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Immunoglobulin repletion during blinatumomab therapy does not reduce the rate of secondary hypogammaglobulinemia and associated infectious risk

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Background
Blinatumomab has demonstrated efficacy in minimal residual disease (MRD) positive and relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) by inciting rapid and sustained B-cell depletion.

Methods
Owing to its effect on B-cells, blinatumomab is associated with a higher rate of secondary hypogammaglobulinemia compared to chemotherapy. To mitigate blinatumomab-induced hypogammaglobulinemia, patients were pre-emptively repleted with intravenous immune globulin (IVIG) during blinatumomab therapy. In this retrospective study, we compared outcomes of 23 blinatumomab treated adults with ALL. Seventeen patients routinely received IVIG and 6 patients were in the control cohort.

Results
Our findings demonstrated no difference between the two cohorts in immunoglobulin G (IgG) nadir (338 mg/dL vs. 337 mg/dL, P=0.641), days to IgG nadir (120.5 vs. 85.5 days, P=0.13), infection rate (82.4% vs. 66.7%, P=0.58), infections requiring ICU admission (23.5% vs. 16.7%, P=1), and infection related mortality (17.6% vs. 16.7%, P=1).

Conclusion
Pre-emptive IVIG repletion during blinatumomab did not prevent hypogammaglobulinemia and associated infection risk.

Key Words Acute lymphoblastic leukemia, Blinatumomab, Hypogammaglobulinemia, ALL, Intravenous immunoglobulin

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is an aggressive disease with a poor prognosis in adults with 5-year overall survival (OS) depending heavily on post-treatment measurable residual disease (MRD) status [1, 2]. In patients who do achieve MRD negativity, median 5-year OS is approximately 60% [1]. The presence of MRD in B-precursor ALL prognosticates chemotherapy-refractory disease and relapse, with a rate of subsequent relapse in 90% of cases [3, 4]. In the relapsed/refractory setting, the 5-year OS is dismal at 3–10% [5]. Identifying actionable targets, such as CD19 which is expressed on over 90% of B-cell ALL blasts provides opportunity for targeted therapy aimed at improving outcomes [6, 7]. Blinatumomab (Blincyto) is a bispecific T-cell engaging antibody which binds to CD19 on B-cells and CD3 on T-cells to activate cytotoxic killing of malignant and healthy B-cells [8]. Blinatumomab has demonstrated efficacy in MRD positive, or relapsed/refractory B-ALL by inciting rapid and sustained B-cell depletion [8, 9].

Therapy-induced depletion of CD19-positive B-cells, plasmablasts, and plasma cells can lead to a prolonged state of hypogammaglobulinemia including immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG), which play a central role in pathogen elimination

in the humoral immune response [10, 11]. In a phase III trial, the incidence of secondary hypogammaglobulinemia was reported in 16% of blinatumomab treated patients with relapsed/refractory ALL compared to 1% in patients who received chemotherapy [12]. Despite the higher rate of hypogammaglobinemia in blinatumomab treated patients, the lower rates of both ≥ grade 3 neutropenia (37.8% vs. 57.8%) and ≥ grade 3 infections (34.1% vs. 52.3%) were observed in blinatumomab group compared to the patients who were treated with chemotherapy [12]. The duration of hypogammaglobulinemia post-blinatumomab treatment has been shown to last for over a year, though this does not account for the baseline hypogammaglobulinemia some patients have prior to the initiation of blinatumomab [11]. Interestingly, a reduction in IgG level post-blinatumomab was observed in patients with ALL who achieved treatment response but not in patients who did not respond to blinatumomab, suggesting a correlation between development of secondary hypogammaglobulinemia and blinatumomab treatment response [11].

Secondary hypogammaglobulinemia and associated infections were shown to be highly prevalent in patients with chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) as a result of disease-related and/or treatment-related factors, and the beneficial effects of monthly IVIG repletion in these patients with low IgG level (<500 mg/dL) for the prevention of recurrent bacterial infections has been well established [13]. In contrast, there is a paucity of clinical data supporting IVIG replacement therapy in patients with ALL for the reduction of infectious complications associated with secondary hypogammaglobulinemia [14].

The objective of this study was to evaluate the utility of IVIG repletion during blinatumomab therapy in patients with MRD positive or relapsed/refractory B-ALL to reduce the risk of hypogammaglobulinemia and associated infectious complications.

