



## Review Article

# Biosimilars in Treatment of Multiple Sclerosis in Iran

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**Background:** Biological drugs are manufactured via some changes made to the living organisms by genetic engineering. Notably, biological drugs are very expensive and their importation can impose economic pressure, especially on poorer countries. Thereafter, manufacturing these drugs has been considered by policymakers in many countries, resulting in the production of biosimilars. Iran requires a wide range of biological drugs due to the growing number of patients with multiple sclerosis. On the other hand, the poor economic situation of Iran due to repeated sanctions has had a great impact on the health care system, which has prevented the allocation of sufficient financial resources in this regard. Therefore, manufacturing biosimilar drugs due to their lower cost has received much attention in various fields of treatment.

**Keywords:** Biosimilars, Iran, Multiple sclerosis

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**Introduction**

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that mainly affects young people. According to the published statistics and studies, the incidence of MS is increasing in Iran.<sup>1</sup> Therefore, due to this increasing prevalence in Iran, more attention must be paid to the treatment of these patients. From 1993 up to the end of 2019, several drugs have entered the global drug market, most of which are classified as biological drugs.<sup>2</sup> Biological drugs are manufactured via some changes made to the living organisms by genetic engineering. Notably, biological drugs are very expensive and can impose economic pressure, especially on poorer countries. Therefore, manufacturing these drugs has been considered by policymakers in many countries, resulting in the production of biosimilars.<sup>3</sup> Biosimilars are biological drugs that are very similar in structure, function, side effects, and efficacy to the prototype.<sup>3</sup>

Iran needs to use a wide range of biological drugs due to the growing number of MS patients. In this regard, manufacturing biosimilar drugs due to their lower cost has received much attention in various fields of treatment.<sup>3</sup>

This article aimed to review biosimilar drugs produced and used in recent years in Iran to treat MS. Having a glance at these drugs and the studies conducted on them reveals the importance of biosimilar drugs in the treatment of patients with MS in Iran and reinforces the necessity of developing this industry.

**Biosimilars in Treatment of MS in Iran**

During past years, several biosimilar drugs have been produced by Iranian companies in Iran. By introducing

these drugs, this section discusses studies performed on their different aspects. Unfortunately, despite the production of various biosimilar drugs in Iran, a limited number of studies have been conducted on them.

**CinnoVex**

CinnoVex is the first biosimilar produced in Iran for MS. It is an intramuscular and biosimilar interferon beta-1a drug developed by CinnaGen in collaboration with the Fraunhofer Institute in Germany in 2006. Currently, CinnoVex is used by nearly 11 000 patients.<sup>4</sup> Nafissi et al compared the efficacy and side effects of CinnoVex with Avonex, and after two years of monitoring patients, they reported no significant difference in terms of effectiveness and side effects between these two drugs.<sup>5</sup>

In a similar study by Pakdaman et al, 182 patients were randomly assigned to be treated with either CinnoVex or Avonex and then followed up for four and a half years. This study also showed no difference between these two drugs in terms of complication rate, magnetic resonance imaging (MRI), and clinical results.<sup>6</sup>

In another study, the cost-effectiveness of CinnoVex was compared with that of Avonex, and it was found that the cost per person for CinnoVex was \$2410 compared to \$4515 for Avonex, showing a significant difference.<sup>7</sup> Later, these two drugs were compared regarding other aspects. For example, Hatem et al found no difference in terms of quality of life among the consumers of Avonex and CinnoVex.<sup>8</sup> In addition, Abolfazli et al observed no difference in quality of life between CinnoVex and Avonex recipients after 30 months of follow-up.<sup>9</sup>

Shahkarami et al compared the levels of neutralizing

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antibodies (NABs) in patients consuming these two drugs. Correspondingly, these patients were monitored for a 24-month period and had their NABs measured every 6 months. Also, the amounts of antibodies were separately evaluated in two different laboratories, one in Iran and the other in Canada. The results for both drugs were similar in both laboratories, indicating that CinnoVex and Avonex have identical immunogenetic profiles in addition to having similar efficacy and safety.<sup>10</sup>

In another study on the level of cytokines in CinnoVex recipients and its relationship with patients' responses to treatment, it was found that the IFN- $\gamma$  level was significantly higher in the responder group compared to the non-responder group.<sup>11</sup>

### ReciGen

ReciGen is a biosimilar product modeled after Rebif (interferon beta-1a subcutaneous) which was produced in 2009 by CinnaGen. Etemadifar et al compared ReciGen with Rebif and found no meaningful difference between these two drugs in terms of effectiveness and side effects.<sup>12</sup>

In a study conducted by Shokrollahi et al, the recipients of ReciGen and Rebif were studied for the amount of NABs, and as a result, it was found that there was no significant difference between the consumers of these two drugs in terms of neutralizing antibody positivity.<sup>13</sup>

Unfortunately, despite the high consumption of this drug in Iran, few studies have evaluated the effect of ReciGen on MS patients. In 2020, following the use of interferons in the treatment of COVID-19, three studies examined the effectiveness of ReciGen in the treatment of COVID-19 indicating that the use of ReciGen could significantly reduce the severity of COVID-19.<sup>14-16</sup> An observational study examined the effect of ReciGen on the incidence, hospitalization, and mortality in 75 MS patients taking the drug. Correspondingly, the mean duration of ReciGen consumption was 6 years in these patients. Among them, one patient was infected with COVID-19 who did not need hospitalization and whose symptoms rapidly improved within five days. This study showed that although the use of ReciGen in these patients did not reduce the incidence of COVID-19, the rates of hospitalization and death were significantly decreased.<sup>17</sup>

