

ORIGINAL RESEARCH

Obinutuzumab Infusion-Related Reactions: Multicenter Retrospective Evaluation of Incidence, Severity, and Risk Factors

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Introduction: Despite standard prevention strategies, obinutuzumab carries a significant risk of infusion-related reactions (IRRs) for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Reported rates of IRRs vary in phase III clinical trials evaluating obinutuzumab-containing regimens. Although obinutuzumab has a higher rate of severe (grade 3 and higher) IRRs than rituximab, clinical risk factors predicting IRR have not been identified, and therefore strata informing patient-specific risk of IRR have not been applied in practice. **Methods:** This multicenter, retrospective evaluation of patients with CLL/SLL estimated the incidence of obinutuzumab-related IRRs and evaluated risk factors for the development of IRR in a real-world population. **Results:** 68 patients with untreated or previously treated CLL/SLL were included in the analysis, with the majority being older adult (median age = 70) males (61.8%) with Rai stage III and IV CLL. All-grade IRRs occurred in 25% of patients, and severe IRRs occurred in 1.5% of patients. Of the variables evaluated, absolute lymphocyte count was a significant predictor ($p \leq .05$) of the odds of experiencing an IRR in patients receiving obinutuzumab. **Conclusion:** Obinutuzumab IRR rates in a real-world population were comparable to most phase III clinical trial results succeeding implementation of split dosing and standard premedication. Absolute lymphocyte count is a statistically significant predictor for increased odds of experiencing an IRR. Future research evaluating risk-adapted obinutuzumab administration strategies is needed to recommend a specific approach.

Obinutuzumab (Gazyva)-containing regimens for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) yield response rates of 71% to 96% and have improved patient survival in the first-line setting (Fischer et al., 2019; Goede et al., 2014; Moreno et al., 2019; Sharman et al., 2020). Obinutuzumab is currently US Food and Drug Administration (FDA)-approved for the treatment of patients with untreated CLL in combination with chlorambucil or chemotherapy, and as monotherapy for the treatment of patients with relapsed or refractory follicular lymphoma. Despite their efficacy, anti-CD20 monoclonal antibodies like obinutuzumab carry a high risk of infusion-related reactions (IRRs), which ranged from 13.5% to 67.1% in phase III trials evaluating obinutuzumab for the first-line treatment of CLL (Fischer et al., 2019; Leblond et al., 2018; Moreno et al., 2019; Sharman et al., 2020). Infusion-related reactions to monoclonal antibodies are usually nonallergic systemic reactions within hours of infusion initiation that result from cytokine release and inflammation associated with drug-target binding. Characterized by cutaneous, cardiovascular, respiratory, gastrointestinal, and neurological symptoms, IRRs differ in symptomology, severity, and impact on the patients and their plan of care. Common symptoms resulting from IRRs to monoclonal antibodies include flushing, rash, chills, tachycardia, hypotension, and dyspnea. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 grades IRRs according to duration and severity of symptoms and responsiveness to symptomatic treatment (U.S. Department of Health and Human Services, 2017). Mild to moderate (grade 1 or 2) IRRs may simply necessitate pausing the infusion temporarily with or without administration of symptomatic treatment with antihistamines or corticosteroids, while severe (grade 3 or higher) IRRs result in life-threatening symptoms prompting hospitalization and require permanent discontinuation of the agent (Roselló et al., 2017).

