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Received: October 4, 2023.

Accepted: December 7, 2023.

Citation: Corrado Girmenia, Fabio Ciceri, Paolo Corradini, Antonio Cuneo, Fortunato D'Ancona, Pellegrino Musto, Antonio Maria Risitano, Maria Teresa Voso, Adriano Venditti, and Giovanni Barosi. Towards a personalized preventive strategy of Herpes zoster infection in patients with hematologic diseases or hematopoietic stem cell transplant recipients: a position paper from an *ad hoc* Italian expert panel. *Haematologica*. 2023 Dec 14. doi: 10.3324/haematol.2023.284417 [Epub ahead of print]

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Running head: Herpes zoster prevention in hematologic diseases

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Contributions: CG and GB coordinated the expert panel. All authors contributed to the literature review. CG and GB wrote the manuscript. All authors actively participated to the group discussion

Disclosures: no disclosure for all authors

Funding: this project was not supported by any funding

Abstract

The identification of patients at high risk of herpes zoster (HZ) requiring a prevention strategy with antiviral prophylaxis and anti-HZ vaccine is a clinically relevant issue in patients with immunological impairment. Absence of trials comparing vaccination to pharmacological prophylaxis or defining their sequential use makes the optimal prevention strategy uncertain. This article presents the results of group discussion among an *ad hoc* constituted panel of experts aimed to review the literature regarding antiviral prophylaxis and vaccine efficacy and safety in populations with malignant and non-malignant hematological diseases, and submitted to hematopoietic stem cell transplantation. The panel used the consensus methodology and proposed solutions for prevention strategy producing advice for the management of the most relevant unmet clinical needs. Such a comprehensive overview aims to support at the practice of HZ pharmacological and vaccine prevention and informing the design and the need of implementation of new studies in the field.

Key words: Herpes zoster, prophylaxis, vaccination, hematological diseases

Introduction

Herpes zoster (HZ) is a painful, infectious, cutaneous eruption, usually involving one to three adjacent dermatomes, resulting from reactivation of latent varicella-zoster virus (VZV). Although mortality is low, HZ causes high morbidity, occasionally threatening manifestations (e.g. encephalitis, hepatitis) and a high societal cost mainly related to complications such as postherpetic neuralgia ¹. Various hematologic diseases (HD) and hematopoietic stem cell transplant (HSCT) are historically considered at high risk of HZ due to immunological impairment ².

Strategies to prevent symptomatic reactivation of VZV include risk-adapted pharmacological antiviral prophylaxis (AVP), and vaccination. Now, two different types of HZ vaccines have been approved worldwide and in Europe: a 1-dose live-attenuated vaccine not indicated in subjects with impaired immune conditions and an adjuvanted recombinant vaccine (aRZV) that was recommended for immunocompetent adults aged ≥ 50 years and for immunocompromised adults aged ≥ 18 years at increased risk of HZ ³⁻⁹. The aRZV vaccination schedule consists of two doses of 0.5 mL each: an initial dose followed by a second dose between 2 and 6 months after the first dose. For subjects who are or might become immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose ³.

However, absence of trials comparing vaccination to pharmacological prophylaxis or defining their sequential use makes the overall prevention strategy in high-risk patients uncertain. Indeed, recommendations issued in 2022 by the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) ¹⁰ and by the National Comprehensive Cancer Network (NCCN) ¹¹ advise to use AVP in certain diseases and conditions and generically recommend vaccination with aRZV in hematologic and HSCT patients without going into details on strategies for concomitant/sequential use of vaccine and AVP (supplementary Table 1).

In this work, a panel of experts *ad hoc* constituted in view of their expertise in the management of specific hematologic diseases or conditions and of their experience in consensus conference and guidelines projects tried to work out a position paper aimed at reviewing the current literature on vaccines efficacy and safety and AVP in immunocompromised populations with malignant and non-malignant HD submitted to chemotherapy and/or immune-suppressive therapy and autologous or allogeneic HSCT. The aim is to identify, in this setting of patients, critical unmet clinical needs in the

prevention of HZ infections and to identify the optimal strategy for prevention, by exploiting the consensus methodology approach.

Methods

Two chairmen (CG and GB) appointed an expert panel (EP) of 9 members, selected as opinion leaders of the following hematologic diseases or conditions: myeloproliferative diseases (GB, MTV, AV), lymphoproliferative diseases (PC, PM, AC), non-oncologic hematological diseases (AMR), stem cell transplant (FC, AMR) and infections in hematology (CG). In addition, a member of the panel with expertise in clinical epidemiology (GB) assured the methodological congruence of the process and an infectious diseases and epidemiology specialist member of the Italian National Institute of Health (Istituto Superiore di Sanità) (FD) dealt with the vaccine legislative and regulatory aspects.

A consensus-based project requires that the methodology of group discussion (questionnaires and nominal group technique) is applied. This means that the generated statements, advises and recommendations are not primarily evidence-based (they do not derive from a systematic review and grading of the evidence) because of the limited number of interventional, clinical studies dealing with HZ prevention in hematologic populations.

During an initial meeting, in April 2022, the outline of the project was discussed and the topics forming the structure of the present document were decided. The EP agreed on the major relevant issues by generating and rank-ordering clinical key-questions, using the criterion of clinical relevance, through a Delphi process ¹². In a further phase of the process, the chairmen reviewed evidence about the selected key questions by PubMed searches of English-language literature (from January 2012 to June 2023). Afterwards, panelists drafted statements that addressed one identified relevant issue, while the remaining panelists scored their agreement with those statements and provided suggestions for modification. The EP convened in a consensus meeting where final proposals and recommendations were prepared; in a round-robin fashion, participants were asked to comment their disagreements with the proposed issues and then to vote for a final statement. For consensus we required 80% votes in favour

Results

A narrative literature review on epidemiology, AVP and vaccination of HZ in HD and HSCT published since 2012 is detailed in supplementary Table 2 and supplementary Table 3. The following paragraphs describe a synthesis of the most significant data on the epidemiology and strategies for HZ prevention in various categories of haematological patients. Proposals and/or recommendations of the EP on the prevention of HZ in patients with various hematologic diseases and conditions are summarized in table 1. All the final proposals and recommendations received >80% consensus.

Herpes zoster risk and prevention in myeloid disorders

Data on incidence of HZ infection specifically in myeloid disorders were derived from three retrospective observational studies in acute promyelocytic leukemia (APL) ¹³⁻¹⁵, two others in chronic myeloproliferative neoplasm (MPNs) and one in myelodysplastic syndromes (MDS) ¹⁶⁻¹⁸. APL patients treated with arsenic trioxide are at high risk of HZ if not receiving AVP; indeed, the incidence ranges from 11.6% to 45.7% within the first 6 months of therapy ¹³⁻¹⁵. The risk is particularly high for older patients and for those with a previous history of HZ. AVP was shown to significantly reduce the risk of HZ, or delay its onset ^{14,15}.

