bjh short report

Efficacy and safety of heterologous booster vaccination with Ad26.COV2.S after BNT162b2 mRNA COVID-19 vaccine in haemato-oncological patients with no antibody response

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Summary

Patients with haemato-oncological malignancies are one of the high-risk groups for a severe course in case of COVID-19 infections. Furthermore, vaccination results in significantly lower response rates in haematological malignancies and lower antibody levels in patients with solid cancer. We investigated efficacy and safety of a heterologous booster vaccination with Ad26.COV2.S DNA vector vaccine in haemato-oncological patients without antibody response after double-dose BNT162b2 messenger (m-)RNA COVID-19 vaccine. A total of 32 haemato-oncological non-responders to double-dose BNT162b2 received a heterologous booster vaccination with Ad26.COV2.S. Blood samples were assessed directly before the vaccination (T0) and four weeks after (T1). Safety assessment was performed using a standardised questionnaire. The overall response rate was 31%, with a mean (SD) antibody titre of 693·79 (1 096·99) binding activity units (BAU)/ml. Patients with chronic lymphocytic leukaemia or lymphoma showed a significantly lower response rate ($P = 0{\cdot}048$). Adverse events were reported in 29·6% of patients, of which 7·1% were graded as severe, including grade III and IV events following the Common Terminology Criteria of Adverse Events (CTCAE). The heterologous booster vaccination with Ad26.COV2.S led to a serological response in nine out of 29 patients without response after double-dose BNT162b2. Furthermore, the vaccination was safe in our cohort, leading to mainly mild local and systemic reactions. Overall, this vaccination regimen should be further evaluated to increase the response rate in the highly vulnerable population of haemato-oncological patients.

Keywords: COVID-19, serological response, haemato-oncological patients, heterologous booster vaccination, non-responders.

Introduction

Despite rapid advances in vaccination, the coronavirus disease 2019 (COVID-19) is an ongoing pandemic with >230 million infections worldwide, causing more than 4·8 million deaths.[1]

Initial studies demonstrated 70–95% efficacy in preventing symptomatic COVID-19 infection in the general population, following immunisation with BNT162b2 messenger (m-)RNA COVID-19 vaccine (Comirnaty®) from Pfizer/BioNTech and Ad26.COV2.S DNA vector vaccine (Janssen®) from Johnson & Johnson.[2,3]

In our previous study we demonstrated that patients with haematological malignancies had a 6·4-fold increased risk of serological non-response, which increased to 14-fold in case of systemic treatment.[4] Overall, in our cohort 28·6% of the haematological patients did not respond to two doses BNT162b2·[4] Also, Roeker *et al.*[5] reported that only half of the vaccinated chronic lymphocytic leukaemia (CLL) patients developed antibodies after immunisation with BNT162b2

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and Moderna's mRNA-1273 vaccine (mRNA-1273). Further data from Malard *et al.*[6] and Pimpinelli *et al.*[7] confirmed those poor response rates in haematological patients compared to the overall population, especially in those receiving systemic treatment. Lower immunogenicity was also demonstrated in solid-organ transplant recipients, with a positive antibody response in 54% of patients after two doses of a SARS-CoV-2 mRNA vaccine.[8]

In patients with solid cancer we showed response rates comparable to those in the general population, a fact supported by several other studies.[4,9,10] Despite these promising results, current data imply that these high-risk patients have lower antibody levels compared to the healthy population.[9,10]

Therefore, further strategies to improve protection against COVID-19 are urgently needed for the high-risk group of haemato-oncological patients. One approach currently under investigation is the use of heterologous vaccination schedules.[11] The Com-COV trial conducted by Liu *et al.*[12] presented first results of a heterologous vaccination regimen combining ChAdOx1 nCoV-19 vaccine and BNT162b2, showing ChAdOx1/BNT162b2 to be non-inferior in immunological response compared to double-dose ChAdOx1 and therefore supporting previously published data from Borobia *et al.*[13]

