Ocrelizumab: its efficacy and safety in multiple sclerosis

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Introduction. Ocrelizumab is a humanised monoclonal antibody that targets the CD20 antigen on B cells. It has recently been approved by the US (Food and Drug Administration) and European health agencies (European Medicines Agency) for the treatment of multiple sclerosis (MS) and is the first drug marketed for both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). The clinical trials conducted for both the relapsing forms (OPERA I/II) and the progressive forms of the disease (ORATORIO) have demonstrated its efficacy. The aim of this review is to address the main aspects of the efficacy and safety of ocrelizumab in MS.

Development. Using PubMed, a literature review was conducted of studies published at the ECTRIMS 2017 Congress and of active studies in ClinicalTrials. In order to evaluate the efficacy and safety of ocrelizumab in MS, both randomised clinical trials and their extension and follow-up studies were reviewed, and information about its safety obtained from monitoring programmes of the Food and Drug Administration and European Medicines Agency was included.

Conclusions. Ocrelizumab is the first drug that has been shown to be able to significantly slow disability progression at 12 and 24 weeks in patients with PPMS. It is also effective in controlling clinical and radiological activity in patients with RRMS forms, and it is approved and indicated for both phenotypes of the disease. To date, the safety profile of ocrelizumab matches that observed in clinical trials, without any unexpected alerts.

Key words. CD20 antigen. Multiple sclerosis. Ocrelizumab. Primary progressive multiple sclerosis. Relapsing-remitting multiple sclerosis.

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Introduction

Multiple sclerosis (MS) is an autoimmune disease characterised by inflammation, demyelination and neurodegeneration of the central nervous system [1]. Onset usually occurs between 20 and 40 years of age and is the first cause of non-traumatic disability among young people [2]. The prevalence of the disease in our country stands at around 100 cases per 100,000 inhabitants [3-5], and it is calculated that 2.5 million people currently suffer from it around the world [6], which entails high healthcare, occupational and social costs [7,8].

In the new classification of MS by phenotypes published in 2014 two disease profiles are defined [9]: one in which activity (either clinical or radiological) is predominant, and the progressive phenotype, which may or may not be associated with activity. This way of conceptualising the disease involves accepting the fact that even in progressive forms there may be an activity component, possibly amenable to treatment. This is what we are witnessing in recent years: the incorporation of new off-label or already approved therapeutic options for patients who, with the classic approach, did not receive treatment for their clinically progressive behaviour.

There is no treatment to cure MS. Since the first interferon was commercialised in 1993 many therapeutic strategies have been investigated and today there are 16 disease-modifying drugs (DMD) that have been approved by the European Medicines Agency. All of them have a predominantly anti-inflammatory profile, focused on reducing the risk of new lesions in magnetic resonance, the risk of new relapses and, potentially, the progression of the disability [10]. All of these DMD are indicated in relapsing-remitting forms of MS (RRMS), but none have been approved for primary progressive multiple sclerosis (PPMS). Despite this extensive therapeutic arsenal, a considerable percentage of patients continue to present relapses, and up to 59% undergo a significant exacerbation of their disability [11]. This leads us to a therapeutic race with many milestones still to be reached.

The pathogenesis of MS is complex and, although the exact mechanism of action of the drugs approved for MS remains unknown, the majority of them predominantly affect, either directly or indirectly, T cells. Yet, for several decades researchers suspected that B cells are directly involved in the physiopathogenesis of MS. Today, we know that this is indeed so, and that they act as antigen-pre-

senting cells, as well as playing a role in the production of autoantibodies, the regulation of cytokines and the formation of ectopic lymphoid aggregates in the meninges, all of which probably contribute to cortical damage, neurodegeneration and disability progression [12-15].

Previous studies conducted with rituximab – a chimeric anti-CD20 monoclonal antibody – showed that depletion of B cells could be a potentially effective treatment in MS, reducing the number of relapses and inflammatory lesions in MRI in MSRR forms [16,17] and slowing disability progression in the more active subgroups of patients with PPMS [17, 18]. Rituximab is a more economical drug, the protective patent of which has expired and with little commercial interest, and therefore its development is very unlikely to continue with the design of pivotal clinical trials. Based on these results, the line of research with anti-CD20 molecules has continued with a humanised antibody, ocrelizumab, and another human one, ofatumumab, which are expected to entail a lower risk of immunogenic reactions.

Ocrelizumab has been tested for both RRMS and PPMS forms [19]. Based on the results of pivotal clinical trials, ocrelizumab (Ocrevus ®) is the first drug approved for use in people with active RRMS and PPMS by the US Food and Drug Administration and the European Medicines Agency in March and November 2017, respectively. Work on defining the ideal profile of patients – with either the progressive phenotype or the activity phenotype – for whom the risk-benefit balance of the drug is appropriate is expected to be completed in the near future [20].

