An update on cladribine for relapsing-remitting multiple sclerosis

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Abstract

Introduction. Despite recent progress, currently available therapies for relapsing remitting multiple sclerosis (MS) are only partly effective, and their use is limited by tolerability and safety issues, as well as high cost. Cladribine was originally rejected by the regulatory authorities in both the European Union and USA in 2011, but in June 2017 the European Medical Agency recommended marketing authorization for treatment of aggressive relapsing MS.

Areas covered. We provide an update on chemistry, mechanism of action, efficacy and safety of cladribine for the treatment of MS.

Expert opinion. Cladribine is well tolerated, it is dosed orally in cycles of one year, the need for regular blood testing during treatment is likely limited, and the two-year efficacy data for treatment of relapsing MS are at least in the same range as the most efficient licensed treatments. The increased risk of malignancies reported in the pivotal trial seems to be caused by unexpectedly low numbers of malignancies in the placebo group. Cladribine could therefore be an alternative for many patients with relapsing remitting MS. The main caveat is the lack of long term efficacy and safety data. Currently there are insufficient data to guide further treatment of patients who have completed two treatment cycles of cladribine.

Keywords

Multiple sclerosis, cladribine, treatment, review

1.Introduction

The number of people living with multiple sclerosis (MS) increased from 2.1 million in 2008 to 2.3 million in 2013 [1] . Immunomodulatory drugs are used to prevent relapses and disability progression mainly in the relapsing forms of the disease, and are most effective if started early when the inflammation mediated by migration of lymphocytes across the blood-brain barrier is most pronounced [2]. In these patients, drugs usually dominate cost of illness, whereas informal care and production losses dominate during advanced disease [3]. Drug costs and access to MS treatment is highly variable, and immunomodulatory treatment is still unaffordable for many MS patients, even within the European Union [4].

Cladribine for the treatment of MS was reviewed in 2013 [5], after the drug was rejected by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Merck later filed a new application to EMA based on additional clinical data, and in June 2017 EMA recommended marketing authorization. Another review is therefore relevant.

2. Overview of the market

More than 10 therapies are available for the treatment of relapsing remitting MS (RRMS) [6,7]. There are however, important unmet needs, in particular for those approximately 50% of MS patients having progressive disease forms. The B cell depleting monoclonal antibody ocrelizumab has shown some efficacy also in primary progressive MS [8], and was recently approved as the first treatment for this subtype of MS by FDA. The effect on disease progression was however modest, and so far no drugs are approved for secondary-progressive MS.

For RRMS, drugs with an improved balance between efficacy, side effects and cost are still needed. The injectable drugs interferon beta-1a and -1b, peginterferon beta-1a and glatiramer acetate are safe, but have limited efficacy and are often poorly tolerated [6,7]. The monoclonal antibodies natalizumab, alemtuzumab, daclizumab and ocrelizumab have more pronounced efficacy and are often better tolerated. Their use is, however, restricted by serious adverse effects such as progressive multifocal leukoencephalopathy (PML) for natalizumab [9], secondary autoimmunity and opportunistic infections including fatal cases of listeriosis for alemtuzumab [10,11], and liver damage for daclizumab [12]. Among the oral drugs teriflunomide and dimethyl fumarate have an efficacy that is comparable to the injectables,

whereas fingolimod is more effective [6,7]. The advantage of oral administration is, however, to some extent outweighed by the need for frequent blood sampling, tolerability issues, and for dimethyl fumarate and fingolimod also opportunistic infections, including PML that is possibly related to lymphopenia [13,14]. Most immunomodulatory drugs lose their effect rapidly when stopped, and severe rebound disease activity has been reported for natalizumab and fingolimod [15,16]. MS preferentially affects young women, and none of the drugs can be recommended unconditionally during pregnancy [17]. There is thus a need for drugs with high efficacy, safety and tolerability, and with prolonged clinical effect that can protect women when trying to become pregnant as well as during pregnancy.

For many MS patients across the world an affordable treatment is the most obvious unmet need. The costs of drugs for MS has accelerated more than comparable treatments for other diseases [18]. The introduction of generics has so far not reduced prices substantially, possibly because there are too few generics on the market [19].

2. Introduction to the compound

2.1 Chemistry

Cladribine is a small molecular drug with a molecular weight of 285.687 g/mol and belongs to the group of chemotherapeutic agents known as antimetabolites. The chemical name is 2-chloro-2'-deoxyadenosine (2CdA) ($C_{10}H_{12}ClN_5O_3$). It is a purine analogue that mimics the nucleoside adenosine. It is phosphorylated by deoxycytidine kinase to 2-chloro-2’-deoxy-ß-D-adenosine monophosphate (2-CdAMP). CdAMP is resistant to deamination by adenosine deaminase. Since there is little deoxynucleotide deaminase in lymphocytes and monocytes, the metabolite accumulates intracellularly and is converted into the active triphosphate deoxynucleotide,2-chloro-2’-deoxy-ß-D-adenosine triphosphate (2-CdATP), leading to cell death [20].

2.2 Pharmacodynamics

Cladribine differs structurally from deoxyadenosine by the presence of a chlorine atom at position two the purine ring. This results in resistance to degradation by adenosine deaminase and a more prolonged cytotoxic effect against resting and proliferating lymphocytes. Cladribine passively crosses the cell membrane and is phosphorylated by deoxycytidine kinase [21]. The ratio of deoxycytidine kinase to deoxynucleotidase is high in lymphocytes and monocytes, leading to phosphorylation to the active compound triphosphate deoxynucleotide, 2-chlorodeoxyadenosine-ATP. Cells with high levels of deoxynucleotides are unable to repair single-strand DNA breaks, leading to subsequent DNA damage and cell death. Cladribine thus induces a rapid and prolonged decrease in circulating B and CD4+ T-lymphocytes [22,23], including both resting and dividing cells [24]. It was early reported that B cells are particularly sensitive to cladribine [25]. Notably, oral cladribine in doses used in clinical trials suppressed CD19 B cells by 70-90% with repopulation to 15-20% of baseline values before redosing, suppression of CD4 and particularly CD8 T cells were much less pronounced [26,27]. . Thus, memory B cells have recently been suggested to be particularly important for disease control in MS, including during treatment with cladribine [26,27]. Because of its cytotoxic effect on lymphocytes, cladribine is used in cancer therapy and is indicated against Hairy Cell Leukemia and B-cell chronic lymphocytic leukemia [28]

