MEDICATION FOR MULTIPLE SCLEROSIS

Ocrelizumab effect and safety

Alsa Oudah
Abstract

Multiple sclerosis (MS) is an autoimmune inflammatory disease induced by immune cell attack on oligodendrocytes causing the loss of myelin and leading to degeneration of neuron function. The disease is divided into four subgroups based on inflammatory activity and disease progression, relapsing-remitting MS, primary progressive MS, secondary progressive MS and progressive relapsing MS. Available drugs today do not cure the disease; instead, they regulate inflammatory cytokines to decrease the demyelination process. This study takes a closer look at the newly approved medication ocrelizumab that has shown a promising effect on disease progression in comparison to baseline treatments. This study aimed to provide a better understanding of the new medication regarding effect, safety and comparison to other MS treatments.

Data in this study was obtained from several high-value sources such as; Pubmed for clinical trial and review papers, medical databases including Medibas, internetmedicin, 1177.se. Books on human anatomy and disease provided the background information on multiple sclerosis.

The results from 3 clinical studies and 2 review papers indicated effect of ocrelizumab in MS patients. Comparison of ocrelizumab effect to placebo groups and interferon-beta 1 groups favoured ocrelizumab in the progression and efficacy data. The disease progression was measured with three methods: Expanded disability status scale (EDSS) score, using a tracer that cannot cross a normal, intact blood brain barrier revealing Gadolinium-enhanced lesions (GEL) in the brain on magnetic resonance imaging (MRI) and the inflammation marker immunoglobulin G (IgG) index. Participants were aged 18-55 and had confirmed MS diagnose before trial start.

Adverse events (AEs) were not absent and the most reported AE was the infusion-related reaction in ocrelizumab groups. Reports of infections were registered and were anticipated due to the drugs mechanism of action—suppression of immune response.

In conclusion, results show that ocrelizumab is an effective treatment for multiple sclerosis. The drug is associated with better disability progression, MRI, and clinical rates in the treated population. Even comparison to baseline treatment showed a pronounced efficacy and lower disease activity in ocrelizumab group.

Key words: Multiple sclerosis, Ocrelizumab, Primary progressive MS, Interferon beta-1a, Vitamin D.
Table of Contents

Ocrelizumab effect and safety ................................................................. 0

Introduction ......................................................................................... 1

  Diagnoses ......................................................................................... 3

Treatment ............................................................................................... 3

Pregnancy .............................................................................................. 5

Treatment expenditure ........................................................................... 5

Objective ................................................................................................. 5

Method ..................................................................................................... 6

Results ...................................................................................................... 7

1.1 Ocrelizumab versus Placebo in Primary Progressive multiple sclerosis ....... 7

  1.1.1 Inclusion and exclusion criteria .................................................. 7

  1.1.2 Trial end points, statistical analysis and Patients ......................... 8

  1.1.3 Efficacy ...................................................................................... 8

  1.1.4 Safety .......................................................................................... 9

1.2 Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis ......... 9

  1.2.1 Inclusion and exclusion criteria .................................................. 9

  1.2.2 Trial end points and Patients ...................................................... 9

  1.2.3 Efficacy ...................................................................................... 10

  1.2.4 Safety .......................................................................................... 10

1.3 Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomized, placebo-controlled, multicentre trial ........................................... 10

  1.3.1 Inclusion, exclusion criteria and Patients .................................. 11

  1.3.2 Efficacy ...................................................................................... 11

  1.3.3 Safety .......................................................................................... 11

1.4 Ocrelizumab: A B-cell depleting therapy for multiple sclerosis ............... 11

1.5 The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects ............................................... 12

Discussion ............................................................................................... 12

  Method discussion .............................................................................. 12

  Diagnosis .............................................................................................. 12

  Mechanism .......................................................................................... 13

  Pregnancy .............................................................................................. 13

  Result discussion .................................................................................. 13

  Safety ...................................................................................................... 14
Expenditure
Future of treatment
Conclusions
Acknowledgement
References
Introduction

Multiple sclerosis (MS) debuts between the ages 20 to 45 years old and statistics show that more women become ill with MS than men. The prevalence in Sweden is 190/100 000, which equals 20 000 individuals living with MS. Meanwhile the incidence is 10 per 100 000 and that is the equivalent to 900 persons falling ill yearly. Symptoms caused by the disease vary depending on the location of the autoimmune reaction and development of plaques. (4)

MS is an autoimmune, inflammatory disorder that affects the central nervous system (the brain and the spinal cord) (2). The disease causes the rise of inflammations and scars on the nerves which effect the signalling paths of the central nervous system (CNS) (1).

Multiple sclerosis can be caused by the following various factors; genetic, immunologic and vitamin D deficiency. When comparing to MS incidences in Asia Australian studies have shown an inverse association between exposure to sun and risk for development of multiple sclerosis (4). Data from a randomized clinical study asserts an association between high vitamin D levels (>50 nmol/L) and reduced MS-activity (4,14). Similarly, Swedish studies present data confirming individuals with vitamin D deficiency have a higher risk of developing MS. Some studies have been able to prove improvement of life quality with usage of vitamin D supplements (38). Genetic factors include transmutation of human leukocyte antigens (HLA) locus on chromosome 6(4).

The nervous system consists primarily of neurons and glial cells. The glial cells main function are structural support and insulation, while neurons are the nervous system’s signalling cells that convey information back and forth in the CNS. Neurons consists of cell body, axon and dendrites; around every axon, there is a protective shaft called a myelin sheath (17). Myelin is composed of protein-lipid layers that spiral around the axon with the purpose to insulate and increase electric conductance (11). There are multiple types of glial cells: oligodendrocytes and Schwann cells. Oligodendrocytes produce myelin in the central nervous system, while Schwann cells produce myelin in the peripheral nervous system (29).