Another approach to improve the serological response in immunocompromised patients, especially in those with haemato-oncological malignancies, is the application of a booster vaccination. Recently, Shroff *et al.*[14] showed that a third dose of BNT162b2 was safe in patients with solid tumours and led to a significant increase in spike receptor binding-domain-specific (S/RBD) antibody titres. Further studies have investigated the additional benefit of a third dose of SARS-CoV-2 mRNA vaccines in transplant recipients. Kamar *et al.*[15] reported an anti-SARS-CoV-2 antibody prevalence of 68% four weeks after the third dose of BNT162b2 compared to 40% before the third dose. Another trial with mRNA-1273 supports these findings by proving a significantly higher serological response, characterised by S/RBD-antibody level ≥100 U/ml, of a third dose compared to placebo (55% vs. 18%, relative risk 3·1, $P < 0{\cdot}001$).[16]

Up to now, there are still many unanswered questions regarding the best vaccination strategy in immunocompromised patients. One group that needs special attention are haemato-oncological patients who did not respond to initial immunisation. The aim of the study was therefore to investigate the efficacy and safety of a heterologous vaccination regimen in patients without antibody response on double-dose BNT162b2 from our previously reported cohort[4] using a booster vaccination approach with the vector vaccine Ad26.COV2.S.

Patients and methods

Objectives, participants and oversight

Between January and March 2021, we conducted two voluntary vaccination campaigns for haemato-oncological patients at the Academic Teaching Hospital Feldkirch, after which 39 of the 259 patients did not respond after two vaccinations with BNT162b2·[4]

In July 2021, we invited the 39 non-responders and three additional haemato-oncological patients who had received the two vaccinations with BNT162b2 elsewhere to voluntarily participate in a heterologous boost with Ad26.COV2.S at the Academic Teaching Hospital Feldkirch. A total of 32 patients participated. The second dose of BNT162b2 was administered either 124 or 167 days before the boost, with the exception of three patients where the intervals were 47, 109 and 139 days. Ad26.COV2.S was administered on the 23 July 2021, at a dose of 5×10^{10} viral particles (0·5 ml) as a single intramuscular injection into the deltoid muscle. Only patients without any signs of infection received the vaccine and the therapy was continued according to the treatment protocol.

The socio-demographic data were extracted from the medical records. Blood samples were taken immediately before the vaccination (T0) and 28 +/− three days after (T1), except for one patient from whom the blood sample was taken 40 days after the first collection due to an interim hospitalisation. Overall, three patients were excluded from the analysis as they already showed positive antibody titres on the day of the third vaccination.

To evaluate serological response we used the Elecsys® Anti-SARS-CoV-2-S immunoassay from Roche (Basel, Switzerland) as well as the SARS-CoV-2 IgG II Quant assay from Abbott (Abbott Park, IL, USA), both of which detect S/RBD-antibodies to the SARS-CoV-2 spike (S) protein RBD.[17,18] Per definition, values >0·82 binding activity units per millilitre (BAU/ml) indicated a positive antibody detection in the Elecsys® immunoassay, whereas the threshold value for the assay from Abbott was 50 arbitrary units per millilitre (AU/ml) which corresponds to 7·1 BAU/ml.[17,19]

In addition, the following laboratory values were recorded: neutrophil count, lymphocyte count, eosinophil count, total immunoglobulin G (IgG), cluster of differentiation 4 ($CD4^+$) count and cytotoxic T-cell ($CD8^+$) count. As in a previous study at our clinic, patients were divided into two groups based on IgG levels, with a cut-off of ≥550 mg/dl, according to Herishanu *et al.*[4,20]

Local and systemic adverse events were evaluated up to seven days after vaccination using a standardised safety questionnaire, according to Polack *et al.*[2] This questionnaire was handed out at the third vaccination and the participants noted every symptom which occurred within seven days after the booster vaccination. Thereafter, the investigators reviewed the returned safety questionnaires and graded the severity from 1 to 5, following the Common Terminology Criteria of Adverse Events (CTCAE), Version 5·0,[21] summarising events of Grades III and IV as severe adverse events. Specifically, the following symptoms were addressed: pain at injection side, local redness and swelling, fever, fatigue, headache, muscle pain, joint pain, diarrhoea, nausea and occurrence of thrombosis. In addition, participants could indicate other symptoms.