In patients with MPN the treatment with ruxolitinib was associated with an increased risk of HZ, which ranges from 3.5 to 6.9 cases per 100 patient-years (PY), ten times higher than in patients not treated with ruxolitinib ^{16,17}. No information was found on AVP efficacy. Compared to an age matched immunocompetent population, patients with MDS have only a modest increased risk of HZ infection (odds ratio, 1.31) ¹⁸.

As far as we know about the protective effect of aRZV, Dagneu et al. ¹⁹ reported 80.4% and 73.7% of humoral and cellular vaccine response, respectively, in an adult immunocompromised population, including patients with AML and MDS (56 patients in the vaccine group). No patient with a MPN who received aRZV developed HZ infection.

Herpes zoster risk and prevention in lymphoproliferative disorders

Lymphoma and myeloma are associated with significantly increased HZ odds, whose magnitude varies widely ²⁰⁻³³. The association was the most significant within 2 years from diagnosis ²⁰.

In patients with non-Hodgkin (NHL) and Hodgkin lymphoma (HL) receiving chemotherapy without AVP the cumulative incidence of herpesvirus infections (93% represented by VZV disease) was 20.2% at 5 years from chemotherapy start, being the high cumulative dose of corticosteroids and the history of neutropenic fever independent

risk factors, in multivariate analysis ²¹. AVP was preferentially effective during the first year of treatment since reactivations were reported up to 51.3 months from initial immunotherapy, particularly in patients treated with rituximab plus bendamustine and in patients with rituximab or obinutuzumab maintenance.

Rituximab-containing regimens were not associated with a high overall incidence density of HZ, although the addition of rituximab to conventional chemotherapy increased the short-term risk of HZ with adjusted odd ratios of 1.38 and 1.37 during the 1-year and 2-year follow-up periods, respectively ²².

In patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib the incidence of HZ was 5% during a long-term follow-up while 2.9 cases per 1000 PY were documented in those treated with various regimens in the pre-ibrutinib era ^{24,25}.

In patients with refractory or relapsed high-grade B-cell lymphoma treated with axicabtagene ciloleucel, a CD19 targeted CAR-T, 16% had HZ skin infection ²⁶. The HZ incidence rate was 14.8% for the entire cohort and 25.8% for the long-term survival cohort. The median time from CD19 targeted CAR-T infusion to the onset of HZ was 15.5 months (range, 8–20 months) and all the HZ infections happened within the first two years. Introducing AVP (200 mg oral acyclovir, three times a day) effectively reduced the incidence of HZ after CAR-T treatment.

The analysis of a UK primary care database showed that multiple myeloma (MM) is associated with the greatest increase in odds (adjusted OR = 4.24) compared to a reference group of subjects without a malignancy diagnosis ²⁰. In patients receiving bortezomib with no AVP, infection occurred after cycle 1 in 32%, after cycle 2 in 23%, after cycle 3 in 23%, after cycle 4 in 13%, and less than 10% in the following cycles. In MM patients who received various schedules of AVP (acyclovir 200 mg/day to 400 mg twice daily or valacyclovir 500 mg/day) no or less than 1% instances of infection were observed for the whole duration of bortezomib treatment and in the follow-up. ²⁷⁻³¹. Patients in whom AVP was interrupted before the end of cancer treatment had a higher risk of developing HZ infection, compared to those who continued AVP (adjusted HR 3.09) ³². The immunogenicity of aRZV vaccination in HM was evaluated in two randomized clinical trials ^{8,34}. The first study ⁸ demonstrated that aRZV elicited a robust humoral and cellular response when administered during and up to 6 months after chemotherapy. Overall, 80.4% of 148 participants with HM other than B-NHL or CLL had a humoral vaccine response at month 2, compared with 0.8% participants in the placebo group. Conversely, the humoral vaccine response was 45% in B-NHL and 22% in CLL patients. Humoral and

cell mediated immune responses persisted above baseline until month 13 in all strata. The frequency of humoral vaccine response was higher among those who were vaccinated after the end of immunosuppressive therapy as compared to those who were vaccinated while still receiving immunosuppressive treatment. One month after the second dose injection, the proportion of participants with a vaccine response in terms of a cell mediated immune response was high (83,7%) in all diseases (including B-NHL and CLL) and it was durable since still measurable after 12 months . A post-hoc analysis revealed that the incidence of HZ was 8.5 per 1000 person-years in the vaccine group and 66.2 per 1000 person-years in the placebo group, resulting in 87.2% efficacy against HZ, including patients with B-NHL and CLL.

Zent et al³⁴ analyzed the vaccine response in patients aged ≥ 50 years and on treatment with a Bruton tyrosine kinase inhibitor (BTKi) because of a diagnosis of CLL or in patients with lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. A certain proportion of patients with CLL or lymphoplasmacytic lymphoma on BTKi therapy prompted a response to aRZV while on BTKi therapy. Twenty-four of 32 patients (75%) had a humoral response to vaccination and 21 of these 24 (87.5%) also mounted a T-cell response. Only 4 (50%) among 8 subjects with no humoral immune response exhibited a T-cell response. A following analysis of the same study evaluated humoral response 24 months (± 3 months) after vaccination³⁵. Among patients responding at 4 weeks from vaccination, 56.5% had a sustained humoral response 24 months after vaccination. The overall humoral response rate for all patients at 24 months compared to prevaccination was 41.9%. There was no significant association between prior rituximab and achieving humoral response. Cellular response was achieved in 81.3% of patients 4 weeks after vaccination and continued to be sustained in 65.4% of patients 24 months after vaccination. The overall cellular response rate in all patients at 24 months was 54.8%.

Real life data on the efficacy and immunogenicity of aRZV in malignant HD are summarized in supplementary table 3. These studies did not provide information on the timing of the vaccination in the course of the disease and on any AVP.

Mutchar al.³⁶ analysed the effects of two doses of aRZV given at a 2-month interval, in individuals with untreated or BTKi-treated CLL. A 3-months antibody response was seen in 45% of participants, which was significantly lower compared to sex and age-matched healthy controls (63%, $p=0.03$). The antibody response did not significantly differ between untreated and BTKi-treated CLL (51% vs. 36%, respectively, $p=0.23$). The CD4+ T-cell response to vaccination was significantly lower in study participants compared to controls

(54% vs. 96%, $p < 0.001$), mainly due to the weaker elicitation among BTKi-treated patients compared to untreated CLL (32% vs. 73%, $p = 0.008$).

In 2 open-label, single-arm clinical trials, Pleyer et al^{37,38} measured the effect of BTKi's on response recall to aRZV in CLL patients who were treatment naïve (TN) or on BTKi cohort. The response rate to aRZV did not differ significantly between the BTKi (41.5%) and TN cohorts (59.1%). The vaccine antibody response rate in CLL patients was significantly higher in the TN cohort (76.8%) compared with patients receiving a BTKi (40%). The cellular response rate was also significantly higher in the TN cohort (70%) compared with the BTKi group (41.3%).

In Multiple Myeloma (MM) patients, Sweiss et al.³⁹ documented that overall rate of seropositivity increased after 1 (87.9%; $p = 0.0002$) and 2 (92.6%; $p = 0.0001$) vaccine doses. Seroconversion from a baseline negative to positive test was observed in 76.2% and 95.8% patients after 1 and 2 doses, respectively.

