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Effectiveness and Safety of Ocrelizumab in Primary Progressive Multiple Sclerosis among Iraqi Patients

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Abstract: Background Multiple sclerosis disorder altering agents are classify into two groups: drugs with medium effectiveness, also known as platform therapies, and high efficacy agent treatments (HEATs). Ocrelizumab (Ocrevus®), a humanized anti-CD20 monoclonal antibody given through veinous line, is approved for adults in deteriorating forms of multiple sclerosis or primary progressive multiple sclerosis.

Aim: The study aims to evaluate Effectiveness and safety of (Ocrelizumab) in Primary Progressive Multiple - Sclerosis among Iraqi patients.

Method: A multi centered, prospective study conducted in 3 hospitals in Iraq. A study analyzed clinical and MRI data in two visits over 6 months period.

Results: A study compromised 151 participants demonstrate 51% males while (49%) females with mean age 41±10; most patients taken (2) doses. Average of Expanded Disability Status Scale score of patients significantly increased from 4.851 to 5.026 with 34 (22.5%) confirmed disability progression. There was significant reduction in the progression index from 1.030 to 0.909 between two visits. Brain MRI experienced a substantial reduction in the number of T2 lesions from 8 to 7 with stable spinal MRI lesions. Ocrelizumab was well tolerated with most common adverse events were infusion related and 99% of them classified as mild.

Conclusion: Ocrelizumab appears effective in delaying the progression of the illness and lowering the development of MRI lesions in people with Multiple - Sclerosis.

Key words: Multiple sclerosis, Ocrelizumab, Neurology

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1. Introduction:

Multiple sclerosis (MS) is an autoimmune disease that destroys myeline, the defending of nerve fibers in the central nervous system CNS. This results in lesions or plaques, particularly in areas like the corpus callosum, brainstem, spinal cord, and cerebellum. The damage to myeline slows or blocks nerve signal transmission, causing neurological deficits. MS is believed to develop in individuals with a genetic predisposition triggered by environmental factors. It predominantly affects young adults, especially women, and often leads to gradual disability [1]. MS has a significantly increased incidence in Iraq, while prevalence is low compared to neighboring countries. [2].

Primary Progressive MS (PPMS) is often perceived as a unique, minimally inflammatory, or even non-inflammatory variant of MS. However, extensive clinical, imaging, and genetic evidence indicates that PPMS falls within the broader range of progressive MS phenotypes. The distinctions between PPMS and the progressive phase of relapsing forms of MS, such as Secondary Progressive MS (SPMS), are more relative than absolute, lacking pathophysiological distinct characteristics.[3]

Frequent relapses often correlate with an escalating disability, with a higher number of relapses signaling rapid deterioration in patients experiencing active symptoms. Age is a predictive factor for worsening disability, even in the absence of active disease symptoms. The combination of both frequent relapses and older age significantly heightens the risk of severe disability. [4]

Ocrelizumab is a humanized anti CD20 monoclonal antibody given intravenously, is authorized for treating adults with relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). Ocrelizumab demonstrated superior efficacy compared to interferon beta-1a in reducing action of illness and progression in patients with deteriorating MS, as observed over a 96-week duration. Ocrelizumab demonstrated a significant reduction in clinical and MRI progression rates compared to placebo in patients with relapsing remitting multiple sclerosis [5]. In primary progressive MS the incidence of confirmed disability progression at the 12-week mark (primary endpoint) was 32.9% for patients treated with ocrelizumab compared to 39.3% for those given a placebo. The proportion of patients experiencing confirmed disability progression at the 24-week mark, which is the first secondary endpoint in the analysis hierarchy, was 29.6% for those treated with ocrelizumab and 35.7% for those given a placebo [6].

2. Method

This A prospective, multi-centered, observational, and analytic design at at Baghdad Teaching Hospital, Saad Al-Witri Neuroscience Hospital, and Shar Teaching Hospital, to determine Effectiveness and safety of (Ocrelizumab) in Primary Progressive Multiple - Sclerosis among Iraqi patients. The study sample compromised One hundred fifty-one patients who met the specified criteria were with the primary objective of enrolling. A convenient sampling technique was used to select samples included as age 18-55 years and Finding of PPMS to the revised Mc-Donald standards (2017). The study analyzed clinical and MRI data in two visits over 6 months period. Data were coded, assigned serial numbers, and analyzed using SPSS version 26 under the guidance of an academic supervisor. Descriptive statistics, including frequency, percentage, mean, and standard deviation, were used, and the significance of differences in qualitative data was tested using Pearson's Chi-square test, Yate's correction, or Fisher's exact test where applicable, with a significance threshold of $P \leq 0.05$. Ethical considerations included obtaining approval from the ethical committee of the Scientific Council for Neurology and the Ministry of Health, maintaining participant confidentiality, and securing verbally informed consent from participants or their relatives after explaining the study's objectives.

