Handscan optical measurements in Rheumatoid Arthritis: an inventory comparing serum levels of CRP, ESR, IL-6, clinical arthritis and reproducibility of DAS28.

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2.1 Primary ObjectiveDescribing the association between Handscan optical scores, markers of inflammation (levels of CRP, serum IL-6) and clinical swollen joint score in three treatment groups with different pharmacokinetic modes of action for RA...

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

Summary

ID

NL-OMON49310

Source
ToetsingOnline

Brief title
HANDRAIL

Condition

- Autoimmune disorders

Synonym
reumatoïd arthritis, rheumatism

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: deze investigator initiated study wordt gefinancieerd met een bijdrage/ Grant van Sanofi,Sanofi-aventis

Intervention

Keyword: DAS28, Handscan, IL-6, Reumatoid Arthritis

Outcome measures

Primary outcome

Sensitivity to change of the Handscan during consecutive visits after initiation of different treatment strategies. In this, the percentage of patients with an initial response detected by the Handscan (= at least 2 points reduction in TOS) at the different moments in time will be determined (% initial response at week 1 (early), week 3 (early), week 6 (intermediate), week 9 (late), week 12 (late), respectively).

Secondary outcome

9.1.2 Secondary study parameters/endpoints

- Sensitivity to change of the currently used parameters SJC, TJC, DAS28, CRP, BSE and IL-6 during the consecutive visits after initiation of different treatment strategies.

In this, the same endpoint parameter will be used with the applicable response definition for each of the instruments.

- Difference in response time between Handscan response detection and response detection by the currently used instruments. Differences will be categorized as within patient difference in response time (Handscan response x weeks earlier to x weeks later)

- Handscan TOS and SJC, TJC, DAS28, CRP, BSE and IL-6 at baseline and during the consecutive visits.

- Defining the Handscan optical scores in untreated early RA patients at baseline

- Establish reproducibility of Handscan measurements with interobserver variability of DAS28

- Association between Handscan total optical score and DAS28

- Describing the effects of Sarilumab therapy in MTX naïve patients compared to the monotherapy MTX group

- Establish IL-6 levels with rate of severity of arthritis activity, DAS28 categories

Study description

Background summary

DAS28 is an internationally accepted composite measurement of RA disease activity. There is one composite for BSE and one for CRP. There are several reasons why a better method for RA disease monitoring should be developed.
The first reason is that in the pivotal DAS study in 1990, the indices for the DAS28 were determined in a group of 113 *early* RA patients with a mean swollen joint count of 14, a tender joint count of 11 and a mean CRP of 30 (2). This group of patients is not representative for our current practice and a more sophisticated measuring tool for the current *early phase* of the disease is needed. In future, our therapeutic intervention might even move forward into the spectrum of clinically suspect arthralgia.
Secondly, the reproducibility of DAS28 measurements in clinical practice is known to vary between rheumatologists(3) (Cheung et al 2013). The concordance in DAS28 (remission/ mild/severe/active) varied between 71% and 87%, with only a kappa of 0.50 of agreement on swollen joint level.
Thirdly, the objective part of the indices may cause overtreatment of patients with chronic pain without inflammation (4)
Another plea for an alternative method for measurement of disease activity is the predicted problematic shortage of health care workers in rheumatology care

in the US. In table 1 it is shown that this shortage will be 4000 health care workers in 2030 (5) An automated method (robotica) for measurement of disease activity in RA might be a solution.

The Handscan is a new (Dutch) non invasive imaging device that visualizes inflammation in the joints of hands and wrists in patients with rheumatoid arthritis (RA). The technique is based on optical spectral transmission measurements (www.hemics.com). By using this technique, the Handscan is supposed to be an objective measurement tool.
The Handscan already demonstrated its ability to visualize subclinical inflammation in studies when compared to ultrasound imaging and DAS28 scores (Onna et al 2015).
At this time, only a few institutes (including both MCL and LUMC) have access to and experience with this new device. Until now no data exist comparing the Handscan with systemic parameters of inflammation such as ESR, CRP, IL-6 and arthritis activity. Also, the range of the optical score in different patients is not known.
With this study proposal we will gather data which may lead to more specific clinical Handscan studies. First we have to define its association with current objective inflammatory parameters and its quality to sense small (subclinical) changes in a short treatment period. If this quality exists, than the Handscan might be a new tool for objective and better measurement of disease activity.
A secondary objective of this study is to evaluate the relationship between serum Interleukin-6 levels with CRP, ESR, swollen joint count over time during treatment with different treatment modes. It is expected that serum IL-6 levels in the Sarilumab treatment group better predict clinical response than in the other treatment groups.
Another secondary objective is to describe the effects of Sarilumab therapy in MTX naïve patients (% remission after 12 weeks and time to remission, compared to the monotherapy MTX group).
If this study shows that the Handscan indeed can measure both subclinical arthritis activity and is more sensitive to change than DAS28 measurement, then more studies are justified. One intriguing application could be the use of the Handscan as a classification tool for early RA patients, who would benefit most from rapid onset biologic treatment at the early stages of the disease (6) Furthermore, use of the Handscan as an instrument for substitution of medical healthcare workers in controlling disease activity could be an important answer to the expected shortage of healthcare workers in rheumatology.

