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Safety and effectiveness of biosimilar of Rituximab CT-P10 in the treatment of cryoglobulinemic vasculitis: the MARBLe study (Mixed cryoglobulinemiA Rituximab BiosimiLar)

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Abstract

Rituximab (RTX) represents a milestone in the treatment of mixed cryoglobulinemic vasculitis (MCV). Despite usually well-tolerated, RTX may induce different types of adverse drug reactions, including exacerbation of vasculitis. Recently, RTX biosimilar CT-P10 has been approved in Europe for the treatment of rheumatoid arthritis, but no data are available about

effectiveness and safety of CT-P10 in the treatment of MCV. In this multicenter open-label study, we analyzed the safety of CT-P10 in patients with MCV treated in first-line or after a shift by RTX originator. Fifty-one consecutive MCV patients (females/males 35/16, median age 68 years, median disease duration 42 months, 51% HCV positive) were included in the study between July and December 2018 and were treated with CT-P10 (group 1). Safety and effectiveness of CT-P10 were compared with a retrospective group (group 2) including 75 consecutive patients treated with RTX originator between July 2017 and July 2018. Thirty-six patients were treated with CT-P10 for the first time, while the other 15 switched from RTX originator. RTX was administrated with high or dosage schemes (375 mg/m^2 four times a week apart/1000 mg twice one week apart or 250 mg/m^2 twice one week apart). During a month period after the last infusion, 13/51 adverse events (AE) were observed in group 1 and 17/75 in group 2 (p not significant). Among them, 7/13 and 6/17 (in group 1 and 2, respectively) could be considered immune-mediated AE (p not significant). At univariate analysis patients with IM-AE were more frequently males ($p = 0.04$) and with a lower disease duration ($p = 0.03$), but both the parameters were not significant at logistic regression. About clinical response after 6 months by the end of the treatment, no differences were observed between patients treated with originator and CT-P10 regarding the response to the therapy. No differences were observed in safety and effectiveness between patients naïve at RTX or switching from originator. Despite the higher prevalence of immune-mediated AE among patients treated with CT-P10 than originator, we have observed no significant differences between the 2 groups. The use of a low-dosage regimen is more common in group 1 than in group 2, representing a possible bias of the study, possibly influencing the appearance of AE. Considering the cost/efficacy ratio of biosimilars, their use could be helpful to treat a large number of MCV patients with an effectiveness and safety comparable to originator. Multicenter studies including a large number of patients and the new RTX biosimilars could be useful to fully elucidate the possible risk of immune-mediated adverse events with biosimilar drugs. Considering the cost/efficacy ratio of CT-P10, its use could help to treat a large number of MCV patients with an effectiveness and safety comparable to originator.

AQ1

AQ2

Introduction

Mixed cryoglobulinemic vasculitis (MCV) is a small-vessel systemic vasculitis involving kidneys, joints, skin, and peripheral nerves, and it is characterized by

the presence of mixed cryoglobulins in the serum often associated with a detectable B cell-lymphoproliferation [1].

Before the development of the direct-acting antiviral agents against hepatitis C virus (HCV), MCV was associated to HCV in almost 90% of cases. As a consequence of an effective treatment of HCV infection in the last years, the prevalence and incidence of HCV-related MCV are overall decreasing [1, 2].

The main manifestations of MCV syndrome are recurrent palpable purpura, weakness and arthralgias; other clinical features include Raynaud's phenomenon, vasculitic skin ulcers, arthritis, glomerulonephritis, peripheral neuropathy or, more rarely, central nervous system or pulmonary involvements. Severe life-threatening conditions are anecdotal and can appear as acute renal failure with oligo-anuria and rapidly progressive renal failure, diffuse alveolar hemorrhage, acute cerebrovascular and cardiovascular events, ischemic colitis, sepsis complicating skin ulcer infection, and critical liver failure [1, 3].

Therapeutic strategies include etiological (antivirals, in HCV-related MCV), pathogenetic and symptomatic drugs, mainly immunosuppressants, corticosteroids, plasma-exchange and apheresis. In particular, anti-human CD20 monoclonal antibody, Rituximab (RTX), represents a milestone in the treatment of MCV, even in the presence of life-threatening conditions. Three unblinded randomized controlled trials and one follow-up study suggested that RTX can be effective in reducing disease activity and preventing vasculitis flares [4, 5, 6, 7]. RTX is generally well tolerated but can lead to drug-related adverse events (AE) that can be infusion related, immune-mediated or due to the immunosuppression [8].