### Ziferon

Ziferon is another biosimilar produced by Zist Daru Danesh Company in 2010, which is modeled after Betaferon (interferon beta-1 $\beta$ ). In order to examine the structural property of this biologic drug, Dadgarnejad et al used the micellar electrokinetic chromatography (MEKC) method and found that Ziferon has an acceptable potency comparable with its brand.<sup>18</sup>

In a study by Gheini et al, the effectiveness of these two drugs was compared in terms of disease progression, the number of attacks, the effect on MRI, and their side effects over a two-year period, and no significant difference was observed between them.<sup>19</sup> In another study conducted

in Isfahan, the authors showed that 9% of patients who enrolled in the study had received Ziferon as the main drug which was comparable with other high dose interferons including ReciGen and Betaferon.<sup>20</sup> The effectiveness of Ziferon as a combination therapy on patients with COVID-19 has been studied in Iran<sup>21</sup> and the results of this study will be published in the future which may increase our knowledge regarding the efficacy and safety of Ziferon.

### Zytux

Besides interferons, monoclonal antibody drugs have also attracted the attention of Iranian pharmacists and have been developed to be used for various diseases. The only biosimilar monoclonal antibody drug, which is available in Iran and is widely used for MS patients, is called Zytux. This drug is actually the MabThera biosimilar (rituximab) which was produced in 2010 by AryoGen Company.<sup>22</sup>

The effectiveness and safety of this drug were compared with MabThera in a study on patients with chronic lymphocytic leukemia (CLL). In the mentioned double-blind study, 70 patients were divided into two equal groups as follows: one group received Zytux and the other one received MabThera. No significant difference was observed between the two groups in terms of drug efficacy and side effects.<sup>23</sup>

In another observational study, 10 patients with CLL and 10 patients with non-Hodgkin lymphoma were treated by Zytux and were followed up for 6 months. In this study, the efficacy and safety of Zytux were acceptable and were comparable with reports of MabThera in the literature.<sup>24</sup> Toosi et al investigated the safety and efficacy of this biosimilar drug in patients with pemphigus vulgaris and reported desirable outcomes in this regard.<sup>25</sup>

Torkashvand et al compared the binding affinity of Fc gamma receptors between Zytux and MabThera. Fc gamma receptors are the most important receptors mediating the antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. These two pathways are the main ways through which rituximab affects diseases. The authors showed that there was not any significant difference between these two drugs in terms of the binding affinity of Fc gamma receptors.<sup>26</sup>

Although Zytux is widely used in treatment of MS patients in Iran, only one observational study has been performed on its efficacy and side effects.<sup>22</sup> This study was conducted on 100 MS patients taking Zytux (20 patients had relapsing-remitting MS, 20 patients had primary progressive MS, and 60 patients had secondary progressive MS). It was found that Zytux has no serious side effects and is effective on all types of MS.

Similarly, Naser Moghadasi and Ghoreyshi Tayyebi have reported a 21-year-old female with highly active MS who was effectively treated by Zytux.<sup>27</sup>

Another observational study examined the outcome of pregnancy in MS patients who became pregnant while taking Zytux. Of 21 pregnancies, 8 pregnancies resulted

in term births and two pregnancies resulted in preterm births. Two spontaneous abortions and 7 miscarriages were performed either in response to the suggestion of their physician or by the request of the mother. Overall, the study showed that despite taking Zytux, pregnancy can be safe for both mother and infant.<sup>28</sup>

In another study, short-term and long-term side effects of Zytux were studied on patients with MS and neuromyelitis optica spectrum disorder, revealing that these side effects were usually mild, except for one case of bradycardia.<sup>29</sup>

### Discussion

Biosimilars are widely used in Iran. Extensive use of biosimilars has practically resulted in using various drugs with reasonable prices by MS patients. Although the number of conducted studies in this field is limited, it seems that Iranian companies have been successful in manufacturing these biosimilars, and the biosimilar sample is identical to the original sample in terms of effectiveness and safety. However, a better understanding of the efficacy of these drugs requires conducting further comprehensive studies. With the exception of CinnoVex that has been assessed from different perspectives to some extent, such studies have not been performed on the other biosimilars despite their widespread use, which makes it difficult to evaluate these drugs. Lack of numerous studies is the most concerning point regarding the wide spread use of biosimilars in Iran that must be immediately addressed. Another crucial issue is the growth of pharmaceutical companies manufacturing monoclonal antibody drugs. As mentioned earlier, the only biosimilar monoclonal antibody drug used to treat MS in Iran is Zytux. Iranians' access to other monoclonal drugs that are not biosimilars, is practically limited due to their high prices. Also, several drugs such as Ocrelizumab, Alemtuzumab, and Natalizumab can be used widely in treatment of MS patients, if they are reasonably priced. Thus, Iranian pharmaceutical companies should plan to manufacture biosimilars of the mentioned drugs.

### Conflict of Interest Disclosures

Abdorrezza Naser Moghadasi has received speaker's honoraria from CinnaGen and AryoGen Companies.

He has collaborated with CinnaGen and Zist Daru Danesh Companies concerning conducting clinical trials.

### Ethical Statement

Not applicable.

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