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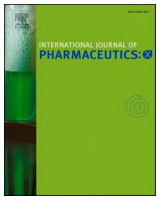

Effect of treatment with original or biosimilar adalimumab on SARS-CoV2 vaccination antibody titers

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ABSTRACT

The technological process of production of biosimilars determines the degree of biosimilarity to the original biological drug. In particular, the focus is on the similarity of immunogenic responses. The primary endpoint of our retrospective study was to find the differences in SARS-CoV-2 antibody amount between patients treated with original adalimumab and biosimilar adalimumab MSB11022 (Idacio) and the differences in the SARS-CoV-2 antibody amount between patients treated with and without biological treatment. We collected the gender, autoimmune disease type, age, and treatment data of the patients in the outpatient clinic MEDICAL PLUS, s.r.o., Uherske Hradiste. These patients suffer from autoimmune rheumatic diseases. All patients received the mRNA vaccine (Pfizer/BioNTech – BNT162b2), with a 21-day (interquartile range, 21–24) gap between the two vaccinations. Patients receiving adalimumab were able to develop cellular immune responses after the second vaccination dose, as well as the individuals without adalimumab. In the period of 6–23 weeks after the second vaccination dose (D63 – D182), the SARS-CoV-2 antibody levels did not change significantly in the patients receiving the original adalimumab, while in the patients receiving biosimilar adalimumab a significant decrease was revealed. A statistically significant difference in the SARS-CoV-2 antibody amount between the patients without biological treatment (median: 504.3 U/mL) and with biological treatment (Original and Biosimilar – median: 47.2 and 28.2 U/mL, respectively) was confirmed on day 182. According to our observation, the effect of the treatment type on the increase/decrease of antibodies over time is dominant, while the impact of other variables (gender, methotrexate treatment, autoimmune disease type, and age) was confirmed as insignificant or minor.

1. Introduction

Several biological disease-modifying antirheumatic drugs (DMARDs) targeted against tumor necrosis factor (TNF), such as adalimumab (ADA), certolizumab pegol, etanercept, golimumab, and infliximab, have been developed and approved for use worldwide in patients with rheumatoid arthritis (RA) and have achieved very positive clinical outcomes (Smolen et al., 2014).

Although biologic DMARDs, such as TNF inhibitors, have been used successfully to treat rheumatoid diseases, they are frequently associated with relatively high costs and a substantial financial burden to patients and healthcare payers (Dörner et al., 2016). The usage of biosimilars offers the potential to reduce costs associated with biological treatment and increase the patient's access to such therapies, which should improve the sustainability of healthcare in the case of rheumatoid diseases (Dörner et al., 2016; Hirsch and Lyman, 2014).

Biosimilars are similar biological products that enter the market after the patent protection of original biological products expires. They cannot be regarded in the same way as generic chemicals because, unlike them, they are not and cannot be chemically identical to the original product. Generic chemical drugs are relatively small molecules prepared by chemical synthesis. Their preparation results in a substance with a specific, clearly defined structure identical to the original drug substance. In contrast, biological drugs are prepared biologically and produced by living systems involving bacteria, yeast, and mammalian cells. They are large complex molecules, usually proteins or polypeptides, practically impossible to characterize unambiguously. As with any product derived from living systems, the resulting structure of biological drugs is variable. Their variability is determined by the spatial shape of the molecule and the type and length of each attached carbohydrate or

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hydrocarbon group. Amino acid sequences of the proposed biosimilar drug should be identical to that of the reference product (RP); however, minor differences may exist in terminal amino acid sequences since biologics are produced in living systems. Four potential differences between a biosimilar and the RP include posttranslational modifications, such as glycosylation, oxidation, deamidation, and protein aggregation, caused by the different host cell and expression systems. The bioprocess from the production to purification and formulation for long-term storage should be assessed to determine the clinical impact on pharmacokinetics, efficacy, and safety (Weise et al., 2012; Schreiber et al., 2020). Different regulatory authorities consistently define biosimilars as being highly analytically similar to the originator RP, with no clinically significant differences in purity, potency, pharmacokinetics (PK), pharmacodynamics (PD), clinical efficacy, safety, and immunogenicity, notwithstanding the presence of minor differences in clinically inactive components (Food and Drug Administration, n.d., European Medicines Agency, n.d.).

Five studies were conducted on healthy volunteers with immunogenicity data available in publications or regulatory documents for five biosimilars of adalimumab (BI 695501) (Wynne et al., 2016), SB5 (Shin et al., 2017), ABP 501 (Markus et al., 2019; Kaur et al., 2017), FKB327 (Puri et al., 2017) and GP2017 (Assessment Report: Hyrimoz (Procedure No. EMEA/H/C/004320/0000), 2018) and one adalimumab's biosimilar candidate (MSB11022) (Hyland et al., 2016). Subsequently for rheumatic diseases, six biosimilars were identified with adalimumab as the reference product biosimilars BI 695501 (Cohen et al., 2018), SB5 (Weinblatt et al., 2018), ABP 501(Cohen et al., 2017), FKB327 (Puri et al., 2017; Alten et al., 2020), GP2017 (Wiland et al., 2020), MSB11022 (Edwards et al., 2019) and two biosimilar candidates PF-06410293 (Fleischmann et al., 2018), and ZRC-3197 (Jani et al., 2016). According to (Strand et al., 2020), immunogenic responses to the approved biosimilars or biosimilar candidates have been shown to be similar to those of their reference products. These results indicate that the biosimilar development guidelines in the US and Europe have led to the approval of biosimilars with highly similar within-class immunogenicity and have not resulted in immunogenic differences between biologic agents of the same class. However, it is also necessary to note that subtle differences in clinical responses and adverse events between the reference and biosimilar products were noted despite meeting the pre-defined equivalence criteria (Zhao et al., 2018).

The COVID-19 pandemic is an ongoing global pandemic of coronavirus disease 2019 (COVID-19) caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to (Siemieniuk et al., 2020), no specific and effective treatment is available for COVID-19. The vaccine seems to be an effective tool for controlling the epidemic, so several vaccines have been developed in the last two years (Soleimanpour and Yaghoubi, 2021).

