A PHASE 0 SINGLE DOSE STUDY TO EVALUATE THE PHARMACOKINETICS/-DYNAMICS AND SPECIFIC TARGETING PROPERTIES OF 124-I-F8IL10 IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INFLAMMATORY BOWEL DISEASE

Published: 04-03-2013
Last updated: 04-05-2024

Primary objective:Pharmacokinetics/-dynamics of 124I-F8IL10 Secondary objective:Dosimetric parameters of arthritic joints and internal organs.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON39620

Source
ToetsingOnline

Brief title
phase 0 PET-CT study with 124-I-F8IL10 in RA and IBD

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders
- Joint disorders

Synonym

rheumatoid arthritis and inflammatory bowel disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Philogen S.p.A.

Intervention

Keyword: F8IL10, Inflammatory bowel disease (IBD), positron emission tomography-computed tomography (PET-CT), rheumatoid arthritis (RA)

Outcome measures

Primary outcome

Pharmacokinetics and -dynamics of F8IL10 in RA (including uptake in joints)

Secondary outcome

Radiation dosimetry of 124-I-F8IL10 in joints and internal organs.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease that affects 0.5-1% of the population in the industrialized world and commonly leads to significant disability and a consequent reduction in quality of life.

Traditional therapy of RA included anti-inflammatory treatment with low-dose systemic glucocorticoids as well as symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), which alleviate the disease but may induce significant damage to the upper and lower gastrointestinal tract and do not provide a complete control of the disease. Disease modifying drugs (DMARDs) have been used since the beginning of the 20th century in order to avoid disease progression; a number of molecules have been developed and used in RA patients (gold salts, chloroquine and hydroxychloroquine, salazopyrine, leflunomide, cyclosporine) Until today Methotrexate (MTX) is the most commonly

used DMARD and continues to be the gold standard of therapy of rheumatoid arthritis.

More recently, biological compounds that target TNF-* and other inflammatory cytokines, B-cells or T-cells have been used successfully to treat RA patients with an inadequate response to MTX; however, approximately 30-40% of patients do not respond to these treatments or had to stop treatment due to drug-related adverse events, resulting in an unmet need for alternative therapies.

Inflammatory bowel diseases (IBD), which include Crohn*s disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the intestinal tract characterized by a succession of periods of clinical relapse and remission. The pathogenesis of IBD likely involves multifactorial interactions among genetic and immunological factors and environmental triggers. IBD causes significant gastrointestinal symptoms, including diarrhea, abdominal pain, bleeding, anemia and weight loss. Several score systems to measure disease activity have been developed [3], the most widely adopted being Mayo score [4] and CDAI [1] for UC and CD, respectively. Treatment is aimed at maintaining a normal quality of life for the patient by rapidly inducing and sustaining remission and avoiding complications of the disease itself and its treatment. Corticosteroids, aminosalicylates, immunosuppressive drugs as well as TNF* blockers are the mainstay of medical treatment.

Interleukin-10 (IL-10) is a cytokine produced by activated monocytes and T cells which is deeply involved in the regulation of inflammatory responses and immune reactions. IL-10 has been considered an attractive candidate for therapeutic use based on its potent in vitro immunomodulating activities and proven effects in animal models of acute and chronic inflammation, autoimmunitiy, cancer and infectious disease. Schering-Plough developed recombinant human IL-10 (ilodecakin, Tenovil®) for clinical trials in patients suffering from inflammatory bowel disease, psoriasis or rheumatoid arthritis. A combination of IL-10 and Methotrexate in a multicenter, placebo-controlled, dose escalation study in RA patients was described where 8 or 20 µg / kg three times weekly resulted in ACR 20 responses in 50-60 % of patients compared to 10 % for placebo. However, the development of recombinant IL-10 as a therapeutic drug for chronic inflammation was discontinued in 2003 probably due to insufficient response rates in the medium-high responder group and/or to problems with manufacturing.

In the F8IL10 molecule, IL-10 is coupled to the antibody fragment F8 which binds to the extra-domain A of fibronectin, selectively expressed at sites of inflammation. Upon administration to a patient, F8IL10 is supposed to accumulate at the site of arthritis and exhibit its biological function there. Such antibody-mediated targeted delivery of cytokines to sites of disease is a novel therapeutic concept which is largely unexplored for the treatment of chronic inflammatory conditions but has been investigated successfully in the cancer setting over the last few years.

In the frame of the preclinical analysis of the drug candidate, F8IL10 displayed an impressive ability to selectively localize at sites of arthritis in the CIA mouse model upon intravenous and subcutaneous injection. Furthermore, F8IL10 showed a therapeutic activity, which was superior to the one of IL-10 fused to an antibody of irrelevant specificity in the mouse and was highly synergistic when administered in combination with Methotrexate (MTX).

Study objective

Primary objective:
Pharmacokinetics/-dynamics of 124I-F8IL10

Secondary objective:
Dosimetric parameters of arthritic joints and internal organs.

Study design

The presented trial is a phase 0 single dose study of the arthritic targeting human monoclonal-antibody cytokine fusion protein 124I-F8IL10 in 5 patients with active rheumatoid arthritis and 5 patients with active IBD.
It is a uncontrolled, open-label study in one clinical center.
5 patients with active rheumatoid arthritis and 5 with active IBD will be enrolled.
A single dose of 0.4 mg F8IL10 labeled with Iodine-124 (with a maximum radiation burden of the scanning procedure of 13 mSv)will be administered to consenting patients with arthritis. Target localization will be analyzed by PET/CT scans.

