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Targeting immunoglobulin deficiency in CLL: A retrospective evaluation of IgM/IgA-enriched IVIg use in a small cohort of patients from Argentina.

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Introduction

Infectious complications represent a major cause of morbidity and mortality in CLL due to both, intrinsic immune dysfunction and detrimental effects of anti-leukemic therapies on the patient´s immune system. Hypogammaglobulinemia is the most common immune defect. Its prevalence ranges between 20 and 70% depending on the cohort analysed, with a decrease of all immunoglobulin (Ig) isotypes usually starting with IgM, then IgG and IgA (Freeman, Crassini et al. 2013, Parikh, Leis et al. 2015, Andersen, Vojdeman et al. 2016, Ishdorj, Streu et al. 2019). The administration of immunoglobulin replacement therapy (IgRT) is not recommended as routine prophylaxis, and is only reserved for patients with severe recurrent infections in the presence of hypogammaglobulinemia (Hallek, Cheson et al. 2018). Remarkably, Ig preparations used in CLL contain more than 95% IgG and as a result, IgA and IgM deficiencies persist unaddressed. An analysis of the factors associated with infections in CLL patients showed a stronger association between major infections and combined Ig deficiency rather than isolated IgG deficiency (Visentin, Compagno et al. 2015), thus an IgA/IgM-enriched Ig preparation may offer enhanced benefits. Moreover, we have previsoulsy reported that in contrast to standard IgRT, IgA- and IgM-enriched IVIg (IVIg-GAM) preparation showed a significantly lower inhibitory effect on T cells, a feature highlighted as a potential benefit of this particular preparation with the potential to preserve T cell function when administered in vivo (Khan, Molica et al. 2022). **This study evaluates the impact of IVIg-GAM on infection rates and antimicrobial use in a small cohort of CLL patients.**

Methods

This was a retrospective study of a group of 6 CLL patients that initiated treatment with a IVIg-GAM preparation, Pentaglobin, between 2018 and 2022 and were followed up for 24 months after IVIg-GAM initiation. Patients were diagnosed with CLL and treated according to the IWCLL criteria. IVIg-GAM administration was indicated according to local guides based on the presence of hypogammaglobulinemia (defined as IgG levels <400 g/L) and/or at least three infections per year. The universally accepted dose of common IVIg is 400 mg x Kg of weight every 21 to 28 days. In general, doses of 25 g are used in clinical practice once a month. Pentaglobin contains 38 mg of IgG, 6 mg of IgA and 6 mg of IgM per ml. Therefore, the dose equivalence compared to common IVIG would be: 5 to 6 ml x Kg of weight (350 to 420 ml for a 70 kg adult). Patients received IV administration of 400 ml of Pentaglobin, which is equivalent to 15.2 g of IgG, 2.4 g of IgA and 2.4 g of IgM, every 25 to 28 days, independently from their body weight. The study was carried out according to the Helsinki Declaration and approved by the local Ethical Committee. Patient basal characteristics are depicted in Table 1.

Results

Patient basal characteristics

Patient	Sex	Age	Year Dx	Rai/Binet Dx	IGVH	FISH	Treatment: Type	Treatment: Year	Treatment: Response	Infecious events 1y pre-IgRT (number/type)	Ig leveles prior IVIg-GAM treatment (IgG/IgA/IgM; mg/dl)	IVIg-GAM started	Infecious events 2y post-IgRT (number/type)	COVID-19
1	M	55	2016	II/A	UM	del 13q complex cariotype	Ibru	2019	PHR	3 (colitis*, pharyngitis*, pneumonia#)	428/19/10	2018	1 (sinusitis*)	No
2	M	47	2001	IV/C	M	trisomy 12	FCR, RB, Ven, Ibru	2006, 2015, 2019, 2024	CHR, PHR, CHR, PHR	2 (pneumonia#)	410/10/<5	2017	1 (sinusitis*)	Yes
3	M	70	2019	II/B	UM	del 13q	Ibru	2023	CHR	3 (bronchitis*, sinusitis*, pneumonia#)	473/30/<5	2020	1 (pharyngitis*)	No
4	M	45	2020	II/B	M	no	Ibru	2022	CHR	5 (onychomycosis&, UTI*, sinusitis*, pneumonia#, COVID#)	432/25/13	2022	1 (pharyngitis")	Yes
5	M	71	2020	II/B	UM	del 13q	Ibru	2022	CHR	3 (folliculitis#, pneumonia#, bronchtis*)	300/26/14	2020	1 (COVID")	Yes
6	F	66	2005	I/A	M	del 13q	No	-	-	2 (bronchitis*, pneumonia#)	404/30/8	2018	0	No

Table 1. Patient basal characteristics. IVIg-GAM: Immunoglobulin preparation of IgG, IgA and IgM (pentaglobin); **y:** year; **M:** male; **F:** female; **Dx:** diagnosis; **IGHV:** immunoglobulin heavy-chain variable; **UM:** unmutated; **Mut**: mutated; **Ibru:** ibrutinib; **FCR:** fludarabine, cyclophosphamide, rituximab; **RB:** rituximab, bendamustine; **Ven:** venetoclax; **PHR**: Partial Hematological Response; **CHR:** Complete Hematological Response; ***** oral antibiotics; **#** hospitalization and/or intravenous antimicrobial use; **&** oral anti-fungal; **"** symptomatic treatment.

