

Updates in Rheumatology and Autoimmunity in the *Israel Medical Association Journal (IMAJ)* 2018

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Every year the *Israel Medical Association Journal (IMAJ)* publishes many studies covering relevant issues of autoimmunity and rheumatology. In 2018, *IMAJ* especially focused on the following topics:

BIOLOGICAL THERAPIES IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

The symptoms of many patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS) are maintained and well-controlled with disease-modifying anti-rheumatic drugs (DMARDs). However, when the symptoms remain active, treatment is usually switched to biological therapies such as anti-tumor necrosis factor (TNF) drugs, tocilizumab, and rituximab. All of these therapies have been found to improve prognosis and reduce the need for steroids and immunosuppressive drugs.

In general, 30% to 40% of RA patients treated with different biological therapies discontinue these drugs either because of insufficient outcome or due to adverse events. In this case, first line anti-TNF non-responders may benefit from switching to a second anti-TNF treatment (second-line strategies). Another option (supported by many real-life studies) is to switch to different drugs with a different mechanism of action other than blocking TNF such as abatacept, rituximab, tocilizumab, or Janus kinase inhibitors. One of the case studies showed the beneficial outcome of using a reduced dose regimen of rituximab in a patient with RA and Raynaud's syndrome. However, results from many prospective randomized studies supported the advantage of switching to a second anti-TNF therapy rather than starting a new alternative agent [1-3].

A relevant issue in this aspect is how patients with RA or AS are maintained on different DMARDs or biologicals for long periods of time. In a large study comprised of 11,642 patients with RA, 2241 were treated with anti-TNF drugs and 9401 with

other DMARDs. During the first year of follow-up, 63.5% of patients continued on their treatment with anti-TNF drugs, and 54.1% continued their treatment with DMARDs. Assessing the persistence on therapy in 1251 patients with AS, 79% maintained their anti-TNF treatment and only 41% remained on DMARDs. A similar trend was noticed at the end of the second year. The study demonstrates higher rates of therapy persistence with anti-TNF drugs compared to DMARDs. Higher persistence was also observed in patients with AS than in RA patients. It is possible that this mode of persistence on anti-TNF therapy is mainly attributed to the extent of the beneficial effects and/or lack of side effects [4]. The fact that 20% to 30% of patients presenting with RA or AS stop their beneficial response to TNF inhibitors over time suggests that neutralizing antibodies to these drugs (acting as antigens) may develop. In these cases, clinicians should consider assessing these neutralizing antibodies [5].

In an earlier study, the development of antibodies against TNF-blocking drugs such as antibodies to infliximab, etanercept, or adalimumab and the relation of this result to their beneficial effect during long-term therapy (3, 6, and 12 months of therapy) was analyzed. Anti-infliximab, anti-etanercept, and anti-adalimumab antibodies were found in 20%, 0%, and 30% of patients, respectively. Patients with antibodies to anti-TNF drugs had lower serum infliximab or adalimumab compared to patients in whom neutralizing antibodies were not detected.

The outcome of all available biological therapies in autoimmune diseases should be evaluated carefully

In addition, the formation of antibodies to these drugs was found to be in negative correlation with disease activity. In a study published this year, RA patients were found to be poorly responsive to anti-TNF drugs due to the development of anti-drug antibodies (ADA). Total ADA serum levels were significantly higher in patients with treatment failure, suggesting the importance of applying tests for the early detection of these antibodies to prevent therapy failure [6,7].

Fatigue is one of the common distressing symptoms in patients presenting with RA, systemic lupus erythematosus (SLE), and other autoimmune diseases. There is not sufficient data on how different therapeutic regimens are effective in reducing fatigue. Biological therapies are widely reported to improve fatigue and other symptoms, such as the reduction of

joint damage and bone density in RA. The effect of long-term treatment with tocilizumab on fatigue and bone mineral density (BMD) was assessed in 145 patients presenting with active RA. Of these, 88 patients (61%) completed a 2 year treatment period. Fatigue score improved continuously starting from one month after the initiation of therapy. Bone mineral density of femoral neck remained stable in addition to a significant decrease in disease activity [8].

The effect of tocilizumab on BMD in patients with active RA was assessed in another study by Kume and co-authors [9]. In their study, 86 patients who were not sufficiently responsive to methotrexate treatment were treated with tocilizumab (8 mg/kg every 4 weeks). After 1 year, 33 patients with osteopenia at baseline, showed a significant increase in BMD of the lumbar spine, suggesting that tocilizumab is highly efficient in improving BMD in active RA patients.

