Clinical considerations on the introduction of ocrelizumab in Mexico

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Abstract

Multiple sclerosis (MS) is the leading cause of neurological disability among young adults. The disease-modifying treatments (DMTs) have been a breakthrough in the care of this patients, becoming a treatable disease. Today, we face a broad spectrum of treatment possibilities, which should be used rationally to provide the maximum benefit for the patients. In the context of the introduction of ocrelizumab as a treatment option in the Mexican MS DMT portfolio, a group of neurologists was convened to analyze the potential transition among DMT from their experience, through a desk research and expert opinion. As a result, here we describe the different considerations suggested for switching from different DMT to ocrelizumab that includes profiling studies, washout periods, and follow-up considerations. We concluded that the switch from other DMT previously used to ocrelizumab could be convenient and safe, as long as there is an adequate selection and profiling of the patients.

Introduction

Multiple sclerosis (MS) is the main neurological cause of disability in young adults around the world. The diagnosis of MS has increased substantially in the past few decades, with a prevalence of 1.6/100,000 habitants in 1972. According to the previous studies, it has been estimated that there are at least 15,000 people in Mexico who suffer from MS, with a prevalence of 7.5-30/100,000 habitants.

Treatment aimed at modifying the natural history of MS has progressed considerably. The first disease-modifying treatment (DMT) approved was interferon beta-1b in 1993, since then, we have had major changes in the understanding of the disease and now much more is known about environmental risk factors and genetic susceptibility, and the specific pathogenesis of MS may be explained in more detail. That is why there is now a wide range of treatment options available that should be used rationally to better benefit patients.

This work was carried out in the context of the introduction of ocrelizumab (Ocrevus®) to the Mexican market. Ocrelizumab is an IgG1 humanized monoclonal antibody that depletes B lymphocytes that express the CD20+ surface protein in their membrane. This limits immunological events linked to autoimmune conditions, specifically, MS. Having a new DMT available, it makes it possible to debate over its use, which is why Roche has brought together a group of Mexican neurologists to examine the therapeutic transition from different points of view, based on their experience. The opinions given herein are the responsibility of the physicians who gave them and are independent from the unrestricted support given.

Materials and methods

This analysis was carried out in the second half of 2017. Eleven neurologists considered as opinion leaders in MS, highly experienced in DMT and its mechanism of action (MoA), who understood the implications of changing treatment and were asked to give their point of view.

The group was made up of 11 neurologists who worked at some of the major public and private health institutions and hospitals in Mexico (INNN, IMSS, Hospital Español, Hospital Ángeles Lomas, INCNSZ, ISSSTE, ISSEMyM, etc.)

The work was carried out in two hands-on sessions, each lasting 2 days. Points to be considered included: (a) defining the guidelines for the proper use of ocrelizumab; (b) establishing the medical reasons for why a switch in treatment could be considered and its implications; (c) suggested paraclinical studies according to the treatment from which they are switching; (d) suggested washout period to migrate each DMT to ocrelizumab; and (e) suggested paraclinical control studies.

The work has been carried out for academic purposes, design as a non-experimental and documentary research that involved open discussion in teams and reflections as a group.

Results

Placing ourselves in the MS treatment algorithm context, in Mexico, we have beta-1b interferon, beta-1a interferon, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, natalizumab, and alemtuzumab. Ocrelizumab is now one of the many drugs available.

Treatment guidelines around the world say that the choice of DMT depends on the characteristics of patients, comorbidities, activity/severity of the disease, safety profile, access to treatment, and other aspects.
**Table 1. Recommendations to switch from an oral disease-modifying treatment to ocrelizumab**