MATERIALS AND METHODS

Study design and population

This is a single-center, retrospective study that was performed between July 2015 and June 2020 at the Mount Sinai Hospital (MSH). The study was institutional review board (IRB)-approved, and the IRB approved a waiver of informed consent. Patients who received at least 1 cycle of blinatumomab were identified by a report generated by the electronic health record (EHR) and screened for study inclusion. IVIG administration during blinatumomab therapy was defined by the administration of IVIG starting a month prior to the first cycle of blinatumomab, during blinatumomab therapy, and until the initiation of the next line of therapy. Patients who received IVIG for at least 1 cycle of blinatumomab therapy were assigned to the IVIG cohort, and patients who did not receive IVIG during blinatumomab therapy were assigned to the control cohort. In relapsed/refractory ALL, complete response (CR) was defined as <5% bone marrow (BM) lymphoblasts with or without count recovery. In MRD positive ALL, response was defined as achieving MRD negative status [based on flow cytometry with sensitivity of 0.01%, and/or undetectable *BCR-ABL* by PCR in patients with Philadelphia chromosome-positive (Ph [+]) disease]. For the purpose of this study, we have utilized a novel definition of partial response (PR) in patients with Ph+ ALL with MRD positive disease, as achieving a 1 to 2 log reduction in *BCR-ABL* transcript level but that remained above 0.01 in order to further illustrate if there is a relationship between hypogammaglobulinemia and treatment response. We collected data on microbiologically documented infections that were determined to be clinically significant.

Blinatumomab was administered as a continuous intravenous (IV) infusion over 28 days per cycle, with at least 2 weeks of treatment-free intervals. The total number of treatment cycles depended on the indication and/or other factors [i.e. plan for hematopoietic stem cell transplant (HSCT), treatment response]. Starting in 2018, the Adult Leukemia Program at our institution implemented a practice change to administer IVIG 400 mg/kg (using ideal body weight and rounded to nearest vial size) prior to the initiation of each cycle of blinatumomab in patients with MRD positive or relapsed/refractory ALL in an attempt to reduce the risk of severe hypogammaglobinemia and associated infection risk. In the event that a patient's blinatumomab cycle was delayed, IVIG administration was likely held until the blinatumomab cycle was initiated.

Inclusion and exclusion criteria

Patients were included in the study if they were at least 18 years of age and received blinatumomab for B-ALL. Patients were excluded if they: (i) received blinatumomab for indications other than B-ALL, or (ii) were initiated on blinatumomab during an active infection and died.

Data collection

Data collection included patient demographics, prior history of a microbiologically documented clinically relevant infection with a multi-drug resistant organism (MDR), known risk factors for hypogammaglobulinemia (prior anti CD20 therapy, MM, CLL), immunoglobulin levels, blinatumomab treatment details, infections and infection related mortality, infections necessitating intensive care unit (ICU) admission, and blinatumomab treatment response. Common Terminology Criteria for Adverse Events (CTCAE) v5 was used to grade adverse events and infections.

Outcomes

The primary outcome was to evaluate the utility of IVIG administration during blinatumomab in MRD+ or relapsed/refractory B-ALL to reduce the risk of hypogammaglobulinemia-associated infectious complications. Secondary outcomes included the correlation between IgG levels and blinatumomab treatment response. All endpoints were assessed from the start of blinatumomab therapy until last

available follow up at data cut-off or up to a maximum of 1 year after the last dose of blinatumomab.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics. Variables were expressed as median values with ranges of minimum and maximum values. Comparisons between the control and IVIG cohorts were conducted using Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. *P*-value of ≤0.05 denoted statistical significance.

RESULTS

A total of 23 patients were included in the study, of whom 17 patients (74%) received at least 1 dose of IVIG during blinatumomab therapy and 6 patients (26%) did not. Patient characteristics were similar between the two cohorts (Table 1). Excluding 3 patients who received blinatumomab for consolidation or maintenance therapy, 75% of the patients (15/20) received blinatumomab for MRD positive B-ALL indication. Patients received a median of one (range, 1–5) prior line of treatment. Known risk factors for hypogammaglobulinemia were present in 10 patients (43.5%), all of whom had prior rituximab therapy with one patient having a history of MM. Notably, patients in the control cohort received a higher median cumulative number of doses of rituximab than the IVIG cohort [6.5 doses (range, 6–7) vs. 3 doses (range, 1–5), *P*=0.044]. The median number of blinatumomab treatment cycles administered was 2 (range, 1–8) in the IVIG cohort and 2 (range, 1–2) in the control cohort. The median length of each blinatumomab cycle was 55 days (range, 22–163) in the IVIG cohort and 56 days (range, 41–78) in the control cohort. In the IVIG cohort, a median percent of blinatumomab treatment cycles administered with IVIG repletion was 100% (range, 50–100%), with 13 patients (76.5%) receiving IVIG for all blinatumomab cycles. Patients in the IVIG group received a median of 1 dose of IVIG (range, 0–12) per each cycle of blinatumomab. Infusion related reactions (IRR) during IVIG occurred in 4 patients (23.5%) with a median of one IRR per patient. All IRRs were grade 2 reactions.

