SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Immunogenicity of vaccines in rheumatoid arthritis and COVID-19

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1. Introduction and literature review – Part I

1.1. The importance of pneumococcal vaccination

In 2015, lower respiratory tract infections affected 3.2 million people, these infections were on the third place on the "top 10 causes of death" list published by the World Health Organization (WHO). The position of these infections has not changed between 2000 and 2015; as the number of affected people (3.4 versus 3.2 million) decreased by only 200000. The annual incidence of community acquired pneumonia (CAP) in the general adult population is between 1.6 and 13.4 cases per 1000 inhabitants.

The most common pathogen of community and hospital acquired pneumonia is *Streptococcus pneumoniae* (pneumococcus). A European systematic review showed that pneumococcus was the most common isolated pathogen between 1990 and 2007 with variable incidence (11.9% - 68.3%) and mortality (1 - 48%) in different countries. During seasonal and pandemic influenza, the leading cause of death is bacterial pneumonia caused by pneumococcus. Due to its resistance to antibiotics, treatment is more and more difficult and challenging.

Risk factors for pneumococcal pneumonia include older age, chronic medical conditions including diabetes mellitus, chronic liver and renal failure, pulmonary asthma, as well as secondary immunodeficiency including splenectomy, gravidity, hemato-oncological disorders, organ transplant, Human Immunodeficiency Virus (HIV) infection, and autoimmune rheumatic diseases (AIRD).

Pneumococcal vaccines are crucial in preventing severe pneumococcal disease. For vulnerable populations, such as the elderly, individuals with certain health conditions, pneumococcal vaccination is particularly important as they are at higher risk of developing severe complications from pneumococcal infections. The diverse recommendations encompass factors like age groups, risk categories, types of vaccines, vaccination schedules (including single or sequential vaccinations), and reimbursement policies. Such variations can result in complexities for healthcare providers and patients alike. Therefore, comprehensive evidence becomes crucial to streamline recommendations and optimize vaccination strategies.

1. 2. Lower respiratory tract infections in AIRD

The group of AIRD involves; among others, rheumatoid arthritis (RA), idiopathic inflammatory myopathies, Sjögren's syndrome, systemic lupus erythematosus (SLE), systemic sclerosis and mixed connective tissue disease. Patients with AIRD are more vulnerable to infections due to their underlying disease and immunosuppressive therapy, compared to the general population.

The mortality of respiratory infections in RA patients corrected for age and gender is 2-5-times higher than that in the general population. In the general population, the annual incidence of CAP is 1.07-1.20/1000 person-years (PY) and the incidence among patients with AIRD treated with tumor necrosis factor α (TNF-α) inhibitors is 5.97/1000 PY.

1.3. Biologic therapy of RA

RA is the classical example of AIRD. RA has a prevalence of 0.5-1%. Disease-modifying antirheumatic drugs (DMARDs) decrease the progression of inflammation and joint destruction, and improve physical function in RA.

DMARDs include conventional, synthetic (csDMARD), biologic (bDMARD) and targeted synthetic (tsDMARD) compounds. Methotrexate (MTX) is the most used csDMARD. Based on recent guidelines, the standard therapy has been replaced by early, aggressive DMARD therapy. Targeted therapies have been introduced for the treatment of RA in the early 2000s. Biologics have significantly changed the outcome of RA, improved physical function and quality of life of the patients. By 2006, the number of bDMARD-treated Hungarian patients increased to 900. In 2016, approximately 5000 patients were treated with biologics.

Most of the available bDMARDs suppress pro-inflammatory cytokines, primarily tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6). Some biologics also inhibit B- and T-cells.

1.4. Pneumococcal vaccination

1.4.1. Pneumococcal virulence factors: the capsular polysaccharide

Pneumococcus is a Gram-positive bacterium, a common commensal inhabitant of the nasopharynx. Colonization of the nasopharynx by pneumococcus is asymptomatic, and starts during infancy, with a prevalence of 40-95%, persisting at 1-10% in adulthood.

Nasopharyngeal carriage is a special step along the path of pneumococcal disease. The essential virulence factors of pneumococcus, which are responsible for severe invasive infections, are capsular polysaccharides. Out of more than 90 serotypes of capsular polysaccharide, there are only 25-30 serotypes responsible for pneumococcal infections in humans.

1.4.2. Pneumococcal vaccine developments

While pneumococcal capsular polysaccharides play the most important role in the pathogenesis of the given disease, they are also a target for vaccine development. The aim of pneumococcal vaccine design is to cover the most common serotypes associated with severe disease and ensure effective long-term immunogenicity.

Two types of pneumococcal vaccines; namely, polysaccharide (PPV) and protein conjugated (PCV) pneumococcal vaccines have been developed. PPV was introduced first in 1977 with 14 serotypes, which was expanded to 23 in 1983.

1.4.3. Different pneumococcal vaccines: different immunogenicity

The 13-valent conjugated vaccine (PCV-13) had been developed by 2010, initially recommended only for children. Based on the increasing evidence, PCV-13 had been gradually approved for all ages by 2013. The PCV-13 vaccine includes the same 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) as PPV-23, the only difference is the 13th serotype (6A).

In the newly developed PCVs, the polysaccharide antigens are covalently linked to a protein. Due to protein binding, PCVs induce B-cell memory by T-cell-dependent immune responses leading to stronger induction of memory B-cells compared to PPV-23. It has been confirmed that although it covers a higher number of serotypes, PPV-23 lacks the booster effect of revaccination. PPV-23 is also unable to trigger long-standing immunological memory, which limits its use in all age groups. Accordingly, WHO has declared and hastened that PCV-13 is required to prevent severe pneumococcal disease.

1.4.4. Pneumococcal vaccination - general considerations and sequential scheme

There are three main aspects of vaccination that play a vital role in the protection of the population against pneumococcal infection:

1. Herd immunity

2. To cover the most common pathogen-related serotypes of vaccine
3. Good immunogenicity of vaccine

The incidence of serious invasive pneumococcal infection in the adult population can be modified by childhood vaccination. The good pneumococcal vaccination coverage in children can reduce transmission of the infection to adult contacts.