While the incidence of IRR rates for both rituximab (Rituxan) and obinutuzumab in CLL range from 25% to 70% in the literature, a higher proportion of obinutuzumab reactions are severe. In contrast to rituximab, which has well-defined

risk factors used in clinical practice to preemptively identify patients at greater risk for experiencing IRRs, such as bulky disease or absolute lymphocyte count (ALC) greater than 25×10^9 cells/L, risk factors for obinutuzumab IRRs have not been clearly elucidated (Wierda & Tambaro, 2020). The most relevant studies identify CD20 expression, FCγR genotype, ALC, white blood cell (WBC) count, lactate dehydrogenase (LDH), and respiratory comorbidities as factors that increase a patient's likelihood of experiencing an IRR, from post-hoc analysis of CLL-11 clinical trial data (Freeman et al., 2015, 2016; Leblond et al., 2018). However, meaningful differences in clinical trial data and real-world evidence may exist, and a strategy for those in clinical practice to identify patients at risk for experiencing IRRs to obinutuzumab has not been developed or adopted.

Due to the severity of these IRRs, the FDA package insert recommends that the first dose (total dose = 1 g, 1,000 mg) of obinutuzumab for CLL/SLL be split into two divided doses over 2 days, with 100 mg given on day 1 and 900 mg given on day 2. The recommended rate for day 1 is 25 mg/hour over 4 hours, and the rate for day 2 is 50 mg/hour for 30 minutes, increased in increments of 50 mg/hour to a maximum rate of 400 mg/hour as tolerated (Genentech, Inc., 2017). However, across the US, many different strategies for obinutuzumab have anecdotally been used. These practices include inpatient admission for administration of the total first dose, administering the recommended split dose over 1 day in the outpatient setting, or administering two 500-mg split doses in the same day. Because these strategies have mostly been reported within professional forums and communities, a robust analysis of alternative administration strategies is lacking in published literature. Pharmacologic strategies to minimize these IRRs include premedication with a glucocorticoid (e.g., dexamethasone or methylprednisolone), antihistamine (e.g., diphenhydramine), and acetaminophen at least 30 minutes prior to the first dose of obinutuzumab. Antihypertensive medications should be held 12 hours before infusion due to the risk of hypotension with obinutuzumab IRR (Genentech, Inc., 2017).

This multicenter retrospective analysis will estimate the incidence of obinutuzumab-related

IRRs in patients with CLL/SLL and investigate risk factors for the development of IRR in a real-world population. Defining real-world incidence of obinutuzumab IRRs could allow for identification of at-risk patients and allow for exploration of more convenient dosing strategies in the future. Clarifying and publishing the frequency of IRRs and identifying risk factors for IRRs in a real-world population at two centers will contribute to the literature base used to make decisions regarding infusion schedule, premedication, and monitoring for patients with CLL/SLL.

METHODS

This was a multicenter, Institutional Review Board–approved retrospective cohort study including adult patients with a CLL/SLL who received their first dose of obinutuzumab at one of two academic medical centers in the Southeast United States from January 1, 2013, to April 30, 2021. The primary endpoint was the incidence and severity of IRRs in patients receiving obinutuzumab for a cancer diagnosis of CLL/SLL. Secondary endpoints included odds ratios for association of disease and patient-specific factors with IRR to obinutuzumab. Baseline characteristics (e.g., disease- and patient-specific factors) included Rai stage of disease, age, sex, comorbidities, performance status, pretreatment LDH, ALC, and creatinine clearance, chemotherapy regimen, administration schedule, CD20 expression, line of therapy, and number of previous therapies. The severity of IRRs was evaluated per the Common Terminology Criteria for Adverse Events (CTCAE) version 5 grading system for IRRs. Descriptive statistics were used to classify incidence and severity of IRRs, and a binomial regression completed with SAS version 9.0 was used to determine associations between IRRs and patient characteristics.