The relevance of vaccination against COVID-19 for patients with autoimmune diseases is recommended by studies suggesting that this patient population is at increased risk of developing a severe course of COVID-19 (Gianfrancesco et al., 2020). Nevertheless, the induction of protective immunity after COVID-19 vaccination could be affected due to treatment with immunosuppressive medication in patients with autoimmune diseases (Furer et al., 2021). Published data suggest that TNF inhibitors, glucocorticoids, methotrexate, and anti-CD20 therapies reduce the immunogenicity of COVID-19 vaccines (Spiera et al., 2021; Michiels et al., 2021).

Although studies investigating the effect of biological DMARDs as well as adalimumab on SARS-CoV-2 antibody responses in patients with immune-mediated inflammatory diseases are slowly accumulating (Chanchlani et al., 2022; Smetanova et al., 2022), a comparison of the original and biosimilar adalimumab on the development of immune responses to COVID-19 vaccines is still lacking.

2. Materials and methods

2.1. Patients

We collected the gender, autoimmune disease type, age, and treatment data of the patients in the outpatient clinic MEDICAL PLUS, s.r.o., Uherske Hradiste. These patients suffer from autoimmune rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). Sixty-three individuals received the mRNA vaccine (Pfizer/BioNTech) between March 2021 and April 2021 (Table S1 in the Electronic Supplementary Material [ESM]). The Inclusion and Exclusion criteria for data choice were the following:

Inclusion criteria: (1) age $\geq$ 18 years; (2) active autoimmune rheumatic diseases: rheumatoid arthritis (RA) patients fulfilling either the 1987 ACR or the 2010 ACR/EULAR Classification Criteria; ankylosing spondylitis (AS) patients fulfilling the Modified New York criteria; psoriatic arthritis (PsA) patients fulfilling the CASPAR criteria; (3) SARS-CoV-2 – mRNA vaccine (Pfizer/BioNTech – BNT162b2); (4) treatment with adalimumab and/or methotrexate 10–25 mg/week simultaneously for at least 12 weeks before their first dose of SARS-CoV-2 vaccine (D0).

Exclusion criteria: (1) treatment with any other biologic therapy than adalimumab; (2) treatment with other conventional DMARD than methotrexate (MTX); (3) interruption of the rheumatic disease therapy during the D0 until D182 with the exception of one omitted dose of methotrexate after receiving the first and second dose of the SARS-CoV-2 vaccine in accordance with the ACR recommendation; (4) treatment with any corticosteroids; (5) treatment with any immunomodulating therapy during the last 3 months; (6) treatment with any immunosuppressive therapy (with the exception of methotrexate and adalimumab); (7) SARS-CoV-2 disease before the first dose of SARS-CoV-2 vaccine (patients with positive SARS-CoV-2 antibodies at D0); (8) SARS-CoV-2 disease between the D0 until D182; (9) receiving any other vaccine during the last 6 months prior to the first dose of SARS-CoV-2 vaccine (D0); (10) participants with known unusual immunogenicity reaction history to any vaccine; (11) participants with known malignancy within the last 5 years prior to the first dose of SARS-CoV-2 vaccine (D0).

2.2. Data collection overview

The data collection overview is shown in Fig. 1. Three groups of patients were selected: The “Original” group – these patients were treated with the adalimumab original 40 mg every two weeks subcutaneously. The “Biosimilar” group – these patients were treated with the adalimumab's biosimilar MSB11022 (Idacio) 40 mg every two weeks subcutaneously, and the last group, “Without Biological Treatment (WBT)” – these patients were not treated with any biologic therapy. Some patients from all groups were treated with conventional DMARD methotrexate (MTX) 10–25 mg/week simultaneously (as shown in Table 1). Patients using MTX omitted one dose of methotrexate after receiving the first and second doses of the vaccine in accordance with the ACR recommendation (Curtis et al., 2021). All included patients had been on their immunosuppressive therapy for at least 12 weeks before their first vaccination. No one of the selected patients received corticosteroids. No deaths were recorded during the monitored period. All patients received the mRNA vaccine (Pfizer/BioNTech – BNT162b2), with a 21-day (interquartile range, 21–24) gap between the two vaccinations. The results of SARS-CoV-2 antibodies from the following sampling period were available for our analysis: before the first vaccination (D0), three weeks after the first vaccine dose – before the second vaccination (D21), then six weeks after the second vaccine dose (D63) and finally 23 weeks after the second vaccine dose (D182). Data from patients previously exposed to SARS-CoV-2 infection, as indicated by positivity for SARS-CoV-2 antibodies before the vaccination on D0 (before the first vaccination), were not collected for this analysis.

