Biologics: Targets and Therapy

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ORIGINAL RESEARCH

Certolizumab Can Also Be Effective in Monotherapy for the Treatment of Rheumatoid Arthritis Patients

Pedro Santos-Moreno[1]
Susan Martinez[2]
Linda Ibatá[2]
Laura Villarreal[1]
Manuel Rivero[3]
Adriana Rojas-Villarraga[4]

[1]Rheumatology, Biomab IPS, Bogotá, DC, Colombia; [2]Epidemiology, Biomab IPS, Bogotá, DC, Colombia; [3]Pharmacy, Biomab IPS, Bogotá, DC, Colombia; [4]Rheumatology, Research División, Fundación Universitaria de Ciencias de la Salud – FUCS, Bogotá, DC, Colombia

Objective: Although it is known that methotrexate (MTX) increases the effectiveness of biological drugs (mainly anti-TNFs) in patients with rheumatoid arthritis (RA), in real life, it is known that many patients using anti-TNFs are on monotherapy due to many causes. This article compares the effectiveness of certolizumab as monotherapy as combined with MTX or leflunomide (LFN) in RA patients with failure to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in a real-world setting.

Methods: A retrospective observational cohort study was conducted at a specialized centre for RA management in Colombia. Patients treated with certolizumab as monotherapy or in combination with MTX, LFN, or MTX+LFN, between 2011 and 2020 with a minimum 3-month follow-up were included. Demographics and RA clinical characteristics were recorded; effectiveness was assessed as the improvement in Disease Activity Score (DAS28) getting remission or low disease activity at 3, 6, and 12 months of treatment.

Results: A total of 181 patients were included, 24 received certolizumab as monotherapy, 62 certolizumab plus MTX, 47 certolizumab plus LFN and 48 certolizumab plus MTX+LFN. At 3 months of follow-up, 80% of the patients showed decreased disease activity, with no significant differences between groups; at 12 months of treatment, response in certolizumab monotherapy group was 94.4% compared to 81.8% in combination with MTX, 80.5% in combination with LFN and 51.4% in combination with MTX+LFN. Response at 3 months (OR 4.04; 95% CI 1.28–12.69) and positive anti-CCP (OR 3.83; 95% CI 1.11–13.21) were associated with 12-month response.

Conclusion: Certolizumab seems to be effective as monotherapy in the treatment of RA patients with failure to csDMARDs.

Keywords: rheumatoid arthritis, treatment, anti-TNFs, certolizumab, monotherapy

Background

Tumour necrosis factor inhibitors (antiTNFs) are one of the most commonly used biological therapy for Rheumatoid Arthritis (RA) patients who do not show an adequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).[1] Although some anti-TNF inhibitors could be effective as monotherapy in the treatment of RA, current guidelines recommend that biological DMARDs (bDMARDs), including anti-TNFs, should be used in combination with methotrexate (MTX).[2]

Despite evidence suggests improved efficacy of TNF inhibitors in combination with MTX, some patients receive monotherapy because of intolerance to MTX or

Correspondence: Pedro Santos-Moreno
Rheumatology, Biomab IPS, Calle 48 # 13-86, Bogotá, Colombia
Email pedrosantosmoreno@hotmail.com

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contraindication for its use.[3,4] It is well known that MTX remains the csDMARD of the first choice in RA, but response varies depending on demographic, clinical and psychosocial predictors.[5] While it is true that MTX cessation due to an adverse event is possible, some studies have demonstrated reasons for inefficacy and cessation; rheumatoid factor positivity, age, and higher baseline disease activity have an increased risk of MTX failure due to inefficacy.[6] In addition, other studies have demonstrated that specific polymorphisms in some genes are involved in MTX monotherapy discontinuation.[7]

Although certolizumab, a PEGylated, Fc-free molecule, has been proven effective and safe in combination with MTX in the treatment of patients with RA after failure to csDMARDs, there is scarce information about its effectiveness as monotherapy in real life.[8]

Knowing the effectiveness of monotherapy with certolizumab versus certolizumab combined with MTX and other csDMARDs is of vital importance for patients and their health care providers. This article presents real-world clinical practice results of a cohort of patients with RA and failure to csDMARDs who received certolizumab as monotherapy, combined with MTX, or leflunomide (LFN), or MTX plus leflunomide (MTX+LFN).

