The Rate Of Disease Progression In MS Patients Treated With Rituximab And Ocrelizumab: A Comparative Study

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Abstract
New disease-modifying treatments (DMTs), like monoclonal antibodies (mAbs), have improved clinical outcomes and led to major shifts in MS treatment guidelines. Since these mAbs like rituximab and ocrelizumab have varying degrees of efficacy; our study aimed to evaluate and compare rituximab and ocrelizumab by terms of their potency in lowering disability scores, slowing disease progression and clinical relapse, and depleting B cells in Iraqi patient with MS. Fifty-eight Iraqi patient with MS were enrolled, and divided equally based on the medication used into two groups; 29 patients medicated with Rituximab and 29 patients medicated with Ocrelizumab. Each of EDSS, PI and clinical relapse were calculated, moreover serum Albumin was measured using Biosystem kit, while CRP measured by using immunoturbidimetric assay. B- cell depletion was measured by using flowcytometry technique. EDSS mean (before and after treatment) among patients treated with RTX didn't show any difference (EDSS1=3.19 vs. EDSS2=3.2), while the patients treated with OCR showed a notable deterioration in EDSS even after treatments (EDSS1= 3.93 vs. EDSS2= 5.1). Moreover, there was a significant decrease in clinical relapses among RTX treated-patients (27.6%) compared to OCR treated-patients (17.17). The percent of PI in RTX group showed significant decrement than that of OCR group (44% vs. 56%), also, a high significant depletion in B cell was noticed in RTX group compared to OCR group (0.48 vs. 0.70). In contrast to OCR, which revealed a substantial worsening of EDSS following treatment, RTX demonstrated no statistically significant difference in EDSS (pre- and post-treatment). Also, patients treated with RTX had much lower rates of PI, relapses, and higher B cell depletion as compared to patients treated with OCR. So, these findings indicate that rituximab exceeds ocrelizumab in slowing the course of illness.

Keywords: Multiple sclerosis, Rituximab, Ocrelizmub, EDSS, $CD20^{+}$, progression index.

1. Introduction

Multiple sclerosis (MS) is a long-term autoimmune inflammatory disorder of the central nervous system (CNS), and it has vital epidemiological and social effects. Among young people, MS is the most common cause of neurological disability that affect 50-300 individual per 100,000 people [1, 2]. On a neuropathological level, MS is characterized by three hallmarks: neuroinflammation, demyelination, as well as axonal degeneration. In spite of recent advances, the pathogenesis of MS still unknown in many aspects. Prior research suggested that T lymphocytes were the primary autoimmune response promoters in MS, however, recent studies have shown that B lymphocytes play an important role as well, and that targeting these cells with targeted medications may help reduce inflammation and disease progression [3]. Since B cells play vital role in MS pathology, B cell-depleting treatments have been developed and used to target components specific to B cells, most notably CD20 [4]. With the exception of pro -B cells, critically differentiated plasma-blasts, and plasma cells; CD20 defined as a transmembrane, non-glycosylated phosphoprotein

which is mainly expressed on the surface of the cell through nearly all of the phases of B-cell development [5]. Because it is only found on some B cell populations, CD20 could be a better target for B cell reduction in autoimmune disorders like MS and malignancies related with B cells [6].

Additionally, anti-CD20 mAbs are already certified for use in clinical trials for a variety of autoimmune illnesses, such as rheumatoid arthritis, polyangiitis, systemic lupus erythematosus, and different stages of MS [7-11]. For the treatment of multiple sclerosis, five anti-CD20 treatments are either already licensed or are in the clinical development phase [12-16]:

- Rituximab, commercially known as Rituxan, which is often used off-label as it is not yet certified for use in multiple sclerosis.
- Ocrelizumab, commercially called Ocrevus; both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have given their approval for this drug as treatment of relapsing-remitting multiple sclerosis (RRMS), active secondary progressive MS (SPMS), and primary progressive multiple sclerosis (PPMS).
- Ublituximab and Ofatumumab, had been approved by EMA and FDA for treating clinically isolated syndrome (CIS), RRMS and efficient SPMS.
- BCD-132 is currently being studied in clinical trials but has not yet received approval for the treatment of MS.