During the four-week observation period, patients presenting with symptoms of respiratory or gastrointestinal infection were tested for COVID-19 with a polymerase chain reaction test and the result was documented. Also, occurrence and cause of death was noted.

Our trial was conducted according to the Declaration of Helsinki of 1975 (revised 2013) and Good Clinical Research Practice. The study was approved by the Ethics Committee of the Medical University of Innsbruck (EC No: 1088/2021) and the Institutional Review Board.

Statistical evaluation

The aim of this study was to assess the safety and serological response to a heterologous boost with Ad26.COV2.S in haemato-oncological patients without seroconversion following vaccination with double-dose BNT162b2. Sample size was not pre-specified. The baseline characteristics were described using percentages, means, medians, standard deviations and interquartile ranges. Serological non-responding was defined as no detectable S/RBD-antibodies at T1. The Clopper–Pearson method was used to calculate a 95% confidence interval for response rate. Using descriptive statistics, patient characteristics were compared regarding serological response. The association between serological response and gender, therapy as well as adverse events was tested for statistical significance using cross tabulation and Fisher's exact test. The non-normal distributed variables were compared regarding serological response using the Mann–Whitney *U*-test. A P value <0·05 was considered statistically significant. All analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS), version 27 (IBM, Armonk, NY, USA).

Results

We observed all patients from the day of heterologous boost with a median follow-up of 28 days. Socio-demographic characteristics are shown in Table I. None of the participants died and we lost no patient during follow-up. In addition, no cases of COVID-19 occurred in any of the patients after they received the booster vaccination. Patient flow is shown in Fig 1.

Serological response

Among the 29 participants analysed in our study, the third dose was administered a median of 124 days after the second BNT162b2 vaccination. The antibody response was measured a median of 28 days thereafter with a positive serological response in nine patients (31%, 95% CI 15·3–50·8). The mean (SD) antibody titre of responders was 693·79 (1096·99) BAU/ml (Fig 2). A subgroup of patients with CLL or lymphoma was less likely to develop serological response compared to the other patients (efficacy 16·7%, P = 0·048, Fig 3).

Table I. Demographic characteristics of the patients.

Characteristic	Value
Number of patients	29
Gender, *n* (%)	
Female	8 (27·6)
Male	21 (72·4)
Age, years, median (IQR)	72 (60–78)
Tumour entity, *n* (%)	
CLL/lymphoma*	18 (62·1)
Other haematologic malignancies§	8 (27·6)
Solid cancer¶	3 (10·3)
Time between second and third vaccination, days, median (IQR)	124 (124–167)
Time between first and second blood sample, days, median (IQR)	28 (28–28)
Active therapy at third vaccination, *n* (%)	
Yes	20 (69)
No	9 (31)

CLL, chronic lymphocytic leukaemia; IQR, interquartile range;
*This group comprises: low-grade non-Hodgkin lymphoma (CLL, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma) and high-grade non-Hodgkin lymphoma (diffuse large B-cell lymphoma).
§This group comprises: multiple myeloma, amyloidosis of the lung and acute myeloid leukaemia.
¶This group comprises: melanoma, adrenal carcinoma and breast cancer.

Due to the limited number of participants, we summarised the patients with multiple myeloma (n = 6), amyloidosis of the lung (n = 1) and acute myeloid leukaemia (n = 1). There was no significant difference in serological response according to gender, therapy, age, adverse events and immune status (all P not significant, Table II).