Development

We conducted a literature review using the PubMed database, as well as the manuscripts published at the ECTRIMS Congress in October 2017 and the active studies in ClinicalTrials. In order to evaluate the efficacy and safety of ocrelizumab in MS, we analysed randomised clinical trials together with their extension and follow-up studies. We also included safety data from the Food and Drug Administration and European Medicines Agency monitoring programmes.

B cells as a therapeutic target in MS

MS has traditionally been considered a disease mediated by T lymphocytes. This concept has been based on traditional animal model studies of the disease, experimental autoimmune encephalitis, where the main mediator is the autoreactive T lymphocyte. For several decades, however, speculation has grown concerning the role of B lymphocytes. The oligoclonal bands present in most patients with MS have always been one of the most solid arguments put forward when it comes to defending an active role of B cells in the disease. Today we know that the activated plasmablast, derived from the B lymphocyte, can remain in MS patients' cerebrospinal fluid for very prolonged periods of time, unlike what occurs in other central nervous system diseases such as infections. This cell would be responsible for secreting immunoglobulins and oligoclonal bands, an independent marker of the medium-term prognosis of the disease [21].

Most of the treatments approved for MS have a direct or indirect effect on the control over the functioning of T cells, and the majority of them also partially exert their mechanism of action by acting upon B cells.

Advances in the knowledge available about the disease have made it possible to develop therapies against this cell line. CD20 antibodies trigger destruction of circulating CD20+ B cells that continues for over six months [22]. However, the extent to which these therapies are effective in their action on the B cells of the central nervous system, upon lymphoid tissue and upon bone marrow remains unknown.

The effect of the depletion of these B cells has been tested in MS with different anti-CD20 monoclonal antibodies. CD20 is a B lymphocyte surface antigen which is present from pre-B cells to B lymphocyte memory cells, but is absent in lymphoid stem cells and plasma cells [23,24]. For this reason, CD20+ B cell depletion could reduce the immunogenicity of MS without affecting the capacity to reconstitute the B cell populations or the pre-existing humoral immunity [25,26].

Anti-CD20 antibodies

The different anti-CD20 monoclonal antibodies can be distinguished from each other by their molecular structure, the epitope to which they attach themselves and the mechanism of destruction of the B cell. These differences are what are expected to condition immunogenicity with the prolonged use of the drug and the perfusion responses. Rituximab, ocrelizumab and ofatumumab are anti-CD20 drugs in active use or under study for MS, with a good safety profile and the capacity to reduce the formation of new lesions in MRI and the frequency of relapses. The effect of these drugs on the disabil-

Table I. Phase II and III clinical trials of ocrelizumab.

	Characteristics	Eligibility criteria	Primary objective	Was the primary objective fulfilled?
NCT00676715 (WA21493)	600 mg OCR versus 2,000 mg OCR versus Avonex versus placebo (1:1:1:1) Phase II	RRMS EDSS: 1-6.6 ≥ 2 relapses in the previous three years (1 relapse in the previous year) ≥ 6 T_2 lesions	Number of gadolinium enhancing lesions in T_1 in magnetic resonance imaging	Yes 600 mg OCR: ↓ 89% (CI 95%: 68-97%) 2,000 mg OCR: ↓ 96% (CI 95%: 89-99%) $p < 0.0001$
NCT01412333 (OPERA I/II)	600 mg OCR versus 44 µg Rebif (1:1) Phase III	RRMS EDSS: 0-5.5 ≥ 2 relapses in the previous two years or 1 relapse in the previous year	Annualised relapse rate at 96 weeks	Yes OPERA I: ↓ 46% (CI 95%: 28-60%) OPERA II: ↓ 47% (CI 95%: 29-60%) $p < 0.001$
NCT01194570 (ORATORIO)	600 mg OCR versus placebo (2:1) Phase III	PPMS EDSS: 3-6.5 If EDSS > 5: < 15 years If EDSS ≤ 5: < 10 years	Increase of the EDSS maintained at 12 weeks	Yes 600 mg OCR: ↓ 24% (CI 95%: 2-41%) $p = 0.03$
NCT03085810	OCR naïve patients (single group) Phase III Open label	RRMS ≤ 3 years EDSS: 0-3.5 Clinical or radiological activity in the last 12 months	Time until confirmed disability at 24 and 48 weeks	Ongoing
NCT02637856	OCR in refractory patients (single group) Phase III Open label	RRMS ≤ 12 years ≤ 3 previous DMD for ≥ 6 months The last interrupted due to inefficacy	NEDA	Ongoing

DMD: disease-modifying drug; EDSS: Expanded Disability Status Scale; NEDA: no evidence of disease activity; OCR: ocrelizumab; PPMS: primary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

ity progression is more modest, and the greatest benefit could be gained by young patients with signs of activity [18].