Herpes zoster risk and prevention in HSCT

HZ incidence ranges from 8% to 25% in autologous HSCT^{40,41}, and 13% to 28% in allogeneic HSCT recipients^{42,43}. Indeed, AVP is commonly administered to patients after HSCT in order to prevent HZ-associated infections. According to literature data the incidence of HZ reactivation appears similar in the two transplant procedures, however it should be underlined that the above data refer to heterogeneous populations with different transplant risks and the epidemiological data are affected by the use of AVP. In general, after allogeneic HSCT the risk is particularly high and prolonged over time even for years after the transplant. In 2017 the available literature was systematically reviewed to determine the optimal duration of AVP as a prevention of HZ in allogeneic and autologous HSCT recipients⁴⁴. Six observational studies were analyzed comprising a total of 3420 patients. In all HSCT recipients, the overall incidence of HZ in the AVP group and the control group was 7.8% and 25.6%, respectively, with a pooled RR of 0.31. The incidence of HZ in the prophylaxis subgroup that was given for at least 1 year and the incidence in the subgroup who received prophylaxis for less than 1 year were 2.1% and 15.4%, respectively, with a pooled RR of 0.23. These data demonstrate that AVP can significantly reduce HZ in HSCT recipients and that prophylaxis should be given for at least 1 year.

The more recent literature on anti HZ prophylaxis analysed the effect of transplant type, and the optimal antiviral therapy and dose⁴⁵⁻⁵⁶. In a study of Kawamura et al.⁴⁷ in patients who underwent autologous HSCT the first consecutive 30 patients received oral

acyclovir at 1000 mg/day until engraftment, whereas the following 69 patients received oral acyclovir at 200 mg/day. After engraftment, acyclovir was continued at 200 mg/day at the discretion of the attending physicians in both groups. Patients were next divided into three groups according to the timing at which acyclovir prophylaxis was stopped after transplant (at engraftment, between engraftment and 1 year after transplant, and later than 1 year). The cumulative incidence of HZ was 25.8, 7.7, and 0.0 % at 1 year, respectively. No difference was observed in the incidence of HZ according to AVP dosing suggesting that low-dose acyclovir prophylaxis may be effective for preventing HZ after autologous HSCT. Zhang et al.⁴⁹ documented that duration of AVP and HZ incidence were inversely correlated. Compared with patients who were on AVP for 1-89 days, those with AVP duration of 180-269 days [hazard ratio (HR) = 0.576, $p = 0.019$], 270-359 days (HR = 0.594, $p = 0.023$), and ≥ 360 days (HR = 0.309, $p < 0.001$) had a significantly lower risk of HZ. Abbasov et al.⁵¹ documented that no patient with low dose acyclovir prophylaxis (400 mg per day) developed HZ in the first year after autologous HSCT while 2.8% of patients developed HZ in the second year after AVP discontinuation.

The impact of longer-term AVP on HZ incidence after cord blood transplantation (CBT) was studied by Xue et al.⁵². HZ occurred in 44 patients (19%) at a median of 23.6 months. The cumulative incidence of HZ by 1 year after CBT was 1.8% but increased to 26% by 5 years. A high incidence of HZ after CBT despite AVP for > 1 year was found. Based on these findings, the authors suggested longer duration of prophylaxis for HZ after CBT.

A randomized observer-blind phase III trial study analyzed the role of anti HZ vaccination in autologous HSCT populations⁷. 1846 adult autologous HSCT recipients were randomized to receive a first dose of either aRZV or placebo 50–70 days post-transplant, followed by the second dose at 1–2 months later. Compared to placebo group, aRZV was associated to 68.2% efficacy in preventing HZ infection and 89.3% in minimizing the incidence of postherpetic neuralgia. Stadtmauer et al. (57) provided an in-depth description of humoral and cell-mediated immune responses by age or underlying disease as well as efficacy by underlying disease of the aRZV in the above study. Despite the lower anti-gE antibody in B-NHL patients, CD4 T-cell frequencies were similar between B-NHL and other underlying diseases. Vaccine efficacy against HZ ranged between 42.5% and 82.5% across underlying diseases and was statistically significant in B-NHL and MM patients.

Two real life studies on the efficacy of aRZV were published in allogeneic HSCT population^{58,59}. In a single-center prospective observational cohort study, safety and reactogenicity of aRZV, as well as incidence of graft-versus-host disease (GVHD) and confirmed cases of HZ after vaccination were assessed in 158 volunteer allogeneic HSCT recipients⁵⁸. The cumulative incidence of GVHD in the peri-vaccination period was no different than in historical controls. There were 4 cases of HZ in the total vaccinated cohort who received at least 1 vaccine dose (2.5%) and 3 cases in the modified total vaccinated cohort who received 2 vaccine doses (28.3/1000 person-years). In a study including 79 allogeneic HSCT recipients who received aRZV, cellular immunity against various VZV antigens was analyzed by interferon-gamma ELISpot and patients with versus without previous shingles were compared⁵⁹. Multivariate analysis showed that previous shingles and sex both impacts significantly on VZV immunity being responses against the glycoprotein E significantly higher in males than females.

In conclusion, two aRZV doses, administered 50–70 days post-transplant, induced robust and durable humoral and cellular mediated immune responses irrespective of age and underlying diseases, in adults who had undergone autologous HSCT. Glycoprotein E-specific CD4 T-cell responses were polyfunctional, and the proportion of polyfunctional CD4 T cells expanded in the 2 years following vaccination. In a post-hoc analysis, it was demonstrated that, in each underlying disease, the efficacy against HZ reflected that observed in the overall population and that such an efficacy was robust also in patients with B-NHL, despite the weaker humoral immune response. Conversely, in allogeneic HSCT population the efficacy data of aRZV are less evident and future clinical trials are needed to better investigate the rate and timing of aRZV immunogenicity in this population.

Herpes zoster risk and prevention in immune-mediated non malignant hematologic diseases

Few data are available on the risk of HZ reactivation in patients with immune mediated non-malignant hematological disease, like autoimmune hemolytic anemia and immune thrombocytopenia. Recent studies have shown that the prolonged use of corticosteroids in the geriatric population (>65 year old) can increase the risk of developing HZ (threefold increase of odds) due to its immunosuppressing effects⁶⁰. There is a duration-related effect between oral corticosteroids administration and the risk of HZ.

