# Prolonged methylprednisolone premedication prior to obinutuzumab in patients with chronic lymphocytic leukemia

**Pejša, Vlatko; Lucijanić, Marko; Vrkljan Vuk, Anamarija; Štoos-Veić, Tajana; Jakšić, Ozren; Jonjić, Željko; Piršić, Mario; Prka, Željko; Ivić, Marija; Fazlić Džankić, Amina; ...**

*Source / Izvornik:* **Leukemia & Lymphoma, 2020, 61, 934 - 939**

**Journal article, Accepted version**
**Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)**

https://doi.org/10.1080/10428194.2019.1702182

*Permanent link / Trajna poveznica:* https://urn.nsk.hr/urn:nbn:hr:105:272145

**Title:** Prolonged methylprednisolone premedication prior to obinutuzumab in patients with chronic lymphocytic leukemia

**Authors:** Vlatko Pejsa[1,2], Marko Lucijanic[1], Anamarija Vrkljan Vuk[1], Tajana Stoos-Veic[3,4], Ozren Jaksic[1,2], Zeljko Jonjic[1], Mario Pirsic[1], Zeljko Prka[1], Marija Ivic[1], Amina Fazlic Dzankic[5], Zdravko Mitrovic[1,2]

**Affiliations:**

[1]Hematology Department, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia.

[2]School of Medicine, University of Zagreb, Salata 3, 10000 Zagreb, Croatia.

[3]Department of Clinical Cytology and Cytometry, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia

[4]University of Osijek, Faculty of Medicine, Josipa Huttlera 4, 34000 Osijek, Croatia

[5]Hematology Department, General Hospital Sisak, Josipa Jurja Strossmayera 74, 44000 Sisak, Croatia.

**Corresponding author:** Vlatko Pejsa, MD, PhD, Professor, Department of Hematology, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia. mail: vpejsa@kbd.hr

**Funding:** none.

**Informed consent:** All subjects provided written informed consent for treatment.

**Ethical approval:** The study was approved by the Institutional Review Board.

**Word count:** 2343

**Abstract:**

First obinutuzumab application is associated with infusion related reactions (IRRs) that may discourage further continuation of the drug. During our clinical practice we have observed that chronic lymphocytic leukemia (CLL) patients with autoimmune hemolytic anemia (AIHA) prolongedly receiving corticosteroids do not develop obinutuzumab IRRs. Therefore, we decided to apply prolonged corticosteroid premedication with methylprednisolone in dose 1-1.5 mg/kg for ≥7 days to all further obinutuzumab candidates. Here we present non-randomized comparison of 28 consecutive previously untreated CLL patients receiving prolonged corticosteroid premedication (15 patients) or standard premedication (13 patients) prior to the first obinutuzumab infusion.

Prolonged corticosteroid premedication resulted in significant reduction of all-grade (20% vs 61.5%; P=0.025) and grade III (0% vs 23.1%; P=0.049) obinutuzumab IRRs. Prolonged corticosteroid premedication did not significantly affect occurrence of infective complications. Patients with CLL and AIHA receiving obinutuzumab showed continuous and stable increase in hemoglobin levels concomitantly with decrease in parameters of hemolysis.

**Keywords:** chronic lymphocytic leukemia; obinutuzumab; infusion related reactions; premedication; corticosteroids; methylprednisolone

**Introduction:**

Obinutuzumab is a humanized anti-CD20 monoclonal antibody that has shown remarkable efficacy and acceptable safety profile in combination with chlorambucil in the first line treatment of B chronic lymphocytic leukemia (CLL) patients that are unfit for fludarabine based therapy [1,2]. However, first obinutuzumab application is associated with infusion related reactions (IRRs) developing in 69% of patients and which range from grade I-II events that either do not require intervention or resolve promptly to symptomatic treatment to grade III-IV events that might be life threatening and may require hospitalization and occur in 21% of patients [3]. Pathophysiology of obinutuzumab IRRs remains poorly understood and IRRs are considered to be multifactorial events with some of identified risk factors being drug dose and speed of infusion, premedication, concomitant medications, comorbidities, genetic predisposition and tumor burden, and some of purported biologic mechanisms being release of vasoactive and proinflammatory mediators by target CD20 positive cells, effector cell activation and immunoglobulin E mediated immunity [1,3]. Obinutuzumab IRRs represent serious clinical problem, may discourage further continuation of the drug and affect clinical decision making, consequently depriving patients from potential benefit of this highly potent therapy.