In multiple sclerosis patients, the immune system starts to attack the myelin encasing the axons (2,12). (See figure 1). The cells behind the demyelination and autoimmune reaction are T- and B-cells. B-cells matures in the bone marrow while T-cells mature in the thymus. Every immune cell undergoes recognition of self-peptides before becoming activated (3). The immune cells in MS patients lose their tolerance to self-proteins. Most recent studies indicate polymorphism in the genes encoding for inflammatory cytokines interleukin-2 (IL-2) and interleukin-7 (IL-7) cytokines that are responsible for activating and regulating T-cell mediated responses. (2)

The disease takes time before surfacing due to the function of regulatory T-cells (T_{Reg}-cells). T_{Reg}- cells inhibit and decrease the inflammatory process. This gives oligodendrocytes time to recover and heals the damage caused to myelin in a process called remyelinating. In time, as the disease progresses, the damage intensifies and becomes irreversible ending in the death of axons and termination of signalling pathways (4,29)

The autoimmune reaction is activated when T-cells bind to myelin antigens inducing the inflammatory process and demyelination of the protective sheath (See figure 1). The blood-brain barrier protects the central nervous system from cellular infiltration, nonetheless activated T-cells can express adhesion molecules and chemokines that make it easier for these cells to pass through the barriers. Activated T-cells secrete cytokines (IL-1, IL-6, TNF- Alfa, INF-gamma), inducing inflammatory processes and dilating the surrounding vessels to attract and increase the numbers of immune cells (B-cells and macrophages). Recent studies verify
that previously activated T-cells activate again when binding to major histocompatibility complex II (MHC II) presented antigens. Antibodies produced by B-cells bind and mark myelin sheath proteins, innate immune cells use antibodies marking the myelin to target and destroy the oligodendrocytes. This process leaves behind sciera (plaques) (3,12).

Multiple sclerosis is divided into four subtypes that differ from each other based on the disease course and symptoms (5).

1. **Relapsing-remitting MS (RRMS)**
   Periods of immune attacks happening with months or years of symptom free intervals. Symptoms improve after the attack thanks to remyelinating process; but the remyelinating is not complete, which leaves residual disability. With each attack the disease will worsen, and the demyelination becomes irreversible. What differs between this type of multiple sclerosis, and the others, is that between exacerbations there is no increase in disability (9). See figure 2.

2. **Primary progressive MS (PPMS)**
   PPMS is one constant immune attack on myelin proteins which causes steady disease progression (8). See figure 2.

3. **Secondary progressive MS (SPMS)**
   Similar to RRMS but in time the immune attacks become more persistent causing steady progression of disability (10). See figure 2.

4. **Progressive relapsing MS (PRMS)**
   One constant attack with periods super imposed which means the disease progression is even faster (30) See figure 2.

![Normal nerve cell](image1)

![MS affected nerve cell](image2)

Figure 1: Normal Nerve cell free of MS in Comparison to MS affected nerve cell. Demyelination can be seen in the MS affected nerve cell (38).
Diagnoses

MS diagnoses are based on medical history and neurologic clinical analysis, MRI and cerebrospinal fluid (CSF) analysis. Diagnosis is established after symptom evaluation is made to exclude differential diseases, neurologic loss in two lesions in the central nervous system and electrophoresis of CSF proving Oligoclonal IgG-bands (4).

Due to the disease effects on the CNS, it is better to diagnose with MRI images of the brain and spinal cord, than using clinical examination methods. MRI shows multiple lesion disseminated in space. MS diagnoses are based on findings of a minimum of two out of four MS-typical regions in CNS (4,28):

- Periventricular
- Juxta cortical
- Infratentorial
- Spinal

RRMS is diagnosed in the presence of two separate lesions disseminated in space that have occurred at different periods. PPMS is diagnosed by progression observation (retro- or prospective) over a minimum of a year with evidence of one of the following: brain lesion MRI of >1 t2-lesions, Spinal MRI-lesions >2 t2-lesions or electrophoresis of CSF confirming oligoclonal IgG-bands. After first diagnoses of subtype an assessment of following is made (4.28):

- Lapse period (secondary or primary progressive)
- Active or inactive disease
- Continuous evaluation of lapse period in case of sudden progression

Treatment

Swedish national guidelines for treatment of MS include disease-modifying medications for multiple sclerosis subdivisions. The guidelines cover treatment of exacerbations, children,
elderly, pregnancy and nursing, as well as treating MS symptoms (6). Currently, when this study was conducted there is no cure for MS, only medications that slow the progression of the disease and possibly prolong the life of the patient. The intention of treatment is to reach good control of the inflammatory activity and decrease exacerbations thus averting disease progression. Choice of treatment is based on the severity of the disease, progression, exacerbation and disease activity in addition to treatment of symptoms. The severity of MS is evaluated with the help of clinical tests and MRI (1, 4).

The intention is to further improve life quality of afflicted individuals (4,6). In Sweden, as recommended by National board of health and welfare- Socialstyrelsen (6). The available medications consist of the following groups: beta-interferons, immunosuppressants, and immunomodulating (1) (See Table 1). In March of 2017 there was a breakthrough in the search for effective medications and a new drug was approved for treatment of PPMS (4). See Table 2. Newest available treatment Ocrelizumab (Ocrevus) is a humanized CD20 antibody, the drug targets and selectively depletes surface antigen CD20 on B cells which decreases immunogenicity in MS patients (28).

Table 1: Table showing available medications in Sweden used for treatment of MS and how they are chosen for treatment (4, 13,15-16,18-27).

<table>
<thead>
<tr>
<th>Medication Group</th>
<th>Substance name</th>
<th>Product name</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>Interferon beta- 1a</td>
<td>Avonex</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Immunomodulation, immune stimulation</td>
<td>Glatiramer acetate</td>
<td>Capoxone</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Selective Immunosuppressive</td>
<td>Teriflunomide</td>
<td>Aubagio</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Effect on CNS</td>
<td>Dimethylfuran</td>
<td>Tecfidera</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Interferon</td>
<td>Interferon beta- 1b</td>
<td>Betaferon</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Interferon</td>
<td>Interferon beta- 1b</td>
<td>Extavia</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Interferon</td>
<td>Interferon beta- 1a</td>
<td>Rebif</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Interferon</td>
<td>Peginterferon beta- 1a</td>
<td>Plegridy</td>
<td>First Treatment</td>
</tr>
<tr>
<td>Selective Immunosuppressive</td>
<td>Natalizumab</td>
<td>Tysabri</td>
<td>Second Treatment</td>
</tr>
<tr>
<td>Selective Immunosuppressive</td>
<td>Fingolimod</td>
<td>Gilenya</td>
<td>Second Treatment</td>
</tr>
<tr>
<td>Selective Immunosuppressive</td>
<td>Alemtuzumab</td>
<td>Lemtrada</td>
<td>Third Treatment</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>Rituximab</td>
<td>Mabthera</td>
<td>PPMS</td>
</tr>
<tr>
<td>Selective Immunosuppressive</td>
<td>Ocrelizumab</td>
<td>Ocrevus</td>
<td>PPMS</td>
</tr>
</tbody>
</table>

