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ORIGINAL ARTICLE

Humoral immunity to varicella zoster virus is altered in patients with rheumatoid arthritis

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Abstract

Introduction The prevalence of herpes zoster (HZ) is high in patients with rheumatologic diseases. The incidence in patients with rheumatoid arthritis (RA) is at least twice as high as in healthy people. Nevertheless, little is known about humoral immunity against varicella zoster virus (VZV), in particular in patients with RA.

We, therefore, aimed to retrospectively compare VZV antibody concentrations in a collective of patients with RA in a German outpatient clinic with age- and sex-matched controls without RA.

Methods We included $n = 247$ patients with RA from one single university centre as well as $n = 250$ age- and sex-matched controls from the in-house routine in this retrospective analysis. The concentration of VZV IgG antibody concentration was either available from the records or was measured using an enzyme-linked immunosorbent assay (ELISA). Additionally, avidity for specific IgG was analysed for some of the samples. The antibody concentrations have been compared between the two groups. Moreover, a consecutive subgroup analysis after stratification by age was performed.

Results A total of 68.4% ($n = 169$) of the included patients were treated with conventional synthetic DMARDs, either as monotherapy or in combination. Biological originator DMARDs were used in 45.8% ($n = 113$) of the patients, with the majority (85%, $n = 96$) of them being on tumour necrosis factor (TNF)–inhibiting agents. As the main result of this study, antibody titres for VZV were found to be significantly lower in RA patients compared with healthy controls ($p < 0.0001$). The observed difference was most pronounced for the older patients being in the sixth and seventh decade. Antibody avidity was high in both groups with a significantly higher avidity among the controls ($p = 0.0006$).

Conclusions A possible explanation for the low VZV antibody concentration in RA patients might be premature immunosenescence, which most likely also effects the B cell compartment and humoral immunity. This thesis is emphasised by the significantly higher antibody avidity among the controls. The data also suggest that the increased HZ risk is a consequence of a poor humoral immunity. The available HZ vaccinations should contribute to decreasing the elevated HZ risk in RA patients.

Key Points

- *Humoral immunity to varicella zoster virus seems to be reduced in patients with RA.*
- *This impaired immunity might contribute to the increased herpes zoster susceptibility in RA patients.*
- *An accelerated immunosenescence in RA could be causative for this finding.*

Keywords Herpes zoster · Rheumatoid arthritis · Shingles · Vaccination · Varicella zoster virus · VZV antibodies

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Introduction

The relevance of herpes zoster (HZ, shingles) is high in patients with autoimmune disorders, in particular in rheumatic diseases. While its incidence is approximately 3–5/1.000 person-years in the general population [1, 2], the incidence in patients with rheumatoid arthritis (RA) is estimated to be 12/1.000 person-years [2]. In systemic lupus erythematosus (SLE), the incidence is even higher, reaching up to 91/1.000 person-years [1]. Interestingly, HZ not only occurs more frequently in patients with a recent RA diagnosis but is also associated with disease severity (e.g. previous joint surgery due to erosive disease) [2].

A live vaccine to prevent HZ was already licenced in 2006 in the United States (US) for immunocompetent adults [3]. Effectiveness and safety have been demonstrated for healthy adults [4]. A reduced incidence of HZ in vaccinated SLE patients has been shown prospectively [5]. Moreover, retrospective analyses indicate a reduced incidence also for other patients using immunosuppressive drugs, including patients with RA [6, 7]. The safety profile of the live HZ vaccine was evaluated favourable, following 10 years of post-marketing use [8]. In 2017, an effective subunit vaccine [9, 10] was approved in the US, which was followed by approval in the European Union in 2018.

Nevertheless, vaccination indications in patients with rheumatic diseases remain unclear and vaccination rates are reported to be low [11–13]. While the European League Against Rheumatism (EULAR) only recommends a vaccination in patients with inflammatory rheumatic diseases and less severe immunosuppression [14], the American College of Rheumatology (ACR) recommends a vaccination in RA patients even under treatment with disease-modifying antirheumatic drugs (DMARDs) but not under any biologic therapy [15]. These recommendations are based on the live vaccine.

The knowledge concerning humoral VZV immunity in RA patients is limited. We, therefore, compared VZV IgG titres in RA patients with healthy controls to help increasing this knowledge, which might contribute to establish proper indications for HZ vaccination.