Immunoglobulin levels

Immunoglobulin data are provided in Table 2. Prior to starting blinatumomab, 47.6% patients had some component of hypogammaglobulinemia; 47.6% had documented IgG hypogammaglobulinemia, 9.5% had IgA hypogammaglobulinemia, and 42.9% had IgM hypogammaglobulinemia. Additionally, 42.9% had combined immunoglobulin deficiencies; 7 of these patients had both IgG and IgM hypogammaglobulinemia, and 2 patients had deficiency in all 3 immunoglobulins (IgG, IgA, and IgM). Eleven patients did not have IgG hypogammaglobulinemia at baseline (IgG levels >700 mg/dL) prior to starting blinatumomab; 10 (91%) of these patients

Table 1. Baseline characteristics.

	All (N=23)	Control (N=6)	IVIG (N=17)	*P*
Demographics				
Age at blinatumomab initiation, median, years (range)	56 (25–74)	57.5 (50–64)	48 (25–74)	0.32
Male	9 (39.1)	3 (50)	6 (35.3)	0.64
BMI, kg/m^2, median (range)	24.47 (18.48–31.89)	25.49 (21.84–31.89)	24.27 (18.48–29.87)	0.43
Total follow up from blinatumomab initiation, days, median (range)	393 (108–926)	354.5 (147–453)	424 (108–926)	0.32
Disease characteristics				
MRD (+)[a]	15 (75)	5 (83.3)	10 (71.4)	1
Relapsed/refractory[a]	5 (25)	1 (16.7)	4 (28.6)	1
Number lines of prior therapy, median (range)	1 (1–5)	2 (1–2)	1 (1–5)	0.76
Philadelphia chromosome (+)	7 (30.4)	1 (16.7)	6 (35.3)	0.62
HSCT prior to blinatumomab	3 (13)	0 (0)	3 (17.6)	0.54
Infectious disease history				
History of MDR infection	5 (22.7)	2 (40)	3 (17.6)	0.55
ESBL	1 (4.3)	1 (16.7)	0 (0)	0.26
MRSE	4 (17.4)	1 (16.7)	3 (17.6)	1
Hypogammaglobulinemia Risk factors				
Prior anti-CD20 therapy	10 (43.5)	2 (33.3)	8 (47.1)	0.66
Number of doses, median (range)	3.5 (1–7)	6.5 (6–7)	3 (1–5)	0.04
Multiple myeloma	1 (4.3)	0 (0)	1 (5.9)	1

All values listed as N (%) unless otherwise noted.
[a]Excluding 3 patients who received blinatumomab for consolidation/maintenance therapy.
Abbreviations: BMI, body mass index; ESBL, extended spectrum beta-lactamase; HSCT, hematopoietic stem cell transplant; MDR, multidrug resistant organism; MRD, minimal residual disease; MRSE, methicillin-resistant staphylococcus epidermidis.

Table 2. Immunoglobulin data.

	Ref range (mg/dL)	All (N=23)	Control (N=6)	IVIG (N=17)	*P*
Baseline values (mg/dL)					
Baseline IgA, mg/dL, median (range)	70–400	128 (40–544)	117.5 (54–149)	132 (40–544)	0.18
Baseline IgA hypogammaglobulinemia		2 (9.5)	1 (16.7)	1 (6.7)	0.5
Baseline IgM, mg/dL, median (range)	40–230	41 (8–144)	44 (8–117)	41 (12–144)	0.73
Baseline IgM hypogammaglobulinemia		9 (42.9)	2 (33.3)	7 (46.7)	0.66
Baseline IgG, mg/dL, median (range)	700–1,600	716 (321–1,783)	836.5 (404–1,262)	716 (321–1,783)	0.97
Baseline IgG hypogammaglobulinemia		10 (47.6)	3 (50)	7 (46.7)	1
Nadir values (mg/dL), median (range)					
IgA Nadir[a)]	70–400	18 (<5–42)	11 (9–33)	19 (<5–42)	0.4
Time to nadir	-	101 (35–688)	82 (48–109)	119 (35–688)	0.14
IgM Nadir[a)]	40–230	9.5 (<5–47)	10 (<5–47)	9 (<5–38)	0.93
Time to nadir	-	86 (35–688)	82 (48–109)	93 (35–688)	0.45
IgG, Nadir	700–1,600	338 (221–1,006)	337 (221–587)	338 (258–1,006)	0.64
Time to nadir	-	103 (28–435)	85.5 (48–109)	120.5 (28–435)	0.13
IgG <500 mg/dL, N (%)	-	19 (86.4)	5 (83.3)	14 (87.5)	1
Last available immunoglobulin follow-up data, median (range)					
IgA[a)]	70–400	31 (<5–325)	20 (10–325)	36 (<5–313)	0.5
Day from blinatumomab initiation, days	-	244.5 (35–912)	109 (48–382)	285 (35–912)	0.31
IgM[a)]	40–230	27.5 (<5–211)	12 (<5–90)	30 (<5–211)	0.53
Day from blinatumomab initiation, days	-	244.5 (35–912)	109 (48–382)	279 (35–912)	0.35
IgG	700–1,600	591.5 (221–2,346)	787 (221–1,679)	547 (268–2,346)	0.91
Day from blinatumomab initiation, days	-	243 (35–912)	141.5 (48–445)	276.5 (35–912)	0.49
ANC <500 cells/μL at any time point, N (%)	-	19 (82.6)	6 (100)	13 (76.5)	0.54
Time to ANC <500 cells/μL, days, median (range)	-	71 (2–249)	65.5 (2–109)	96 (14–249)	0.35