VITAMIN D INSUFFICIENCY IN AUTOIMMUNE/IMMUNE-MEDIATED DISEASES

Vitamin D insufficiency is a frequent finding in many autoimmune diseases, namely in SLE. It plays a crucial role both in reducing BMD and in the progression of osteoporosis and the development of fractures. The etiology of reduced BMD and vitamin D insufficiency in SLE is not clear. The reasons for this are related to the persistence of inflammation as well as to the side effects of long-term usage of steroids. As such, it is important to monitor vitamin D serum levels to prevent and treat these co-morbidities [10]. Vitamin D insufficiency was also reported in fibromyalgia, which suggests the importance of supplementation for fibromyalgia. Patients with fibromyalgia and vitamin D levels below 30 ng/ml were given 50000 IU of oral vitamin D once every week for 3 months. The 25 (OH) D levels increased significantly in correlation with a significant improvement in symptoms [11].

BIOLOGICAL THERAPIES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER IMMUNE-MEDIATED INFLAMMATORY DISEASES

Despite the wide usage of combined immunosuppressive therapies and steroids in treating severe SLE, end-stage organ damage and poor prognosis in many cases remain therapeutically challenging. In addition, SLE is a disease with much co-morbidity, such as recurrent infections, low levels of vitamin D, and osteoporosis. These conditions should be carefully monitored and treated to improve the prognosis of SLE. Although only one biologic agent, belimumab, has been approved for active and steroid-dependent SLE, other off-label biologics are frequently administered. Lacking evidence-based data for many of these drugs, such as rituximab and abatacept, specialists in the field of SLE are frequently encouraged by real-life experience. One of these real-life based

Many immune-mediated disorders have recently been found to be autoinflammatory in origin

recommendations was supported by the opinion of 59 French speaking SLE experts from three clinical networks dedicated to autoimmune diseases.

Overall, 17 recommendations supporting the usage of biologics other than belimumab, provide guidance for clinicians in daily practice [12]. Rituximab (monoclonal anti-CD20 antibody) is widely and efficiently used in many immune-mediated renal diseases, including SLE lupus. Although recognized as a safe drug, rare but serious adverse events have been reported, such as severe hypogammaglobulinemia, increased rate of infections, and the reactivation of hepatitis B. Nephrologists who recommend long-term rituximab should consider these side effects mainly when optimal doses are prescribed. New therapeutic combinations and novel drugs against a variety of molecules are under continuous evaluation, to help reduce SLE disease activity and organ damage. This caution is especially important when strategies such as treat-to-target are the right approach for achieving best results; however, many clinical and therapeutic issues are still unresolved [13-15].

AUTO-INFLAMMATORY DISEASES: DIAGNOSIS AND THERAPY

Auto-inflammatory diseases are usually diagnosed during childhood. However, these diseases are occasionally documented in adults as well. They are usually manifested with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. Other diseases present with recurrent pericarditis, familial Mediterranean fever (FMF), or cryopyrin-associated periodic syndromes. Overall, the final diagnosis is achieved in all cases after a delay of a mean of 12 years. When compared to children, adult patients with auto-inflammatory diseases presented more frequently with mild manifestations and none developed amyloidosis [16]. Idiopathic recurrent acute pericarditis (IRAP) is a disease of suspected immune-mediated pathogenesis, also defined as an auto-inflammatory disease. IRAP patients test negative for mutations associated with FME, but a few may have a mutation in the gene encoding the receptor for TNF. IRAP is treated with nonsteroidal anti-inflammatory drugs or aspirin at high doses and with steroids when sufficient response is not achieved. When the tapering of steroids is not possible, colchicine is administered to achieve a long-lasting remission and the discontinuation of steroids. When pericarditis is not controlled, anakinra is a good solution [17,18]. Myocarditis, myositis, and eosinophilic granulomatosis with polyangiitis can also be symptoms of auto-inflammatory disorders. In such cases, interleukin (IL)-1 and IL-6 inhibitors have shown to be highly effective. The aberrant stimulation of interferon signaling is followed by a clinical spectrum of auto-inflammatory disorder a concept called "type I interferonopathies". Questions as how type I interferon can drive

Advanced diagnostic assays for detecting antinuclear antibodies are useful for early diagnosis

systemic inflammation are still unsolved, but symptoms can still be treated with anti-IL-1 or anti-IL-6 [18-21].