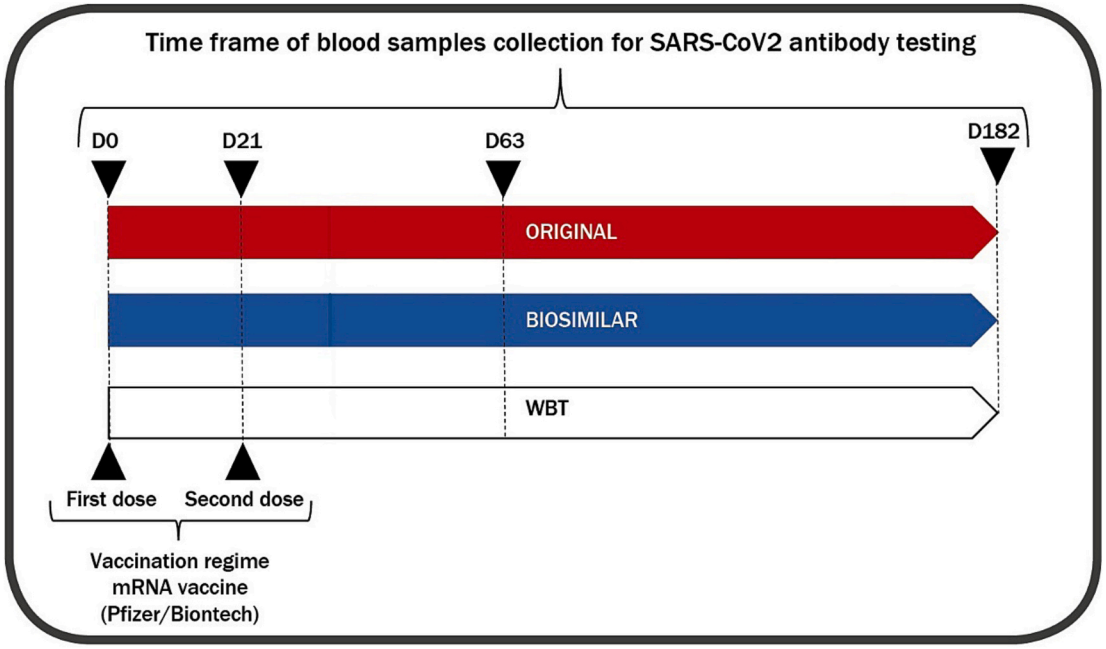

Fig. 1. Data overview including vaccination regime and time frame of blood results for SARS-CoV2 antibody testing.

2.3. SARS-CoV-2 antibody testing

All collected data of SARS-CoV-2 antibodies was determined according to (Muench et al., 2020), using the Cobas e411 instrument (Roche Diagnostics International Ltd., Switzerland) and the Roche Elecsys® Anti-SARS-CoV-2 S quantitative kit by following the manufacturer's instructions (Elecsys® Anti-SARS-CoV-2 S, 2020).

Our obtained data were adapted to address the right truncation of titers, in which the exact titer value was known for some participants and was only known to have exceeded a particular value (>250·0 units per mL or > 2500·0 units per mL [i.e., censorship]) for others. This methodology was used to calculate the medians and interquartile ranges (IQR) (Frey et al., 2022).

2.4. Statistical analysis

There were included 63 patients in the subsequent data analysis. In cases where the patients' antibody levels exceeded the upper limit of quantification (ULoQ) after sample dilution, the data were replaced by a value equal to ULoQ. As the Shapiro-Wilk test did not confirm the data normality, either for the original data or for the $\log_{10}$ transformed data, methods of nonparametric statistics were further used. Data visualization was performed on $\log_{10}$ transformed data using a box and whisker plot showing the median (a middle line that divides the box), IQR (a box), minimum/maximum score (whiskers), and individual measured points. Robust parameters of descriptive statistics, median, and IQR were used to summarize the antibody concentration in the whole data set and selected groups and subgroups stratified by variables treatment, gender, diagnosis, MTX, and age.

Nonparametric tests to assess the statistical significance of the differences in the antibody levels were employed. The Wilcoxon test for paired data was used to compare the antibody levels between the two consecutive sampling points. The antibody concentrations between different data subsets at individual sampling points were compared by the Mann-Whitney *U* test (in case of two subgroups) or the Kruskal-Wallis test (in case of three subgroups as well as CRP comparison) with subsequent Dunn's multiple comparisons testing (in case of significant effect detected by Kruskal-Wallis). The Spearman's rho (r_s) as a nonparametric correlation coefficient, which does not require normal distribution, was used to evaluate the association between the antibody concentration and age. For the correlation analysis, age was treated as a continuous variable; in other cases, age was converted into subgroups of the following intervals: < 45, 45–60, and > 60 years. These intervals were chosen as a compromise to achieve simple data segmentation with the evenest distribution of patients in the age subgroups and, at the same time, a sufficient age difference between younger and older patients. Only groups and subgroups with an adequate number of patients (≥ 5) were tested and assessed to avoid bias. The data analysis was carried out in software R, version 4.1.2 (R Core Team, 2021).

3. Results

3.1. Primary aims of analysis

The primary aims were to find the differences in the SARS-CoV-2 antibody amount between the patients treated with and without biological treatment and the differences in the SARS-CoV-2 antibody amount between patients treated with the original adalimumab and biosimilar adalimumab.

When comparing the level of SARS-CoV-2 antibodies depending on the type of treatment at D21, there was no observable difference between patients treated with the original and biosimilar adalimumab with median values of 10.2 and 11.1 U/mL, respectively. It was found that the level of antibodies in patients treated with the biological treatment is higher than in the WBT group (median: 2.9 U/mL), as can be seen in boxplots (Fig. 2A, Table 1). However, the mutual differences among all three groups differentiated by the treatment type were identified as statistically insignificant (Table 3).

Then, at D63, a significant increase in antibodies was found (Table 2), regardless of the type of treatment (Table 3). At D63 and D182, higher levels of antibodies were observed in the WBT group than in the biological treatment groups, regardless of the drug type (Fig. 2A, Table 1). However, a significant difference between the WBT (median: 504.3 U/mL) and biological treatment (Original and Biosimilar – median: 47.2 and 28.2 U/mL, respectively) was confirmed only in D182 (Tables 1 and 3).

In the period of 6–23 weeks after the second vaccination dose (D63–D182), it was found that the antibody levels did not change

Table 1
Descriptive statistics: median (IQR) of SARS-CoV-2 antibody concentration values (U/mL) at each sampling point for the whole data set and selected groups and subgroups stratified by variables treatment, gender, MTX, diagnosis, and age.