Methods

This retrospective observational cohort study was conducted at a specialized centre for RA management in Colombia. Patients treated with certolizumab as monotherapy or in combination with MTX, or LFN, or MTX+LFN, between 2011 and 2020 were included in this study, regardless of their previous treatment or disease status. All participants met either the 1987 ACR criteria or the 2010 ACR/EULAR criteria for RA diagnosis.[9,10] The indication of certolizumab was a medical decision based on disease activity. Patients could be taking other drugs like non-steroidal anti-inflammatory drugs, COX2 inhibitors and/or opioids and corticosteroids. Patients who did not complete 3 months of follow-up or patients with change or addition of other csDMARDs or dosing adjustments were excluded.

Certolizumab was administered 400 mg SC monthly after three induction doses at weeks 0, 2 and 4, as a monotherapy or in combination with MTX (until 25 mg/week), LFN (20 mg/day) or MTX (until 25 mg/week) plus LFN (20 mg/day) as a first-line treatment after failure with csDMARDs or as a second-line treatment after failure with one or more biological drugs.

For each patient, demographic characteristics, and RA characteristics, such as duration and activity level according to DAS28 scores, were recorded. Patients were classified as remission (DAS28 <2.6), low disease activity (DAS28 between 2.6 and 3.2), moderate activity (DAS28 >3.2 and ≤5.1), or high activity (DAS28 >5.1.). Effectiveness was assessed as the change in DAS28 at 3, 6, and 12 months of treatment. The response was defined as a decrease >1.2 in activity level using DAS28 or to remain in low activity or remission. A DAS28 ≤3.2 was considered an indicator of disease control.

Analysis Methods

Frequencies and proportions were calculated for qualitative variables and central tendency and dispersion measures for quantitative variables based on the distribution (Shapiro–Wilk test). Exploratory comparisons of numeric variable data between groups were made through one-way ANOVA or Kruskal–Wallis test. Chi-square test and Fisher's exact test were used for categorical variables. For all tests, a p-value <0.05 indicates statistical significance. Variables with statistical significance or clinical interest related to response to therapy were included in multivariate analyses. Logistic regressions were performed to analyze individual, clinical, and pharmacological factors on the response at 6 and 12 months. All calculations were performed using PASW Statistics software version 25.

Results

Of the 181 enrolled patients, 24 received certolizumab as monotherapy, 62 certolizumab combined with MTX, 47 certolizumab in combination with LFN and 48 certolizumab in combination with MTX+LFN. In 55.2% of the patients, these interventions were first-line treatment (after csDMARDs) and 44.8% second-line treatment (bDMARDs), without significant differences between groups. All the patients were treated before the study with MTX at a 25 mg/per week dose. MTX was suspended by gastric or hepatic adverse events or lack of efficacy. Table 1 describes the characteristics of patients at the time of diagnosis based on the type of treatment. The mean age of subjects included was 57.87 ± 12.33 years, with significant differences between groups, with a mean age of around 60 years in patients treated with CTZ+MTX and CTZ+LFN. Women predominated in all groups (84.0% of the total). The most common comorbidities at the time of RA diagnosis were osteoporosis (31.5%) and Sjogren's syndrome (31.5%). Overall, comorbidities were similar