IMMUNE-MEDIATED UVEITIS: DIAGNOSIS AND TREATMENT

By conducting a literature review and considering the epidemiology of uveitis, a multidisciplinary panel of 14 experts, including ophthalmologists, rheumatologists, and internists instituted recommendations for the diagnosis of uveitis. The team established that diagnosis should be guided by the medical history and serologic screening for syphilis in all patients. When this method is not sufficient for a diagnosis, then other assessments are required such as assays for human leukocyte antigen (HLA) B27, serum angiotensin-converting enzyme (ACE), interferon-gamma release, chest computed tomography (CT), and cerebral magnetic resonance imaging (MRI). Other investigations in the absence of the clinical or laboratory analyzes were found to be of no diagnostic value. In another study, the relevance of these procedures for the etiological diagnosis of uveitis was further established. The study comprised 300 patients. Chest CT scans were valuable in the diagnosis of sarcoidosis in 83 patients (29%). Findings such as snowballs in ocular examination, blood lymphopenia, and increased ACE levels were found to be associated with abnormal CT scans. Cerebral MRI was abnormal in 15 patients (9%) and in most of them snowballs and retinal vasculitis were also present. The main etiology of uveitis was latent tuberculosis (25%) and sarcoidosis (22%), but 34% remained of unknown origin [22,23]. Uveitis has a strong impact on quality of life (QoL) following the development of severe visual impairment. Eighty patients presenting with uveitis and 23 healthy controls completed a 36-item short-form healthy survey (SF-36). QoL was significantly decreased in patients with uveitis compared to healthy controls, mainly due to physical and clinical functioning [24]. Careful evaluation is always required by specialists or physicians experienced in treating uveitis. The approach to assessment is based on the experience of clinicians and a review of the literature with regard to the use of steroids, immunosuppressive drugs, and biologic drugs in the management of patients with inflammatory eye disease [25].

Increased IL-6 production has been found to be involved in the development of many systemic immune-mediated inflammatory diseases. With respect with ocular diseases, increased levels of IL-6 was found in ocular fluids derived from diseases such as retinal vein occlusion and chronic uveitis. Ongoing clinical trials are assessing new anti-IL-6 monoclonal antibodies and their potential use in clinical practice [26]. The efficacy of dexamethasone implants on ocular, clinical, and morphological parameters was evaluated in patients presenting with Behçet's disease related uveitis. A single intravitreal dexamethasone injection was applied into each eye of five Behçet's disease patients. At baseline, all eyes showed marked macular edema, and in four out of all, active retinal vasculitis was documented. Best corrected visual acuity and central macular thickness were

significantly improved from baseline at 6 months of follow-up. At the end of the study, retinal vasculitis resolved in all eyes [27].

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Capsule

Adult neurogenesis and Alzheimer's disease

Alzheimer's disease (AD) pathology destroys neurons and synapses in the brain, leading to dementia. The brain generates new neurons throughout life in the hippocampus, a process called adult hippocampal neurogenesis (AHN). **Choi** et al. found that blocking AHN exacerbated cognitive impairment in an AD mouse model. Inducing neurogenesis alone did not improve cognition in AD mice; whereas, inducing neurogenesis while simultaneously ameliorating the neuronal environment via

exercise did. The use of genetic or pharmacological treatments that simultaneously induced neurogenesis and increased levels of brain-derived neurotrophic factor (BDNF) mimicked the benefits of exercise on cognition. Thus, inducing both neurogenesis and providing BDNF may be useful as an AD therapeutic.

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Capsule

Emicizumab prophylaxis in patients who have hemophilia A without inhibitors

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis. In a phase 3, multicenter trial, **Mahlangu** and co-authors investigated its use as prophylaxis in individuals who have hemophilia A without factor VIII inhibitors. A total of 152 participants were enrolled. The annualized bleeding rate was 1.5 events in group A and 1.3 events in group B, as compared to 38.2 events in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($P < 0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those

in group B had no treated bleeding events, compared to those in group C, who all had treated bleeding events. In the intra-individual comparison involving 48 participants, emicizumab prophylaxis resulted in an annualized bleeding rate that was 68% lower than the rate with previous factor VIII prophylaxis ($P < 0.001$). The most frequent adverse event was low-grade injection-site reaction. There were no thrombotic or thrombotic microangiopathy events, development of antidrug antibodies, or new development of factor VIII inhibitors.

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Capsule

Synthesizing a therapeutic probiotic

Phenylketonuria is a disease caused by an inability to metabolize the amino acid phenylalanine, which can accumulate in the blood and brain and cause neurotoxicity. Patients are treated by restricting phenylalanine intake through a low protein diet, but this can cause failure to thrive. To improve the therapeutic options, **Isabella** and colleagues developed a probiotic that meets the current requirements for clinical testing. They engineered a strain of *Escherichia coli* with a strong safety profile in humans to inducibly express a phenylalanine-

degrading enzyme. Oral administration of this probiotic in a mouse model of phenylketonuria prevented increased phenylalanine concentrations in the blood when the mice were injected with phenylalanine, suggesting that gastrointestinal degradation can regulate circulating phenylalanine concentrations. Thus, this synthetic probiotic could have potential in clinical trials.

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