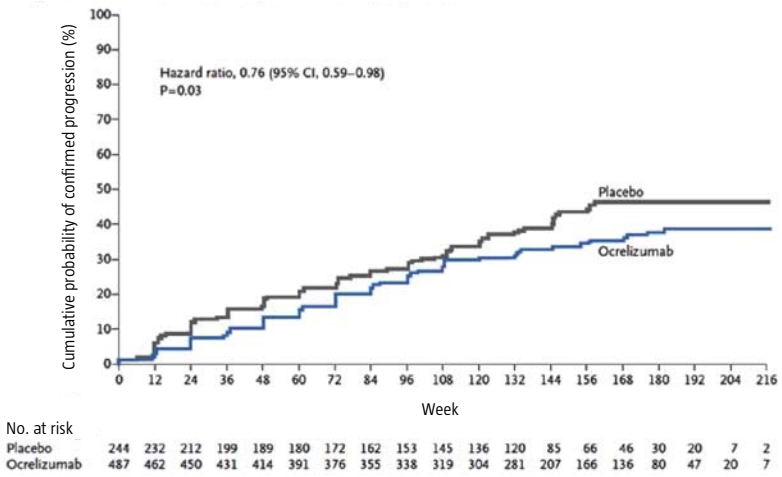
Ocrelizumab in MS with relapses (RRMS)

The first study on ocrelizumab in MS to be published was WA21493. This was a phase II, multicentre, randomised, double-blind clinical trial, with four treatment arms 1:1:1:1, two ocrelizumab arms (total doses of 600 mg and 2,000 mg), one active comparator arm (interferon β-1a, Avonex®) and one placebo arm. The study included a total of 220 patients with clinically and radiologically active RRMS (two or more relapses over the last three years, at least one of them during the previous year, and more than six lesions in T_2 in the baseline MRI). The main objective at six months was a reduction in the number of gadolinium enhancing lesions versus placebo. This aim was achieved for the two ocrelizumab arms: reduction of 89% (95% confidence interval, CI 95%: 68-97%) for the 600 mg dose and by 96% (CI 95%: 89-99%) for the 2,000 mg dose ($p < 0.0001$), and the difference was also significant versus Avonex ($p < 0.0001$). As secondary aims, differences were also observed in the annualised relapse rate in both dosages of ocrelizumab versus placebo – a reduction of 80% (CI 95%: 45-99%; $p = 0.0005$ for the 600 mg dose, and 73% (CI 95%: 29-97%; $p = 0.0014$) for the 2,000 mg dose – and versus Avonex for the 600 mg dose ($p = 0.03$). The results of the extension studies were in line with the previous outcomes [27].

The clinical development programme continued by means of the OPERA I/II studies, which had the same design. They consisted in two phase III, multicentre, triple-blind clinical trials that were randomised in a proportion of 1:1 over a period of two years to 600 mg of ocrelizumab versus an active comparator arm (interferon β-1a, 44 µg Rebif®). The two trials included a total of 1,656 patients with RRMS and clinically active disease (the presence of two or more relapses over the past two years or one relapse in the last year). The primary objective, to reduce the annualised relapse rate after 96 weeks, was achieved in both trials, with a reduction of 46% (CI 95%: 28-60%) and 47% (CI 95%: 29-60%), respectively, versus Rebif ($p < 0.001$ in both cases).

The data from the clinical trials are summarised in Table I.

Figure 1. Primary aim of the ORATORIO clinical trial of ocrelizumab in primary progressive multiple sclerosis (adapted from [33]): confirmed disability progression for 12 weeks.



As part of these secondary aims of the OPERA I/II studies, an analysis was performed to determine the frequency of patients who reached no evidence of disease activity (defined as the absence of relapses, progression and radiological activity at 12 weeks), which was significantly higher in the ocrelizumab group than in the Rebif group (47.7% versus 27.1%; $p < 0.0001$). Differences in favour of ocrelizumab were also observed in the following secondary objectives: number of gadolinium enhancing lesions (reduction of 94%; $p < 0.001$), confirmed disability progression at 12 weeks (9.1% versus 13.6%; hazard ratio: 0.6; CI 95%; 0.45-0.81; $p < 0.001$) and confirmed disability progression at 24 weeks (6.9% versus 10.5%; hazard ratio: 0.6; CI 95%: 0.43-0.84; $p = 0.003$) [28]. In the post hoc analyses, for the annualised relapse rate and no evidence of disease activity depending on the baseline characteristics, a reduction in the annualised relapse rate was observed in all the subgroups analysed, with a smaller benefit in patients ≥ 40 years old (relative risk, RR: 0.76; CI 95%: 0.56-1.03; $p = 0.073$) and in the patients without gadolinium enhancing lesions (RR: 0.74; CI 95%: 0.56-0.96; $p = 0.025$) [29]. For no evidence of disease activity, a benefit from ocrelizumab was observed in all the subgroups, with a smaller effect in patients with an Expanded Disability Status Scale (EDSS) score ≥ 4 (RR: 1.31; CI 95%: 0.98-1.75; $p = 0.064$) and in patients with no radiological activity (RR: 1.55; CI 95%: 1.35-1.78; $p < 0.001$) [30].

