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COVID-19 in patients with inborn errors of immunity - the current state of knowledge, diagnostic and therapeutic dilemmas

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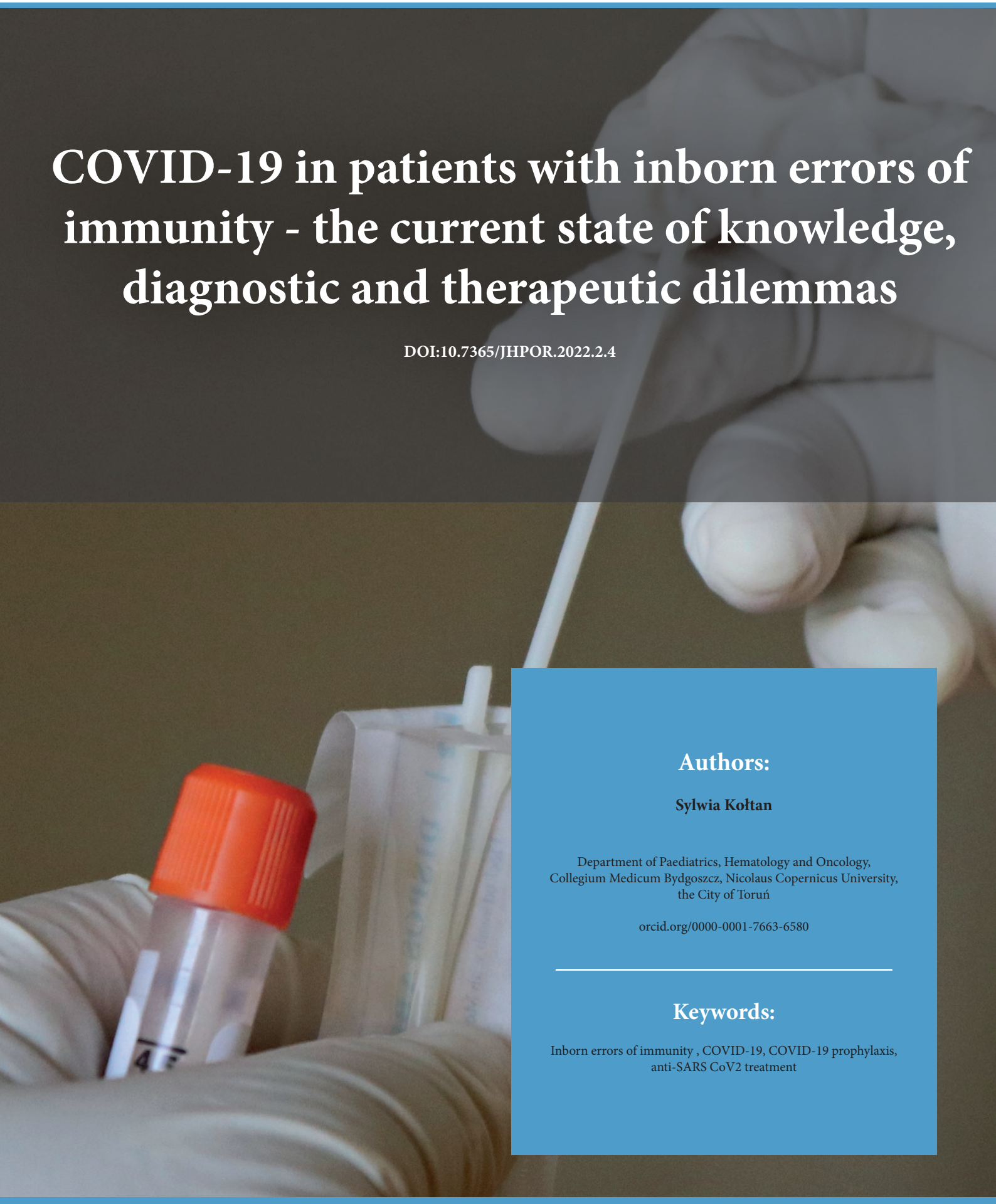

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Abstract

Patients with inborn errors of immunity (IEI) are at risk of contracting the SARS CoV2 virus, as are all humans. The risk of a serious course of COVID-19 related to the type of IEI concerns patients with combined immunodeficiencies, immune dysregulation syndromes, and certain inborn immunity defects, including type I interferon defects. Adult patients with severe humoral immunodeficiency are also at the increased risk (for example CVID or agammaglobulinemia). The additional risk results from the frequent occurrence of many comorbidities and the treatment used.