Table 1 Baseline Characteristics of Patients According to Treatment

	CERTOLIZUMAB		CERTO +MTX		CERTO +LFN		CERTO+MTX +LFN		Total		P value
	n=24		n=62		n=47		n=48				
Age, mean (SD)	52.7	(16.8)	60.9	(12.0)	59.1	(10.8)	55.4	(10.3)	57.87	(12.33)	0.014†
Female, n (%)	22	(91.7)	55	(88.7)	37	(78.7)	38	(79.2)	152	(84.0)	0.275*
Comorbidities	19	(79.2)	45	(72.6)	35	(74.5)	42	(87.5)	141	(77.9	0.269*
Arterial hypertension, n (%)	5	(20.8)	24	(38.7)	15	(31.9)	7	(14.6)	51	(28.2)	0.033*
Diabetes mellitus, n (%)	2	(8.3)	7	(11.3)	4	(8.5)	2	(4.2)	15	(8.3)	0.613*
CVD, n (%)	3	(12.5)	4	(6.5)	2	(4.3)	0	(0)	9	(5.0)	0.126*
CKD, n (%)	1	(4.2)	1	(1.6)	1	(2.1)	0	(0)	3	(1.7)	0.615*
Osteoporosis, n (%)	7	(29.2)	24	(38.7)	13	(27.7)	13	(27.1)	57	(31.5)	0.511*
Sjögren's Syndrome, n (%)	2	(8.3)	6	(9.7)	4	(8.5)	2	(4.2)	57	(31.5)	0.744*
RA duration, median (IQR)	6.0	(13)	5.0	(11)	5.0	(13)	4.0	(8)	5.00	(11)	0.846‡
Baseline DAS 28											0.787*
Remission, n (%)	3	(12.5)	10	(16.1)	4	(8.5)	5	(10.4)	22	(12.2)	
Low activity, n (%)	2	(8.3)	8	(12.9)	3	(6.4)	4	(8.3)	17	(9.4)	
Moderate activity, n (%)	12	(50.0)	30	(48.4)	26	(55.3)	21	(43.8)	89	(49.2)	
High activity, n (%)	7	(29.2)	14	(22.6)	14	(29.8)	18	(37.5)	53	(29.3)	
Baseline DAS 28, median (IQR)	4.08	(1.99)	4.01	(1.77)	4.49	(1.42)	4.58	(1.91)	4.32	(1.83)	0.272‡
Positive Hand radiograph, n (%)	7	(53.8)	10	(41.7)	6	(30.0)	4	(22.2)	27	(36.0)	0.269*
Positive Foot radiograph, n (%)	6	(46.2)	4	(23.5)	3	(30.0)	2	(20.0)	15	(30.0)	0.488*
Positive Rheumatoid factor, n (%)	17	(70.8)	52	(83.9)	38	(80.9)	35	(72.9)	142	(78.5)	0.422*
Positive Anti-CCP, n (%)	15	(62.5)	33	(53.2)	31	(66.0)	34	(70.8)	113	(62.4)	0.546*
Treatment characteristics											
Treatment line											0.958*
First, n (%)	14	(58.3)	33	(53.2)	27	(57.4)	26	(54.2)	100	(55.2)	
Second, n (%)	10	(41.7)	29	(46.8)	20	(42.6)	22	(45.8)	81	(44.8)	
Previous bDMARDs (number)											0.046*
None, n (%)	14	(58.3)	33	(53.2)	27	(57.4)	26	(54.2)	100	(55.2)	
One, n (%)	8	(33.3)	23	(37.1)	15	(31.9)	13	(27.1)	59	(32.6)	
Two, n (%)	0	(0.0)	4	(6.5)	2	(4.3)	8	(16.7)	14	(7.7)	
Three, n (%)	0	(0.0)	0	(0.0)	3	(6.4)	0	(0.0)	3	(1.7)	
Corticoids use, n (%)	11	(45.8)	32	(51.6)	28	(59.6)	36	(75.0)	107	(59.1)	0.042*

Notes: *Ji cuadrado. †One-way ANOVA. ‡Kruskal–Wallis Test.

among groups, except for hypertension, which was more common (38.7%) in the group of patients treated with CTZ+MTX.

The duration of arthritis on average was 8.27 ± 8.73 years, without significant differences between treatment groups. In terms of disease activity, at baseline, 78.5% of the patients were in moderate or high disease activity according to DAS28, without significant differences between the groups. There were no statistically significant differences in hand and foot x-ray results, initial C-reactive protein (CRP), rheumatoid factor, and anti-citrullinated antibodies (anti-CCP) values. Differences in the number of biologicals and corticoid use were observed; patients in the combination groups had used in a higher proportion two or more biological than in the monotherapy group and had used corticosteroids more frequently. The dose in patients receiving corticoids was low (7.5 mg/day), and there were no changes during the observed period.