All values listed as N (%) unless otherwise noted.
[a)]A value of <5 indicates a result below the detectable level.
Abbreviations: ANC, absolute neutrophil count; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

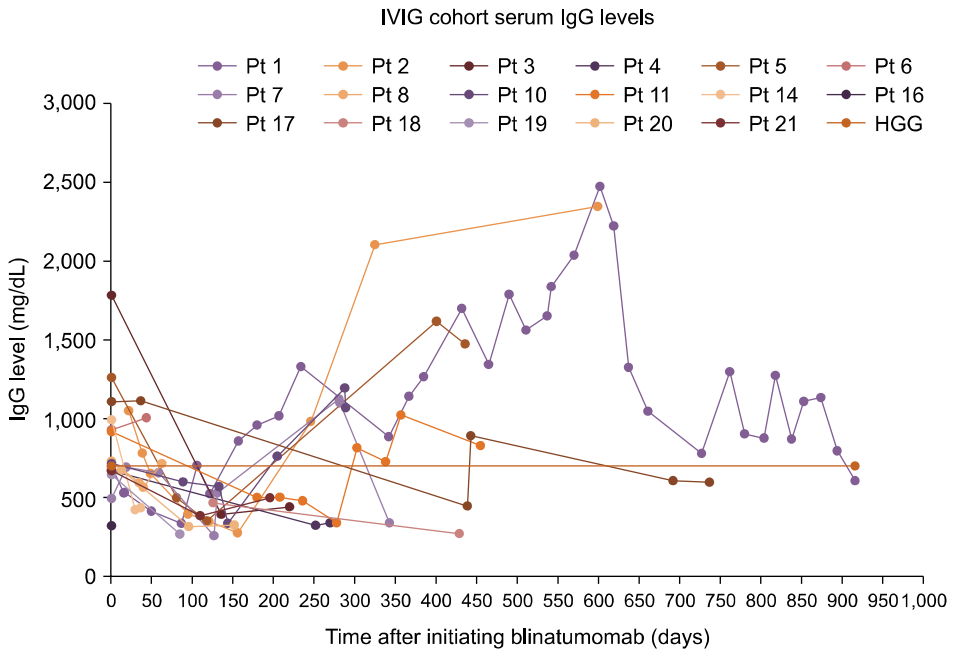

Fig. 1. Serum IgG levels for patients in the IVIG cohort collected at baseline and to end of follow-up. Abbreviation: HGG, hypogammaglobulinemia.

developed IgG hypogammaglobulinemia during the study period. The median time to nadir in IgG, IgA, and IgM was similar between the IVIG and control cohorts. Our findings demonstrated no difference between the two cohorts in IgG nadir (338 mg/dL in the IVIG cohort vs. 337 mg/dL in the control cohort, P=0.641). Of note, the majority of patients (86.4%) had a documented IgG level <500 mg/dL. Median IgG level at 8 months was also similar between the two cohorts. Fig. 1 depicts serum IgG levels at all available time points during the time of baseline serum IgG level collection and up until 1 year after the last dose of blinatumomab for the IVIG cohort, and Fig. 2 depicts this information for the control cohort. Patients in both cohorts with baseline hypogammaglobulinemia had stable IgG levels throughout the evaluated period. Neutropenia [defined as absolute neutrophil count (ANC) <500 cells/μL] was common amongst patients during the study period, occurring in 19 patients (82.6%) at any time point.