Infusion anti-CD20 medicines, such as Rituximab and Ocrelizumab, are among the most popular second-line treatments for MS. It considered as the most effective treatments currently available, which have been shown a significant reduction in disease relapse by 46–47% every year [17]. Rituximab (RTX) is a chimeric murine-human IgG1 kappa mAb that binds to the large extracellular loop of CD20 amino acid residues 168-175, and has a molecular weight of about 145 kDa [18]. For treating MS; an intravenous (IV) infusion of rituximab is usually started with a 1000 mg dosage on day 1 and repeated with another 1000 mg dose on day 15. Following that, a 1000 mg dose will be given to the patient every six months [19]. The monoclonal antibody RTX lyses CD20 cells and leads to the long-term reduction of B lymphocytes in circulation. In disorders like MS where autoantibodies play a significant role in the pathophysiology, RTX therapy is beneficial. Once second-line treatments like Natalizumab (NTZ) and fingolimod (FTY) have been stopped, RTX has proven to be a very effective substitute [20]. Ocrelizumab is an IgG1 kappa mAb that has been recombinantly humanized and glycosylated to target the long extracellular loop of CD20 binding to amino-acid residues 165-180 and has a molecular weight of 145 kDa [21]. The recommended dosage of ocrelizumab is 300 mg given intravenously over 2.5 hours on day 1, with a repeat dose of 300 mg given intravenously on day 15. Every six months after that, give another 600 mg over at least 3.5 hours (or 2 hours if there were no major infusion reactions before) [22]. Before each infusion of these medications, it is recommended to take an antihistamine and an intravenous dose of 100 (mg) of methylprednisolone or comparable corticosteroid [21, 22]. The progressive and disabling nature of MS has led to the approval of these drugs for the management and reversal of the disease's progression. However, the neurological capabilities of MS patients gradually deteriorate over time, and none of the DMTs completely stop or reverse this process [23].

Hence, the main objective of this study is to evaluate and compare rituximab and ocrelizumab by terms of their efficiency in lowering disability scores, slowing disease progression and clinical relapse, and depleting B cells in Iraqi patient with MS.

2. Material and Methods

2.1.Patients' selection

Fifty-eight MS patients with different stages (RRMS and PPMS), whom attended to Baghdad Teaching Hospital, were participated in the study and divided equally according to the medication used into two groups; 29 patients were administered Rituximab and 29 patients were administered Ocrelizumab. At least 18 months of treatment were administered to these individuals. Each patient's Expand disability status scale (EDSS) was determined by the neurologist. To measure the effect of diseases progression, we divided each patient's EDSS value by their disease duration to yield their progression index (PI). Individuals' full names, ages, addresses, medical histories, and prescription histories were recorded. The excluded cases were individuals with any other autoimmune diseases, any other medical condition or who were on any form of medication. This study was approved by the human research ethics committee at the college of science/university of Baghdad. Prior to participation, all patients were asked to provide written consent.

2.2.Sample collection and Methods

Fifty-eight blood sample of Iraqi patient with MS were collected, and the withdrawn portion was divided into EDTA-containing tube, and other tube with clotting activator gel to obtain serum. Serum Albumin was measured using Biosystem kit, while CRP measured by using immunoturbidimetric assay. The sample portion in the EDTA tube was used for measuring the complete blood count using fully automated hematology analyzer. The same sample was used for counting the B cells using BD FacsCanto™ II flow cytometer (manufactured by BD Biosciences, Germany). Several clinical parameters such as; duration of MS, MS type, history of previous used therapy, clinical relapse (before and after DMT), and EDSS (which was measured at baseline and after at least 18 months) were recorded.

The effectiveness of RTX and OCR treatments was evaluated by measuring the disease progression index (PI), and comparing the number of clinical relapses as well as EDSS at more than 18 months following treatment to the number at baseline before treatment began.

2.3.Statistical Analysis

In order to analyze all of the data, SPSS version 27.0 was used. For categorical factors including gender, age, family history, disease incidence and DMT history, frequencies and percentages were used. While means and percentages were recorded for quantitative variables like the progression index, number of clinical relapses and EDSS before and after therapy at 18 months follow-up. Student T-Test was used for analyzing the differences in CD20 percentage, absolute and percentage of lymphocytes, serum albumin and CRP between the study groups.

