



Przemysław Kotyla<sup>1</sup>, Włodzimierz Samborski<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Rheumatology and Clinical Immunology, Medical University of Silesia, Katowice, Poland

<sup>2</sup>Department and Clinic of Rheumatology, Rehabilitation and Internal Medicine, Poznań University of Medical Sciences, Poznań, Poland

# What does immunology say to rheumatologists that it does not say to others?

At the beginning of this century a real breakthrough process in understanding complex mechanisms of autoimmunity was observed [1]. That was mainly due to enormous progress in genetics, basic, and clinical immunology. That progress translated directly to the introduction to the clinical practice new class of drugs commonly referred to as biological disease-modifying drugs or biologics. This new class of drugs possesses the unique ability to interact with key elements of inflammatory pathways and thus can modify the clinical picture and course of inflammatory and autoimmune diseases.

Interaction with the immune system is not restricted to immunosuppressive or immunomodulatory properties of these compounds drugs. The role of immune active drugs—both large molecular weight proteins as well as small compounds can be recognized in the wider context of modulation of the immune system. Being rheumatologists, we recognize the immune system primarily as the effector arm of autoimmunity, however, the fundamental role of the immune system is to recognize invaders, pathogens, and cancer cells to save the integrity of the host. Immune check point inhibitors are newly developed immune active drugs aimed to enforce immune response mainly by T cells. The cellular immune response is tightly controlled by several mechanisms aimed to halt or even reverse the immune response in a situation when such an activity is not needed. This is realized mainly by the presence of several molecules (check points) on the surface of the T and B cells interacting with each other and transmitting so-called co-stimulatory signals necessary for full T cell activation. In

the case of cancer, the host's immune system may be stunned by cancer cells and thus could work insufficiently to promote cancer spread. Among many potential mechanisms, cancer cells may use, activation of negative stimulation via check-point is one of the most effective methods to reduce immune system response against the cancer cells. The philosophy of anticancer drugs recently introduced to oncology is to block check points thus reducing the risk of immune system inactivity. The deep interaction in the immune system may bring however many negative consequences. The check-point inhibitors usage can include uncontrolled activation of the immune system leading directly to an autoimmune response. That was the background of work by Janiak et al. — “Rheumatic manifestations in cancer patients treated with immune checkpoint inhibitors” [2]. Analysis of clinical and epidemiological data strongly suggests that rheumatic diseases and autoimmune disorders can occur in the context of the treatment with immune check points inhibitors. Patients treated with immune check point inhibitors may show a wide spectrum of rheumatic conditions including inflammatory arthropathies, connective tissue diseases mimics, vasculitides and others. The clinical picture may be additionally complicated by the co-presence of rheumatic symptoms caused directly by cancer (paraneoplastic rheumatic syndromes).

The intervention in a tightly controlled system such as the immune system is, always may bring many negative consequences. Apart from the activation of the immune system via immune checkpoint inhibitors, immunosuppression with the use of biologics contribute to the development of autoimmune conditions

and predisposes to the development of thyroid disorders. It may be surprising that biologics — designed to ameliorate immune response and halt the progression of rheumatic conditions could in some instances generate an autoimmune response. This is mainly due to an imbalance between Th1 and Th2 responses but more generally between humoral and cellular responses. The excellent example may serve the development of psoriasis after anti-tumour necrosis factor (TNF) therapy or generation of anti-nuclear antibodies and the development of lupus-like disorders. In this issue Sawicka-Gutaj and colleagues reviewed the current concepts on development of autoimmune thyroid diseases caused by treatment with biologics [3]. The development of autoimmune reaction is a well-known clinical entity since the introduction of biologics to general clinical practice. The precise pathophysiological background is generally not fully elucidated. It is supposed that cytokine imbalance caused by amelioration of the cytotoxic response mediated by TNF may play a role. The other potential mechanism is lymphocyte migration and inflammatory reaction evoked by the reduction of TNF levels in the course of anti-TNF treatment. The role of TNF as a key cytokine in this process is supported by the observation of the lack of such an effect in the course of the treatment with other biologics targeting IL-6, IL-17, or IL-23. Regardless of the pathophysiological background of thyroiditis caused by anti-TNF treatment thyroid disorders represent a real challenge for both endocrinologists and rheumatologists/immunologists. Moreover autoimmune thyroid diseases represent the most frequent autoimmune diseases and we may simply face the overlapping the sex-related autoimmunity and treatment with the use of biologics.

Not all rheumatic drugs used in the treatment of inflammatory arthritides may exert negative impact on body functioning. The example may serve the pleiotropic effects of some disease-modifying antirheumatic drugs (DMARDs) used for the treatment of rheumatoid arthritis, psoriatic arthritis and spondyloarthropathies. As it was elegantly reviewed by Targońska-Stępniać inflammation is linked to a higher risk for the development of insulin resistance and overt diabetes [4]. Some DMARDs may exert protective potential in this field. This is especially true for hydroxychloroquine which was proven to reduce the risk of diabetes development. Unfortunately, it

is not the case as far as the most common drug in rheumatology-methotrexate is concerned. Methotrexate therapy is not associated with a reduction in the risk of diabetes. As methotrexate is one of the most potent synthetic DMARDs it may only be speculated that other mechanisms apart from reduction of inflammation may play a role. Some discrepancies consist regarding the use of TNFi. Generally TNFi seems to reduce the risk for diabetes development especially when given in combination with HCQ, although not all studies confirmed that. Taking into account promising data from studies with abatacept it is plausible the deep interaction in immune response may result in a reduction of the diabetes risk in patients with connective tissue diseases.

