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Evaluating the efficacy and safety of Zytux™ (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: An observational study

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ABSTRACT

Background: Anti-CD20 monoclonal antibodies such as ocrelizumab, rituximab, and ofatumumab target B-cell lineage. Clinical trials have demonstrated their effect on reducing both magnetic resonance imaging (MRI) active lesion burden as well as clinical activity. Zytux™ (Rituximab, AryoGen Pharmed) used in the present study for multiple sclerosis (MS) patients is basically a biosimilar rituximab. In this observational study, a total of 100 patients receiving Zytux™ were collected to see its effect on the clinical course of the disease.

Materials and Methods: The files of 100 MS patients, who received Zytux™ in a referral center (Sina MS Clinic in Tehran, Iran), were analyzed as a hospital-based observational study. Patients' age and disease duration until the start of Zytux™, expanded disability status scale (EDSS) at the baseline and in the last visit after administration of the drug, and annual relapse rate (ARR) before and after initiating Zytux™ were studied. Disease activity was evaluated both clinically and via MRI.

Result: A total of 100 MS patients including 36 males and 64 females participated in the present study. The patients included 20 relapsing remitting MS (RRMS), 20 primary progressive MS (PPMS), and 60 secondary progressive MS (SPMS) patients. Totally, the mean of EDSS score before and after the administration of drug was 5.50 ± 1.04 (ranging from 1 to 7) and 5.11 ± 1.59 (ranging from 0 to 7), respectively, with the difference between them being very significant (p-value: 0.000). Also, the mean of ARR before and after the initiation of the medication was 0.47 and 0.10, respectively, whose difference was also significant (p-value: 0.000). In our study, the greatest effect of Zytux™ was observed in RRMS patients. At the time of injection, 70 patients indicated some reactions including limb pain, skin sensitivity, and throat irritation. One month after the injection, one of the patients suffered from pneumonia and two patients had a urinary tract infection.

Conclusion: The observed results revealed that the Zytux™ could have a positive and significant effect on all types of MS.

1. Introduction

Multiple sclerosis (MS), the most prevalent neurodegenerative disease of the young (Staun-Ram and Miller, 2017), was thought to be the result of T-cell mediated pathology, but emerging data support the importance of B-cell activation as well. The presence of oligoclonal bands (OCBs) is a considerable hint for this idea which are antibodies synthesized by cerebrospinal fluid (CSF) B-cells in more than 98% of MS patients. This marker has even prognostic values (Obermeier et al., 2008). Further, the pattern II of Lucchinetti is the dominant pathology of MS plaques in most patients which involves specific antibodies and complement activation in the lesion (Lucchinetti et al., 2000). As shown in recent years, the major effect of B-cell targeted treatments in MS patients is the clearest evidence. It is believed that B-cells are not only the key cells in antibody secretion but also play an important role in T-cell activation and proinflammatory cytokine secretion, which may justify their role in the pathogenesis of diseases such as MS and neuromyelitis optica (NMO) (Moreno Torres and Garcia-Merino, 2017).

Anti-CD20 monoclonal antibodies such as ocrelizumab, rituximab, and ofatumumab target B-cell lineage (Barun and Bar-Or, 2012). Clinical trials have demonstrated their effect on reducing both magnetic resonance imaging (MRI) active lesion burden as well as clinical activity (Moreno Torres and Garcia-Merino, 2017; Sorensen and Blinkenberg, 2016; Hauser et al., 2017; Kappos et al., 2011;

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Hauser et al., 2008; Bar-Or et al., 2008; Castillo-Trivino et al., 2013; de Flon et al., 2016; Sorensen et al., 2014). Rituximab first approved for non-Hodgkin's B-cell lymphoma in 1997 and since has been used for the treatment of several autoimmune disorders. Various studies have indicated almost complete (> 98%) depletion of circulating CD19+ *B* cells within two weeks of initiation (Hauser et al., 2008; Bar-Or et al., 2008; Bar-Or et al., 2010). It has been even reported that rituximab could also reduce T cells in CSF (Cross et al., 2006).