3. Results

Fifty-eight MS patients; 24 male and 34 female with age range of 18-62 years were participated in this study. These patients, with both RRMS and PPMS types, were subdivided into two equal groups according to the treatment used; 29 patients of them were on RTX and

the other 29 patients were on OCR. Seven of total patents had a family history (3 of RTX group and 4 of OCR group). As shown in Table 1; different durations of disease were recorded among the participitants;10 patients had at least 1 year, 30 of them had durations between 5-10 years and 18 patients had more than 10 years. The duration of treatments was divided into; less than 2 years (36 patients), between 2-4 years (16 patients), and more than 4 years (6 patients).

Table (1): The baseline characteristics of MS patients (N=58)

characteristic	RTX group N=29	OCR group N=29	Frequency (%)
Gender (n, %)			
Male	11 (37.9)	13 (44.8)	24 (41.4)
Female	18 (62.1)	16 (55.1)	34 (58.6)
Age (n, %)			
20 -30 (year)	10 (34.4)	2 (6.9)	12 (20.7)
30-40 (year)	9 (31)	11 (37.9)	20 (34.5)
40-50 (year)	7 (24.1)	7 (24.1)	14 (24.1)
50-60 (year)	3 (10.3)	9 (31)	12 (20.7)
Family History (n, %)			
Yes	3 (10.3)	4 (13.8)	7 (12.1)
NO	26 (89.6)	25 (86.2)	51 (87.9)
Duration of Disease, (n, %)			
≤ 2 years	6 (20.7)	4 (13.7)	10 (17.2)
5-10 year	15 (51.7)	15 (51.7)	30 (51.7)
10-15 year	4 (13.7)	9 (31)	13 (22.4)
> 15year	4 (13.7)	1 (3.4)	5 (8.6)
Duration of Treatment, (n,%)			
≤ 2year	14 (48.3)	22 (75.9)	36 (62.1)
2-4 year	10 (34.4)	6 (20.7)	16 (27.6)
> 4 years	5 (17.2)	1 (3.4)	6 (10.3)

The disease progression index percentage of patients with RTX treatment showed a notable reduction compared to that of patients on OCR treatment, Figure 1. Moreover, there was a significant decrease in clinical relapses among patients those administered RTX (27.6%) compared to patients administered OCR (17.17), Figure 2.

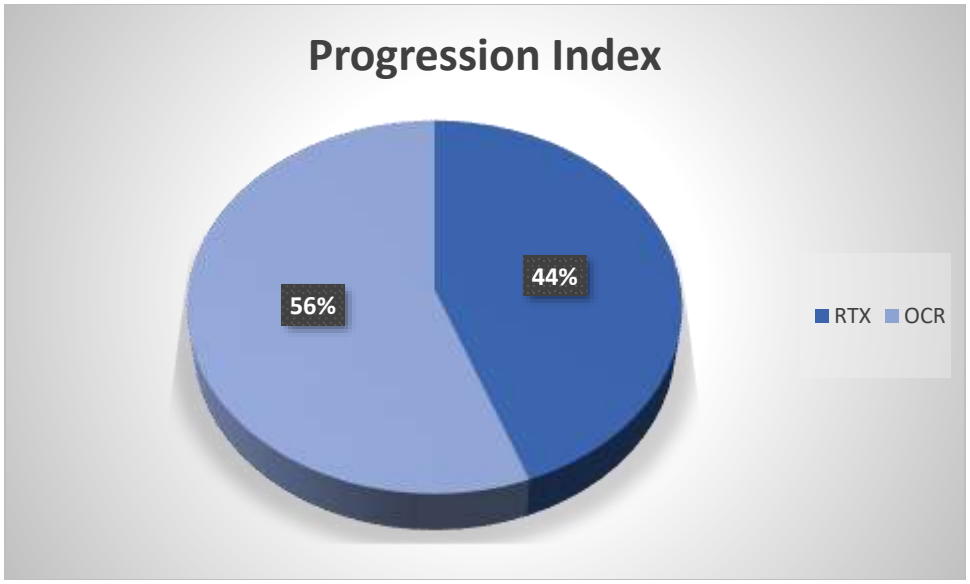


Figure 1: Progression Index (PI) between RTX and OCR groups.