The so-called herd immunity occurs when unimmunized individuals get into contact with immunized ones. In Hungary PCV-13 had been included in the mandatory childhood schedule since 2014.

Based on the more evident immunogenicity of PCV-13, two studies confirmed immunological advantage in vaccine-naive individuals if PCV-13 was given first, followed by PPV-23. T-cell-dependent immunogenicity of PCV-13 and coverage of 23-serotype PPV sequential pneumococcal vaccination sequential vaccination has to be applied. Based on the immunization history (previously PPV-23 vaccinated or not) of the patient suggested sequential pneumococcal vaccination scheme is recommended.

In 2012, ACIP recommended PCV-13 for adults aged ≥19 years with immunocompromised conditions. Several observational studies were published about the safety and immunogenicity of PPV-23 vaccination administered in AIRD patients, there has been no published data about the PCV-13 vaccine in that group treated with biologics.

2. Introduction and literature review – Part II

2.1. The COVID-19 pandemic

The first confirmed case of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection in humans can be traced back to November 17, 2019, in China. On December 31, 2019, the Chinese Health Authority informed the WHO about 41 individuals who exhibited pneumonia of unknown origin. Most of these patients had visited the Huanan seafood market, which was subsequently closed the following day. On January 7, 2020, Chinese researchers identified the pathogen causing the pneumonia, revealing it to be a new type of coronavirus responsible for the infection. January 11, 2020, marked the world's first acknowledgment of a fatality due to the novel coronavirus infection, and on the same day, Chinese researchers identified the genetic makeup of the virus.

SARS-CoV-2 primarily targets the respiratory system, binding to the human Angiotensin-Converting Enzyme 2 (hACE2) receptors found on mucosal cells within the airways. The interaction between the receptor-binding domains (RBDs) of the spike proteins and hACE2 can result in various pathological consequences, which vary among patients. Based on current research and clinical observations, the infection can manifest symptoms of varying severity. In some cases, individuals may experience mild symptoms, such as fever, cough, fatigue, and loss of taste or smell. Others might develop moderate symptoms involving difficulty breathing, chest pain, and persistent fever. Severe cases can lead to acute respiratory distress syndrome (ARDS), pneumonia, organ failure, and in some instances, death. The severity and specific symptoms experienced by individuals often depend on various factors, including the patient's overall health, age, and any underlying medical conditions. Understanding these different levels of disease severity is crucial for appropriate medical management and intervention strategies.

As of August 2022, over 6.4 million people has died of a total of 608 million infected patients. As we continue to navigate this situation, it's crucial to prioritize safety measures, vaccination, and healthcare support to minimize further spread and loss of life.

While specific antiviral therapies for SARS-CoV-2 continue to be researched and developed, vaccination remains a key strategy in building immunity against the virus and curbing its spread within communities.

2.2. Efficacy of COVID-19 booster vaccination

2.2.1. COVID vaccination: the first messenger ribonucleic acid vaccine

Traditional vaccine development often involves growing and inactivating a virus or using a weakened form of it, which can be time-consuming and challenging. In contrast, messenger ribonucleic acid (mRNA) vaccines can be designed and produced relatively quickly once the genetic sequence of a virus is known. While mRNA vaccines had been studied for other diseases, the urgency of the pandemic accelerated their development and brought them to the forefront of public attention. The successful application of mRNA as a vaccine agent has brought about a revolution in vaccine development, especially highlighted by the rapid development of mRNA-based COVID-19 vaccines. The Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) was one of the first to receive Emergency Use Authorization (EUA), initially for individuals 16 years and older, and later expanded to include adolescents aged 12 through 15. This authorization was granted after rigorous evaluation of available data from clinical trials, which demonstrated the vaccine's safety and efficacy in preventing COVID-19.

2.2.2. Hungarian vaccination protocol for citizens

For instance, if a particular vaccine like BNT162b2 was not universally accessible, Hungary might have opted to administer alternative vaccines to ensure continued vaccination efforts and protection against COVID-19. The Hungarian Public Health Centre (NPH) guide prioritized four groups targeting those most in need or with heightened exposure included (I.) healthcare workers; (II.) high risk patients (elderly patients and people with chronic comorbidities); (III.) individuals in critical infrastructure roles, ensuring the functioning of essential services and maintaining societal stability (e.g., education); and (IV.) covers those who don't fall into the previous categories, focusing on the broader population aged 18-59 who are not included in the higher priority groups.

In Hungary, the second available anti-SARS-CoV-2 vaccine was the BBIBP-CorV inactivated vaccine after the BNT162b2 mRNA vaccine; therefore, the second risk group was immunized by the largest quantity of the BBIBP-CorV vaccine. Based on early studies that did not involve individuals over 65 and the latest clinical findings indicating decreased effectiveness of this vaccine in this age group, the anticipation for the use of heterologous boosters (utilizing different vaccines for the initial and subsequent booster doses in a vaccination regimen) suggests an interest in exploring whether combining different types of

vaccines for initial and booster shots could provide additional benefits in terms of immunity and protection against COVID-19.

2.2.3. Third vaccination of COVID-19

The introduction of a third dose during the third wave of the COVID-19 pandemic in 2021 was a response to emerging data on waning immunity. The introduction of third dose was a part of the broader strategy to adapt vaccination campaigns in response to the changing nature of the virus and the dynamics of the pandemic, aiming to maintain high levels of protection.

The need for further research and clinical data in this area underscored the importance of ongoing studies to determine the efficacy, safety, and immune response elicited by mixed vaccine schedules. This information was vital for optimizing vaccination approaches, especially when considering third doses, and ensuring broad and robust protection against COVID-19 across different demographic groups. The comparison between BNT162b2 and BBIBP-CorV vaccines regarding their efficacy has been a focus of some studies. These studies suggested that BNT162b2 might offer higher efficacy in terms of raising antibody titres compared to BBIBP-CorV.

Therefore, it becomes crucial to ascertain whether using a third dose of BNT162b2 after the initial BBIBP-CorV doses or vice versa could effectively improve the humoral immune response against the virus. The latest available information, there's limited clinical data specifically addressing the efficacy and safety of using a combination of the BBIBP-CorV inactivated vaccine and the BNT162b2 mRNA vaccine as a third dose in non-Caucasian populations.

