Attenuated antibody responses to respiratory syncytial virus vaccination in hematologic malignancies: impact of anti-CD20 therapy

Respiratory syncytial virus (RSV) is a leading cause of severe lower respiratory tract infections, particularly in older adults and individuals with comorbidities. Recently approved vaccines; Arexvy (recombinant subunit with stabilized prefusion F protein), Abrysvo (bivalent recombinant protein), and mRESVIA (mRNA-based), represent a major advance in RSV prevention. Phase III trials showed robust efficacy, with 80-85% protection against severe RSV-associated lower respiratory tract disease in adults ≥60 years during the first year post-vaccination,[1-3] leading to broad vaccination recommendations.[4]

Patients with hematologic malignancies such as chronic lymphocytic leukemia (CLL), B-cell non-Hodgkin lymphoma (B-NHL), and multiple myeloma (MM) face disproportionately high risk of severe RSV outcomes due to both disease-related immune dysfunction and immunosuppressive treatments.[5] RSV infection in these patients is linked to slower viral clearance, prolonged hospitalization, and higher mortality compared with the general population.[6,7] Although RSV vaccines are highly effective in immunocompetent adults, their immunogenicity in hematologic malignancy patients is poorly defined. Experience with COVID-19 vaccines underscores this challenge: seroconversion rates are markedly reduced, particularly in patients with CLL and B-NHL, and in those previously exposed to B-cell-depleting therapies. Reported seroconversion rates range from 38-76%, with the lowest in CLL and higher in MM.[8,9] These findings underscore the need to characterize RSV vaccine responses in this vulnerable population.

This study aimed to assess the antibody response and safety profile of the RSV vaccine in patients with lymphoproliferative diseases.

In this prospective observational study, adults aged ≥60 years with CLL, B-NHL, or MM who were scheduled to receive Arexvy as part of routine clinical care were enrolled. Individuals with prior RSV vaccination were excluded. Demographic and clinical data including hematological diagnosis, disease status, prior/current therapy, lymphocyte counts, and immunoglobulin levels were collected. The study was approved by the institutional review board, and all participants provided written informed consent.

Peripheral blood samples were prospectively pre-planned for collection at baseline (T0, pre-vaccination) and 4-6 weeks post-vaccination (T1, peak response). RSV-specific immunoglobulin G (IgG) antibodies were measured using the SERION enzyme-linked immunosorabant assay classic Respiratory Syncytial Virus IgG (Serion Diagnostics, Germany). The assay provides qualitative classification as negative, positive, or indeterminate. For the primary immunogenicity analysis, seroconversion was defined as a change from a negative pre-vaccination result to a positive post-vaccination result. Patients with indeterminate results at baseline or post-vaccination were excluded from the seroconversion analysis. Patients reported local and systemic symptoms within 7 days post-vaccination. All adverse events (AE) were graded using standard criteria and assessed for relationship to vaccination. During the follow-up period, patients were actively monitored for respiratory illness via systematic medical record review and structured self-reporting.

The primary endpoint was seroconversion defined by transition to RSV-specific IgG positivity. Analyses were prespecified by subgroup (CLL, MM, B-NHL); overall summaries are descriptive, and subgroup comparisons were exploratory without multiple-comparison adjustment. A two-sided $P<0.05$ was considered significant

A total of 102 patients were enrolled in the study between January and April 2025. Of these, 79 (77.5%) qualified for the prespecified efficacy cohort, while 23 (22.5%) were excluded from efficacy analyses due to baseline seropositivity (N=13), borderline post-vaccination serology (N=6), borderline baseline serology (N=3), or missing baseline serology with a positive post-vaccination result (N=1). All 102 patients (Table 1) were included in the safety cohort The study population comprised 43 patients with CLL (42.2%), 37 with MM (36.3%), and 22 with B-NHL (21.6%). The median age at vaccination was 74 years (interquartile range [IQR], 68-78). Overall, 66% of participants were male, with higher proportions in CLL (72%) and MM (70%) compared with B-NHL (46%).

Within the efficacy cohort (N=79; Tables 2; *Online Supplementary Tables S1* and *S2*), 33 patients (41.8%) had CLL, 29 (36.7%) had MM, and 17 (21.5%) had B-NHL. The median time from diagnosis to vaccination was 84 months (interquartile range [IQR], 47.0-127.5), and was longest among patients with CLL (122 months; IQR, 74.0-181.0). At the time of evaluation, 11 patients (13.9%) were treatment-naïve, whereas 46 (58.2%) were receiving active therapy. The most common regimens included BTK inhibitors, administered either as monotherapy (N=14) or in combination with anti-CD20 antibodies (N=4) or with venetoclax (N=1), and anti-CD38-based combinations in MM (N=12). Further treatment details are provided in *Online Supplementary Table S2*.