RESULTS

A total of 68 patients received obinutuzumab at either institution for the indication of CLL/SLL from January 1, 2013, to April 30, 2021. Baseline characteristics for the study population are reported in Table 1. Both institutions have standard premedication protocols with acetaminophen 650 mg by mouth, diphenhydramine 50 mg by mouth or intravenously, and dexamethasone 20 mg intravenously

Table 1. Baseline Demographics and Clinical Characteristics (N = 68)

Characteristic	n (%)
Age (years), median (range)	70 (53–89)
Sex, male	42 (61.8)
Rai stage	
0	8 (11.8)
I	6 (8.8)
II	10 (14.7)
III	21 (30.9)
IV	26 (38.2)
Previous lines of therapy	
0	33 (48.5)
1	17 (25.0)
2	9 (13.2)
3+	9 (13.2)
Charlson Comorbidity Index, median (range)	5 (3–12)
ECOG PS, median (range)	1 (0–4)
Regimen	
Obinutuzumab + chlorambucil	25 (36.8)
Obinutuzumab monotherapy	16 (23.5)
Obinutuzumab + venetoclax	24 (35.3)
Obinutuzumab + ibrutinib	2 (2.9)
Previous lines of therapy, (median, range)	2 (0–6)
Pretreatment LDH (units/L), median (range)	207 (110–776)
Pretreatment ALC ($\times 10^9$ cells/L), median (range)	12.9 (0.4–277.9)
Pretreatment CrCl (mL/min), median (range)	62.5 (14–125)
CD20 expression	
Negative	1 (1.5)
Partial to negative	1 (1.5)
Partial	0
Positive dim	9 (13.2)
Positive	53 (69.8)

Note. ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ALC = absolute lymphocyte count; CrCl = creatinine clearance.

on cycle 1, day 1 60 minutes prior to obinutuzumab administration, which were implemented upon obinutuzumab FDA approval and first institutional use. Roughly half of the patients (48.5%) received

Table 2. Frequency of Infusion-Related Reactions Among Patients With CLL Treated with Obinutuzumab

	n (%)
IRR	17 (25.0)
IRR grade, median (range)	
Grade 1	1 (1.5)
Grade 2	15 (88.2)
Grade 3	1 (1.5)
Grade 4	0
Grade 5	0
IRR grade ≥ 3	1 (1.5)

Note. IRR = infusion-related reaction.

obinutuzumab as part of a first-line treatment regimen for CLL. The most common combination regimen was obinutuzumab in combination with chlorambucil (36.8%), followed by obinutuzumab plus venetoclax (35.3%).

Seventeen patients (25%) experienced IRRs (Table 2). Of these patients, 12 patients (70.6%) successfully completed obinutuzumab after symptoms

improved on the same therapy day. Four patients (23.5%) were successfully rechallenged with obinutuzumab at a later date, and one patient (5.8%) discontinued obinutuzumab. Most (94.1%) reactions were grade 1 or 2 (median grade = 2, range = 1–3), but one patient (1.5%) experienced a grade 3 IRR. The patient who experienced a grade 3 IRR received the drug in the inpatient setting due to having a pretreatment ALC of 108×10^9 cells/L, considered high-risk for tumor lysis syndrome.

Sixty-seven (98.5%) patients received obinutuzumab via package insert–recommended split dosing strategy. One patient received an initial cycle 1, day 1 starting dose of 1,000 mg and did not experience an IRR. Of the disease- and patient-specific factors collected and analyzed, only ALC was a significant predictor ($p \leq .05$) of the odds of experiencing an IRR in patients receiving obinutuzumab (Table 3).

DISCUSSION

In this real-world evaluation, the incidence of obinutuzumab IRRs was lower than rates reported in most phase III first-line clinical trials of

Table 3. Binomial Regression Analysis of Select Patient and Clinical Characteristics

	OR	Lower	Upper	p value
Age	0.92	0.83	1.01	.094
Sex = male reference	0.81	0.18	3.66	.781
CCI = 3	Reference			
CCI = 4	0.42	0.02	9.1	.578
CCI = 5 or more	2.14	0.38	12.04	.387
Stage 0	Reference			
Stage I	0.95	0.05	18.21	.973
Stage II	0.12	0.01	1.84	.127
Stage III	0.28	0.04	2.15	.223
Stage IV	0.45	0.06	3.66	.431
Pretreatment ALC	1.01	1.002	1.004	.027
Pretreatment LDH	0.99	0.99	1.00	.765
CD20 positive	0.00	0.00	0.00	1.00
CD20 positive dim	1.064	0.123	9.195	.955
ECOG = 0	Reference			
ECOG = 1	0.15	0.011	2.20	.153
ECOG = 2–4	0.052	0.003	1.05	.054

Note. OR = odds ratio; CCI = Charlson Comorbidity Index; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; ALC = absolute lymphocyte count; CrCl = creatinine clearance.