Variable	Group	Subgroup	Patients (n)	D21	D63	D182
	All data set	–	63	6.7 (1.5–24.3)	250.0 (116.8–274.4)	53.1 (7.7–215.5)
Treatment	Original	–	18	10.2 (2.2–18.1)	250 (90.7–274.5)	47.2 (8.7–189.5)
	Biosimilar	–	31	11.1 (2.1–25.5)	232.6 (90.0–250.0)	28.2 (4.4–81.7)
	WBT	–	14	2.9 (0.5–6.5)	407.2 (203.3–656.8)	504.3 (164.3–765.8)
Gender	F	–	26	7.2 (1.3–22.0)	250.0 (120.0–282.6)	100.7 (20.0–740.6)
	M	–	37	4.8 (1.8–24.9)	229.7 (82.0–250.0)	25.7 (2.7–123.8)
MTX	Yes	–	39	3.6 (0.3–18.1)	196.0 (72.2–266.3)	50.9 (5.5–232.6)
	No	–	24	15.8 (4.5–29.5)	250.0 (238.1–293.8)	95.7 (28.6–197.5)
Diagnosis	AS	–	16	12.2 (2.5–21.7)	250.0 (140.4–293.8)	72.2 (8.8–137.1)
	PsA	–	11	18.0 (2.2–44.1)	232.6 (61.5–266.3)	36.2 (1.5–571.4)
	RA	–	34	5.0 (1.0–20.3)	249.5 (120.4–332.0)	62.9 (8.7–234.2)
Age (years)	< 45	–	13	23.2 (14.9–46.2)	266.1 (232.6–402.1)	100.7 (28.2–134.8)
	45–60	–	33	6.7 (2.6–25.5)	250.0 (138.0–359.3)	90.7 (8.7–267.9)
	> 60	–	17	0.9 (0.0–1.9)	85.2 (70.0–250.0)	33.8 (4.9–114.0)
Treatment/Gender	Original	F	8	17.2 (5.81–35.2)	250.0 (98.6–258.2)	91.9 (33.9–411.2)
	Original	M	10	3.8 (2.2–14.4)	231.4 (113.5–634.1)	15.1 (4.7–121.5)
	Biosimilar	F	17	13.4 (3.6–36.2)	249.0 (117.7–250.0)	28.2 (6.0–90.7)
	Biosimilar	M	14	8.1 (1.9–24.9)	170.8 (74.3–250.0)	21.3 (2.1–51.6)
	WBT	F	12	2.9 (0.6–6.2)	352.75 (184.1–691.3)	745.9 (184.8–797.6)
	WBT	M	2	N/A	N/A	N/A
Treatment/MTX	Original	MTX Yes	11	14.9 (1.3–18.1)	120.0 (40.2–250.0)	17.5 (5.3–91.9)
	Original	MTX No	7	7.2 (3.8–27.3)	250.0 (250.0–795.2)	144.0 (33.2–511.8)
	Biosimilar	MTX Yes	17	3.6 (0.0–36.2)	121.6 (69.8–249.0)	6.3 (1.7–50.9)
	Biosimilar	MTX No	14	19.7 (10.7–24.9)	250.0 (183.2–250.0)	61.7 (15.0–103.9)
	WBT	MTX Yes	11	1.3 (0.3–5.8)	455.5 (210.5–708.5)	740.6 (195.0–838.0)
	WBT	MTX No	3	N/A	N/A	N/A
Treatment/Diagnosis	Original	AS	6	8.1 (2.4–34.4)	506.1 (96.9–811.8)	98.9 (26.6–189.5)
	Original	PsA	1	N/A	N/A	N/A
	Original	RA	11	7.2 (1.9–17.3)	212.8 (100.5–250.0)	12.7 (5.3–91.9)
	Biosimilar	AS	9	13.4 (10.5–21.2)	250.0 (148.0–250.0)	33.8 (8.7–100.7)
	Biosimilar	PsA	9	5.1 (0.9–36.6)	179.5 (37.8–250.0)	6.3 (1.5–50.9)
	Biosimilar	RA	13	8.4 (0.7–36.2)	162.1 (94.9–250.0)	28.2 (6.0–72.7)
	WBT	AS	1	N/A	N/A	N/A
	WBT	PsA	1	N/A	N/A	N/A
	WBT	RA	10	2.9 (0.7–5.9)	455.3 (258.6–656.8)	504.3 (205.3–756.8)
Treatment/Age (years)	Original	< 45	6	17.2 (15.3–39.2)	379.4 (229.1–690.6)	92.8 (52.5–2256.7)
	Original	45–60	10	3.8 (2.2–15.4)	250.0 (87.6–250.0)	30.0 (4.7–189.5)
	Original	> 60	2	N/A	N/A	N/A
	Biosimilar	< 45	7	25.5 (18.3–43.6)	250.0 (241.3–321.6)	100.7 (17.3–132.5)
	Biosimilar	45–60	14	19.7 (6.4–33.5)	197.3 (118.7–250.0)	22.5 (4.8–81.3)
	Biosimilar	> 60	10	0.8 (0.0–3.0)	79.9 (70.0–232.4)	13.0 (3.6–46.7)
	WBT	< 45	0	N/A	N/A	N/A
	WBT	45–60	9	5.5 (0.5–6.7)	605.2 (359.3–743.0)	755.1 (235.9–918.6)
	WBT	> 60	5	1.3 (0.6–1.9)	196.0 (115.8–250.0)	195.1 (154.0–740.6)

* N/A – Not applicable due to the low number of patients in the relevant group.

significantly in the Original and WBT groups, while in the Biosimilar group, a significant decrease was revealed (Table 2).

3.2. Secondary aims of analysis

The secondary aim was to evaluate the differences in the amount of the SARS-CoV-2 antibody produced in the dependence on the adalimumab and methotrexate treatment, gender, diagnosis, and the age of the patients.

Regarding the effect of other variables on the SARS-CoV-2 antibody levels after the first dose of the COVID-19 vaccine (D21), no significant association between the autoimmune disease type and gender was identified (Table 3, Fig. 2B and D). In contrast, lower levels of antibodies were found in patients treated with MTX than in those without the MTX treatment. The age of patients also proved to be a statistically significant parameter; the lower levels of antibodies were confirmed in elderly patients (Table 3, Figs. 2C and E).

Regarding the situation after the second dose of vaccine, in D63, the negative effect of the MTX treatment and age (lower antibodies in patients over 60 years than in younger patients) on the antibody levels and no influence of other parameters (diagnosis, gender) was confirmed. In D182, a significantly higher amount of antibodies was found in the Female group than in the Male group, and no effect of other parameters (diagnosis, age, MTX) was revealed (Tables 1 and 3, Fig. 2B–E).

In terms of evaluating the change of antibodies over time, in the period D21–D63, an increase in the antibody concentration was observed in all groups stratified by diagnosis, gender, MTX treatment, and age. The antibody level was maintained or decreased in the final analysis period, D63–D182. For example, there was a decline in the Male group as opposed to the Female group or in patients with AS/RA as opposed to patients with PsA (Table 2, Fig. B–E).