Regarding aplastic anemia, the risk of HZ in subjects not treated with HSCT has been generically reported without mentioning specific evidence-based information. Clinical

experience indicates that patients with aplastic anemia may develop HZ reactivation while on therapy with anti-thymocyte globulin (ATG) and cyclosporine, when a global suppression of T-cell function and numbers can occur. Indeed, according to guidelines on the management of aplastic anemia, AVP is not routinely recommended in untreated patients while it is during and after ATG therapy.⁶¹

Herpes zoster antiviral prophylaxis and vaccination schedule in patients with hematological diseases or submitted to HSCT

Comparison of different doses of acyclovir or comparison of different drugs are secondary objectives of observational studies on AVP. Lin et al. reported that the delivery of different dosages and types of anti-HZ drugs resulted in equivalent protective effects (32). Zheng et al. documented that the rate of HZ infection was similar between AVP with intermittent oral famciclovir at a dose of 250 mg twice daily for 9 days, and the continuous oral acyclovir group (8.4% vs 7.9% P=0.835)³³. Kawamura et al.⁵² documented that the number of patients who developed HZ before day 100 after HSCT was not different in the acyclovir 1000 and in the acyclovir 200 group. Mascarenhas et al.⁵⁴ documented that the use of low dose acyclovir prophylaxis was associated with a low rate of VZV reactivation in the first year after HSCT, with no evidence of clinically significant rebound at 2 years after transplant.

Two doses of aRZV are necessary regardless of the previous history of shingles or previous receipt of live zoster vaccine. The second dose of aRZV should typically be given 2–6 months after the first. However, for persons who are or will be immunodeficient or immunosuppressed and who would benefit from completing the course in a more condensed period of time, the second dose can be administered 1–2 months after the first. If a supplementary dose of aRZV is given sooner than 4 weeks after the first, a second valid dose should be repeated at least 4 weeks after the dose that was given early. The vaccine course should not be resumed if >6 months have elapsed since the first dose.

When possible, patients should be vaccinated before becoming immunosuppressed. If vaccination before immunosuppression is not possible, physicians should consider timing vaccination when the immune response is likely to be most robust.

Vaccination deferral in immunodeficient patients should be carefully weighed against the potential decline of aRZV response, occurring during the most aggressive phases of immunosuppression, therefore resulting in missing a “window of opportunity”.

In theory, laboratory tests to measure vaccine immunoprotection elicited for both B- and T-cell compartments might be exploited to guide post vaccination AVP, however, at the present the few literature data do not allow to define post-vaccination AVP strategy based on immunological monitoring.

Conclusion

The availability of new recombinant vaccine for HZ prevention has boosted great impetus for its use in immunocompromised patients at high risk of HZ reactivation. Lack of randomized trials considerably limits the quality of the evidence that should inform advises and recommendations. Consensus-based statements we provided in this project assume that the experts have an implicit and comprehensive mastery of scientific and practical information to help the most appropriate decisions. Applying these recommendations could not only improve outcomes but also enable data collection to inform future practice. Randomized clinical trials and large prospective epidemiological surveys are needed to better define some aspects of HZ prevention in hematological populations with the aim of optimizing the harmonization of the antiviral prevention strategy in terms of duration of AVP after vaccination in specific disease or conditions and eventual use of AVP late after vaccination particularly for chronic haematological disease undergoing prolonged treatments. Finally, literature data and personal experience of the experts demonstrate the continuous variation in the risk of HZ reactivation related both to the underlying disease or condition and the different treatments. It is therefore necessary to re-evaluate the prevention strategies over time in step with new therapeutic strategies for individual hematological diseases.

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Table 1. Proposals and/or recommendations on the prevention of *H.zoster* in patients with hematologic diseases

Herpes zoster prevention in myeloid disorders
<ul style="list-style-type: none"> • APL is considered at high risk for HZ reactivation during arsenic trioxide therapy and until 6 months from its discontinuation. In this setting, AVP is recommended from APL diagnosis and at least up to 6 months after discontinuation of arsenic trioxide. Considering the high efficacy of AVP and that the risk of HZ is limited in time, vaccination during active APL treatment is not recommended. • In patients with acute myeloid leukemia other than APL the risk of HZ infection is standard: thus HZ AVP and vaccination are not required at least during intensive leukemia treatment. HZ vaccination should be considered after leukemia treatment discontinuation, particularly in elderly patients. • HZ risk in patients with MDS is mainly related to the age risk. In this population AVP is not recommended and aRZV is recommended in elderly subjects. • Patients with BCR-ABL negative chronic MPNs are at high risk for HZ reactivation during ruxolitinib (or other JAK2 inhibitor) treatment. aRZV is recommended early when ruxolitinib therapy is planned, and AVP should be administered from the start of ruxolitinib, until at least one month after second vaccine dose. • Patients with chronic MPNs not treated with JAK2 inhibitors are at standard risk for HZ. AVP is not required and vaccination is recommended in elderly subjects.
Herpes zoster prevention in lymphoproliferative disorders
<ul style="list-style-type: none"> • In patients with lymphoma and CLL, HZ reactivation is frequently observed but distributed over a prolonged risk period, even years after treatment discontinuation. There is no clear evidence that HZ risk is highly increased after rituximab and other anti-CD20 treatments. The Expert Panel agrees that aRZV is highly recommended in patients with lymphoma and CLL possibly at the onset of the disease while planning hematologic treatment, and particularly in elderly patients, although low immunogenicity after anti CD-20 treatment is expected. • In patients treated with fludarabine or bendamustine, AVP is indicated at least until one month after the second vaccine dose. • In acute lymphoblastic leukemia the risk of HZ is standard and generally chemotherapy protocols do not consider AVP. The EP agrees that AVP is not recommended in ALL patients and aRZV may be considered in elderly patients in disease remission after leukemia treatment discontinuation. • MM is at high risk for HZ in general and particularly during proteasome inhibitors treatment and both AVP and vaccination are recommended. • In patients with MM not eligible for auto-HSCT aRZV is recommended possibly at the onset of disease before start of hematologic treatment. AVP is also recommended during proteasome inhibitors treatment at least until one month after the second vaccine dose. • In patients with MM eligible for auto-HSCT the Expert Panel agrees to delay aRZV administration two months after transplant, while AVP should be administered from the onset of induction treatment to one month after the second vaccine dose. • In the event of MM relapse late after vaccination there are no data on the risk of breakthrough HZ and no recommendation on AVP strategy can be made until more scientific data is available. However, AVP should be still considered if proteasome inhibitors are employed as salvage therapies
Herpes zoster prevention in the stem cell transplant setting
<ul style="list-style-type: none"> • The Expert Panel agrees to administer aRZV in all auto-HSCT patients two months after transplant. AVP should be administered from the start of conditioning regimen and until one month from the second vaccine dose. • In view of the very few data on the efficacy of aRZV in the allo-HSCT setting and the variable immune reconstitution in the different diseases and types of transplant it is not possible to give a definite recommendation on the timing of vaccination and the duration of AVP. A certain immunogenicity of the vaccine can be hypothesized six months after transplantation, but the