Autoimmune cytopenias develop in 4-10% of CLL patients, mostly during disease course, but also at the time of diagnosis (27% of autoimmune cytopenias present at the time of diagnosis) [4]. Most common autoimmune cytopenia is an autoimmune hemolytic anemia (AIHA) developing in 2.3-4% of CLL patients [4]. CLL associated autoimmune cytopenias are usually managed by immunosuppression but require active CLL treatment if they remain unresponsive to immunosuppressive therapy. Currently, there is limited experience with obinutuzumab in the treatment of AIHA associated with CLL due to the fact that patients with prior history of AIHA were not considered eligible for enrollment in the obinutuzumab clinical trials [5].

During our clinical practice, we have noticed that patients presenting with CLL associated AIHA standardly treated with methylprednisolone in dose 1-1.5 mg/kg for ≥7 days did not experience obinutuzumab IRRs when starting obinutuzumab and chlorambucil treatment. This led to our hypothesis that prolonged corticosteroid premedication might mitigate frequency and severity of obinutuzumab IRRs. Therefore, we decided to apply prolonged corticosteroid premedication with methylprednisolone in dose 1-1.5 mg/kg for ≥7 days in patients that were candidates for obinutuzumab and chlorambucil treatment in similar fashion as in patients with AIHA although they did not present with autoimmune cytopenias. Here we present evaluation of our CLL patients receiving prolonged corticosteroid premedication in comparison to CLL patients receiving only standard premedication prior to the first obinutuzumab infusion.

**Patients and methods:**

We analyzed a cohort of 28 consecutive, previously untreated CLL patients with the indication for the start of active treatment [6] but ineligible for fludarabine based therapy that received first administration of obinutuzumab in University Hospital Dubrava, Zagreb in period from 2017 to 2019. All patients were intravenously and perorally hydrated, antihypertensive medications were temporary withheld and all patients were given standard premedication on the first day of obinutuzumab administration [7] consisting of intravenous corticosteroid (methylprednisolone 125 mg intravenously), oral analgesic/anti-pyretic (paracetamol 1000 mg per os) and anti-histaminic drug (chloropyramine 20 mg intravenously). Obinutuzumab was administered in dose of 100 mg intravenously at 25 mg/hour rate over 4 hours during first application on day 1. Patients presenting with AIHA and patients receiving prolonged corticosteroid premedication started with methylprednisolone in dose 1-1.5 mg/kg for ≥7 days prior to the first obinutuzumab administration. Choice of prolonged steroid premedication was non-randomized and was based either on presence of AIHA or on ordinating physician's discretion. Consecutive patients prior to our observation that patients with AIHA did not experience obinutuzumab-related IRRs did not receive prolonged corticosteroid premedication and received standard premedication only, and most of consecutive patients post this observation received prolonged corticosteroid premedication. Therefore, most patients receiving different treatments came from different chronological time frames of the study. Post first administration, obinutuzumab was given in standard doses (900 mg on day 2 of cycle 1; 1000 mg on day 15 of cycle 1; 1000 mg on days 1 of cycles 2-6) and chlorambucil was given either as per protocol (0.5 mg/kg on days 1 and 15 of each cycle) [1] or adjusted for age per physician's discretion (fixed dose of 10 mg daily for 5 days per each cycle). All patients received obinutuzumab and chlorambucil combination. Patients received acyclovir, fluconazole and co-trimoxazole per physician's discretion. Obinutuzumab IRRs were graded by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [8]. Obinutuzumab IRRs were managed according to current recommendations [3]. Patients were followed for development of infectious and other events for the duration of obinutuzumab treatment (6 months). The study was approved by the Institutional Review Board. All patients provided written informed consent for treatment.

Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. Normally distributed numerical variables were presented as mean ± standard deviation and were compared between two groups using the t-test. Non-normally distributed numerical variables were presented as median and interquartile range (IQR) and were compared between two groups using the Mann

Whitney U test. Categorical variables were presented as proportion and percentage and were compared between two groups using the $\chi^2$ test. For comparison of laboratory parameters prior and after treatment in same patients, the t-test for paired samples for normally distributed and the Wilcoxon test for paired samples for non-normally distributed variables were used. P values <0.05 were considered statistically significant. All analyses were done using the MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium).

