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Altered cellular and humoral immunity to varicella-zoster virus in patients with autoimmune diseases

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2

ABSTRACT

Objective

Patients with autoimmune diseases such as systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (Wegener's) (GPA) have a 3–20-fold increased risk of herpes zoster compared to the general population. The aim of this study was to evaluate if susceptibility is due to decreased levels of cellular and/or humoral immunity to the varicella-zoster virus (VZV).

Methods

A cross-sectional study of VZV-specific immunity was performed in 38 SLE patients, 33 GPA patients, and 51 healthy controls. Levels of IgG and IgM antibodies to VZV were measured using an in-house glycoprotein enzyme-linked immunosorbent assay (ELISA). Cellular responses to VZV were determined by interferon-γ (IFNγ) enzyme-linked immunospot (ELISpot) assay and carboxyfluorescein succinimidyl ester (CFSE) dye dilution proliferation assay.

Results

Levels of IgG antibodies to VZV were increased in SLE patients as compared to healthy controls, but levels of IgM antibodies to VZV were not. Antibody levels in GPA patients did not differ significantly from levels in healthy controls. In response to stimulation with VZV, decreased numbers of IFNγ spot-forming cells were found among SLE patients (although not GPA patients) as compared to healthy controls. Proliferation of CD4+ T cells in response to stimulation with VZV was decreased in SLE patients but not GPA patients.

Conclusion

SLE patients have increased levels of IgG antibodies against VZV, while cellular immunity is decreased. In GPA patients, antibody levels as well as cellular responses to VZV were comparable to those in healthy controls. These data suggest that increased prevalence of herpes zoster in SLE patients is due to a poor cellular response. Vaccination strategies should aim to boost cellular immunity against VZV.

INTRODUCTION

Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV) [1,2]. It presents as an acute neurocutaneous disease characterized by severe pain and rash in a dermatomal distribution [3]. Postherpetic neuralgia, defined as pain lasting >90 days after onset of rash, is the most common complication of herpes zoster and is estimated to occur in 8–27% of patients [4-7]. Herpes zoster and postherpetic neuralgia can have a major impact on quality of life and productivity of a patient [4,5]. In particular, elderly individuals and individuals with compromised immune systems are at increased risk of developing herpes zoster and, accordingly, postherpetic neuralgia [3,6].

Systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (Wegener's) (GPA) both are autoimmune inflammatory rheumatic diseases. Patients with an autoimmune inflammatory rheumatic disease are at increased risk of infections including herpes zoster, as a result of the immunosuppressive effect of the disease and/or the use of immunomodulatory medication [8-10]. Herpes zoster is found in 15–91 cases per 1000 patient-years among SLE patients and 45 cases per 1000 patient-years among GPA patients [3,11,12]. Since the incidence of herpes zoster in developed countries is estimated at 3–5 per 1000 person-years in the general population [11], there is at least a 3–20-fold increase in risk among these patient groups.

In the US, a vaccine to prevent herpes zoster was licensed in 2006 for use in older immunocompetent adults [13]. It was proven to be safe and effective in preventing herpes zoster and postherpetic neuralgia in this group [6]. A prospective study of varicella vaccination in children and adolescents with SLE who were previously exposed to VZV showed a lower incidence of herpes zoster in the vaccinated SLE group, while the frequency of flares and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score [14] were similar [15]. Although the Advisory Committee on Immunization Practices (ACIP) stated in 2008 that the zoster vaccine should not be administered to persons with primary or acquired immunodeficiency [16], the short-term risk of herpes zoster did not appear to be increased in vaccinated patients. In fact, vaccination against herpes zoster was retrospectively associated with a lower incidence of herpes zoster in patients with inflammatory and autoimmune diseases, including patients receiving immunosuppressive medication [17,18].

Despite these promising results, it remains unclear if vaccination against herpes zoster is safe and effective in patients with an autoimmune inflammatory rheumatic disease [19]. The American College of Rheumatology (ACR) recommended vaccination against herpes zoster in patients with rheumatoid arthritis even during treatment with disease-modifying antirheumatic drugs (DMARDs) [20]. The European League Against Rheumatism (EULAR) stated that vaccination against herpes zoster may be considered in patients with an autoimmune inflammatory rheumatic disease, but only among those with less severe immunosuppression [8]. However, the level of evidence for both the ACR and EULAR recommendations was classified as C, the lowest level of evidence [20].