In the intention-to-treat analyses, a reduction in the disability progression was observed at weeks 12 and 24 in the ocrelizumab group versus Rebif: 34% ($p < 0.001$) and 31% ($p = 0.002$), respectively. A reduction in the proportion of patients with progression at weeks 12 and 24 was also observed, regardless of the relapses: 25% ($p < 0.008$) and 23% ($p = 0.039$), respectively, versus Rebif. In the subgroup of patients with a higher risk of suffering from secondary progressive MS (EDSS ≥ 4 and Pyramidal Score ≥ 2) [31], ocrelizumab reduced progression regardless of the relapses over 12 and 24 weeks by 40% ($p = 0.022$) and 36% ($p = 0.063$), respectively, compared to Rebif [32].

Ocrelizumab in PPMS

The OLYMPUS study, a clinical trial in phase II/III conducted with rituximab in 439 patients with PPMS, did not fulfil its primary objective – confirmed disability progression – probably due to sample size. The analysis by subgroups, however, showed a slow progression in younger patients (< 51 years of age) and with evidence of inflammatory activity (gadolinium enhancing lesions) [18].

These results led to a new study, with ocrelizumab, through the clinical trial ORATORIO. This was a multicentre, triple-blind clinical trial, randomised in a proportion of 2:1 to ocrelizumab (600 mg every 24 weeks, with a minimum of five doses) or placebo. The study included patients diagnosed with PPMS, EDSS 3-6.5 and moderate duration of the disease (< 15 years if the EDSS > 5 or < 10 years if the EDSS ≤ 5). The primary aim of the study was to determine the proportion of patients with confirmed disability progression at week 12 (defined as a sustained increase of the EDSS ≥ 1 if the baseline EDSS ≤ 5.5, or a sustained increase of the EDSS ≥ 0.5, if the baseline EDSS > 5.5) [33]. The study included 732 patients over a period of 120 weeks. The primary aim was fulfilled in 32.9% of the ocrelizumab arm versus 39.3% in the placebo arm (hazard ratio: 0.76; CI 95%: 0.59-0.98; RR reduction: 24%; $p = 0.03$) (see the data from the study in Table I and the primary objective in Fig. 1.)

One of the secondary aims of the OPERA study was to determine the proportion of patients with confirmed disability progression at 24 weeks (29.6% ocrelizumab versus 35.7% placebo; hazard ratio: 0.75; CI 95%: 0.58-0.98; RR reduction: 25%; $p = 0.04$), changes in the 25-foot-walk test at 120 weeks (RR reduction: 29.3%; CI 95%: –1.6-51.5; $p = 0.04$), change in the volumes of lesions in T_2 between weeks 24 and 120 (–3.4% ocrelizumab versus 7.4% placebo; $p < 0.001$) and change in brain volume

(–0.9% ocrelizumab versus –1.09% placebo; RR reduction: 17.5%; $p = 0.02$) (Fig. 2).

The extension study involved a follow-up lasting at least another six months and allowed the results to be confirmed with a RR reduction of confirmed disability progression [34].

Monitoring CD19+ cells

CD19 is a surface antigen present in B-strain cells, from immature B cells to plasmablasts [35]. The measurement of CD19+ cells by means of flow cytometry is a surrogate measure of B lymphocytes in patients treated with anti-CD20 antibodies [28].

In clinical practice with rituximab, the measurement of CD19+ cells is used, in some centres, to programme the drug administration schedule. As the levels of CD19+ are undetectable from the second week of rituximab administration onwards and take up to 9-12 months to become normalised, the administration of a new dose of anti-CD20 is often considered unnecessary while these levels remain undetectable. This practice allows longer intervals to be introduced between the dates of rituximab administration without, theoretically, reducing its effectiveness [36].

In the data currently available for ocrelizumab, the CD19+ cells were at undetectable levels from the second week until the end of the study (the last determinations were carried out at week 96 in OPERA I/II and at week 216 in ORATORIO) [28,33]. The average time taken to regain the levels of CD19+ cells was 72 weeks [20].

