When and in whom to stop etanercept after successful treatment of Juvenile Idiopathic Arthritis

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Hypothesis:A substantial proportion of the JIA patients in remission (according to the Wallace criteria) will be able to discontinue etanercept successfully.Goals:To investigate in a randomized controlled trial:- which proportion of JIA patients in...

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

Summary

ID

NL-OMON34350

Source
ToetsingOnline

Brief title
Withdrawal of etanercept after successful treatment

Condition

- Autoimmune disorders

Synonym
juvenile arthritis, juvenile idiopathic arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Reumafonds

Intervention

Keyword: Etanercept, Juvenile Idiopathic Arthritis, Remission, Withdrawal

Outcome measures

Primary outcome

Part 1:

- Flare-rate (adjusted for time in remission before discontinuation and JIA subtype)

Part 2:

- Prediction model for successful discontinuation of etanercept (variabels: duration of remission till withdrawal etanercept, MTX comedication at inclusion, optimal dosage of MTX given before start, subtype JIA, MRP8/ MRP14, presence of pre-existent radiological damage)

Secondary outcome

Part 1:

- Patient- and disease characteristics of the patients with a exacerbation
- Flare-rate in the subgroups 3-9 en 9-18 months in remissie with etanercept.
- Number of patients with protocol violence.

Deel 2:

- Number of patient with persistent remmission 12 months after discontinuation fo therapy.
- Course of the disease after re-introduction of etanercept in case of a exacerbation (using ACR pedi 30/50/70 criteria).

- Number of patients with protocol violence.

- Response of psoriatic skin lesions (if possible).

Study description

Background summary

Juvenile Idiopathic Arthritis (JIA) is the most common cause of chronic arthritis in childhood. The term JIA encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown cause. It is a heterogeneous disease comprising several disease subtypes. Evidence is accumulating that early disease control is important to prevent joint destruction, growth deformities and even blindness (from JIA-associated chronic uveitis). Therefore, JIA therapy has changed in favour of the early introduction of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and biologicals.
Since its introduction in 1999 etanercept, a TNF-alpha-blocker, has become an important treatment for patients with refractory JIA. It is currently the most frequent prescribed biological, and is proven to be effective in JIA patients who previously had not respond to DMARDs, including methotrexate. (Lovell 2000 en Prince 2009) However, despite this success there are also concerns regarding the long-term use of etanercept, since it suppresses the immune system of young children.
After reaching remission, it is a logical step to try to reduce or discontinue etanercept in order to prevent unnecessary side-effects and costs and to reduce the burden of weekly injections. Unfortunately, no guidelines on when or how to stop etanercept therapy are currently available and little is known about the course of the disease in JIA patients after discontinuation.
Only one study (our pilot study) has been published on the subject when and how to stop etanercept after successful treatment of JIA patients (Prince 2009).
All 19 JIA patients from the ABC-register who discontinued etanercept because of a sustained good clinical response were evaluated. Ten of these patients retained remission during follow up during a median of 0.8 years. All patients who retained remission fulfilled the Wallace remission criteria at time of discontinuation in contrast to only one third of the patients who flared. Patients with a longer remission period and carefully tapering had a better chance retaining remission. Nine patients flared after discontinuation of etanercept, five within the first 6 months and 3 more in the following 3 months after discontinuation. All eight patients who restarted etanercept after disease flare regained a good clinical response which is reassuring. However due to the fact that these data are from an observational study we can not exclude that reasons related to patient and disease characteristics have influenced the decision to stop etanercept at a certain moment causing