Scheme:

Visit 1: screening visit, thyroid prophylaxis is provided for day -1 and day -2 for start of the study.

Visit 2:
- thyroid prophylaxis
- infusion 124-I-F8IL10
- PET-CT at 0.5-1h after infusion
- blood sampling for laboratory parameters, pharmacokinetics and pharmacodynamics

Visit 3:
- thyroid prophylaxis
- PET-CT at 24h after infusion
- blood sampling for pharmacokinetics and pharmacodynamics

Visit 4: (This PET-CT will be cancelled if the burden for the patient is too large)
- thyroid prophylaxis
- PET-CT at 72h after infusion
- blood sampling for laboratory parameters, pharmacokinetics and pharmacodynamics

Study burden and risks

Burden and risks
- Collection of blood; can cause local bruises
- Drip (2x); can cause local bruises
- 3x PET-CT scan; radiation burden of in total 13 mSv
- Very small chance of allergic reaction to F8IL10

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

For patients with Rheumatoid Arthritis:;1. Diagnosis of RA according to ACR criteria;2. Active RA (Disease Activity Score 28 * 3.2);3. Treatment with disease modifying anti-rheumatic drugs (DMARDS), biologicals and in addition, corticosteroids up to 10 mg daily and non-steroidal anti-inflammatory drugs (NSAIDs) is permitted, provided that there is a stable dose for at least 2 weeks.;For patients with Inflammatory Bowel Disease:;1. diagnosis of IBD to clicinico -pathologic criteria;2. clinically active IBD:
a. Crohn*s disease: active Crohn*s disease, with a CDAI (Crohn*s Disease Activity index) > 220 [Best et al. Gastroenterology 1976] with CDEIS (Crohn*s disease endoscopic index of severety) > 15 [Mary et al. Gut, 1989] assessed via colonoscopy or MRI enteroclysis within 4 weeks of dosing.;b. Ulcerative Colitis: active ulcerative colitis, Mayo score > assessed via colposcopy within 4 weeks of dosing.;3. Treatment with aminosalacylates, immunomodulators, biological and corticosteroids up to 20 mg. dialy is permitted, provided that there is a stable dose for at least 2 weeks.;For ALL patients;1. Patients aged *18 years;2. All acute toxic effects of any prior therapy returned to classification mild according to MedDRA;3. Sufficient hematologic, liver and renal function: total white cell count as well as ANC should be normal prior to start the treatment, as well as liver function tests:;a. Absolute neutrophil count (ANC) * 1.5 x 109/L, platelets * 100 x 109/L, haemoglobin (Hb) * 9.5 g/dl;b. Alkaline phosphatase (AP), alanine aminotransferase (ALT) and/or aspartate aminotransferase < 3 x upper limit of reference range (ULN), and total bilirubin < 2.0 mg/gL;c. Creatinine < 1.5 ULN or 24 h creatinine clearance > 50 mL/min;4. Negative serum pregnancy test for females of childbearing age prior to starting treatment;5. Male patients, who are potentially fertile, must agree to use adequate contraceptive methods at the beginning of the screening visit and continue until 3 months following the last treatment with the study drug.;6. Evidence of a personally signed and dated Ethics Committee-approved Informed Consent form indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the study;7. Willingness and ability to comply with the scheduled visits, treatment plan, laboratory tests and other study

Exclusion criteria

Patients must not be enrolled in the study if, at the time of enrollment, they have any of the following. ;1. Presence of active infections (e.g. requiring antibiotic therapy) or other severe concurrent disease, which, in the opinion of the investigator, would place the patient at undue risk or interfere with the study;2. Chronic active hepatitis (hepatitis B/C) or active autoimmune diseases other than RA;3. Known primary or secondary immonodeficiency;4. HIV positive patient;5. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years;6. History within the last year of acute or subacute coronary syndromes including myocardial infarction, unstable or severe stable angina pectoris;7. Heart insufficiency (> Grade II, New York Heart Association (NYHA) criteria);8. Irreversible cardiac arrhythmias requiring permanent medication;9. Uncontrolled hypertension;10. Ischemic peripheral vascular disease (Grade IIb-IV);11. Severe diabetic retinopathy;12. Recovery from

major trauma including surgery within 4 weeks of administration of study treatment;13. Known history of allergy to IL-10 or other intravenously administered human proteins/peptides/antibodies;14. Pregnancy or breast feeding;15. Any conditions that in the opinion of the investigator could hamper compliance with the study protocol;16. Previous exposure to radioactivity with a yearly cumulative dose of * 5 mSv. ing:;17. For patient undergoing MRI:
a. electronically, magnetically and mechanically activated implants.
b. cardiac pacemakers
c. ferromagnetic haemostatic clips in the central nervous system (CNS) or in the body.
d. cochlear implants or stapedial implants.
e. insulin pumps and nerve stimulators.
f. prosthetic heart valves
g. ferromagnetic or electrically operated active devices like automatic cardioverter defebrillators.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-06-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	F8IL10
Generic name:	F8IL10

Ethics review

Approved WMO Date:	04-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-023114-32-NL
CCMO	NL33778.029.10