Treatment is divided into three groups, the first is targeted towards moderate disease with moderate symptoms. The second treatment group has a better anti-inflammatory effect and is used when first treatment does not give the desired effect. The third line of treatment has the most potent effect yet comes with serious side effects (13). See table 2. Treatment choice is based on clinical findings and disease progression (6). Symptoms include paralysis with
spasticity, muscle pain, ataxia, and dysarthria. Sensory symptoms, fatigue, depression, affected cognitive ability and paroxysmal symptoms are not unusual in MS patients (4).

Until recently, treatments for primary progressive MS did not have the desired effect on the disease. No study has shown effect of interferon or glatiramer acetate treatment when treating primary progressive MS, while Rituximab had shown some effect on patients above 50 years old or with lesions visible on MRI (28).

**Pregnancy**
Fertile women should avoid pregnancy during treatment for MS as most medications have a risk of inducing fetus deformation or abortion. Hence conceiving should only occur 4 months after cessation of therapy (when using Lemtrada). These drugs should not be used when nursing, due to pharmacodynamic attributes enabling active molecules to cross into breastmilk and to the infant (4,13,15-16,18-28). During pregnancy the immune activity adjusts to maintain a healthy and risk-free pregnancy, which leads to decreased MS exacerbations on the mother. After pregnancy the exacerbations increase during the first three months after delivery (28). See table 2.

**Treatment expenditure**
Immunosuppressants are included in the Swedish health benefits system (Förmånsystemet). The medications included in the list are agreed upon by TLV in consideration of cost and benefit to the receiving patient. The cost for treatment one MS patient per year in Sweden is between 85 000-200 000 Swedish crowns, but health economical (Hälsoekonomiska) studies showed that medication cost is about 10% of the total disease expenditure (6-7). See table 7.

**Objective**
The aim of the project is to study the newly approved medication for multiple sclerosis including mechanism and effect. What are the pros and cons of the medication and how safe is it; how does ocrelizumab compare to other medication currently used for treatment.

- Multiple sclerosis; symptoms etc?
- What available treatments are out on the market and their effect in comparison to Ocrelizumab?
- Is the medication available in Sweden and is it included in the benefit system (Förmånsystemet)?

Table 2: Presentation of available drugs for treatment with indications, contraindications, and most common side effects associated with the medication. Data in this table is from FASS and internetmedicin, the categories A-D describe the risk on the fetus with A being adequate and well controlled studies the provided no fetus risk and D providing evidence of risk on fetus (13,15-16,18-27).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Pregnancy Category</th>
<th>Side effects</th>
<th>Contra indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex</td>
<td>RRMS</td>
<td>B:3</td>
<td>Headache, reduced lymphocytes, increase in Potassium levels, Vomiting, diarrhoea, Muscle cramps.</td>
<td>Depression, Pregnancy/nursing, Sensitivity to substance</td>
</tr>
<tr>
<td>Betaferon</td>
<td>RRMS, SPMS</td>
<td>D</td>
<td>Anaemia, hypothyroidism, confusion, tachycardia, elevated bilirubin levels, alopecia.</td>
<td>Depression, Pregnancy/nursing, Liver diseases</td>
</tr>
</tbody>
</table>
### Method
The information in this document was found using diverse databases, books available at Malmo city library and lectures from previous courses.

- PubMed was used for scientific articles with the application of filters to narrow the search and to only include specific up to date articles in this study. The articles where chosen based on the title and abstract with relevancy to my questions. See table 3.
- Robbins Basic pathology by Elsevier provided the detailed mechanism behind the disease. To search for information keyword Multiple sclerosis was looked up in the boom index.
- Läkemedelsverket and läkemedelsboken with keywords multiple sclerosis.
- FASS.se Swedish drug data base with information submitted by drug companies and approved by Swedish Medicine agency. Search used drug names from the medications used for multiple sclerosis treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Class</th>
<th>Conditions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extavia</td>
<td>RRMS, SPMS</td>
<td>D</td>
<td>Anaemia, hypothyroidism, weight gain, confusion, tachycardia, elevated bilirubin levels.</td>
<td>Depression, Pregnancy/nursing, Liver diseases</td>
</tr>
<tr>
<td>Rebif</td>
<td>RRMS</td>
<td>B:3</td>
<td>Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia, depression, insomnia,</td>
<td>Depression, Pregnancy/nursing, Sensitivity to substance</td>
</tr>
<tr>
<td>Plegridy</td>
<td>RRMS</td>
<td>B:3</td>
<td>Thrombocytopenia, alopecia, headache, fever, pain and irritation in application area, depression.</td>
<td>Depression, Pregnancy/nursing, Sensitivity to substance</td>
</tr>
<tr>
<td>Tysabri</td>
<td>RRMS</td>
<td>B:3</td>
<td>Urinary tract infection, nausea, headache, nasopharyngitis, Progressive multifocal leukoencephalitis.</td>
<td>Progressive multifocal leukoencephalitis, Malignity</td>
</tr>
<tr>
<td>Gilenya</td>
<td>RRMS</td>
<td>D</td>
<td>Infections with influenzas herpes virus, pneumonia, basal cell cancer, malign melanoma, lymphopenia, thrombocytopenia.</td>
<td>Patients with high infection risk, Liver failure, Cardiac diseases</td>
</tr>
<tr>
<td>Aubagio</td>
<td>RRMS</td>
<td>D</td>
<td>Infections, pharyngitis, oral herpes, laryngitis, neutropenia, anaemia, hypertonia, nausea, elevated ALAT.</td>
<td>Sensitivity to substance, Liver failure and Kidney failure, Nephrotic syndrome</td>
</tr>
<tr>
<td>Lemtrada</td>
<td>RRMS</td>
<td>B:3</td>
<td>Infections, insomnia, depression, nausea, hypotonia, elevated ASAT and ALAT, Hyperhidrosis, menorrhagia.</td>
<td>HIV, Active infection</td>
</tr>
<tr>
<td>Capoxone</td>
<td>RRMS</td>
<td>B:1</td>
<td>Infection, depression, anxiety, head ache, dyspnoea.</td>
<td>Sensitivity to substance</td>
</tr>
<tr>
<td>Tecfidera</td>
<td>RRMS</td>
<td>B:3</td>
<td>Gastritis, diarrhoea, leukopenia, elevated ALAT.</td>
<td>Sensitivity to substance</td>
</tr>
<tr>
<td>Mabthera</td>
<td>PPMS</td>
<td>C</td>
<td>Sepsis, Anaemia, Nausea, Cardiac infarction, Arrhythmia, Hypertension. Constipation.</td>
<td>Active infections, Acute immunosuppression</td>
</tr>
</tbody>
</table>
Table 3: Data search table showing the filters applied and how it affects the quantity of articles. Clinical trial filter was applied to filter away reviews and other short not original articles while publication date, 5 years, was used to only include the newest available and up to date studies (2-3, 11-12, 14, 30-36, 38).