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Teriflunomide(^{9-11})</th>
<th>Dimethyl fumarate(^{12-15})</th>
<th>Fingolimod(^{14,16-20})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MoA to consider before switching</strong></td>
<td>Inhibits the mitochondrial DHO-DH enzyme selectively and reversibly; reduces rapid replication of lymphocytes; blocks proliferation of the activated T and B lymphocytes</td>
<td>Reduces oxidative stress and inhibits pro-inflammatory cytokines, causing lymphopenia</td>
<td>As it is a functional antagonist of the S1P receptor, it blocks the capability of lymphocytes to exit the lymph nodes, causing lymphopenia. Specifically, the MoA to be considered on circulating B cells is the potential decrease in activated B memory cells (CD38)</td>
</tr>
<tr>
<td><strong>Possible switching scenarios</strong></td>
<td>No response to treatment (clinical activity and/or in MRI) after 6 months of continuous use and having checked adherence to treatment</td>
<td>No response to treatment (clinical activity and/or in MRI) after 6 months of continuous use and having checked adherence to treatment</td>
<td>No response to treatment (clinical activity and/or in MRI) after 6 months of continuous use and having checked adherence to treatment. Patients who do not adhere to treatment</td>
</tr>
<tr>
<td></td>
<td>Patients who do not adhere to or are intolerant to treatment</td>
<td>Patients who do not adhere to treatment because of dosage</td>
<td>Adverse events of fingolimod that makes it difficult to continue treatment</td>
</tr>
<tr>
<td></td>
<td>Inherent adverse effects of teriflunomide</td>
<td>Adverse events of DMF that makes it difficult to continue treatment</td>
<td>Choice of patient in dosage due to convenience</td>
</tr>
<tr>
<td></td>
<td>Choice of patient because of convenience of dose</td>
<td></td>
<td>In patients who do not respond after switching from natalizumab to Fingolimod due to the risk of PML. Literature reports positive outcomes switching to anti-CD20 therapy(^{15})</td>
</tr>
<tr>
<td><strong>Additional screening</strong></td>
<td>Standard screening previously described for ocrelizumab, including pregnancy test</td>
<td>Standard screening previously described for ocrelizumab, including pregnancy test</td>
<td>Standard screening previously described for ocrelizumab</td>
</tr>
<tr>
<td></td>
<td>If needed serum level of teriflunomide</td>
<td></td>
<td>Rule out chicken pox</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rule out skin cancer and breast cancer in patients at risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-JCV antibody index recommended, as we are aware that there have been reported cases of PML associated with fingolimod treatment(^{19})</td>
</tr>
<tr>
<td><strong>Washout time</strong></td>
<td>Immediate if all screening paraclinics are normal</td>
<td>It is recommended to wait for total lymphocyte recovery and, ideally, measure sub-populations of lymphocytes by flow cytometry, and check status of liver function tests. If the parameters are normal, you may switch immediately</td>
<td>Given the MoA, 6-12 weeks are recommended. It is important to check recovery of total lymphocyte count (at least 800 cell/ml) in blood count and, ideally, measure sub-populations of lymphocytes by flow cytometry</td>
</tr>
<tr>
<td></td>
<td>If there is an alteration to the liver function</td>
<td>A washout time of 6-12 weeks is recommended depending on recovery of lymphocytes and liver function tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If lymphocytes are below normal limits, consider accelerated elimination</td>
<td></td>
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<tr>
<td></td>
<td>Consider induced washout with activated carbon or cholestyramine</td>
<td></td>
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<tr>
<td><strong>Monitoring when switching to ocrelizumab</strong></td>
<td>Monitor disease’s activity (EDSS and MRI) every 6 months</td>
<td>Monitor disease’s activity (EDSS and MRI) every 6 months</td>
<td>Monitor disease’s activity (EDSS and MRI) every 6 months</td>
</tr>
<tr>
<td></td>
<td>Monitor liver function</td>
<td>Monitor lymphocyte count</td>
<td>Monitor lymphocyte count</td>
</tr>
<tr>
<td></td>
<td>Convenience of whether to carry out anti-JVC antibodies or not is still in debate</td>
<td></td>
<td>Monitor cancer</td>
</tr>
<tr>
<td></td>
<td>Convenience of whether to carry out anti-JVC antibodies or not is still in debate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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The following aspects were analyzed as part of the work to consider switching from other DMT to ocrelizumab:

a. The MoA to be considered and its clinical implications
b. The most relevant safety and efficacy considerations of each DMT for which a switch may be needed
c. Elimination time of the previous DMT from which the switch is made and, therefore, washout time, if necessary. Paraclinical studies before the switch is made
d. Paraclinical follow-up studies to monitor safety
Table 2. Recommendations to switch from a monoclonal antibody group disease-modifying treatment to ocrelizumab

