The course of Disease Activity, infliximab serum concentrations and anti-infliximab antibody concentrations measured, between two standard infliximab infusion time- periods, in patients with rheumatoid arthritis.

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Primary Research Question:Is the disease activity halfway through the infusion significant higher compared to the disease activity at the start if infusion or lower compared to the disease activity at the end of infusion?Secundary Research Questions...

Ethical review	Approved WMO
Status	Pending
Health condition type	Joint disorders
Study type	Observational invasive

Summary

ID

NL-OMON31619

Source
ToetsingOnline

Brief title
Disease activity and (anti)infliximablevels between two infliximabdoses

Condition

- Joint disorders

Synonym
Rheumatoid Arthritis

Research involving

Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: Sint Maartenskliniek

Intervention

Keyword: Disease Activity, Infliximab, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

DAS28

Secondary outcome

infliximab serum levels and anti-inflximab serum levels

Study description

Background summary

Infliximab is a chimeric monoclonal antibody that binds with high affinity and specificity to TNF-alpha and neutralizes its biological activity. Several studies in both early as refractory rheumatoid arthritis demonstrate that infliximab gives rapid and sustained clinical response, delays radiographic progression, and improves functional status and health-related QOL

Despite the success of infliximab and other biological therapies, approximately 14-30% of the patients treated with infliximab fail to respond. Furthermore, in clinical practice 22-51% of the patients with RA receive within 1 year higher doses of infliximab. This is in contrast to the two pivotal randomised clinical trials (ASPIRE and ATTRACT) in which at most 17% of the patients seems to benefit from a higher dose infliximab. A higher dose of infliximab could however increase dose dependent side effects and will increases the costs of the therapy.

Therefore a more individualized approach is needed to tailor the infliximab-dose. Possible solutions for avoiding individual overdosing of antiTNF-alpha could be titration of the infliximab dose based on actual disease activity scores. The use of DAS28 scores, as measure of disease activity, will

help to identify responders and non-responders objectively and quickly.

In addition to dose titration based on disease activity, data derived from both rheumatology and gastro-enterology patients suggest that the determination of serum trough concentrations of infliximab and anti-infliximab antibodies may help to optimize treatment. Low serum trough levels of infliximab have been associated with reduced clinical efficacy. Furthermore, clinical response in RA decreases rapidly with serum infliximab trough levels under 1 mg/l. The pharmacokinetics of infliximab can be altered by the formation of antichimeric antibodies against infliximab (HACA). HACA*s have been found in 8% to 43% of RA patients treated with infliximab and have been associated with less efficacy and higher adverse event rates. Knowledge of the (anti-) infliximab serum-concentrations could therefore provide auxiliary information for the decision whether a dose escalation or de-escalation is necessary. Currently we are conducting a cohort study to determine the added value of pharmacokinetic parameters above disease activity guided treatment.

Although cross sectional data about the relationship between (anti)infliximab levels and response are available, longitudinal data about the relation between pharmacokinetics and disease activity are absent. Therefore, the right moment to measure disease activity and serum (anti)infliximab levels is still unknown. The most practical moment to collect disease activity and pharmacokinetic information is just before the administration of a new course of infliximab (trough levels). Besides practical arguments, there is also evidence that serum trough levels are associated with reduced clinical efficacy. However, the infusion interval of infliximab is 4-8 weeks. Therefore, it cannot be ruled out that disease activity changes over times during the infusion course: theoretically decreasing infliximab levels could lead to increased disease activity.

More information is therefore needed about the course of the disease activity between two infusions, and how disease activity is related to (anti-)infliximab serum levels. More information is also needed about the moment of anti-infliximab formation. Knowledge of these pharmacokinetic and pharmacodynamic parameters could help us to determine the position of therapeutic drug monitoring infliximab therapy in rheumatoid arthritis.

Therefore, this observational, descriptive open-label pharmacokinetic-pharmacodynamic cohortstudy describes the relationship between disease activity and (anti)infliximablevels in patients with rheumatoid arthritis.

Study objective

Primary Research Question:
Is the disease activity halfway through the infusion significant higher compared to the disease activity at the start if infusion or lower compared to

the disease activity at the end of infusion?

Secundary Research Questions:
1) What's the relationship between infliximab serum levels and disease activity?

2) How progresses the anti-infliximab levels in time and how are these anti-infliximab levels related infliximab serum levels and disease activity.

Study design

Observational, descriptive open-label pharmacokinetic-pharmacodynamic cohortstudy

Study burden and risks

Participants of this study are patients who are already treated with infliximab for rheumatoid arthritis, an authorized indication for infliximab. Before each infusion, as part of the standard treatment in our hospital, DAS28-scores are assessed and blood samples collected.

In this study one dose interval will be observed. During this interval three additional blood samples are collected: one our after the infusion started, one after 50% of the infusion interval and after 75% of the infusion interval. At 50% and 75% of the DAS28 score will also be assessed. Both interventions will lead to a minimal burden or risk.

Contacts

Public
Sint Maartenskliniek

Hengstdal 3
6522JV NIJMEGEN
Nederland
Scientific
Sint Maartenskliniek

Hengstdal 3
6522JV NIJMEGEN
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients who had fulfilled the 1987 ACR criteria and had started infliximab therapy for at least 3 months

Exclusion criteria

There are no exclusioncriteria for this study other than the regulatory contraindications

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2008

Enrollment:	25
Type:	Anticipated

Ethics review

Approved WMO 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
CCMO	NL20709.091.08