Infections

Infection data are provided in Table 3. Overall, 78% of the patients developed infectious complications. No difference was seen between the IVIG and control cohorts in the rates of infection (82.4% vs. 66.7%, P=0.58), infections requiring ICU admission (23.5% vs. 16.7%, P=1), and infection related mortality (17.6% vs. 16.7%, P=1). The median time to first microbiologically documented infection occurred in both cohorts was similar [89 days (range, 20–131) in IVIG cohort vs. 99.5 days (range, 15–429) in control cohort, P=0.72]. Causative organisms were similar between IVIG and control cohorts for viral microbes (46.5% vs. 75%, P=0.33), bacterial microbes (47.9% vs. 20%, P=0.38), fungal microbes (2.8% vs. 5%, P=0.8), and parasites (2.8% vs. 0%, P=0.88). Of the total 88 microbiologically documented infectious events, 50 (56.8%) were severe infections (grade ≥3). There was no statistically significant difference between the IVIG and control groups in overall infection rate. Twelve patients (85.7%) in the IVIG group and three patients (75%) in the control cohort had one or more severe infections. The rates of total events of severe infections were also similar between the IVIG and control cohorts, [44/68 (64.7%) vs. 6/20 (30%), P=0.45].

Treatment response to blinatumomab

Details for treatment response to blinatumomab are provided in Table 4. Overall, 16 (80%) achieved treatment response to blinatumomab, and 14 patients (60.9%) proceeded to HSCT. One patient in the IVIG group who received blinatumomab for MRD+ disease achieved a partial response to blinatumomab. Two patients (10%) received additional chemotherapy for relapsed disease. In our study, there was no association between a reduction in IgG levels post-blinatumomab treatment and blinatumomab treatment response. The percent drop in IgG level from baseline was similar regardless of their response to blinatumomab therapy (52% in CR cohort vs. 53.6% in non-responders, P=0.43). Similarly, no difference was seen in the absolute reduction in IgG level from baseline to nadir between the CR cohort and non-responder cohort (368 mg/dL in CR cohort vs. 379 mg/dL in non-responders, P=0.77).

DISCUSSION

Multiple studies demonstrated benefits of IVIG repletion in preventing infections related to hypogammaglobulinemia in patients with CLL and MM, however there is a lack of data supporting clinical benefit in patients with B-ALL. This study is the first to report the clinical outcomes of IVIG repletion to reduce the risk of secondary hypogammaglo-

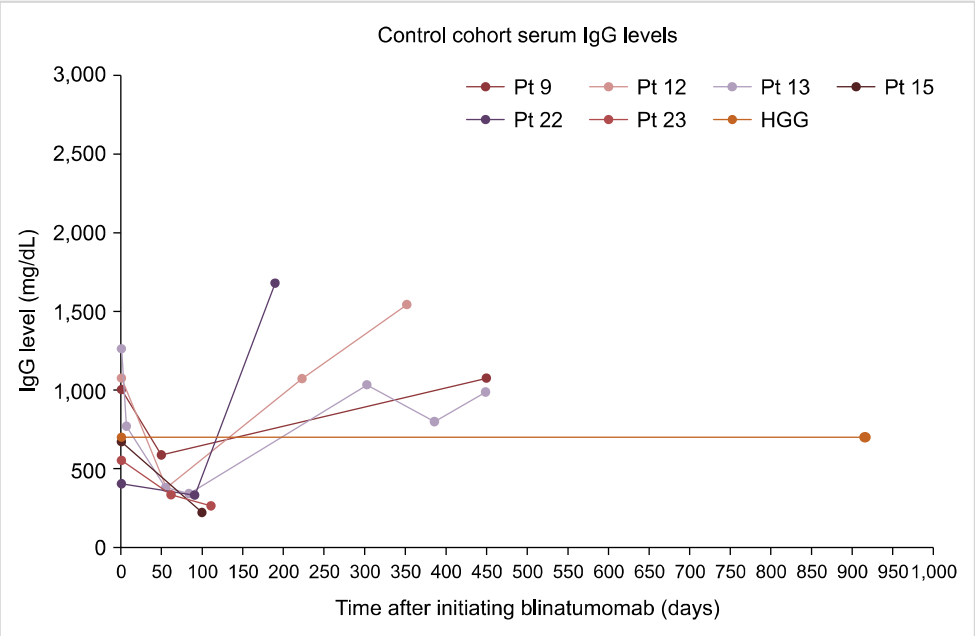

Fig. 2. Serum IgG levels for patients in the control cohort collected at baseline and to end of follow-up. Abbreviation: HGG, hypogammaglobulinemia.

Table 3. Infection outcomes.