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Natalizumab&lt;sup&gt;8,16,20&lt;/sup&gt;</th>
<th>Alemtuzumab&lt;sup&gt;20-24&lt;/sup&gt;</th>
<th>Rituximab&lt;sup&gt;16,25&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoA to be considered before switching</td>
<td>Humanized α4-integrin antagonist mAb, inhibiting migration of lymphocytes through the blood–brain barrier. Its MoA should be considered when switching treatment due to the risk of IRIS</td>
<td>Anti-CD52 mAb that depletes T and B lymphocytes. The effect of alemtuzumab on B cells may be transitory and there may be an early rebound, so anti-CD20 would be a suitable option</td>
<td>Anti-CD20 mAb</td>
</tr>
<tr>
<td>Possible switching scenarios</td>
<td>No response to treatment (clinical activity and/or in MRI) after 6 months of continuous use and having checked adherence to treatment. Risk of PML in patients with &gt; 24 infusions of natalizumab and/or a high JCV index Patients who do not adhere to treatment Adverse effects of natalizumab that makes it difficult to continue treatment Choice of patient because of convenience of dose</td>
<td>Disease activity (clinical and/or radiological) after the 2nd year of treatment Reconstitution syndrome measured by B lymphocytes; it is recommended to check sub-populations of lymphocytes by flow cytometry Adverse effects that make it difficult to continue with infusions (incomplete cycles) Choice of patient Patients in transitional/progressive disease. Approved as therapy for active secondary progressive and PPMS in adults by the FDA. Consider the local labeling in Mexico is approved for RMS and PPMS</td>
<td>Adverse reactions (infusion related) Off-label use may limit insurance approval</td>
</tr>
<tr>
<td>Additional screening</td>
<td>Anti-JCV antibody titers recommended, particularly in patients who switch due to the risk of PML MRI no &gt; 3 weeks, with FLAIR/T2, DWI sequence to discard PML Monitoring MRI every 3 months during the 1st year to assess risk of PML Rule out syphilis and chicken pox</td>
<td>Lymphocyte count, considering flow cytometry to measure cell sub-populations, bearing in mind that immunosuppression in these patients is greater Tests to rule out cancer (mastography, papanicolaou, APE, SOH, skin cancer) Tests to rule out other autoimmune conditions Consider prophylaxis with acyclovir, TMP-SMX</td>
<td>If profiling carried out previously for rituximab, continue with routine monitoring</td>
</tr>
<tr>
<td>Washout time</td>
<td>4-12 weeks, discarding lesions suggestive of PML by MRI. Risk of IRIS should be taken into account</td>
<td>At least 6 months after the last infusion</td>
<td>Unnecessary, should continue with application scheme established (every 6 months)</td>
</tr>
<tr>
<td>Monitoring when switching to ocrelizumab</td>
<td>Monitor disease activity (EDSS and MRI) every 6-12 months Monitor PML data up to 6 months after latest infusion of de natalizumab Lymphocyte counts Monitoring cancer Convenience of carrying out anti-JCV antibodies questioned once again</td>
<td>Monitor disease activity (EDSS and MRI) checking patient’s stability Lymphocyte count Monitoring cancer, including skin cancer Continue monitoring alemtuzumab’s potential side effects for 5 years</td>
<td>Monitor disease activity (EDSS and MRI) every 1-12 months Lymphocyte counts Monitoring cancer</td>
</tr>
<tr>
<td>Evidence</td>
<td>Literature reports improved efficacy results in patients who switched from natalizumab to anti-CD20 treatment versus oral DMT</td>
<td>Cases have been reported in literature of patients not responding to alemtuzumab who benefited from switching to anti-CD20 therapy Anti-CD20 therapy has been used in cases of early B lymphocyte reconstitution rebound</td>
<td>Still no evidence</td>
</tr>
</tbody>
</table>