Methods and study design

Throughout 3 months, any adult RA patient (≥ 18 years) being scheduled for routine consultation in our outpatient clinic has been asked for participation in this retrospective cohort study. To acquire a realistic sample of patients from the outpatient setting, no further restrictions to gender, age or the particular therapy have been applied.

Any RA diagnosis was based on a rheumatologist's clinical judgement and according to the 2010 criteria of the ACR/EULAR [16]. Our clinic belongs to a University Hospital and is providing outpatient rheumatologic care.

All vaccination data and HZ history presented have been obtained from the patient's record, the vaccination documents or from interviewing the patient. The antibody titres were available from the individual patient record.

To compare the VZV antibody titres, non-RA controls without any history of autoimmune diseases have been randomly selected from the in-house diagnostic routine and were age- as well as sex-matched. No details about chickenpox or HZ history were available from the controls. VZV IgG antibody concentrations have been measured using an IgG enzyme-linked immunosorbent assay (Euroimmun, Lübeck, Germany; cut-off 100 mIU/ml, assay range 12–5.000 mIU/ml, sensitivity 100%, specificity 100%) employing highly purified whole virus lysate strain Ellen. For some of the samples, avidity for specific IgG was analysed (DiaSorin, Dietzenbach, Germany; cut-off 100 mIU/ml, assay range 10–4.000 mIU/ml, sensitivity 100%, specificity 97.1%) using 3.6-M urea.

The ethics committee of the University of Leipzig has approved the design of the study, and written informed consent was obtained from each patient before enrolment.

Biostatistical analysis

Continuous data were described using mean and standard deviation (SD). Categorical data were described using absolute or relative frequencies. Fisher's exact test was performed to compare frequencies of categorical variables. To compare continuous data, Student's t test or Mann-Whitney U test, as appropriate, was used after performing the Kolmogorov-Smirnov normality test. For the subgroup investigation, analysis of variance (ANOVA) with Šidák's correction for multiple post hoc comparisons was used. A significant statistical difference was assumed when the p value was found to be < 0.05.

Analyses were conducted using GraphPad PRISM Version 6 for Mac (GraphPad Software Inc., San Diego, CA, USA). Recommendations of the STROBE group have been applied when reporting the findings of this survey [17].

Results

In total, $n = 247$ RA patients (mean age 60.2 ± 13.1 years) have been enrolled and evaluated. Varicella zoster virus (VZV) antibodies have been positive in 245 patients. In total, 66 patients had a past history of HZ. None of the patients ever had a HZ vaccination.

At baseline, 68.4% ($n = 169$) were treated with conventional synthetic (cs) DMARDs, either as monotherapy or in combination, and 9.7% ($n = 24$) received glucocorticoids only. Biological originator (bo) DMARDs were used in 45.8%

($n = 113$) of the patients with 85% ($n = 96$) of them being on tumour necrosis factor (TNF)–inhibiting agents and 6.2% ($n = 7$) on rituximab.

A total of $N = 250$ controls (60.7 ± 10.2 years) have been randomly selected from the diagnostic in-house routine and were matched for age and sex.

Avidity for specific VZV IgG was measured in retained samples in $n = 71$ patients and $n = 36$ controls.

Details on the epidemiology of the patients as well as controls can be obtained from Table 1. For further patient's characteristics, see Table 2.

RA patients show significantly lower VZV IgG concentrations

The enrolled patients were matched according to age and gender to randomly selected healthy controls from the in-house routine. When comparing both groups, we found the VZV IgG concentrations to be significantly lower in the studied RA patients compared with the control group ($p < 0.0001$, see Fig. 1). No influence of the respective RA medication on the antibody titre could be revealed. Moreover, neither individual HZ nor chickenpox history did have any effect on the antibody concentration (data not shown).

The antibody avidity was high in both groups with the measured relative avidity index (RAI) not falling short of 50% in any of the samples (Fig. 2). Comparing the RAIs between the two groups, avidity was significantly higher among the controls (82.6% ± 9.5 in controls, 76.4% ± 8.1 in patients, $p = 0.0006$).

Further investigating the difference in VZV IgG concentrations, patients and controls have been divided by age into six subgroups (< 30 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years and > 70 years). The following subgroup analysis revealed the difference in concentration being most pronounced in the sixth ($p < 0.0001$) and seventh ($p = 0.0032$) decade, see Fig. 3.