Study objective

2.1 Primary Objective
Describing the association between Handscan optical scores, markers of inflammation (levels of CRP, serum IL-6) and clinical swollen joint score in three treatment groups with different pharmacokinetic modes of action for RA activity. Each of these groups has its own time to response due to differences in pharmacodynamic properties of the used medication. If the Handscan is really

sensitive to early response then a difference between treatment groups should be detected in Handscan scores.

2.2 Secondary Objectives
- Comparing differences in time to response in the three treatment groups for swollen joint count, tender joint count, DAS28, CRP, ESR and IL-6
- Defining the Handscan optical scores in untreated early RA patients at baseline
- Establish reproducibility of Handscan measurements with interobserver variability of DAS28.
- Association between Handscan total optical score and DAS28
- Describing the effects of Sarilumab therapy in MTX naïve patients compared to the monotherapy MTX group
- Establish IL-6 levels with rate of severity of arthritis activity, DAS28 categories.

Study design

The HANDRAIL study is a randomised open label trial with three different treatment groups. This study compares the characteristics of different modes for measuring disease activity in three randomized treatment groups with expected different spatial response patterns during 12 weeks.

Intervention

Investigational product/ treatment
Early MTX naive RA patients will be randomized in three subgroups:
I. methotrexate 15 mg once a week monotherapy
II. methotrexate plus methylprednisolone 120 mg IM (depomedrol)
III. methotrexate 15 mg once a week plus Sarilumab 200 mg SC every 2 weeks
After randomisation the study is an open label observational study, which focusses on the characteristics of different modes for scoring RA disease activity during 12 weeks.

Study burden and risks

Participation in this study entails a total of 7 study visits at Screening, baseline, week 1, 3, 6, 9 en 12.
This means 3 to 4 visits more than patients would have had in standard of care in the same period after starting a csDMARD. This is a time burden but also a chance for early detection of persisting disease activity and an oppertunity to adjust medication if necessary.
Blood drawal is slightly more frequent than in regular care, but at the start of methotrexate patients also have to draw blood every three to four weeks in the first three months. (and sometimes more frequently, for example if they start csDMARDs leflunomide of sulfasalazine)

Patients do not experience the Handscan measurements as painful.
Repeating the Joint examination for showing interobserver variability of the DAS28 can be experienced as unpleasant, particularly if patients have a lot of tender joints
All patients have active RA for which a DMARD would be started, regardless of if the patient decides or not to participate in a study. In this study all patients will receive medication with proven efficacy and known side effects, which are deemed acceptable. The therapeutic effect (and the burden of persisting active disease without starting medication) weighs up to the chance of potential side effects.
Also patients have the chance of reaching early remission of RA as a result of the start of Sarilumab early in the course of the disease, this has been shown to have the benificial effect of reaching and maintaining longterm remission.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Able and willing to give written informed consent
- Patients aged >= 18 years
- Recent (< 2 yr) diagnosis of Rheumatoid Arthritis (RA) according to the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR/ACR) classification criteria
- At least two swollen joints of wrists, PIP or MCP joints.
- No previous methotrexate and/or biologic treatment
- No systemic steroids within 6 weeks prior to baseline

Exclusion criteria

- Deformity of the hand or an allergy to light is an exclusion criteria for valid use of the Handscan
- A recent (< 2 months) or planned carpal tunnel operation
- Female who is pregnant, breastfeeding, or is considering becoming pregnant during
the study or a male planning to father a child.
- Any active or recurrent viral infection that, based on the Investigator's clinical
assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes
simplex, or human immunodeficiency virus (HIV).
- History of any malignancy within the last five years except for successfully treated NMSC or localized carcinoma in situ of the cervix.
- Laboratory values meeting the following criteria within the Screening period prior
to the first dose of study drug:
Serum aspartate transaminase (AST) > 2 × ULN
Serum alanine transaminase (ALT) > 2 × ULN
Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m2
Total white blood cell (WBC) count < 2,500/µL
Absolute neutrophil count (ANC) < 1,500/µL
Platelet count < 100,000/µL
Absolute lymphocyte count < 850/µL
Hemoglobin < 5.8 mmol/L
- Uncooperative patients, or any condition that could make the patient potentially noncompliant to the study procedures
- Patients for whom Sarilumab is contra-indicated as described in the local label

- Patients currently participating in any interventional clinical trials
- Previous experience with Sarilumab either through a clinical trial or treatment
- Concomitant use of any biologic DMARDs or any tsDMARDs, including but not limited to etanercept, adalimumab, infliximab, anakinra, rituximab, abatacept, tociluzumab, certolizumab, golimumab, tofacitinib

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:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2020
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Generic name:	Handscan
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	depomedrol
Generic name:	methylprednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kevzara

Generic name:	Sarilumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	methotrexate
Generic name:	methotrexate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-12-2020
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2019-005022-30-NL
CCMO	NL72546.099.20