More data on comorbidities in connective tissue diseases comes from the paper of Ptak et al. [5] Gout and more general hyperuricaemia is a growing problem in well-developed countries. However contrary to the XIX century description the face of hyperuricaemia has been changed and nowadays is usually linked to cardiovascular system complications. The final result of hyperuricaemia is a gout attack that may be present in a limited patient population. For unknown reasons the coexistence of gout and connective tissue diseases is very rare suggesting the involvement of other immunological mechanisms responsible for the inflammasome activation and gout-related cytokine storm. We may only speculate that as was stated by the Authors, some drugs used in the treatment of connective tissue diseases may exert a protective role in gout attraction. That may not be necessarily true as far as the cyclosporine activity is concerned. Cyclosporine reduces the renal exertion of uric acid thus predisposing to accumulate it in the body. Moreover, cyclosporine for connective tissues disease treatment is generally used for the treatment of connective tissues diseases-related glomerulonephritides. In that case deterioration of a renal function itself may result in a significant increment of uric acid thus predisposing to the gout attack.

The team from Katowice presented the fight for the patients with diffuse alveolar hemorrhage (DAH), one of the most severe medical emergencies in rheumatology, characterized by the presence of fresh blood in lung alveoli [6]. This case report is really up to date as we often see such a clinical picture in the context of probable SARS-CoV-19 infection.

The described case may be an excellent example of fatal overlapping autoimmune dis-

ease and possible SARS-CoV-19 infection. In the COVID era one should remember that patients suffering from connective tissue diseases are prone to develop several serious complications including viral bacterial and fungal infections. Although the patient was COVID-19 negative as it was established on the base of the polymerase chain reaction test the rapid clinical picture suggested otherwise. DAH may be sometimes the first presentation of connective tissue disease, therefore in the presented case one cannot exclude the induction of DAH by the viral infection and such a relationship has been already described in the literature. On the other hand, a substantial body of evidence showed that

SARS-CoV-19 is able to generate ANCA antibodies which may be an element of the cytokine storm [7]. Many controversies exist as far as the treatment of the patients is concerned. Immunosuppressive treatment although contraindicated in the course of infection may be a risky option but in some cases result in remission attainment [8].

The last paper in the issue described a favorable effect of wrist arthroplasty in 43 years female patients with Juvenile idiopathic arthritis. The Authors emphasized that the last generation of wrist implants is really stable and provides a satisfactory range of motions. In the conclusion it was stated that this surgical procedure should not be recognized as a “last choice option” [9].

## References

1. Kotyla P. Primary immunodeficiency syndromes-beginning of autoimmunity. *Rheumatol Forum*. 2015; 1(1): 30–37.
2. Janiak P, Smoleńska Ż, Zdrojewski Z. Rheumatic manifestations in cancer patients treated with immune checkpoint inhibitors. *Rheumatol Forum*. 2022; 8(3): 98–104, doi: [10.5603/RF.2022.0015](https://doi.org/10.5603/RF.2022.0015).
3. Sawicka-Gutaj N, Wietrzyk D, Zawalna N, et al. Autoimmune disorders and thyroid function in patients with rheumatoid arthritis after biological treatment. *Rheumatol Forum*. 2022; 8(3): 111–121, doi: [10.5603/RF.2022.0016](https://doi.org/10.5603/RF.2022.0016).
4. Targońska-Stępnik B. Antidiabetic effect of disease-modifying antirheumatic drugs. *Rheumatol Forum*. 2022; 8(3): 120–126, doi: [10.5603/RF.2022.0017](https://doi.org/10.5603/RF.2022.0017).
5. Płak I, Grygiel-Górniak B, Samborski W. Gout in the course of systemic lupus erythematosus: Literature review and case study report. *Rheumatol Forum*. 2022; 8(3): 105–110, indexed in Pubmed: [10.5603/RF.2022.0014](https://pubmed.ncbi.nlm.nih.gov/3718165/).
6. Kopeć-Medrek M, Brońska Z, Pieczyrak R. Diffuse alveolar hemorrhage. *Rheumatol Forum*. 2022; 8(3): 133–137, doi: [10.5603/RF.2022.0018](https://doi.org/10.5603/RF.2022.0018).
7. Kronbichler A, Geetha D, Smith RM, et al. The COVID-19 pandemic and ANCA-associated vasculitis — reports from the EUVAS meeting and EUVAS education forum. *Autoimmun Rev*. 2021; 20(12): 102986, doi: [10.1016/j.autrev.2021.102986](https://doi.org/10.1016/j.autrev.2021.102986), indexed in Pubmed: [34718165](https://pubmed.ncbi.nlm.nih.gov/34718165/).
8. Bołtuć K, Bielejewska A, Coloma-Millar A, et al. Case report: Cyclophosphamide in COVID-19 — when an absolute contraindication is an absolute necessity. *F1000Research*. 2021; 10: 829, doi: [10.12688/f1000research.55625.1](https://doi.org/10.12688/f1000research.55625.1).
9. Brębowicz M, Kaczmarek L, Brębowicz E, et al. Wrist arthroplasty, good alternative for rheumatoid wrist: case report with literature review. *Rheumatol Forum*. 2022; 8(3): 129–134, doi: [10.5603/RF.2022.0019](https://doi.org/10.5603/RF.2022.0019).