3.results

Table (3.1): EDSS score at 1st and 2nd visits:

Statistics		EDSS 1st visit	EDSS 2nd visit
Mean		4.851	5.026
Median		5.000	5.000
Std. Deviation		1.5414	1.5703
Percentiles	25	3.500	4.000
	50	5.000	5.000
	75	6.000	6.500
Wilcoxon Signed Ranks Test (non-parametric paired)	p-value	<.001	

The average EDSS score of the participants at their initial visit was 4.851. However, during their second visit, it significantly increased to 5.026, as indicated by the Wilcoxon Signed Ranks Test with a p-value of less than 0.001.

Table (3.2): Progression index between visits:

Statistics			Wilcoxon Signed Ranks Test
	Progression index 1	Progression index 2	P-value
Mean	1.030	0.909	< 0.001
Median	0.929	0.818	
Std. Deviation	0.697	0.493	

During the second visit, there was a statistically significant reduction in the progression index, scored as 0.808, as revealed by the Wilcoxon signed ranks test with a p-value of < 0.001.

Table (3.3): Progression events during consecutive visits:

Patients		Frequency	Percent	Valid Percent	Cumulative Percent
		111	73.5	73.5	73.5
	CDI	6	4.0	4.0	77.5
	CDP	34	22.5	22.5	100.0
	Total	151	100.0	100.0	

Calculating number of patients who attained a confirmed disability progression, 4% of the patients had a confirmed disability improvement, while 22.5% had confirmed disability progression.

Table (3.4): Brain MRI number of lesions in the 1st and 2nd visits:

Brain MRI number of lesions					
		1ST visit		2nd visit	
		T2	GDEL	T2	GDEL
Mean		8	0	7	0.05
Median		7	0	7	0
Std. Deviation		2.097	.535	2.087	.570
Percentiles	25	6	0	6	0
	50	7	0	7	0
	75	9	0	9	0

During the initial brain MRI examination, participants exhibited an average of 1 lesion in T1, eight in T2,

and 0 in GDEL. During the second visit, T2 experienced a significant drop of the lesion number, with only seven remaining. Additionally, there was a noteworthy increase in GDEL, reaching a value of 0.05. These findings were determined to be statistically significant using the Wilcoxon Signed Ranks Test, with p-values of less than .001 and 0.006, respectively.

Table (3.5): Spinal MRI number of lesions in the first and second visits:

Spinal MRI number of lesions					
		1st visit		2nd visit	
		T2	GDEL	T2	GDEL
Mean		3.87	.05	3.89	.00
Median		4.00	.00	4.00	.00
Std. Deviation		1.060	.253	1.049	.000
Percentiles	25	3.00	.00	3.00	.00
	50	4.00	.00	4.00	.00
	75	4.00	.00	5.00	.00

During the first spinal MRI, the average lesions were 0.04 in T1, 3.87 in T2, and 0.05 in GDEL. On the second visit, there was a significant increase in the average number of lesions in T1 to 0.08 and a decrease in GDEL to 0. These findings were determined by the Wilcoxon Signed Ranks Test, with p-values of 0.034 and 0.011, respectively.

Table (3.6): Number of individuals who could perform the LLT25FW test on them:

Statistics	1st visit	2nd visit
Mean	26.52	21.89
Median	19.00	19.00

Regarding the LLT25FW test, only 136 individuals were able to complete it, with an average time of 26.52 seconds. This number decreased to 126 individuals, with an average time of 21.89 seconds.

Table (3.7): UL9HP and LLT25FW at first and second visits:

		1st visit	2nd visit
UL9HP test (in sec.)	Mean	38	38
	Median	37	36
	Standard Deviation	13	14
LLT25FW test (in sec.)	Mean	27	22
	Median	19	19
	Standard Deviation	18	13

During the UL9HP test, the mean value on the first visit was 38, the same as recorded on the second visit. In contrast, the LLT25FW test decreased from 27 seconds on the first visit to 22 seconds, although this decrease was not statistically significant.

Table (3.8): Treatment adverse effects:

Classification	N	%
Mild	150	99.3
Moderate	1	.7
Total	151	100

Most adverse effects were classified as mild (99.3%), with only a small portion categorized as moderate (0.7%).