It seems that the heterologous approach, using the BNT162b2 mRNA vaccine as a third dose after an initial BBIBP-CorV inactivated vaccine regimen with a temporal separation, resulted in notable improvements in anti-spike antibody production.

Clinical laboratory tests help measure antibody levels and evaluate the effectiveness of vaccines in generating an immune response against SARS-CoV-2. Clinical studies have looked at the serological (antibody-related) responses in different populations under various conditions. These studies compare the immune responses in individuals who received different types of vaccinations - either as primary doses or third shots - and also consider whether these individuals had previous SARS-CoV-2 infections.

There have been limited trials or studies assessing the use of different vaccine combinations involving BBIBP-CorV. This vaccine has been used in a restricted number of countries, with limited data available from these specific regions. The original phase I/II trial for BBIBP-CorV demonstrated efficacy in the 18–59-year-old age group. The lack of specific data on efficacy among the elderly might result in cautious recommendations regarding the use of BBIBP-CorV in this age group until more evidence becomes available. The comparative data highlighting lower efficacy and faster waning of effectiveness for BBIBP-CorV in comparison to vaccines like BNT162b2, mRNA1273 and Ad26.COV2.S underscores the differences observed among various COVID-19 vaccines. The study by Blanco et al indicating a significantly lower neutralizing response when BBIBP-CorV was used as a second dose in comparison to other protocols, is crucial in understanding the dynamics of mixed vaccine schedules. Their suggestion against recommending BBIBP-CorV as a second dose aligns with their findings regarding the diminished neutralizing response.

3. Objectives, specific aims

Study I.

Patients suffering from autoimmune rheumatologic diseases (AIRD) are at risk of acquiring respiratory infections, because of their immunocompromised status. The most common respiratory pathogen in community acquired pneumonia is *Streptococcus pneumoniae*. It is therefore advantageous for such patients to receive pneumococcal vaccines. However, administration of biologic therapy can modify the immune response to the vaccine. We therefore wanted to explore the effectiveness of such vaccines in patients with RA treated with biologic therapy.

Specific aims:

1. We aimed to investigate whether the 13-valent conjugated pneumococcal vaccine, Prevenar 13 (PCV-13) administered to rheumatoid arthritis (RA) patients treated with biologic therapy is effective.
2. The PCV-13 vaccine had been investigated in the general population, however, there has been little amount of safety data gathered in RA patients treated with biologics. Therefore, our research investigated whether the PCV-13 vaccine was safe in RA patients undergoing biologic therapy with etanercept (ETA).
3. Based on our results we aimed to compile a set of recommendations for pneumococcal vaccination in RA patients.

Study II.

Specific aims:

1. We aimed to compare immunization regimens of homologous (2 basic and third dose of BNT162b2) and heterologous (2 basic BBIBP-CorV vaccines and third dose of BNT162b2 vaccine) COVID vaccination schemes.
2. We investigate whether a third dose of BNT162b2 administered after two doses of BBIBP-CorV effectively boosts anti-SARS-CoV-2 RBD humoral immune responses more than a homologous regimen of three BNT162b2 doses.
3. We investigate immune responses through subgroup analysis how different age groups react to vaccines.

4. We investigate if heterologous regimen of COVID vaccination is effective and safe

4. Patients and methods

4.1. Study I.

4.1.1. Study population and epidemiological data

The study was a prospective observational study evaluated in patients who presented to the University of Debrecen Clinical Centre, Department of Internal Medicine, Division of Rheumatology. The study group included 22 adult patients with an established diagnosis of RA according to the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria. All patients received ETA biological therapy. We included a control group of 24 patients with osteoarthritis. Patients with primary immunodeficiency and secondary immunodeficiency (e.g. chronic alcohol intake, bronchial asthma, chronic hepatitis, diabetes mellitus, malignancy, splenectomy or other AIRD) that may influence the antibody response to vaccination were excluded. The plasma immunoglobulin G, A and M levels of all participants were in a normal range. None of the patients showed signs of infection (at least 2 weeks prior to vaccination). All participants in the study and control groups were naive to pneumococcal vaccine. An Institutional Review Board approval had been obtained before the initiation of the study. All enrolled patients gave written consent for participation.

Most of the RA patients were female (n=17; 77%) with mean age of 55.1±10.4 years; 5 male enrolled RA patients (23%) of the study group were younger than female patients with a mean age of 52±11.07 years. The control group of 24 patients with OA included 18 females and 6 males (mean age 63.9±9.7 years). There were no significant differences with respect to male: female ratio between the study and control group. Cardiovascular diseases (coronary heart disease, hypertension) were more common in the control group than in RA patients (88% vs 55%, p=0.034). The incidence of metabolic (hyperlipidaemia, obesity) and gastrointestinal (duodenal ulcer, gastro-oesophageal reflux) co-morbidities did not differ significantly between the two groups (p=0.46; p=0.403).

Immuno-laboratory tests revealed IgM rheumatoid factor seropositivity in 13 RA patients (59%) and anti-cyclic citrullinated peptide (anti-CCP) seropositivity in 11 RA patients (50%). All enrolled RA patients had low disease activity as defined by EULAR [75] before vaccination. The mean DAS28-CRP value at baseline was 2.78 ± 0.62. OA patients were taking non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics only, no patient was treated with any type of immunosuppressive drugs. All RA patients were treated with 50 mg ETA administered subcutaneously (SC) once a week for at least one year. Out of these 22 RA patients, 15 patients (68%) received combination therapy of ETA plus oral MTX; 7 patients (32%) received ETA monotherapy. In patients treated with ETA+MTX combination, the mean MTX dose was 12.3±4.5 mg/week. In the RA group, five patients (23%) received oral corticosteroids. The mean corticosteroid dose was 2.8 ±1.1 mg/day.

4.1.2. Vaccination of patients

PCV-13 vaccination was applied to all RA patients 5 days before administering the next dose of ETA. The vaccination was performed after obtaining written informed consent and after fulfilling the contraindication checklist (fever, signs and symptoms of infection). All subjects were vaccinated with a single dose (0.5 ml) of the PCV-13 vaccine (Prevenar 13, Pfizer^{TM}) IM into the upper arm.