3.3. Interactions

Furthermore, the data analysis focused comprehensively on the influence of all variables (described within the primary and secondary endpoints) and their interactions. For this purpose, the data testing results after the data subdivision into subgroups (according to the treatment type and selected second variable) are presented in the lower part of the tables (Tables 1 and 2).

Six weeks after the second dose (D63), compared with the previously measured time point (D21), a significant increase in the SARS-CoV-2 antibodies was found in all subgroups without the distinction of gender, diagnosis, MTX treatment, and age. The only exception where

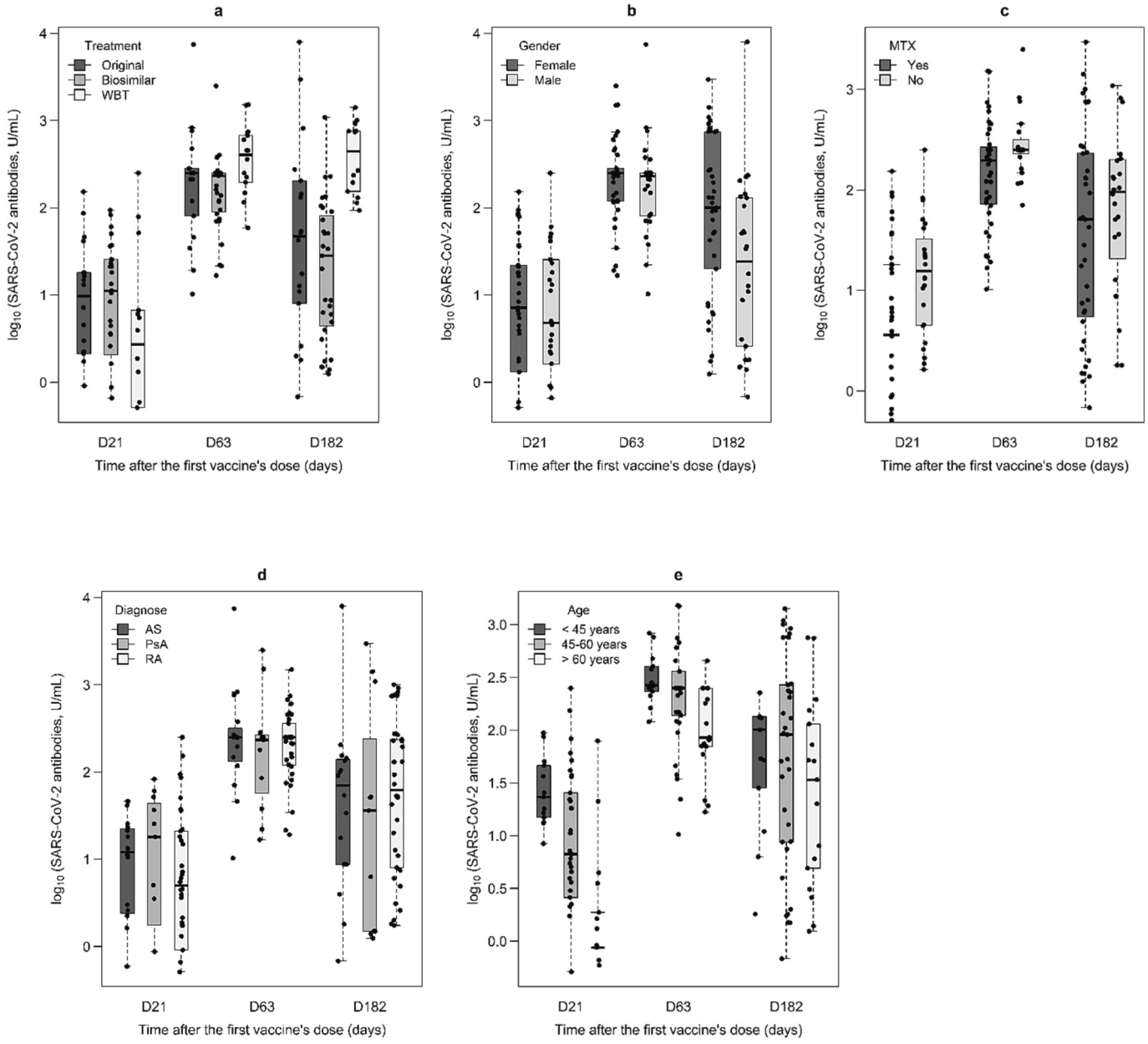

Fig. 2. Box and whisker plots showing the $\log_{10}$ transformed concentration of SARS-CoV-2 antibodies (U/mL) depending on time after vaccination for individual data groups stratified by a factor: treatment (A), gender (B), MTX (C), diagnose (D) and age (E) differentiated by box colors; individual measured values are also plotted.

no further antibody increase was present was in the WBT patients over 60 years (Table 2). In the period D63–D182, the antibody level showed no change in the WBT and Original groups. At the same time, there was a statistically significant decline of antibodies in the Biosimilar group, without the influence of gender, MTX treatment, autoimmune disease type, and age (Table 2). Therefore, the effect of the treatment type on the increase/decrease of antibodies over time is dominant, while the impact of other variables was confirmed as insignificant or minor.

3.4. Correlation analysis

A correlation analysis was performed to determine the effect of age on the development of immune responses to the COVID-19 vaccine.

In general, the SARS-CoV-2 antibody amount is negatively affected by the patient's age, especially in D21 (statistically significant negative correlation coefficients are in Table 4), indicating a slower increase in the antibody levels after the first vaccination dose in the elderly compared to younger patients. This dependence applies to patients treated with biological treatment, while in the WBT group, the antibody values were not correlated with the patient's age (Table 4). On the other hand, a significant correlation of the antibody level with age is no longer demonstrated at the end of testing (D182) for the Original and WBT groups. In contrast, in the Biosimilar group, the effect is still significant (Table 4).

The correlation analysis for the Original group at individual sampling points revealed a statistically significant correlation only in D21, indicating a slower increase in antibodies in elderly patients compared to younger patients, whereas, after the second dose, the age no longer affects the antibody levels. In contrast, for the Biosimilar group, the significant effect of age on antibodies during the whole monitored period was revealed (Table 4).