substantial bias. There were not enough patients in the study to evaluate other predictors for successful stopping. This underlines the need for a study with an interventional design and more patients to answer the research questions.
The National Institute for Clinical Excellence (NICE), UK, recommend in their guidelines a 2 years disease-free period before discontinuation of etanercept (NICE 2005). However, it is not clear on what data they based their recommendation.
Foell et al. published data on when to stop methotrexate (MTX) after successful treatment and at the same time they investigated the usefulness of myeloid related proteins 8 and 14 (MRP8/ MRP14) (Foell 2004). Conclusions were that residual synovial inflammation seemed to influence the rate of disease flares and that MRP in clinical inactive arthritis may help to identify patients in whom MTX can be safely withdrawn. But they also mention that they cannot exclude the possibility that reasons related to patient characteristics influenced the decision for MTX earlier or later, which might have influenced the subsequent occurrence of flares.
Also, data on Rheumatoid Arthritis (RA) treatment on this subject are limited. Miyamura et al. published results on two patients who had prolonged clinical and radiographic remission of RA after the discontinuation of etanercept (Miyamura 2010). Brocq et al. reported on 21 RA patients in remission who were taken of anti-TNF-alpha (14 of etanercept) (Brocq 2009). Only 25% of patients retained remission. Patients still in remission had a longer mean period of anti-TNF-alpha use and longer mean period of remission before discontinuation.
Concluding from published data; no consensus has been established concerning the important clinical question when and in whom to stop etanercept therapy in JIA after successful treatment.

Study objective

Hypothesis:
A substantial proportion of the JIA patients in remission (according to the Wallace criteria) will be able to discontinue etanercept successfully.

Goals:
To investigate in a randomized controlled trial:
- which proportion of JIA patients in remission can successfully discontinue etanercept compared to JIA patients in remission who continue etanercept;
- if time in remission on etanercept is an important factor in retaining remission after discontinuation of etanercept;
- if flare-rate is different between the subgroups 3-9 months and 9-18 months in remission on etanercept.

To evaluate
- predicting factors (patient or disease characteristics (including time in remission) and MRP8/MRP14) for successfully discontinuing etanercept;
- the disease course after discontinuation of etanercept therapy (time to

flare) and the effect of restarting etanercept after flaring.

Study design

The study consists out of 2 parts:
1. A randomized controlled trial. Intervention: discontinuation etanercept
2. An observational study of all patients discontinuating etanercept.

1. A randomized controlled trial (intervention: discontinuation of etanercept)
All eligible patients selected from the ABC-register and during a 12 month inclusion period will be stratified into 2 subgroups (3-9 and 9-18 months in remission under etanercept treatment) and than randomized in 2 arms; an intervention and a control group. Stratification in these 2 subgroups will ensure an equal representation of time in remission in both arms and therefore avoid confounding. We will test for interaction between the 2 subgroups. Both subgroups (3-9 and 9-18 months in remission under etanercept treatment) will be analyzed together, with adjustment for time in remission.
Patients from the ABC-register who already meet the in- and exclusion criteria before beginning of the study will be included directly after approval of the Medical Ethical Committee and depending on their time in remission enrol in the different subgroups.
Patients meeting the in- and exclusion criteria during the inclusion period, will be included as soon as these criteria are met.
The study will be open (not blinded for both patients and physicians).
Randomization, in block sizes of 6 patients, will be coordinated from the Erasmus MC Sophia Rotterdam, and will be confirmed by email or fax within 24 hours.
Duration of this randomized part will be 9 months in total; 3 months tapering off and 6 months follow-up from discontinuation. We consider a follow-up of 6 months from discontinuation long enough, since in our pilot study more than 50% of the patients flared within 6 months.

Intervention: Patients will first taper the etanercept medication. If patients are on a dosing schedule of twice a week 0.4 mg/kg (with a maximum of 50 mg/week) frequency will be lowered to once a week 0.4 mg/kg (with a maximum of 25 mg/week) for 3 months. If patients are on a dosing schedule of once a week 0.8 mg/kg (with a maximum of 50 mg/week) frequency will be lowered to once a week 0.4 mg/kg (with a maximum of 25 mg/ week) for 3 months. If patients don*t experience a flare during tapering of etanercept it will be discontinued completely 3 months after start of the study. After discontinuation of etanercept, patients will be followed for another 6 months for this study part.
Concomitant medication: MTX, if used, will be kept stable through the study course, with adjustment for growth allowed. In case of complaints and not meeting the criteria of a flare, it is allowed to start or raise the dosage of NSAIDs. No corticosteroids (including intra-articular corticosteroids up to 6 months prior to inclusion) and other synthetic and biologic DMARDs are allowed.