HZ frequency in RA patients increases with age

Of the RA patients investigated ($n = 247$), 66 patients ever had HZ (mean age 46.3 ± 17.8 years). There was no relationship between HZ incidence and the particular antirheumatic medication (data not shown). The relative frequency was highest in older RA patients (Fig. 4).

Table 1 Characteristics of the studied patients and controls. Means are given with standard deviation (SD)

	RA patients $N = 247$	Controls $N = 250$	p value
Mean age, years	60.2 ± 13.1	60.7 ± 10.2	0.64
Female, *n* (%)	197 (79.8)	181 (72.4)	0.06

Table 2 Clinical characteristics of the studied patients with rheumatoid arthritis (RA) ($n = 247$). Means are given with standard deviation (SD). Medians are given with interquartile range (IQR)

Characteristics	Result
Positive varicella history[1], *n* (%)	130 (52.6)
HZ history, *n* (%)	66 (26.7)
Mean RA duration, years	14.1 ± 13.1
RF-positive, *n* (%)	173 (70.1)[2]
ACPA-positive, *n* (%)	173 (70.1)[2]
Median ACPA (RU/ml)	100.0 (4.98–300)
Median RF IgM (IU/ml)	35.9 (10.6–134)
Median CRP (mg/l)	3.04 (1.31–9.26)
Mean HAQ	1.1 ± 0.8
Mean DAS28-CRP	3.3 ± 1.7
Smoker, *n* (%)	16 (6.5)
Medication, *n* (%)	
csDMARDs only	107 (43.2)
boDMARD	113 (45.8)
TNF inhibitor	96 (38.9)
Glucocorticoid monotherapy	24 (9.7)
csDMARDs, *n* (%)	
any csDMARD	169 (68.4)
MTX	147 (59.5)
Leflunomide	8 (3.2)
Azathioprine	4 (1.6)
Sulfasalazine	4 (1.6)
MTX + Leflunomide	3 (1.2)
MTX + sulfasalazine	1 (0.4)
MTX + ciclosporin A	1 (0.4)
Hydroxychloroquine	1 (0.4)
boDMARDs, *n* (%)	
Any agent	113 (45.8)
Adalimumab	41 (16.6)
Etanercept	40 (16.2)
Abatacept	8 (3.2)
Rituximab	7 (2.8)
Golimumab	7 (2.8)
Infliximab	5 (2.0)
Tocilizumab	1 (0.4)
tsDMARDs, *n* (%)	
Tofacitinib	1 (0.4)
Glucocorticoids, *n* (%)	
All users	191 (77.3)
Low-dose[3] users	186 (75.3)

ACPA, anti-citrullinated proteins/peptides antibodies; *boDMARD*, biological originator disease-modifying antirheumatic drug; *csDMARD*, conventional synthetic disease-modifying antirheumatic drug; *DAS28-CRP*, disease activity score 28 joints; *HAQ*, Health Assessment Questionnaire; *IU*, international units; *HZ*, herpes zoster; *RU*, relative units; *RF*, rheumatoid factor; *TNF*, tumour necrosis factor; *tsDMARD*, targeted synthetic disease-modifying antirheumatic drug; *VZV*, varicella zoster virus

[1] According to the personal patient history and documentation (actual disease rates are thought to be higher since most of the patients were born before the availability of a proper vaccination)

[2] Numbers are indeed identical

[3] The dose was considered being low when not exceeding 7.5-mg prednisolone equivalent [18]

Discussion

Most investigations regarding varicella zoster virus (VZV) immunity focus on cellular immunity [19, 20]. Contrary to

