Anakinra versus treatment as usual in the treatment of acute gout

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

Summary

ID

NL-OMON47178

Source
ToetsingOnline

Brief title
ATTACG

Condition

- Other condition

Synonym
acute gout, arthritis urica

Health condition

Inflammatoire gewrichtsaandoening

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Twente (prof. dr. M.A.F.J. van de Laar)
Source(s) of monetary or material Support: ZonMW,Swedish Orphan International

Intervention

Keyword: anakinra, gout, interleukin 1, pain

Outcome measures

Primary outcome

Change in patient-reported pain in the index joint from baseline to the average

of pain values at 24, 48 and 72 hours

Secondary outcome

Time to 50% reduction in pain in the primary affected joint

Time to remission of pain

Decrease of primary joint swelling according to patient across day 2-5

Decrease of primary joint tenderness according to patient across day 2-5

Decrease in C-reactive protein (CRP) levels after 7 days of treatment

Decrease of serum uric acid concentration after 3 months

Treatment response according to patient across day 2 -7

% dropout due to adverse event (AE)

% dropout due to serious adverse event (SAE)

Level of physical functioning

Health related quality of life (HR-QOL)

Experienced side effects

Direct and indirect costs

Time to first reoccurrence of flare

Number of new flares

% patients starting with canakinumab treatment

% patients with serum uric acid concentration * 0.36 mmol/l

Study description

Background summary

Acute Gout is a common form of inflammatory arthropathy characterized by severe pain and reduced physical functioning. The predominant risk factor for gout is hyperuricemia. When left untreated, elevated uric acid levels in the blood can lead to formation and precipitation of monosodium urate crystals in and around the joints, stimulating and initiating a local inflammatory response. The current standard treatments, colchicine, corticosteroids or NSAIDs, are therefore designed to rapidly relieve the pain and inflammation in the affected joints. Although gout is one of the most well understood rheumatic diseases, currently available treatment options are frequently contra-indicated or poorly tolerated by gout patients, which frequently presents in the presence of significant multi-morbidity (hypertension, diabetes mellitus, renal disease). For this complex group of gout patients, the finding of interleukin-1* (IL-1*) in the pathophysiology of gout was promising. In 2013, a new agent, the IL-1* inhibitor canakinumab, was registered in the Netherlands for the treatment of acute gout. However, this agent is limited by the high cost per treatment (> ¤ 10,000). It is reimbursable for patients in whom conventional treatments are not suitable and who are faced with more than two gout attacks each year.

Anakinra (Kineret), a DNA recombinant IL-1 receptor antagonist, is a medicinal product currently registered for the treatment of rheumatoid arthritis. It acts by competitively inhibiting the binding of IL-1* and IL-1* to IL-1 type I receptors, causing the biological activity of these interleukins to be neutralized. The clinical efficacy and safety of anakinra in acute gout have been investigated and reported in a handful of case series or small open-label studies. These studies provide a proof of concept of the plausibility and clinical importance of a large scale clinical trial. The goal of this project is to determine whether anakinra could be a safe, more applicable and possibly more effective agent to treat gouty arthritis.

Study objective

The primary aim of this research is to demonstrate the noninferiority of anakinra compared with the standard of care in the treatment of acute gout flares.

Secondary objectives are to compare the cost per quality-adjusted life day between anakinra and standard of care and to evaluate the safety of ankinra use in gout. Also to compare the 3 and 12 months clinical outcome of patients initially treated with anakinra versus Standard of care and starting Urate lowering therapy.

Study design

The total study duration is 12 months. The initial 3 month study is a multi-center randomized, double (dummy)-blinded, placebo controlled NI trial, followed by a 9 month open label extension study.

Intervention

200 patients diagnosed with crystal proven acute gout, will be randomly allocated in the ratio 1:1 to either:

1. 5 consecutive days of 100 mg daily anakinra injection and standard of care pill placebo
2. one of the standard of care treatment options (colchicine, naproxen, corticosteroids) and 5 consecutive days of 100 mg anakinra injection placebo.The dose and duration of the standard treatment options will be as follows:
- colchicine (active or placebo): 3 daily dosages of 0.5 mg for 90 days
- naproxen (active or placebo): 2 times daily 500 mg for 90 days
- prednisolon (active of placebo): 35 mg / day for 5 days.

