Efficacy and safety of canakinumab in Schnitzler syndrome

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Primary: To determine whether IL-1 inhibition by Canakinumab is efficacious in treatment of Schnitzler syndrome.Secondary:1. To assess the effect of canakinumab on Schnitzler syndrome (clinical signs/symptoms and inflammatory biomarkers C-reactive...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON34354

Source
ToetsingOnline

Brief title
Canakinumab in Schnitzler syndrome

Condition

- Haematological disorders NEC
- Immune disorders NEC
- Angioedema and urticaria

Synonym
Schnitzler syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: VIDI stipendium AS,Novartis

Intervention

Keyword: Anti-IL-1, Canakinumab, Schnitzler syndrome

Outcome measures

Primary outcome

Complete or clinical remission at Day 14.

Secondary outcome

1. Complete or clinical remission at Day 3 and Day 7

2. The prevention of disease relapse in patients who demonstrated complete remission at Day 14

3. The change in biomarkers (CRP and SAA) and clinical parameters (physician and patient global assessment of disease activity) during the treatment and follow-up periods

4. Time to relapse after the last canakinumab dose

5. Safety and tolerability as well as PK/PD properties of canakinumab in the treatment of patients with Schnitzler syndrome.

Exploratory:

1. Changes in patient quality of life by using: Medical Outcome Short Form (36) Health Survey (SF-36®).

2. Optimal canakinumab dose and frequency in patients with Schnitzler syndrome

Study description

Background summary

Schnitzler syndrome is a disabling inflammatory disease, characterized by chronic urticaria, fever, arthralgia, bone pain and gammopathy, which can so

far only be effectively treated with anakinra, an interleukin-1 receptor antagonist. However, this drug is not registered for use in Schnitzler syndrome, and it needs to be injected daily, which is uncomfortable and unpractical. Therefore other treatments targeting IL-1 are needed. Canakinumab is a long-acting monoclonal antibody against IL-1β that has been registered for bimonthly use in the rare autoinflammatory disease Cryopyrin-associated periodic syndrome. We hypothesize that it will be effective in Schnitzler syndrome.

Study objective

Primary: To determine whether IL-1 inhibition by Canakinumab is efficacious in treatment of Schnitzler syndrome.
Secondary:
1. To assess the effect of canakinumab on Schnitzler syndrome (clinical signs/symptoms and inflammatory biomarkers C-reactive protein and serum amyloid A).
2. To evaluate the safety and tolerability of canakinumab in the treatment of patients with Schnitzler syndrome.
3. To assess PK/PD properties of canakinumab by measuring canakinumab and IL-1beta levels
Exploratory:
1. To explore the changes in patient quality of life during canakinumab treatment in patients with Schnitzler syndrome by using: Medical Outcome Short Form (36) Health Survey (SF-36®).
2. To explore potential biomarkers and pharmacogenomic characterization of these patients at baseline as predictors of total clinical response with canakinumab treatment
3. To explore an optimal canakinumab dose frequency in patients with Schnitzler syndrome.

Study design

Study design: This is a 6-month open-label, single treatment arm, safety and efficacy study of canakinumab subcutaneous injection in patients with active Schnitzler syndrome, with a maximum 6 month run-out observation period after cessation of treatment.
Study dose: Canakinumab 150mg/month or 2mg/kg/month for patients <40kg.

Intervention

Monthly subcutaneaous administration of Canakinumab 150mg.

Study burden and risks

In view of specific analogies of CAPS and Schnitzler syndrome, e.g. chronic

urticaria and systemic inflammation and complete remission of symptoms upon anakinra treatment, we expect canakinumab to be highly effective in Schnitzler syndrome as well. This would eliminate the burden of daily injections, which are required in anakinra treatment, and offer more insight in which cytokines - IL-1α and/or IL-1β - are critically involved in the pathophysiology of Schnitzler syndrome. Namely, a major difference between anakinra an canakinumab is that the former blocks the effects of both IL-1α and IL-1β, whereas the latter specifically inhibits IL-1β. Theoretically, it could have less side effects by being more specific. As yet, it is unclear if in Schnitzler syndrome, blocking solely IL-1β is as effective as blocking both IL-1α and IL-1β. It is therefore important to find this out.
Interleukin -1 blockade may interfere with the immune response to infections. Clinical data with anakinra and rilanocept have demonstrated a slight increase in the overall risk for serious infections, the majority of which are upper respiratory tract infections. Other reported side effects were gastrointestinal symptoms, such as abdominal pain, and vertigo. No deaths were attributed to canakinumab use. One could question the use of an anti-inflammatory agent in a disease in which in 12% of patients a lymphoproliferative disorder ensues after 10 years of symptomatic disease (de Koning et al., 2007). However, we rather expect a protecting effect of anti-IL-1 therapy, if any, since a recent study showed that in patients with smoldering or indolent multiple myeloma who were at risk of progression to active myeloma, treatment with IL-1 inhibitors decreased the myeloma proliferative rate and CRP levels in those who responded (Lust et al., 2009a).
For further information we refer to the Canakinumab Investigator*s Brochure Ed 7.