4.1.3. Laboratory methods

Serum samples were separated for the following tests: total anti-PPV23 antibody levels produced against the various serotypes at baseline before vaccination, 30 than 60 days after vaccination. Pre-vaccination anti-PPV23 levels were compared to those 4 weeks and 8 weeks after vaccination. Pneumococcal antibody levels were assessed by a VaccZymeTMAnti-PCP IgG (immunoglobulin G) Enzyme Immunoassay Kit (produced by The Binding Site Group Ltd., Birmingham, United Kingdom). This specific assay is designed for the *in vitro* measurement of IgA antibodies against Pneumococcal Capsular Polysaccharide present in human serum. According to the recommendations of the American Academy of Allergy, Asthma & Immunology, at least a twofold increase in antibody level was an indicator of an adequate immune response (AIR).

4.1.4. Safety assessments

All vaccinated patients were observed for 30 minutes after vaccination to ensure if there were any need for urgent medical attention following vaccination due to serious allergic reaction (generalized rash, angioedema, anaphylaxis). After the observation period, asymptomatic and complaint-free patients were discharged and asked to record the temperature (feverish, fever), any injection site reactions (e.g. pain, redness, swelling), any adverse event (fatigue, nausea, vomiting, diarrhoea, myalgia, headache) or any other unusual events until the next follow-up visit (30 days after vaccination).

4.1.5. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v20), USA. Categorical variables are reported as counts (percentages) and continuous variables as mean and standard deviation (SD). The distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Data obtained in the RA and control groups were compared by independent samples t-test, Mann-Whitney U test, χ^2 test or Fisher's exact test. Changes of IgG levels were evaluated by Wilcoxon test separately in patients and control group. Correlations were determined by Spearman's test. Regression analysis was used to determine the relation between the change of IgG level and epidemiological data as prognostic factors. The used p-value threshold for significance was a two-sided value of 0.05 in all statistical tests.

4.2. Study II.

4.2.1. Study population and epidemiological data

This prospective observational study with 122 participants all together compared the antibody response for third dose of BNT162b2 vaccine after two, basically different COVID vaccine in two groups of 61 patients each. Both group was vaccinated by basic COVID vaccination; the first group by BBIBP-CorV and the second group by BNT162b2.

Adult patients (≥ 18 years) with primary immunodeficiency, or those undergoing immunosuppressive therapy, or with malignancy were excluded. All patients have no signs and symptoms of COVID-19 at least one week before third-dose vaccine. During the study patients with any suspicion of infection were monitored and tested by SARS-CoV-2 PCR.

In our provided data, while the mean ages of the two groups were close (the first group: 63.9± 12.61 years, the second group: 59.9 ± 12.92 years) there was a statistically non-significant difference (p = 0.090) between them. In the first group, there were 39 female patients, constituting 62.9% of that group, while the second group had 41 female patients, comprising 67.2% of that group. The p-value of 0.849 indicates that there was no statistically significant difference in gender distribution between the two groups.

For instance, diabetes mellitus was the most common comorbidity in both groups had similar proportions: 21.3% in the study group and 16.4% in the control group, with a p-value of 0.643, indicating no statistically significant difference. Additionally, other comorbidities such as cardiovascular disease, autoimmune diseases, chronic respiratory diseases, chronic renal insufficiency didn't show significant differences in prevalence between the study cohorts.

4.2.2. Vaccination of patients

In this study administering the first and second doses of both the BBIBP-CorV and BNT162b2 vaccines 21 days apart for all participants in both groups helps standardize the vaccination process. According to the NPH guideline, at least four month later (132–309 days) following the basic immunization the third dose, the BNT162b2 mRNA COVID vaccine was given.

Focusing on evaluating the total immunoglobulin (Ig) levels against the SARS-CoV-2 spike protein 1 receptor-binding domain (anti-SARS-CoV-2 S1-RBD) we compared them administering a third dose of the BNT162b2 vaccine in two different groups: the BBIBP-CorV vaccinated group following a heterologous regimen and the other group receiving three doses of BNT162b2 in a homologous regimen. The first sample was taken at the same time of administering of third vaccine, the second sample was collected after one month.

We performed a subgroup analysis based on age groups (≤60 years and >60 years) within the study cohort to find out how age influences the antibody responses to the vaccination regimen, specifically focusing on the correlation between antibody responses and time intervals after vaccination.

Patient questionnaires helped to analyze and review any possible infection and hospitalization due to COVID-19.

4.2.3. Laboratory methods

We used the Cobas® Anti-SARS-CoV-2 S serology test from Roche Diagnostics, (Mannheim, Germany) for measuring total Ig levels in serum samples to determine SARS-CoV-2 S1-RBD-specific antibody titres before and after the third dose of vaccination. The cut-off value used for seropositivity was ≥0.8 BAU/mL.

4.2.4. Statistical analysis

Normality Testing: The Kolmogorov–Smirnov test was employed to assess whether the data followed a normal distribution. This test is used to determine if a dataset significantly differs from a normal distribution.

Descriptive Statistics: Results were presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. This provides a comprehensive view of the central tendency and spread of the data.

Comparison of two groups: The Wilcoxon test, a non-parametric test for comparing two independent groups, was used for analysing serology results. This test is suitable for non-normally distributed data and assesses if there is a significant difference between groups.

Chi-Squared Test: For comparing demographic parameters between the two groups, the chi-squared test was used. This statistical test assesses whether there is an association between categorical variables.

Correlation analysis: Spearman's correlation analysis was performed to examine relationships between variables. This non-parametric test assesses the strength and direction of monotonic relationships between variables.

Significance level: A significance level of $p < 0.05$ was chosen, indicating that results with a probability value below this threshold were considered statistically significant.

Software: The statistical analysis was conducted using the "R project" mathematical software via RStudio (Boston, MA, US).