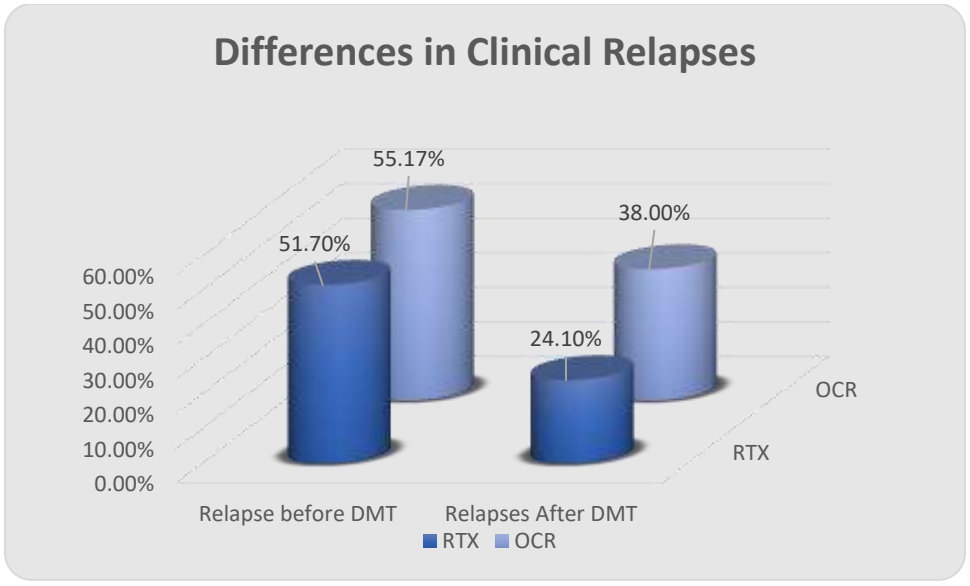


Figure 2: Clinical relapses percentage before and after using DMT.

Figure 3 showed that there wasn't any difference in EDSS mean (before and after treatment) among patients medicated with RTX, while the patients medicated with OCR showed a notable deterioration in EDSS even after treatments.

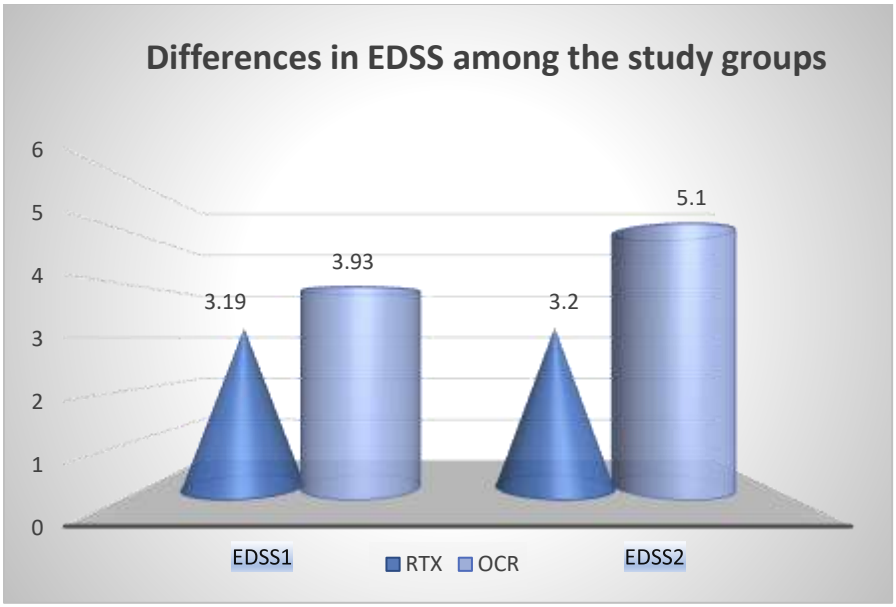


Figure 3: Mean of EDSS values before and after using DMTs.

Table 2 showed a high significant decrease the percentage of CD20 RTX group compared to OCR group (0.48 vs. 0.7) respectively. In addition, both absolute and percentage of lymphocytes showed significant difference between RTX and OCR groups. Serum albumin didn't show any significant difference among patients, while serum CRP showed a highly significant rise in OCR group compared to RTX group (2.08±0.87 vs. 1.17±0.58) respectively.