<table>
<thead>
<tr>
<th>Keywords</th>
<th>No filter</th>
<th>Clinical trial</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis pathophysiology</td>
<td>13355</td>
<td>874</td>
<td>189</td>
</tr>
<tr>
<td>Multiple sclerosis disease pathophysiology</td>
<td>6940</td>
<td>299</td>
<td>54</td>
</tr>
<tr>
<td>Ocrelizumab multiple sclerosis</td>
<td>103</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Multiple sclerosis disease</td>
<td>36758</td>
<td>1397</td>
<td>311</td>
</tr>
<tr>
<td>Immune system and inflammatory process</td>
<td>12032</td>
<td>169</td>
<td>33</td>
</tr>
<tr>
<td>Multiple sclerosis treatment</td>
<td>35050</td>
<td>3091</td>
<td>712</td>
</tr>
<tr>
<td>Multiple sclerosis treatment metabolism</td>
<td>9180</td>
<td>745</td>
<td>156</td>
</tr>
<tr>
<td>Multiple sclerosis vitamin D</td>
<td>1149</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
<td>Immunosuppressive drug mechanism</td>
<td>13599</td>
<td>410</td>
<td>66</td>
</tr>
<tr>
<td>Neurons and glial cell function</td>
<td>55007</td>
<td>99</td>
<td>24</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>176</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

- *Fysiologi med relevant anatomi* by studenlitteratur book from a previous course attended by the author gives background facts about the physiology of the human body. This book was used for information about the nervous system.
- 1177.se public site with disease informative guides presenting a simpler approach to the disease directed to patients and their relatives.
- Medibas Swedish data base where specialists in their professions provide the newest available fact about the disease based on PubMed and other primary studies. Key words used were Multiple sclerosis. Articles referred to in the database were also used to provide further information and elevate the confidence in presented facts.

Results

1.1 Ocrelizumab versus Placebo in Primary Progressive multiple sclerosis
Montalban X et al. describes a randomized controlled multicentre trial on a large patient group (Phase III) where Ocrelizumab is compared to a placebo group. The trial was designed with double-blind treatment (5 doses). Randomisation is stratified based on geographic regions and each trial centre had their own independent and expert investigator who was blinded as to whom received placebo and Ocrelizumab. The investigators measured expanded disability status scale (EDSS) scores on centre patients. MRI scans were sent to MRI-centres for analysis by staff who were unaware of trial groups. After the randomized trial an open label extension (OLE) study was conducted with participants who completed the randomized trial. Patients who did not completed the OLE were included in the safety follow up. The trial follows international guidelines for good clinical practice and declaration of Helsinki (30).

1.1.1 Inclusion and exclusion criteria
The study had inclusion and exclusion criteria for patients. Participants in the study at the beginning were 732 patients diagnosed with primary progressive multiple sclerosis (PPMS). The patients had to be between the ages of 18 to 55 years. To be included they had to have a
score varying between 3.0 to 6.5 on the EDSS. EDSS has a score range from 0 to 10 and higher score indicates greater disability. Pyramidal function component of the functional system scale ranging from intervals 0 to 6 with a higher score indicating greater disability. The participants with disease diagnoses scoring <5 on the EDSS scale had to have been living with PPMS for 15 years or 10 years for patients with a score >5. Patients must have a documented elevated IgG index or IgG oligoclonal band in the cerebrospinal fluid (30).

Exclusion criteria included; relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, contraindications to MRI, contraindications to oral or intravenous glucocorticoids and previous treatment with B-cell targeting or immunosuppressants (30).

Participants received 100 mg Methylprednisolone through intravenous infusion before administration ocrelizumab, the intention of the administration was to counteract infusion related reactions. Patients received 600 mg ocrelizumab intravenously in two 300mg infusions 14 days apart or matching placebo. Infusions occurred with infusion adjustments to evade infusion related reactions (30).

1.1.2 Trial end points, statistical analysis and Patients

Montalban X et al. study lasted 120 weeks with two primary endpoints. The first endpoint was percentage of confirmed disability progression at week 12 in a time to event analysis. The secondary endpoint is change from baseline to week 120 in timed performance 25-foot walk (30).

Primary endpoint measured disability progression with increase in EDSS of at least 1.0 points or minimal baseline increase of 0.5 sustained for 12 weeks from baseline 5.5. Primary point with significance level of P<0.05 induced secondary point test (30).

Et al Montalban X was conducted between March 2011 to December 2012 with 732 participants who went through randomization. The randomization was based on demographic and disease characteristics to further balance the trial groups (see table 4).

Table 4: Et al Montalban X, this figure presents the total participant and how they were divided between drug and placebo groups, the percentage shows what percentage of the total assigned patients completed the 120-week trial and the duration of the trial (30).