5. Results

5.1. Study I.

5.1.1. Antibody response to PCV-13 vaccine

At baseline, pneumococcal antibody levels (IgG t = 0) in RA patients and in controls were 110.1 ± 68.2 mg/l and 124.0 ± 99.0 mg/l, there were no statistically significant difference. One month after vaccination, antibody levels (IgG t = 1) increased in both groups (RA: 247.7 ± 155.6 mg/l; controls: 417.7 ± 198.3 mg/l) compared to baseline ($p < 0.001$).

The mean increase in antibody levels between baseline and 4 weeks was 2.63-fold in the RA and 6.13-fold in the control group ($p= 0.016$). After two months, antibody levels (IgG t = 2) somewhat decreased in both groups, however, still remained significantly higher compared to baseline (RA: 207.6 ± 127.6 mg/l; control: 356.4 ± 171.2 mg/l, $p=0.002$). The mean increase in antibody levels after 8 weeks were 2.08-fold and 5.2-fold in the RA and control groups, respectively, compared to baseline ($p=0.039$).

5.1.2. Subgroup analysis: treatment with or without MTX

When comparing RA patients receiving ETA-MTX combination (n=15) and those receiving ETA monotherapy (n=7), the subgroup treated with combination produced a higher rate of increase in pneumococcal antibody levels after one month (2.89-fold increase) compared to the ETA monotherapy group (2.07-fold increase), however, the difference was not statistically significant ($p = 0.503$). After 2 months, the combination and monotherapy groups had 2.22-fold and 1.76-fold increases in antibody levels, respectively. The difference between the two subgroups was not significant ($p= 0.245$).

5.1.3. Correlations between change of IgG and epidemiological data

Pneumococcal antibody levels (at 0, 1 and 2 months) were analyzed using various methods; results are shown in Table 8. There was no significant correlation between changes of IgG levels and DAS28, RF levels, anti-CCP levels and MTX dose.

Also indicated in Figure 3., the increase in antibody levels between baseline and week 8 negatively correlated with age (Spearman's R = −0. 431; p = 0.045) in the RA group. Such significant correlation was not observed in the control group.

5.1.4. Vaccine safety and side effects

In the RA group, MTX treatment was stopped in two patients due to gastrointestinal side effects one month after vaccination, otherwise, their condition was stable, and they did not need any supplementary treatment. The average dose of MTX after vaccination increased (12.33±4.48 mg/week to 13.08±4.23 mg/week), but this change was not significant (p=0.337). During the treatment follow-up period after vaccination, the median value of DAS28 did not increase over 3.2; PCV-13 vaccination did not increase disease activity.

During the post-vaccination follow-up period, patients had no complaints, such as fever, pain or infections. In summary, there were neither clinically significant side effect nor local or systemic reactions were observed in any of the patients during the 2-month follow-up period.

Considering the very small number of steroid treated subgroup, statistical analysis was not performed. The corticosteroid dose was stable in 4 patients, only one patient (No 3) needed higher dose of corticosteroids after vaccination (increased from 2 mg to 4 mg). Comparing patients treated with corticosteroids (5 patients) and those without corticosteroids (17 patients), DAS28 value did not change significantly before (2.94±0.93 and 2.78±0.62; p=0.564) and after (2.79±0.45 and 2.97±0.87; p=0.673) vaccination.

None of the RA patients needed the introduction of corticosteroids after vaccination. In the control OA group, there were no changes in medications within 2 months after PCV13 administration.

5.1.5. Predictive factors and antibody response in RA patients

We aimed to determine prognostic factors, which predict antibody response. We performed univariate logistic regression analysis and investigated how different parameters affected the inadequate antibody responses in one and two months after vaccination in the RA group. There were no correlations between gender, age, treatment strategy (ETA with or without MTX, with or without corticosteroids), immunolaboratory tests (RF levels, anti-CCP levels), disease activity (DAS28-CRP) and inadequate antibody responses.

5.1.6. Practical recommendations of pneumococcal vaccination in RA patients

Firstly, conjugated pneumococcal vaccination (PCV-10, PCV-13) is recommended from 2 months of age. This has been accepted in most of European Union (EU) countries and in the United States, however, only 6 EU countries (Bulgaria, France, Hungary, Latvia, Poland, Slovakia) included it in their mandatory childhood vaccination protocol.

The country-specific adulthood pneumococcal vaccination guidelines are even more problematic in the EU. Ten countries have absolutely no guidelines. In another 10 countries, only PPVs are recommended. In 6 countries, only PCVs are recommended. There are only 5 countries (Finland, Greece, Hungary, Italy, Luxemburg) where the recently approved international, sequential pneumococcal vaccination protocol has been introduced. In addition, there is no specific clinical guideline for pneumococcal vaccination of patients with AIRD.

For the optimal decision making about pneumococcal vaccination, there are three issues that must be assessed by a multidisciplinary team (rheumatologist, experienced infectious disease specialist in vaccinology, general practitioner): 1. disease activity, 2. ongoing immunosuppressive therapy, 3. vaccination history. In order to prevent flare of autoimmune diseases, pneumococcal vaccines have to be administered in the state of low disease activity (DAS28 $\leq$ 3.2). The optimal timing of administration of vaccines would be 2 weeks before initiation of DMARDs. During anti-TNF-α, abatacept or tocilizumab therapy, the immunisation can be started. Patients treated with rituximab; due to B-cell depletion, must be vaccinated more than 5 months after the last rituximab dose, and at least 4 weeks before the next dose. Review of the immunisation history is important to decide how sequential pneumococcal vaccination should be conducted. Immunologically, the best option in vaccine-naive AIRD patient is to start with PCV-13 first, followed by PPV-23 administration after 2 months.

5.2. Study II.

5.2.1. Antibody response in heterologous and homologous vaccination groups

The baseline comparison of anti-SARS-CoV-2 S1-RBD antibody levels between the BBIBP-CorV and BNT162b2 groups (20.8 [6.6–98.7] BAU/mL vs 903,4 [528.8–1811.7] BAU/mL, respectively) (Figure 4.) yielded a statistically significant ($p < 0.0001$) difference. It's notable that both the BBIBP-CorV cohort and the BNT162b2 group showed a significant

increase in antibody levels after receiving the third dose of vaccine. The anti-SARS-CoV-2 S1-RBD antibody levels substantially rose in both groups compared to their respective baseline levels ($p < 0.0001$). The BBIBP-CorV cohort exhibited a median antibody level of 27,195 [15,604–42,754] BAU/mL after the third dose, while the BNT162b2 group displayed a median level of 24,492 [13,779–42,671] BAU/mL.