	All (N=23)	Control (N=6)	IVIG (N=17)	*P*
N of patients with infection	18 (78.3)	4 (66.7)	14 (82.4)	0.58
Change in antibacterial agent or received antibiotic agent[e)]	22 (95.7)	6 (100)	16 (94.1)	1
Change in antifungal agent[e)]	5 (21.7)	1 (16.7)	4 (23.5)	1
Change in antiviral agent[e)]	10 (43.5)	4 (66.7)	6 (35.3)	0.34
N of infections per patient who had ≥1 infection, median (range)	4.5 (1–19)	4.5 (4–7)	4.5 (1–19)	0.65
Time to first infection, days median (range)	99.5 (15–429)	89 (20–131)	99.5 (15–429)	0.72
Organism type, median (range)	N=91	N=20	N=71	
Viral[a)]	48 (52.7)	15 (75)	33 (46.5)	0.33
Bacterial[b)]	38 (41.8)	4 (20)	34 (47.9)	0.38
Fungal[c)]	3 (3.3)	1 (5)	2 (2.8)	0.8
Parasite[d)]	2 (2.2)	0 (0)	2 (2.8)	0.88
Site, N (%)	N=89	N=20	N=69	
Bloodstream	33 (37.1)	9 (45)	24 (34.8)	0.28
Upper respiratory tract	20 (22.5)	9 (45)	11 (15.9)	0.16
Lower respiratory tract	11 (12.4)	1 (5)	10 (14.5)	0.96
Urinary	6 (6.7)	1 (5)	5 (7.2)	0.8
Gastrointestinal	13 (14.6)	0 (0)	13 (18.8)	0.23
Bone	1 (1.1)	0 (0)	1 (1.4)	0.88
Intra-abdominal	2 (2.2)	0 (0)	2 (2.9)	0.72
Mouth	1 (1.1)	0 (0)	1 (1.4)	0.88
SSTI	2 (2.2)	0 (0)	2 (2.9)	0.72
Patients with infection by severity, N (%)				
Grade 1	8 (44.4)	3 (75)	5 (35.7)	0.28
Grade 2	10 (55.6)	3 (75)	7 (50)	0.59
Grade 3	12 (66.7)	3 (75)	9 (64.3)	1
Grade 4	6 (33.3)	1 (25)	5 (35.7)	1
Grade 5	4 (22.2)	1 (25)	3 (21.4)	1
Severe infection (grade ≥3)	15 (83.3)	3 (75)	12 (85.7)	1
Infection severity incidence, N (%)	Total=88	Total=20	Total= 68	
Grade 1	22 (25)	8 (40)	14 (20.6)	1
Grade 2	16 (18.2)	6 (30)	10 (14.7)	0.38
Grade 3	29 (33)	3 (15)	26 (38.2)	0.21
Grade 4	17 (19.3)	2 (10)	15 (22.1)	1
Grade 5	4 (4.5)	1 (5)	3 (4.4)	1
Severe infection (grade ≥3)	50 (56.8)	6 (30)	44 (64.7)	0.45
Patients requiring ICU admission due to infection	5 (21.7)	1 (16.7)	4 (23.5)	1
Occurring while on blinatumomab	1 (20)	0 (0)	1 (25)	1
Patients with infection related mortality	4 (17.4)	1 (16.7)	3 (17.6)	1
Occurring while on blinatumomab	0 (0)	0 (0)	0 (0)	-

All values listed as N (%) unless otherwise noted.
[a)]Adenovirus, BK virus, cytomegalovirus, Epstein Barr virus, herpes simplex virus, human herpes virus 6, influenza A and B, metapneumovirus, norovirus, parainfluenza, respiratory syncytial virus, rhinovirus, rhinovirus/enterovirus, and Sars-COV-2. [b)]Bacteroides ovatus, Clostridioides Difficile, Enterococcus faecium, Escherichia coli, Helicobacter pylori, Klebsiella pneumonia, Lactobacillus rhamnosus, methicillin sensitive staphylococcus aureus, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus epidermidis, Staphylococcus hominis, and Stenotrophomonas. [c)]Candida glabrata, Rhizopus, and a probable invasive fungal infection. [d)]Babesia. [e)]To treat a known or suspected infection.
Abbreviations: ICU, intensive care unit; SSTI, skin and soft tissue infection.

bulinemia post-blinatumomab therapy and associated infection risk. Our study did not demonstrate beneficial effects of IVIG repletion during blinatumomab on the rate of infections, severity of infections, infectious complication requiring ICU admissions, or infection related mortality. Furthermore, we did not observe a correlation between development of secondary hypogammaglobulinemia and blinatumomab treatment response.

Hypogammaglobulinemia in patients with hematologic malignancies originates from disease-related immune dysfunction, and/or occurs secondary to antineoplastic and other B-cell targeting therapies [13, 15, 16]. In the long-term follow

Table 4. Response to blinatumomab.