The response to treatment was assessed at 3, 6 and 12 months according to the decrease in DAS28 (see Table 2). Overall, approximately 80% of the patients had responded to treatment with decreased disease activity, and 63% were in remission or low activity within 3 months of follow-up, with no significant differences between groups. This trend

Table 2 Response at 3, 6 and 12 Months by Treatment Group

	CERTO		CERTO+MTX		CERTO + LFN		CERTO + MTX + LFN		Total		P value
	n=24		n=62		n=47		n=48				
Response at month 3											
DAS 28											0.081
In remission, n (%)	14	(63.6)	26	(44.8)	20	(43.5)	16	(34.8)	76	(44.2)	
Low activity, n (%)	2	(9.1)	13	(22.4)	12	(26.1)	6	(13.0)	33	(19.2)	
Moderate activity, n (%)	6	(27.3)	19	(32.8)	11	(23.9)	22	(47.8)	58	(33.7)	
High activity, n (%)	0	(0.0)	0	(0.0)	3	(6.5)	2	(4.3)	5	(2.9)	
3-month DAS 28, median (IQR)	2.44	(1.43)	2.76	(1.43)	2.92	(1.19)	3.37	(1.78)	2.89	(1.4)2	0.144
Response*											0.150
Negative, n (%)	3	(13.6)	10	(17.2)	8	(17.4)	15	(32.6)	36	(20.9)	
Positive, n (%)	19	(86.4)	48	(82.8)	38	(82.6)	31	(67.4)	136	(79.1)	
Control**											
Negative, n (%)	6	(27.3)	19	(32.8)	14	(30.4)	24	(52.2)	63	(36.6)	0.080
Positive, n (%)	16	(72.7)	39	(67.2)	32	(69.6)	22	(47.8)	109	(63.4)	
Response at month 6											
DAS 28											0.152
In remission, n (%)	14	(66.7)	34	(59.6)	24	(55.8)	17	(37.8)	89	(53.6)	
Low activity, n (%)	3	(14.3)	11	19.3)	8	(18.6)	9	(20.0)	31	(18.7)	
Moderate activity, n (%)	4	(19.0)	12	(21.1)	8	(18.6)	14	(31.1)	38	(22.9)	
High activity, n (%)	0	(0.0)	0	(0.0)	3	(7.0)	5	(11.1)	8	(4.8)	
6-month DAS 28, median (IQR)	2.24	(0.81)	2.51	(0.77)	2.53	(0.99)	3.22	(1.78)	2.52	(1.12)	0.028
Response*											0.132
Negative, n (%)	1	(4.8)	8	(14.0)	7	(16.3)	12	(26.7)	28	(16.9)	
Positive, n (%)	20	(95.2)	49	(86.0)	36	(83.7)	33	(73.3)	138	(83.1)	
Control**											
Negative, n (%)	4	(19.0)	12	(21.1)	11	(25.6)	19	(42.2)	46	(27.7)	0.076
Positive, n (%)	17	(81.0)	45	(78.9)	32	(74.4)	26	(57.8)	120	(72.3)	
Response at Month 12											
DAS 28											0.007
In remission, n (%)	11	(61.1)	36	(65.5)	25	(61.0)	17	(45.9)	89	(58.9)	
Low activity, n (%)	6	(33.3)	9	(16.4)	8	(19.5)	2	(5.4)	25	(16.6)	
Moderate activity, n (%)	1	(5.6)	7	(12.7)	8	(19.5)	14	(37.8)	30	(19.9)	
High activity, n (%)	0	(0.0)	3	(5.5)	0	(0.0)	4	(10.8)	7	(4.6)	
12-month DAS 28, median (IQR)	2.35	(1.08)	2.24	(1.03)	2.43	(0.84)	3.10	(1.80)	2.38	(1.07)	0.058
Response*											0.010
Negative, n (%)	1	(5.6)	8	(14.5)	3	(7.3)	12	(32.4)	24	(15.9)	
Positive, n (%)	17	(94.4)	47	(85.5)	38	(92.7)	25	(67.6)	127	(84.1)	
Control**											
Negative, n (%)	1	(5.6)	10	(18.2)	8	(19.5)	18	(48.6)	37	(24.5)	0.001
Positive, n (%)	17	(94.4)	45	(81.8)	33	(80.5)	19	(51.4)	114	(75.5)	

Notes: *Decreased disease activity or maintenance in mild activity/remission. **DAS 28 ≤3.2.

continued until the sixth month. At 12 months of treatment, although the response was maintained in most patients, in the Certolizumab monotherapy group, this was 94.4% compared to 81.8% in combination with MTX, 80.5% in combination with LFN and 51.4% in combination with MTX+LFN.