The comparison of the increase in antibody titers (after/before total antibodies) between the heterologous (BBIBP-CorV) and homologous (BNT162b2) vaccination cohorts revealed a significant difference (Figure 5.). Specifically, the ratio of antibody levels after the third vaccination to baseline levels was notably higher in the heterologous vaccination group compared to the homologous group ($p < 0.0001$). This finding suggests that the increase in antibody levels following the third-dose vaccination was more pronounced in the heterologous vaccination group (BBIBP-CorV) compared to the homologous group (BNT162b2). The higher ratio of post-third dose to baseline antibody levels in the heterologous cohort indicates a potentially stronger immune response elicited by the mix-and-match (BBIBP-CorV + BNT162b2, heterologous) vaccination approach.

5.2.2. Age-related subgroup analysis of SARS-CoV-2 total Ig levels

That's an interesting and somewhat unexpected finding that age didn't appear to influence the anti-SARS-CoV-2 total Ig levels in either the pre-third dose or post-third dose stages within these cohorts. The subgroup analysis confirmed further that only the type of vaccine significantly influenced the baseline anti-SARS-CoV-2 total Ig levels aligns.

5.2.3. Time-related analysis of SARS-CoV-2 total Ig levels after the third-dose vaccination

The observed moderate but significant correlation between anti-SARS-CoV-2 total Ig levels after the third-dose vaccination and the time interval between the second and third doses in both groups is an important finding. A Spearman's correlation coefficient of 0.22 ($p = 0.015$) suggests a positive relationship between these variables. This correlation indicates that the efficacy of the third-dose vaccine, as measured by the increase in antibody levels, was most pronounced when the time interval between the basic (initial) and third-dose vaccinations ranged from around 6 to 8 months (Figure 7.). In the BBIBP-CorV

group, the peak of antibody levels following the third-dose vaccination occurred approximately 8 months later than in the BNT162b2 group.

5.2.4. Vaccine safety and side effects

The administration of three vaccine doses to all subjects was both safe and well-tolerated in our study. Additionally, the incidence of COVID-19 infection during the basic immunization regimen was notably low, with only one patient (1.7%) acquiring a mild case of the infection in the BBIBP-CorV group, occurring shortly after the second vaccine dose. Importantly, this individual did not require hospitalization.

6. Discussion

6.1. Study I.

6.1.1. Studies of PPV-23 in RA patients treated with biologics

Previously, in the PPV era, there were more studies in which similar or mild immune responses were detected in biologics-treated versus non-treated patients. Between 2004-2012, ETA and infliximab were the first studied anti-TNF-α agents in relation with pneumococcal vaccination. The mean antibody response to PPV-23 vaccination was not impaired in patients on ETA or infliximab in most studies. In 2007, Kaine et al investigated PPV-23 vaccination in adalimumab-treated RA patients. They concluded that adalimumab had no negative effect on PPV-23 vaccination, and that patients responded well to the vaccine.

Since 2014, the efficacy of PPV-23 vaccine administered to biologic-treated RA patients has been investigated. These studies using certolizumab pegol and golimumab confirmed a protective immune response to the PPV-23 vaccine in these patients. Other biologics, such as tocilizumab and abatacept, did not impair antibody responses to PPV-23 in RA patients.

Two studies included rituximab-treated RA patients. These studies suggested that the B-cell inhibitor rituximab impaired immune responses to PPV-23. Izumi et al published a prospective, multicentre, double-blind, randomized, placebo-controlled trial of PPV-23 vaccination in RA patients. Altogether, 900 RA patients were randomized to two groups (464 PPV-23-vaccinated and 436 non-vaccinated). The vaccinated group included 257, while the non-vaccinated group included 253 biologic-treated RA patients. The incidence of pneumococcal pneumonia was one of the primary endpoints of the study. The results showed no effectivity of PPV-23 vaccination in RA patients treated with any DMARDs or corticosteroids, regardless of dose. Moreover, there was no significant difference in the incidence rate of pneumonia caused by pneumococcus between vaccinated and non-vaccinated groups.

6.1.2. Studies of PCV in RA patients treated with biologics

There have been limited data available about the immunogenicity of the 13-valent PCV-13 administered in immunocompromised conditions. In recent literature, only one completed study investigated the immunogenicity of PCV-13 in patients suffering from immunocompromised condition. The vaccine showed good effectivity in chronic lymphocytic leukaemia patients.

Kapetanovic et al compared the heptavalent conjugated pneumococcal vaccine (PCV-7); approved for children only, in adult RA patients receiving ETA, rituximab and adalimumab with PPV-23. There were no differences in antibody responses.

PCV-7 was also investigated in RA patients with concomitant rituximab, abatacept and tocilizumab treatment. The result of the study concluded that rituximab and abatacept; but not tocilizumab, might impair antibody responses to PCV-7 (50).

Based on the poor clinical data, we evaluated the immunogenicity and safety of the PCV-13 vaccine in RA patients undergoing ETA therapy. Our results showed a clinically significant (> 2-fold) elevations of antibody levels, as a protective level was observed after one- and two-months post-vaccination, compared to baseline in both RA and control groups. Pneumococcal antibody levels significantly increased four weeks after vaccination in both groups, then it somewhat decreased by week 8, however, these levels remained significantly higher compared to baseline antibody concentrations. Our investigation was the first to show protective pneumococcal antibody levels after using the PCV-13 vaccine in RA patients treated with ETA.

Since January 2024, two new conjugate vaccines with broader serotype coverage have been introduced in Hungary. The 15-valent vaccine, PCV-15 (Vaxneuvance®), was approved in the EU on December 13, 2021, and has been available in Hungary since January 2024 for individuals aged six weeks and older. In 2024, this vaccine replaced PCV-13, which had previously been part of the mandatory childhood immunization schedule in Hungary. The other vaccine, PCV-20 (Apexxnar®/Prevenar 20), containing 20 serotypes, was approved in the EU on February 14, 2022, and also became available in Hungary in January 2024 for administration from six weeks of age.

