A Randomized, Controlled Trial of *Panax quinquefolius* Extract (CVT-E002) to Reduce Respiratory Infection in Patients With Chronic Lymphocytic Leukemia

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ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) patients are at high risk for acute respiratory illness (ARI).

Objective: We evaluated the safety and efficacy of a proprietary extract of *Panax quinquefolius*, CVT-E002, in reducing ARI.

Methods: This was a double-blind, placebo-controlled, randomized trial of 293 subjects with early-stage, untreated CLL conducted January–March 2009.

Results: ARI was common, occurring on about 10% of days during the study period. There were no significant differences of the 2 *a priori* primary end points: ARI days (8.5 ± 17.2 for CVT-E002 vs 6.8 ± 13.3 for placebo) and severe ARI days (2.9 ± 9.5 for CVT-E002 vs 2.6 ± 9.8 for placebo). However, 51% of CVT-E002 vs 56% of placebo recipients experienced at least 1 ARI (difference, −5%; 95% confidence interval [CI], −16% to 7%); more intense ARI occurred in 32% of CVT-E002 vs 39% of placebo recipients (difference, −7%; 95% CI, −18% to 4%), and symptom-specific evaluation showed reduced moderate to severe sore throat ($P = .004$) and a lower rate of grade ≥3 toxicities ($P = .02$) in CVT-E002 recipients. Greater seroconversion (4-fold increases in antibody titer) vs 9 common viral pathogens was documented in CVT-E002 recipients (16% vs 7%, $P = .04$).

Limitations: Serologic evaluation of antibody titers was not tied to a specific illness, but covered the entire study period.

Conclusion: CVT-E002 was well tolerated. It did not reduce the number of ARI days or antibiotic use; however, there was a trend toward reduced rates of moderate to severe ARI and significantly less sore throat, suggesting that the increased rate of seroconversion most likely reflects CVT-E002-enhanced antibody responses.

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, accounting for nearly one-third of all leukemias.[1,2] Almost all cases of CLL occur in adults 50 and older with a median age at diagnosis in the mid-60s.[2,3] Median survival is 4-5 years after initiation of treatment, but early-stage patients often do not require treatment for many years after diagnosis.[1] Both the underlying CLL and its treatment result in immune compromise, particularly poor antibody responses; infection is common.[1,4] The most common infections in CLL patients are acute respiratory infections (ARIs).[4] Many of these ARIs are viral, but antibiotics are frequently prescribed because it is difficult to differentiate viral from bacterial infection. The rate of major infection (ie, infection severe enough to require hospitalization or treatment with parenteral antibiotics) is 0.04, 0.06, and 0.14 per patient per month in patients being treated with

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chlorambucil, fludarabine, and the combination, respectively.[3] Untreated CLL patients are more prone to infection than are similar-age patients with nonmalignant comorbidity (eg, myocardial infarction) based on data published more than 30 years ago;[5] but there are no more recent data, and those data included patients with a mix of CLL stages. Because the vast majority of CLL patients are older than age 60, it is likely that immune senescence (ie, the waning of immunity with advanced age) also a risk factor for infection.[6] Recent studies[7] suggest that the mean number of ARI days during the winter respiratory illness season within this age group is about 8.

Strategies to prevent infection are problematic in CLL. Inadequate antibody responses render vaccines less effective.[1-4] Infusion of intravenous immunoglobulin (IVIG) has been used in subjects with low serum immunoglobulin G (IgG) (<500 mg/dL). However, IVIG use is controversial due to supply issues, lack of consensus on frequency of administration or dose, and the questionable cost-effectiveness of this very expensive therapy (approximately $11,000,000 per quality-adjusted life year gained).[2] Prophylactic antibiotics are much less expensive, but this strategy likely enhances antimicrobial resistance and has poor compliance; prophylaxis for common viral pathogens is not available.[1-4] Thus, there is a pressing need for effective, low-cost interventions that enhance immunity, reduce infection risk, and limit antibiotic use in CLL patients.