Vaccination is the most effective way to prevent a severe course of COVID-19. An additional dose is required in the selected patients with IEI. The vaccine response in selected IEI groups may be ineffective. Therefore, the pre-exposure prophylaxis with the use of long-acting monoclonal antibodies is justified.

With regard to the Omicron variant, there are no recommendations for the post-exposure prophylaxis - no effective preparations.

Treatment of COVID-19 in patients with IEI, especially those at risk of severe disease, should be started not later than 5-10 days after the infection. It is advisable to use in paralel,the antiviral drugs and monoclonal antibodies, effective for the currently dominant variants of the virus. It is important to continue treatment of the inbornerrors of immunity, especially human immunoglobulin replacement therapy.

Introduction

SARS CoV2 infection and COVID-19 disease have had an impact and continue to affect all aspects of people's lives around the world. They have become the leading topic of research by scientists and clinicians. Every person can become infected at any stage of their life. You can fall ill many times. For these reasons, every doctor should have access to updated knowledge about SARS CoV2 virus and the disease it causes, i.e. COVID-19. Despite the publication of thousands of studies and clinical analysis conducted since the end of 2019, it still cannot be said that the complete knowledge about the virus, its variability and the clinical consequences of infection is at our hands. Moreover, the generally accepted standards of management have not been developed. Although the risk groups of serious infection have been defined, the course of the disease in individual cases is unpredictable. In addition, there are complications of COVID-19, described both in the case of severe and asymptomatic or mild course of the disease, which significantly impair health-related quality of life.[1, 2] Moreover, in the time of the pandemic, the new health problems arose that are difficult to unambiguously associate with the infection caused by SARS CoV2, but the influence of the virus on their etiology cannot be ruled out (e.g. acute hepatitis in children of unknown etiology).[3]

From a medical point of view, the most important issues are: identifying the risk factors for serious course of COVID-19 infection in specific populations, developing rules for the prevention of the infection and severe course of COVID-19, and treatment of the disease and its complications.

In the present study, all these issues will be discussed in relation to the patients with inborn errors of immunity (IEI).

Immune response to SARS CoV2 infection

The typical immune response to viral infection involves the activation of innate immunity, which aims to limit the expansion of the microorganism in the infected person and inhibit its replication. Type I interferons (INF I) have been attributed an important role in performing this task. The induction of acquired cellular and humoral immunity is expected to destroy virus-infected cells. For many viruses, this organised immune defence is very effective.

SARS CoV2 virus shatters these dogmas of classical immunological knowledge. It has the unique ability to dysregulate the immune response from virus recognition by pathogen recognition receptors (PRRs), through inhibition and apoptosis of NK cells, resulting in an excessive inflammatory response, inhibition of type I interferon production by viral proteins and effects on both cellular and humoral acquired immunity. The degree of immune

dysregulation induced by SARS CoV2 is particularly exacerbated in infected individuals in whom, for various reasons, the functioning of individual elements of innate and/or acquired immunity is already impaired prior to infection. An example is the severe course of COVID-19 in patients with INF I-associated innate immune defects or elderly people with the presence of antibodies to type I interferons. Similarly, the accumulation of impaired immune regulation due to inborn error and dysregulation caused by SARS CoV2 virus results in an increased risk of a severe course of COVID-19.[4]

Inborn errors of immunity

Inborn errors of immunity include about 500 identified diseases/syndromes, the vast majority of which are genetically determined. Depending on the dominant clinical picture, 2 large groups are distinguished:

- Primary Immunodeficiency Disorders (PIDD) with a dominant infectious phenotype
- Primary Immune Regulatory Disorders (PIRD) with a predominant autoimmune, allergic and/orcancer phenotype; special subgroup is Primary Atopic Disorders (PAD)[5]

In clinical practice, the most commonly used division is developed by the International Union of Immunological Societies (IUIS). It is updated every 2 years. The last update took place in 2022. There are 10 IEI groups in this classification:

- inborn errors of cellular and humoral immunity
- combined immunodeficiencies with associated or syndromic features
- predominant antibody deficiencies
- diseases of immune dysregulation
- congenital defects of phagocyte number or function
- defects in intrinsic and innate immunity
- autoinflammatory disorders
- complement deficiencies
- bone marrow failure
- phenocopies of inborn errors of immunity[6,7]

The aim of this study is not to provide an understanding of the different groups of inborn errors of immunity, nor a detailed analysis of the course of SARS CoV2 infections in each of the 10 IEI groups, and therefore such information is not presented.