Before immunization against herpes zoster among patients with autoimmune inflammatory rheumatic diseases can be considered and to understand the increased susceptibility of these patients to herpes zoster, more knowledge regarding basic immunity against VZV is necessary. Therefore, we evaluated VZV-specific immunity to determine if the increased susceptibility to herpes zoster among patients with SLE and GPA is due to decreased levels of humoral and/or cell-mediated responses to VZV.

PATIENTS AND METHODS

Study population

Consecutive patients with SLE and GPA, most of them with quiescent disease, were recruited from the University Medical Centre Groningen outpatient clinic, and healthy controls were matched for age and sex. SLE patients eligible for the study fulfilled the ACR criteria for SLE [21]. GPA patients eligible for the study fulfilled the ACR criteria for GPA [22]. Pregnancy was an exclusion criterion for both patients and controls. Disease characteristics, including use of immunosuppressive medication, were recorded. The study was approved by the institutional medical ethics committee, and informed consent was obtained from all participants.

Serum was stored at –20°C, and peripheral blood mononuclear cells (PBMCs) were stored in liquid nitrogen until use. Only PBMCs with a minimum cell viability of >90% after thawing, as evaluated by trypan blue staining, were used in enzyme-linked immunospot (ELISpot) assays and proliferation assays.

Antibody response to VZV and diphtheria

For quantitative detection of IgG VZV antibodies, an in-house glycoprotein enzyme-linked immunosorbent assay (ELISA) was developed. VZV purified glycoproteins (EastCoastBio) were used as antigen, and a pooled serum with known levels of anti–glycoprotein VZV was used as standard. The in-house IgG glycoprotein ELISA was validated by comparing and statistically evaluating results of a quantitative Serion classic Varicella-Zoster Virus IgG ELISA (Institut Virion\Serion) and results of a VIDAS assay, the institution's standard diagnostic test for VZV serology.

VZV IgM antibodies were measured using the same methods. The in-house IgM glycoprotein ELISA was validated using a Serion classic VZV IgM ELISA (Institut Virion\Serion). Because there is evidence of polyclonal hypergammaglobulinemia in SLE patients [23], as a control, IgG antibody responses to diphtheria were measured using a commercial kit according to the instructions of the manufacturer (IBL International). Diphtheria was chosen because it is nonendemic in The Netherlands.

Interferon-γ (IFNγ) ELISpot assay

MultiScreen Filter Plates (Merck Millipore) were coated overnight with 50 µl of anti-human IFNγ (Mabtech) at 4°C. Frozen PBMCs were thawed and incubated overnight in

culture medium (RPMI 1640 with 10% fetal calf serum [FCS]) to allow the cells to rest. Subsequently, 2×10^5 PBMCs per well were added to 200 µl of medium and stimulated with 1.5 µl of ultraviolet (UV)–inactivated varicella vaccine (Provarivax; Sanofi Pasteur) in duplicate. PBMCs stimulated with concanavalin A (5 µg/ml) were used as a positive control, and PBMCs in culture medium alone were used (in duplicate) as a negative control. After 48 hours, plates were washed, and 50 µl of 1 µg/ml biotinylated anti-human IFNγ was added per well. Subsequently, 50 µl of streptavidin–alkaline phosphatase (1:1,000; Mabtech) was added. Plates were stained with BCIP/ nitroblue tetrazolium substrate. After washing and drying, spots were counted using an automated reader (ELISpot Reader; A.EL.VIS). The mean number of spots in the negative control sample was subtracted from the mean number of spots in the VZV-stimulated wells. Results are referred to as the number of IFNγ spot-forming cells.