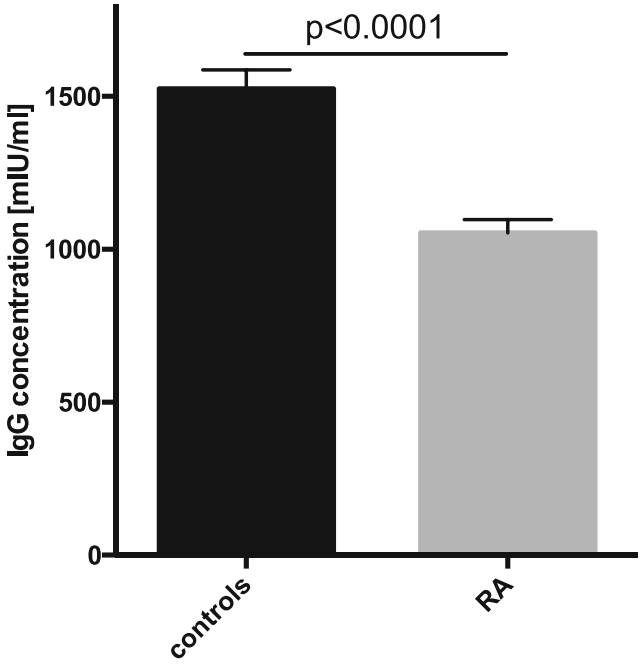

Fig. 1 Comparison of varicella zoster virus IgG antibody concentration between RA patients ($n = 245$) and controls ($n = 250$). RA patients have significantly lower specific VZV IgG concentration than controls. Given are means with standard error of the mean (SEM)

systemic lupus erythematosus [1, 21, 22], knowledge about humoral immunity against VZV in RA is limited. Patients are clearly at an increased risk of HZ [2, 23]. This risk is further increased by age, usage of csDMARDs, TNF inhibitors and prednisone therapy [24, 25]. Moreover, also therapy with tofacitinib seems to increase HZ risk, in particular, if being combined with prednisone but not MTX [26, 27]. A recent trial indicates that vaccination just a few weeks before initiating a therapy with tofacitinib might be safe and induces a proper immune reaction [28]. Conducting the study at hand, we aimed to further investigate humoral immunity against VZV in RA patients.

Our study revealed significantly lower VZV IgG serum concentrations in RA patients in comparison with a matched control group without RA. No influence of the immunosuppressive RA medication or individual varicella/HZ history on VZV immunity was found. To our best knowledge, this is the first paper addressing VZV IgG antibody concentrations in patients with RA. Of particular importance is the finding that the difference is most pronounced in the sixth and seventh decade of life. This difference diminishes beyond the age of 70 with both groups having similar antibody titres.

One possible explanation for the observed reduced antibody concentrations might be the ageing of the immune system, called immunosenescence [29]. Immunosenescence affects both branches of the immune system, innate and adaptive immunity [30–33]. The immune system in RA patients is thought to be prematurely aged by more than 20 years [31] and has been extensively studied as a model system for the molecular mechanisms of immune ageing [30]. Mortality models are consistent with the thesis of accelerated ageing in RA [34]. The hallmark of immunosenescence in RA is the ageing of T cells with loss of the costimulatory molecule CD28, premature shortening of telomeres, increased DNA breakage and a metabolic reprogramming resulting in an energy deficit [30]. Additionally, the loss of CD28 negatively impacts CD40L expression, which actually is important for B and T cell interaction and consecutive antibody production [35]. The B cell compartment also changes with healthy ageing and the reduced T cell help further deteriorates its function. It is thought that these changes are both qualitative and quantitative of nature [36, 37]. Concerning RA, actual B cell senescence is poorly examined [38], although a reduced number of peripheral B cells could be demonstrated [39]. In contrast, a study of newly diagnosed RA found no changes in B cell characteristics [40]. In healthy elderly people, bone marrow houses significantly decreased numbers of plasma cells, which were found to be consecutively reduced in peripheral blood [41]. This finding is in line with the proposition that humoral immunity is altered in the elderly leading to a reduction in overall antibody levels and contributing to ageing by producing inflammatory cytokines [42–44].

Consistent with the hypothesis of immunosenescence-mediated reduced antibody levels, a recent large-scale study