The influence of other variables plays no role in D21 and D182, and

Table 2
Effect of time: differences in the SARS-CoV-2 antibody levels between each two consecutive sampling points for the whole data set and selected groups and subgroups stratified by variables treatment, gender, MTX, diagnosis, and age; an increase/decrease in antibody concentration over time or a statistically insignificant difference with the corresponding *p*-value of Wilcoxon paired test (significant differences are indicated in bold).

Variable	Group	Subgroup	Patients (n)	D21–D63	D63–D182
	All data set	–	63	**Increase (p < 0.001)**	**Decrease (*p* < 0.001)**
Treatment	Original	–	18	**Increase (p < 0.001)**	NS (*p* = 0.130)
	Biosimilar	–	31	**Increase (p < 0.001)**	**Decrease (*p* < 0.001)**
	WBT	–	14	**Increase (p < 0.001)**	NS (*p* = 0.715)
Gender	F	–	26	**Increase (p < 0.001)**	NS (*p* = 0.149)
	M	–	37	**Increase (p < 0.001)**	**Decrease (p < 0.001)**
MTX	Yes	–	39	**Increase (p < 0.001)**	**Decrease (*p* = 0.014)**
	No	–	24	**Increase (p < 0.001)**	**Decrease (*p* = 0.023)**
Diagnosis	AS	–	16	**Increase (p < 0.001)**	**Decrease (p = 0.004)**
	PsA	–	11	**Increase (*p* = 0.005)**	NS (*p* = 0.054)
	RA	–	34	**Increase (p < 0.001)**	**Decrease (*p* = 0.037)**
Age (years)	< 45	–	13	**Increase (p < 0.001)**	NS (*p* = 0.191)
	45–60	–	33	**Increase (p < 0.001)**	**Decrease (p = 0.004)**
	> 60	–	17	**Increase (p < 0.001)**	NS (*p* = 0.207)
Treatment/ Gender	Original	F	8	**Increase (*p* = 0.008)**	NS (*p* = 0.945)
	Original	M	10	**Increase (p = 0.002)**	NS (*p* = 0.064)
	Biosimilar	F	17	**Increase (p < 0.001)**	**Decrease (p < 0.001)**
	Biosimilar	M	14	**Increase (p < 0.001)**	**Decrease (*p* = 0.001)**
	WBT	F	12	**Increase (p < 0.001)**	NS (*p* = 0.266)
	WBT	M	2	N/A	N/A
Treatment/ MTX	Original	MTX Yes	11	**Increase (p < 0.001)**	NS (*p* = 0.102)
	Original	MTX No	7	**Increase (*p* = 0.016)**	NS (*p* = 0.578)
	Biosimilar	MTX Yes	17	**Increase (p < 0.001)**	**Decrease (p < 0.001)**
	Biosimilar	MTX No	14	**Increase (p < 0.001)**	**Decrease (p < 0.001)**
	WBT	MTX Yes	11	**Increase (p < 0.001)**	NS (*p* = 0.765)
	WBT	MTX No	3	N/A	N/A
Treatment/ Diagnosis	Original	AS	6	**Increase (*p* = 0.031)**	NS (*p* = 0.313)
	Original	PsA	1	N/A	N/A
	Original	RA	11	**Increase (p < 0.001)**	NS (*p* = 0.083)
	Biosimilar	AS	9	**Increase (p = 0.004)**	**Decrease (p = 0.004)**
	Biosimilar	PsA	9	**Increase (*p* = 0.020)**	**Decrease (*p* = 0.004)**
	Biosimilar	RA	13	**Increase (p < 0.001)**	**Decrease (p = 0.008)**
	WBT	AS	1	N/A	N/A
	WBT	PsA	1	N/A	N/A
	WBT	RA	10	**Increase (p = 0.002)**	NS (*p* = 0.922)
Treatment/ Age (years)	Original	< 45	6	**Increase (p = 0.031)**	NS (*p* = 1.000)
	Original	45–60	10	**Increase (p = 0.002)**	NS (*p* = 0.106)
	Original	> 60	2	N/A	N/A
	Biosimilar	< 45	7	**Increase (p = 0.016)**	**Decrease (p = 0.031)**
	Biosimilar	45–60	14	**Increase (p < 0.001)**	**Decrease (p = 0.002)**
	Biosimilar	> 60	10	**Increase (p = 0.002)**	**Decrease (*p* = 0.002)**
	WBT	< 45	0	N/A	N/A
	WBT	45–60	9	**Increase (p = 0.004)**	NS (*p* = 0.570)
	WBT	> 60	5	NS (*p* = 0.063)	NS (*p* = 0.125)

*N/A – Not applicable due to the low number of values in the relevant group of patients.
*NS – Not significant difference.

the identified dependencies apply uniformly in all groups (negatively correlated age and antibodies in D21, as well as an absence of correlation in D182) (Table 4). Therefore, the immune response to the vaccine in elderly patients was rather delayed than impaired, as was also confirmed by other statistical methods (Tables 2 and 3).

The correlation analysis further suggested that age plays an important role primarily when monitoring the entire age range of patients. If the data set is divided into subgroups according to age (< 45, 45–60, and >60 years), then within these subgroups, the age has not a significant effect on the antibody levels (almost all relevant *p*-values at all sampling times are higher than 0.05; Table 4).

4. Discussion

In this retrospective study, we evaluate the SARS-CoV-2 antibody response after immunization with the Pfizer/BioNTech mRNA vaccine by three groups of patients suffering from rheumatoid autoimmune

Table 3
Effect of variables (treatment, gender, MTX, diagnosis, and age): differences in SARS-CoV-2 antibody levels between different data subsets at individual sampling points; *p*-values of Mann-Whitney *U* test in case of two subgroups or Kruskal-Wallis test with subsequent Dunn's multiple comparisons testing in case of three subgroups (significant differences are indicated in bold).