Prior or current exposure to anti-CD20 antibodies was documented in 34 patients (43.0%), including, eight (23.5%) treated within the past 12 months. The median serum IgG level was 580 mg/dL (IQR, 374.0-878.0), and 18 (22.8%) were receiving intravenous Ig replacement. The median absolute lymphocyte count on the day of vaccination was 1.5×10^9/L (IQR, 1.0-2.6).

Overall, 22 of 79 patients (27.8%) achieved RSV-specific IgG seropositivity following vaccination. Seroconversion was numerically higher in MM (12/29, 41.4%) than in CLL (8/33, 24.2%) or B-NHL (2/17, 11.8%), though the difference did not reach statistical significance (P=0.08). The only variable significantly associated with antibody response was prior anti-CD20 exposure, with seroconversion observed in three of 34 exposed patients (8.8%) *versus* 19 of 45 unexposed patients (42.2%) (P=0.004), corresponding to an odds ratio (OR) of 0.13 (95% confidence interval [CI]: 0.04-0.50). No significant associations were found for age, sex, current treatment status, anti-CD20 exposure (within 12 months before vaccination), BTKi-monotherapy, anti-CD38 exposure, serum IgG level, serum IgM level or lymphocyte count. In a multivariable logistic regression model including disease type and prior anti-CD20 exposure (variables with P<0.1 in univariate analyses), prior anti-CD20 therapy remained the strongest predictor of reduced serologic response (adjusted OR=0.19; 95% CI: 0.03-1.15; P=0.07), although the association did not reach conventional statistical significance. During follow-up (median 6 weeks post-vaccination), no patient developed a documented RSV infection.

In the safety cohort of 102 patients, AE were predominantly mild and localized (Table 3). The most common AE included injection-site pain in 30 patients (29.4%), redness in 16 (15.7%), muscle pain in 13 (12.7%), rash in 12 (11.8%), and fatigue in 11 (10.8%). Grade 2 events were rare, each occurring in only one patient (1.0%) and included fever, injection-site pain, and muscle pain. No grade ≥3 AE and no serious AE attributable to vaccination were reported (Table 3).

This prospective study evaluated the immunogenicity and

Table 1. Baseline demographic and clinical characteristics of the entire study cohort.

Characteristic	CLL N=43	MM** N=37	B-NHL* N=22	Total N=102
Age at vaccination, years, median (IQR)	73 (68-77)	74 (71-79)	74 (68-80)	74 (68-78)
Sex, N, (%)				
Males	31 (72.1)	26 (70.3)	10 (45.5)	67 (65.7)
Females	12 (27.9)	11 (29.7)	12 (54.5)	35 (34.3)
Time from diagnosis to vaccination, months, median (IQR)	120.0 (72.5-175.0)	66.0 (38.0-98.0)	81.5 (5-350)	82.0 (45.3-122.8)
Time from T0 to T1, days, median (IQR)	41 (35-46)	45 (38-54)	42 (35-55)	43 (35-50)
Treatment status at the time of vaccination, N (%)				
Treatment naïve	8 (18.6)	1 (2.7)	3 (13.6)	12 (11.8)
On treatment	28 (65.1)	27 (73.0)	9 (40.9)	64 (62.7)
Post treatment	7 (16.3)	9 (24.3)	10 (45.5)	26 (25.5)
Any exposure to anti-CD20 treatment, N (%)				
Yes	25 (58.1)	0 (0)	21 (95.5)	46 (45.1)
No	18 (41.9)	37 (100.0)	1 (4.5)	56 (54.9)
Within 12 months before vaccination	5/25 (20.0)	0 (0)	9/21 (42.9)	14/46 (30.4)
Exposure to anti-CD38 treatment within 24 months before vaccination, N (%)	0 (0)	14 (37.8)	0 (0)	14 (13.7)
Active BTKi monotherapy, N (%)	14 (32.6)	0 (0)	4 (18.2)	18 (17.7)
Receiving IVIG treatment, N (%)	9 (20.9)	12 (32.4)	2 (9.1)	23 (22.6)
IgG level at time of vaccination, mg/dL, median (IQR)	627.0 (454.0-1,026.3)	504.0 (363.0-770.8)	605.0 (509.3-740.8)	586.0 (375.0-890.0)
IgM level at time of vaccination, mg/dL, median (IQR)	25.0 (18.0-66.0)	19.0 (<16-26.5)	48.0 (24.0-178.5)	21.5 (<16-51.8)
Lymphocyte count at time of vaccination, x10^9/L, median (IQR)	2.4 (1.4-5.3)	1.2 (0.8-1.5)	1.1 (0.8-1.8)	1.5 (0.9-2.6)