All patients had low levels of IgA and IgM concomitant with their IgG hypogammaglobulinemia . Regarding anti-leukemic treatment, 5 out of 6 patients had to receive treatment due to progression of the disease. 3 patients received ibrutinib as first line of treatment and obtained complete haematological response (CHR), and remained in remission during the follow up. Patient #1, who belongs to the stereotyped BCR Ig subset #2 and presents with a complex karyotype, received ibrutinib treatment one year after IVIg-GAM treatment, was started. He obtained partial haematological response (PHR) after 6 months of ibrutinib treatment and remained stable throughout the follow up. Patient #2, with more than 20 years of evolution and 3 relapses, obtained PHR to the fourth line of treatment with ibrutinib. Patient #6, who presented 136 x 109 L lymphocytes at the beginning of his follow-up in stage Binet A Rai II, after 12 months of IVIg-GAM administration obtained PHR with disappearance of splenomegaly and a decrease in the lymphocyte count to 14 x 109 L, according to a stage Binet A Rai 0, without specific treatment for the disease.

Immunoglobulin levels before and after IVIg-GAM treatment

At the time of IVIg-GAM treatment initiation, median basal immunoglobulin levels were 419 (300-473) mg/dl for IgG, 25.5 (10-30) mg/dl for IgA and 9 (4-14) mg/dl for IgM. As shown in Figure 1 A-C, the increase in all Ig isotypes was evident at 6 months after IgRT treatment initiation, rising to median levels of IgG of 591 (524-699) mg/dl, 48 (38-77) mg/dl of IgA and 23 (12-25) mg/dl of IgM at 24 months of continuous IVIg-GAM treatment.

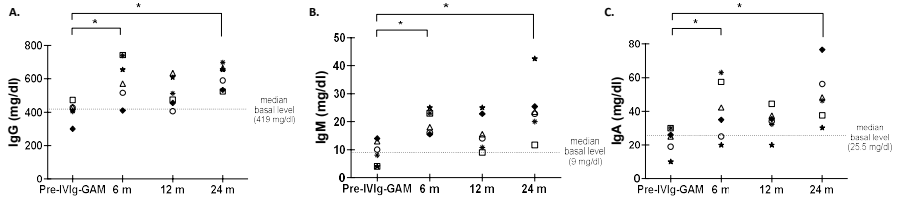

Figure 1. Immunoglobulin levels before and after IVIg-GAM treatment. A-C. Serum IgG, IgA and IgM levels prior IVIg-GAM and during the following 24 months. Levels of Ig at month 6, 12 and 24 were obtained form laboratory test results closest to the date mentioned. If multiple tests were taken during that period, then the average test result was calculated. Each symbol represent a different patient. *p<0.05. Friedman test, Dunn´s multiple comparisons test 6, 12 and 24 months vs pre-IgRT. Doted line represent the median level of immunoglobulin pre - IVIg-GAM.

Infection events and anti-microbial use before and after IVIg-GAM treatment and safety.

Before IVIg-GAM administration, the mean of any infection was 3 (2-5) infection/year, the mean of anti-microbial use due to infection was 2.8 (2-4) event/year and all patients suffered at least one severe infection, defined as infection with the need of intravenous antimicrobial treatment and/or hospitalization. The most prevalent severe infection before IVIg-GAM administration was grade 3-4 pneumonia. During the 2 years of follow up with IVIg-GAM treatment, patients had a good quality of life (QoL), no patient suffered an infection that required intravenous antimicrobial treatment or hospitalization, and both grade 1 infections and anti-microbial use were significantly decreased. During the SARS-Cov-2 pandemic, 5 of the 6 patients were under IVIg-GAM treatment and only 2 of them suffered from the infection in a mild form without requiring hospitalization, while the others, despite not having obtained a response to vaccination, did not present withany symptoms of COVID.

Importantly, Pentaglobin treatment was safe and few adverse events (AEs) were observed in our patients, primarily limited to mild rash and transient hypotension during the first infusion. All patients received 1 g of paracetamol one hour before infusion, along with 4 mg of dexamethasone and 30 mg of diphenhydramine administered prior to each infusion.

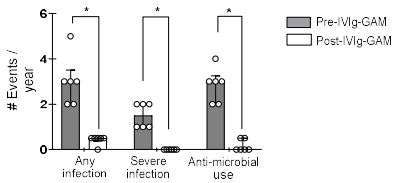

Figure 2. nfection events and anti-microbial use before and after IVIg-GAM treatment. Number of any infection, severe infection and event requiring anti-microbial use during the year prior and the two years after of IgRT with IVIg-GAM is expressed as event/year. Severe infection was defined as an infection requiring administration of intravenous antimicrobial and/or hospitalization. Detail of infection events are depicted in table 1. *p<0.05. Two-way ANOVA, Sidak's multiple comparisons test.

Discusion

This is the first report to our knowledge reporting infection events, use of anti-microbial treatment and IgGs levels of CLL patients under IgRT treatment with an IgM and IgA enriched IgG preparation, (Pentaglobin). Our results are encouraging, since during the 2 years of follow-up treatment with Pentaglobin all patients suffered only mild infections without the need of hospitalization or administration of intravenous antimicrobials. Antimicrobial use significantly decreased during IVIg-GAM treatment. Notably, during the SARS-Cov-2 pandemic, only two patients undergoing IgRT had COVID-19. Immunoglobulin replacement therapy with an IgA and IgM enriched Ig preparation, Pentaglobin, was safe and effective in a small cohort of CLL patients as infection prophylaxis with an increase in all Ig isotypes. Given that most CLL patients with hypogammaglobulinemia exhibit reduced levels across all immunoglobulin isotypes, further research to explore the potential benefits of an enriched IgM-IgA preparation in larger cohorts is warranted.