The substantial beneficial effects of rituximab on B-cells have prompted researchers to consider it as an effective drug in the treatment of MS (Salzer et al., 2016). Over recent years, a good number of studies have been published in order to address the effect of rituximab on MS patients (Salzer et al., 2016; Durozard et al., 2018; Scotti et al., 2018; Alcalá et al., 2018; Alldredge et al., 2018; Granqvist et al., 2018). It has been found that the mentioned drug can be regarded as an appropriate option in patients with treatment-resistant relapsing-remitting MS (RRMS) (Durozard et al., 2018). Furthermore, in case of the presence of a concurrent autoimmune disease, this drug should be considered as a serious choice (MK.Berenguer-Ruiz et al., 2016). In a number of other studies, it has been reported that the efficacy of this drug in RRMS cases can be equal to that of natalizumab (Scotti et al., 2018). Furthermore, rituximab is a very good choice for cases where natalizumab administration cannot be continued for any reasons (Alping et al., 2016). Other studies have addressed the effect of rituximab on secondary progressive MS (SPMS), especially in active cases (Rommer et al., 2011). Furthermore, this medication may be effective in primary progressive MS (PPMS) patients aged under 51 and with enhancing lesions on MRI (Hawker et al., 2009).

Given the high prevalence of MS in Iran (Rezaali et al., 2013; Eskandarieh et al., 2017), especially central regions (around 115.94 per 100,000 populations in Tehran), more efficient treatments are highly needed (Eskandarieh et al., 2018). Rituximab has become a treatment of choice in tertiary clinics, although it is not still approved for MS.

Zytux™ is a biosimilar product with the generic name of Rituximab which is a product of AryoGen Pharmed. Zytux™ is an anti-CD20 chimeric monoclonal antibody. Note that AryoGen is an Iranian pharmaceutical company which was established in 2010 with the aim of producing biological drugs.

In a study, there were no clinical differences between two groups regarding the effectiveness of Zytux™ and Mabthera (Rituximab, Roche) in patients with chronic lymphocytic leukemia (Toogeh et al., 2018). With increasing propensity to use this drug worldwide, Iranian physicians have considered its application in MS treatment, thereby popularizing Zytux™ application. However, no studies have yet been published on the efficacy and safety of this drug on MS patients.

In this observational study, the total of 100 patient files receiving biosimilar rituximab have been collected to examine its effect on clinical course of the disease.

2. Materials and methods

The files of 100 MS patients, who received Zytux™ in a referral center (Sina MS Clinic in Tehran, Iran) were analyzed as a hospital-based observational study. MS diagnosis was based on 2010 Mc Donald's criteria (Polman et al., 2011) and rechecked by 2017 version of the criteria (Thompson et al., 2018). The files had been filled by MS specialist and included demographic data, clinical course, and MRI characteristics.

Written informed consent was gained for drug administration and using the data, after explaining all the risks and benefits of drug administration, based on the Declaration of Helsinki protocols.

Patients' age and duration of the disease until the start of Zytux™, expanded disability status scale (EDSS) at the beginning and at the last visit after administration of the drug, as well as the annual relapse rate (ARR) before and after starting Zytux™ were studied. Disease activity was evaluated both clinically and through MRI.

Based on the inclusion criteria, only patients with clinically definite MS diagnosis who had received at least one dose of Zytux™ over the last six months were included in the study. The type of MS was not a criterion for inclusion in the study, and patients with any type of MS who had received Zytux™ during their treatment period were included in the study. All progressive patients had a progressive course lasting for at least two years before injection. Further, their data in terms of ARR, EDSS score, and MRI records were recorded over these two years. Note that sustained progression is defined as the rise of at least one point in EDSS over 3–6-month follow-ups if the patient's initial EDSS has been between 1 and 5.5. If EDSS is above 5.5, this definition refers to an increase of 0.5 points in EDSS (Berntsson et al., 2018; Healy et al., 2013).