CVT-E002, a patented mixture of polysaccharides isolated from *Panax quinquefolius* (Afexa Life Sciences, Edmonton, Canada), has been investigated as an immunomodulatory compound. The accumulated data on the mechanism of action indicate that CVT-E002 is an innate immune modulator, acting through toll-like receptors on the surfaces of these cells. This activation leads to increased numbers and function of cells within both the innate and adaptive immune systems.[8-11] CVT-E002 reduces the incidence of ARIs in adults.[7,12-14] Importantly, 3 of these studies[7,12,14] were performed in older adults, the population most affected by CLL. One study in healthy, community-dwelling seniors showed that CVT-E002 reduced the number of days with respiratory illness symptoms by more than 50%.[12] Another study was conducted in long-term care (nursing home) residents,[7] with the main end point being laboratory-confirmed symptomatic influenza; of 101 placebo recipients, only 7 had confirmed influenza or respiratory syncytial virus (RSV) illness, compared with only 1 of 97 CVT-E002 recipients ($P = .033$). In the third study, conducted in 783 community-dwelling seniors,[14] the incidence of respiratory illness was decreased by one-third in the CVT-E002 recipients ($P = .04$).

In addition to older age, there are important parallels of subjects in published CVT-E002 studies[7,12,14] with CLL patients. Subjects in two studies[7,14] were highly immunized (>90% received an influenza vaccine within 2 years); thus, most cases of influenza represented vaccine failure. Also, the characteristics of long-term care residents—older age, multiple comorbidities, and impaired immunity including ineffective vaccine responses—closely resemble the population and immune milieu of CLL patients. Based on these parallels and the need for effective preventive measures for ARI in CLL patients, we performed a randomized, double-blind, placebo-controlled trial of CVT-E002 to reduce ARI and the need for antibiotic treatment in CLL patients.

MATERIALS AND METHODS

Subject Selection and Enrollment

Subjects were enrolled between November 1 and December 31, 2008, at sites affiliated with the Community Clinical Oncology Program Research Base of Wake Forest University's Comprehensive Cancer Center or the National Cancer Institute's (NCI's) Cancer Trials Study Unit. Inclusion criteria were age ≥18 years, phenotypic evidence of CLL (flow cytometry or bone marrow), Eastern Cooperative Oncology Group (ECOG, Zubrod) performance status ≤2, life expectancy >12 months, and ability to provide informed consent. Exclusion criteria were human immunodeficiency virus; cirrhosis; autoimmune disease (eg, multiple sclerosis); malignancy other than CLL (nonmelanoma skin cancer and carcinoma in situ of the cervix were allowed); creatinine clearance ≤50 mL/min; serum glutamic oxaloacetic transaminase (SGOT, aspartate aminotransferase) or serum glutamic-pyruvic transaminase (SGPT, alanine aminotransferase) ≤2.5 times upper limit of normal (ULN); total bilirubin ≤1.5 times ULN; current or prior treatment with fludarabine, alemtuzumab, or rituximab; IVIG; hematopoietic stem cell transplantation; current or recent (within 3 months) therapy with chlorambucil; current treatment with corticosteroids equivalent to ≥20 mg/day prednisone; use of antibiotic prophylaxis other than trimethoprim-sulfamethoxazole (TMP-SMX); current use of warfarin; allergy to ginseng products; or current use of other herbal products (and unwillingness to discontinue).

Subjects were stratified by use of prophylactic TMP-SMX (yes/no), serum IgG (≤500 vs >500 mg/dL), and influenza vaccine status for the enrollment year (yes/no) and randomized (1:1) to receive CVT-E002 (200 mg twice daily) or matching placebo (microcrystalline cellulose) orally. Treatment continued from the time of enrollment through April 30, 2009, to allow for a consistent period of time during which all subjects were on protocol (January 1 through April 30). This period encompassed the time of maximal respiratory tract infection and influenza risk (January to April) regardless of geography in the United States.

Definitions and Main Outcomes

The main outcome measured was ARI days during a fixed 3-month period (January 1 through March 31). Subjects took CVT-E002 or placebo for an additional month to ensure that secondary end points were met and to encompass a potential late influenza season in the treatment period. All subjects were seen at enrollment, week 4, week 10, and the end of the study; a follow-up phone call was performed 4 weeks later to assess any adverse events.

Subjects kept a daily symptom diary to determine the number of ARI days, and study personnel instructed subjects at enrollment regarding each item in the diary. Symptoms specifically queried daily included cough, sore throat, nasal/sinus congestion, runny nose, feverishness, chills/sweats, myalgias (muscle aches), fatigue, headache, poor endurance, and increased shortness of breath. Each symptom was rated on a 0-3 scale of severity (0 = absent, 1 = mild, 2 = moderate, 3 = severe). If they felt feverish, subjects were asked to take their temperature orally with a home thermometer. Subjects also indicated whether symptoms limited their participation in usual activities.