<p>Panel agrees that it is not currently possible to define in which patients AVP should be recommended despite aRZV and how long prophylaxis should be administered due to lack of evidence-based data. The Expert Panel underlines the importance to investigate this aspect in the real life when aRZV will enter the common clinical practice of allo-HSCT.</p>
<p>Herpes zoster prevention in immune-mediated non malignant hematologic diseases</p> <ul style="list-style-type: none"> • Few data is available on the risk of HZ reactivation specifically in patients with autoimmune hemolytic anemia and immune thrombocytopenia, although an increased risk can be hypothesized during the first months of steroid treatment. The HZ risk is unknown also for cases of second-line treatment with drugs other than steroids (i.e. rituximab, TPO mimetics, SYK inhibitors). The Expert Panel agrees that AVP is not generally recommended in immune-mediated hematologic diseases but it could be considered in elderly patients during the first two months of steroid treatment. aRZV is recommended in elderly patients, possibly at the onset of disease. • Also for bone marrow hypoplastic disorders there is few data on the risk of HZ reactivation although immunosuppressive therapy exposes to increased risk of herpetic infection. The Expert Panel agrees that in patients with aplastic anemia treated with ATG and cyclosporine (plus eltrombopag), AVP is recommended during and until at least six month after treatment, irrespective of indication to allo-HSCT. aRZV is recommended after immunosuppressive therapy discontinuation particularly in elderly patients. • Patients with paroxysmal nocturnal hemoglobinuria treated with complement inhibitors targeting C5 (i.e. eculizumab or ravulizumab) are not at increased risk of viral infections, therefore no specific HZ prevention strategy is recommended. Data on proximal complement blockers are not available yet.
<p>Herpes zoster antiviral prophylaxis and vaccination schedule in patients with hematological diseases or undergoing HSCT</p> <ul style="list-style-type: none"> • Acyclovir at a dose of 400 mg per day is an appropriate anti HZ viral prophylaxis in malignant and non malignant HD and in subjects undergoing autologous and allogeneic HSCT. • In the case where anti HZ vaccination is indicated, the double dose of aRZV should be considered in all hematological settings, since live attenuated formulation is contraindicated in immunocompromised subjects • Though with no strong evidence-based conclusion, aRZV is indicated also in patients who previously received live attenuated HZ vaccination, for whom poor vaccine response is expected. • The second dose of aRZV should be preferably early administered one/two month after the first dose. • In hematologic populations for which a good vaccine response (at least greater than 60%) is expected (see the above literature data), AVP could be discontinued one month after the second vaccine dose. Until adequate data is available, a personalized post-vaccination AVP based on laboratory immunological response does not seem a viable strategy at the moment. Future investigation in this setting is advised. • Uncertainty remains on the best AVP strategy after the second vaccine dose in conditions where a poor immune response is expected. The Panel agreed on recognizing this as an unmet clinical need, requiring more scientific data. In this setting the extension of AVP may be actually considered. • In patients with a breakthrough HZ reactivation despite previous vaccination, HZ treatment should be followed by prolonged secondary AVP. It is not possible to define how long secondary AVP should be continued due to the lack of clear evidence in literature.

APL: acute promyelocytic leukemia; AVP: antiviral prophylaxis; HZ: herpes zoster; MDS; myelodysplastic syndromes; MPNs: myeloproliferative neoplasms; aRZV: adjuvanted recombinant vaccine; MM: multiple myeloma; CLL: chronic lymphoid leukemia; ALL: acute lymphoid leukemia; ATG: anti-thymocyte globulin

Supplementary Table 1. Hematologic diseases and conditions at high risk for HZ infections for which antiviral prevention is recommended: summary of recent international guidelines

Disease condition	or AGIHO 2022 (1)	NCCN 2022 (2)
Acute myeloid leukemia	For patients with acute promyelocytic leukaemia treated with arsenic trioxide pharmacological prophylaxis during the time of treatment till 6 months thereafter is recommended to reduce VZV disease (BIr)	
Acute lymphoid leukemia	Antiviral prophylaxis to reduce reactivation of VZV is recommended for patients with acute lymphoblastic leukaemia while on treatment (BI)	
Chronic Myeloproliferative neoplasms	Antiviral prophylaxis to reduce reactivation of VZV is recommended for patients treated with ruxolitinib while on treatment (BIru)	Prophylaxis during ruxolitinib therapy
Non Hodgkin Lymphoma	Pharmacological prophylaxis to reduce VZV disease in non-Hodgkin lymphoma patients treated with immuno-chemotherapy is recommended (BIlu).	
Hodgkin lymphoma	There is no general recommendation for antiviral prophylaxis in patients with first line therapy of Hodgkin's lymphoma (treated with ABVD or BEACOPPesc) according to study protocols. Decision about antiviral prophylaxis has to be made on individual case basis, referring to treatment intensity and duration (CIII).	Consider prophylaxis during CD-20 targeted therapy
Chronic lymphocytic leukemia	Pharmacological prophylaxis to reduce VZV disease in CLL patients treated with immuno-chemotherapy is recommended (BIlu). In Patients with CLL (and other Non- Hodgkin lymphoma) receiving BTK or BCL2 inhibitors antiviral prophylaxis may be recommended particularly in patients in advanced lines of therapy (CIIu). In patients receiving idelalisib high risk of infections persists for several months after therapy (BIII). The existing	Consider VZV prophylaxis in patients treated with BTK inhibitors depending on additional risk factors. Consider prophylaxis during CD-52 targeted therapy

	data about venetoclax are not sufficient to consider a specific risk for VZV reactivations and to recommend antiviral prophylaxis.	
Myeloma	Antiviral prophylaxis in patients receiving bortezomib-based treatment regimens is strongly recommend (Allu). Prophylaxis is also recommended in patients receiving carfilzomib and ixazomib (Allu). The existing data about IMiDs are not sufficient to consider a specific risk for VZV reactivations and to recommend antiviral prophylaxis. Prophylaxis may be considered in selected cases, taking in account the patient's individual VZV disease risk (CIlh; CIIt)	VZV prophylaxis during active therapy with proteasome inhibitors including periods of neutropenia. Consider prophylaxis during CD-38 targeted therapy.
Stem cell transplant	No specific recommendations	Consider antiviral prophylaxis for at least 6–12 months after autologous HCT. Prophylaxis should be considered for at least 1 year after allogeneic HCT.
Indications for the use of HZ vaccination	Vaccination with the adjuvated recombinant zoster vaccine (aRZV) is recommended due to safety and immunogenicity, although data on clinical efficacy in certain malignancies are preliminary and long-term protection rates are sparse.	The administration of aRZV is recommended for adult patients age ≥ 50 years and those ≥ 18 years who are at increased risk for herpes zoster disease. aRZV is recommended 50–70 days after autologous HCT. aRZV may be considered after allogeneic HCT (Efficacy in allogeneic HCT, in the presence of GVHD, or ongoing immunosuppression has not been established). The aRZV vaccine is given in 2 doses ≥ 2 –6 months apart. For at-risk adults ≥ 18 years of age, a second dose can be given 1–2 months after the first dose if they will benefit from a shorter vaccination schedule. For patients who have previously received the live attenuated herpes zoster vaccine (ZVL), aRZV should be given at least 2 months after the last ZVL dose.

Supplementary Table 2. Main results of studies published since 2012 focused on the epidemiology and antiviral prophylaxis of HZ in HD and HSCT populations.