It has been suggested that cladribine also exert effects independently of deoxycytidine kinase activity and cell proliferation. Thus, it has been shown in vitro that cladribine exposure may prevent T cell activation and proliferation also in the presence of deoxycytidine, which allows T cells to survive in the presence of cladribine [29]. The clinical importance of this observation is uncertain, particularly as the clinical effect of cladribine (table 1) persists for many months after clearance of the drug [30]. Moreover, In a recent study cladribine did not impair proliferation in surviving mononuclear cells, but rather induced an anti-inflammatory cytokine profile with increased IL4/INF-gamma ratio and a trend towards increased IL-10 production [31].

Although the clinical effects of cladribine are mainly attributed to the effects on lymphocytes, other mechanisms may also operate. It has thus been suggested that induction of interferon alpha producing myeloid dendritic cells could account for some of the effects in MS [23].In the experimental autoimmune encephalomyelitis (EAE) model of MS cladribine interferes with the synaptic effects of IL-1beta, indicating that it could also have neuroprotective properties independent of its effects on peripheral lymphocytes [32].

2.3 Pharmacokinetics and metabolism

The bioavailability of cladribine is 100% when administered intravenously and 37-51% when given orally [21]. A bioavailability of 45.6% when administered without food and 40.5% when administered with food was recently reported in MS patients. The half- life is 5.7 to 19.4 hours and distribution volume varies from 54 to 357 L/m2. Protein binding is 20% [21]. The concentration in cerebrospinal fluid (CSF) is 25 % of that in plasma in patients without central nervous system disease, and exceeds the plasma level in patients with meningeal disease. [21]

About 18% of the administered dose has been reported to be excreted in urine in patients with solid tumors. The major catabolite measured in plasma and urine, 2-chloroadenine, has also been shown to be cytotoxic *in vitro*, although less so than cladribine [33]. About five times more 2-chloroadenine were measured in urine after oral compared to intravenous administration, and it has been suggested that this metabolite may contribute to the clinical effect after oral administration of cladribine. [33] Renal clearance of cladribine seems to be correlated with creatinine clearance, with a decrease of 19% and 40% in patients with mild and severe renal impairment respectively [34].

3. Clinical efficacy

3.1. Parenteral administration

There has never been a true phase I study of cladribine in MS. Safety and dose finding decisions have been based on studies of patients with malignancies [35,36]. From these studies and previous clinical experiences, Sipe and colleagues initiated a pilot study of four patients with progressive MS with intravenous cladribine in 1990 [36-39].

The results of clinical studies are shown in Table 1. The promising pilot results triggered the first randomized study to evaluate the efficacy and safety in MS in 1992, with 51 patients and crossover design [37,38]. The inclusion criteria were defined as clinically definite or laboratory supported definite MS according to the Poser criteria [40], with chronic progressive disease for more than 2 years [37,40]. The baseline mean EDSS was 4.6 and 4.7, and mean age 42.7 and 43.0 years in the placebo and cladribine group respectively. The authors have later stated that most patients had relapses, and thus secondary progressive MS [36,41]. The study population was matched according to age, sex, and disease severity into pairs of patients, and randomized to receive 4-monthly doses of one week with 0.10 mg/kg/day (a total dose of 2.8 mg/kg) or placebo the first study year. In the second year the original cladribine patients received placebo, and the original placebo patients were crossed over to cladribine 0.10 mg/kg for 7 days in month 1 and 0.05 mg/kg for 7 days during months 2 and 3 (total dose 1.4 mg/kg), followed by 7 days of placebo in month 4. The cladribine dose was thus 50% of that given to the cladribine arm the first year [38,39]. Results from the first year showed highly significant clinical effects of cladribine 2.8 mg/kg as measured by the Scripps Neurologic Rating Scale (SNRS) and the Extended Disability Status Scale (EDSS) scores. Analyses of the patient pairs revealed a treatment effect in favor of cladribine after 12 months as evaluated by both EDSS ($p<0,004$) and SNRS ($p<0.001$) [37]. Time to EDSS progression of 1 ($p=0.012$) or 1.5 ($p=0.024$) steps, and SNRS progression by a loss of 10 ($p=0.004$) or 15 ($p=0.009$) points during the first year was lower in the cladribine arm compared to placebo [39]. The findings were confirmed by reduction of contrast enhancing MRI lesions at month 12 (8 % among the patients in the cladribine arm compared to 50 % in the placebo arm; $p<0.001$) [39]. The effects on clinical outcomes were less pronounced during the second year at the lower dose of 1.4 mg/kg, possibly indicating a dose–response effect [36,39]. However, there was a highly significant reduction of contrast enhancing MRI lesions from month 12 (50 %) to month 24 (5 %) in the original placebo arm that received cladribine 1.4 mg/kg during the second year. None of the patients who received cladribine 2.8 mg/kg during the first year and placebo the during second year had contrast enhancing lesions at month 24, indicating a prolonged treatment effect [39].

A second phase II randomized, placebo-controlled, double-blind study included 52 patients with RRMS, who either received subcutaneous cladribine 0.07 mg/kg daily (n=27) at 5 consecutive days for 6-monthly courses (total dose 2.1 mg/kg) or placebo (n=25) for 18 months [42]. Patients should have a RRMS diagnosis for at least one year, at least two

relapses the preceding two years prior to inclusion, and a baseline EDSS score ≤ 6.5. Primary outcome measures were combined frequency and severity of relapses after one year, and the number of contrast enhancing MRI lesions at 12 monthly scans. Secondary outcome measures included change in EDSS and SNRS scores, and relapse rate and MRI disease activity after 18 months.