T cell proliferation assay

Thawed PBMCs were stained with carboxyfluorescein succinimidyl ester (CFSE; Molecular Probes/LifeTechnologies) at a final concentration of 6.25 µg/ml and incubated for 10 minutes in the dark at 37°C. The reaction was stopped by adding RPMI plus 10% FCS. Next, 96-well U-bottomed plates (Greiner Bio-One) were filled with 1.0×10^5 CFSE-stained PBMCs, which were stimulated with 1.5 µl UV-inactivated varicella vaccine. As a positive control, cells were stimulated with CD3-specific and CD28-specific antibodies (obtained from a hybridoma culture supernatant). Cells were incubated for 7 days at 37°C in an atmosphere containing 5% CO_2. Subsequently, cells were harvested and 5 µl of allophycocyanin-conjugated mouse anti-human CD3 and 5 µl of peridinin chlorophyll protein–conjugated mouse anti-human CD8 (both from BD PharMingen/BD Biosciences) were added to the tubes. Cells were washed and analyzed on a Calibur flow cytometer using CellQuest Pro Software (both from BD Biosciences).

Using ModFit software (Verity Software House), CD4+ and CD8+ T cell populations were gated as CD3+CD8– and CD3+CD8+, respectively. Proliferation indices (sum of the cells in all generations divided by the calculated number of original parent cells) were determined.

Statistical analysis

Data were analyzed using SPSS 20 (IBM). For correlations, Spearman's rho was used. Analysis of age, which was normally distributed, was performed using Student's t-test. For analysis of all other variables, Mann-Whitney U test and Fisher's exact test were used as appropriate.

Levels of antibodies against VZV and proliferation indices of the positive control samples were logarithmically transformed, and ELISpot data (number of IFNγ spot-forming cells in response to VZV) were square root transformed, in order to use linear regression to assess the influence of different immunosuppressive drugs and the SLEDAI score on humoral and cellular immunity outcome measures.

To test the influence of immunosuppressive medication in GPA patients, outcome variables were compared between GPA patients who were taking immunosuppressive medications and GPA patients who were not taking these drugs. P values less than 0.05 (2-sided) were considered significant.

RESULTS

Characteristics of the patients and healthy controls

Characteristics of the patients and healthy controls are shown in Table 1. There were no significant differences in age and sex between the patient groups and the healthy control group.

Validation of the in-house glycoprotein ELISA

Validation of the in-house IgG glycoprotein ELISA was performed by comparing results of 127 samples with the results of both a Serion ELISA and a Vidas assay. The results of the in-house IgG glycoprotein ELISA showed a highly significant correlation with the results of the Serion ELISA, which is also glycoprotein based ($\rho = 0.79$, $P < 0.0001$). In addition, a strongly significant correlation was shown between results of the in-house IgG glycoprotein ELISA and results of the Vidas assay ($\rho = 0.68$, $P < 0.0001$).

Table 1. Characteristics of patients and healthy controls

	HC (n=51)	SLE (n=38)	GPA (n=33)
Sex, males, n (%)	16 (31)	9 (24)	12 (36)
Age, mean (± SD), in years	45.1 (10.4)	43.3 (10.3)	48.0 (8.9)
Patients not using immunosuppressives, n (%)	NA	5 (13)	18 (55)
Prednisone, n (%)	NA	16 (42)	11 (33)
In users, median (range) mg/day[a]		5,0 (2,5-10)	5 (2,5-10)
Azathioprine, n (%)	NA	13 (34)	14 (42)
In users, median (range) mg/day[a]		125 (50-200)	87.5 (14.3-150)
Hydroxychloroquine, n (%)	NA	22 (58)	NA
In users, median (range) mg/day[a]		400 (200-800)	
Other immunosuppressive drugs, n (%)	NA	5 (13)[b]	3 (9)[c]
Disease duration, (± SD), in months	NA	111.8 (82.1)	117.2 (91.4)
SLEDAI/BVAS, median (range)	NA	2 (0-7)[d]	0 (0-6)[e]

NA=not applicable; HC=healthy controls; SLE=systemic lupus erythematosus; GPA=granulomatosis with polyangiitis; SD=standard deviation; SLEDAI=systemic lupus erythematosus disease activity index; BVAS=Birmingham vasculitis activity score.
[a] Among patients receiving the treatment
[b] Five patients received methotrexate (15 mg/week in 4 patients 7,5 mg/week in 1 patient).
[c] One patient received mycophenolate mofetil (2 g/day), 1 patient received cyclosporine (150 mg/day), and 1 patient received prednisolone eye drops and prednisolone eye ointment,
[d] Two patients had a SLEDAI score of >4.
[e] One patient had a BVAS of >0. This patient had a score of 6.