Author, year (reference)	Hematologic disease or condition (N. of pts)	Rate of HZ infection	Details on antiviral prophylaxis data
Yamakura 2014, (3)	APL (25)	HZ was documented in 7 of 15 (46.7%) pts treated with ATO but in none of 10 patients without ATO treatment. The median time of VZV reactivation was 72 days from the start of ATO	No data
Freyer 2021 (4)	APL (112)	HZ occurred in 13/112 (11.6%) pts within 6 months of completing ATO, including one case of HZ encephalitis.	HZ occurred in 17.5% of patients without versus in 4.1% of patients with AVP (RR 0.24). AVP reduced the incidence of HZ (17.5% vs. 4.1%, RR 0.24 [95% CI 0.05–1.0, p = .025]) with a number needed to treat of 7.7. HZ despite AVP occurred later than HZ in patients without AVP (7.8 vs. 2.3 months from starting ATO, p = .11). Older age and prior HZ increased the risk of HZ in patients not receiving AVP. Routine AVP should be considered in patients with APL receiving ATO, particularly in older patients and those with a history of HZ.
Glass, 2021 (5)	APL (155)	Of 102 pts treated with ATO and 53 not treated with ATO a HZ infection was documented in 14 (14%) and 1(2%) cases, respectively. The majority of these cases occurred within the first 6 months of treatment. In a multivariate analysis, ATO treatment showed a significant association with HZ infection (HR: 9.25, p = 0.04).	Of the 102 pts treated with ATO, 14 (13.7 %) received AVP at the start of therapy. Four of the 14 pts receiving AVP still developed HZ infection with a trend toward a higher proportion of herpes zoster infections among patients receiving AVP). This would suggest that prophylaxis in this cohort was used disproportionately in higher risk patients.

Barraco 2020 (6)	Myelofibrosis (426)	HZ was documented in 3.5 cases per 100 PY in 259 patients exposed to ruxolitinib versus 0.3 cases per 100/PY in 167 patients not exposed to ruxolitinib.	No data
Te Linde, 2022 (7)	Myelofibrosis and polycythemia vera (128)	Overall, 19,5% of patients treated with ruxolitinib developed HZ during treatment, in an average follow-up time of 37 months. The incidence rate was 6.9 of 100 PY being the risk to develop HZ more or less constant over the first 5 years.	No data
Cho, 2015 (8)	NHL (2188)	The overall incidence of HZ was 11.79% of the patients who received conventional chemotherapy and 12.76% of those who received rituximab-containing chemotherapy. The majority of the HZ episodes occurred within the first two years after the diagnosis of NHL.	No data
Goenaga Vázquez 2019 (9)	NHL and HL (415)	During a median follow-up of 8.9 years, the overall HZ incidence was 11.1%. Higher rates of HZ were associated with lymphocytopenia, autologous HSCT, multiple courses of chemotherapy, and fludarabine therapy. Those who received highly immunosuppressive chemotherapy had 2.9 times the risk to develop HZ than those who did not receive this therapy.	No data
Steingrímsson 2020 (10)	CLL (8989)	The incidence rate of HZ per 1000 PY in CLL pts was 2.94 compared to 0.26 in a age-/sex-/residence-matched control group.	When HZ in the calendar period 2002-2008 was compared to 1994-2001, there was a significantly decreased risk (HR 0.59). which importantly suggests that the use of AVP has resulted in decreased HZ infections despite increased risk associated with fludarabine treatment.

Coutre, 2019 (11)	CLL (330)	An integrated safety analysis of single-agent ibrutinib from randomized phase 3 studies was conducted. HZ was documented in 5% of pts treated with ibrutinib during long-term follow-up	No data
Minarik, 2012 (12)	MM (169)	There were 78 pts not receiving any AVP (46%), and 92 pts (54%) who received prophylactic ACV 200 mg/day for the whole course of bortezomib treatment and stopped with the last dose of bortezomib. Overall, 22 patients (13%) were diagnosed with HZ during bortezomib treatment, 68% of cases occurring during the first 3 cycles.	HZ occurred in only 1 patient (1%) who received AVP and in 27% of pts patients who did not. Later inspection revealed that the single patient that developed HZ despite AVP had poor adherence to the treatment, and the reactivation was caused by skipped medication. A subgroup analysis of pts with HZ history showed even higher incidence of HZ reactivation (33%).
Fukushima 2012 (13)	MM (32)	32 patients treated with bortezomib received 500 mg/day VACV prophylaxis for a median duration of 301 days. VZV reactivation developed in only one patient during AVP.	VACV at a dose of 500 mg daily appears to be effective at preventing VZV reactivation and was well-tolerated by patients with MM who received bortezomib.
Swaiika 2012 (14)	MM (100)	All patients treated with bortezomib-based therapies and treated with >4 weeks of ACV prophylaxis (400 mg twice daily), which was initiated prior to starting treatment with bortezomib and discontinued 4 weeks following bortezomib, were considered.	None of the 100 MM patients receiving AVP developed HZ during treatment with bortezomib
Konig 2014 (15)	MM (93)	All pts treated with lenalidomide. VZV infection occurred in 10.7% of pts. Again, VZV infection was documented in 132 consecutive MM patients who received autologous HSCT (7.6 %) MM patients within 1 (n =5) and 2 (n =5) years after transplant.	After routine ACV prophylaxis was introduced in 2012 no further VZV infection case was documented

Leng 2018 (16)	MM (6934)	Pts treated with bortezomib or carfilzomib for ≥ 3 months were considered. Among them, 52.4% were dispensed zoster prophylaxis at least once.	Amongst users of AVP, 2.4% developed HZ, and amongst non-users 5.8%. In the cohort of patients who used PIs ≥ 6 months, both use of prophylaxis (2.6% in users versus 6.9% in nonusers) and adherence to prophylaxis (2.0% in adherent versus 4.7% in nonadherent) were independently associated with lower risk for HZ.
Lin 2023 (17)	MM (551)	AVP was given to 283 patients. Overall, 49.8% of AVP MM patients had received VACV 500 mg per day, 35.6% received ACV 200 mg per day, while the remaining 14.6% received 400 mg ACV per day. The incidence rate of HZ infection was 6.5 cases per 100 PY in the 500 mg VACV group, and 6.2 and 8.1 cases per 100 PY in the 200 mg and the 400 mg ACV groups, respectively. Pts without prophylaxis had incidence rate up to 20.6 cases per 100 PY (HR 3.28, $p < 0.001$).	The cumulative incidence of HZ infection was remarkably higher in the group who ended AVP before first-line treatment. This suggests that the use of AVP should be continued at least until the end of cancer related treatment. Non-prophylaxis group (HR: 2.37, 95% CI 1.57–3.57) had higher risk of HZ infection. The difference in dosage and types of anti-HZ drugs showed similar protective effects. In patients who stopped anti-HZ prophylaxis before active cancer-related treatment, a higher risk of getting HZ infection compared to the corresponding group was also observed (adjusted HR 3.09, $p = 0.008$).
Zheng 2022 (18)	MM (719)	The incidence of bortezomib treatment-related HZ was evaluated in pts receiving intermittent oral famciclovir prophylaxis (250mg twice daily for 9 days after finishing the last dose of bortezomib therapy every cycle) (250 pts), continuous oral ACV prophylaxis (216 pts) or no prophylaxis (253 pts).	The incidence of HZ was significantly higher in the non-prophylaxis group compared with the prophylaxis group (22.9% vs 8.2% $P < 0.001$), while the rate was similar between the intermittent oral famciclovir group and the continuous oral acyclovir group (8.4% vs 7.9% $P = 0.835$). Univariate analysis showed that HZ infection is strongly associated with no AVP. Other factors such as gender, age, ISS stage, type of M protein, baseline of ALC, ANC and AMC had no relationship with VZV reactivation.
Kamber 2015 (19)	Autologous HSCT (191)	Pts affected by MM. VZV reactivation occurred in 30% of patients, in 8.5% during induction and in 21.5% after HSCT, peaking at 8 months after HSCT	AVP comprised 500 mg of oral acyclovir twice daily starting on the first day after ASCT and continued for 3 weeks. As a consequence of this study internal guidelines were

