccination auto-inflammatory disorders and autoimmune diseases such as SLE, Sjögren's syndrome, and systemic vasculitis. Other reports pointed to the possible association between vaccines, infectious diseases, and lymphomas [28]. Studies have tried to explain how adjuvants could possibly disrupt the immune system balance, leading to increased B cell proliferation, autoantibody production, cytokine release, and tissue infiltration [29]. Attempts to establish well-accepted predictive markers, which could define susceptible individuals at risk of developing post-vaccination autoimmune syndromes, are essential. By defining individuals who are at risk for autoimmune/inflammatory syndrome (ASIA) induced by adjuvants, we may be able to lower the number of individuals who develop post-vaccination problems. Patients with a higher risk of ASIA include those with a medical history of autoimmunity or a history of allergic diseases, patients who carry autoantibodies but still asymptomatic, and individuals carrying certain genetic profiles [30].

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