Table 4. Comparison of IRR rates and Mitigation Strategies in Select First-Line CLL Obinutuzumab Combination Regimens

Study	CLL11 (2014)	GREEN (2018)	iLLUMINATE (2019)	ELEVATE-TN (2019)	CLL14 (2020)
	Obinutuzumab + chlorambucil vs. Rituximab + chlorambucil OR chlorambucil monotherapy	Obinutuzumab +/- chemotherapy ^a	Obinutuzumab + ibrutinib vs. Obinutuzumab + chlorambucil	Obinutuzumab + acalabrutinib vs. Acalabrutinib monotherapy OR obinutuzumab + chlorambucil	Obinutuzumab + venetoclax vs. Obinutuzumab + chlorambucil
Mitigation strategies for IRR	• Pre-medication (antihistamine, APAP) • Protocol amendment for pre-medication with steroid for ALC > 25, then all patients • Protocol amendment for split dosing scheme D1&2	• IRR mitigation cohorts^b	• Pre-medication • Split dose D1&2	• Pre-medication • Split dose D1&2 • Acalabrutinib administered x 1 cycle prior to obinutuzumab	• Pre-medication • Full dose on D1 or split dose • D1&2 per splitting rules
IRR (all grades)	69% (O+C)	59.5% (1) 67.1% (2) 63.6% (3)	24.8% (O+I) 58.2% (O+C)	13.5% (O+A) 39.6% (O+C)	44.8% (O+V) 51.4% (O+V)
IRR (grade 3+)	21% (O+C)	19.0% (1) 18.0% (2) 24.5% (3)	2.0% (O+A) 7.8% (O+C)	2.2% (O+A) 5.3% (O+C)	9.0% (O+V) 10.3% (O+C)

Note. IRR = infusion-related reaction; APAP = acetaminophen; ALC = absolute lymphocyte count.

^aChemotherapy = fludarabine, cyclophosphamide; chlorambucil; bendamustine.

^bCohort 1: 25 mg at 12.5 mg/h on day 1 and 975 mg at 50–400 mg/h on day 2; Cohort 2, 100 mg at 25 mg/h on day 1 and 900 mg at 50–400 mg/h on day 2, with oral dexamethasone 20 mg or equivalent given 12 h pre-dose; Cohort 3: 25 mg at 12.5 mg/h on day 1 and 975 mg at 50–400 mg/h on day 2, with oral dexamethasone 30 mg or equivalent given 12 h pre-dose.

obinutuzumab combinations for the treatment of CLL/SLL (Table 4). Patients in the CLL-11 trial evaluating obinutuzumab + chlorambucil vs. rituximab + chlorambucil or chlorambucil monotherapy experienced high rates of all-grade and grade 3 and 4 IRRs early in the trial, resulting in a protocol amendment instituting split dosing as described in the package insert (Genentech, Inc., 2017; Goede et al., 2014, p. 11). Therefore, patients who experienced an IRR prior to the amendment likely contributed to this high rate of reactions. Notably, split dosing was consistently employed for patients in this real-world population, and premedication with antihistamine, acetaminophen, and dexamethasone for cycle 1 was completed for patients throughout the included timeframe. This supports the use of these mitigation strategies and could explain why the incidence of IRR in this real-world