			modified our and prolonged antiviral prophylaxis was recommended.
Mawatari, 2015 (20)	Autologous HSCT (97)	The cumulative incidence of VZV reactivation after a median of 1027 days after autologous HSCT was 30.7% at 1 year and 51.2% for the total observation period. The median time of the onset was 239.5 days (range 20–1798 days; IQR 126–498 days).	97% of pts received oral ACV (200 mg 5 times per day) which started at the beginning of the preparative regimen and continued until a median duration of 32 days (interquartile range 27–35 days) of HSCT. Almost all cases of HZ occurred after ACV discontinuation.
Kawamura 2015 (21)	Autologous HSCT (83)	As AVP, before August 2009, patients received oral ACV at 200 mg five times daily (ACV1000) from day 7 to engraftment, whereas after September 2009, patients received oral ACV at 200 mg once daily (ACV200). After engraftment, ACV was continued at 200 mg at the discretion of the attending physicians in both groups. Overall, 17% of pts developed VZV disease at a median of 125 days (range 38–1334) after auto-HSCT. The cumulative incidence of VZV disease after auto-HCT was 14.8 % at 1 year and 18.5 % at 2 years.	No HZ case was observed during AVP. In 62 pts who discontinued ACV before the onset of VZV disease the cumulative incidence of VZV disease after the cessation of ACV was 19.2 % at 1 year and 23.6 % at 2 years. Comparing patients who discontinued AVP at engraftment, between engraftment and 1 year after auto-HSCT, and beyond 1 year the cumulative incidence of VZV disease was 25.8 %, 7.7 %, and 0.0 % at 1 year, respectively, and 28.9 %, 17.2 % , and 0.0 % at 2 years, respectively.
Sahoo, 2017 (22)	Autologous HSCT (1000)	VZV seropositive autologous HSCT recipients with up to five years of follow up were considered. AVP with ACV 800 mg by mouth twice daily or VACV 500 mg by mouth twice daily for one year after HSCT was routinely prescribed. Post-HCT maintenance therapy protocols, especially those using steroids or bortezomib, recommended continuation of AVP for 2 months beyond completion of maintenance therapy. Over a period of five years post-autologous HSCT, 194 patients developed at least one HZ episode with a	Of the 194 patients who developed HZ 82% were not on AVP at the time of HZ. Patients taking ACV/VACV had reduced risk for HZ (adjusted hazard ratio 0.59). The median time to first HZ episode after stopping ACV/VACV prophylaxis was 4 months. Post-herpetic neuralgia was common and reported in 24% of patients with well-documented follow up.

		cumulative incidence of 21%. The incidence rate per person years over the entire follow up period was 0.06. The highest incidence rate was 0.13 in the second year.	
Zhang, 2017 (23)	Autologous HSCT, (1959)	93.0% were prescribed AVP. Average AVP duration was 220 days, while 200 (11%) patients had AVP for >1 year. HZ incidence was 42.4/1000 PY for the overall auto-HSCT cohort.	The incidence of HZ in the different AVP groups is the following: for pts who did not receive AVP HZ it was 41.3/1000 PY; for those who received AVP during the post-transplant first year HZ incidence ranged from 61.8/1000 PY for patients with AVP duration of 1–89 days to 22.6/1000 PY for patients with AVP duration of >360 days. Compared with patients who were on AVP for 1–89 days, patients with AVP duration of 180–269 days [HR = 0.576, p = 0.019], 270–359 days (HR = 0.594, p = 0.023), and >360 days (HR = 0.309, p<0.001) had significantly lower risk of HZ. Patients who did not have AVP prescriptions were probably at lower perceived risk of HZ.
Shinohara, 2019 (24)	Autologous HSCT (72)	Pts who received auto-HSCT between 2005 and 2014, without the use of AVP, were included in this study. The one-year cumulative incidence of HZ was 26.4 % (8% disseminated disease) and half of them developed post-herpetic neuralgia. A second episode of HZ occurred in 31/194 (16%) patients.	No patient received AP.
Abbasov 2022 (25)	Autologous HSCT, (107)	Pts with MM and NHL treated with autologous HSCT who received 12 months prophylactic low-dose ACV (400 mg/day) compared to 162 patients who did not receive AVP and were controlled regularly regarding HZ for at least 24 months following transplant. Overall, HZ was observed in 2.8% of patients who received AVP and in 20% in	In the group of pts who received AVP HZ occurred after prophylaxis discontinuation, in the group who received AVP 14% and 5.6% of pts developed the viral infection during the first and second year after transplant, respectively. Neither an increase of HZ cases following AVP nor ACV refractory HZ cases were observed.

		those who did not. 30% of lymphoma pts and 14% of myeloma pts developed HZ in the first 24 months after ASCT without AVP, but only 6.3% and 0% of pts with AVP, respectively.	
Kawamura 2013 (26)	Allogeneic HSCT (141)	Pts received long term ultra low-dose ACV (200 mg/day) prophylaxis until the end of immunosuppressive therapy and for at least 1 year after HSCT. The cumulative incidence of VZV disease after HSCT was 4.5% at 1 year and 18.3% at 2 years.	Six patients experienced breakthrough VZV disease, but four of these six had not taken ACV for several weeks before breakthrough VZV disease. The cumulative incidence of VZV disease after the cessation of ACV was 28.4% at 1 year and 38.0% at 2 years.
Blennow 2014 (27)	Allogeneic HSCT (802)	VZV reactivation without routine AVP was evaluated for a median of 2.4 years. ACV prophylaxis (400 mg 2 times daily) was only used in pts who had an IgG antibody titer to herpes simplex virus of >10,000, and it was administered until engraftment. Overall, 21.4% of pts reactivated VZV at a median of 175 days after HSCT (range, 1 to 2198), resulting in a total cumulative incidence of 22.6%. There was no difference in VZV reactivation between patients receiving myeloablative conditioning or reduced intensity conditioning	No breakthrough infection during AVP could be identified.
Mascarenhas 2019 (28)	Allogeneic HSCT, (889)	All pts underwent ACV prophylaxis until 1 year after transplant or 3 months after immunosuppression discontinuation. The cumulative incidence of VZV infection was 2.8% at 1 year, and 5.8% at 2 years following HSCT	The principal finding from this study was that the use of lower dose acyclovir prophylaxis was associated with a low rate of VZV reactivation in the first year after HCT, with no evidence of clinically significant rebound at 2 years after HCT.