Safety results

Overall, 29·6% of the patients reported adverse events following the heterologous vaccination, and two side effects (7·1%) were graded as severe (Fig 4). The most commonly reported side effects were fatigue (25%), followed by pain at the injection site (7·1%) as well as headache, fever and joint pain (3·6% each). The two patients with severe adverse events suffered from fatigue and fever, respectively. Furthermore, one participant was hospitalised due to a hypertensive crisis. Apart from this, no thrombotic event or anaphylactic reaction occurred. Side-effect rates did not differ according to gender, tumour entity or therapy (P not significant, respectively). However, there was a trend towards more adverse events in younger patients (P = 0·075).

Discussion

This study was able to demonstrate that a heterologous boost with Ad26. CoV2.S was safe and led to a serological

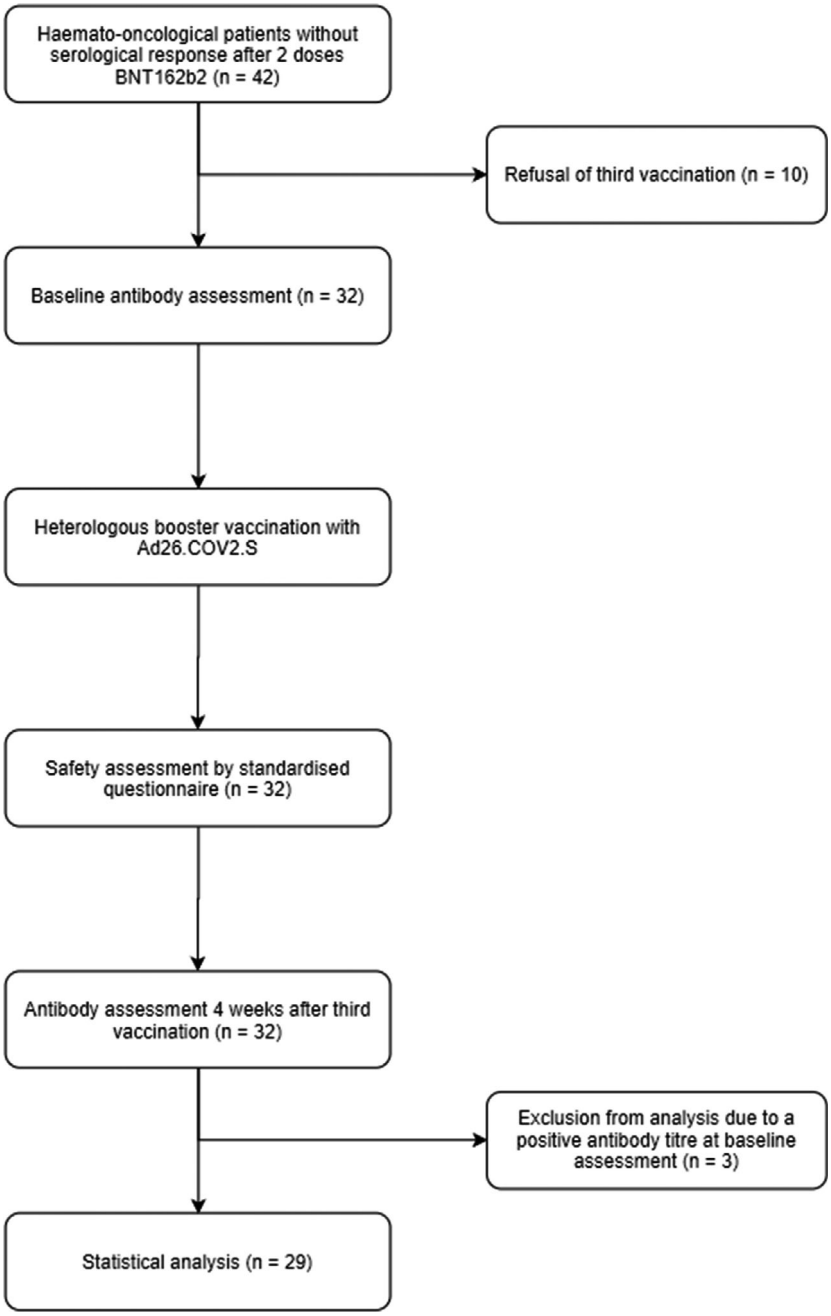

Fig 1. Study profile. The number of patients (*n*) at key target points is indicated. The reasons for and time points of dropouts are shown. BNT162b2 = BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech), Ad26.COV2.S = Ad26.COV2.S vaccine (Johnson & Johnson).