Patients will be requested to visit our clinic 12-15 times, and to complete a diary of symptoms and potential adverse effects. 12-15 blood samples will be taken of 20-60 ml each. In order to start this study, treatment with the IL-1 receptor antagonist anakinra will have to be withdrawn; we expect patients to experience symptoms within 72 hours of this withdrawal. As soon as they are symptomatic, patients will start on canakinumab treatment. Rescue treatment has been stipulated in the event that canakinumab is not as efficacious as anakinra; if treatment fails, patients are returned to anakinra treatment. The benefit of this study: if canakinumab is as effective as anakinra, it will mean one subcutaneous injection a month instead of a painful injection once a day. If this study shows good results, steps will be taken towards registration of canakinumab for use in Schnitzler syndrome.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients with a diagnosis of Schnitzler syndrome as fulfilling the criteria (see table 1).
2. Patients with Schnitzler syndrome who have been treated with the biological agent Anakinra must have demonstrated a partial or complete clinical response with an associated decrease in their biomarkers of inflammation (CRP and SAA) below 10mg/L.
3. Active Schnitzler syndrome (if applicable after stop of current treatment) at time of start of study treatment.
4. Male and female patients at least 18 years of age at the time of the screening visit.
5. Patient*s informed consent prior to the study
6. Negative QuantiFERON test or negative Purified Protein Derivative (PPD) test (< 5 mm induration) at screening or within 1 month prior to the screening visit, according to the national guidelines. Patients with a positive PPD test (>= 5 mm induration) at screening may be enrolled only if they have either a negative chest x-ray or a negative QuantiFERON test (QFT-TB G In-Tube.
7. Adequate contraception in premenopausal women

Exclusion criteria

1. Pregnant or nursing (lactating) women
2. History of being immunocompromised, including a positive HIV at screening (ELISA and Western blot).
3. Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose
4. History of significant medical conditions, which in the Investigator*s opinion would exclude the patient from participating in this trial
5. History of recurrent and/or evidence of active bacterial, fungal, or viral infection(s)
6. Use of any other medication to control the symptoms of active Schnitzler syndrome.
7. Corticosteroids > 0.1 mg/kg/day in the 1 week prior to the baseline visit
8. Use of the following therapies:
• Anakinra within 24 hours prior to Baseline visit
• Rilonacept within 1 week prior to Baseline visit
• Toclizumab within 3 weeks prior to Baseline visit
• Etanercept within 4 weeks prior to Baseline visit
• Adalimumab within 8 weeks prior to the Baseline visit
• Infliximab within 12 weeks prior to the Baseline visit
• Rituximab within 26 weeks prior to the Baseline visit
• Leflunomide within 4 weeks prior to the Baseline visit. Documentation of a completion of a full cholestyramine elimination treatment after most recent leflunomide use will be required.
• Thalidomide within 4 weeks prior to the Baseline visit
• Cyclosporine within 4 weeks prior to the Baseline visit
• Intravenous immunoglobulin (i.v. Ig) within 8 weeks prior to the Baseline visit
• 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil within 12 weeks prior to the Baseline visit
• Dapsone, mycophenolate mofetil within 3 weeks prior to the Baseline visit
• Growth hormone within 4 weeks prior to the Baseline visit
• Corticosteroids (oral prednisone (or equivalent)) > 1.0 mg/kg/day (or greater than the maximum of 60 mg/day for children over 60 kg) within 3 days prior to the Baseline visit
• Intra-articular, peri-articular or intramuscular corticosteroid injections within 4 weeks prior to the Baseline visit
• Any other investigational biologics within 8 weeks prior to the Baseline visit
• Any other investigational drugs, other than investigational biologic treatment, within 30 days (or 3 months for investigational monoclonal antibodies) or 5 half-lives prior to the Baseline visit, whichever is longer
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
10. Severe co-morbidity (as judged by investigator).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-12-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ilaris
Generic name:	Canakinumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-10-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2010-021166-30-NL
CCMO	NL32191.091.10