Exploratory open label study to investigate the effect of teriflunomide on immune cell subsets in the blood of patients with relapsing forms of multiple sclerosis

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Primary:- To measure the effect of Teriflunomide on lymphocytes subsets in patients with relapsing forms of multiple sclerosis as compared with baseline values and those of a reference population of untreated healthy subjects.Secondary:- To assess...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON40257

Source
ToetsingOnline

Brief title
TERI-DYNAMIC

Condition

- Demyelinating disorders

Synonym
MS, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: multiple sclerosis, open label, relapsing, teriflunomide

Outcome measures

Primary outcome

Change from baseline in lymphocyte subset parameters as measured by flow

cytometry. [Time frame for evaluation: At 12 weeks and 24 weeks]

Secondary outcome

- Change from baseline in biased T cell clonal repertoire based T cell receptor

(TCR) spectratyping [Time frame for evaluation: At 12 weeks and 24 weeks]

- Change from baseline in serum cytokine as measured by multicytokine array

tool [Time frame for evaluation: At 12 weeks and 24 weeks]

- Change from baseline in Mitogen/TCR-specific T cell proliferation as measured

by flow cytometry [Time frame for evaluation: At 12 weeks and 24 weeks]

Study description

Background summary

The purpose of this study is to investigate the effect of teriflunomide on immune cell subsets in the blood of patients with relapsing forms of multiple sclerosis.

Study objective

Primary:
- To measure the effect of Teriflunomide on lymphocytes subsets in patients with relapsing forms of multiple sclerosis as compared with baseline values and

those of a reference population of untreated healthy subjects.

Secondary:
- To assess if Teriflunomide treatment results in biased T cell clonal diversity.
- To assess the effect of Teriflunomide on the function of peripheral blood mononuclear cells (proliferation and cytokine production in situ).
- To assess the circulating cytokines profile in the serum of Relapsing Multiple Sclerosis (RMS) patients during a 24-week treatment versus baseline and healthy controls.
- To assess the reversibility of all parameter changes in patients who discontinue treatment after accelerated elimination procedure with cholestyramine or activated charcoal.

Study design

The LPS13539 study is an open-label, parallel design, phase 3 study.

Intervention

* Drug: teriflunomide (HMR1726); Pharmaceutical form: tablet; Route of administration: oral
* Drug: cholestyramine; Pharmaceutical form: powder; Route of administration: oral
* Drug: charcoal; Pharmaceutical form: granule; Route of administration: oral

Study burden and risks

The most common side effects reported for teriflunomide: nasopharyngitis (upper respiratory infection), flu symptoms, hair thinning/loss, nausea, elevated liver function test, paresthesia and hypoesthesia, pain (limb, joint or back), diarrhea, constipation, rash, abdominal pain, (usually mild) increase in blood pressure, mild decrease in the number of white blood cells, increase susceptibility to infections.

The most common side effects reported for cholestyramine: constipation, stomach pain, nausea, diarrhea, heartburn or indigestion, abdominal gas, vomiting, belching, dizziness, headache; and rare include: bleeding tendencies, and weight loss.

The most common side effects reported for charcoal: black stools, nausea and constipation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients:
Patients (male and female) with relapsing forms of multiple sclerosis meeting McDonald criteria for MS at the screening visit and having either one of the following treatment status:
- Naïve to disease modifying (DM) treatment or no DM treatment for more than 2 years
- Or currently (not more than 3 months interruption) on MS therapy with IFN *-1 or Glatiramer acetate and a period of at least 2 weeks without IFN *-1 or Glatiramer acetate before switching to teriflunomide.
- Male and female patients, between 18 and 56 years of age, exclusive.;Healthy volunteers:
- Male and female subjects, between 18 and 56 years of age, exclusive.
- Body weight between 50.0 and 95.0 kg, inclusive, if male; and between 40.0 and 85.0 kg, inclusive, if female, body mass index between 18.0 and 30.0 kg/m2, inclusive.
- Certified as healthy by a comprehensive clinical assessment (detailed medical history and

complete physical examination).
- Normal vital signs after 10 minutes resting in supine position:
* 95 mmHg < systolic blood pressure (SBP) <140 mmHg
* 45 mmHg < diastolic blood pressure (DBP) <90 mmHg
* 40 bpm < heart rate (HR) <100 bpm
- Normal standard 12-lead electrocardiogram (ECG) after 10 minutes resting in supine position; 120 ms < PR <220 ms, QRS <120 ms, QTc * 430 ms if male, * 450 ms if female.
- Laboratory parameters within the normal range (or defined screening threshold for the Investigator site), unless the Investigator considers an abnormality to be clinically irrelevant for healthy subjects; however liver function parameter(s) should not exceed the upper laboratory norm.