population was more consistent with trials that followed CLL-11 and implemented these practices. Split dosing and premedication protocols were routinely implemented into subsequent first-line clinical trials following CLL, and IRR rates ranged from 13.5% to 67.1%, with severe IRRs occurring in 2% to 24.5% of cases (Fischer et al., 2019, p. 14; Leblond et al., 2018; Moreno et al., 2019; Sharman et al., 2020). Additionally, IRR rates may be lower than phase III trial rates because many patients evaluated in this study (51.4%) received obinutuzumab as a second- or later-line therapy. This is likely reflective of initial regulatory approval of obinutuzumab in the United States in late 2013. Many who were included in this study likely did not yet have access to obinutuzumab as a therapy option outside of a clinical trial at the time of their first-line CLL therapy (Genentech, Inc., 2017).

There are well-established risk factors to predict infusion reactions to rituximab in non-Hodgkin lymphoma and CLL (Byrd et al., 1999; Winkler et al., 1999). Specifically, patients with bulky disease or pretreatment ALC of greater than 25×10^9 cells/L have a higher probability of experiencing an IRR. It is common to monitor patients at high risk for IRR in an escalated treatment setting (e.g., inpatient), intensify premedications, and implement slower titration rates or split dosing for patients who meet these criteria (Plante et al., 2021). Conversely, ALC as a risk factor has been used to increase rituximab infusion rates for low-risk patients with CLL (Moore et al., 2021; Swan et al., 2014). Implementation of a rapid infusion rituximab conversion protocol at a multisite cancer institution allowed 49 of 180 patients to safely convert to a rapid 90-minute infusion. Patients who were eligible for conversion included those with ALC less than 5×10^9 cells/L who received a previous rituximab infusion without interruption due to IRR and premedication with at least acetaminophen and an antihistamine. No patients experienced IRRs (Moore et al., 2021). As previously mentioned, risk factors allowing for risk-adapted infusion strategies for obinutuzumab have not been published and are needed.

An additional real-world, retrospective evaluation of obinutuzumab IRRs as part of first-line regimens was recently published. In 67 patients treated with obinutuzumab, Bourrier and colleagues (2022) found a 43.3% rate of all-grade IRRs and 6% rate of grade 3 to 4 IRRs. Notably, this institution utilized slower infusion rates for obinutuzumab (6 mg/hour to 24 mg/hour on day 1) than the package insert recommends. The authors also used logistic regression to detect univariable associations between IRRs and age, pretreatment lymphocyte count, cumulative illness rating scale, and receipt of prior chemotherapy. Of these variables, only pretreatment lymphocyte count was found to be statistically significant, which is consistent with the presented findings from this evaluation. The authors also modeled the relationship between pretreatment lymphocyte count and log odds of IRR, and found that risk increases until the ALC reaches 100×10^9 cells/L (Bourrier et al., 2022).

The current evaluation provides further information that real-world IRRs to obinutuzumab are comparable to or lower than those reported in clinical trials, especially clinical trials run prior to the institution of split-dosing practices. The significance of higher ALC as a risk factor for obinutuzumab IRR is further elucidated. This finding could allow for the study of risk-adapted strategies for patients receiving obinutuzumab for CLL based on an ALC boundary. For example, strategies, pending future studies, could include the omission of split dosing or shortened infusions for low-risk patients and provision of heightened monitoring and stringent adherence to premedication and split-dose strategies for high-risk patients, similar to those implemented for rituximab. Improving infusion parameters and decreasing IRR rates may ultimately impact cost to institutions, patient quality of life, and quality of care for patients.

CONCLUSION

Obinutuzumab IRR rates in a real-world population were comparable to most phase III clinical trial results succeeding implementation of split dosing and standard premedication. Absolute lymphocyte count is a statistically significant predictor for increased odds of experiencing an IRR. Future research evaluating risk-adapted obinutuzumab administration strategies is needed to recommend a specific approach. ●

Disclosure

Dr. Moore has served on advisory boards for AstraZeneca, Janssen, and Pfizer.

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