According to Hungary's current vaccination guidelines the choice and sequence of vaccination for adults depend on the individual’s prior immunization history and the serotype count of the vaccine to be administered. Sequential immunization remains recommended with the 23-valent polysaccharide vaccine (PPSV23), with some adjustments incorporating

the newer, higher-valency PCV-15 and PCV-20 vaccines. Of the two main international guidelines currently in place (EULAR-2019 and ACR-2022), only the updated American guidelines address the use of these newer pneumococcal vaccines for patients with AIRD. EULAR is set to review its guidelines in October 2024.

For further insights into the effectiveness of these vaccines in adults with impaired immunity, future studies will provide necessary data, as current literature is still lacking on this topic.

6.1.3. Concomitant immunosuppressive treatment affecting antibody response: MTX

Several studies and meta-analyses investigated antibody response for PPV-23 during biologic therapy with concomitant MTX treatment in RA patients. Most of them demonstrated a decreased antibody response for PPV-23. Studies investigating PCV-7 in RA patients treated with combined biologic + MTX therapy showed similar results. Immunological responses to PCV-7 were reduced with concomitant MTX treatment. Kapetanovic et al performed a comparative study in which they analysed the immune response to PCV-13 in RA patients treated with or without MTX. This group demonstrated a decreased immune response to PCV-13 during MTX therapy.

In our study surprisingly, after 1 and 2 months of the vaccination, patients in the subgroup with MTX combined therapy had better responses than those receiving ETA monotherapy, but the differences were not significant. This observation investigated by univariate analysis showed that patients on biologics with concomitant MTX therapy had similar antibody response compared to those not treated with MTX combination.

MTX promotes cell apoptosis. Apoptosis affects the highly activated T-cells in a dose- and time-dependent manner. Van Aalst et al reviewed the effect of MTX and biologics (anti-TNF-α, rituximab) in RA patients during pneumococcal vaccination (PPV-23, PCV-7 or PCV-13). Decreased initial antibody responses were observed in all vaccines compared to controls during the administration of all immunosuppressive drugs. However, patients treated with anti-TNF-α had stronger immune responses than those treated with other immunosuppressive agents.

6.1.4. Concomitant immunosuppressive treatment affecting antibody response: corticosteroids.

Visvanathan et al investigated PPV-23 vaccinated RA patients on infliximab in two groups treated with or without oral corticosteroids. The surprising result confirmed that added the corticosteroid elicited superior antibody response after PPV-23 vaccination.

Kapetanovic et al confirmed better immune responses to PCV-7 in RA patients treated with anti-TNF-α combined with concomitant corticosteroid therapy (mean doses of 8.8-14 mg/week). Nagel et al analysed if there was any correlation between antibody levels and increasing of subsequent events of serious pneumococcal infections after vaccination in 248 PCV-7 vaccinated RA patients. Higher dose of corticosteroid (≥7.5 mg/day) was found to be a significant predictor of serious infections. In this trial, neither biologics nor MTX monotherapy nor combination treatment were predictive factors for serious pneumococcal infections.

In our study, we did not analyse statistically corticosteroid-treated patients separately, due to the small number of this subgroup. In our univariate regression analysis, added corticosteroid therapy did not predict an impaired antibody response. Thus, our PCV-13 vaccinated RA patients had a good immune response. The immune response had not been impaired by MTX combination. Protective immune response was seen 2 months after vaccine administration.

6.1.5. Older age as a predictive factor for antibody response

Two studies using PCV-7 vaccine in RA patients concluded that older age was an independent predictor of inadequate antibody response. As we observed, significant negative correlation was found between the increasing antibody level (IgG2/IgG0) and age, 2 months after vaccination in the RA group. These results suggest that early initiation of pneumococcal vaccination in younger age produces a more robust adequate antibody response in RA patients.

6.1.6. Limitations of the study

RA patients treated with MTX monotherapy or without immunosuppressive drugs were not enrolled in the study, because the number of these patients at our department is

limited. The control group included OA patients. Possibly another control group of RA patients would have been useful (e.g. drug-naive new RA patients), but infeasible for this purpose. We did not want to include patient population treated with different biologics.

The number of patients within the RA group; especially in the combination versus monotherapy subgroups, were relatively low. However, it was not easy to do an at least two months' prospective vaccination study using ETA monotherapy only.

In this study, we only assessed total antibody level; any specific IgGs against pneumococcal polysaccharide serotypes were not measured.

Moreover, the 2-month post-vaccination follow-up period was not enough to determine long term antibody response. The duration of protection after PCV-13 vaccination is still unknown, but it probably lasts at least several years. Long-term follow-up in order to assess the clinical occurrence of pneumococcal infections was not performed.

6.2. Study II.

6.2.1. The effect of third-dose BNT62b2 vaccination on the heterologous (BBIBP-CorV) and homologous (BNT162b2) groups

The scarcity of heterologous vaccination studies—specifically those involving the use of BNT162b2 after two initial BBIBP-CorV vaccinations—in non-Caucasian populations highlights an important gap in our understanding of vaccine interactions and effectiveness across diverse demographic groups.

Kanokudom et al applied a protein subunit vaccine following a two-dose basic vaccination regimen involving BBIBP-CorV, seems to explore the potential of a heterologous vaccination strategy. Using a different type of vaccine, such as a protein subunit vaccine, after completing the initial BBIBP-CorV regimen, aims to assess the immune response generated in this sequence.

The study conducted by Hueda-Zavaleta et al in Peru, which involved a temporal separation of 7 months between BBIBP-CorV and BNT162b2 vaccinations for healthcare workers, appears to focus on the effects of a heterologous vaccination schedule on humoral immunity. The findings indicating a more pronounced increase in humoral immunity among individuals without prior SARS-CoV-2 infection after receiving the heterologous BNT162b2 regimen are noteworthy. This suggests that the sequential use of different vaccines, especially with a considerable time gap, might induce a more robust immune response in individuals who haven't had prior exposure to the virus.