Inborn errors of immunity predisposing to a severe course of COVID-19

At the beginning of COVID-19 pandemic, it was assumed that all patients suffering from IEI would be at risk of severely developing the infection. This quickly turned out to be untrue. Only patients from the selected IEI groups are predisposed to the severe course of COVID-19. These are the patients:

- with combined immunodeficiencies (defects of cellular and humoral immunity)
- with syndromes of immune dysregulation
- with the selected defects of innate immunity, especially regarding the immune response with type I interferons[8, 9, 10]

Many studies have confirmed that regardless of the diagnosis of IEI, the risk of a serious course of COVID-19 increases with age and is correlated with the selected cardiological diseases, diabetes, chronic lung diseases, and lymphopenia diagnosed prior to SARS CoV2 infection. The risk of a severe course of COVID-19 increases in patients with IEI who require immunosuppressive or biologic drugs for the treatment of concomicant diseases. In this situation, IEI patients develop a secondary immunodeficiency. An example is the diversion of anti-CD20 programmes in patients with cytopenias refractory to other therapies. The use of these monoclonal criteria increases the risk of severe COVID-19 (reported risk factors of 1.7 to 5.5).[8, 9, 11, 12]

In Europe, immunodeficiencies from the group of dominant antibody defects are most often diagnosed - they account for over 50% of all IEI. If only adults were taken into account, this percentage would increases even above 70%.[13-15] In the meta-analysis presented by Buciol et al., the risk of a complicated course of COVID-19 in this group of patients is estimated at approx. 14%, and of death - 8-9%, regardless of the diagnosed disease unit (including common variable immunodeficiency - CVID and agammaglobulinemia). In comparison, among patients with immune dysregulation syndromes, the risk of severe COVID-19 is higher at 28% and the risk of death at 15%, among patients with innate immunity defects at 62% and 10% respectively. The highest risk was shown in patients with severe combined immunodeficiency before allogeneic haematopoietic cell transplantation (57% and 57%, respectively).[8] In Poland, in the general population, the highest risk of death was reported in May 2020. (5.05%); it is currently much lower at 1.86%.[16]

Diagnosis of SARS-CoV2 infection in patients with IEI

The gold standard for the identification of SARS CoV-2 infection in patients with IEI is RT-PCR nasopharyngeal swab testing. During the epidemic, being in force in Poland as from March 2020 to May 15, 2022, the access to this test was satisfactory. From May 16, 2022, an epidemiological emergency was announced and the rules for access to the diagnostic tests aimed at identifying people infected with SARS CoV-2 virus were changed. The access to molecular testing as part of the public health care system has been significantly restricted; Currently, such tests are performed on doctor's recommendations in the case of suspected COVID-19 infection, at the admission to the hospital or during hospitalization.

In patients with inborn errors of immunity, it should be remembered that there is a possibility of obtaining false negative results more often than in the population of immunocompetent people.[17] It appears that false-negative results may be related to the very low SARS CoV2 load of the nasopharyngeal mucosa in some patients, especially in the early stages of infection.[18]

The tests should be repeated several times if the results are negative, but epidemiological and clinical data indicate the possibility of COVID-19.

The antigen tests show lower diagnostic efficiency compared to the molecular tests. Less sensitivity was shown in the infected but asymptomatic people, as well as in the situation of a lower SARS CoV2 virus load on the upper respiratory tract mucosa from which swabs are collected. This situation applies to the patients vaccinated against COVID-19 and some patients with inborn errors of immunity.[18]

The serological tests, based on the detection of anti-SARS CoV2 antibodies, are the least reliable in the patients with inborn immunity errors, and completely unsuitable for the diagnostic purposes in the patients with severe humoral immunity defects, especially with agammaglobulinemia or CVID. However, in some IEI groups where humoral and/or cellular immunity is not deficient, serological tests can be used to reliably assess both infection and vaccine response. Such immunodeficiencies include, but are not limited to, inborn error of immunity of phagocyte number or function or complement deficiencies.