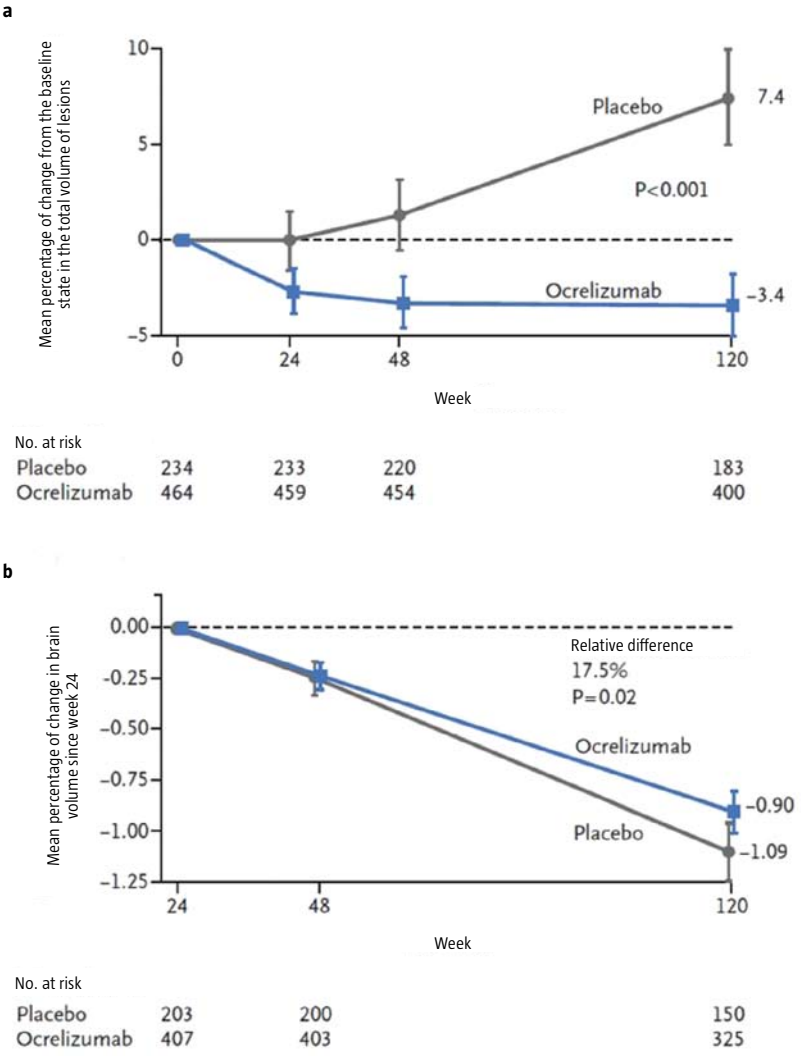
Ocrelizumab is probably more powerful than its predecessor and a 600 mg dose of ocrelizumab would be biologically superior to a 1,000 mg dose of rituximab [37]. Despite this evidence, however, which in some way would be indicating the ideal personalised dosage regimen, there are no recommendations on monitoring the effect of ocrelizumab, and the administration regimen is weekly, in equal doses, for all patients.

Serodiagnosis and vaccinations

Cases of reactivations of the hepatitis B virus (HBV) have been detected in patients who received anti-CD20 antibodies, which resulted in fulminant hepatitis, liver failure and death. The summary of product characteristics recommends determining the immunisation status against HBV in patients who are going to start treatment with ocrelizumab and their prior vaccination if they have not been inoculated. HBV vaccine was included in the vaccination schedule in the 80s, which means that most people who were born before then will not have been vaccinated. The drug would be contraindicated in actively infected patients and it is recommended that those with a positive serum test and HBV carriers should be referred to specialists in liver pathology and be given monitoring and treatment, if appropriate, with the aim of preventing the reactivation of HBV.

According to the summary of product characteristics of ocrelizumab, and in accordance with its mechanism of action, inoculation with live or at-

Figure 2. Radiological objectives of ORATORIO in primary progressive multiple sclerosis by intention-to-treat (adapted from [33]): a) Total volume of brain lesions in T_2 weighted sequences; b) Brain volume.



tenuated live vaccines is not recommended during treatment and until B-cell repletion. The absence of data on the effects of vaccinating these patients makes it recommendable to review the immunisation status of patients who are going to receive ocrelizumab and to update the vaccination schedule if necessary, at least six weeks before starting treatment with the drug [20,38].

Once the treatment phase had been completed in the clinical trials, it was observed that ocrelizumab did not bring about any changes in the pre-existing immunity to mumps, German measles, chickenpox or pneumococcus [39].