Recently, the RTX biosimilar CT-P10 has been approved in Europe in all indications held by reference RTX, including rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis, pemphigus vulgaris and hematological malignancies such as non-Hodgkin’s lymphoma and chronic lymphocytic leukemia [9, 10, 11, 12], providing a new threshold for patient access to effective biologic treatments for chronic diseases, including some rheumatic inflammatory diseases [9]. On the other hands, the availability of different biosimilar drugs is also accompanied by possible safety concerns [9].

No data are currently available about the effectiveness and safety of RTX biosimilars in the treatment of MCV. In the context of the Italian Group for the study of cryoglobulins, a multicenter open-label study was proposed aiming to evaluate the safety and the effectiveness of CT-P10 in patients affected by MCV.

Patients and methods

Patients

A multicenter open-label prospective study was conducted in ten Italian centers with expertise in the management of MCV. The study was approved by the local ethical committee. All enrolled patients satisfied the preliminary classification criteria for the disease [13]. Both clinical and laboratory parameters were carefully evaluated according to standard previously described methodologies [14].

The study included all consecutive MCV patients treated with CT-P10 (Truxima®) in first-line therapy or after a shift by RTX originator. All patients must have been at least 18 years of age or older, without any upper age limit. All patients gave written consent for the use of data. Previous or concurrent treatments with glucocorticoids, immunosuppressants, antiviral treatment, hydroxychloroquine, gabapentin and pain management therapy were accepted. For patients already treated with RTX originator, the switch to CT-P10 was allowed only in absence of previous AE.

The protocol for the infusion of RTX, both originator and CT-P10, was standardized in every center and included premedication with methylprednisolone 100 mg intravenously and acetaminophen 30 min prior to each infusion; the infusion was initiated at a rate of 50 mg/h and increased by 100 mg/h increments at 30-min intervals, to a maximum of 400 mg/h. RTX, both biosimilar and originator, was administrated with high-dosage schemes (375 mg/m^2 four times a week apart or 1000 mg twice one week apart) [8] or low-dosage scheme (250 mg/m^2 twice one week apart) [15]. In absence of shared protocols, the scheme was decided according to the expert physician.

Safety and effectiveness of CT-P10 were compared with an historical cohort extrapolated from the same centers composed by MCV subjects treated with RTX originator in the previous years.

Inclusion and exclusion criteria were the same for both groups; therefore, they were retrospectively evaluated for historical group.

Clinical and immunological assessment

Patients' baseline evaluation included clinical and serological assessment.

Regarding clinical aspects, we evaluated cutaneous involvement (purpura, distal ulcers), arthralgia, arthritis, gastrointestinal tract involvement, renal involvement [proteinuria, hematuria and abnormal reduction of glomerular filtration rate

(GFR)], neurological involvement (peripheral and/or central nervous system) and clinical signs of hepatic insufficiency and/or portal hypertension. The diagnosis of lymphoid neoplasms was based on the World Health Organization (WHO) criteria [16]. Eventual life-threatening manifestations, such as glomerulonephritis and kidney failure, pulmonary alveolitis and interstitial lung disease, gastrointestinal or central nervous system vasculitis and heart failure, were recorded [3].

Furthermore, laboratory evaluation at baseline included the virologic profiling, rheumatoid factor (RF), C3 and C4 fraction of complement, and the detection and characterization of cryoglobulins (II or III type).

Clinical response of MCV was evaluated at 6 months after CT-P10 and RTX originator treatment on the basis of the main treatment indication (see Table 1). Clinical picture stabilization was defined as a lack of significant clinical changes regarding the main treatment indication.

Table 1

Evaluation of clinical response in mixed cryoglobulinemia vasculitis patients

	Improvement	**Worsening**
Skin involvement (physician's assessment)	Disappearance of purpura; healing or disappearance of ulcers and/or skin necrosis	Worsening or relapsing of purpura
		Worsening or relapsing of ulcers and/or skin necrosis
Joint involvement (VAS and DAS-28-PCR)	Disappearance or improvement of arthralgia by VAS (improvement of at least of 50% of VAS)	Worsening or relapsing of arthralgia by VAS
	Disappearance or improvement of arthritis by DAS-28 CRP (improvement of at least of 50% of DAS-28 CRP)	Worsening or relapsing of arthritis by DAS-28 PCR
Renal involvement (bio-humoral parameters)	Disappearance or significant improvement of proteinuria (Proteinuria < 0.3 g/24 h or improvement of at least of 50% of proteinuria)	Worsening or relapsing of proteinuria;
	Disappearance of glomerular hematuria	Relapsing or no response of glomerular hematuria (≥ 10 RBCs/hpf)
	Improvement of GFR > 20% at week 24 if GFR < 60 mL/min/1.73 m^2 at diagnosis	Rise in serum creatinine > 30% or fall in creatinine clearance > 25%