response in 31% of our haemato-oncological patients who did not respond after a previous double dose of BNT162b2. Similar results were reported by Kamar and colleagues[15] who investigated a third dose of BNT162b2 in solid-organ transplant recipients, with 44% of patients who were sero-negative prior to the third vaccination showing a serological response four weeks after the third dose. In addition, another trial regarding transplant recipients reported a substantially higher immunogenicity after a third dose of mRNA-1273 compared to placebo.[16] Haemato-oncological patients and transplant recipients seem to be comparable, as both groups are considered immunosuppressed, a fact known to lead to poorer response after COVID-19 vaccination.[4,6–8,22,23]

Previous studies reported markedly impaired serological response after two doses of BNT162b2 in patients with CLL. In the present cohort we showed preliminary data indicating a significantly lower response rate in patients with CLL or lymphoma even after a heterologous booster vaccination with Ad26.COV2.S following immunisation with BNT162b2·[4,20]

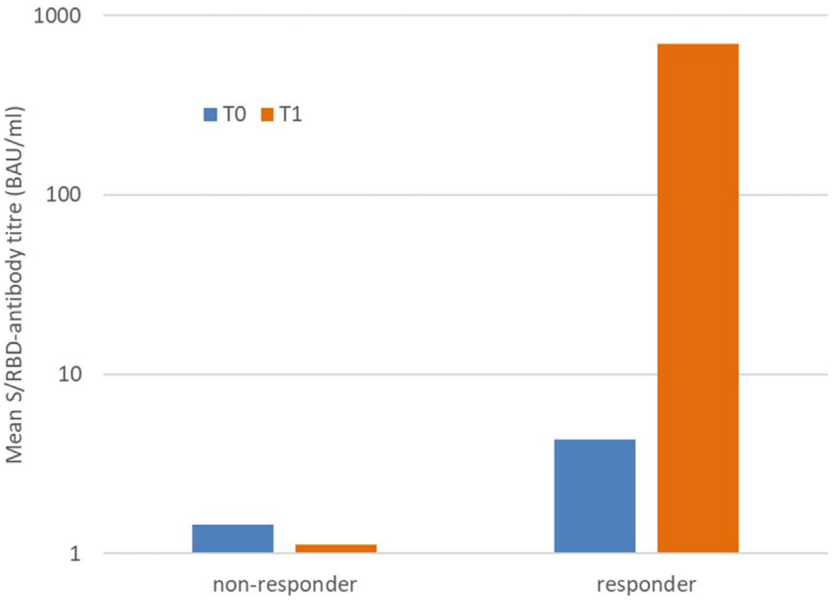

Fig 2. Mean S/RBD antibody titre at T0 and T1 regarding serological response four weeks after the heterologous booster vaccination. The mean antibody titres of the responders were 4·31 (SD = 3·31, *R* = 6·28) BAU/ml at T0 and 693·79 (SD = 1096·99, *R* = 2566·16) BAU/ml at T1. In the group of non-responders the mean antibody titres were 1·45 (SD = 1·93, *R* = 6·28) BAU/ml at T0 and 1·13 (SD = 1·40, *R* = 6·28) BAU/ml at T1. Responders and non-responders are determined using the Elecsys® Anti-SARS-CoV-2-S immunoassay (Roche) as well as SARS-CoV-2 IgG II Quant assay (Abbott). BAU/ml, binding activity units per millilitre; *R*, range; S/RBD-antibody, antibody to the SARS-CoV-2 spike protein receptor binding domain; SD, standard deviation; T0, immediately before the booster vaccination; T1, four weeks after booster vaccination. [Colour figure can be viewed at wileyonlinelibrary.com]