Cladribine treated patients experienced lower number and severity of relapses, with an estimated annual relapse rate from month 6 to month 12 at 0.77 compared to 1.67 in the placebo arm (p=0.021). The difference remained significant at month 18 (0.66 in the cladribine arm compared to 1.34 in the placebo arm; p=0.010). Cladribine treated patients also had fewer contrast enhancing MRI lesions at month 12 compared to the placebo group (p=0.0001). The difference was already present at month 7 (p=0.0001), and remained at month 18 (p=0.002). No differences were detected in the EDSS and SNRS scores [42].

A third cladribine study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group design study that evaluated the safety and efficacy of two subcutaneous cladribine doses in a population of progressive MS patients (70% SPMS and 30 % PPMS) [43]. Altogether 159 patients were included and received in total 0.7 mg/kg (n=53) or 2.1 mg/kg (n=52) cladribine or placebo (n=54). Treatment evaluation was performed after one year and was further planned for a 6-year open-label extension [43]. Patients were aged 21–60 years, had clinically definite or laboratory supported MS according to the Schumacher criteria [44] or Poser criteria [40]. They had a chronic progressive disease, defined as slowly progression of signs and symptoms over the preceding 12 months prior to inclusion, and a baseline EDSS score between 3.0 and 6.5. The primary outcome measure was the mean change in EDSS score from baseline to the final evaluation. Secondary outcome measures included mean change from baseline in SNRS score and time to progression (increase in EDSS score of ≥1.0 step for patients with baseline scores from 3.0 to 5.0 or ≥ 0.5 step for those with baseline scores from 5.5 to 6.5, confirmed at the next scheduled visit). Additional secondary outcome measures included the proportion of patients with contrast-enhanced T1-weighted MRI lesions at the final evaluation, the number and volume of enhanced T1-weighted lesions and volume of T2-weighted lesions.

The results revealed no differences in mean changes of EDSS and SNRS scores during the 12-month double-blind phase of the study. EDSS scores in the SPMS placebo subgroup increased modestly (0.3) compared to stable scores in the SPMS cladribine subgroups, but the difference was not statistically significant. Even smaller differences were found for the PPMS subgroups. A total of 33% of the patients in the SPMS placebo subgroup experienced EDSS progression, compared to 24% and 27% in the SPMS cladribine subgroups (not statistically significant). However, fewer patients had contrast-enhanced T1-weighted MRI lesions at month 12 in the cladribine 2.1 mg/kg arm (6 %; p=0.0017) and the 0.7 mg/kg arm (10 %; p=0.013) compared to placebo (32 %). The mean number and volume of contrast-enhanced T1-weighted MRI lesions were also lower in both cladribine arms at month 12 compared to placebo ($p<0.001$ for high dose and $p\leq0.004$ for low dose). The mean change in T2 lesion volume from baseline to month 12 was significantly lower in the cladribine high dose arm (p=0.040), but not in the low dose arm (p=0.055) compared to placebo [43].

Subcutaneous cladribine was also studied in a Polish crossover study that included 84 treatment-naive patients with relapsing MS [45]. The patients should have at least one contrast enhancing MRI lesion (timing not specified), EDSS score of 1.0–7.0, and no clinical relapse the last three months. Patients were randomized to receive seven courses of cladribine 5 mg daily for five consecutive days at month 1-6 and at month 9 or placebo the first year, and crossed-over for the same dosing regimen the second year. The mean dose for all patients was 2.45 mg/kg. The results showed a reduction in relapse rate during the first year in the cladribine group, and an improvement in EDSS score that were not sustained throughout the study period of two years. The original placebo group that received cladribine the second year did not experience reduction in relapse rate, but had stable EDSS score. MRI was not included as an efficacy endpoint [45].

3.2. Oral administration

Oral administration of cladribine was studied in the first phase 3 study in RRMS (CLARITY) [30]. This double-blind, multicenter, randomized study randomized 1326 patients to receive either cladribine 5.25 mg/kg (n=456), cladribine 3.5 mg/kg (n=433), or placebo (n=437) for 96 weeks from April 2005 to January 2007. The study medication was administered as four courses (4-5 days) during the first 48 weeks (week 1, 5, 9, and 13), and two courses during the next 48 weeks (week 48 and 52). Patients were aged 18–55 years, with RRMS according to the McDonald criteria [46], MRI lesions consistent with MS [47], at least one relapse during

the 12 months before study entry, EDSS score ≤ 5.5 [40], and normal hematologic status. The primary end point was relapse rate at 96 weeks. Main secondary efficacy endpoints included proportion of relapse free patients, time to 3 months sustained disability progression ≥ 1 EDSS step (≥ 1.5 steps if the baseline EDSS score was 0), mean number of gadolinium-enhancing T1-weighted MRI lesions per patient per scan; active T2-weighted lesions, and combined unique MRI lesions [30]. The results showed that cladribine reduced the annualized relapse rate at week 96 to 0.15 (0.12–0.17) for 5.25 mg/kg and 0.14 (0.12–0.17) for 3.5 mg/kg, compared to 0.33 (0.29–0.38) for placebo, corresponding to 58 % and 55% relative reduction respectively ($p < 0.001$ for both). More patients in the cladribine groups were relapse free (80 % for 3.5mg/kg and 79 % for 5.25 mg/kg versus 61 % for placebo; $p < 0.001$ for both). The risk for 3-month sustained disability progression was also reduced by about 30% in both cladribine arms (hazard ratio 0.67 [95% CI: 0.48, 0.93; $p = 0.018$] for 3.5 mg/kg and 0.69 [95% CI: 0.49, 0.96; $p = 0.026$] for 5.25 mg/kg). Clinical outcomes were confirmed by reductions in MRI activity in both cladribine arms (T1 gadolinium-enhancing lesions 86-88 %, active T2 lesions 73-77 % and combined unique lesions 74-78 %; $p < 0.001$ for all).