VAS visual analogue scales, *DAS-28-PCR* disease activity score on 28 joints calculated with C-reactive protein, *GFR* glomerular filtration rate, *RBC* red blood cell, *hpf* hight performance field (400×)

	Improvement	Worsening
Peripheral neurological involvement (clinical and electro-physiological evaluation)	Clinical evaluation: Improvement or resolution of pain and paresthesia by VAS (improvement of at least of 50% of VAS); Improvement of manual muscular testing in case of motor impairment at baseline	Clinical evaluation: Worsening or relapsing of pain and paresthesia by VAS; Worsening of muscular testing in case of motor impairment at baseline
	Electro-physiological evaluation: Improvement of electromyogram abnormalities	Electro-physiological evaluation: Appearance or worsening of electromyogram abnormalities

VAS visual analogue scales, *DAS-28-PCR* disease activity score on 28 joints calculated with C-reactive protein, *GFR* glomerular filtration rate, *RBC* red blood cell, *hpf* hight performance field (400×)

Safety assessment

Immune-mediated drug-related AE (IM-AE) such as urticaria-like cutaneous reactions, sick serum syndrome, autoimmune hemolytic anemia, vasculitic re-exacerbation, angioedema, fever and hypotension were recorded. Vasculitic re-exacerbation was defined as the onset of a new organ involvement or worsening of the autoimmune disease, within 4 weeks following RTX [17]. When an IM-AE occurred, we reported the outcome and the management.

AQ3

IM-AE are classified by severity according to Hartwig et al. [18]. An AE is considered serious when it causes death, hospitalization or its prolongation, serious or permanent disability or endangers the patient's life [18].

Finally, to evaluate effectiveness and safety of CT-P10, we compared the actual group with an historical cohort extrapolated from the same centers composed by MCV subjects treated with RTX originator.

Statistical analysis

The baseline variables were expressed as percentages or median and interquartile ranges (IQR). Analyses were made using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA), with a p value ≤ 0.05 considered to be statistically significant. The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables (absolute numbers and percentages) regarding baseline characteristics. The univariate and multivariate analyses were performed using logistic Cox regression model.

Results

A total of 51 patients, 35 females and 16 males, were included in the study between July and December 2018 and were treated with CT-P10 (group 1). The historical control group (group 2) included 75 consecutive patients, 58 females and 17 males, treated with RTX originator between July 2017 and July 2018 (see Table 2). Median disease duration was 42 months (interquartile range—IQR—96) in group 1 and 96 months (IQR 96) in group 2 (see Table 2).

Table 2

Baseline evaluation of MCV patients treated with CT-P10 biosimilar (group 1) or RTX originator (group 2)

	Group 1 (51 pt)	**Group 2 (75 pt)**	***p* value**
Median age (years)	68 (21)	65 (16)	0.038
Median disease duration (months)	42 (96)	96 (96)	0.006
Sex (M/F)	16/35	17/58	ns
HCV (%)	26 (51)	70 (93.3)	< 0.001
Clinical features			
Skin involvement (%)	41 (80.4)	51 (68)	0.01
Renal involvement (%)	15 (29.4)	35 (46.7)	0.05
Peripheral neurological involvement (%)	30 (58.8)	54 (72)	ns
Lymphoma (%)	9 (17.6)	13 (17.3)	ns
Life-threatening involvement (%)	6 (11.8)	1 (1.3)	ns
RTX main indication			
Skin involvement (%)	33 (64.7)	26 (34.7)	ns
Renal involvement (%)	6 (11.8)	29 (38.7)	0.002
Peripheral neurological involvement (%)	12 (23.5)	19 (25.3)	ns

Numeric parameters are reported as median (interquartile range); Dicotomic parameters are reported as number (percentage)

MCV mixed cryoglobulinemic vasculitis, *Pt* patient, *M* male, *F* female, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *RTX* Rituximab, *AE* adverse event

[a]Glucocorticoids, azathioprine, colchicine, hydroxychloroquine

[b]Prednisone < 7.5 mg; The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables regarding baseline characteristics