4. Discussion

By comparing the patients' characteristics in this study with relevant studies, one can gain valuable insights into the similarities and differences in patient demographics, disease progression, and treatment

strategies. Our current investigation indicates a nearly equal distribution of males (51%) and females (49%). While Deleu et al. [7] (2012) determined that the prevalence of multiple sclerosis (MS) is higher in females than in males, with a female-to-male ratio of 1.33:1 among Qatari patients. Yamout et al. (2008) [8] found that the gender distribution was balanced, with females making up around two-thirds of the patients, given that our cohort is mainly primary progressive phenotype our results is consistent with the epidemiology of PPMS which have male predominance. Our study revealed a noteworthy progression in disability over time, as evidenced by the average EDSS score of 4.851 at the initial visit and 5.026 at the second visit. This aligns with the intricate correlation between disease activity and disability in multiple sclerosis, as well as the demand for more efficient and well-tolerated treatments [9].

Clara G. Chisari et al [10] observed that there were no discernible disparities in terms of PI (Progression Index) at 12 and 24 months between the ORATORIO and non-ORATORIO group, which was a comparative study between two groups of primary progressive MS. Our study showed a significant decrease in progression index which reflects a potential role for Ocrelizumab in slowing down disease activity. In the study conducted by Xavier Montalban et al [6], the rate of patients experiencing confirmed disability progression at the 24-week mark was 29.6% for those treated with ocrelizumab, compared to 35.7% for those given a placebo.

In a real-world setting like in our study, 4% of our cohort experienced confirmed disability improvement, while 22.5% experienced confirmed disability progression which is lower than the percentage achieved in the clinical trial. Our study assessed the brain and spinal MRI results of participants during two visits over a period of 6 months, with particular emphasis on variations in the quantity of lesions. While the research conducted by Marina Boziki et al. examined the individuals who exhibited a positive response to the treatment over 12 and 24 months. The study assessed clinical outcomes, specifically relapse rates and lesion burden. [11] Our study found a reduction in T2 lesions and an increase in GDEL between the first and subsequent brain MRI visits among the participants. The observed changes were determined to have a high level of statistical significance. While spinal MRI on the second visit revealed significant decrease in GDEL and stable T2 lesion burden.

In the study conducted by Boziki et al. After 24 months, 20 patients (90.9%) did not have any new or enlarged T2 lesions on their brain and cervical MRI scans. The study conducted by Boziki et al. reveals that a significant percentage of patients displayed favorable responses to the treatment, which maintained its efficacy for a duration of 24 months. [11] Xavier Montalban's study demonstrated that after 120 weeks, the performance on the timed 25-foot walk deteriorated by 38.9% with ocrelizumab compared to 55.1% with placebo (P=0.04). In our study, the time taken for the walk decreased from 27 seconds on the initial visit to 22 seconds, although this reduction did not have statistical significance. [6] To evaluate a real-world experience of effectiveness we calculated mean time for walking speed, in contrast to the trial conducted by Montalban et al. as they were evaluating efficacy in head-to-head with placebo. Such a decrease in walking time may reflect improvement and response to treatment or can be attributed to smaller size sample as compared to 1st visit.

In Edward J Fox's study [12], it was found that ocrelizumab had a significant impact on reducing the change in 9HPT time over a period of 120 weeks. It also reduced the risk of having a 20% or higher increase in 9HPT time for both hands, as well as the risk of experiencing more severe progression in 9HPT compared to a placebo. Our study uncovered During the UL9HP test, the average value on the initial visit was 38, which was also observed on the subsequent visit. By considering the variations in studies emphasis, groups of patients, length of treatment, and specific outcomes, it becomes clear that the findings of each study offer valuable understanding of the effects of ocrelizumab in the context of multiple sclerosis. These disparities underscore the necessity for a thorough assessment and analysis of the impact of treatments on multiple sclerosis, considering diverse clinical metrics and patient attributes. Victoria Prockl et al [13] conducted a study where they administered a combination of steroids, antihistamines, and antipyretics as premedication to over 90% of patients. The findings from a retrospective observational study in Qatar provide valuable insights into using ocrelizumab for treating

multiple sclerosis in an Arab population. The study, encompassing 60 patients predominantly with relapsing-remitting MS, demonstrates that ocrelizumab is an effective and well tolerated treatment option, with a significant proportion of patients achieving no evidence of disease activity (NEDA) status at the one-year mark. The safety profile of ocrelizumab was confirmed by the mild nature of reported infusion related reactions and infections, with no severe side effects noted. These results, reflecting real-world clinical practice, reinforce the potential of ocrelizumab as a valuable therapy for managing multiple sclerosis in diverse patient populations. [14]

Conclusion: The relationship between disease activity and disability emphasized the necessity for more efficacious treatments also Ocrelizumab's impact in reducing disability progression and functional decline risk was emphasized through comparisons in functional tests. and low incidence of moderate side effects when used with premedication. and .The implications for managing multiple sclerosis indicate that ocrelizumab is a highly effective treatment for controlling the progression of the disease and enhancing overall outcomes.

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