Active immunization against COVID-19 in patients with IEI

At present, there is no more effective and safer way to prevent infectious diseases than preventive vaccinations. This also applies to COVID-19. However, preventing SARS CoV-2 infections has proved to be a difficult task. While the prevention of severe COVID-19 is a goal that has been achieved, the protection against symptomatic infections with a milder course is still unsatisfactory. This is due to the relatively short duration of immune protection, resulting in the need for booster doses, and the variability of the virus causing it to "escape" the immune surveillance. As a result, it is necessary to modify the vaccines already in use to better function with new SARS CoV2 variants (e.g. Omicron). The new vaccines containing adjuvants (Novavax) are also introduced, the actual effectiveness of which in relation to patients with IEI will be assessed in the studies.[16, 17, 18] **Table 1** presents the latest vaccination schedules recommended by the CDC (Centre for Disease Control) and the current Polish recommendations for people with moderate or severe dysfunctions of the immune system.[19, 20, 21]

IEI patients with severe humoral deficiency, undergoing human immunoglobulin replacement therapy, should be vaccinated with an additional dose in the primary series and booster doses, according to current national recommendations. The vaccinations can be carried out at any time interval in relation to the immunoglobulin transfusions.

Patients with combined immunodeficiencies, including syndromic immunodeficiencies, should also be vaccinated with a booster dose to the primary vaccination series. Patients in other IEI groups according to the IUIS, including those with complement defects, innate immunodeficiencies, defects in the number or function of phagocytic cells, should be vaccinated as healthy individuals.

Regardless of the type of inborn errors of immunity, the coexistence of comorbidities and their treatment, especially with immunosuppressive and/or biological drugs, is an indication for vaccination according to the rules for persons with moderate or severe immune deficiencies (in regimens using an additional dose in the primary vaccination).[23, 24]

It is important for clinicians and patients with the inborn errors of immunity to be aware that the response to vaccines may be suboptimal despite the addition of an additional dose and booster doses of COVID-19 vaccines. This applies especially to the patients with severe humoral immunodeficiency (e.g. agammaglobulinemia, CVID), as

Tab. 1 Protective vaccinations for people with moderate or severe immunodeficiency: CDC recommendations and Polish recommendations (as of December 1, 2022) [CDC, PZH]

Vaccination	Age group	CDC recommendations					Polish recommendations				
		Basic dose (1-2) and additional dose)minimum interval(			Booster dose)minimum interval(		Basic dose (1-2) and additional dose)minimum interval(			Booster dose)minimum interval(	
		1	2	additional	1	2	1	2	additional	1	2
Moderna	6 months 4 –years		4 + weeks	4+weeks			#	#	#		
	511 – years		4 + weeks	4+weeks				4 + weeks	4+weeks		
	1217 – years		4 + weeks	4 +weeks				4 + weeks	4 +weeks	3 +* months	4 +** months
	18 ≤ years		4 + weeks	4 +weeks	3 +* months	4 +** months		4 + weeks	4 +weeks	3 +* months	4 +** months
Novavax	18 ≤ years		3 + weeks					3 + weeks	4 +weeks	3 +* months	4 + ** months
Pfizer - BioN-Tech	6 months 4 –years		3 + weeks	4 +weeks							
	511 – years		3 + weeks	4 +weeks	3 + * months	4 +** months		3 + weeks	4 +weeks	3 +* months	4 +** months
	1217 – years		3 + weeks	4 +weeks	3 + * months	4 +** months		3 + weeks	4 +weeks	3 +* months	4 +** months
	18 ≤ years		3 + weeks	4 +weeks	3 + * months	4 +** months		3 + weeks	4 +weeks	3 +* months	4 + ** months
AstraZeneca	18 ≤ years							4-12 + weeks	4 + ** weeks	3 +* months	4 + ** months
Janssen) J&J(	18 ≤ years			4 +*weeks	3 + * months	4 +** months			4 + ** weeks	3 +* months	4 + ** months

Vaccines recommended in the primary vaccination and as an additional dose

Vaccines recommended in the primary vaccination, excluding selected risk groups for complications