	Group 1 (51 pt)	Group 2 (75 pt)	*p* value
Abdominal vasculitis (%)	–	1 (1.3)	ns
Laboratory assessment			
Type II cryoglobulins positive (%)	45 (88.2)	71 (94.7)	ns
Rheumatoid factor positive (%)	35 (68.6)	69 (92)	ns
Rheumatoid factor titer (U/ml)	185 (497)	144 (402)	ns
C4 (mg/dl)	6.8 (10.8)	3 (4.9)	0.04
C4 decreased (%)	33 (64.7)	58 (77.3)	ns
Previous or concomitant treatment			
Previous immunosuppressive treatment[a] (%)	7 (13.7)	9 (12)	ns
Concomitant low-dosage steroid treatment[b] (%)	21 (41.1)	37 (49.3)	ns
RTX dosage			
1 g × 2 (%)	6 (11.8)	16 (21.3)	ns
375 m^2 × 4 (%)	12 (23.5)	58 (77.3)	< 0.001
250 mg m^2 × 2 (%)	33 (64.7)	1 (1.3)	ns
Switch (%)	15 (29.5)	–	
Adverse events (%)	13 (25.5)	17 (22.7)	ns
Immuno-mediated AE (%)	7 (13.7)	6 (8)	ns
Numeric parameters are reported as median (interquartile range); Dicotomic parameters are reported as number (percentage)			
MCV mixed cryoglobulinemic vasculitis, *Pt* patient, *M* male, *F* female, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *RTX* Rituximab, *AE* adverse event			
[a]Glucocorticoids, azathioprine, colchicine, hydroxychloroquine			
[b]Prednisone < 7.5 mg; The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables regarding baseline characteristics			

Thirty-seven patients were treated with CT-P10 for the first time, while the other 14 subjects were switched to CT-P10 after a previous treatment with RTX originator.

Regarding the therapeutic regimen, in the group 1, 33 subjects received low-dosage treatment (64.7%) and 18 high-dosage treatments (33.3%), in particular 6 received RTX 1000 mg twice one week apart and 12 received RTX 375 mg/m^2 four times a week apart. All patients in the group 2 were treated with high-dosage schemes, 16 received RTX 1000 mg twice one week apart and the remaining 59 received RTX 375 mg/m^2 four times a week apart.

Baseline clinical, bio-humoral characteristics and main treatment indications are summarized in Table 2. Other treatments associated were glucocorticoids, azathioprine, colchicine, antiviral treatment, hydroxychloroquine, gabapentin and pain management therapy (Table 2).

Safety

No differences were observed between group 1 and 2 according to the number of AE (0.87 and 0.37 for the total number of AE and immune-mediated AE, respectively).

Within one month from the infusion, 13 adverse events were recorded in group 1; among them, 7 were immune-mediated and could be directly related to the treatment, namely 3 skin vasculitis exacerbation, 2 serum sickness syndromes, 1 urticaria and 1 neutropenia. Other 4 patients developed nonspecific adverse events (arrhythmias in 2 patients, blood pressure disorders in 2, infection in the other 2) (see Table 3).

Table 3

Advers events in MCV patients treated with CT-P10 biosimilar (group 1) or RTX originator (group 2)

Group 1 (51 pts)		**Group 2 (75 pts)**	
Immuno-mediated AE	Num.	Immuno-mediated AE	Num.
Vasculitis exacerbation	3	Vasculitis exacerbation	1
Serum sickness syndrome	4	Serum sickness syndrome	1
Neutropenia	1	Neutropenia	2
Urticaria	1	Urticaria	1
		Hemolytic anemia	1
Total	7	Total	6
Non-IM-AE		Non-IM-AE	

MCV mixed cryoglobulinemic vasculitis, *pt* patient; *AE* adverse event, *IM* immuno-mediated, *Num.* number of AE

Group 1 (51 pts)		Group 2 (75 pts)	
Arrythmias	2	Increase of liver enzymes	2
Infection	2	Infection	5
Hypotension	1	Hypotension	2
Hypertension	1	Hypogammaglobulinemia	2
Total	6	Total	11

MCV mixed cryoglobulinemic vasculitis, *pt* patient; *AE* adverse event, *IM* immuno-mediated, *Num.* number of AE

In the historical group, we recorded 17 adverse events and 6 with immune-mediated features (see Table 3).

No severe advent events occurred in group 1 and all patients recovered within 2 weeks, while 2 severe AE, needing hospital admission (serum sickness syndrome and pneumonia), were observed in group 2.