VZV and diphtheria antibody levels

SLE patients had significantly increased IgG VZV antibody levels (median 1300 IU/ml [range 210–10,950]) compared to healthy controls (median 670 IU/ml [range 70–6,340]), as measured with the in-house glycoprotein ELISA (P = 0.0051). Among GPA patients, VZV antibody levels (median 750 IU/ml [range 20–11,540]) did not differ significantly from VZV antibody levels in healthy controls (P = 0.4309) (Figure 1A). In contrast to IgG VZV antibody levels, diphtheria antibody levels in both SLE and GPA patients were significantly lower than in healthy controls (P = 0.0004 and P = 0.0288, respectively) (Figure 1B). No significant differences were found in IgM VZV antibody levels between patients and controls (Figure 1C).

IFNγ ELISpot

The median number of IFNγ spot-forming cells per 2×10^5 PBMCs in response to VZV stimulation was 19.5 (range 0–74) among healthy controls, 8.5 (range 0–61) among SLE patients, and 12.8 (range 0–66.8) among GPA patients. The number of IFNγ spot-forming cells in response to VZV was significantly lower among SLE patients as compared to healthy controls (P = 0.033). No significant difference was found between GPA patients and healthy controls (Figure 2).

CD4+ T cell proliferation

CD4+ T cell proliferation indices in the positive control samples from the SLE patients (median 3.18 [range 1.22–10.84]) and positive control samples from the GPA patients (median 3.40 [range 1.35–12.00]) were lower than proliferation indices in the positive control samples from the healthy control subjects (median 4.19 [range 1.32–9.65]) (both P = 0.023) (Figure 3A). The median proliferation index in the VZV-stimulated CD4+ T cells was 1.07 (range 1.00–2.86) in SLE patients, 1.08 (range 1.00–3.84) in GPA patients, and 1.17 (range 1.00–4.36) in healthy controls. The proliferation index in VZV-stimulated CD4+ T cells from SLE patients was significantly lower than that in cells from healthy controls (P = 0.034), whereas the decrease in the index in cells from GPA patients was not significant (Figure 3B).

CD8+ T cell proliferation

The CD8+ T cell proliferation index in the positive control samples from SLE patients (median 2.64 [range 1.27–5.54]) was significantly lower than that in positive control samples from the healthy control subjects (median 3.97 [range 1.4–7.78]) (P = 0.002). Among GPA patients (median 2.79 [range 1.53–11.18]), there was a trend toward a lower proliferation index compared to healthy controls (P = 0.063) (Figure 3C).

There was no statistically significant difference between the proliferation index in VZV-stimulated CD8+ T cells from either patient group and cells from the healthy control group. However, a trend toward a lower proliferation index among SLE patients versus
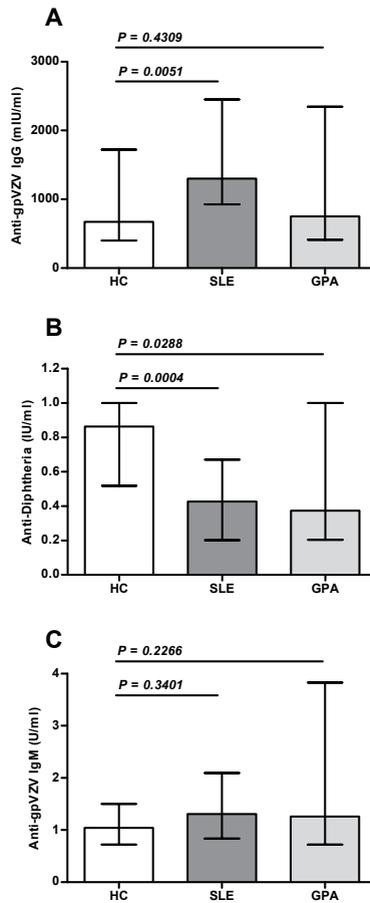
Figure 1. Levels of antibodies against varicella-zoster virus (VZV) (A and C) and diphtheria (B) among 38 systemic lupus erythematosus (SLE) patients, 33 granulomatosis with polyangiitis (Wegener's) (GPA) patients, and 51 matched healthy control (HC) subjects. Bars show the median and interquartile range. gp = glycoprotein.

healthy controls was observed (P = 0.071). The median proliferation index was 1.05 (range 1.00–2.02) in SLE patients, 1.13 (range 1.00–3.15) in healthy controls, and 1.11 (range 1.00–2.79) in GPA patients (Figure 3D).