	All (N=23)	Control (N=6)	IVIG (N=17)	*P*
Achieved disease response to blinatumomab[a),b)]	16 (80)	5 (83.3)	12 (85.7)	1
Proceeded to HSCT	14 (60.9)	5 (83.3)	9 (52.9)	0.34
Time to HSCT, days, median (range)	105 (58–289)	1 04 (64–129)	106 (58–289)	0.61
Proceeded to other line of therapy	4 (17.1)	1 (16.7)	3 (17.6)	-
Time to next therapy, days, median (range)	123 (108–608)	123 (123–123)	123 (108–608)	1
If MRD (+) disease, achieved MRD (-)[a),b)]	N=15	N=5	N=10	
	12 (80)	4 (80)	8 (80)	1
Time to response, days, median (range)	39.5 (29–83)	46.5 (32–83)	37 (29–85)	0.65
If relapsed/refractory disease, achieved CR[a)]	N=5	N=1	N=4	
	5 (100)	1 (100)	4 (100)	-
CR with MRD (+)	2 (40)	1 (100)	1 (25)	0.4
Time to result, days, median (range)	34 (30-89)	89	33 (30-35)	0.5

All values listed as N (%) unless otherwise noted.
[a)]Excluding 3 patients who received blinatumomab for consolidation/maintenance therapy. [b)]One patient in the IVIG cohort achieved partial response, defined as 1–2 log reduction in BCR-ABL PCR.
Abbreviations: CR, complete response; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease.

up data on immunoglobulin levels in 6 blinatumomab treated patients with B-ALL for MRD+ disease indication, all 6 patients had hypogammaglobulinemia at study entry, attributed to prior chemotherapy and/or the underlying ALL [11]. Similarly, about half of the patients in our study (47.6%) had IgG hypogammaglobulinemia prior to starting blinatumomab. Although the majority of our patients were not heavily pre-treated (median of one prior therapy), almost half of our patients (43.5%) received prior anti-CD20 therapy for a median of 3.5 doses. The clinical relevance of hypogammaglobulinemia is well-described in patients with CLL and MM, both of which are diseases more chronic in nature necessitating multiple lines of sequential therapies and longer follow ups, with reported rates of infection related mortality of 65% and 30%, respectively [16]. Historical data highlights the clinical utility of IVIG in patients with CLL, by demonstrating benefits in preventing serious bacterial infections for a longer period of time [17]. In our study, both the time to first microbiologically documented infection and infection severity, as well as the distribution of infections were similar between the IVIG and control cohorts. In CLL, a positive correlation was shown between low IgG levels and the frequency/severity of infections [15]. In B-ALL, however, a relationship between low levels of immunoglobulins and infections or infection-related mortality from hypogammaglobulinemia has not been well established. In fact, most infections in ALL have been attributed to disease- and/or chemotherapy-related granulocytopenia [14]. The lack of association between hypogammaglobulinemia and infection risk in ALL patients was shown in a phase III trial in which the overall rate of hypogammaglobulinemia was shown higher in the blinatumomab arm at 6% (grade ≥3, 2.6%) compared to 0.9% in the chemotherapy arm, whereas the rate of infection was lower in the blinatumomab arm than the chemotherapy arm (34% vs. 52%) [12]. In our study, 61% of patients were neutropenic (ANC <500 cells/μL) at any time point, and/or have proceeded to allogeneic HSCT, both of which are associated with increased infectious risk. Additionally, all but one ICU admission due to infections and infection-related deaths occurred after patients had proceeded to HSCT and/or next line of chemotherapy.

The development of B-cell targeted therapies has contributed to the increased prevalence of iatrogenic hypogammaglobulinemia [13]. Studies have shown a rapid ablation of B-cells to undetectable level within 2 days of starting blinatumomab, which remained undetectable for the duration of a treatment cycle [18]. Following blinatumomab, recovery of B cells can take more than a year as a result of CD19 depletion, leading to hypogammaglobulinemia [6]. To best capture the nature of reduction in immunoglobulin levels in our patients, all measured IgG levels were collected during the follow-up period, which included period during/after HSCT and/or next line of therapy (Fig. 1, 2). Fifteen (68.2%) patients had IgG nadir values recorded during blinatumomab, occurring at a median of 2 cycles of therapy.