An *ARI day* was defined as any day on which the subject experienced 1 or more respiratory symptoms (cough, sore throat, nasal or sinus congestion, or runny nose) and 1 or more systemic symptoms (feverishness, chills/sweats, myalgias, fatigue, headache, poor endurance, or increased shortness of breath). Use of the rating scale for each symptom allowed the first validation of the instrument in CLL patients with other commonly used scales, such as the modified Jackson criteria for "colds"[15] as later refined by Gwaltney et al.[16] *Severe* ARI days were defined as an ARI day plus one of the following: fever (oral temperature >100°F) or limited participation in usual activities.

Antibiotic use days were defined as days on which systemic (oral/parenteral) antibiotics were given once or multiple times for any reason, excluding prophylactic TMP-SMX. Subjects recorded the information on antibiotic-use forms, and entries were confirmed by study personnel during visits.

Toxicities were evaluated by the standard Common Toxicity Criteria–NCI Version 3.0. Any untoward adverse events were reported to the institutional review board and the Comprehensive Cancer Center of Wake Forest University Clinical Research Oversight Committee for further review.

Serologic Responses to Common Respiratory Viruses

Enzyme immunoassay was performed to detect virus-specific serum IgG for 9 respiratory viruses: influenza A and B, RSV, parainfluenza virus (PIV) serotypes 1-3, human metapneumovirus (hMPV), and coronaviruses 229E and OC43 per published methods.[17-20] Briefly, antigens were produced from virally infected whole-cell lysates for all viruses except RSV. Purified viral surface glycoproteins were used as antigen for RSV enzyme immunoassay according to a published method.[17] Paired serum samples were screened at a single dilution, and those showing a ≥1.5 increase in optical density reading from baseline to the end of study were further tested by full dilution to determine antibody titer. Serial 2-fold dilutions of each sample were tested in duplicate. Seroconversion was defined as a ≥4-fold rise in antibody from baseline to end of study.

Statistical Analyses

Chi-squared and Wilcoxon rank-sum tests were used to assess baseline group differences in categorical and continuous variables, respectively. Fisher's exact test and Poisson regression were used to compare toxicities in the 2 groups. Efficacy outcomes were assessed over the 3-month period between January and March (primary analyses) and toxicity outcomes over the entire study. Negative binomial regression was used to assess the effect of treatment arm on the rate of events. Exposure times were included in the models, as not all subjects returned all diaries. The negative binomial model was used, as the variances of the outcomes were greater than what was predicted by a Poisson model. In these models, age, sex, and strata were used as covariates. Fisher's exact test was used to assess differences in the proportion of subjects with seroconversion vs measured viral pathogens, and Poisson regression was used to compare seroconversion rates.

Originally designed for a sample size of 112 patients per group (which would allow detection of a 30% difference in the number of ARI days with 90% power at the 5% 2-sided level of signif-

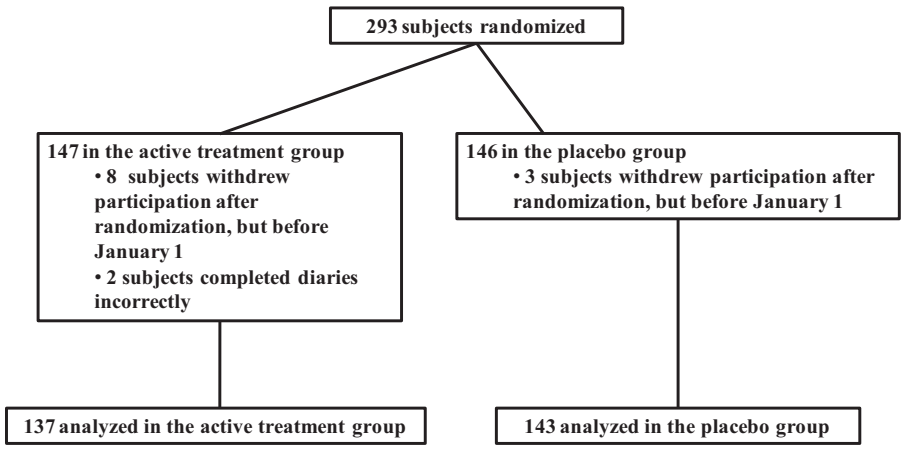

Figure 1

The CONSORT Diagram is a breakdown of subjects enrolled in the study.