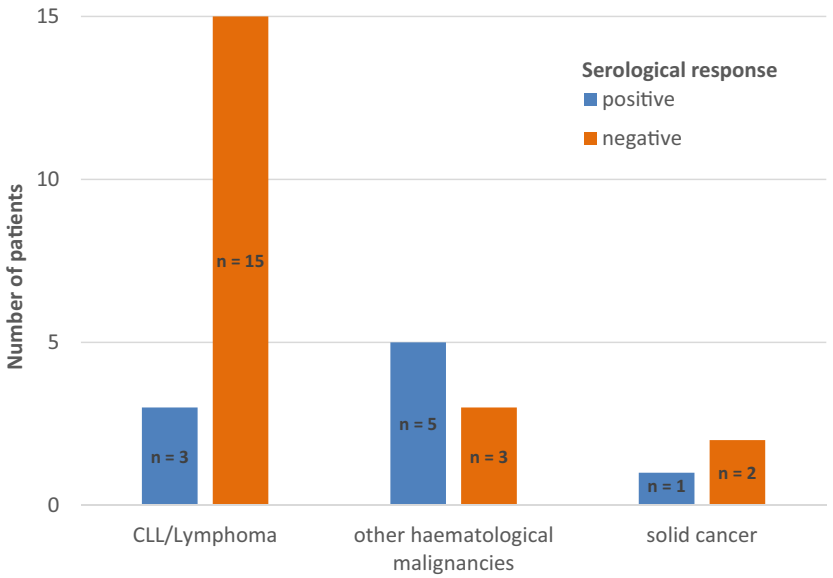

Fig 3. Serological response four weeks after heterologous booster vaccination (T1) regarding tumour entity. Tumour entity is differentiated into patients with lymphoma or chronic lymphocytic leukaemia (CLL) *versus* participants with other haematological malignancies and solid cancers. The number of patients (*n*) in each group is shown. Responders and non-responders are determined using Elecsys® Anti-SARS-CoV-2-S immunoassay (Roche) as well as SARS-CoV-2 IgG II Quant assay (Abbott). [Colour figure can be viewed at wileyonlinelibrary.com]

Furthermore, in our cohort, there was no correlation between serological response and immunoglobulin G level. Also, no association between systemic treatment and response occurred in our analysis. Despite the limitation of a small sample size this result could lead to the indication for a third vaccination regardless of therapy in haemato-oncological patients without response to prior immunisation.

Heterologous vaccination with Ad26.COV2.S was safe in our cohort, with a total of 29·6% of patients reporting mainly mild local and systemic reactions. Two participants

Table II. Association between patient characteristics, laboratory values and serological response after the booster vaccination with Ad26.COV2.S following double-dose BNT162b2.

Variables	Serological response		*P**
	Positive	Negative	
Gender, *n* (%)			
Female	3 (33·3)	5 (25)	0·675
Male	6 (66·7)	15 (75)	
Active therapy at third vaccination			
Yes	8 (88·9)	12 (60)	0·201
No	1 (11·1)	8 (40)	
Age, years, median (IQR)	73 (69–77)	70 (59–79)	0·627
Adverse events, *n* (%)§			
Yes	3 (33·3)	5 (27·8)	1·000
No	6 (66·7)	13 (72·2)	
IgG (mg/dl) at T0, median (IQR)	688 (537–770)	542 (342–666)	0·153
IgG (mg/dl) ≥550 at T0, *n* (%)			
Yes	5 (55·6)	9 (45·0)	0·700
No	4 (44·4)	11 (55)	
Neutrophil count (G/L) at T0, median (IQR)	3·2 (2·0–4·3)	3·93 (2·65–5·7)	0·317
Lymphocyte count (G/L) at T0, median (IQR)	1·5 (0·9–1·9)	1·2 (0·8–2·1)	0·871
CD4 cell count (cells/µl) at T0, median (IQR)	550 (244–637)	345 (188·5–570·5)	0·501
CD8 cell count (cells/µl) at T0, median (IQR)	448 (246–601)	494 (261–1048·5)	0·660
Eosinophil count (G/L) at T0, median (IQR)	0·21 (0·07–0·25)	0·05 (0·01–0·17)	0·062

Ad26.COV2.S, Ad26.COV2.S vaccine (Johnson & Johnson); BNT162b2, BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech); IQR, interquartile range; T0, blood samples collected directly before vaccination.
*Significance: $P < 0·05$.
§Data available only for 27 patients.