An attack or relapse denotes a new clinical episode, which lasts at least 24 h and is confirmed by clinical examinations and objective evidence. This early episode should occur due to the demyelinating inflammations of the central nervous system and should not be accompanied by fever or infection (Thompson et al., 2018).

Patients underwent cerebral and cervical MRI imaging annually with and without contrast injection, and all the obtained data were recorded including the number of new and enhancing plaques. The patients' follow-up visits were performed every three months. The complications were recorded by a nurse during the injection period. Further, long-term complications were examined and recorded at each visit. These complications included allergies, infections, and the development of possible cancers and new autoimmune diseases.

As one-sample Kolmogorov-Smirnov test showed, the data did not have normal distribution, and Wilcoxon signed ranks test was used to compare EDSS and ARR before and after Zytux™ administration.

3. Results

A total of 100 MS patients including 36 males and 64 females participated in the present study (Table 1). The patients in this research included 20 RRMS, 20 PPMS, and 60 SPMS patients with the female-to-male ratio of 18:2, 8:12, and 38:22, respectively. The mean age of the patients was 38.60 ± 8.23 years (with the age range of 19–63), the average disease duration was 10.66 ± 6.25 years (ranging from 6 months up to 29 years), and the average follow-up length after the injection of Zytux™ was 9.9 months (Table 2).

The injection regimen of Zytux™ for all patients was one injection of 1 g Zytux™ on the first and 14th days. Drug injection was repeated every six months. Before injection, all patients received premedication, which included intravenous injection of 125 mg of methylprednisolone, intramuscular injection of chlorpheniramine, and two oral acetaminophen tablets.

The mean of EDSS score before and after the drug administration was 5.50 ± 1.04 (ranging from 1 to 7) and 5.11 ± 1.59 (ranging from 0 to 7), respectively, and the difference between them was very significant (p-value: 0.000).

Furthermore, the mean of ARR before and after the initiation of the medication was 0.47 and 0.10, respectively. The difference between them was also significant (p-value: 0.000).

All of the patients had undergone MRI for six months before starting

Table 1
Patient's baseline characteristics
F: female; M: male; m: months; y: years.

Sex	Number of patients	Age range (Mean,SD), y	Disease duration range (Mean,SD), y	Average follow-up length after the injection, m
F	64	19–58 (37.67, 8.70)	05–25 (10.90, 6.10)	3–18 (9.98, 4.18)
M	36	28–63 (40.25, 7.16)	2–29 (10.20, 6.60)	3–18 (9.97, 3.38)

Table 2
Characteristics of different MS groups.
PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; y: years.

MS subtype	Age range (Mean,SD), y	Disease duration range (Mean,SD), y	Female/ male ratio
RRMS	19–47 (31.05,8.66)	0.5–16 (6.17,4.79)	18 / 2
PPMS	26–56 (38.50,7.26)	3–29 (8.80,6.05)	8 / 12
SPMS	30–63 (41.15,6.84)	2–27 (12.78,5.81)	38 / 22

Zytux™, and 27 patients had enhancing lesions prior to the initiation of injection. Of these 27 patients, 10, 4, and 13 patients were categorized as RRMS, PPMS, and SPMS, respectively. The MRI status in different groups after the injection was as follows:

Five patients in the RRMS group did not undergo MRI. Of the remaining 15 patients, two patients had enhancing plaque, and in the remaining 13 patients, neither new nor enhancing plaques were observed.

Ten patients in the SPMS group did not undergo MRI. None of the remaining 30 patients indicated any new or enhancing plaques in their MRI.

In the PPMS group, ten patients did not undergo MRI. The MRI results of the remaining 10 patients revealed neither new nor enhancing plaques.

Clinical outcomes were individually examined in all three groups to better evaluate the efficacy of the mentioned drug.