<table>
<thead>
<tr>
<th>Participants</th>
<th>Total</th>
<th>Percentage</th>
<th>Weeks</th>
<th>Median trial duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocrelizumab</td>
<td>488</td>
<td>82%</td>
<td>120</td>
<td>2.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>244</td>
<td>71%</td>
<td>120</td>
<td>2.8</td>
</tr>
</tbody>
</table>

1.1.3 Efficacy

Disability progression in the primary endpoint in the ocrelizumab group was 32.9% versus 39.3 in the placebo, with a hazard ratio of 0.76; 95% confidence interval [CI], 0.95 to 0.98; relative risk reduction 24%; P= 0.03. (30).

In the first secondary endpoint patient disability progression (24-week) the percentage of ocrelizumab was 29.6% and 35.7% with placebo (hazard ratio, 0.75; 95% CI, 0.58 to 0.98; relative risk reduction, 25%; P = 0.04. In the second secondary end the change from baseline to week 120 in the timed 25-foot performance was 38.9% with ocrelizumab versus 55.1% with placebo (relative reduction with ocrelizumab, 29.3%; 95% CI, −1.6 to 51.5; P = 0.04. No significant change in the physical component summery score at the end of the 120-week trial (30).
Ocrelizumab infusion showed stabilization of CD4-expressing T cell levels during therapy. CD3+ or CD8+ cell count decreased in the peripheral blood by 2 to 6% from baseline at week 2 of treatment. Over the 2-120 weeks there was a further reduction by 6% in CD8-expressing cells. Placebo group expressed an increase in CD3+ or CD4+ cell with 4% to 5% at week 2. The treatment had no effect on natural killer cell and during the treatment, there was an increase of (CD16+ or CD56+) cells with 3% (30).

1.1.4 Safety

Adverse events (AE), in percentage for at least one AE, was 95.1% for ocrelizumab versus 90.0% with placebo. More serious reports of AEs in ocrelizumab was 20.4% and with placebo was 22.2%. Side effect in 100 patient years was not significantly different from placebo, Ocrelizumab group AEs was 260.5 [95% CI, 252.2 to 269.1] versus placebo 267.0 [95% CI, 254.7 to 279.8] (30). The infusion-related reaction was not so uncommon under the trial process, for patients who received at least one dose, Ocrelizumab infusion-related reactions were reported to be 39.9% compared to placebo with 25.5%. This lead to infusion modification to rate or interruption. There were no life-threatening AEs, but respiratory tract infections were higher in ocrelizumab participants with 10.9 versus 5.9 for placebo (30).

Montalban X. et al. reported five deaths under the trial that were considered not drug-related. In ocrelizumab, 0.8 % patients died of pulmonary embolism, pneumonia, pancreatic carcinoma and aspiration pneumonia, Placebo had one death related to a road traffic accident (30).

1.2 Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis

Hauser SL et al. describes a phase 3 trial over 96 weeks. The study was conducted in multiple centres, is a randomized, double-blind, double-dummy-active controlled and a parallel-group trial. The purpose of the trial is to compare two separate multiple sclerosis treatment effects on relapsing-remitting MS in two non-overlapping trial sites. Trial centres had separate examination investigators to conduct neurologic assessments, MS functional composite, EDSS and MRI analysis (31).

Participants were divided into 1:1 ratio to receive 600 mg ocrelizumab intravenously every 24 weeks as two 300 mg injections on day 1 and day 15 as the first dose and continuing with 600 mg throughout the trial. Interferon beta-1a was to be administered subcutaneously at a dose of 44 µg three times in a week over 96 weeks. Before administrations of drug patients received methylprednisolone 100 mg intravenously (31).

1.2.1 Inclusion and exclusion criteria

The inclusion age is between 18 to 55 years with Ms diagnoses and EDSS score from 0 to 5.5 and a minimum of two documented clinical relapses in previous 2 years or one in the previous year before MRI. Patients had to have had no disease deterioration in at least 30 days before the trial start. Exclusion criteria were a diagnosis of PPMS, earlier B-cell-targeted treatment or immunosuppression, sick with MS for more than 10 years and low EDSS <2 scores at screening (31).

1.2.2 Trial end points and Patients

The primary endpoint is the annual relapse rate at week- 96 to follow patient response to the drug. The Secondary endpoints were disability progression by week 12 in time to event analysis and gadolinium-enhanced lesions in the brain on MRI at 24, 48, and 96 weeks (31).
Hauser SL et al. had 1656 participants that were randomized into two groups, OPERA I with 821 patients and OPERA II with 835 patients. The groups then where divided into subgroups with ocrelizumab and interferon beta-1a in each subgroup (see table 5). Both groups were similar in demographic and disease characteristics. The percentage of patients completing the 96-week trial was in OPERA I 89.3% in ocrelizumab group and 82.7% in interferon beta-1a group. Meanwhile, OPERA II had 86.3% in ocrelizumab versus 76.6% in interferon beta-1a complete the trial (31).

Table 5: Hauser SL et al. Participants included in the randomization, with trial sites and countries where the study was conducted and trial duration (31).

<table>
<thead>
<tr>
<th></th>
<th>Ocrelizumab</th>
<th>Interferon beta-1a</th>
<th>Trial sites</th>
<th>Countries</th>
<th>Duration from - to</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPERA I</td>
<td>410</td>
<td>411</td>
<td>141</td>
<td>32</td>
<td>31-08-2011 - 12-02-2013</td>
</tr>
<tr>
<td>OPERA II</td>
<td>417</td>
<td>418</td>
<td>166</td>
<td>24</td>
<td>20-09-2011 - 28-03-2013</td>
</tr>
</tbody>
</table>

### 1.2.3 Efficacy

OPERA I trial MRI, clinical and reported patients’ outcome in yearly relapse rate was 0.16 in ocrelizumab in comparison to 0.29 in interferon beta-1a. OPERA II reports of yearly relapse rate at 0.16 in ocrelizumab versus 0.29 in interferon beta-1a group. The rating result indicates a decrease of 46% with ocrelizumab in OPERA I compared to 47% decrease in ocrelizumab group in the OPERA II, P<0.001 for both trial comparisons. Progression in disability was confirmed in the ocrelizumab groups (31). See table 6.