Safety

During the development phase of ocrelizumab in MS, 600 mg and 2,000 mg doses were tested. Following the death of one patient in the treatment arm with the higher dose due to systemic inflammatory response syndrome, it was decided that the research should continue with just the 600 mg dose [27]. Experience in other diseases shows us that ocrelizumab, in combination with other immunosuppressants, could increase the risk of severe opportunistic infections. Accordingly, development of the drug for rheumatoid arthritis was stopped [24].

In MS, and in an accumulated manner, the rate of severe side effects in the clinical trials was 6.9% for the ocrelizumab arm in RRMS and 8.7% for the Rebif arm, 20.4% for the ocrelizumab arm in PPMS and 22.2% for the placebo arm. The most frequent side effects in patients who received ocrelizumab were infusion-related reactions, urinary tract infections, nasopharyngitis and upper respiratory tract infections.

The drug was withdrawn due to side effects in 2-4% of the patients in the clinical trials. Of the total number of patients who had received ocrelizumab up until February 2017, the drug was withdrawn due to side effects in 3.9% of them (1.24 per 100 patient-years; CI 95%: 1-1.51). The most frequent causes of withdrawals were infusion-related reactions (1%), neoplasias (0.8%) and infections (0.5%).

In the clinical trials in phase II and III, there were a total of nine deaths, six of them in the ocrelizumab arm. In the OPERA I/II trials there was one death due to suicide in the ocrelizumab arm (0.1%), and one death due to suicide and another owing to mechanical ileus in the Rebif arm (0.2%). Four patients died in the ocrelizumab arm in the ORATORIO study (0.8%) due to pulmonary thromboembolism, pneumonia, adenocarcinoma of the pancreas and aspiration pneumonia, respectively, and in the placebo arm one patient died (0.4%) in a road accident [28,33,40].

Infusion-related reactions

Infusion-related reactions with ocrelizumab are common and generally take place within 24 hours of drug administration [28,38]. They occurred in 34.4% of the OPERA I/II patients and 39.9% of the ORATORIO patients. They were more frequent during the first infusions than in subsequent ones (27.5% versus 6.8% in OPERA I/II; 27.4% versus 12.6% in ORATORIO) and went on to become severe in 2.4% in the OPERA I/II studies and 1.2% in ORATORIO. One patient in the OPERA I/II trial presented a life-threatening reaction in the form of a severe bronchospasm during the first infusion [28,33,41].

These reactions are believed to be a type 2 hypersensitivity model due to the release of cytokines. As a result, recommendations include monitoring, premedication (endovenous methylprednisolone, with or without prophylactic treatment with analgesics/antipyretics and antihistamines) and dividing the first 600 mg dose into two 300 mg doses administered with an interval of two weeks between them [28,38].

Infections

The rate of infection in the clinical trials was 75.6 per 100 patient-years (CI 95%: 73-78.2), a rate that remained stable in the extension studies. In February 2017, the rate of infection was 71.3 per 100 patient-years (CI 95%: 69.5-73.2), above all in the urinary tract, nasopharyngitis, upper respiratory tract infections and herpes infections.

The accumulated rate of severe infections in all the clinical trials was 1.3% for the ocrelizumab arm in RRMS and 2.9% for the Rebif arm, 6.2% for the ocrelizumab arm in PPMS and 5.9% for the placebo arm [28,33,40].

Due to compromised humoral immunity during treatment with ocrelizumab, it is recommended that the vaccination schedule should be updated prior to beginning treatment [20].

Neoplasias

In the clinical trials with ocrelizumab in MS, an increase in the incidence of cancer was observed in the ocrelizumab arms versus placebo or interferon β-1a. In these studies, in which data collection ended in July 2015, the rate of incidence of malignant tumours in patients with ocrelizumab per 100 pa-

tient-years was 0.43 (CI 95%: 0.26-0.66; 6,467 patient-years of exposure). Six cases of breast cancer were recorded, one case of renal cell carcinoma, one case of malignant melanoma, three cases of basal cell skin carcinoma, one case of endometrial carcinoma, one anaplastic giant cell lymphoma, one case of malignant fibrous histiocytoma and one pancreatic carcinoma [28,33,42].

As part of the extension studies, and up until February 2017, altogether 2,301 patients with MS had been exposed to ocrelizumab, with a total of 7,748 accumulated years of exposure. The incidence ratio of malignant tumours per 100 patient-years in the population exposed to ocrelizumab was 0.45 (CI 95%: 0.32-0.63), above all due to breast cancer and non-melanoma skin cancer. The data are similar to those found in previous studies and are also similar to the known incidences of cancer in MS in different cohorts [42]. A prolonged follow-up of the drug would provide us with further information. Yet, to date there is no specific alarm or any special recommendation, except performing screening tests in keeping with the different age groups.

