Biomarker-guided treatment-and-stop-strategy for recombinant IL-1receptor antagonist (anakinra) in patients with systemic Juvenile Idiopathic Arthritis.

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This study has been transitioned to CTIS with ID 2024-518684-35-00 check the CTIS register for the current data. The current project proposal continues on our findings of the performed prospective cohort study, aiming to develop a biomarker guided...

Ethical review	Approved WMO
Status	Completed
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON43845

Source
ToetsingOnline

Brief title
ESTIS trial: Early Stop of targeted Treatment in children with Systemic JIA

Condition

- Autoimmune disorders
- Joint disorders

Synonym
Still's disease, systemic JIA

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw;goed gebruik geneesmiddelen grant nummer 836041005,SOBI AB, Stockholm, Sweden,SOBI levert een bijdrage voor monitoring van de studie en ontwikkeling van het CRF en een vergoeding per geincludeerde patient.

Intervention

Keyword: anakinra, biomarker-guided therapy, Stop-strategy, systemic Juvenile Idiopathic Arthritis

Outcome measures

Primary outcome

* The total (mean/median) number of injections of anakinra per patient during

the first year of treatment;

Secondary outcome

* The number of patients with *clinically inactive disease* without medication

at time point 1 year.

* The total number of disease flares during or after tapering and stop of

therapy in the first year;

* The number of patients with remission off medication at time point 2 years;

* The number of patients needing to switch treatment because of treatment

failure during the first year (to calculate reduction in treatment costs)

* The number of (serious) adverse events in the first year.

Study description

Background summary

Systemic Juvenile Idiopathic Arthritis (sJIA) is a rare disease, affecting
20-40 new patients in the Netherlands each year. SJIA

is currently classified as a subtype of JIA, characterised by chronic arthritis as well as signs of systemic (auto-) inflammation.
Until recently, the cornerstone in the treatment of sJIA consisted of corticosteroids, often necessary in high doses during prolonged time. This resulted in significant side effects like growth retardation, hypertension etc.
Since 2005, understanding of the pathophysiology of sJIA has increased, showing the importance of IL-1 and IL-6 in the inflammatory cascade of this disease. These findings have resulted in the use of recombinant IL-1 receptor antagonist (rIL-1RA or anakinra), still an unregistered drug for this indication, as well as the registration of tocilizumab (anti-IL-6) in 2011 and Canakinumab (anti-IL-1) in 2013 for the indication sJIA.
However, Tocilizumab and Canakinumab are registered as 2nd line treatment, for children with unsatisfactory responses to corticosteroids. This means that patients with sJIA still suffer from major side effects of corticosteroids and ultimately many of these patients need to switch to anti-IL-1 or anti-IL-6 in the chronic phase of sJIA, when proven steroid dependent. As no known stop-strategies for these drugs are currently available, these patients face long-term immunosuppressive treatment at high costs and uncertain risks.
We recently performed a prospective cohort study, treating new-onset sJIA patients with r-IL-1RA as first line treatment in corticosteroid naïve sJIA patients. We showed high response rates and importantly, also tested a stop-strategy that associated succesful stopping with low levels of several biomarkers.

Study objective

This study has been transitioned to CTIS with ID 2024-518684-35-00 check the CTIS register for the current data.

The current project proposal continues on our findings of the performed prospective cohort study, aiming to develop a biomarker guided stop strategy for the use of rIL-1RA in sJIA: short and targeted therapy early in the disease course with a yet unregistered drug for sJIA.

The main hypothesis of this study is that the (average) number of injections rIL- 1RA per patient in order to achieve and maintain clinically inactive disease in the first year after the start of rIL- 1RA , by making additional use of the biomarker IL -18, is lower than the average number of injections rIL-1RA that was necessary per patient in the first year after the start of rIL- 1RA in our historical cohort (in which the decision to taper and stop with rIL- 1RA was done only on clinical judgment of the treating physician).

Study design

non-randomised, biomarker-driven, tapering and stop study (intervention trial)

Intervention

Tapering and discontinuation of treatment if patients on rIL- 1RA therapy at D90 (after 3 months of therapy) show a good clinical response (adapted ACRPed score 90 or clinically inactive disease) and have a biomarker value below the treshold (IL-18).

Study burden and risks

Concerning burden: nil.
- No extra visits / outpatient visits because of the study (following the current clinical practice)
- Only iin case blood is drawn because of clinical indication in the first year after start of therapy, an additional quantity of blood is taken (up to 10 times in the first year) for the determination of the biomarker IL -18
- Standardized and validated questionnaires (JAMAR) will be collceted at multiple time points during the study. These are currently already used in clinical practice to monitor patient reported disease activity .

Regarding risk : low risk.
- It is a tapering and stop study of a specific biological (rIL- 1RA). Early cessation of treatment will have no measurable increased risk for the patient. Since it can not be excluded that patients show disease activity again after discontinuation of treatment, there will be close monitoring during the study in order to be able to start therapy asap again if needed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Open label lead-in (observational part):
1. Children and adolescents diagnosed with sJIA (ILAR 2004 classification criteria);;2. Both male and female patients, aged 8 months - 16 years (anakinra is approved in children aged 8 months and older who suffer from CAPS, and as per definition, JIA has an onset before the age of 16); ;3. Parents or legal guardian (and the subject when age is appropriate) who are willing to sign the consent/assent forms.;Intervention part (tapering and stop phase):
1. patients treated with rIL-1RA as first line therapy showing an initial beneficial response (no fever on day 7) to rIL-1RA monotherapy (concomitant NSAID allowed);

2. Achieving at least an ACRPed90 response without fever around point 90 days after start of therapy on rIL-1RA mono therapy (concomitant NSAID allowed).

Exclusion criteria

Open label lead-in (observational part):
1. An onset of Macrophage Activation Syndrome (MAS) simultaneously with sJIA or after the diagnosis of sJIA will lead to exclusion of a (potential) subject from participation in this study;;2. Previous systemically administered corticosteroid treatment within 6 weeks before diagnosis and enrollment.;3. Known exclusion criteria for the use of rIL-1RA (renal failure, with a creatinin clearance rate of < 30 ml/min or neutropenia with neutrophil counts of < 1,5 * 10e9/L).;Intervention part (tapering and stop phase):
1. An onset of Macrophage Activation Syndrome (MAS) after the diagnosis of sJIA will lead to exclusion of a (potential) subject from participation in this study;2. Patients with a relapse of sJIA in the open label lead-in phase of the study will be excluded for the tapering and stop phase, and will switch treatment to concomitant corticosteroid treatment and/or other biological therapy (Tocilizumab or Canakinumab) upon the decision of the treating physician.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-03-2017
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kineret
Generic name:	Anakinra
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-07-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-10-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-11-2016

Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2024-518684-35-00
EudraCT	EUCTR2015-004393-16-NL
CCMO	NL55231.041.16