Baumrin 2019 (29)	Allogeneic HSCT (2163)	All patients received prophylaxis with acyclovir for at least 12 months following transplant, but 22 (1.0%) developed severe HZ at a rate of 1 per 228 person-years. Severe HZ infection occurred in a bimodal distribution during the early peri-HSCT period and at 12 to 24 months post-HSCT.	54.5% of pts were receiving ACV prophylaxis at the time of reactivation Of the 8 patients who had severe HZ at 12 to 24 months post-HSCT, 3 patients were on standard ACV dosing and concurrent immunosuppression for GVHD and the other 5 patients were not on ACV prophylaxis and were not receiving immunosuppressive medications.
Xue 2021 (30)	Cord blood transplant (227)	Cumulative incidence of HZ up to 5 years post-transplant in seropositive CBT recipients who were transplanted between 2006 and 2016 were retrospectively analyzed. Among 1-year survivors, 91% were still receiving antiviral prophylaxis, for a median duration of 20.6 months. HZ occurred in 44 patients (19%) at a median of 23.6 months. The cumulative incidence of HZ by 1 year after CBT was 1.8% (95% confidence interval [CI], .1%–4%), but increased to 26% (95% CI, 19%–33%) by 5 years.	From 2006 to 2009, institutional guidelines recommended HZ prophylaxis until immunosuppression withdrawal; after 2009, guidelines recommended HZ prophylaxis for at least 1 year and at least 8 months after immunosuppression withdrawal. Additionally, HZ prophylaxis was recommended in patients restarted on immunosuppressive therapies. In a multivariable analysis, AVP was associated with reduced risk for HZ (adjusted hazard ratio, 0.19 [95% CI, .09–.4]). in patients with a follow-up > 3 years 88% of HZ episodes occurred after AVP discontinuation.

ACV= acyclovir; AVP= antiviral prophylaxis; APL= acute promyelocytic leukemia; ATO= arsenic trioxide; CLL= chronic lymphocytic leukemia; HR=hazard ratio; HZ= Herpes zoster; MM= multiple myeloma; NHL= non Hodgkin lymphoma; Pts= patients; PY= person/years; VACV= valacyclovir; VZV= varicella zoster virus

Supplementary Table 3. Main results of real life studies on the efficacy and immunogenicity of adjuvated Recombinant Zoster Vaccine (aRZV) in hematologic malignancies (HM) and hematopoietic stem cell transplant populations (HSCT).

Author, year	Hematologic disease or condition (N. of pts)	Results of the study and comments
Mughtar, 2021 (31)	Monoclonal B-cell lymphocytosis (MBL) and CLL (37 MBL and 25 CLL pts)	The immunogenicity of aRZV was investigated and compared to historic controls matched by age and sex. An antibody and CD4+ cell response at 3 months was seen in 45% and 54% of participants, respectively, which was significantly lower compared to historic controls (63% and 96%, respectively). Lower CD4+ cell responses were observed among BTKi-treated patients compared to untreated MBL/CLL (32% vs. 73%, p = .008).
Pleyer, 2021 and 2022 (32,33)	CLL patients who were treatment naïve or receiving Bruton tyrosine kinase inhibitor therapy (106 and 96 pts evaluable for antibody and cellular response, respectively)	The antibody and cellular response rate was significantly higher in the treatment naïve cohort (76.8% and 70.0%, respectively) compared with patients receiving a BTKi (40.0% and 41.3%, respectively). Antibody titers and T-cell responses were not correlated with age, absolute B- and T-cell counts, or serum immunoglobulin levels. A concordant positive humoral and cellular immune response was observed in 69.1% of subjects with a humoral response, whereas 39.0% of subjects without a humoral response attained a cellular immune response (P = .0033). Antibody titers and T-cell responses were not correlated with age, absolute B- and T-cell counts, or serum immunoglobulin levels.
Zent, 2021 and Brady 2023 (34, 35)	CLL or lymphoplasmacytic lymphoma (32 pts)	Of the 24 (75%) subjects with a humoral immune response, 21 (87.5%) also achieved a T-cell response at 4 weeks from vaccination. For the eight subjects without a humoral immune response, only four (50%) had a T-cell response. Four patients did not meet criteria for either a humoral or T-cell response. Among patients responding at 4 weeks from vaccination, 56.5% had a sustained humoral response 24 months after vaccination. The overall humoral response rate for all patients at 24 months compared to prevaccination was 41.9% . There was no significant association between prior rituximab and achieving humoral response. Cellular response was achieved in 81.3% of patients (90% CI, 66.4–91.5) 4 weeks after vaccination. Among patients who mounted T cell response at 4 weeks from vaccination, the response continued to be sustained in 65.4% of patients 24 months after vaccination. The overall cellular response rate in all patients at 24 months was 54.8%.

		This prospective study shows that patients with CLL or LPL on BTKi therapy can respond to aRZV vaccine while on BTKi therapy.
Sweiss, 2020 (36)	Multiple myeloma (85 pts)	Overall rates of seropositivity increased after 1 (87.9%; p=0.0002) and 2 (92.6%; p=0.0001) doses. Seroconversion from a baseline negative to positive test was observed in 16 (76.2%) and 23 (95.8%) patients after 1 and 2 doses, respectively
Baumrin, 2021 (37)	Allogeneic HSCT (158 pts)	In a single-center prospective observational cohort study 2 doses of aRZV were administered between 9 and 24 months after HCT, with the doses separated by ≥ 8 weeks. There were 4 cases of HZ in the total vaccinated cohort (2.5%) and 3 cases in the modified total vaccinated cohort (28.3/1000 person-years) which was higher than that seen after RZV in healthy older adults (IR, 0.8/1000 PYs) but similar to autologous HSCT recipients (IR, 30.0/1000 PYs). All 4 HZ cases occurred during the second and third year after transplant, 10, 51, 102, 115 days after the second vaccine dose and 9, 10, 41, 206 days after antiviral prophylaxis discontinuation. No patient was taking immunosuppressive medications at the time of HZ.
Koldehoff, 2022 (38)	Allogeneic HSCT (79 pts)	Patients received aRZV after 37 median months (range, 8–402) from transplant. Cellular immunity against various VZV antigens was analyzed by interferon-gamma ELISpot and VZV (g-E) specific immunity tested prior and post 2nd vaccination were compared. Response to VZV g-E peptide were significantly higher (from 3.2 to 5.7 fold according to measurement method) after the 2nd vaccination. Peripheral blood mononuclear cells of recipients with versus without prior shingles (n = 36 and n = 43, respectively) showed approximately twofold higher VZV-specific responses prior to and post vaccination. Immunity against glycoprotein E after the first and second vaccination, was significantly higher in males versus females. Multivariate analysis showed that shingles and sex both impacts significantly on VZV immunity. No significant correlation with the interval between transplantation and vaccination was observed. Whether the higher ELISpot responses correlate with better protection against VZV infection and reactivation needs to be clarified.

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