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(54) **CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS**

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(57) **ABSTRACT**

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be orally administered and wherein re-treatments are possible.

48 Claims, No Drawings

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CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATION

This application is the U.S. national stage application of International Patent Application No. PCT/EP2005/056954, filed Dec. 20, 2005, which claims the benefit of U.S. Provisional Patent Application No. 60/638,669, filed Dec. 22, 2004, the disclosures of which are hereby incorporated by reference in their entireties, including all figures, tables and amino acid or nucleic acid sequences.

FIELD OF THE INVENTION

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

BACKGROUND OF THE INVENTION

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (Lublin and Reingold, *Neurology*, 1996, 46:907-911).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exacerbation but also from insidious progression between exacerbations (Lublin and Reingold above). 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5% of patients have PRMS and are often considered to have the same prognosis as PPMS. It is sug-

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cations for disease classification (Lassmann et al., 2001, *Trends Mol. Med.*, 7, 115-121; Lucchinetti et al., *Curr. Opin. Neurol.*, 2001, 14, 259-269).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnosis (Noseworthy et al., *The New England Journal of Medicine*, 2000, 343, 13, 938-952). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (Mc Donald et al., 2001, *Ann. Neurol.*, 50:121-127).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatiramer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'-deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (EP 626853B1 and U.S. Pat. No. 5,506,214).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (Selby et al., 1998, *Can. J. Neurol. Sci.*, 25:295-299) and Relapsing-Remitting MS respectively (Romine et al., 1999, *Proceedings of the Association of American Physicians*, 111, 1, 35-44).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07 mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (Rice et al., 2000, *Neurology*, 54, 5, 1145-1155). In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (Beutler et al., 1996, *Proc. Nat. Acad. Sci. USA*, 93, 1716-1720; Romine et al., 1999 above). Phase II study results, were positive on the significant reduction of MRI-measured brain lesions (Rice et al., 2000, above).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (Selby et al., 1998, above; Beutler et al., 1994, *Acta hematol.*, 91:10-15). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been

33, 1(S1), 45-52) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Grieb et al. reported a small trial in 11 patients with relapsing-remitting multiple sclerosis (Grieb et al., 1995, *Archivum Immunologiae et Therapiae Experimentalis*, 43 (5-6), 323-327) wherein Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4-5.7 mg/kg (patients of about 52 and about 75 kilos, respectively) i.e. a total effective dose of 2-2.85 mg/kg. For some patients, a single re-treatment of 5 days was performed at a cumulative dose of 0.4-0.66 mg/kg after a cladribine free-period of 3 or 6 months. The side effects observed with the regimen above were said to be less severe than the ones observed in the study on patients suffering from chronic progressive multiple sclerosis treated by i.v. infusion of Cladribine (Sipe et al., 1994, *Lancet*, 344, 9-13) but were still present. In addition, the therapeutic efficacy of the oral regimen above versus the i.v. infusion therapy was questioned (Grieb et al., 1995, above) and a group of "non-responders" has been identified (Stelmasiak et al., 1998, *Laboratory Investigations*, 4(1), 4-8).

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of Cladribine treatment between the treatment periods is also desirable.

SUMMARY OF THE INVENTION

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

- (i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);
- (iv) A Cladribine-free period wherein no Cladribine is administered.

administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

- (i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- (iii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);
- (iv) A Cladribine-free period wherein no Cladribine is administered.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg or the total dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days is 1.7 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg or the total effective dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 0.7 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments. Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of (i) an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and (ii) a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine

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dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months, typically at least of about 8 months.

A "Maintenance Treatment" consists in the sequential succession of (i) a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and (ii) a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria (Schumacher et al., 1965, *Ann. NY Acad. Sci.* 1965; 122:552-568; Poser et al., 1983, *Ann. Neurol.* 13(3): 227-31).

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (Miller et al., 1996, *Neurology*, 47(Suppl 4): S217; Evans et al., 1997, *Ann. Neurology*, 41:125-132).

The observation of the reduction and/or suppression of MRI T₁ gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T₁ enhanced brain lesion volume, MRI T₁ enhanced lesion number, MRI

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T₁ enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (Sipe et al., 1984, *Neurology*, 34, 1368-1372). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in Mattson, 2002, *Expert Rev. Neurotherapeutics*, 319-328.

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983, *Neurology*, 33, 1444-1452). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (WO 96/19230; WO 96/19229; U.S. Pat. Nos. 6,194,395; 5,506,214; WO 2004/087100; WO 2004/087101), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (EP 173,059; WO 04/028462; WO 04/028462; U.S. Pat. No. 5,208,327; WO 00/64918) and Robins et al., *J. Am. Chem. Soc.*, 1984, 106: 6379. Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maize starch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycolate. Wetting agents include, but are not limited to, sodium lauryl sulfate).

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