Variable	Group	D21		D63		D182	
Treatment	Original vs. Biosimilar	0.435	NS	0.058	NS	**< 0.001**	0.054
	Original vs. WBT		NS		NS		**0.012**
	Biosimilar vs. WBT		NS		NS		**< 0.001**
Diagnosis	AS vs. PsA	0.834	NS	0.864	NS	0.500	NS
	AS vs. RA		NS		NS		NS
	PsA vs. RA		NS		NS		NS
Age (years)	< 45 vs. 45–60	**< 0.001**	**0.023**	**0.018**	1.000	0.517	NS
	< 45 vs. >60		**< 0.001**		**0.028**		NS
	45–60 vs. > 60		**0.043**		**0.049**		NS
Gender	F vs. M	0.911	–	0.513	–	**0.020**	–
MTX	Yes vs. No	**0.008**	–	**0.025**	–	0.292	–

*NS – Not significant difference.

Table 4
Correlation analysis: correlation between SARS-CoV-2 antibody concentration and age for the whole data set and selected groups and subgroups stratified by variables treatment, gender, MTX, diagnosis, and age; Spearman's rho and the corresponding p-value indicating the statistical significance of the correlation (significant r_s values are indicated in bold).

Variable	Group	Patients (n)	D21	D63	D182
	All data set	63	**−0.61 (p < 0.001)**	**−0.37 (p = 0.003)**	−0.17 (p = 0.172)
Treatment	Original	18	**−0.69 (p = 0.001)**	−0.46 (p = 0.053)	−0.47 (p = 0.050)
	Biosimilar	31	**−0.61 (p < 0.001)**	**−0.48 (p = 0.007)**	**−0.39 (p = 0.003)**
	WBT	14	−0.33 (p = 0.249)	**−0.64 (p = 0.014)**	−0.35 (p = 0.222)
Gender	F	26	**−0.60 (p < 0.001)**	**−0.40 (p = 0.013)**	−0.18 (p = 0.276)
	M	37	**−0.66 (p < 0.001)**	−0.35 (p = 0.079)	−0.31 (p = 0.124)
MTX	Yes	39	**−0.63 (p < 0.001)**	−0.31 (p = 0.054)	−0.20 (p = 0.216)
	No	24	**−0.44 (p = 0.029)**	**−0.48 (p = 0.018)**	−0.13 (p = 0.541)
Diagnosis	AS	16	**−0.54 (p = 0.030)**	**−0.56 (p = 0.023)**	−0.12 (p = 0.663)
	PsA	11	**−0.75 (p = 0.007)**	−0.39 (p = 0.233)	−0.36 (p = 0.272)
	RA	34	**−0.61 (p < 0.001)**	−0.26 (p = 0.142)	−0.14 (p = 0.440)
Age (years)	< 45	13	0.11 (p = 0.717)	0.54 (p = 0.057)	0.02 (p = 0.957)
	45–60	33	−0.31 (p = 0.083)	0.03 (p = 0.885)	0.07 (p = 0.708)
	> 60	17	−0.13 (p = 0.613)	**0.53 (p = 0.029)**	−0.36 (p = 0.157)

*N/A – Not applicable due to the high number of values above the ULoQ.

diseases treated with the original adalimumab, with the biosimilar adalimumab and treated without the biological treatment.

Our observation showed no statistically significant difference between patients treated with the original adalimumab and biosimilar adalimumab at D21. The lower level of antibodies by subjects treated with biologics was expected based on the previous studies. Salinas et al., 2013 demonstrated a severe defect in the humoral response to primary vaccination against hepatitis B in anti-TNF-treated SpA patients.

A significant increase in antibodies, regardless of the type of treatment, was found at D63, which is in line with (Askling et al., 2014), who highlighted the effectiveness of the second vaccination against other pathogens, such as hepatitis A. A significant increase in antibodies was found in addition, regardless of the type of treatment. This finding was confirmed by a study performed by (Smetanova et al., 2022). Their presumption was confirmed at our sampling point D182, where a significantly higher level of antibodies was observed in the WBT group than in the biological treatment groups, regardless of the drug type. This finding is consistent with the observations of (Chanchlani et al., 2022) and (Vollenberg et al., 2022). Our findings also agree with (Chen et al., 2021), where the longitudinal analysis showed the most significant reductions in the SARS-CoV-2 antibodies in individuals treated with tumor necrosis factor-alpha inhibitors.

In D63, the presence of a high number of values above the ULoQ (Table 1, Fig. 2) must also be considered when interpreting the statistical testing outputs. The slightly higher increase in antibodies between D21 and D63 than indicated in the results can be assumed. However, this does not change the findings on statistical significance, as the increase in antibodies between these sampling points was also found with the current right-censored data.

Further, some gender differences in response to the COVID-19 vaccination were found. In D182, a significantly higher level of antibodies in the Female group than in the Male group was confirmed. Our observation contradicts the work of (Vollenberg et al., 2022) – their unpaired *t*-test analysis revealed no statistically significant differences between vaccinated males and females in anti-RBD and anti-S1 antibody levels after the first and second doses and at the later time points, that is, 45 and 75 days after the second shot. Equally, (Wheeler et al., 2021) revealed a compatible efficacy of the Pfizer-BioNTech and Moderna vaccines in the induction of various anti-SARS-CoV-2 antibodies, a similar immune response to vaccination in males and females. On the other hand, our observation is confirmed by (Pellini et al., 2021); in their recent study, women were found to generate higher antibody levels than men in multivariate analyses.

Six weeks after the second dose (D63), antibodies for all subgroups were significantly increased without the influence of diagnosis. No statistically significant difference between Inflammatory Rheumatic Diseases was observed. Our observation agrees with (Simon et al., 2021), who did not detect any significant difference between the diseases based on adjusted mean differences in immune-mediated inflammatory diseases. (Schreiber et al., 2022) also achieved the same observation results; their proportional odds model showed no significant differences across the diagnosis groups.

In contrast, the negative effect of the MTX treatment on antibody levels throughout the entire observed period was confirmed. This negative influence of MTX was observed in the past by (Subesinghe et al., 2018). A similar result was confirmed by (Haberman et al., 2021), who observed that individuals with immune-mediated inflammatory diseases on methotrexate demonstrate up to a 62% reduced rate of adequate immunogenicity to BNT162b2 mRNA vaccination. The case study (Lukaszuk et al., 2021) indicates that the humoral response to vaccination of a patient taking MTX can be lower and delayed.