Overall, we did not observe significant differences in the number of adverse events between CT-P10 and originator group, although the frequency of immune-mediated AE was higher in CT-P10 group (13.7% and 8% in CT-P10 and originator group, respectively). At univariate analysis patients with IM-AE were more frequently males ($p = 0.04$) and with a lower disease duration ($p = 0.03$) (see Table 4), but both the parameters were not significant at logistic regression (see Table 5, NOT TABLE 4 4).

Table 4

Clinical demographic features of MCV patients with or without adverse events

	Adverse events			Immune-mediated AE		
	No	Yes	*p* value	No	Yes	*p* value
Number	*96*	*30*		*113*	*13*	

Numeric parameters are reported as median (interquartile range); Dichotomic parameters are reported as number (percentage)

The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables regarding baseline characteristics

MCV Mixed cryoglobulinemic vasculitis, *AE* adverse event, *M* male, *F* Female, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *RTX* rituximab

	Adverse events			Immune-mediated AE		
	No	**Yes**	***p* value**	**No**	**Yes**	***p* value**
Median age (years)	65 (16.8)	66.5 (13.5)	0.29	66 (15.5)	78 (106.5)	ns
Median disease duration (Months)	75 (99.3)	60 (110.3)	0.45	64 (17)	48 (102.5)	0.03
Sex (M/F)	24/72	9/21	0.64	26/86	7/6	0.04
HCV	73 (76)	23 (76.7)	0.85	86 (76.1)	10 (76.9)	ns
Organ involvement						
Skin involvement	73 (76)	19 (63.3)	0.37	84 (74.3)	8 (61.5)	ns
Renal involvement	36 (37.5)	14 (46.7)	0.37	45 (39.8)	5 (38.5)	ns
Joint involvement	18 (18.8)	4 (13.3)	0.59	19 (10.8)	3 (23.1)	ns
Peripheral neurological involvement	64 (66.7)	20 (66.7)	1.00	76 (67.3)	8 (61.5)	ns
Lymphoma	18 (18.8)	4 (13.3)	0.59	19 (16.8)	3 (23.1)	ns
RTX main indication						
Skin involvement	46 (47.9)	13 (43.3)		54 (47.8)	5 (38.5)	ns
Renal involvement	25 (26)	10 (33.3)	0.83	31 (27.4)	4 (30.8)	ns
Peripheral neurological involvement	24 (25)	7 (23.3)		27 (23.9)	4 (30.8)	ns
Abdominal vasculitis	1 (1)	–		1 (0.9)	–	ns
Laboratory assessment						
Type II cryoglobulins (positive)	89 (92.7)	27 (90)	0.7	104 (92)	12 (92.3)	ns

Numeric parameters are reported as median (interquartile range); Dichotomic parameters are reported as number (percentage)

The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables regarding baseline characteristics

MCV Mixed cryoglobulinemic vasculitis, *AE* adverse event, *M* male, *F* Female, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *RTX* rituximab

	Adverse events			Immune-mediated AE		
	No	**Yes**	***p* value**	**No**	**Yes**	***p* value**
Rheumatoid factor (positive)	82 (85.4)	22 (73.3)	0.17	93 (82.3)	11 (84.6)	ns
Rheumatoid factor titre (U/ml)	150 (454)	185 (581)	0.9	150 (403)	251 (811)	ns
C4 (mg/dl)	4 (10)	4.2 (4.5)	0.84	4 (8)	3 (15)	ns
C4 decreased	66 (68.7)	25 (80.3)	0.14	79 (69.9)	12 (92.3)	ns
RTX dosage						
1 g × 2	15 (15.6)	7 (23.3)		21 (18.6)	1 (7.7)	ns
375 m^2 × 4	55 (57.3)	15 (50)	0.61	63 (55.8)	7 (53.8)	ns
250 mg m^2 × 2	26 (27.1)	8 (26.7)		29 (25.7)	5 (14.7)	ns
Biosimilar/originator	38/58	13/17	0.71	44/69	7/6	ns
Numeric parameters are reported as median (interquartile range); Dichotomic parameters are reported as number (percentage)						
The differences between continuous variables were analyzed using the Mann–Whitney nonparametric test. The chi-squared test was used for categorical variables regarding baseline characteristics						
MCV Mixed cryoglobulinemic vasculitis, *AE* adverse event, *M* male, *F* Female, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *RTX* rituximab						

Finally, among patients treated with high-dosage regimens, no differences were observed between the 2 groups regarding the overall AEs, while a trend for a higher frequency of IM-AE was observed in CT-P10 group ($p = 0.056$).