**Results:**

***Patients' characteristics***

We analyzed a total of 28 previously untreated B-CLL patients that received either prolonged corticosteroid premedication [15/28 (53.6%)] or standard premedication [13/28 (46.4%)] prior to the first obinutuzumab infusion. Mean age was 74.1 ±8.4 years, there was similar proportion of male and female patients [14/28 (50%) of each gender]. Indications for treatment were Rai stage III or IV [19/28 (67.9%)], significant disease related symptoms [5/28 (17.9%)] and corticosteroid refractory AIHA [4/28 (14.3%)]. All included patients were considered unfit/ineligible for fludarabine due to presence of comorbidities (CIRS >6). Patients' characteristics are shown in Table 1. Median dose of methylprednisolone received was 96 mg per day (corresponding to 1-1.5 mg/kg per day). Median duration of corticosteroid therapy was 7 days.

Patients receiving prolonged corticosteroid premedication had shorter time from diagnosis to the start of treatment (median 0.9 years for prolonged premedication vs 4.4 years for standard premedication; P=0.003), were more likely to have AIHA [4/15 (26.7%) for prolonged premedication vs none for standard premedication; P=0.044], lower hemoglobin levels prior to (94.1 g/L for prolonged premedication vs 110.9 g/L for standard premedication; P=0.036) and post prolonged premedication (98.4 g/L for prolonged premedication vs 110.9 g/L for standard premedication; P=0.023), higher absolute neutrophil counts post prolonged premedication (median 9.3 $x10^9$/L for prolonged premedication vs 3.8 $x10^9$/L for standard premedication; P=0.001), and lower absolute eosinophil counts post prolonged premedication (median 0 $x10^9$/L for prolonged premedication vs 0.1 $x10^9$/L for standard premedication; P=0.005). Two groups did not significantly differ in other characteristics (P>0.05 for other comparisons).

Among patients receiving prolonged corticosteroid premedication, significant rise in absolute neutrophil counts (median 7.1 $x10^9$/L vs 9.3 $x10^9$/L prior and post prolonged premedication; P=0.022) and significant fall in absolute eosinophil counts (median 0.1 $x10^9$/L vs 0 $x10^9$/L prior and post

prolonged premedication; P=0.012) were observed prior to the first obinutuzmab application. Also, statistically non-significant rises in hemoglobin, platelets, WBC, absolute lymphocyte, monocyte and basophil counts were observed during prolonged premedication (P>0.05 for all comparisons).

***Obinutuzumab IRRs during first application***

All-grade obinutuzumab IRRs during first application of monoclonal antibody were significantly less frequent among patients receiving prolonged corticosteroid premedication (P=0.025) and developed in total of 3/15 (20%) patients with prolonged corticosteroid premedicationand 8/13 (61.5%) patients with standard premedication. Rates of grade I [2/15 (13.3%) vs 3/13 (23.1%); P=0.639] and grade II [1/15 (6.7%) vs 2/13 (15.4%); P=0.583] obinutuzumab IRRs did not significantly differ between patients with and without prolonged corticosteroid premedication. However, none of patients receiving prolonged corticosteroid premedication experienced grade III IRRs in comparison to 3/13 (23.1%) patients with standard premedication (P=0.049). There were no grade IV obinutuzumab IRRs. Frequencies of first obinutuzumab application IRRs are depicted in Figure 1. There were no obinutuzumab IRRs during later obinutuzumab applications.

We did not encounter any infective complications during prolonged corticosteroid premedication, nor was incidence of neutropenia and febrile neutropenia during first cycle and later during treatment significantly different between these two subgroups (P>0.05 for both comparisons). Incidence of infective complications and rate of hospitalizations related to infections did not significantly differ between two subgroups as well (P>0.05 for both comparisons). Regarding hospitalizations due to infections, one patient developed herpes zoster, one patient developed pneumonia and one patient experienced cholangitis later during treatment in the prolonged corticosteroid premedication group, whereas two patients developed pneumonia and one patient developed urinary tract infection during treatment in the standard premedication group. One elderly patient with multiple comorbidities that initially presented with AIHA and received the prolonged corticosteroid premedication died after 2 cycles of obinutuzumab+chlorambucil therapy due to unknown cause and one patient that received standard premedication developed progressive multifocal leukoencephalopathy (PML) shortly after completion of 6 cycles of obinutuzumab and chlorambucil [9].