Table 1

Baseline Demographics and Clinical Characteristics of Evaluable Subjects

CHARACTERISTIC	CVT-E002, NO. (%)	PLACEBO, NO. (%)	*P*
Total	137 (100)	143 (100)	
Age (years)			.810
Median (range)	65 (43–87)	66 (44–82)	
<50	6 (4)	9 (6)	
50–59	37 (27)	30 (21)	
60–69	46 (34)	56 (39)	
70–79	36 (26)	44 (31)	
80+	12 (9)	4 (3)	
BMI (kg/m^2)			.927
Median (range)	27.9 (17–47)	28.2 (18–41)	
Underweight-normal (<25)	30 (22)	34 (24)	
Overweight (25–30)	57 (42)	61 (43)	
Obese (>30)	50 (36)	48 (34)	
Strata			—
3: TMP/SMX, yes; IgG, >500; influenza vaccine, yes	1 (1)	1 (1)	
4: TMP/SMX, yes; IgG, >500; influenza vaccine, no	1 (1)	0 (0)	
5: TMP/SMX, no; IgG, ≤500; influenza vaccine, yes	11 (8)	13 (9)	
6: TMP/SMX, no; IgG, ≤500; influenza vaccine, no	3 (2)	2 (1)	
7: TMP/SMX, no; IgG, >500; influenza vaccine, yes	94 (69)	99 (69)	
8: TMP/SMX, no; IgG, >500; influenza vaccine, no	27 (20)	28 (20)	
Race			.623
Hispanic	0 (0)	2 (1)	
Asian	0 (0)	1 (1)	
Black	1 (1)	2 (1)	
White	136 (99)	138 (97)	
Sex			
Female	59 (43)	59 (41)	.760
Male	78 (57)	84 (59)	
ECOG Performance Status			.583
0	125 (91)	133 (93)	
1	12 (9)	10 (7)	

icance, assuming a coefficient of variation of 80%), the accrual was bolstered to account for an assumed 20% dropout rate.

RESULTS

From November 1, 2008, through December 31, 2008, 293 subjects were enrolled; 147 subjects were randomized to active drug and 146 to placebo (Figure 1). Diaries were not completed by 12 patients, 11 of whom decided not to participate in the study after being randomized and 1 of whom refused to complete the diary. An additional patient completed the diary incorrectly. These 13 subjects were excluded, leaving 280 analyzed subjects (137 in the active treatment group and 143 in the placebo arm). Table 1 shows subject characteristics in each group; there were no significant differences between groups in any of the characteristics. The study was completed by 120 subjects in the active treatment group and 125 subjects in the placebo arm. Reasons for withdrawal were similar between groups; only 2 subjects in the active group and 1 subject in the placebo group withdrew due to toxicity. In both groups, 92% of all daily diaries were completed and returned. Mean adherence with prescribed medication (by patient self-report on completed diaries) was 97% in both groups.

ARI Days and Antibiotic Use

An ARI occurred in 54% of subjects overall during the 3-month primary study period of interest. The overall rate of ARIs was 0.09 per patient day; or, on average, subjects experienced an ARI approximately 1 of every 11 days. There were no significant differences in the 2 *a priori* primary end points—: ARI days were 8.5 ± 17.2 in the CVT-E002 recipients vs 6.8 ± 13.3 in the placebo group (10.5% ± 20.1% vs 8.2% ± 15.6%, respectively; $P = .23$), and severe ARI days were 2.9 ± 9.5 in CVT-E002 recipients vs 2.6 ± 9.8 in placebo recipients (3.4% ± 11% vs 3.1% ± 12%, respectively; $P = .78$). There were also no significant differences in the 2 *a priori* secondary end points: Antibiotic use days were 1.8 ± 5.0 for CVT-E002 vs 2.3 ± 7.1 for placebo ($P = .37$),

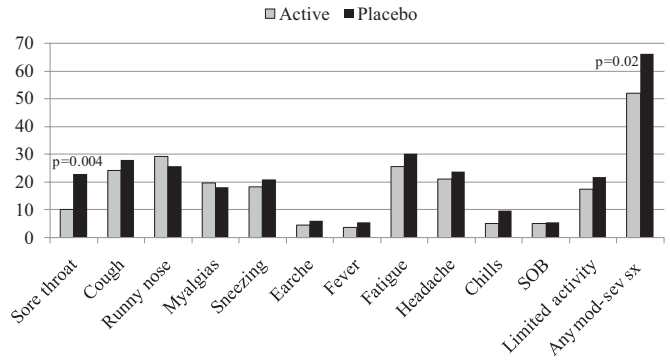

Figure 2

Respiratory Illness Symptoms Reported as Moderate to Severe. The percentage of subjects in each group reporting moderate to severe ARI symptoms (worst reported severity, January to March) is shown.

and Jackson-defined cold days were 2.1 ± 6.6 for CVT-E002 vs 1.2 ± 3.2 for placebo (P = .23).