A simple and multiple logistic regression analysis was performed to explore the relationship of different variables with the DAS28 response at 6 and 12 months (see Tables 3 and 4). There was no association between a positive rheumatoid factor and DAS28 response at 6 or 12 months. No differences were observed in the response at 6 and 12 months between the treatment groups, and the only variable associated with these outcomes is the response at 3 months. In the multivariate analysis, the response at 3 months was the only one associated with the 6-month

Table 3 Simple Regression Analysis to Estimate the Risk of Response at 6 and 12 Months by Treatment Group

Factor	Response at Month 6			Response at Month 12		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.02	0.99–1.06	0.101	1.02	0.98–1.06	0.190
Sex (female)	1.21	0.41–3.54	0.726	1.59	0.52–4.80	0.408
Duration of RA	1.06	0.99–1.13	0.070	1.00	0.95–1.05	0.927
Positive rheumatoid factor	0.81	0.21–2.97	0.746	0.61	0.13–2.90	0.543
Positive anti-CCP	1.03	0.31–3.42	0.954	2.40	0.83–6.91	0.103
Baseline DAS28	1.08	0.79–1.48	0.592	0.94	0.67–1.31	0.731
Second line	0.84	0.37–1.89	0.674	1.14	0.47–2.75	0.771
Previous bDMARDs (number)	0.94	0.59–1.49	0.820	1.19	0.66–2.15	0.556
Corticoids use	0.76	0.32–1.78	0.536	0.81	0.33–1.99	0.648
Treatment group						
CTZ monotherapy	–	–	–	–	–	–
CTZ + MTX	0.30	0.04–2.61	0.279	0.34	0.04–2.97	0.333
CTZ + LFN	0.26	0.03–2.24	0.219	0.74	0.07–7.69	0.805
CTZ + MTX + LFN	0.14	0.02–1.13	0.066	0.12	0.01–1.03	0.054
Response at Month 3	5.88	2.40–14.42	0.000	4.96	1.91–12.89	0.001

Table 4 Multiple Regression Analysis to Estimate the Risk of Response at 6 and 12 Months by Treatment Group

Factor	Response at Month 6			Response at Month 12		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.02	0.98–1.07	0.214	1.03	0.97–1.08	0.262
Duration of RA	1.06	0.98–1.14	0.115			
Positive anti-CCP				3.83	1.11–13.21	0.033
Previous bDMARDs (number)	0.97	0.53–1.79	0.939	1.32	0.63–2.75	0.450
Treatment group						
CTZ monotherapy	–	–	–	–	–	–
CTZ + MTX	0.25	0.02–2.60	0.245	0.48	0.04–5.33	0.548
CTZ + LFN	0.25	0.02–2.63	0.246	0.80	0.06–10.73	0.869
CTZ + MTX + LFN	0.16	0.02–1.61	0.122	0.18	0.02–1.94	0.159
Response at Month 3	5.46	2.08–14.32	0.001	4.04	1.28–12.69	0.017

response (OR 5.46; 95% CI 2.08–14.32). The response at 3 months (OR 4.04; 95% CI 1.28–12.69) and positive anti-CCP (OR 3.83; 95% CI 1.11–13.21) were associated with 12-month response.

Discussion

Rheumatoid arthritis requires for its control the use of disease-modifying medications. According to EULAR recommendations, MTX plus glucocorticoids should be initiated as the first line of treatment in the short term to achieve an improvement of at least 50% at 3 months and remission at 6 months; if this is not achieved, treatment should be modified according to the presence of prognostic markers. If there are no unfavourable prognostic factors, other csDMARDs could be added. On the contrary, if there are unfavourable prognostic factors, a bDMARD or JAK inhibitor should be added.[11]

Although EULAR recommends combination therapy with biological DMARDs, a significant proportion of patients are treated with monotherapy due to csDMARDs intolerance or adherence failure to MTX in real life.[4] This study included patients with MTX failure who received CTZ alone, CTZ combined with methotrexate or leflunomide, and CTZ combined with MTX and LFN. Several studies have reported that approximately 25% to 30% of the patients are treated with monotherapy.[3,12] In our study, this proportion is lower (13%) probably related to the scarce information available regarding the effectiveness of certolizumab monotherapy.