All four patients with AIHA discontinued corticosteroids soon after start of obinutuzumab and experienced continuous and stable increase in hemoglobin levels, paralleled with decrease in parameters of hemolysis (LDH, bilirubin) during first several cylces.

**Discussion**

Here we present novel and safe approach that results in significant reduction in frequency and severity of obinutuzumab IRRs that are representing significant clinical problem in everyday practice. Also, to the best of our knowledge, our paper is first do describe efficacy of obinutuzumab in treatment of B-CLL associated AIHA.

Several author groups described different therapeutic contexts that might affect severity and frequency of obinutuzumab IRRs. Since obinutuzumab IRRs have been demonstrated to be associated with the release of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, interferon γ) [10], an attempt to inhibit IL-6 signaling by monoclonal antibody tocilizumab has been made [11]. Although feasible, this approach did not significantly reduce obinutuzmab IRRs in comparison to placebo (all-grade IRRs in 72% vs 77% of patients with and without tocilizumab), resulted in prolonged increase in IL-6 levels due to displacement from IL-6 receptors by the antibody, and was deemed ineffective. On the other hand, reduced incidence of obinutuzumab IRRs (grade I and II IRRs in 17% and grade III IRRs in 4% of patients) was reported with the ibrutinib and obinutuzumab combination [12]. Significant increases in IL-10, TNF-α, interferon γ, CCL-3 and CCL-4, but not IL-6 post obinutuzumab infusion have been observed with the concurrent use of ibrutinib suggesting important roles of IL-6 and B-cell signaling in development of obinutuzumab IRRs. It is also worth to note the retrospective analysis of the real-life cohort of CLL patients from Poland treated with obinutuzumab and chlorambucil where low rate of grade III obinutuzumab IRRs (2.3%) was reported [13]. Although the analysis was limited by retrospective approach, observed rate might be affected by higher dose of corticosteroids used to treat autoimmune cytopenias present in real-life patient cohorts.

Potential mechanisms behind observed effects of prolonged corticosteroid premedication in our study remain elusive at the moment. We speculate that corticosteroid exposure of sufficient duration might lead to reduced production of inflammatory cytokines (IL-6, IL-8, TNF-α, interferon γ) and their lower levels at the time of first obinutuzumab administration. As we observed, prolonged corticosteroid premedication led to redistribution of different subsets of white blood cells and resulted in significant rise in absolute neutrophil counts and significant fall in absolute eosinophil counts, but not clinically evident disease debulking. Reduced levels of eosinophils and their potent vasoactive mediators can at least in part influence reduced IRR severity and frequency. However, it should be noted that absolute change in eosinophil counts that we observed was small, and therefore of uncertain clinical meaning. Since corticosteroid have direct effects of lipid metabolism, we also speculate that prolonged corticosteroid premedication might affect cholesterol content of plasma membrane and consequently influence buoyancy and antigenicity /availability of different epitopes of membrane proteins. This phenomenon has already been described in the case of CD20 molecule where expression of particular epitopes was profoundly affected by varying cholesterol content of plasma membrane [14]. Further

studies investigating these potential molecular mechanisms behind observed corticosteroid effects are ongoing.

Experience with obinutuzumab in AIHA treatment is limited since patients with AIHA were considered ineligible for enrollment in the obinutuzumab clinical trials. Our initial experience shows that obinutuzumab is a potent and effective therapy for AIHA associated with CLL and is able to quickly achieve control over hemolytic process. Our encouraging data suggest that obinutuzumab might be an option for patients with AIHA ineligible to receive rituximab or other CD20 antibodies (e.g. developing anaphylactic reaction, shortage of drug on the market, etc.). However, clinical data on this topic are missing and further studies are surely needed prior to such recommendation.