Table 6: Hauser SL et al. Disability progression at week-12 in a pooled trial with total participants in both ocrelizumab and interferon beta-1a groups with progression percentage, risk, hazard ratio, confidence interval and p-value (31).

<table>
<thead>
<tr>
<th>Week 12</th>
<th>Pooled trials</th>
<th>P – value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ocrelizumab</td>
<td>Interferon beta-1a</td>
</tr>
<tr>
<td>Participants</td>
<td>827</td>
<td>829</td>
</tr>
<tr>
<td>Percentage</td>
<td>9.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Risk</td>
<td>40% lower in ocrelizumab</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.60 (0.45 to 0.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>

### 1.2.4 Safety

Reports of adverse events in OPERA I group ocrelizumab was 80.1% (327 of 408) versus 80.9 (331 of 409) in interferon beta-1a group. In OPERA II trials the percentage in ocrelizumab was 86.3% (360 of 417) and 85.6% (357 of 417) in interferon beta 1-a. Most reported AEs were infusion-related reactions, upper respiratory infections, urinary infections, headache, and nasopharyngitis in ocrelizumab groups. Meanwhile, interferon beta 1-a reported AEs were injection-site erythema, urinary tract infection, headache, upper respiratory tract infection, and influenza-like illness (31).

### 1.3 Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomized, placebo-controlled, multicentre trial

Ludwig Kappos et al. describes a phase 2, randomized, placebo-controlled study conducted in multiple centres. The objective of the trial was to assess drug efficacy and safety with two dose regimes of ocrelizumab, a low dose 600mg and high dose 2000mg with trial ongoing for 48 weeks. The drug was administered on day 1 and 15. The primary endpoint of the trial was the
The total number of gadolinium enhancing lesions and T1-weighted MRI at week 12, 16, 20, and 24. The trial follows international guidelines for good clinical practice and declaration of Helsinki with a written consent from participating patients. The participants received ocrelizumab dose in two infusions 600mg with two 300mg and 2000mg with two 1000mg intravenous administrations (32).

### 1.3.1 Inclusion, exclusion criteria and Patients

The trial was carried out in 79 centres spread over 20 countries with an international multicentre RCT, parallel, double-blind, placebo-controlled, dose-finding ocrelizumab trial. In the international trial, 58 participated from North America, 120 from central Europe, 34 from western Europe, and 8 from Latin America. Participants were aged 18-55 years with confirmed RRMS and had documented relapses in the previous three years before screening, EDSS score of 1-6, MS inflammatory disease activity in 6 T2 lesions or more per MRI. Exclusion criteria were diagnosis with PPMS or SPMS, more than 15 years disease duration and EDSS score <2. (32).

The study had 273 patients screened for eligibility who then were randomly assigned to different groups, Ocrelizumab 600 mg had 56 patients compared to placebo with 54, ocrelizumab 2000 mg had 55 participants in comparison to interferon beta-1a with 55 patients. All patients received methylprednisolone 100 mg half an hour before each infusion (32).

### 1.3.2 Efficacy

Relapse rates during the 24 weeks were lower, 80% in 600mg ocrelizumab group with 95% CI 45–99 than in placebo. In the high dose ocrelizumab (2000mg) relapse was 73%, lower than placebo. GEL was lower in both high and low dose ocrelizumab in comparison to placebo with p-value P<0.0001. MRI t2 lesions volume had no significant changes. Ocrelizumab in comparison with interferon beta-1a showed lower disease activity (32).

Low-dose ocrelizumab resulted in decreased relapse rate in comparison with high-dose. Low-dose ocrelizumab 600 mg had relapse rate 0.09, 95% CI 0.04–0.20 versus high-dose ocrelizumab 2000 mg group 0.28, 0.17–0.47. (32).

### 1.3.3 Safety

Drug safety was appraised at 2, 4, 8, 12, 16, 20, 24 and 48 weeks. Reported AEs were infusion-related reactions that were estimated to be mild to moderate. Infusion-related reaction in low-dose was 35%, 95% CI 22–47, high-dose 44%, 31–57 versus 9%, 2–17 in placebo (32).

### 1.4 Ocrelizumab: A B-cell depleting therapy for multiple sclerosis

Jakimovski D. et al. published a drug evaluation review on ocrelizumab effect in MS patients. Ocrelizumab targets CD20 IgG1 monoclonal antibodies. The drug has been proven to reduce immunogenicity when compared to chimeric monoclonal antibodies such as rituximab. When comparing the two drugs (ocrelizumab to rituximab) rituximab has shown that 6 out of 18 patients developed neutralizing antibodies whereas in ocrelizumab that occurred in only one patient (33).

The effect of ocrelizumab is dose-related. Depletion of B-cells at a dose administration of 200 mg/m² will lead to baseline recovery in 3 months from dose administration. A dose of 375mg/m² or 750mg/m² activates a persistent B-cell count to 12-months succeeding dose intervention. When comparing single dose versus double dose infusion, results showed that at 24 weeks B-cell count was higher in single dose infusion, hence the correlation between B-cell depletion and ocrelizumab dosage (33).
Comparison between ocrelizumab and baseline treatment (Interferon beta-1a) proved the effect of the new medication when treating MS patients. Ocrelizumab resulted in clear GEL reduction in comparison to Interferon beta-1a group and disability progression (33).

1.5 The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects

Sorensen PS. Et al.’s review of ocrelizumab effects based on clinical trials and how it affects MS treatment future was analysed. Ocrelizumab is a second generation humanized MAB. Previously ocrelizumab has been used in trials for other diseases such as; rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) but the trials have been suspended due to the high risk and low therapeutic benefit. The drug did not perform well when combined with methotrexate in RA patients or with glucocorticoids and mycophenolate mofetil in SLE. this therapy combination resulted in serious infections amongst RA and SLE patients (34).

In Ludwig Kappos et al. ocrelizumab was used as a monotherapy and resulted in lower GEL lesions in comparison to placebo population. The drug proved even to have lower GEL lesions when compared to interferon beta-1a treatment. The study even had an OLE at week 144 which confirmed a low annual relapse rate and minimal MRI activity. Most reported AEs with ocrelizumab treatment are infusion-related reactions (34).