To assess the effect of another two years of oral treatment, an extension phase of the CLARITY study started in February 2008 [48]. After a variable treatment gap (median 40 weeks), patients in the cladribine arms were randomized to further treatment with either cladribine 3.5 mg/kg or placebo, and the original placebo patients received cladribine 3.5 mg/kg for another two years. The results have so far only been presented as abstracts. The annual relapse rate was 0.15 (97.5% CI 0.09-0.21) in patients treated with cladribine 3.5mg/kg in the original study and placebo in the extension study, and 0.10 (97.5% CI 0.06-0.13) in those who received cladribine 3.5mg/kg in both studies (P=0.059) [49]. The MRI findings support that effect of two years treatment is maintained over four years, although some disease activity recurs. Thus, the proportion of patients without gadolinium-enhancing lesions was 85.1-89.9 % in cladribine-treated groups in the extension study versus 73.0-80.2% in placebo-treated groups. The respective proportions without active T2 lesions were 37.6-43.7% and 27.6-34.4%. The mean numbers of new gadolinium-enhancing lesions/subject/scan were lower (0.03±0.08) in patients treated with cladribine 3.5mg/kg in both studies than in those treated with cladribine 3.5mg/kg in CLARITY and placebo in the extension study (0.28±0.87; $p<0.001$) [50]. As only 284 of the 433 originally cladribine 3.5 mg/kg treated patients were included in the extension study [30,49] the generalizability of the results could be questionable.

The effect on brain atrophy in the CLARITY study was recently reported [51]. To avoid confounding from pseudo atrophy, annualized brain volume change was assessed from months 6 to 24. This was significantly reduced in patients treated with cladribine 3.5 mg/kg (−0.77% ± 0.94%; p = 0.02) and 5.25 mg/kg (−0.77% ± 0.95%; p = 0.02) compared to placebo (−0.95% ± 1.06%)

Oral cladribine was examined in clinically isolated syndrome (CIS) in the ORACLE study [52]. In a double-blind, multicenter, randomized, phase-3 study, 204 patients received oral cladribine 5.25 mg/kg, 206 received oral cladribine 3.5 mg/kg, and 206 received placebo for pre-planned 96 weeks. The study medication was given as four courses (4-5 days) during the first 48 weeks (week 1, 5, 9, and 13) and two courses during the next 48 weeks (week 48, 52). Patients were aged 18–55 years, and had a first clinical demyelinating event within 75 days before screening, at least two clinically silent brain lesions of at least 3 mm on a T2-weighted MRI scan, and an EDSS score ≤ 5·0. A total of 616 patients were included from October 2008 to October 2010. Due to regulatory authorities expression of concern, Merck choose to stop further development of the cladribine-program and initiated early-termination of the study in October 2011, with the last patient visit in April 2012. The primary efficacy endpoint was time to conversion to clinically definite MS (second clinical event) according to the Poser criteria [40]. The main secondary efficacy endpoint was time to conversion to MS according to the 2005 McDonald criteria, meaning the time to a new MRI lesion or a second clinical event [53]. Secondary MRI endpoints included numbers of new or persisting T1 gadolinium-enhancing lesions and new or enlarging T2 lesions. Overall, 363 (59%) patients completed six treatment courses, and at the end of the study 149 (24%) patients had permanently discontinued treatment. The most common reasons for discontinuation were patient's decision, termination of the trial program, or a Health Authority or sponsor request to stop treatment.

Cladribine significantly delayed the time to conversion to clinically definite MS, with 62% risk reduction for 5.25 mg/kg (HR 0.38; 95% CI 0.25–0.58; p<0.0001) and 67% for 3.5 mg/kg (HR 0.33; 95% CI 0.21–0.51; p<0.0001) versus placebo. Cladribine also significantly reduced conversion to "McDonald MS" versus placebo; with 57% risk reduction for 5.25 mg/kg (HR 0.43; 95% CI 0.33–0.55; p<0.0001), and 50% risk reduction for 3.5 mg/kg (HR 0.50; 95% CI 0.39–0.63; p<0.0001). The cladribine high dose resulted in a 91 % risk reduction for new or

persisting T1 gadolinium-enhancing lesions, and 73 % for new or enlarging T2 lesions compared to placebo. The low dose resulted in 89 % risk reduction new or persisting T1 gadolinium-enhancing lesions and 79 % for new or enlarging T2 lesions compared to placebo.

Yet another study (ONWARD) was a phase 2 study of cladribine add-on therapy to IFN-beta [54]. The patients were aged 18 to 65 years and had definite RRMS or SPMS with superimposed relapses according to the revised 2005 McDonald criteria [53]. They should be treated with either of the available IFN-beta formulations (subcutaneous IFN-beta-1a or 1b, intramuscular IFN-beta-1a) and had experienced at least one relapse within 48 weeks prior to screening. The patients were randomized to add-on therapy with oral cladribine for 4-5 consecutive days at weeks 1, 5, 48, and 52 to a total dose of 3.5 mg/kg (n=124) or identical placebo (n=48) tablets during a double blind period of 96 weeks. The results have not been published in a full-length article, but preliminary data indicate lower mean number of relapses in the cladribine 3.5 mg/kg-IFN-beta arm (0.23) compared to the placebo- IFN-beta arm (0.54; $p<0.001$) [54]. The relapse rate was 0.13 in the cladribine 3.5 mg/kg-IFN-beta arm and 0.32 in the placebo- IFN-beta arm, and the corresponding mean number of T1 gadolinium-enhancing lesions per scan was 0.06 and 0.34 (statistical analyses not available). The frequency of lymphopenia seems to be unacceptable high (grade 3 or 4 lymphocyte toxicity were recorded in 63.7% in the cladribine 3.5 mg/kg-IFN-beta group and 2.1% in the placebo-IFN-beta group).

All patients who participated in one of the oral cladribine trials have been offered participation in a prospective long-term observational safety registry; The PREMIERE (PRospective observational long-term safEty registry of Multiple sclerosis patIEnts who have participated in CladRibinE clinical trials) registry) [55]. The registry started ten years recording in November 2009, and aims to evaluate the long-term safety of oral cladribine in MS. No results have so far been posted.