In every case, the suggested paraclinical studies for patients to start treatment with ocrelizumab include the following:

- Blood count
- Blood chemistry
- Liver function tests
- Hepatitis testing – surface antigen and anti-core antibodies of the virus (AgHBVs and anti-HBVs).
- Rule out tuberculosis – recommend for the population exposed.
- Rule out HIV – recommend for the population exposed.
- Magnetic resonance imaging (MRI) – it is recommended to have a baseline MRI of no more than 3 weeks, ruling out any suspected progressive multifocal leukoencephalopathy. The following sequences must be taken into consideration: T1, T1 with gadolinium, T2, and fluid-attenuated inversion recovery, according to the international standard recommended by the MAGNIMS group. The frequency and make-up of each follow-up is determined by the needs of the individual patient.

If switching from other DMT, specific recommended studies may be added based on what is known about the MoA, as shown in tables 1 and 2. Therapies were divided into two large DMT groups: (a) oral DMT and (b) monoclonal antibodies (mAb). The tables below summarize the considerations made in the discussion groups.

We should point out that there is currently not enough evidence to draw final conclusions, so in this study, we will look at recommendations based on evidence available of the MoA and the recommendations to switch from each DMT. The vast experience of clinical neurologists in using innovative DMT for MS was taken into account.

Conclusions

Some 25 years after the introduction of the first interferon for treating MS, we have witnessed how DMT has evolved, aiming to adjust the pathological processes of this disease that we understand better than before. We are well aware that there is no single treatment algorithm and decisions should be made based on the knowledge of the MoA and the experience gained with these therapies.

When discussing DMT, we may classify its development in three eras: (i) from 1993 to 2003, when the first interferons were introduced and drugs were developed to better understand the immune physiopathological process of MS; (ii) the second was from 2003 to 2009 with the advent of more efficacious DMT, such as natalizumab, the first monoclonal antibody, and fingolimod, the first oral DMT; and (iii) the third from 2009 to date, in which not only were biological therapies developed but also small molecules, such as dimethyl fumarate. The range of MoA from the DMT has been expanded during this time, the results are encouraging.

Bearing this in mind, it is of particular interest to reflect on the experience and opinions of clinical neurologists about the potential switching from other DMT to those recently approved, such as ocrelizumab.

The group concludes that the switch of current DMT to ocrelizumab may be convenient and safe, as long as the patients are selected and evaluated correctly. We should bear in mind that the patients should be monitored closely during the first 24 h after the switch.

Real-life evidence is needed by means of several cases and evidence of safety in the medium and long term.

Ethical declaration

This work was carried out with the unrestricted support of Roche de México, including transport, travel expenses, and the fees of each person attending meetings.

Acknowledgments

The authors would like to thank Drs. Maria Pia Roque, Mariana Arzate, Roxana Flores, Carlos Pla, and Asdrubal Huerta of Roche México for assisting in the logistics of the activities carried out and Dr. Jose de Jesus Flores Rivera for his support.

Conflicts of interest

Dr. Ordoñez reports personal fees and non-financial support from Roche Servicios de Mexico, during the conduct of the study, personal fees and non-financial support from Novartis, personal fees and non-financial support from Stendhal, personal fees and non-financial support from Teva, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Merck, grants and personal fees from Biogen, and grants and personal fees from Synthon, outside the submitted work. Dr. Velazquez Quintana reports personal fees and non-financial support from Roche Servicios de Mexico, during the conduct of the study. Dr. Skromne Eisenberg reports personal fees and non-financial support from Roche Servicios de Mexico, during the conduct of the study, personal fees and non-financial support from Merck.
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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References