Discussion

Method discussion

The search for drug information through mainly PubMed. The only difficulty faced when searching for the substance was finding clinical articles with relevance to multiple sclerosis. When searching for ocrelizumab clinical trials there are only 10 available clinical trials and out of these 10, only 3 were relevant to my literature study of more recent results. When searching for reviews I was able to find many reviews but due to the low number of clinical trials, most of them were reviewing the same studies. The similarity of the reviews and different authors coming to the same conclusion elevates the reliability of ocrelizumab efficacy.

Books and databases provided background information about multiple sclerosis and what we know today about the disease. To strengthen the quality and reliability of presented information multiple databases were used to confirm every written fact.

Based on the available information in 2018 this assay should give an idea of what we now know and a glimpse into CD20 therapies.

The study designs were randomized, double-blinded with geographic stratification. The trials were conducted internationally providing data from all over the world. Data were analysed by independent investigators with no knowledge of group assignments.

Data were analysed with time to event analysis, and intention to treat populations score, MRI scans and disability progression. the diversity in tests provides higher accuracy of drug efficacy. The population was aged between 18-55 with specific inclusion criteria. All trials had a declaration of interest and followed the international guidelines.

Diagnosis

Multiple sclerosis diagnoses are very extensive, ranging from clinical examination and tests to eliminate any differential diseases, to MRI and CSF electrophoresis assays. This broad form of diagnoses provides high and better diagnoses of the disease. In addition to clinical tests,
doctors measure electrical conductivity nerves to assess the damage caused to nerves and how
the patient’s body experiences sensation such as touch, sound, and light, etc (4,28).

**Mechanism**

Interferon beta is an endogenous cytokine with immunomodulating quality to decrease
exacerbations and disease progression. Interferon beta-1a medications such as Avonex exercise
their effect by binding to specific receptors on the surface of cells. This process initiates a
complex cascade of intercellular events resulting in interferon reducing markers, thus
decreasing inflammatory activity in the CNS (4,16).

Rituximab is a chimeric monoclonal anti-CD20 antibody that targets B-cells. The antibody
Fab-domain binds to CD20-antigen on B-lymphocyte and the Fc-domain induces b-cell lysis.
The mechanism induces cell apoptosis and leading to lower disease progression (4,16).

Ocrelizumab is a humanized monoclonal antibody which leads to depletion of CD20 B-cells,
Thus its immunosuppressive effect. CD20 depleting medications are proving to be the
treatment of the future as they have the best-documented effect in comparison to other MS
treatment (31-36).

**Pregnancy**

Fertile females should use effective contraceptives to avoid pregnancy during treatment with
ocrelizumab and continue with contraceptives up to 12 months after therapy termination. That
is due to the long half-life of the drug. The half-life of ocrelizumab is 33 weeks. Women should
avoid breastfeeding because of the study limitations on drug passage via breastmilk (36).

**Result discussion**

Ocrelizumab is a new compound that has been used in clinical trials for the past 10 years. The
oldest clinical trial found in the database PubMed is dated September 2008. The trial is a phase
I/II RCT, blinded and placebo-controlled rheumatoid arthritis. The substance did not provide
the wished results when treating RA and SLE hence the suspension of trials in those disease
groups (34-35).

Clinical trials of Ocrelizumab suggests effective therapy for multiple sclerosis. As of 2017 is has
been approved by the FDA and will soon be available in Europe and the rest of the world.
Montalban X et al, Hauser SL. et al. and Ludwig Kappos et al. have been able to confirm the
efficacy of ocrelizumab in patients with very significant results in comparison to placebo and
interferon beta-1a (30-34).

The trials provide no max dosage for the drug, the highest administrated dose was 2000mg
divided by two infusions. I would like to see more studies about dosage adjustments in the case
of kidney- and liver failure. No data is available for patients with other diseases in combination
with multiple sclerosis (32-36).

Multiple sclerosis has for a while only been connected to a T-cell mediated autoimmune attack
on myelin, but the confirmed efficacy of an anti-CD20 drug proves the role of B-cells in disease
activity. The drug is favourably better for patients than its chimeric sister rituximab due to the
low incidence of anti-drug bodies and the High benefit to risk profile (33-34).

Immunogenicity has been tested in patients at baseline and every 6th month after treatment
with the regard to drug antibodies. Out of 1311 participants treated with ocrelizumab, 12
patients showed drug antibodies and out of these only 2 had confirmed neutralizing antibodies.
This means that it is better to use ocrelizumab to avoid cultivation of drug antibodies that could
affect therapy outcome. Evaluation of efficacy assessment is not possible due to the low incidence in ocrelizumab groups (34,36).

**Safety**

Adverse events included neoplasms and infections in ocrelizumab group. Malignancies were higher in ocrelizumab therapy group in comparison to placebo. Therefore, it is important to scan MS patients for malignity risk factors before initiating therapy. Patients should undergo breast cancer screening and controls if it is impossible to avoid treatment. Patients with known malignancy shall therefore not be treated with ocrelizumab (32-36).

Infections were higher in the Ocrelizumab group when compared to placebo, which can be connected to the pharmacodynamics of the drug and its immunosuppressant characteristics. The infections were treatable without therapy termination. Ocrelizumab is contraindicated in patients with already suppressed immunity. Vaccination safety is not assessed on the trials and it is thus risky for MS patients to receive live attenuated vaccines, or inactivated vaccines until B-cell recovery (32-36).

Infusion-related reactions were counteracted by administration of methylprednisolone before ocrelizumab infusion. this leads to minimization of infusion-related reactions. According to the study, the reaction decreased in the following drug infusions and was most prominent at first administration of ocrelizumab (32-36).

Ocrelizumab safety in long-term treatment is yet to be assessed, this can be done with the help of AE reports done by patients and healthcare centres where the drug is administrated (32-36).

**Expenditure**

At the beginning of this literature study, there was no information on Ocrelizumab in FASS, but at the end of February 2018, I was able to find a FASS page and ATC code for the drug. Ocrelizumab is under the ATC group LA4AA selective Immunosuppressants, unlike its chimeric sister substance rituximab which is under ATC L01XC monoclonal antibodies (36).