4.0 Safety and tolerability

4.1. Overview

The tolerability of oral cladribine in doses tested in MS seems to be very good [56]. In CLARITY, 86.6% of the patients in the cladribine groups and 86.3% of the patients in the placebo group completed the study [30]. Among the most common adverse effects, headache,

nausea, urinary tract infection and nasopharyngitis occurred in comparable frequencies in the placebo and cladribine groups. There were four deaths during the CLARITY study and two after study discontinuation, two in each treatment arm. Causes of death were acute myocardial infarction and metastatic pancreatic carcinoma in the cladribine 3.5 mg/kg arm, drowning and cardiopulmonary arrest, secondary to exacerbation of latent tuberculosis in the cladribine 5.25 mg/kg arm, and suicide and hemorrhagic stroke in the placebo arm. No deaths occurred in the ORACLE study [52].

4.2. Lymphopenia

Depletion of T- and B cells is a mechanism of cladribine [24,27]. In CLARITY cladribine rapidly decreased lymphocyte counts, which reached nadir at 3 – 4 weeks following the first treatment course [30]. Recovery was incomplete at week 48. At week 96 median lymphocyte counts were 56% of baseline values in the 3.5 mg/kg group and 52% in the 5.25 mg/kg groups. Median neutrophil counts at week 96 were 85% and 82% of baseline values in the 3.5 and 5.25 mg/kg groups, respectively. Grade 3 and 4 lymphopenia ($< 0.5 \times 10^9$ lymphocytes/l) were recorded in 25.6% patients in the 3.5 mg/kg group and 44.9% of patients in the 5.25 mg/kg group and 0.5% of patients in the placebo group, compatible with a dose-effect response [56]. Accordingly, in ORACLE lymphopenia occurred in 48 (24%) in the high dose, 25 (12%) in the low dose and none in the placebo arm [52], and was reported as a severe event in 10 (5%) patients in the 5.25 mg/kg group and four (2%) patients in the 3.5 mg/kg group. The effect on neutrophils was less pronounced.

4.3. Infections

An increased risk of opportunistic infections is expected from the high risk of pronounced lymphopenia associated with cladribine. Uppsala Monitoring Centre (UMC) has recorded 5 cases of PML associated with cladribine [57]. The reported indications for treatment were Waldenstrøm's macroglobulinemia (2 cases), hairy cell leukemia, aggressive systemic mastocytosis, and non-hodgkin's lymphoma. No cases of PML have been reported in the MS studies. In CLARITY infections occurred in 48.3% of patients in the cladribine groups compared to 42.5% in the placebo group. The vast majority (99%) of these were graded as mild or moderate [56]. Herpes zoster infections were reported in eight patients in the cladribine 3.5 mg/kg group and 12 patients in the 5.25 mg/kg group, and was inversely correlated with the lymphocyte counts (p=0.003). None herpes zoster infections were reported

in the placebo group. In ORACLE herpes virus infections were reported in 6 % in the high dose, 8 % in the low dose and 1 % in the placebo arm [52]. All cases of herpes infection in CLARITY were cutaneous, whereas three cases of systemic herpes zoster infection have been reported to UMC, again most likely in patients treated for malignancies. Three cases of tuberculosis are recorded by UMC, and one case of tuberculosis was reported in CLARITY.

4.5. Malignancies

Both interference with DNA repair and reduced tumor surveillance could in theory lead to increased risk of malignancies during treatment with cladribine. The effect of tumor surveillance is not routinely addressed in preclinical studies, but has been shown for fingolimod in a mouse model of myeloma [58]. Long-term mice studies revealed a significant increase in Harderian gland tumours, including adenocarcinomas. This was not considered clinically relevant, as humans do not have a comparable anatomical structure [59]. Cladribine also induced chromosomal effects in an *in vivo* bone marrow micronucleus assay in mice and also in an *in vitro* assay, and was mutagenic in mammalian cells in culture [28].

In CLARITY three malignancies (ovarial carcionoma, pancreatic carcinoma and melanoma) occurred in the cladribine groups, and none in the placebo groups during the study, and one case of choriocarcinoma occurred during post trial surveillance. Benign uterine leiomyomas occurred in 9 women in the cladribine groups and one in the placebo groups [56]. The risk of cancer (0.34%) was thus significantly higher in the cladribine groups than in the placebo groups. This was, however, likely driven by the unexpectedly low occurrence of cancers in the placebo group. A meta-analysis showed that the risk of malignancies in CLARITY was not different from that in other phase III studies in MS [60]. In ORACLE neoplasms (all types; benign; malignant; unspecified) occurred in one (<1%) patient in the cladribine 5.25 mg/kg arm, three (1%) in the cladribine 3.5 mg/kg arm, and six (3%) in the placebo arm [52].

5. Fertility and pregnancy

Whereas preclinical studies did not show effects on female fertility, cladribine induced lethal effects in the offspring of female mice at all stages during *in utero* development, and was clearly teratogenic in mice and rabbits [28,59]. The offspring of some male mice had skeletal deformities. EMA concluded that cladribine interferes with spermatogonial cells, implying a minimal risk of inheritable genetic damage after discontinuation of treatment for a period long enough for a new spermatogenetic cycle to achieve completion [59]. The data in humans are restricted to case reports. Pregnancy and lactation should be considered contraindicated during treatment. An official recommendation for the washout period after oral cladribine in doses relevant for MS is pending, but women and men treated with cladribine for malignancies are currently advised not to become pregnant or father a child until six months after the last dosing [28,61-63].

6. Regulatory affairs

Merck applied for market authorization in Europe in and in the United States in 2009 [63], but did not achieve regulatory approval. EMA expressed safety concerns, especially related to malignancies [64]. Moreover, EMA considered the efficacy not sufficiently well established in the subgroup of patients most likely to use cladribine. After the rejection Merck announced in 2011 to no longer pursue the global approval process for cladribine tablets [65]. However, since then more follow-up data on safety and efficacy have been collected through the ORACLE study [52], the Premiere Registry [54], the CLARITY Extension study [48] and meta analyses [60]. Merck submitted in 2016 a new application for marketing authorization for cladribine tablets for the treatment of MS [66]. In June 2017 the Committee for Medicinal Products for Human Use in EMA recommended marketing authorization for patients with highly active relapsing MS as defined by clinical or imaging features [61].