Our findings are limited by small sample size, single center experience and lack of randomization of two patient groups. Exploratory and retrospective nature of our analyses originated from the clinical observation that AIHA patients previously prolongedly treated with corticosteroids do not develop obinutuzumab IRRs and inclusion of AIHA patients inevitably introduced selection bias into our study and can affect interpretation of certain findings (differences in hemoglobin, parameters of hemolysis, etc.). Also, we performed numerous group comparisons without adjustments for multiple hypothesis testing and due to lack of statistical power some of our findings are near significance threshold of P=0.05, further adding to the uncertainty and prompting for future confirmatory research. Nevertheless, our findings suggest beneficial effects of prolonged corticosteroid administration which seems to be safe and feasible. Mitigation of obinutuzumab IRRs is an important clinical goal since impressive clinical presentation might discourage further continuation of this potent and clinically proven drug.

In conclusion, prolonged methylprednisolone premedication in dose 1-1.5 mg/kg for at least 7 days prior to the first application of obinutuzumab significantly reduces frequency and severity of IRRs in patients with previously untreated CLL. Independent replication of our findings and investigation of potential molecular mechanisms behind observed effects are needed.

**Acknowledgements:** none

**Disclosure of interest:** VP, ML, OJ, ZP, ZM have received speaker honoraria from Roche.

**References**

1. Goede V, Fischer K, Busch R, et al. . Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-1110.
2. Prica A, Crump M. Improving CD20 antibody therapy: obinutuzumab in lymphoproliferative disorders. Leuk Lymphoma 2019;60:573-582.
3. Dawson K, Moran M, Guindon K, Wan H. Managing Infusion-Related Reactions for Patients With Chronic Lymphocytic Leukemia Receiving Obinutuzumab. Clin J Oncol Nurs 2016;20:E41-48.
4. Tsang M, Parikh SA. A Concise Review of Autoimmune Cytopenias in Chronic Lymphocytic Leukemia. Curr Hematol Malig Rep 2017;12:29-38.
5. Molica S, Polliack A. Autoimmune hemolytic anemia (AIHA) associated with chronic lymphocytic leukemia in the current era of targeted therapy. Leuk Res 2016;50:31-36.
6. Hallek M, Cheson BD, Catovsky D, et al. . iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
7. GAZYVA® (obinutuzumab) Highlights of prescribing information, revised: 11/2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125486s017s018lbl.pdf.
8. National Cancer Institute Common terminology criteria for adverse events [v.4.03]. Retrieved from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. 2010.
9. Pejsa V, Lucijanic M, Jonjic Z, Prka Z, Vukorepa G. Progressive multifocal leukoencephalopathy developing after obinutuzumab treatment for chronic lymphocytic leukemia. Ann Hematol 2019;98:1509-1510.
10. Freeman CL, Morschhauser F, Sehn L, et al. . Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions. Blood 2015;126:2646-2649.
11. Freeman CL, Böttcher S, Serna JDL, et al. . Tocilizumab to prevent infusion related events in patients with chronic lymphocytic leukemia and comorbidities treated with obinutuzumab and chlorambucil: results from the randomized Phase Ib GALACTA trial. 60th ASH Annual Meeting & Exposition, December 1 4 2018, San Diego, California, USA.
12. Velez Lujan J, Lengerke-Diaz PA, Jacobs C, et al. . Ibrutinib reduces obinutuzumab infusion related reactions in patients with chronic lymphocytic leukemia and is associated with changes in plasma cytokine levels. Haematologica 2019.
13. Dlugosz-Danecka M, Jurczak W, Latka-Cabala E, et al. . Efficacy and safety of the obinutuzumab-chlorambucil combination in the frontline treatment of elderly CLL patients with comorbidities - Polish Adult Leukemia Group (PALG) real-life analysis. Pol Arch Intern Med 2018;128:421-426.
14. Polyak MJ, Ayer LM, Szczepek AJ, Deans JP. A cholesterol-dependent CD20 epitope detected by the FMC7 antibody. Leukemia 2003;17:1384-1389.