Colchicine and naproxen have a treatment duration of 90 days because they are used/extended prophylactically when initiating urate lowering therapy at baseline. Both groups will also be given urate lowering therapy (standard care) at baseline. This will be allopurinol and if not applicable then febuxostat or benzbromaron will be given, also according to the dose/duration recommendations by the gout guidelines from the NVR.

Study burden and risks

During the 12 month study period, patients will need to at 6 different time points fill in questionnaires. In total, patients will need to give blood 3 times. 5 days longs patients will receive a treatment whereby they will need to inject themselves with a anakinra placebo or verum and need to orally take a standard of care pill or standard of care pill placebo. During the gout flare, patients will need to 7 days long fill in daily a short questionnaire regarding the gout flare. For diagnostic purposes and to determine if a patient is eligible for study participation, aspiration of the main joint will be done (if needed).

The potential risks associated with anakinra for the treatment of acute gouty arthritis are:
* Physical discomfort of SC treatment injection
* Local (skin) injection site reaction associated with pain, inflammation, erythema, or ecchymoses, rash
* Serious infections including respiratory infections and skin infections, Influenza infections
* Allergic reaction and anaphylaxis (angioedema, urticarial and pruritus) to anakinra or other constituents, including latex
* Decreased neutrophil count, potentially leading to neutropenia
* possible drug interaction between Urate lowering therapy and anakinra
* Elevated levels of liver enzymes
* Increased total blood cholesterol levels
* Thrombocytopenia (low level of blood platelets)
* Gastrointestinal disturbances related to liver disorders (yellow skin and eyes, nausea, loss of appetite, dark-colored urine, light-colored stools)
* Headaches
* NSAIDs and colchicine are intended as prophylactics for gout flares when initiating ULT. Patients receiving anakinra treatment or prednisolone treatment (when allocated into the SoC group) will not receive colchicine or NSAID prophylactics when initiating ULT. Relapse of a gout flare might occur sooner in this population compared to the other study arm that will receive prophylactics.

To ensure the risks associated with the intake of anakinra remain limited, the inclusion and exclusion criteria of this study are strict. Eligible patients will be excluded from the study if contraindicated to anakinra or any of its constituents. Additionally, patients with pre-existing neutropenia or with untreated infections will not be included in the study to ensure the chance for worsening of or getting neutropenia are decreased in the study population. Also, a DSMB will be established to ensure the safety of the participants. Also, active safety monitoring will take place by the different centres/rheumatologists of reported side effects/complications/AE/SAE and these will be evaluated for seriousness and relatedness to anakinra or treatment as usual. At last, the long use of this product in RA patients has resulted in a good description of its safety profile and the possible side effects. Such information has contributed to clearly defining the potential risks associated with using anakinra in the present study. The group not receiving prophylactic agents will receive the same optimal care as patients receiving prophylactics. In some cases it might be needed to break the randomization (treatment) code to be able to provide the patient the best care. The strain for patients participating in this study will remain limited as questionnaires can be filled in digitally from home (or if needed by paper and pencil). Therefore patients will not have to make an additional visit to the center.

Contacts

Public
Universiteit Twente (prof. dr. M.A.F.J. van de Laar)

Drienerlolaan 5
Enschede 7522 NB
NL
Scientific
Universiteit Twente (prof. dr. M.A.F.J. van de Laar)

Drienerlolaan 5
Enschede 7522 NB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* At least 18 years of age
* Signed written informed consent
* Identification of intracellular monosodium urate crystals in primary joint through aspiration of joint

Exclusion criteria

* Absolute contra-indication for all available types of urate lowering therapy (allopurinol, febuxostat and benzbromaron)
Contra-indications allopurinol: Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given).