Table 2: Student T-Test for some clinical parameters of MS patients.

Parameter	RTX group N=29	OCR group N=29	P- value	Confidence Interval	
				Lower	Upper
CD20 %	0.48 ±0.2	0.70 ±0.3	<0.001	-2.2	0.19
LYM #	1.9±0.5	1.5±0.4	0.007	0.09	0.59
LYM %	29.5±9.9	24.2±6.2	0.018	0.94	9.6
Albumin (mg/dl)	37 ±3.3	36.7 ±5.4	0.791	-2	2.6
CRP (mg/dl)	1.17 ±0.58	2.08 ±0.87	<0.001	-1.3	-0.5

CD20 %; cluster of differentiation 20 percentage, LYM#; absolute Lymphocyte, LYM %; Lymphocyte percentage, CRP; C-reactive protein.

The effect of both DMTs; RTX and OCR illustrated in Figure 4 which contain the Flow cytometry plot of two randomly selected cases; one of RTX group (A) which showed a very significant depletion in CD20, and other one of OCR group (B) that showed a lesser depletion in CD20 percentage.

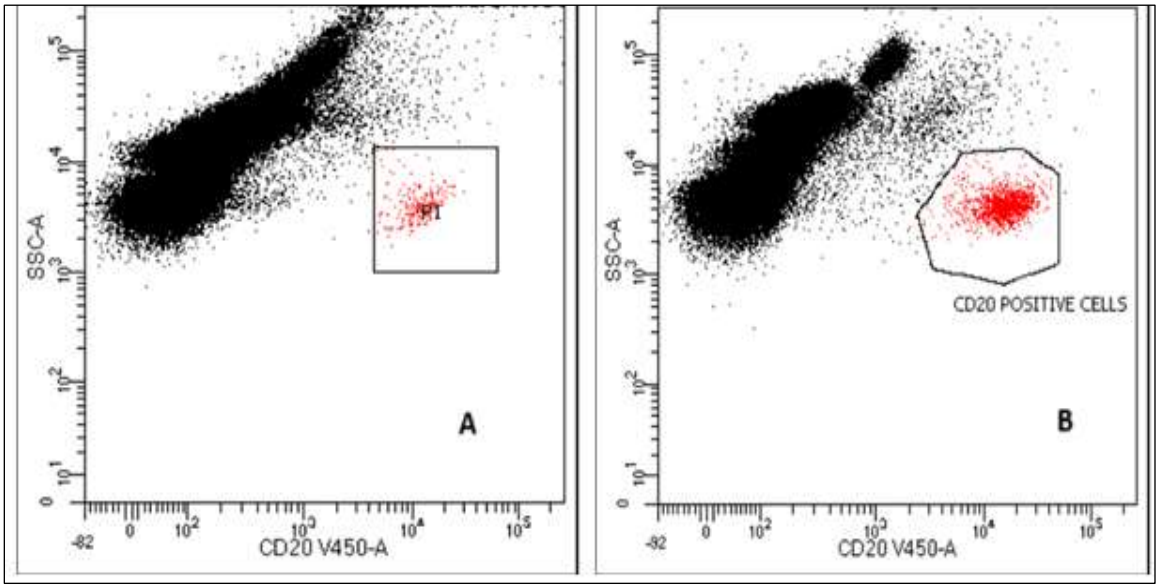


Figure 4: Flow cytometry plot of randomly selected cases of CD20⁺ cells depletion by: A) RTX, and B) OCR.

4. Discussion

This study compared the effectiveness of two commonly prescribed mAbs, rituximab and ocrelizumab, in preventing and controlling the progression of RRMS and PPMS, which was defined as more clinical relapse, increase progression index and disability progression.

Our results showed that MS patients treated with rituximab had significant decrease in clinical relapses among patients treated with RTX (27.6%) compared to patients treated with OCR (17.17). these results agreed with that of Alharbi et al. who found that people treated with ocrelizumab showed higher percentage of clinical relapses than those treated with rituximab [24]. In contrast, Roos et al. showed that the clinical relapse rate was higher in patients treated with RTX than those with OCR [25]. Both rituximab and ocrelizumab have been studied for their effectiveness in contrast to other DMTs using observational data. However, several studies showed that there was notable decline in the number of clinical relapses in RTX- treated patients compared to other DMT [26, 27]. Hellgren et al. showed in his study that rituximab had a great influence on reduction the rate of annual relapses [28]. While other studies found that OCR-treated patients showed a significant decrease in annual relapsing rate compared to those treated with FN-beta-1a [29].