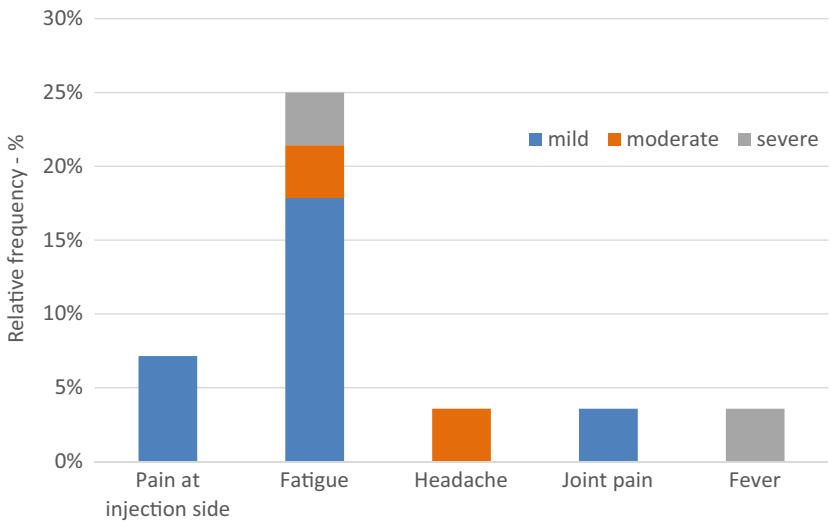

Fig 4. Occurrence of local and systemic adverse events within seven days after heterologous booster vaccination. The relative incidences of local and systemic adverse events are given as percentages. Side effects are collected within seven days after booster vaccination. Severity is differentiated using the Common Terminology Criteria of Adverse Events (CTCAE).[21] No Grade IV or V events occurred. [Colour figure can be viewed at wileyonlinelibrary.com]

reported a severe side effect. These findings are comparable with data from various studies regarding vaccination with BNT162b2 as well as Ad26.COV2.S.[2,3,24] Regarding heterologous immunisation, Hillus *et al.*[25] investigated the safety of heterologous prime-boost immunisation with ChAdOx1 and BNT162b2, demonstrating adverse events in 49% of recipients. In addition, Werbel and colleagues[26] reported a higher rate of adverse events in a small series of patients who

received a heterologous boost with BNT162b2, Ad26.COV2.S or mRNA-1273 after being previously immunised with BNT 162b2 or mRNA-1273. However, both cohorts showed a lower median age compared to the present study, which is known to significantly correlate with higher rates of adverse events.[2,3] Another reason for the lower reactogenicity in our cohort might be the relatively long interval between the second dose and the booster vaccination, a hypothesis also put forward in a previous investigation.[25]

Limitations of this study are the small number of patients and the comparatively short follow-up period as well as the absence of a control group. Also, the relatively long interval between initial immunisation and booster vaccination has to be noted. Furthermore, safety was assessed by means of a questionnaire, which allows for potential bias. Considering the heterogeneity in terms of diagnoses it is difficult to draw conclusions about which diseases respond best to a heterologous booster vaccination.

In conclusion, a heterologous vaccination regimen combining BNT162b2 and Ad26.COV2.S should be further evaluated in haemato-oncological patients to increase the response rates in this highly susceptible population. Further studies are needed to evaluate potential differences between heterologous and homologous vaccination schedules to achieve the very best serological response in these patients.

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