Control: Patients will continue the same dosage of etanercept, as it is at start of the study. Follow-up: 9 months.
The dosage of etanercept and MTX, if used, will be kept stable through the study course, with adjustment for growth allowed. In case of complaints and not meeting the criteria of a flare, it is allowed to start or raise the dosage of NSAIDs. No corticosteroids (including intra-articular corticosteroids up to 6 months prior to inclusion) and other synthetic and biologic DMARDs are allowed.

2. An observational study of all patients discontinuating etanercept (predictive factors for successful discontinuation)
Patients, who were randomized into the control group (continuation of etanercept) and are still in remission at the end of part 1, will discontinue etanercept in the same way as the intervention group in part 1 did. All patients who discontinue etanercept will be followed for 15 months in total . All patients who start tapering off etanercept will be included for this analysis.
We will analyze the following predictive factors for successful discontinuation of etanercept:
- Duration of remission till withdrawal of etanercept (continuous variable)
- MTX comedication at inclusion of the study (yes or no)
- Optimal dosage of MTX given before start of etanercept? (yes or no, optimal dosage MTX defined as 15-20 mg/m2/week, with a maximum of 25mg/week)
- Subtype JIA (systemic vs non-systemic patients)
- Immunological parameters (f.e. MRP8/ MRP14, continuous variable)
- Presence of pre-existent radiological damage before start of etanercept therapy (yes or no)

Flare:
If the local investigator notices (in both study parts) that a patient shows an increase in disease activity, the flare-criteria will be checked and verified by the research physician. Patients will be treated according to the judgement of the treating physician and etanercept therapy can immediately be reintroduced. Response to reintroduction of etanercept will be measured according the ACR pediatric 30, 50 and 70 improvement criteria. If a patient or parent re-introduces etanercept, although the criteria are not completely fulfilled, it is considered as protocol violence.
We consider a patient in remission to flare if one or more of the following occurs (=flare criteria):
- active arthritis in two or more joints;
- ESR > 30 mm/hour not otherwise explained;
- physician*s global of 30mm or more;
- active uveitis;
- fever, rash, serositis or generalized lymphadenopathy (for sJIA patients only);
- signs of SI and spine involvement according the treating physician (for ERA patients only);

Follow-up:
Fixed study visits are at start of the study, during tapering of etanercept, and regularly after discontinuation of etanercept (see protocol).

Intervention

Intervention: withdrawal of etanercept therapy.

Control: continuation of therapy (etanercept).

Study burden and risks

The risk of withdrawal of etanercept is the risk of exacerbation of the disease. However with the continuation of treatment there also remains a (small) risk of exacerbation. In addition there are more risks related to continuation of etanercept, especially with the long-term use of etanercept iwith an increased risk of infection, and possible increased risk of the development of other autoimmune diseases and even malignancies. It is reassuring that in our pilot study all patients in whom etanercept was restarted due to an exacerbation, responded well to the reintroduction of etanercept.

The burden of the patients in this study is negligible because standard usual care is applied.

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

- Diagnosis of Juvenile Idiopathic Arthritis (all subtypes) by the International League of Associations of Rheumatology (ILAR) criteria
- On etanercept therapy
- Concomitant therapy allowed are: NSAIDs, low dose MTX (maximum 10 mg/m2), and other medications not related to the treatment of JIA.
- 3 to 18 months in remission according to the criteria of Wallace (i.e. 9 to 24 months of inactive disease)
- Age >=4 and <18 years at start of study
- Written informed consent from parents and patients 12 years and over

Exclusion criteria

Concomitant medications not allowed are: corticosteroids (including intra-articular corticosteroids up to 6 months prior to inclusion) and other synthetic and biologic DMARDs.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-01-2011
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	02-12-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL33099.078.10