Incidence of ARI

When data were examined as the proportion of subjects experiencing an ARI, 51% of CVT-E002 recipients experienced at least 1 ARI day vs 56% of placebo recipients (difference, −5%; 95% confidence interval [CI], −16% to 7%; P = .42) and 27% of CVT-E002 recipients experienced at least 1 severe ARI day vs 30% of placebo recipients (difference, −3%; 95% CI −13% to 8%; P = .57). *More intense* ARIs, defined as the occurrence of multiple mild symptoms or 1 or more moderate to severe symptoms, were experienced by 32% of CVT-E002 recipients vs 39% in the placebo group (difference, −7%; 95% CI −18% to 4%; P = .22). Analysis of specific moderate to severe symptoms (sore throat, cough, runny nose, congestion, sneezing, earaches, myalgias, fever, fatigue, headache, chills, and shortness of breath) showed a significantly lower rate of sore throat (P = .004) and any moderate to severe symptom (P = .02) in the CVT-E002 group (Figure 2).

Seroconversion vs Common Respiratory Viruses

Of 191 subjects with serum specimens available at baseline and at the end of the study, 22 (15 of 91 CVT-E002 recipients vs 7 of 100 in the placebo group) experienced seroconversion to a common respiratory virus (Table 2; P = .04). As seroconversion to more than 1 virus could occur, we also determined that 27 seroconversions occurred in the 22 subjects, for a seroconversion rate/cold season of 0.22 in CVT-E002 vs 0.07 in placebo recipients (P = .005).

The study design did not allow for serologic sampling before and after each ARI episode, so we cannot match a given ARI event with a specific viral etiology. However, of the 22 subjects experiencing seroconversion, 5 were asymptomatic throughout the study period (that is, 5 in the CVT-E002 group and 1 in the placebo group experienced no ARI days), suggesting asymptomatic conversion. The 5 subjects had seroconversion vs coronavirus 229E or PIV type 2, suggesting that all influenza, RSV, hMPV, and PIV types 1 and 3 were likely symptomatic.

Immune and Disease Activity Parameters

There were no significant differences in either group in pre- vs post-white blood cell count, platelet count, total serum IgG level, percent CD4 T cells, or β_2-microglobulin. Given the short duration of the study, one would not expect progression of CLL in many patients; and there was no difference between groups before and after intervention as measured by Rai stage.

Safety

CVT-E002 was well tolerated. Toxicities were evaluated both as the number of patients experiencing toxicity and as the rate over time, because a subject could experience more than one event; the overall number of subjects and rates of adverse events and serious adverse events were not different between groups. The most commonly reported adverse events

Table 2

Number of Subjects Experiencing a Seroconversion (≥4-Fold Rise in Antibody Titer) vs 9 Common Respiratory Viruses During the Entire Study Period

VIRUS	CVT-E002 (N = 91)	PLACEBO (N = 100)	*P*
Influenza A	1	0	.48
Influenza B	1	1	1.0
Respiratory syncytial virus	1	1	1.0
Human metapneumovirus	6	1	.06
Parainfluenza type 1	1	1	1.0
Parainfluenza type 2	1	0	.48
Parainfluenza type 3	1	1	1.0
Coronavirus 229E	3	1	.35
Coronavirus OC43	5	1	.10
Proportion of subjects with seroconversion/cold season	1591 (16%)	7/100 (7%)	.04
Seroconversion rate/cold season	0.22	0.07	.005

Included in the analysis were 191 subjects who had serum samples available both at baseline and at the end of the study. Totals are given both as proportion of subjects in each group experiencing seroconversion/cold season and, since individuals could seroconvert to more than one virus, as the rate of seroconversions/cold season by group.

in both groups (number of subjects in the active group vs the placebo group) were joint pain (47 vs 58), insomnia (45 vs 31), hyperglycemia (30 vs 39), and headache (31 vs 37). There was, however, a difference in the rate of severe (grade 3 or higher) toxicities reported between groups. From January 1 to April 30, 13 of 142 subjects in the control arm, compared with 8 of 135 in the CVT-E002 arm, experienced at least 1 grade 3 or higher toxicity ($P = .37$). However, control patients experienced a greater cumulative number of grade 3+ toxicities (25 vs 12; $P = .02$).