According to (Schreiber et al., 2022), combining conventional DMARD and biological DMARD revealed a significantly higher risk of

inadequate SARS-CoV2 vaccine response. They showed that patients with the combination therapy may be less likely to develop an immune response compared to those who are in monotherapy with conventional DMARDs or not receiving active treatment (Schreiber et al., 2022). This finding was in our study confirmed by the Biosimilar Group, where the patients treated with the MTX-adalimumab biosimilar combination had a statistically significant decrease of the SARS-CoV-2 antibodies from D63 to D182, in contrast with the patient group without biological treatment where the antibody levels increased (D21–D63) or remained significantly unchanged (D63–D182), respectively.

The SARS-Cov-2 antibody amount is negatively affected by the patients' age, especially in D21, whereas after the second dose (D182), the age no longer affects the antibody levels. Our finding is in full compliance with (Wheeler et al., 2021), who have reported that the Pearson correlation analysis utilizing all age groups revealed a statistically significant relationship between the age and the level of anti-RBD IgG after the first dose of vaccine administration. Then, no age-dependency of the antibody response was seen after the second dose, suggesting that the immune-boosting was significant in all age categories. No correlations between the anti-RBD antibody levels and age were detected at later time points of blood collection (45 and 75 days after the second dose administration) (Wheeler et al., 2021). These results have been recently confirmed by (Jalkanen et al., 2021). In addition to that, (Michiels et al., 2021) show that, even at low doses, the combined methotrexate-adalimumab therapy can be associated with a weak immune response to the mRNA1273 vaccine in elderly patients.

The novel finding of our research, which has never been reported, is that the Biosimilar group revealed the significant effect of age on antibodies during the whole monitored period.

One explanation might be that the administration of adalimumab leads to the suppression of inflammation, which is generally considered to be a catabolic state. Original and biosimilar are not entirely identical medicinal substances (Millán-Martín et al., 2023). Slight differences in complex suppression of inflammation among different preparations might cause differences in SARS-CoV-2 antibody levels since their kinetics (degradation) might be influenced differently.

C-reactive protein (CRP) is a pentameric protein whose circulating concentrations rise in response to inflammation. It was also a clinical parameter collected in adalimumab patients. Thus, we have considered the CRP factor in all subjects during the observed period (Fig. 3). There was a statistically insignificant difference between the original, biosimilar, and without biological treatment groups. This fact may indicate a good response to treatment but does not explain the observed difference between SARS-CoV-2 antibody levels.

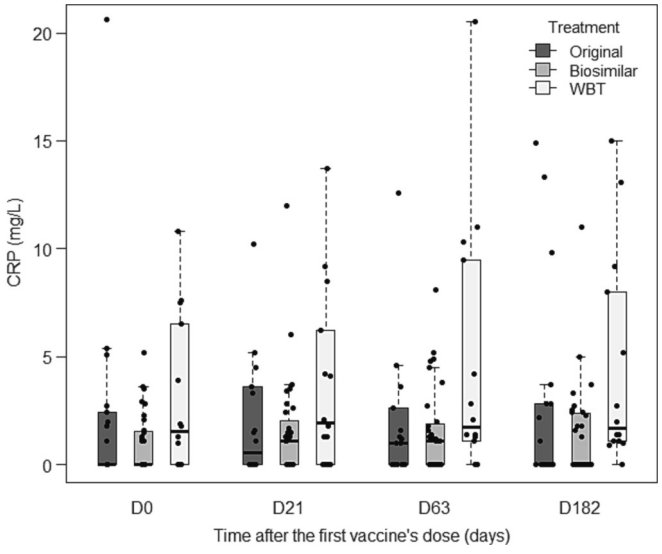

Fig. 3. Box and whisker plots showing the CRP (mg/L) depending on time after vaccination for individual data groups stratified by treatment. Individual measured values are also plotted.

Another explanation of the observed difference in SARS-CoV-2 antibody levels could be an interaction of the treatment antibodies with SARS-CoV-2 antibodies or a more complex immunological process. However, more studies focusing on the observed phenomenon with a large data set will be helpful to clarify this finding.

5. Conclusion

Our retrospective study confirmed that patients receiving adalimumab were able to develop cellular immune responses after the second vaccination dose, as well as healthy individuals. In the period of D63 – D182, the SARS-CoV-2 antibody levels did not change significantly in the patients receiving the original adalimumab, while in the patients receiving biosimilar adalimumab, a significant decrease was revealed. At D182, a significantly higher level of antibodies was observed in healthy individuals.

At D63, the negative effect of methotrexate treatment on the antibody levels was confirmed. At D182, men had lower antibody levels compared to women. During the monitored period, age's significant negative effect on antibody production was revealed in patients receiving biosimilar adalimumab.

This was the first study comparing original and biosimilar adalimumab on developing immune responses to COVID-19 vaccines. Further research is needed to confirm the identified dependencies.

Our study has some limitations. Due to the urgency of the pandemic and the vaccination program, our analysis sample was small. Moreover, more participants than expected fulfilled the exclusion criterium of the SARS-CoV-2 disease before the first dose of the SARS-CoV-2 vaccine. These participants showed no symptoms and did not even know they had undergone the disease.

Author contributions

Eva Dokoupilová and David Vetchý contributed to the design of the analysis; Eva Dokoupilová contributed to the conduct of the analysis; Sylvie Pavloková and Markéta Hanuštiaková contributed to the analysis and interpretation of the results. All authors discussed the results and contributed to the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee Medical Plus s.r.o. (IREC.MP. 2022.0003).

Informed consent statement

Patient consent was waived due to the fact that the study was a retrospective, non-interventional data analysis.

CRediT authorship contribution statement

Eva Dokoupilová: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **David Vetchý:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Sylvie Pavloková:** Formal analysis, Writing – original draft, Writing – review & editing. **Markéta Hanuštiaková:** Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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