3.1. Clinical outcomes of RRMS patients

Twenty patients in this group included 18 female and 2 male participants. The mean age of the group was 31.05 ± 8.66 (ranging from 19 up to 47 years). The average duration of the disease was 6.17 ± 4.79 (ranging from 6 months to 16 years old). The average follow-up length was 8.70 ± 4.87 (ranging from 3 up to 18 months). The mean of treatment cycles was 2.05 ± 1.00 (ranging from 1 to 4).

The mean EDSS score prior to and after initiation of medication therapy was 4.30 ± 1.68 (ranging from 1 up to 7) and 2.97 ± 2.30 (ranging from 0 up to 6), respectively (p-value: 0.001). Furthermore, the mean of the ARR prior to and after the initiation of pharmacotherapy was 1.30 ± 0.92 (ranging from 0 to 4) and 0.15 ± 0.36 (ranging from 0 to 1), respectively, which was very significant (p-value: 0.000).

3.2. Clinical outcomes of SPMS patients

A total of 60 patients had SPMS, of whom 38 were female and 22 were male. The mean age of patients was 41.15 ± 6.84 (ranging from 30 to 63 years old). The average duration of the disease was 12.78 ± 5.81 years (ranging from 2 up to 27 years). The mean of treatment cycles was 2.43 ± 0.77 (ranging from 1 to 4). Finally, the average follow-up length of disease in this group was 10.58 ± 3.72 months (ranging from 3 up to 18 months).

Patients were divided into two groups by considering whether their disease is active or not. The activity of disease was determined based on reports regarding any new attacks over the past year and the presence of any enhancing or new plaques as marked on MRI results. According to this classification, 25 patients had SPMS with activity (SPMS+) while 35 patients had SPMS without activity (SPMS-).

The mean age in the first and second group was 43.16 ± 8.14 yaers (ranging from 30 up to 63 years) and 39.71 ± 5.41 years (ranging from 30 up to 51 years), respectively. The mean EDSS scores prior to the initiation of medication in the first and second group were 5.90 ± 0.45 (ranging from 5 up to 7) and 5.81 ± 0.43 (ranging from 4.5 up to 6.5). The mean EDSS scores after the initiation of Zytux™ in the first and second group were 5.66 ± 0.65 (ranging from 4.5 up to 6.5) and 5.74 ± 0.67 (ranging from 4 up to 7), respectively. There were not any statistical differences before and after injection in each group (p-values: 0.088 and 0.364 respectively).

The means of ARR prior to the initiation of Zytux™ in the first and second group were 0.72 ± 0.61 (ranging from 0 up to 2) and 0 respectively. The means of ARR after the Zytux™ initiation in the first and second group were 0.16 ± 0.47 (ranging from 0 up to 1) and 0.06 ± 0.23 (ranging from 0 up to 1), respectively. As indicated above, the ARR in the first group was significantly lower after the initiation of the medication than the rate in the second group (p-value: 0.001).

3.3. Clinical outcomes of PPMS patients

The mean age of 20 patients in this group was 38.50 ± 7.26 years (ranging from 26 up to 56 years). The average duration of disease in this group was 8.80 ± 6.05 years (3–29 years), and the average follow-up length was 9.45 ± 2.96 months (ranging from 3 up to 13 months). The mean of treatment cycles was 2.20 ± 0.70 (ranging from 1 to 3).

The patients were divided into two groups in terms of whether their disease was active or not. The activity of disease was determined based on the presence of any enhancing or new plaques according to MRI results. None of the 20 patients mentioned any attacks of disease in the previous year. According to the mentioned classification, 8 patients had PPMS with activity (PPMS +), while 12 patients had PPMS without activity (PPMS-).

The mean age in the first and second group was 38.38 ± 6.78 years (ranging from 26 up to 44 years) and 38.58 ± 7.86 (ranging from 29 up to 56). The mean EDSS score prior to the initiation of medication in the first and second group was 5.62 ± 0.64 (ranging from 4.5 up to 6.5) and 5.70 ± 0.45 (ranging from 4.5 up to 6) respectively. The mean EDSS score after the initiation of Zytux™ was 5.37 ± 0.79 (ranging from 4.5 up to 6.5) in the first group and 5.54 ± 0.72 (ranging from 4 up to 6.5) in the second group. According to the results, the value of EDSS was reduced in both groups after the initiation of medication; however, there was no significant difference between them (0.15 and 0.33).