*B-cell non-Hodgkin lymphoma (B-NHL) subtypes include: diffuse large B-cell lymphoma (N=7), marginal zone lymphoma (N=7), mantle cell lymphoma (N=4), follicular lymphoma (N=3), indolent B-cell lymphoma (N=1). **Multiple myeloma (MM) heavy chain characteristics: immunoglobulin (Ig) G=23/37 (62.2%); IgA=7/37 (18.9%); IgM=1/37 (2.7%); none=6/37 (16.2%). CLL: chronic lymphocytic leukemia; T0: pre-vaccination; T1: peak response; BTKi: Bruton tyrosine kinase inhibitor; IQR: interquartile range; IVIG: intravenous Ig.

safety of the RSV vaccine Arexvy in patients with hematologic malignancies, a population at high risk for severe RSV infection but for whom vaccine data are scarce. Our findings reveal markedly impaired antibody responses, with only 27.8% of patients achieving RSV-specific IgG seropositivity following vaccination. Response rates were highest among patients with MM (41.4%), intermediate in those with CLL (24.2%), and lowest in B-NHL (11.8%), all markedly reduced compared with the near-universal seroconversion observed in the phase III Arexvy trial among immunocompetent older adults.[1] In a study of immunocompromised adults, predominantly organ transplant recipients, administration of Arexvy resulted in seroconversion in 61% of participants.[10] These results parallel experience with COVID-19 vaccines, where reduced humoral responses have been consistently reported in hematologic malignancies, particularly in CLL and lymphoma, reflecting both disease-related immune dysfunction and therapy-induced immunosuppression.[8,11]

The most striking result was the profound negative effect of anti-CD20 antibody exposure on vaccine response. Only 8.8% of patients with prior anti-CD20 therapy achieved seropositivity compared with 42.2% of unexposed patients. This observation aligns with extensive evidence that rituximab and obinutuzumab compromise humoral immunity to vaccines including influenza, pneumococcus, and SARS-CoV-2, often for extended periods due to delayed B-cell recovery.[8,11-13] By contrast, no significant

Table 2. Baseline demographic and clinical characteristics of patients included in the efficacy cohort (qualified for respiratory synctial virus serology analysis, N=79).

Characteristic	Serologic response		*P*
	Positive N=22	Negative N=57	
Condition, N (%)			0.08
CLL, N=33	8 (24.2)	25 (75.8)	
MM*, N=29	12 (41.4)	17 (58.6)	
B-NHL, N=17	2 (11.8)	15 (88.2)	
Age at vaccination, years, median (IQR)	73 (67-77)	73 (69-78)	0.460
Sex, N (%)			
Male, N=50	15 (30.0)	35 (70.0)	0.764
Female, N=29	7 (24.1)	22 (75.9)	
Time from diagnosis to vaccination, months, median (IQR)	87.5 (58.5-121.5)	83.0 (46.0-130.0)	0.875
Time from T0 to T1, days, median (IQR)	45 (38-55)	41 (35-47)	0.112
Treatment status, N (%)			
Treatment naïve, N=11	3 (27.3)	8 (72.7)	0.590
Active treatment, N=46	15 (32.6)	31 (67.4)	
Post treatment, N=22	4 (18.2)	18 (81.8)	
Anti-CD20 exposure, N (%)			
Yes, N=34	3 (8.8)	31 (91.2)	0.004
No, N=45	19 (42.2)	26 (57.8)	
Last anti-CD20 within 12 months before vaccination, N (%)			
Yes, N=8	0 (0)	8 (100.0)	0.769
No, N=26	3 (11.5)	23 (88.5)	
Time from last anti-CD20 to vaccination, months, median (IQR)	86.0 (69.0-90.0)	34.0 (14.0-64.0)	0.078
Active BTKi monotherapy, N (%)			
Yes, N=14	6 (42.9)	8 (57.1)	0.167
No, N=65	16 (24.6)	49 (75.4)	
Anti-CD38 exposure within 24 months, N (%)			
Yes, N=12	4 (33.3)	8 (66.7)	0.912
IgG level at time of vaccination, mg/dL, median (IQR)	657.0 (488.0-1145.0)	569.0 (369.3-671.8)	0.105
IgM level at time of vaccination, mg/dL, median (IQR)	21.0 (17.0-49.0)	22.0 (<16-53.0)	0.762
Lymphocyte count at time of vaccination, x10^9/L, median (IQR)	1.8 (1.2-2.6)	1.3 (0.9-2.7)	0.168

*In a sensitivity analysis excluding patients with immunoglobulin (Ig) G-type multiple myeloma (MM), serum IgG levels remained not significantly associated with seroconversion and effect estimates were similar to those of the primary analysis (*P*=0.18). CLL: chronic lymphocytic leukemia; B-NHL: B-cell non-Hodgkin lymphoma; T0: pre-vaccination; T1: peak response; BTKi: Bruton tyrosine kinase inhibitor; IQR: interquartile range; IVIG: intravenous Ig.