Exclusion criteria

Patients:
- Did not consent to HIV testing (the specifics of informed consent process for the HIV testing should be done in accordance with local guidelines).
- A relapse within 30 days prior to screening.
- Clinically relevant cardiovascular, neurological, endocrine, or other major systemic disease making implementation of the protocol or interpretation of the study results difficult or that would put the patient at risk by participating in the study.
- Patients with a congenital or acquired severe immunodeficiency, a history of cancer (except for basal or squamous cell skin lesions which have been surgically excised, with no evidence of metastasis), lymphoproliferative disease, or any patient who has received lymphoid irradiation.
- Human immunodeficiency virus (HIV) positive patients.
- Known history of active tuberculosis not adequately treated or positive QuantiFERON TB Gold test.
- Hypoproteinemia (eg, in case of severe liver disease or nephrotic syndrome) with serum albumin <3.0 g/dL.
- Moderate to severe impairment of renal function, as shown by serum creatinine >133 *mol/L (or >1.5 mg/dL).
- Patients with significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia.
- Acute or chronic infection.
- Liver function impairment or persisting elevations >1.5ULN (confirmed by retest) of serum glutamic pyruvic transaminase/ alanine aminotransferase (SGPT/ALT), serum glutamic oxaloacetic transaminase/aspartate aminotransferase (SGOT/AST), or direct bilirubin greater than 1.5-fold the
upper limit of normal.
- Known history of hepatitis.
- Use of adrenocorticotrophic hormone (ACTH) or systemic corticosteroids for 2 weeks prior to screening.
- Prior or concomitant use of cytokine therapy or intravenous immunoglobulins in the 3 months prior to screening.

- Prior use of alemtuzumab or cladribine.
- Prior use (within 1 year) of fingolimod (Gylenia®).
- Prior use (within 2 years) of mitoxantrone, natalizumab (Tysabri®), or immunosuppressant agents (i.e. azathioprine, cyclophosphamide, cyclosporin, methotrexate or mycophenolate).
- Prior treatment with teriflunomide, and prior or concomitant use of leflunomide (ARAVA®) or hypersensitivity to any of the other ingredients or excipients of the investigational product.
- Prior use of any investigational drug in the 6 months preceding screening.
- Pregnant or breast-feeding women.
- Women of childbearing potential not utilizing effective contraceptive method and /or women of childbearing potential who are unwilling to or unable to be tested for pregnancy.
- Known history of hypersensitivity to teriflunomide or leflunomide.
- Persisting elevations (confirmed by retest) of serum amylase or lipase greater than 2-fold the upper limit of normal.
- Known history of chronic pancreatic disease or pancreatitis.;Healthy volunteers:
- Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecologic (if female), or infectious disease, or signs of acute illness.
- Blood donation, any volume, within 2 months before inclusion or according to local regulations).
- Symptomatic postural hypotension, irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in systolic blood pressure *20 mmHg within 3 minutes when changing from supine to standing position.
- History or presence of drug or alcohol abuse (alcohol consumption more than 40 g per day).
- Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking during the study.
- If female, pregnancy (defined as positive *-HCG blood test), breast-feeding.
- Prior use of any investigational drug in the 6 months preceding screening
- Positive result on any of the following tests: hepatitis B surface (HBs Ag) antigen, antihepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab).
- Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
- Positive alcohol breath test.
- Leukocytes and in particular lymphocytes values below the lower limit of normal range

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-10-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	teriflunomide

Ethics review

Approved WMO Date:	03-05-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-09-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-12-2013
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005324-16-NL
CCMO	NL44560.060.13
Other	Zie sectie J.