Effectiveness

Clinical response was evaluated after 6 months by the end of the treatment. No differences were observed between patients treated with originator and CT-P10 regarding the response to the therapy. Patients treated with CT-P10 improved or remained stable in 100% of cases with skin involvement (95% in the originator group), in 93.3% of patients with renal involvement (97.1% with originator), and in 81.2% of patients with peripheral neuropathy (84% in originator group).

AQ4

No differences were detected according to previous immunosuppressive treatments or ongoing steroid therapy.

Discussion

Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody, used in hematological and autoimmune disorders including B cell-lymphoproliferative diseases, RA, systemic lupus erythematosus and it represents a milestone in the treatment of MCV. Indeed, RTX demonstrated to be effective in the treatment of all clinical manifestations of MCV [8]. Furthermore, is generally well tolerated even if possible severe adverse events, such as serum sickness, immunodeficiency or autoimmune disorders have been reported. Although a large number of patients in the world could benefit from a treatment with RTX, access to this therapy is not universal and the cost of medication can be limiting for some healthcare services. The commercialization of biosimilars of RTX, after the expiration of its patent protection in 2018, led to a better access to the therapy, but also to possible safety concerns, mainly in patients with immune-mediated diseases, such as MCV (Table 5).

Table 5

Logistic regression. Association between clinico-demographic features and adverse events

	Odds Ratio	**95%-CI**	***p***
Disease duration	0.993	0.98–1.00	0.22
Male sex	3.160	0.93–10.69	0.06
CI confidence interval			

AQ5

For the first time, we have compared CT-P10 and originator in MCV patients, obtaining a comparable safety and effectiveness in this population.

Pharmacodynamic studies demonstrated similar profiles of CT-P10 and originator, despite small known differences, which did not modify their clinical efficacy [19, 20]. Pre-marketing studies showed similar safety profiles for CT-P10 and originator (including immunogenicity), despite the incidence of adverse events was generally lower for reference products in rheumatoid arthritis [19, 20].

In our study, despite a higher prevalence of immune-mediated AE among patients treated with CT-P10 than originator [respectively 7/13 (53.8%), and

6/17 (35.3%)], we have observed no significant differences between the 2 groups.

Regarding effectiveness, no differences were observed between the 2 groups in a 6-month period. Only long-term studies could evaluate the persistence of the therapeutic effect over time.

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We can observe that the use of a low-dosage regimen is more common in group 1 than in group 2 and this could possibly influence the incidence of side-effects [17, 21]. Since immune-mediated adverse events have been usually associated to high-dosage schedule (1 g every other week), the high frequency of a low dosage in CT-P10 group could represent a bias in our study, possibly reducing the frequency of IM-AE. Nonetheless in the long-term study analyzing the treatment with low-dose rituximab originator for MC, adverse events were described in 19% of patients (7/37) and IM-AE were more frequently observed (5/37 [13%]) [22]. These percentages are very similar to what observed in patients from group 1 treated with CT-P10 more frequently with a low-dose regimen. In this context, we need large study between originator and CT-P10 with comparable therapeutic schedules to definitively assess the comparability of the two drugs.

The main limitation of our study was represented by the retrospective nature of the control group, the limited number of subjects included and by the absence of shared criteria for the clinical assessment of disease and the comparison of the CT-P10 group with a retrospective cohort of MCV patients treated with RTX originator. Another major limitation is related to the difference between the two groups due to the different historical periods, in particular as regards the use of direct-acting antivirals, the change in therapy schedules administrated and the as regards the treatment proposal on an earlier stage of MCV in comparison to past. In the last years, the treatment of MCV patients with the low-dosage regimen has been approved in Italy, increasing the possibility to treat the patients in an early of the disease [23].

Despite some limitations, our study shows a good safety profile for CT-P10 in MCV patients, maintaining a comparable effectiveness with originator during a 6-month period. Reassuring rheumatologists about biosimilars is nowadays relevant considering the initial concerning about this treatment opportunity [23]. Considering the cost/efficacy ratio of biosimilars, indeed, their use could be helpful to treat a large number of MCV patients with an effectiveness and safety comparable to originator [24]. Multicenter studies including a large number of patients and the new RTX biosimilars could be useful to fully elucidated the possible risk of immune-mediated adverse events with biosimilar drugs.

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