Table 3. Summary of vaccination-related adverse events in the entire study cohort (N=102).

Adverse event	All grades, N (%)	Grade 1, N (%)	Grade 2, N (%)	Grade ≥3, N (%)
Injection-site pain	30 (29.4)	29 (28.4)	1 (1.0)	0 (0)
Redness	16 (15.7)	16 (15.7)	0 (0)	0 (0)
Muscle pain	13 (12.7)	12 (11.8)	1 (1.0)	0 (0)
Rash	12 (11.8)	12 (11.8)	0 (0)	0 (0)
Fatigue	11 (10.8)	11 (10.8)	0 (0)	0 (0)
Dizziness	6 (5.9)	6 (5.9)	0 (0)	0 (0)
Nausea/Vomiting	5 (4.9)	5 (4.9)	0 (0)	0 (0)
Fever	4 (3.9)	3 (2.9)	1 (1.0)	0 (0)
Swelling	4 (3.9)	4 (3.9)	0 (0)	0 (0)
Headache	3 (2.9)	3 (2.9)	0 (0)	0 (0)
Itching	2 (2.0)	2 (2.0)	0 (0)	0 (0)
Lymph node swelling	0 (0)	0 (0)	0 (0)	0 (0)

associations were observed with other therapies such as BTK inhibitors, or anti-CD38 agents, or with demographic and laboratory parameters including age, sex, IgG levels, or lymphocyte counts.

These findings carry important clinical implications. Given the combination of reduced vaccine responses and the high burden of RSV morbidity in hematologic malignancies, vaccination alone may be insufficient to protect many patients, particularly those recently treated with anti-CD20 antibodies. The timing of vaccination in relation to therapy warrants optimization, as administration prior to treatment initiation or, alternatively, deferring vaccination until after partial immune reconstitution may enhance responses.[14] Future vaccination strategies should also consider RSV seasonality, aligning vaccination timing to expected viral circulation periods to maximize protection. In addition, given diminished immunogenicity, booster or repeat vaccination strategies should be considered and formally studied, in line with COVID-19 and influenza evidence that sequential doses can augment serologic responses in immunocompromised populations.[15,16]

Reassuringly, the safety profile in our cohort was favorable. AE were predominantly mild and localized, with no grade ≥3 events or vaccine-related serious AE reported. These results are consistent with pivotal phase III trials in older adults,[1-3] confirming the tolerability of RSV vaccination even in immunocompromised patients. Thus, despite reduced immunogenicity, the safety and feasibility of vaccination remain intact in this population.

Our study has limitations. The use of a qualitative IgG assay did not allow quantification of antibody titers or evaluation of neutralizing activity, which may provide a more precise assessment of protective immunity. By requiring a clear transition from negative to positive and excluding indeterminate results, our definition of seroconversion may underestimate partial or low-level antibody responses. Nonetheless, in the absence of an established correlate of protection and given the qualitative nature of the assay, the clinical significance of borderline titers in this population remains uncertain. Subgroup sample sizes were modest, limiting statistical power to detect additional associations beyond anti-CD20 therapy. For the same reason, the multivariable analysis model was underpowered, and the adjusted associations - while directionally consistent with the univariate findings - should be interpreted with caution. Furthermore, we did not assess T-cell-mediated immunity, which may play an important role in protection when humoral responses are impaired. Cellular immunity is particularly relevant in hematologic malignancies, as T-cell preservation or recovery could compensate for limited antibody production. Future studies incorporating quantitative serology and cellular immunity, as well as evaluating vaccine effectiveness against clinical RSV outcomes, will be essential to inform preventive strategies.

In summary, we demonstrate substantially reduced serologic responses to RSV vaccination in patients with hematologic malignancies, with the poorest responses in those with prior anti-CD20 therapy. These findings mirror vaccine response patterns observed with COVID-19 and other viral vaccines and highlight the urgent need for tailored RSV prevention strategies in this vulnerable population. Optimization of vaccination timing, integration of passive immunization, and further research on immune correlates of protection are needed to improve outcomes for patients with hematologic malignancies.

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YH and IA designed the study, collected data, and wrote the manuscript. YB contributed to data collection and writing. AA performed the serology testing. DG analyzed data. CP and YC contributed to data collection.

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Data-sharing statement
The data that support the findings of this study are available on request from the corresponding author.

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