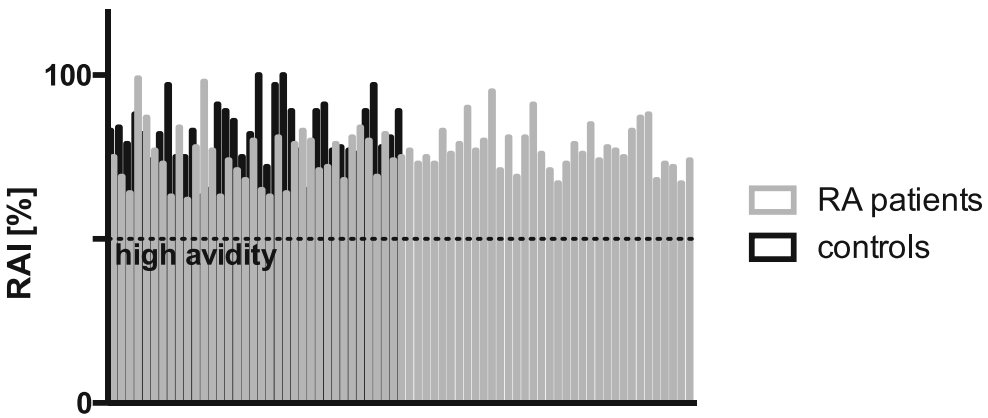

Fig. 2 Varicella zoster virus IgG antibody avidity in RA patients ($n = 71$) and controls ($n = 36$). Given is the relative avidity index (RAI) in %. Every bar represents either one patient (grey bars) or one control (black bars). The antibody avidity is high (> 50%, see dotted line) in any single sample of both groups. RAI is significantly higher though among the controls ($p = 0.0006$)

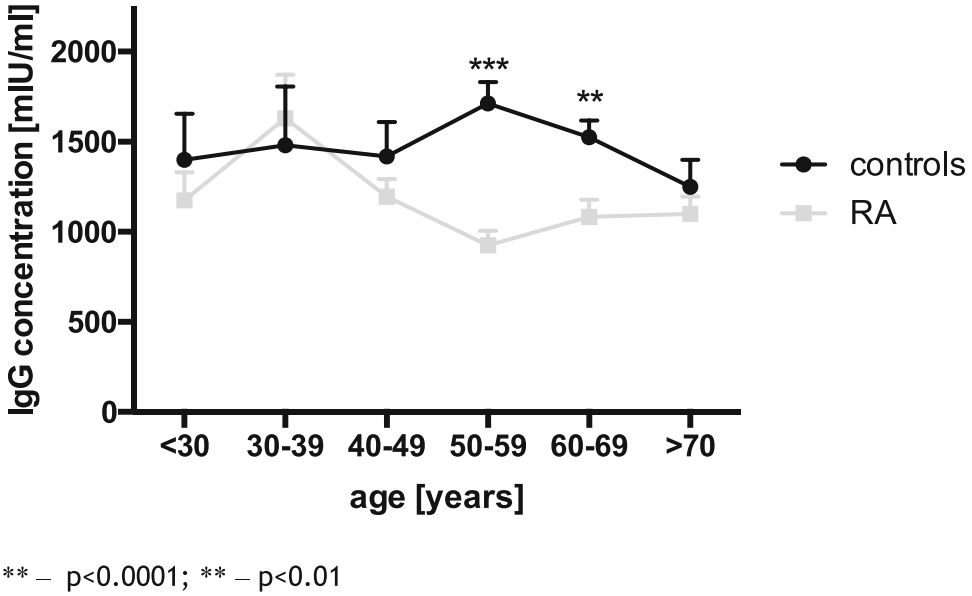

Fig. 3 Comparison of varicella zoster virus IgG antibody concentration between patients and controls after age stratification. Controls in the 6th and 7th decade have significantly higher titres compared with RA patients of the same age group. This difference diminishes in people beyond the age of 70. Given are means with standard error of the mean (SEM). ***$p < 0.0001$; **$p < 0.01$

(990 RA patients) reported comparable results for other common viruses such as Epstein-Barr virus (EBV). Measuring serum levels of EBV, cytomegalovirus and parvovirus B19 (B19) IgG antibodies, the investigation found significantly lower concentrations for both, EBV and B19, in RA patients compared with controls [45]. Unfortunately, no stratification by age has been made. Nevertheless, we speculate that these reduced levels might be the result of an impaired immune response and antibody production being caused by immunosenescence.

Looking into immune response to vaccinations, different outcomes for the efficacy of important vaccines in RA patients have been reported. Response to pneumococcal vaccine has been shown to be altered in one-third of the studied RA patients with no or only response to one of the seven pneumococcal serotypes used [46]. This finding was independent of the individual RA medication. Later investigations found a reduced humoral response to pneumococcal vaccination under MTX and rituximab but not TNF inhibitors [47, 48]. As for influenza, vaccinations in RA patients generally generates a good humoral response, but the overall rate of responders is lower in RA compared with healthy controls [49]. No association between medication and impaired response could be shown except for rituximab [50]. An investigation of the live attenuated HZ vaccine indeed showed a significant induction in VZV IgG antibodies in RA patients, but the cellular response was lower in RA patients than in patients with osteoarthritis who served as controls [51]. A significant immune response upon HZ vaccination was confirmed in another investigation, but a (healthy) non-RA control group was missing [26]. The rise in VZV-specific IgG levels, though, was comparable with known data from healthy individuals [26].