The study conducted by Vargas-Herrera et al in Peru showed a significant increase in geometric mean IgG levels following the administration of the third-dose BNT162b2 after prior BBIBP-CorV vaccination. This finding suggests that using a different vaccine as a third dose, specifically BNT162b2 after BBIBP-CorV, resulted in a notable enhancement of IgG antibody levels.

The study conducted by Moghnieh et al [60] in Lebanon mirrors findings from other research, highlighting the significance of heterologous regimen. This group observed that a heterologous third-dose vaccination—using a different vaccine than the initial one—was significantly associated with higher anti-spike IgG geometric mean titers compared to the levels observed after receiving a homologous third-dose BNT162b2 vaccine.

The research conducted by Park et al involving Korean health professionals revealed that administering a third-dose BNT162b2 after the second dose of BBIBP-CorV provided more effective protection against laboratory-confirmed COVID-19. This comparative analysis indicated that the heterologous approach of using a different vaccine (BNT162b2) as a third-dose after the initial BBIBP-CorV doses offered greater protection against COVID-19 compared to not receiving a third-dose vaccine or receiving a third-dose BBIBP-CorV. The safety and tolerability of heterologous vaccination, particularly using BNT162b2 after BBIBP-CorV were confirmed, as indicated by multiple studies.

Our real-world study provided valuable insights into the immunogenicity and efficacy of the third-dose BNT162b2 vaccination in individuals who had previously received either two BBIBP-CorV vaccinations (heterologous regimen) or two BNT162b2 vaccinations (homologous regimen). Both vaccination regimens resulted in high anti-SARS-CoV-2 Ig levels after the third-dose vaccine compared to baseline.

The 2x BBIBP-CorV + BNT162b2 combination provided adequate catch-up immunization for individuals who did not have access to the 2x BNT162b2 primary vaccination, emphasizing the societal value of heterologous vaccination.

However, the heterologous regimen (BBIBP-CorV followed by BNT162b2) showed a significantly higher increase in antibody levels (after/before total Ig levels ratio) compared to the homologous regimen. Age did not influence anti-SARS-CoV-2 Ig levels in either regimen. There were no significant differences in antibody levels before or after the third-dose vaccination between individuals older than 60 years and younger participants in both groups. The efficacy of the third-dose vaccine was most pronounced around 6–8 months after the initial vaccination schedule. There was a correlation was observed between the timing of

the third-dose vaccination and anti-SARS-CoV-2 Ig levels, suggesting that the most effective reinforcement occurred within this time frame.

A debated question regarding COVID vaccinations was whether the third dose should be considered part of the primary vaccination strategy or viewed as a booster shot. During the pandemic, it became particularly clear in the case of immunosuppressed patient groups that their primary immunization strategy includes three doses, meaning an extended vaccination series, which was also highlighted in the Centers for Disease Control and Prevention's COVID vaccination recommendations. In our study, when compared to several primary immunization recommendations for non-replicating vaccines — where three doses are recommended — the third dose given within a six-month timeframe clearly improved the immune response. We did not specifically study the immunosuppressed population in our paper.

The three doses of vaccines were safe and well-tolerated, affirming the safety profile of the vaccination regimen used in the study.

2. Biomarker measurement: Measuring only the level of anti-SARS-CoV S1-RBD antibodies for the evaluation of humoral immunity might provide an incomplete picture of the immune response, since the applied antibody test is surrogate to the gold standard plaque reduction neutralization test.

7. New findings of studies

7.1. Study I.

Rheumatoid arthritis patients are at risk of pneumonia due to the nature of their disease condition and immunosuppressive therapy. Pneumococcal vaccination can prevent serious pneumococcal infections. Our study confirmed:

1. *Effectiveness of conjugated pneumococcal vaccination:* the PCV-13 was effective 2 months after immunization in RA patients treated with etanercept.

2. *Etanercept combination with MTX therapy* had better immune response to vaccine than those with etanercept monotherapy.

3. Safety and tolerability: The vaccination was safe, did not affect autoimmune disease activity, and the condition of RA patients was stable during, and after immunisation in the follow-up period.

4. Age-dependent response: Vaccination with PCV-13 in younger age produces a more robust AIR in RA patients.

In summary, the most common pneumococcal pneumonia can be prevented in RA patients treated with etanercept and concomitant MTX therapy. The international data about immune response to pneumococcal vaccination during biologics and concomitant MTX or corticosteroids is contradictory. Understanding of immune responses to pneumococcal vaccination in AIRD patients treated with immunosuppressive drugs requires more comparative trials. Effective reduction of pneumococcal vaccine-preventable infections improves quality of life of RA patients. Special issues of immunisation in AIRD have to be assessed in a regular updated country- specific recommendations reviewed by experts.

7.2. Study II.

Our study's conclusions provide critical insights into the efficacy of third dose COVID vaccinations, specifically with BNT162b2 following a BBIBP-CorV vaccination regimen. The list of the key findings is:

1. *Comparison of Immunization Regimens*: we confirmed that two doses of BNT162b2 induce higher anti-SARS-CoV-2 RBD total Ig antibody levels compared to two doses of BBIBP-CorV which establishes a disparity in the immune response generated by these vaccines.

2. Effectiveness of Heterologous Regimen: Demonstrating that a third dose of BNT162b2, administered after two doses of BBIBP-CorV, effectively reinforces anti-SARS-CoV-2 RBD humoral immune responses more than a homologous regimen of three BNT162b2 doses is a crucial finding. This highlights the potential effectiveness of a third vaccine dose in a heterologous regimen for enhancing immune responses.

3. Age-independent response: Highlighting that the humoral immune responses observed were not significantly influenced by age but correlated with the timing of vaccine administration underscores the importance of the vaccination schedule in impacting immune response.

4. Safety and tolerability: Affirming the safety and tolerability of the third-dose vaccination is essential information for healthcare decision-making and public confidence in vaccination strategies.

5.

Future Research Directions: Emphasizing the need for further studies with larger participant numbers is critical for more robust and generalizable findings. Specifically, advocating for additional research involving Caucasian individuals receiving BBIBP-CorV vaccinations acknowledges the importance of diversity in vaccine research.

These findings have significant implications for vaccination policies and clinical decisions, emphasizing the importance of ongoing research for optimizing vaccination protocols.

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