DISCUSSION

ARI is common in CLL. ARI symptoms occurred on 9% of all days from January 1 through March 31 in enrolled subjects. CVT-E002 did not significantly reduce ARI days or antibiotic use, although a trend was noted for CVT-E002–associated reductions in the rate of moderate to severe ARI, and significant reductions were seen in the rates of any moderate to severe symptom and of moderate to severe sore throat. A greater proportion of CVT-E002 recipients experienced seroconversion to common viruses (16% vs 7%; $P = .04$).

Previous studies have noted high rates of respiratory infection in CLL patients,[1-5] but nearly all prior studies examined patients with CLL in later stages that require treatment. To our knowledge, this is the first study to determine the incidence of ARI in untreated, early-stage CLL patients. More than 50% of subjects in this study experienced at least 1 ARI. Furthermore, ARI symptoms were reported on ~9% of the 90 days from January 1 to March 31, a rate similar to previously published data in healthy, community-dwelling older adults.[12] For the vast majority of days, symptoms were mild and did not result in antibiotic use. The average number of antibiotic use days was ~2 in both groups. The mild nature of ARI symptoms may have been due to relatively mild influenza activity during 2008 to 2009 (http://www.cdc.gov/flu/weekly/fluactivity.htm); indeed, of 191 subjects with serologic data, only 3 episodes of influenza seroconversion were confirmed (Table 2). A limitation of this study is that symptoms and serology were used to identify ARIs; prospective surveillance using polymerase chain reaction or viral culture would have been preferable, but was beyond the scope of support available for this study.

In 4 prior randomized, controlled studies in adult populations, CVT-E002 was safe and reduced ARI risk.[7,12-14] This is the first study in CLL subjects; the safety and tolerability of CVT-E002 was again evident in this trial, with no difference compared with placebo recipients. However, there was no effect on ARI illness days or antibiotic use, the *a priori*–defined end points. The lack of efficacy for reaching ARI end points in CLL patients could be due to multiple factors. The accumulated data on the mechanism of CVT-E002 indicate that CVT-E002 is an innate immune modulator, acting through toll-like receptors on the surfaces of these cells. This activation leads to increased numbers and function of cells within both the innate and adaptive immune systems.[8-11] However, there is no current method to measure blood/tissue levels of the "active compound," nor a measurable bioassay to allow a correlation of outcome with evidence of drug effect. It is possible that these pathways are not sufficiently influenced by CVT-E002 at the dose utilized to demonstrate clinical benefit in CLL patients, or that the toll-like receptor pathway is impaired in CLL patients. However, the results regarding seroconversion suggest otherwise (see below), and indicate that further study of higher doses of CVT-E002 is warranted. In addition, it is worth noting that the variability in the symptom-defined measures was far greater than that seen in previous studies in nonleukemic participants, which may have contributed to the failure to reach significance.

To our knowledge, this is the first study in CLL patients treated with an immune modulating agent to comprehensively evaluate seroconversion vs multiple viral pathogens that cause ARI. The serologic data (Table 2) suggest that 4-fold increases in antibodies occurred more frequently in CVT-E002 recipients, reaching statistical significance for combined viral infection rates. Increased viral exposure risk in CVT-E002 recipients seems very unlikely. Furthermore, an increased risk for viral infection is not consistent with the clinical data that show a trend toward lower incidence of moderate to severe ARI in CVT-E002 recipients. The seroconversion data are much more consistent with enhanced immune responses as a result of CVT-E002 therapy. Sensitivity for detecting seroconversion rests on documenting a 4-fold rise in titer. CLL patients generally have impaired antibody responses.[1,3-5] Thus, a more likely explanation for the demonstrated seroconversion rate difference is a manifestation of CVT-E002–enhanced, virus-specific antibody responses, a hypothesis being evaluated by our group and others.

CONCLUSIONS

In summary, ARI is a common complication in patients with untreated CLL, with an average of 1 day in every 11 being an ARI day during the winter respiratory virus season. CVT-E002 was well tolerated but did not reduce the number of ARI days or severe ARI days, the two *a priori* primary end points, or antibiotic use. CVT-E002 therapy, however, was associated with trends toward a reduced rate of more intense ARI and a significant reduction in the percentage of subjects reporting moderate to severe sore throat, any moderate to severe symptom, or grade ≥3 toxicity. A significant increase in the rate of seroconversion vs respiratory viral pathogens in CVT-E002 recipients most likely reflects augmented antibody responses. Future research should examine whether CVT-E002 can affect antibody titers after immunization in CLL patients, and whether higher doses of CVT-E002 might effectively reduce ARI incidence and severity.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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