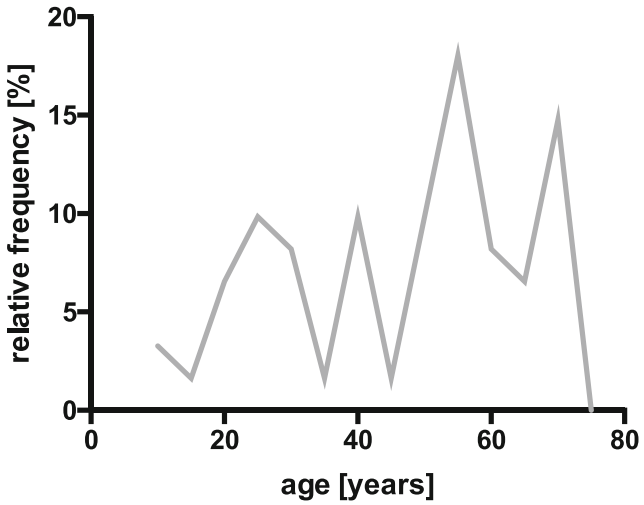

Fig. 4 Relative frequencies of HZ throughout life in the investigated RA patients. Note the increased frequency in later life. Mean age at HZ 46.3 ± 17.8 years, $n = 66$

Little is known about the long-term course of VZV antibodies. Moreover, the cited vaccination results cannot be compared with the natural humoral immunity after common childhood VZV infection we measured in the study at hand. The high affinity of the VZV IgG antibodies we found indicates a first contact with VZV dating back a long time ago. In addition, it cannot be excluded that humoral responses to distinct pathogens might vary in RA patients and could be particularly hampered in VZV.

Taking together, the difference in anti-VZV IgG levels we found in comparison with the controls might be explained by the impact of RA on the immune system of the older patient. That impact could multiply the aberrations the healthy old immune system after a childhood infection already went through. This assumption is supported by the finding that IgG levels in both groups match in early life (up to the fifth

decade) and again in late life (eighth decade). The pronounced differences in the two decades in between might reflect the prematurely aged immune system in RA. Our hypothesis is further encouraged by the high but significantly lower avidity for VZV IgG antibodies we measured in RA patients when being compared with the controls. This could be the result of an impaired B cell maturation process, caused by immunosenescence.

Limitations of our study are the rather high mean age of the patients, the long RA duration and the heterogeneous therapy regimes used.

Consistent with our findings of reduced antibody levels, the incidence of HZ in our RA patients is highest in both the sixth and seventh decade of life. The mean age at onset of HZ was 46.3 years which is considerably lower than the 59.4 years in the general population from a global perspective [52]. One possible confounder here is the rather small sample size of HZ cases, of course.

Conclusions

HZ is a significant problem in RA patients. Our results suggest a reduced humoral immunity in RA and patients might acquire HZ earlier in life than healthy people. One explanation for these findings is a prematurely aged immune system occurring in RA patients. This could cause reduced VZV IgG antibody concentrations in (older) RA patients. These findings contribute to the understanding of the increased HZ risk in people with RA. The available HZ vaccinations might therefore be proper instruments to close the antibody gap and reduce the HZ incidence in RA patients. Of particular interest could be the recently approved subunit vaccine in the context of immunosuppression. Further investigations are needed to substantiate this thesis.

Authors' contributions MK performed the statistical analysis, interpreted the data and drafted the manuscript. CB contributed to data interpretation and was involved in manuscript drafting. UL contributed important intellectual content to the manuscript and was responsible for antibody titre measurement. OS collected the data and was involved in the statistical analysis as well as manuscript preparation. All authors read and approved the final manuscript.

Compliance with ethical standards

Disclosure Dr. Krasselt declares no conflict of interest. Professor Baerwald received lecture fees from Merck, MSD, Mundipharma and Pfizer. Professor Liebert and Dr. Seifert declare no conflict of interest.

Ethical approval All procedures performed in this survey were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with the course of treatment for patients included.

Informed consent Informed consent was obtained from all individual participants included in the study.

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