It can be seen that although the EDSS in SPMS and PPMS groups were reduced after Zytux™ prescription, it significantly decreased only in RRMS group EDSS (Fig. 1).

3.4. Safety

At the time of injection, 70 patients reported some reactions including limb pain, fatigue, skin sensitivity, and throat irritation. Regarding skin sensitivity, intravenous hydrocortisone injection was administrated which provided recovery (8 cases). The prescribed medication continued in these cases. The symptoms of limb pain, fatigue, and throat irritation recovered without any medical treatment.

One month after the injection, one of the patients suffered from pneumonia, which was improved with antibiotic therapy. Furthermore, two patients had a urinary tract infection; oral antibiotics were prescribed for them which led to improvement of patients' conditions.

4. Discussion

To our knowledge this is the first study in Iran which evaluated the effects of Zytux™ on MS patients. Generally, use of rituximab in MS treatment does not have a long history; however, although the mentioned drug has received no approval, it is increasingly used in the treatment of MS (Berntsson et al., 2018). In our study, the greatest effect was observed in RRMS patients. The effect of Zytux™ was also evident in reducing MS patients' disability and relapse rate. The positive effect of rituximab on RRMS patients has also been indicated in a number of other studies, whose effect on MS patients has been considered equal to the impact of natalizumab (Scotti et al., 2018). Furthermore, rituximab can be regarded as a salvage therapy for treatment