Regarding CTZ in monotherapy, there are two clinical trials in patients who did not respond or were intolerant to treatment with csDMARDs. The REALISTIC study compared the efficacy of CTZ monotherapy vs CTZ in combination with csDMARDs and found that patients in the monotherapy group had lower ACR20/50/70 response rates but a slightly greater change in DAS28, although the results were not statistically significant.[13] The FAST4WARD study compared CTZ monotherapy vs placebo at week 24 observed ACR20 response rate was 45.5% with CTZ and 9.3% with placebo.[14] Improvement was also observed in DAS28 and patient-reported outcomes at long-term use.[15] Most adverse events were mild or moderate.

In our study, the response starts to be noted from the third month and is maintained through time. And, 94.4% of monotherapy patients achieved disease control (DAS28 ≤3.2) per year of treatment, compared to approximately 80% in combination groups with csDMARDs and 51.4% of patients in the CTZ + MTX + LFN group. These differences are not explained by the number of previous biologicals received or the use of glucocorticoids. They may be related to adherence issues, not quantified in this study. After adjusting the results by confusion, no differences are observed between the groups to respond at months 6 and 12. Regardless of the treatment group and previous biologics, the 3-month response is strongly associated with a higher probability of response at months 6 and 12. This finding is concordant with the reported results in observational studies where non-response at month 3 is a predictor of failure to achieve the therapeutic target at month 12.[16–18] In our study, we did not find an association with a response and a biologic-naïve status as other studies have reported.[17] Additionally, it is observed that having positive anti-CCP is associated with a greater probability of response at month 12; this finding is similar to that reported with abatacept.[19] However, this finding is debatable as other studies have linked high anti-CCP levels with decreased response to anti-TNF.[20] Regarding disease progression, a study (C-OPERA) comparing a group of patients under CTZ+MTX combo versus a group of placebo + MTX patients showed a trend of greater modified Total Sharp Score change from baseline independently of positive titres of anti-CCP in both groups.[21] In another study comparing the efficacy of CTZ versus adalimumab, there were no baseline differences in anti-CCP positivity nor in the efficacy endpoints regarding the anti-CCP result.[22]

This study has significant limitations inherent to its design, which implies a selection bias. Some patients were intolerant to MTX and went on monotherapy; others showed a lack of efficacy and therefore used LFN and glucocorticoids. In addition, important variables as body mass index and anti-certolizumab antibodies were not measured. However, these exploratory results show a clear trend of certolizumab being effective as monotherapy in patients previously treated with csDMARDs and even after being treated with one bDMARD. Even though results are not statistically different, it seems that certolizumab in monotherapy could be as least as effective as combination therapy. Prospective studies with a larger sample size and with a structured follow-up are needed to confirm these findings.

Data Sharing Statement

The authors declare that the database and other study materials are available for review at any time. All files,

databases and other documents related to the study are available on a computer in our research office and with access only to the team of researchers. In any case, please contact PSM.

Ethical Aspects

According to Resolution 8430 of 1993 from the Ministry of Health of Colombia, this research presents no risks to patients because no intervention and/or intentional modification of the variables was carried out. Therefore, this study was approved by the Institutional Review Board of Biomab IPS, act number 006-2020, October 2020 (code GC.IN.01.FR.03) without the need of obtaining informed consent of the individuals. In addition, to comply with the principles, rights and guarantees in the treatment of regulated personal data according to Law 1266 of 2008 and Law 1581 of 2012, all the individuals signed a general data protection regulation consent when entering to the specialized centre for RA. The group of researchers adhered to the principles of the Declaration of Helsinki. The database was anonymized to protect the confidentiality and privacy of patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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