Others

Although no cases of progressive multifocal leukoencephalopathy were reported in the clinical trials with ocrelizumab, there is a known risk of suffering progressive multifocal leukoencephalopathy in patients who receive other anti-CD20 antibodies. This is especially true in patients who have previously received other immunosuppressants or who combine drugs. This risk is especially well known in rituximab, where at least 57 cases of progressive multifocal leukoencephalopathy have been reported [43].

In May 2017, Genetech reported the appearance of a case of progressive multifocal leukoencephalopathy in a patient in Germany who was receiving ocrelizumab for compassionate use. The patient had previously been on natalizumab for three years (36 infusions) and presented antibodies against JC virus. Finally it was interpreted as a case of carry-over-progressive multifocal leukoencephalopathy due to natalizumab [40].

Pregnancy

IgG1 type immunoglobulins, such as ocrelizumab, do not cross the placenta during the first trimester of pregnancy and it is assumed that maternofoetal transfer only takes place from week 16 onwards [44]. Hence, the foetus would theoretically be protected from exposure to ocrelizumab during organogenesis [44,45]. Moreover, the mean lifetime of ocrelizumab in blood is 26 days and the elimination half-life is 4.5 months (bearing in mind a variability among patients of up to nine months). Therefore, in order to prevent foetal exposure to ocrelizumab, the summary of product characteristics recommends the use of an effective contraceptive until six months after the last dose of ocrelizumab [46].

Lymphopenia and transitory B-cell depletion have been reported in children born to mothers who have been exposed to anti-CD20 antibodies.

Studies conducted with ocrelizumab in monkeys, and with doses between two and ten times higher, showed transitory B-cell depletion in the mothers and in their offspring, but without a higher risk of maternal toxicity, embryotoxicity or foetal or perinatal mortality. Administration of ocrelizumab from organogenesis until birth caused two perinatal deaths and increased nephrotoxicity, formation of lymph follicles in the bone marrow, severe lymphopenia due to B cells and reduction of testicle size [46].

From 2008 until January 2017 a total of 58 pregnancies were reported in patients who received ocrelizumab within the context of a clinical trial. Of those pregnancies, 25 occurred in patients with MS, 22 in patients with rheumatoid arthritis and 11 in patients with systemic lupus erythematosus. The patients were exposed to ocrelizumab doses of between 20 and 2,000 mg. Intrauterine exposure to ocrelizumab was deemed to have occurred when the last dose had been administered three months before conception, during pregnancy or when the date of conception was unknown. Within the MS group, there were 14 pregnancies with intrauterine exposure to ocrelizumab, of which four went to full term with healthy newborns, one was born preterm due to severe preeclampsia, six ended in voluntary interruption of the pregnancy and two were still ongoing at the time the study was published [47].

Information about the outcome of pregnancies is shown in Table II.

Conclusions

Ocrelizumab is the first pharmacological treatment that has proved its efficacy in patients with progressive forms of the disease, and is the first drug approved by the Food and Drug Administration and the European Medicines Agency for the treatment of MS in both phenotypes: PPMS and RRMS. Its conceptual predecessor, rituximab, opened up the way, revealed a niche in which to act on the pro-

Table II. Pregnancies with ocrelizumab in clinical trials until January 2017 (adapted from [47]).

	Multiple sclerosis		Rheumatoid arthritis	Systemic lupus erythematosus
Ocrelizumab dose exposure	600/2,000 mg every 24 weeks		400/1,000 mg every 24 weeks	800/2,000 mg every 16 weeks
Total no. patients exposed	2,147		2,926	332
Total no. pregnancies	25		22	11
	14 with intrauterine exposure to ocrelizumab [a]	11 without intrauterine exposure to ocrelizumab [a]		
Healthy full-term births	4	7	12	
Births with malformations	0	0	7 [b]	
Preterm births	1 (severe preeclampsia)	1 (34 weeks; benign naso-pharyngeal tumour, jaundice, respiratory disease and low weight)	1 (gestational age unknown)	
Miscarriages	1 (gestational age unknown)	0	10 [c]	
Elective abortions	6	1	2	
Active pregnancies at the time of publication	2	2	0	
Loss to follow-up	0	0	1	

[a] Intrauterine exposure: ocrelizumab three months prior to conception, during pregnancy or with unknown date of conception; [b] All the mothers were receiving or had received concomitant treatment with methotrexate, mycophenolate mofetil, hydroxychloroquine or azathioprine; [c] Eight of the abortions occurred in patients with rheumatoid arthritis in concomitant treatment with methotrexate.

gressive phenotype of the disease and suggested that a subgroup of younger active patients would be ideal to accept the risk/benefit ratio of the treatment. The design of the study with ocrelizumab in PPMS does not allow analysis by subgroups, although it seems that the effect of the drug is obtained regardless of the presence or absence of baseline radiological activity [48].