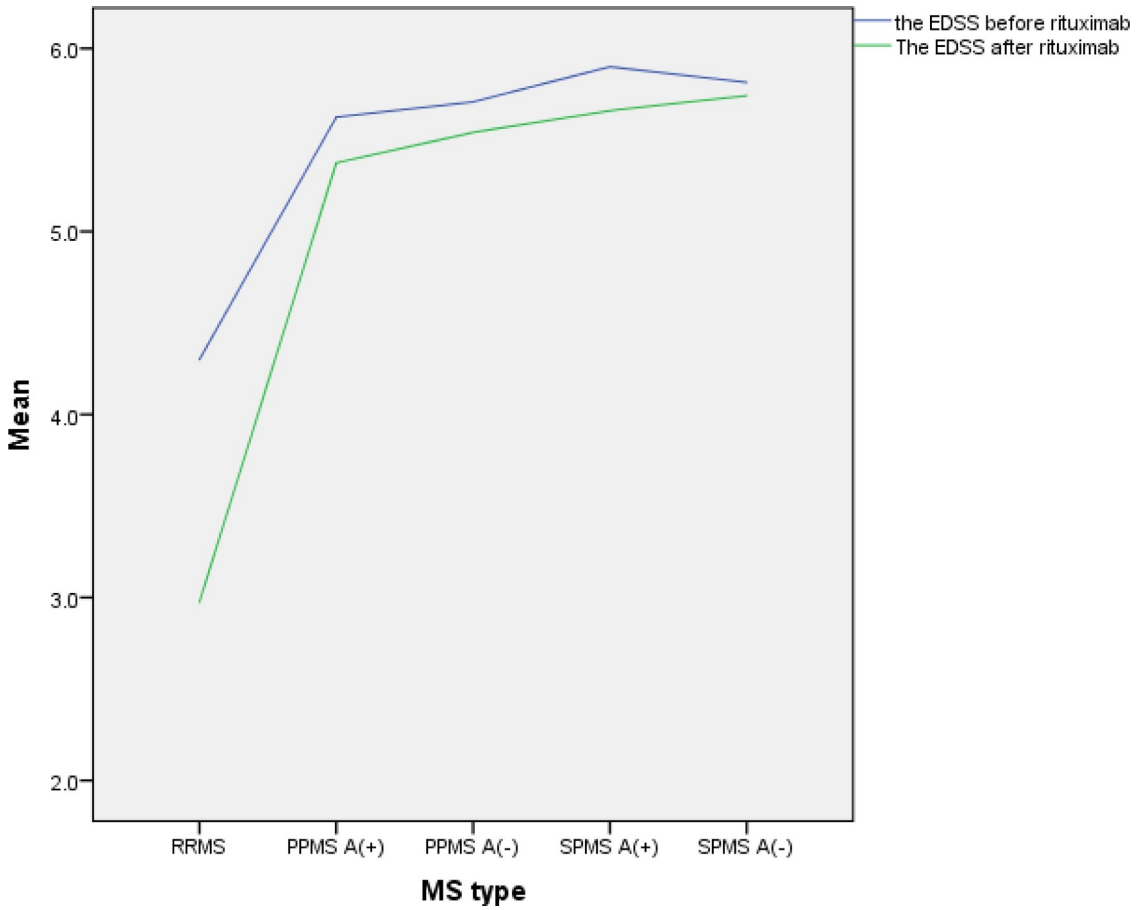

Fig. 1. EDSS before and after the administration of drug in different groups
ARR significantly dropped in RRMS and SPMS+ .

resistant patients, who despite treatment with high efficacy drugs such as fingolimod, natalizumab, and mitoxantrone are still experiencing MS relapses (Durozard et al., 2018).

In patients with an active progressive disease, the ARR significantly improved compared with the reported pre-administration drug. Nevertheless, it must be mentioned that there was no significant difference in the degree of disability before and after the administration of Zytux™. Discrepant results have been reported in studies on the effects of rituximab on degrees of disability among SPMS patients. In some cases, the degree of disability was constant or diminished, while in others it increased (Salzer et al., 2016; Perrone et al., 2014). Perhaps, a meta-analysis with a massive collection of data from MS patients can thoroughly address the mentioned issue.

There was no increase in the EDSS score in the PPMS patients. This was also significant given that the course of disease in all of these patients was progressive over the last two years before the drug administration. In a study previously performed on patients with PPMS, the best effect was observed on patients who were under 51 years old and had enhancing plaques on their MRI results (Hawker et al., 2009). This is in contrary with our results in the present study, which may be attributed to the limited number of patients participating in the present study.

Skin sensitivity was the major adverse drug reaction in patients treated with Zytux during the injection. Furthermore, only one case of pneumonia was observed one month after the injection which was also improved with treatment. The same results have been reported in previous studies (Salzer et al., 2016; Durozard et al., 2018). According to the results presented in already conducted studies, the most commonly reported sensitivity reactions were observed during the injection which had mild to moderate severity.

As already stated rituximab is a monoclonal antibody which acts against the CD20 protein and thereby leading the destruction of B-cells. The positive effect of this medication, as well as its low price, has attracted much attention in recent years (Bourdette, 2016).

Rituximab has been produced in some countries with various names. In Iran, AryoGen company produce this drug under the brand name of Zytux™ in 2013. Zytux™ has been widely used in various fields such as oncology, rheumatology, and neurology. However, this is the first study which evaluated the effects and complications of this drug on MS patients. Although the efficacy of this drug has not been compared with that of Mabthera in a comparative study, the obtained findings indicated its similar efficacy and safety.

A number of limitations existed in this research which should be considered in future studies. Firstly, this study was merely an observational study, and no comparative examinations were performed regarding the effects and complications of Zytux™ and the brand-name drug on MS patients. Secondly, CD19 and CD20 were not measured in the present study. These limitations should be considered in the subsequent studies.

5. Conclusion

The present study examined the efficacy of Zytux™ on Iranian patients with MS. The observed results indicate that the mentioned drug could have a positive effect on all types of MS, regarding relapse rate and disease progression, with the most significant effect in RRMS patients. Zytux™ can be regarded as an appropriate option in the treatment of MS patients thanks to its few side effects, good efficacy, and the increasing incidence of MS disease across Iranian population.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

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