Our results revealed that there wasn't any difference in EDSS mean (before and after treatment) among RTX-treated patients , while OCR-treated patients showed a notable deterioration in EDSS even after treatment. Mazdeh et al. result is in agreement with our results; they reported that the average of EDSS continued to show little to no change after 18 months of rituximab treatment [30]. Mohammadia et al. in his study showed that RTX had a beneficial impact on decreasing the disability score of patients with RRMS and PRMS [31].

Most multiple sclerosis patients had a decline or stability in EDSS scores following the start of RTX [32]. In a study conducted by Houtchens et al., participants with MS were found to have varying degrees of disability when utilizing OCR. Specifically, 25.8% of patients experienced a worsening of disability according to EDSS, 8.1% showed an improvement, and 66.1% stayed stable, with a median end EDSS score of 7.0 (ranging from 6.5 to 9.5). Importantly, 18 individuals (or 29.0%) who took ocrelizumab reported feeling no worse about their clinical conditions [33]. On contrary; Alshawaf et al. showed that MS patients those treated with OCR showed no deterioration in EDSS [34]. Since progression index is directly associated with EDSS; our results showed a high significant increase in progression index among OCR-treated MS patients compared to those treated with RTX. Indirectly, these results may point to a possible efficacy disparity between ocrelizumab and rituximab.

A key component of disease-modifying MS treatments is their impact on B cells, specifically anti-CD20 antibodies. There are three different ways that anti-CD20 mAbs deplete B cells, and their binding to epitopes determines which one is act on. Direct cell death, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC) can all be induced by matching anti-CD20 mAbs. Direct antibody-dependent cell cytotoxicity (ADCC) occurs when immunity-enhancing agents, including natural killer cells and macrophages recognize antibodies through Fc-gamma receptors [35]. According to our finding, RTX as well as OCR showed a great ability to B cell depletion, but RTX had the greater ability to deplete higher percentage of B cells compared to OCR. Also, significant differences were notice in both absolute and percentage of B lymphocytes.

Several studies showed that RTX is more suitable for RRMS, PPMS, as well SPMS in B cell depletion and reduction the disease progression [36, 37]. In accordance with these findings, retrospective investigations have shown that rituximab significantly decreases disease activity, with fewer T2, ARR, and gadolinium-enhancing lesions in patients given the drug [38, 39].

Despite this, higher B-cell depletion and higher ocrelizumab exposure were associated with slower impairment development in RMS and PPMS patients [40- 42]. Numerous studies reported that within two weeks of treatment, ocrelizumab caused a near-total loss of B cells and ninety percent of patients experienced B cell repopulation within 2.5 years of their last treatment, with a median of 72 weeks [15].

Damage to axons and demyelination in MS patients is caused by oxidative stress and inflammation. One indicator of systemic inflammation and oxidative stress in several disorders included MS is the quantity of serum C-reactive protein (CRP) and albumin. Our results showed that there weren't any significant differences in serum albumin among MS patient with both treatments, while serum CRP showed a significant increase in OCR- treated patients. Eren et al, found that PPMS patient with higher EDSS values and more relapses as well, had the higher levels of serum CRP compared to RRMS patients [43]. This result in accordance with our finding, were most of OCR patients are suffering from PPMS whom had increased disease progression index and increased inflammation.

It appears that the severity of disease progression, rather than OCR's capacity to inhibit MS progression, is the primary cause of EDSS worsening, higher relapse %, and elevated serum CRP levels.

Conclusion

In contrast to OCR, which revealed a substantial worsening of EDSS following treatment, RTX demonstrated no statistically significant difference in EDSS (pre- and post-treatment). Also,

patients treated with RTX had much lower rates of PI, relapses, and higher B cell depletion as compared to patients treated with OCR. So, these findings indicate that rituximab exceeds ocrelizumab in slowing the course of illness.

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