*** Moderna, Pfizer - BioNTech, Novavax vaccine allowed; the preferred vaccine used in the primary immunization**

**** in 2nd booster vaccination only with m-RNA vaccine; preferably the same as in the 1st booster vaccination**

Vaccination is not recommended

 # Vaccination in Poland recommended, but the vaccine is not available yet

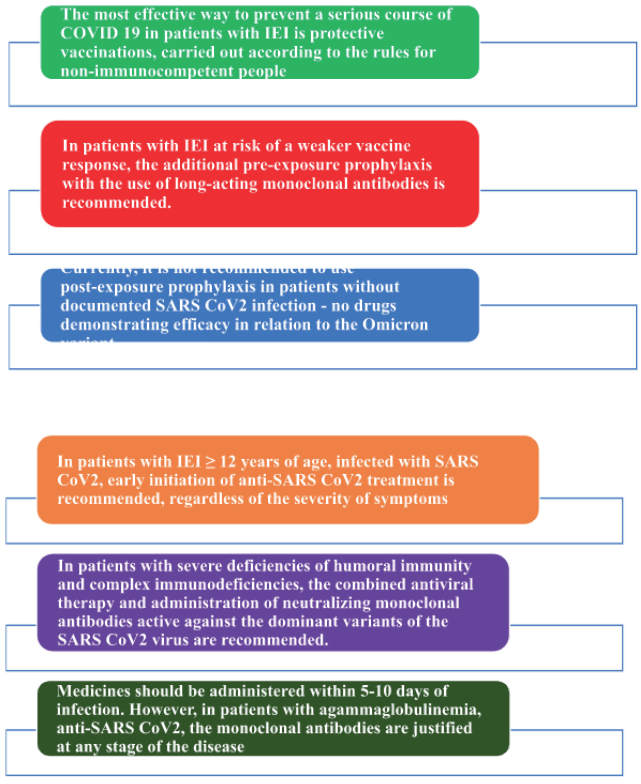

Fig. 1 General principles of anti-SARS CoV2 prophylaxis and treatment in persons ≥ 12 years of age with diagnosed inborn immunodeficiency associated with a high risk of serious course of COVID-19 infection

well as with combined immunodeficiency (defect of both humoral and cellular immunity). It has additionally been shown that in the patients with inborn errors of immunity from any group, who received therapies resulting in a defect in the number and/or function of B lymphocytes (e.g., after treatment with anti-CD20 monoclonal antibodies), the post-vaccination humoral response is weak or even absent.[19] In the above-mentioned groups of patients with IEI, the vaccination does not relieve the doctors from undertaking other methods of pre-exposure and post-exposure prophylaxis of SARS CoV2 infection and early implementation of anti-SARS CoV2 treatment in the symptomatic COVID-19 patients.

The pre-exposure and post-exposure prophylaxis of SARS CoV2 infection and early anti-SARS CoV2 treatment

During the pandemic, the intensive research was carried out on antiviral drugs and passive immunotherapy targeting the SARS CoV2 virus. The general guidelines for the management of the patients with IEI are presented in Fig. 1. The detailed recommendations concerning procedures, drug combinations, modification of preparations to the changing variants are constantly evolving. Therefore, when choosing the methods of treatment in patients with IEI, the Polish recommendations published by the Polish Society of Epidemiology and Infectious Diseases should be used. The recommendations refer to the predominant variants of the virus at a given time, and also take into account the drugs that are available in Poland. The last update is from February 2022.[20]

In this paper, only the therapies that are currently available and recommended for the patients with inborn errors of immunity will be presented.

The prophylaxis not related to active immunization of the patients and antiviral therapy to protect patients from the onset of symptoms of SARS CoV2 infection and from the severe course of COVID-19 face many difficulties. Most preparations should be used at an early stage of the disease (usually recommended to be implemented during the the first 5 days), when the patients usually feel good or have mild symptoms of the infection and often do not go to the doctor. The antiviral drugs have limited efficacy with a relatively high risk of complications. The monoclonal antibody cocktails are proving to be less effective against further variants of SARS CoV2 virus and will most likely need to be modified, as vaccines.

In Poland, the patients do not have access to some drugs approved for use in the European Union, and the access to others is difficult. The system of distribution of preparations to the patients is imperfect, as a result of which the patients at risk are not able to obtain help that would increase their chances of avoiding a severe course of COVID-19 and would improve their situation in this regard.

Pre-exposure prophylaxis with the use of long-acting monoclonal antibodies

It is extremely important to realize that the passive administration of long-acting monoclonal antibodies is not an alternative to immunization, but should complement non-immunocompetent individuals. The indication for their use is the inability to carry out the protective vaccinations against COVID-19 at a given time due to their health condition (e.g. a patient during stem cell transplantation procedure) or the occurrence of severe complications after active immunization against SARS CoV2 (e.g. an anaphylactic reaction), preventing implementation of the full vaccination cycle. It is also an option for the persons who did not respond to vaccinations due to the type of IEI or the treatment they received.