Although ocrelizumab is the first treatment that has proved its efficacy in patients with progressive forms, the real effect upon disability progression is modest, and the long-term clinical relevance in patients with progressive forms remains to be defined. Nevertheless, what we have learnt from the immediate past is that incorporating new therapies is followed by a wide range of studies in clinical practice on the clinical, radiological and biological effect of the molecule, and this in turn furthers our knowledge about the disease. New treatments are the prelude to new evidence.

The path by which the destruction of the B cell has an influence, by modifying the rate of disease progression in PPMS, is unknown. The concept of compartmentalisation of inflammation is particularly relevant in progressive forms of the disease, and a relationship between lymphoid aggregates, meningeal inflammation and progression has been demonstrated [15]. Hence, B-cell control would be slowing antibody synthesis, interleukin release and T-lymphocyte activation, while also controlling predominantly cortical damage. Studies are already underway to quantify the effect of the drug on meningeal inflammation using high-field magnetic resonance imaging [49,50].

In conditions in which the blood-brain barrier is intact, other anti-CD20s, such as rituximab, are known to reach the central nervous system in very low proportions when administered intravenously. It is also known that the magnitude of the biological effect of ocrelizumab at the central level is much lower than that obtained in peripheral blood. Would it therefore be reasonable to suspect that the partially modest effect on disability progression reflects a suboptimal dose of the drug in the central nervous system? This doubt already arose with rituximab, and that was the reasoning behind the

decision to employ intrathecal administration, which was tested in a clinical trial and had to be stopped early on due to negative outcomes in the interim analysis [51].

The benefit of ocrelizumab in patients with RRMS forms, as with other drugs for this indication, is easier to explain: patients with activity, with an open blood-brain barrier and a mechanism of action of the drug which, although predominant in the periphery, has a direct impact on the central nervous system, by indirectly blocking the inflammatory event, the new formation of lesions and the appearance of acute clinical symptoms.

The safety profile of ocrelizumab does not offer any great surprises. Previous biological drugs have gradually opened up the way and, at present, uncertainty about the development of certain infections or neoplasms within the context of these treatments is something with which professionals and patients have to live with, although attempts are made to control it by carefully following risk minimisation plans.

Ocrelizumab gives rise to a new stage in the treatment of MS and this, in addition to a direct effect on patients' quality of life, will lead to an improved understanding of the disease and an improved approach to it in the future [52].

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Ocrelizumab: eficacia y seguridad en la esclerosis múltiple

Introducción. El ocrelizumab es un anticuerpo monoclonal humanizado contra el antígeno CD20 de las células B. Ha sido aprobado recientemente por las agencias sanitarias estadounidense (Food and Drug Administration) y europea (European Medicines Agency) para el tratamiento de la esclerosis múltiple (EM), y supone el primer fármaco comercializado tanto para la EM remitente recurrente (EMRR) como para la EM primariamente progresiva (EMPP). Los ensayos clínicos, tanto para formas recurrentes (OPERA I/II) como para las formas progresivas de la enfermedad (ORATORIO), han demostrado su eficacia. El objetivo de esta revisión es abordar los principales aspectos de eficacia y seguridad del ocrelizumab en la EM.

Desarrollo. Se ha realizado una revisión bibliográfica a través de PubMed de trabajos publicados en el congreso ECTRIMS 2017 y de estudios activos en ClinicalTrials. Con el fin de evaluar la eficacia y seguridad del ocrelizumab en la EM, se han revisado ensayos clínicos aleatorizados, así como sus estudios de extensión y de seguimiento, y se ha incluido información sobre seguridad de los programas de monitorización de la Food and Drug Administration y la European Medicines Agency.

Conclusiones. El ocrelizumab es el primer fármaco que ha demostrado poder frenar de forma significativa la progresión de la discapacidad en 12 y 24 semanas en pacientes con EMPP. Es también eficaz en el control de la actividad clínica y radiológica en pacientes con formas de EMRR, y su aprobación e indicación engloban ambos fenotipos de la enfermedad. Hasta ahora, el perfil de seguridad del ocrelizumab se ajusta a lo observado en los ensayos clínicos, sin alertas inesperadas.

Palabras clave. Antígeno CD20. Esclerosis múltiple. Esclerosis múltiple primariamente progresiva. Esclerosis múltiple remitente recurrente. Ocrelizumab.