While the role of IVIG is well established in primary hypogammaglobulinemia, its role in secondary hypogammaglobulinemia is not as uniformly defined, especially in B-ALL [14, 19]. IVIG is prepared from pooled human plasma, and contains concentrated IgG and trace amounts of IgA and IgM, with half-lives of products ranging from 21 to 33 days [19]. IVIG binds antigen and modifies various effector functions, resulting in modulation of expression and function of Fc receptors, complement activation, complement binding, and anti-inflammatory effects resulting from interference with the cytokine network, and modulation of T and B-cell activation [19]. Within hematologic malignancies, most existing data describes the benefit of IVIG in CLL and MM patients to reduce clinically and microbiologically documented infections [16]. In a study by Arnold *et al.* [20], the utility of monthly immunoglobulin repletion, with first dose administering within 30 days of chimeric

antigen receptor-modified T cell therapy targeting CD19 [CART-19], was assessed in 28 patients [median age, 9.5 yr (range, 3-23 yr)] with B-ALL receiving CART-19. Thirteen patients (46%) developed sinusitis, and 4 patients (14%) developed pneumonia. The median IgG level during infection-free periods was significantly higher compared to the time at which infection occurred. The authors concluded that an IgG level >1,000 mg/dL was associated with a decreased risk of sinopulmonary infections and recommended routine monitoring of IgG levels with goal >1,000 mg/dL in patients with B-ALL receiving CART-19 [20]. Our study from its retrospective nature was not powered to detect correlation between immunoglobulin levels and the time of infection, however pre-emptive supplementation did not correlate to a reduction in infections.

The importance of monitoring IgG levels in patients receiving B-cell depleting therapy has been demonstrated for rituximab, an anti CD20-monoclonal antibody, which is well documented of causing hypogammaglobulinemia [21]. A retrospective review of 4,479 patients, of whom 3,478 (77.7%) received rituximab for the treatment of malignancy, reported a significant increase in severe infections 6 months after rituximab therapy. In addition, higher cumulative doses of immunoglobulin replacement were associated with a reduced risk of severe infections [21]. The authors concluded that routine monitoring of immunoglobulin levels before and after rituximab therapy may help identify patients who may benefit from IVIG [21]. As routine IVIG supplementation didn't lead to reduced infection rate in our series, immunoglobulin data can be used in conjunction with infectious history to determine if IVIG replacement may be beneficial during blinatumomab treatment. Published recommendations suggest a target serum IgG level >400–500 mg/dL with serum IgG levels, antibody titers, and resolution of infections to guide duration of IVIG therapy [13].

In patients with a high risk of hypogammaglobulinemia and history of recurrent infections, periodic monitoring of IgG levels and better patient selection to identify select patients who would most benefit from IVIG repletion will provide opportunities for cost avoidance. Of note, the average cost (based on average wholesale price) of IVIG for an adult is about $4,000 per dose [22]. In addition to the financial aspect of IVIG administration especially for indications without established benefits, there is also a safety component of this therapy as it is a blood product and poses a risk of exposure to pathogens, such as hepatitis B and CMV. The rate of adverse events, including infusion reaction, are reported between 1% and 15%, with <5% of patients experiencing clinically significant reactions [16]. In our cohort, 23% developed IRR all of which were grade 2 events. Taking together, monitoring IgG levels during blinatumomab treatment with history of infection can better direct the use of IVIG rather than pre-emptive administration.

Low immunoglobulin levels have been considered a marker of lymphoblast depletion, and it has been correlated with treatment response from blinatumomab for ALL [11]. Conversely, incomplete B-cell depletion has been observed during blinatumomab infusion at a low doses (0.5 to 1.5 mcg/m^2/day) as well as at higher doses in patients whose disease did not respond to treatment [23]. We did not find an association between decreased IgG levels and blinatumomab treatment response in our study. The percent decrease and absolute reduction in IgG levels were similar between the responders and non-responders to blinatumomab therapy.

There are several limitations to our study, which include the single-center retrospective design and the small sample size. As a result, there were differences in disease characteristics between the control and IVIG groups which, though statistically insignificant, may have impacted the results of our analysis (proportion of patients receiving blinatumomab for R/R disease, Ph status, etc.). There was limited availability of follow-up IgG levels in our study, which precludes a more definitive association between blinatumomab treatment response and reduction in IgG levels. In addition, longer follow-up might be needed to detect a significant difference in infectious complications.

This study is the first to report the clinical outcomes of IVIG repletion for infection prophylaxis secondary to blinatumomab-induced hypogammaglobulinemia in patients with B-ALL. It may be plausible that perhaps a prolonged IVIG repletion may have reduced the rate of infections and demonstrated a difference in the outcomes between the study cohorts. However, our study findings do not support routine IVIG repletion to prevent blinatumomab-induced hypogammaglobulinemia and associated infection risk. In order to make practice recommendations, however, a larger, prospective trial is warranted to further explore potential utility of IVIG repletion for the reduction in blinatumomab-induced hypogammaglobulinemia and associated infection risk.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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