Currently, only one set of two monoclonal antibodies with prolonged action up to 6 months (tixagevimab and

cilgavimab) is registered, approved for use in the USA and the European Union in people ≥ 12 years of age, which is also highly effective in relation to the Omicron variant.[21] It is not reimbursed in Poland. This is bad news for the patients with severe dysfunctions of the immune system, as in the case of the Omicron variant, which is currently most often identified in the infected people, cocktails of monoclonal antibodies, previously used in the post-exposure prophylaxis or at the early stage of the infection treatment, are ineffective.[21]

Post-exposure prophylaxis in non-immunocompetent patients

Regarding the SARS CoV2 variants dominating before Omicron, two monoclonal antibody cocktails (bamlanivimab plus etesevimab and casirivimabplus imdevimab) were effective. Currently, in the era of infections caused in the vast majority by the Omicron variant, they are not recommended in the USA due to their low efficacy. Also, other preparations are not recommended for post-exposure prophylaxis of SARS CoV2 infection, including: convalescent plasma, hyperimmuned immunoglobulins, vitamin D, chloroquine, hydroxychloroquine, interferons, ivemercin, tenofovir).[21]

Anti-SARS CoV2 therapy in patients with inborn immunity errors

The patients with selected inborn errors of immunity are at risk of prolonged active replication of the virus, prolonged infection, the so-called long COVID as well as severe course of the disease [7-9]. Therefore, in this population it is important to early initiate the therapy that inhibits viral replication as well as activates immune mechanisms aimed at inactivating the virus. All therapies are currently dedicated to people ≥ 12 years of age and weighing at least 40 kg (remdesivir, kasirivimab/imdevimab, sotrovimab) or in adults (ritonavir, molnupiravir).

It is a mistake to wait for the apperance of the symptoms, especially the serious ones. It should be remembered that both ritonavir and molnupiravir can be used in the patients who are infected but do not require oxygen therapy. The highest effectiveness of the antiviral drugs as well as the monoclonal antibodies cocktails was demonstrated at the early stage of infection, i.e. during the first 5 days. If within this time, a patient with IEI does not receive the above-mentioned therapy, it is allowed to administer drugs up to the 10th day after the infection (documented prolonged replication of SARS CoV2 virus in non-immunocompetent people) [Polish recommendations]. There are isolated reports that in the patients with severe humoral immunity dysfunction (CVID, agammaglobulinemia) or with combined immunodeficiencies, neutralizing monoclonal antibodies can and should be administered even 10 days after the infection. It is important in this population to use both antiviral drugs and a cocktail of neutralizing monoclonal antibodies. The use of drugs that inhibit the viral replication without the administration of the monoclonal antibodies in the patients with IEI increases the risk of long -COVID (the effect of the persistent replication of SARS CoV2, although usually at lower intensity), while the combined therapy reduces the risk of hospitalization in intensive care units.[22] According to the Polish recommendations, it is prescribed to use either the antiviral therapies or the alternatively monoclonal antibodies.[20] An additional problem is the lack or the declining effectiveness of the monoclonal antibodies against new variants of the SARS CoV2 virus. The cocktail of the monoclonal antibodies casirivimab/imdevimab available in Poland is not effective in relation to the current variants of Omicron, therefore it is not currently recommended neither in the United States nor in Poland. The Polish guidelines of February 2022 recommended the use of the sotrowimab monoclonal antibody as still effective in the infections caused by the Omicron variant (this was true for early sub-variants). However, in the American recommendations of May 2022, this drug is not recommended (loss of efficacy against the BA.2 Omicron subvariant), but the use of another monoclonal antibody, bebtelovimab.[21] This preparation is not available in Poland.

Treatment of inborn immunity error and diseases associated with IEI during COVID-19

It is extremely important that the patients with inborn immunodeficiencies continue to treat their underlying disease as well as the accompanying IEI. It is necessary to continue the replacement therapy with human immunoglobulins in severe deficiencies of humoral immunity; in some cases, consideration should be given to increasing the substitution dose or temporarily changing the form of treatment (e.g. from subcutaneous to intravenous). Any changes in the treatment of diseases accompanying the inborn immunodeficiencies (chronic infections, autoimmune complications, neoplastic diseases) should be determined by a consilium of physicians (clinical immunologist, specialists treating comorbidities and COVID-19 treating physician). Such interdisciplinary approach to the patient with inborn immunodeficiency and COVID-19

will significantly increase the patient's chances of avoiding serious complications of infection and the underlying disease.

Grants, scholarships
none
Conflict of Interest
None

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