The expenditure of ocrelizumab is in the same range as the other medications in the same ATC-group. The price presented in table 7 is for 300mg which means that a total cost for the first infusion will be 102 514 Swedish crowns. this total will double at the next infusion of 600 mg 6 months later.

Table 7: This table present the expenditure of treatments and ATC-group codes. The prices are provided by Lloyds pharmacy in Malmo and ATC- groups from FASS.se (15-16,18-27, 36).

<table>
<thead>
<tr>
<th>Drug name</th>
<th>ATC-group</th>
<th>Cost (SEK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mabthera</td>
<td>L01XC02</td>
<td>3908</td>
</tr>
<tr>
<td>Rebif</td>
<td>L03AB07</td>
<td>6164</td>
</tr>
<tr>
<td>Extavia</td>
<td>L03AB08</td>
<td>6424</td>
</tr>
<tr>
<td>Betaferon</td>
<td>L03AB08</td>
<td>6600</td>
</tr>
<tr>
<td>Aubagio</td>
<td>L04AA31</td>
<td>7103</td>
</tr>
<tr>
<td>Avonex</td>
<td>L03AB07</td>
<td>8532</td>
</tr>
<tr>
<td>Gilenya</td>
<td>L04AA27</td>
<td>15 838</td>
</tr>
<tr>
<td>Tysabri</td>
<td>L04AA23</td>
<td>15 838</td>
</tr>
<tr>
<td>Ocrevus</td>
<td>L04AA36</td>
<td>51 257</td>
</tr>
<tr>
<td>Lemtrada</td>
<td>L04AA34</td>
<td>67 317</td>
</tr>
</tbody>
</table>
The high expenditure of ocrevus will mean that not every patient is going to receive this therapy. Ocrevus might be reserved only for PPMS treatment or when baseline therapy fails in the other subtypes.

**Future of treatment**
Ocrelizumab has a high probability of being an alternative for treatment by rituximab, natalizumab, and alemtuzumab due to its efficacy and low risk.

This therapy opens the way for better life quality for progressive primary multiple sclerosis patients. Ocrevus ability to cross the blood-brain barrier would mean better effect for treatment of PPMS. In trials, Ocrelizumab had a confirmed lower rate than the placebo group. Patients on ocrevus had a 25-foot walk worsening percentage of 38.9% versus 55.1 for placebo; similarly, MRI lesions decreased by 3.4% compared to increase of 7.4% in the placebo (30).

The vast improvement differences between groups prove the importance of this therapy for PPMS and other patients that have had no improvement from their early therapy.

**Conclusions**
In recent years monoclonal antibodies have proven their impact on disease progression. Ocrelizumab proved to be a promising new treatment for MS, especially for PPMS patients. These patients have very few treatment choices, only rituximab.

In the trials of ocrelizumab, the results confirmed the superiority of the substance to placebo and interferon-beta 1a treatment with moderate AEs. Ocrelizumab has undergone a phase I-III trials and been approved by the FDA in 2017 and now is available for phase IV and post marketing trials.

The drug is effective even when compared to baseline treatment. The effect of ocrelizumab proved to be more effective with lower disease progression. Despite the reported AEs, the drug is very therapeutically beneficial for MS treatment with lower disability progression, MRI, and clinical Recidivism.

This breakthrough in the treatment of MS is going to pave the way for newer and even more effective and individualized therapy for patients that to this day did not have an effective and safe drug with disease slowing capacity.

**Acknowledgement**
I would like to extend my thanks to my research mentor for his support, fast response and constructive critics. I would like to thank my family and fiancéd for their support and help.
References

1. Peter Tuominen, Multipel skleros – MS, 1177.se
   Available from: https://www.1177.se/Skane/Fakta-och-rad/Sjukdomar/Multipel-skleros--MS/.
   [Published: 2017-01-31] [Quoted: 2018-01-18]


5. Types of MS. National multiple sclerosis society
   Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS
   [Quoted: 2018-01-20]

6. Läkemedelsverket. Läkemedelsbehandling av multipel skleros (MS)-behandlingsrekommendation. Läkemedelsverket.se
   Available from: https://lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/Lakemedelsbehandling_av_multipel_skleros_MS_beachandlingsrekommendation_webb.pdf [Published: 2016-06] [Quoted: 2018-01-19]

7. Läkemedelsboken, Multipel skleros,
   Available from:

   Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS [Quoted: 2018-01-20]

   Available from: https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS [Quoted: 2018-01-20]


24. FASS. Lemtrada. Available from: 
http://www.fass.se/LIF/product?userType=0&nplId=20121223000012#side-effects 
[Quoted: 2018-01-30]

25. FASS. Aubagio. Available from: 
http://www.fass.se/LIF/product?userType=0&nplId=20120228000034#contraindication
[Quoted: 2018-01-30]

26. FASS. Copaxone. Available from: 
http://www.fass.se/LIF/product?userType=0&nplId=20040312000057#side-effects 
[Quoted: 2018-01-30]

27. FASS. Tecfidera. Available from: 
http://www.fass.se/LIF/product?userType=0&nplId=20120328000057 [Quoted: 2018-01-30]

28. Läkemedelsverket. Läkemedelsbehandling av multipel skleros (MS)- 
Backgrunds dokumentation. Läkemedelsverket.se Available from: 
https://lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/bakg_dok/Lakemedelsbehandling_av_multipel_skleros_MS_bakgrundsdocumentation_webb.pdf [Published: 2016-06] [Quoted: 2018-01-19]

29. Abul K. Abbas, Andrew H, Lichtman, shiv Pillai. Cellular and molecular immunology, 

Giovannoni G, Hartung HP, Hemmer B, Lublin F, Rammohan KW, Selmaj K, 
Traboulsee A, Sauter A, Masterman D, Fontoura P, Belachew S, Garren H, Mairon N, 

Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, 

32. Ludwig Kappos, David Li, Peter A Calabresi, Paul O’Connor, Amit Bar-Or, Frederik 
Barkhof, Ming Yin, David Leppert, Robert Glanzman, Jeroen Tinbergen, Stephen L. 

Opin Biol Ther. 2017 Sep;17(9):1163-1172.


36. FASS. Ocrevus Available from:
http://www.fass.se/LIF/product?userType=0&nplId=20160427000077 [Quoted: 2018-02-25]


Figure