Influence of immunosuppressive medication

Among SLE patients, no influence of immunosuppressive medication on antibody levels was evident (data not shown). A trend toward a higher anti-VZV antibody level was found among GPA patients taking immunosuppressive medication (n = 15) as compared to GPA patients who were not taking immunosuppressive medication (n = 16) (P = 0.086). For both ELISpot and proliferation tests, no influence of immunosuppressive medication or disease activity on outcomes could be found in either patient group (data not shown).
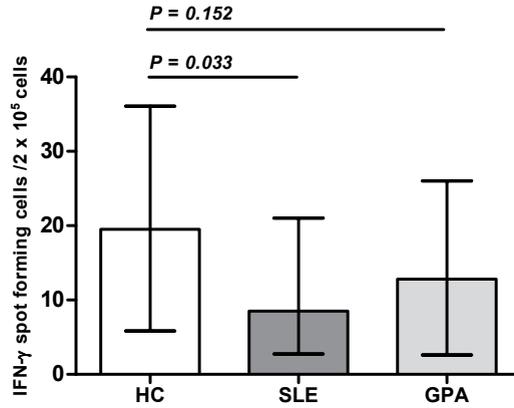
Figure 2. Levels of interferon-γ (IFNγ) spot-forming cells in response to varicella-zoster virus (VZV) stimulation. Numbers of IFNγ spot-forming cells per 2×10^5 peripheral blood mononuclear cells in systemic lupus erythematosus (SLE) patients (n = 34), granulomatosis with polyangiitis (Wegener's) (GPA) patients (n = 28), and healthy control (HC) subjects (n = 45) in response to VZV stimulation were determined. Bars show the median and interquartile range.
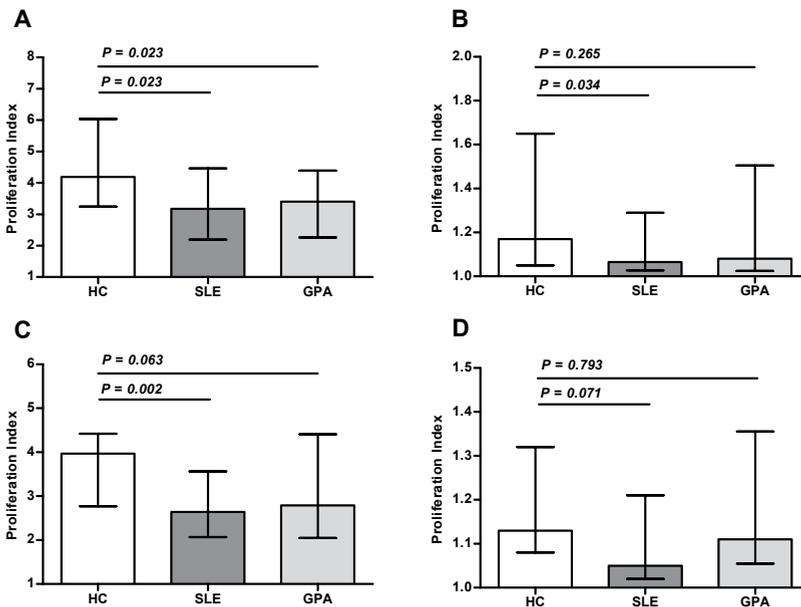

Figure 3. Proliferation indices of CD4+ and CD8+ T cells in response to CD3/CD28 and varicella-zoster virus (VZV) stimulation. Proliferation of CD4+ T cells in response to CD3 and CD28 stimulation (positive control) (A) and in response to VZV stimulation (B) in samples from systemic lupus erythematosus (SLE) patients (n = 38), granulomatosis with polyangiitis (Wegener's) (GPA) patients (n = 33), and healthy control (HC) subjects (n = 51) is shown. CD8+ T cell proliferation in response to CD3 and CD28 stimulation (positive control) (C) and in response to VZV stimulation (D) in SLE patients (n = 23), GPA patients (n = 25), and healthy control subjects (n = 35) is also shown. Bars show the median and interquartile range.