7. Conclusion

The efficacy of cladribine on relapse rate, MRI activity and EDSS progression over two years in RRMS, and the risk of conversion from CIS to RRMS, is well established [30,52]. Cladribine may be regarded as an induction therapy due to prolonged effect after clearance of the drug. The data from extension studies are however limited by risk of attrition bias, and some disease activity seem to recur. Moreover, data on cognition and patient reported outcomes, including fatigue and quality of life, are missing. The risk of serious adverse

events, including malignancies, do not seem to differ substantially from that of other drugs with comparable efficacy [60]. However, as for other immunosuppressive drugs a modest risk associated with prolonged treatment cannot be ruled out.

8. Expert opinion

No evidence of disease activity (NEDA) is an emerging goal in MS treatment [67]. NEDA can be defined in different ways. Including the proportion of patients with no relapses, no EDSS progression over six months (91%), no new gadolinium-enhancing T1-lesions (87%) and no new or enlarging T2 lesions (62%) after two years in CLARITY, the proportion of patients with NEDA at year two was 44% for 3.5 mg/kg and 46% for 5.25 mg/kg [68]. This is in the same range as recently reported with ocrelizumab (47.9% and 47.5% in OPERA I and II at week 96) [69], and possibly higher than for natalizumab (37%) [70], and alemtuzumab (32% in patients who had relapsed on first line treatment) [71]. These numbers must be interpreted carefully, as NEDA does not reflect important aspects such as fatigue, depression, quality of life or or brain atrophy [72]. In a two-year perspective, the efficacy of cladribine on routinely used outcome measures does however seem to be at least as good as the licensed monoclonal antibodies, and in the same range as B cell depleting treatment.

Given that several drugs have comparably high efficacy on clinical and radiological outcomes, safety, tolerability and cost may be decisive for the choice of treatment. Of the licensed drugs with comparable efficacy, natalizumab is also well tolerated but is associated with an unacceptably high risk of progressive multifocal leukoencephalopathy in JCV-positive patients, currently estimated to 6.1 per 1000 after 49 – 72 weeks treatment in patients without previous immunosuppression [73]. The risk of secondary autoimmunity associated with alemtuzumab is high [11], and there is also a growing concern regarding opportunistic infections such as cytomegaolvirus, nocardiosis and listeriosis [10,74-76]. As many MS patients are fertile women, disease protection during pregnancy and lactation is important in treatment decisions. Women are usually advised to stop immunomodulatory treatment before they conceive [17], and women treated with natalizumab and fingolimod may in such cases experience serious rebound disease activity [15,16]. Cladribine must be regarded as teratogenic and should be avoided the last months prior to and during pregnancy. However,

the sustained immunological effects including prolonged B cell depletion will offer protection against disease activity during pregnancy and lactation after the drug is cleared from the body, and are not likely harmful to the fetus. A reasonable washout period in both men and women treated with oral cladribine for MS needs to be established. Given the short half-life [21], a period of 6 months which is recommended after intravenous administration may be unnecessary long.

There are, however, caveats. Opportunistic infections occur, and as for other treatments leading to lymphopenia, rare cases of PML could also appear in MS patients [14], though the risk should be reasonably small given the minor effect of cladribine on the CD8+ T cell population [27].

Notably, the extension trials should be interpreted carefully due to the risk of attrition bias, and there is at present limited data to guide the treatment after year two. Although the extension trials indicate extended clinical efficacy beyond two years, some MRI activity seems to reoccur [50]. Thus, an increasing proportion of patients may also develop new clinical disease activity. The consequences of further cycles of cladribine, either for disease activity or safety are at present unknown. From the prolonged lymphopenia, one would however expect that repeated treatment will lead to prolonged immunosuppression, and thereby to increased risk of infections and possibly also reduced tumor surveillance.

The therapeutic landscape for relapsing MS is likely to change during the next five years. We expect that patients will be treated more actively at an earlier time in their disease course. B cell depleting therapies [26,77,78], and if randomized clinical trials confirm the effect suggested in observational studies [78], also autologous hematopoietic stem cell transplantation, may become standard treatments. The efficacy, tolerability and convenience could still make cladribine competitive. However, data that can guide clinicians and patients beyond two years of therapy, preferentially from a long-term trial, are needed.

References

1. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 2014; 83: 1022-1024.

2. Filippini G, Del GC, Clerico M, et al. Treatment with disease-modifying drugs for people with a first clinical attack suggestive of multiple sclerosis. Cochrane Database Syst Rev 2017; 4: CD012200.

3. Ernstsson O, Gyllensten H, Alexanderson K, et al. Cost of Illness of Multiple Sclerosis - A Systematic Review. PLoS ONE 2016, 11: e0159129. doi: 10.1371/journal.pone.0159129

4. Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. PLoS ONE 2017; 12: e0172753. doi: 10.1371/journal.pone.0172753

5. Comi G, Hartung HP, Kurukulasuriya NC, et al: Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis. Expert Opin Pharmacother 2013; 14: 123-136.

6. Wingerchuk DM, Weinshenker BG. Disease modifying therapies for relapsing multiple sclerosis. BMJ 2016, 354: i3518. doi: 10.1136/bmj.i3518

7. Torkildsen O, Myhr KM, Bo L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol 2016; 23 Suppl 1: 18-27.

8. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med 2017; 376: 209-220.

9. Major EO, Nath A. A link between long-term natalizumab dosing in MS and PML: Putting the puzzle together. Neurol Neuroimmunol Neuroinflamm 2016; 3: e235. doi: 10.1212/NXI.0000000000000235

10. Holmoy T, von der LH, Leegaard TM. Listeria monocytogenes infection associated with alemtuzumab - - a case for better preventive strategies. BMC Neurol 2017; 17: 65.