Contra-indications febuxostat: Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given).
Contra-indications benzbromaron: Hypersensitivity to the active substance or to any of the excipients (see for the excipients the official SPC for the brand given). Patients with known liver disease. Concomitant use of hepatotoxic drugs, particularly antituberculosis agents. Hepatic porphyia. Severe renal impairment (clearance < 30 ml/min.). Patients with secretion of urate higher than 700 mg/24 hours (= 4.2 mmol/24 hour).Urolithiasis. Acute gout flare. ;* Absolute contra-indication for anakinra
Contra-indications anakinra: Hypersensitivity to the active substance or to any of the excipients (citric acid anhydrous, sodium chloride, disodium edetate dihydrate, polysorbate 80, sodium hydroxide, water for injections) or to E. coli derived proteins. Kineret must not be used in patients with severe renal impairment (creatinine clearance rate < 30 ml/minute). Kineret treatment must not be initiated in patients with neutropenia (absolute neutrophil count <1.5 x 109 /l). ;* Presence of liver disease that according to the treating physician precludes participation in the study;* Absolute contra-indication for all three possible standard of care treatments (colchicine, naproxen, prednisolon)
Contra-indications colchicine: Hypersensitivity to the active substance or to any of the excipients (microcrystalline cellulose (E460), lactose, sodium carboxy starch, magnesium stearate (E470b)). Women of childbearing age, unless effective contraceptive measures are taken. Colchicine should not be used in patients with severe renal impairment or severe hepatic impairment.
Contra-indications naproxen: Hypersensitivity to the active substance or to any of the excipients (potato starch, lactose, hydroxypropyl cellulose (200 CP), magnesium stearate, colloidal anhydrous silicon dioxide). Naproxen is contra-indicatied in patients who have previously shown allergic reactions (e.g. asthma, rhinitis or urticaria) in response to acetylsalicylic acid or other prostaglandin-synthesis inhibitors. Severe anaphylactoid reactions have been reported in these patients. In principle, naproxen must not be administered to patients with gastrointestinal ulcerations, congestive gastritis or atrophic gastritis, gastrointestinal bleeding or other bleeding such as cerebrovascular bleeding. Severe renal impairment.
Contra-indications prednisolon: Hypersensitivity to the active substance or to any of the excipients (lactose, magnesium stearate (E470b), silicon dioxide (E551), potato starch, pregelatinized potato starch, sodium (potato) starch glycolate, magnesium stearate (E572), erythrosine (E127)). Gastric and duodenal ulcers. Acute infectious processes, particularly viral infections and systemic fungal infections. Tropical worm infections. Administration after vaccination with a live attenuated virus. Ocular herpes simplex.;* Known history of allergy or sensitivity to latex;* Current use of any ULT (ULT therapies are allopurinol, febuxostat and benzbromaron);* Concurrent use of other IL-1 agents (to this category belong: canakinumab and rilonacept);* Patient reports no to mild gout related pain;* Pregnancy or lactation;* Women who are planning on becoming pregnant within the study period (12 months);* Patients with active or recurrent bacterial, fungal or viral infection ;* Patients using tumor necrosis factor inhibitors (to this category belong: Certolizuman, Golimumab, Adalimumab, Etanercept, Infliximab);* Patient has insufficient knowledge of the Dutch language for completing questionnaire independently

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-02-2016
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Colchicine 0.5 mg PCH
Generic name:	Colchicine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kineret
Generic name:	Anakinra
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Naproxen 500 mg Teva
Generic name:	Naproxen
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolon Teva 30 mg
Generic name:	Prednisolone

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolon Teva 5 mg
Generic name:	Prednisolone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-06-2015
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	06-08-2015
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	11-08-2016
Application type:	Amendment

Review commission:	METC Twente (Enschede)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	21-03-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	08-08-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	29-08-2017
Application type:	Amendment

Review commission:	METC Twente (Enschede)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Twente (Enschede)

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	EUCTR2015-000696-27-NL
CCMO	NL52526.044.15

Study results

Results posted: 02-04-2019

First publication
18-03-2019