DISCUSSION

In this study, antibody levels and cellular immune responses to VZV were evaluated in SLE patients and GPA patients and compared to those in healthy controls. We found that IgG VZV antibody levels were higher among SLE patients than among healthy controls. In contrast, we demonstrated decreased cellular immune responses in general and to VZV in particular among SLE patients as compared to healthy controls. GPA patients also were found to have generally decreased cellular immune responses, although there were no differences in antibody levels and cellular immune responses to VZV compared to healthy controls. No significant differences were found in IgM antibody levels between patients and controls. Furthermore, no influence of immunosuppressive medication could be determined in either patient group.

Many patients with SLE, especially those with active disease, have increased numbers of antibody-forming cells of the IgG class [24]. The observation that SLE patients have increased levels of antibodies against VZV has been previously reported [25]. In addition, increased levels of antibodies to other viruses have been found among SLE patients [26,27]. Because we observed decreased levels of diphtheria IgG antibodies in both patient groups, we believe that polyclonal hypergammaglobulinemia is not a satisfactory explanation of this phenomenon. Data on herpes zoster episodes among the patients and controls who were included in this study were not available, so whether prior herpes zoster episodes are causative could not be tested. Nagasawa et al reported that SLE patients without a history of herpes zoster had increased antibody levels as well [25]. Since stress can induce subclinical virus reactivation in the absence of clinical disease [28-30], we speculate that SLE flares may give rise to subclinical virus reactivations leading to increased VZV antibody levels. Further research is needed to clarify this.

CD4+ and CD8+ T cell responses to CD3-specific and CD28-specific antibodies (i.e., polyclonal activation) were decreased in both patient groups as compared to controls. This seems to indicate that T cells in these patient groups have a lower capacity for proliferating. Since no influence of immunosuppressive medication was found, this could be intrinsic to these diseases. The finding of a lower T cell proliferating capacity among SLE and GPA patients seems to be consistent with the higher prevalence of infections in patients with autoimmune inflammatory rheumatic diseases. Infections are a common cause of morbidity and mortality in these patients. The reason for this has not been fully elucidated, but the immune dysregulation that is characteristic of these diseases is thought to contribute at least in part to higher vulnerability [10]. The generally lower capacity for T cell proliferation could mean that the observed lower response to VZV among SLE patients is not VZV-specific, but a reflection of the lower proliferating capacity of T cells in SLE patients in general. However, this is still compatible with the hypothesis that the increased frequency of herpes zoster in these patients is caused by a decreased cellular immune response.

In this study, we found no influence of immunosuppressive medication on immunity to VZV. Furthermore, no influence of disease activity on cellular immunity could

be determined. It is possible that this is due to the large proportion of patients with quiescent disease. Medication use in both patient groups was restricted to a small number of agents and limited dosages. In a retrospective study by Sayeeda et al. [31], SLE patients with herpes zoster were more likely to be receiving cyclophosphamide, intravenous methylprednisolone pulse therapy, or mycophenolate mofetil than were SLE patients without herpes zoster. These types of immunosuppressive medication were not used by patients participating in the present study. Inclusion of patients who were taking medication that resulted in stronger immunosuppression would possibly have yielded an even larger difference between SLE patients and healthy control subjects with regard to immunity to VZV.

A limitation of this study is that results based upon our group of GPA patients may yield a distorted image of immunity against VZV among these patients. Patients in our GPA group were relatively young, and the group included a higher percentage of women than is typical of GPA. Furthermore, our numbers are relatively small. Therefore, a decrease in cell-mediated response to VZV among GPA patients, which might explain the increased incidence of herpes zoster in these patients, could have been missed.

Despite the limitations, this study has contributed to our knowledge about humoral and cellular immune responses to VZV in patients with autoimmune diseases; this information is necessary before considering herpes zoster vaccination in these patients. Increased IgG VZV antibody levels were found in SLE patients, while cellular immunity against VZV was found to be decreased in these patients compared to healthy controls. Since SLE patients are known to have an increased risk of herpes zoster [3,11,32,33], we can conclude that vaccination strategies in these patients should aim to boost cellular immunity.

2

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