11. Willis MD, Harding KE, Pickersgill TP, et al. Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. Mult Scler 2016; 22: 1215-1223.

12. Giovannoni G, Kappos L, Gold R, et al. Safety and tolerability profile of daclizumab in patients with relapsing-remitting multiple sclerosis: An integrated analysis of clinical studies. Mult Scler Relat Disord 2016; 9: 36-46.

13. Ghadiri M, Rezk A, Li R, et al. Dimethyl fumarate-induced lymphopenia in MS due to differential T-cell subset apoptosis. Neurol Neuroimmunol Neuroinflamm 2017; 4: e340. doi: 10.1212/NXI.0000000000000340

14. Berger JR: Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord 2017; 12: 59-63.

15. Larochelle C, Metz I, Lecuyer MA, et al. Immunological and pathological characterization of fatal rebound MS activity following natalizumab withdrawal. Mult Scler 2016; 23:72-81.

16. Hatcher SE, Waubant E, Nourbakhsh B, et al Rebound Syndrome in Patients With Multiple Sclerosis After Cessation of Fingolimod Treatment. JAMA Neurol 2016;73:790-4

17. Coyle PK. Management of women with multiple sclerosis through pregnancy and after childbirth. Ther Adv Neurol Disord 2016; 9: 198-210.

18. Hartung DM, Bourdette DN, Ahmed SM, et al. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: Too big to fail? Neurology 2015; 84: 2185-2192.

19. Sorensen PS. Multiple sclerosis. Generic glatiramer acetate--a step toward cheaper MS drugs? Nat Rev Neurol 2016, 12: 5-6.

20. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet 1992;340: 952-956.

21. Liliemark J. The clinical pharmacokinetics of cladribine. Clin Pharmacokinet 1997; 32: 120-131.

22. Beutler E, Koziol JA, McMillan R, et al. Marrow suppression produced by repeated doses of cladribine. Acta Haematol 1994; 91: 10-15.

23. Mitosek-Szewczyk K, Tabarkiewicz J, Wilczynska B, et al. Impact of cladribine therapy on changes in circulating dendritic cell subsets, T cells and B cells in patients with multiple sclerosis. J Neurol Sci 2013; 332: 35-40.

24. Carson DA, Wasson DB, Taetle R, et al. Specific toxicity of 2-chlorodeoxyadenosine toward resting and proliferating human lymphocytes. Blood 1983; 62: 737-743.

25. Gorski A, Grieb P, Makula J, et al: 2-Chloro-2-deoxyadenosine--a novel immunosuppressive agent. Transplantation 1993; 56: 1253-1257.

26. Baker D, Marta M, Pryce G, et al. Memory B Cells are Major Targets for Effective Immunotherapy in Relapsing Multiple Sclerosis. EBioMedicine 2017; 16: 41-50. ***Excellent review on the role of B cells in the mechanism of action of MS therapies.**

27. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurol Neuroimmunol Neuroinflamm 2017; 4: e360. doi: 10.1212/NXI.0000000000000360

28. Janssen-Cilag Ltd. Leustat Injection. Summary of Product Characteristics (Updated July 2014; Cited June 2017). https://www.medicines.org.uk/emc/medicine/6737

29. Laugel B, Borlat F, Galibert L, et al. Cladribine inhibits cytokine secretion by T cells independently of deoxycytidine kinase activity. J Neuroimmunol 2011; 240-241: 52-57.

Field Code Changed

30. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010; 362: 416-426. . **** Pivotal trial documenting the efficacy of cladribine in RRMS**

31. Korsen M, Bragado AS, Peix L, et al. Cladribine Exposure Results in a Sustained Modulation of the Cytokine Response in Human Peripheral Blood Mononuclear Cells. PLoS ONE 2015; 10: e0129182. doi: 10.1371/journal.pone.0129182

32. Musella A, Mandolesi G, Gentile A, et al. Cladribine interferes with IL-1beta synaptic effects in experimental multiple sclerosis. J Neuroimmunol 2013; 264: 8-13.

33. Lindemalm S, Liliemark J, Juliusson G, et al. Cytotoxicity and pharmacokinetics of cladribine metabolite, 2-chloroadenine in patients with leukemia. Cancer Lett 2004; 210: 171-177.

34. Savic RM, Novakovic AM, Ekblom M, et al. Population Pharmacokinetics of Cladribine in Patients with Multiple Sclerosis. Clin Pharmacokinet 2017. doi: 10.1007/s40262-017-0516-6

35. Saven A, Kawasaki H, Carrera CJ, et al. 2-Chlorodeoxyadenosine dose escalation in nonhematologic malignancies. J Clin Oncol 1993; 11: 671-678.

36. Sipe JC: Cladribine for multiple sclerosis: review and current status. Expert Rev Neurother 2005; 5: 721-727.

37. Sipe JC, Romine JS, Koziol JA, et al. Cladribine in treatment of chronic progressive multiple sclerosis. Lancet 1994; 344: 9-13.

38. Beutler E, Sipe JC, Romine JS, et al. The treatment of chronic progressive multiple sclerosis with cladribine. Proc Natl Acad Sci U S A 1996; 93: 1716-1720.

39. Beutler E, Sipe J, Romine J, McMillan R, Zyroff J, Koziol J: Treatment of multiple sclerosis and other autoimmune diseases with cladribine. Semin Hematol 1996; 33: 45-52.

40. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227-231.

41. Sipe JC, Romine JS, Koziol JA, et al. Development of cladribine treatment in multiple sclerosis. Mult Scler 1996; 1: 343-347.

42. Romine JS, Sipe JC, Koziol JA, et al. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proc Assoc Am Physicians 1999; 111: 35-44.

43. Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. Neurology 2000; 54: 1145-1155.

44. Schumacher GA, Beebe G, Kibler RF, et al. Problems of Experimental Trials in Multiple Sclerosis: Rewport by the Panel on Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann N Y Acad Sci 1965; 122: 552-568.

45. Stelmasiak Z, Solski J, Nowicki J, et al. Effect of parenteral cladribine on relapse rates in patients with relapsing forms of multiple sclerosis: results of a 2-year, double-blind, placebo-controlled, crossover study. Mult Scler 2009; 15: 767-770.

46. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50: 121-127.

47. Fazekas F, Barkhof F, Filippi M, et al. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. Neurology 1999; 53: 448-456.

48. National Institutes of Health, Clinicaltrials.com. CLARITY extension study (Updated January 24 2014, Cited August 17 2017). Available from: https://clinicaltrials.gov/ct2/show/NCT00641537?term=cladribine+and+multiple+sclerosis&rank=6 .

49. Giovannoni G, Comi G, Cook S, et al. Clinical Efficacy of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS): Final Results from the 120-Week Phase IIIb Extension Trial to the CLARITY Study. Neurology 2016; 86 no. 16 Suppl. P3.028.

50. Comi G, Giovannoni G, Cook S, et al: Magnetic Resonance Imaging (MRI) Outcomes in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS) Treated with Cladribine Tablets: Results from the 120-Week Phase IIIb Extension of the CLARITY Study. Neurology 2016; 86 no. 16 Suppl. P2.11.

51. De Stefano, Giorgio A, Battaglini M, et al. Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets. Mult Scler 2017, 1352458517690269. ***Provides data on brain atrophy**

52. Leist TP, Comi G, Cree BA, et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014; 13: 257-267. ***Demonstrates the clinical efficacy in clinical isolated syndrome**

53. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005; 58: 840-846.

54. National Institutes of Health, Clinicaltrials.com. A Phase 2 Study of Cladribine Add-on to Interferon-beta (IFN-beta) Therapy in Multiple Sclerosis (MS) Subjects With Active Disease (ONWARD). (Updated August 4 2013, Cited August 17 2017). Available from https://clinicaltrials.gov/ct2/show/NCT00436826?term=cladribine+and+multiple+sclerosis&rank=3

Field Code Changed

55. Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials (PREMIERE). (Updated August 9 2017, Cited on August 17 2017. Avalable from https://clinicaltrials.gov/ct2/show/NCT01013350

56. Cook S, Vermersch P, Comi G, et al. Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study. Mult Scler 2011; 17: 578-593.
57. Uppsala Monitoring Centre. VigiBase , the World Health Organization (WHO) international database of suspected adverse drug reactions (Accessed July 12 2017). https://www.who-umc.org/vigibase/vigibase/.

58. Lorvik KB, Bogen B, Corthay A: Fingolimod blocks immunosurveillance of myeloma and B-cell lymphoma resulting in cancer development in mice. Blood 2012; 119: 2176-2177.

59. European Medicines Agency, Committee for Medical Products for Human Use 2011. Withdrawal assessment report for Movectro (cited May 24 2017). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2011/03/WC500104393.pdf

60. Pakpoor J, Disanto G, Altmann DR, wt al. No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. Neurol Neuroimmunol Neuroinflamm 2015; 2: e158. doi: 10.1212/NXI.0000000000000158

61. European Medicines Agency, Commmittee for Medical Products for Human Use 2017. Summary of opinion (initial authorisation) Mavenclad cladribine . Avalable at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004230/smops/Positive/human_smop_001150.jsp&mid=WC0b01ac058001d127

62. Drugsite Trust, Drugs.com. Cladribine Pregnancy and bfreastfeeding Warnings 2017. Available at https://www.drugs.com/cdi/cladribine.html

63. Drugsite Trust, Drugs.com 2017. Cladribine approval status. https://www.drugs.com/history/cladribine.html . 2017.

64. European Medicines Agency, Committee for Medical Products for Human Use 2011. Refusal of the marketing authorisation for Movectro (cladribine). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/001197/WC500101072.pdf

65. Killestein J, Rudick RA, Polman CH: Oral treatment for multiple sclerosis. Lancet Neurol 2011, 10: 1026-1034.

66. EMD Seono 2016. Merck KGaA, Darmstadt, Germany Receives European Medicines Agency Acceptance for Review of Marketing Authorization Application for Cladribine Tablets. Press release. Available at http://www.merckgroup.com/en/media/extNewsDetail.html?newsId=57F6B32E5CD8E3AAC1257FF100307005&newsType=1

Field Code Changed

Field Code Changed

Field Code Changed

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67. Stangel M, Penner IK, Kallmann BA, et al. Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model. Ther Adv Neurol Disord 2015; 8: 3-13.

68. Giovannoni G, Cook S, Rammohan K, et al.: Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol 2011; 10: 329-337.

69. Hauser SL, Bar-Or A, Comi G, Giovannoni G, et al.: Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017; 376: 221-234.

70. Havrdova E, Galetta S, Hutchinson M, et al.: Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol 2009; 8: 254-260.

71. Coles AJ, Twyman CL, Arnold DL, EJ et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012; 380: 1829-1839.

72. Damasceno A, Damasceno BP, Cendes F. No evidence of disease activity in multiple sclerosis: Implications on cognition and brain atrophy. Mult Scler 2016; 22: 64-72.

73. Biogen Idec 2017. Tysabri Prescribing Information (Cited August 17 2017). Available at https://www.tysabrihcp.com/en_us/home/safety/risk-pml-jcv.html

74. Penkert H, Delbridge C, Wantia N, et al. Fulminant Central Nervous System Nocardiosis in a Patient Treated With Alemtuzumab for Relapsing-Remitting Multiple Sclerosis. JAMA Neurol 2016; 73: 757-759.

75. Clerico M, De MS, Artusi CA, et al. Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab. Mult Scler 2017; 23: 874-876.

76. Brownlee WJ, Chataway J. Opportunistic infections after alemtuzumab: New cases of norcardial infection and cytomegalovirus syndrome. Mult Scler 2017; 23: 876-877.

77. Bittner S, Ruck T, Wiendl H, et al. Targeting B cells in relapsing-remitting multiple sclerosis: from pathophysiology to optimal clinical management. Ther Adv Neurol Disord 2017; 10: 51-66.

78. Sormani MP, Muraro PA, Saccardi R, et al. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult Scler 2017; 23: 201-204.

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