**Table 1:** Patients' characteristics.

| | **Overall** | Prolonged corticosteroid premedication | **Standard premedication** | **P value** |
|---|---|---|---|---|
| Number | 28 | 15 | 13 | - |
| Age (years) | 74.1 ±8.4 | 74.4 ±8.9 | 73.8 ±8.2 | P=0.848 |
| Gender<br>Male<br>Female | <br>14/28 (50%)<br>14/28 (50%) | <br>7/15 (46.7%)<br>8/15 (53.3%) | <br>7/13 (53.8%)<br>6/13 (46.2%) | <br><br>P=0.705 |
| AIHA<br>Yes<br>No | <br>4/28 (14.3%)<br>24/28 (85.7%) | <br>4/15 (26.7%)<br>11/15 (73.3%) | <br>0/13 (0%)<br>13/13 (100%) | <br>**P=0.044 *** |
| CIRS >6 | 28/28 (100%) | 15/15 (100%) | 13/13 (100%) | P=1.000 |
| Rai stage<br>I<br>II<br>III<br>IV | <br>3/28 (10.7%)<br>6/28 (21.4%)<br>12/28 (42.9%)<br>7/28 (25%) | <br>0/15 (0%)<br>4/15 (26.7%)<br>8/15 (53.3%)<br>3/15 (20%) | <br>3/13 (23.1%)<br>2/13 (15.4%)<br>4/13 (30.8%)<br>4/13 (30.8%) | <br>P=0.170 |
| Palpable spleen size(cm) | 3 IQR (0.8 - 5.3) | 3 IQR (1.5 - 4) | 4 IQR (0 - 8) | P=0.608 |
| Hemoglobin1 (g/L) | 101.9 ±21.5 | 94.1 ±23.3 | 110.9 ±15.4 | **P=0.036 *** |
| Hemoglobin2 (g/L) | 104.2 ±14.8 | 98.4 ±11.9 | 110.9 ±15.4 | **P=0.023 *** |
| Platelets1 ($x10^9$/L) | 156 ±74.4 | 171.6 ±87.2 | 138 ±54.1 | P=0.240 |
| Platelets2 ($x10^9$/L) | 158.3 ±67.9 | 175.9 ±75.3 | 138 ±54.1 | P=0.144 |
| ALC1 ($x10^9$/L) | 74 ±44.3 | 69.7 ±48.5 | 78.9 ±40.4 | P=0.596 |
| ALC2 ($x10^9$/L) | 79.1 ±45.3 | 79.4 ±50.6 | 78.9 ±40.4 | P=0.977 |
| ANC1 ($x10^9$/L) | 5.2 IQR (3.4 - 8.7) | 7.1 IQR (3.9 - 10) | 3.8 IQR (1.9 - 5.8) | P=0.062 |
| ANC2 ($x10^9$/L) | 6.5 IQR (3.8 - 9.5) | 9.3 IQR (7.3 - 13.2) | 3.8 IQR (1.9 - 5.8) | **P=0.001 *** |
| MDRD estimated creatinine | 67.3 ±22.2 | 64.8 ±22.1 | 70.2 ±22.8 | P=0.533 |

| | | | | |
|---|---|---|---|---|
| clearance (ml/min/1.73 $m^2$) | | | | |
| First obinutuzumab application IRRs<br>Yes<br>No | <br><br>11/28 (39.3%)<br>17/28 (60.7%) | <br><br>3/15 (20%)<br>12/15 (80%) | <br><br>8/13 (61.5%)<br>5/13 (38.5%) | <br><br><br>**P=0.025 *** |
| Neutropenia after cycle I | 9/28 (32.1%) | 3/15 (20%) | 6/13 (46.2%) | P=0.228 |
| Febrile neutropenia after cycle I | 5/28 (17.9%) | 2/15 (13.3%) | 3/13 (23.1%) | P=0.639 |
| Neutropenia during treatment | 16/28 (57.1%) | 10/15 (66.7%) | 6/13 (46.2%) | P=0.274 |
| Febrile neutropenia during treatment | 6/28 (21.4%) | 3/15 (20%) | 3/13 (23.1%) | P=1.000 |
| Hospitalizations due to infections | 6/28 (21.4%) | 3/15 (20%) | 3/13 (23.1%) | P=1.000 |

*statistically significant at P<0.05

Some hematological parameters are shown at the start of corticosteroid pre-phase (labeled as 1) and at the start of first cycle of obinutuzumab (labeled as 2).

Abbreviations: AIHA=autoimmune hemolytic anemia; CIRS=Cumulative Illness Rating Scale; ALC=absolute lymphocyte count; ANC=absolute neutrophil count; MDRD=Modification of Diet in Renal Disease predicted glomerular filtration rate; IQR=interquartile range.

**Figure 1:** Frequencies of obinutuzumab infusion related reactions (IRR) during first application in patients with and without prolonged corticosteroid premedication.