axSpA International Outcome Assessment (AXIOMA)

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HYPOTHESESi. An ldCT-score that includes syndesmophyte formation and facet joint ankylosis will outperform a score that only includes syndesmophytes (CTSS).ii. ldCT has superior *psychometric properties* to CR in the assessment of progression of...

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

Summary

ID

NL-OMON54129

Source
ToetsingOnline

Brief title
AXIOMA

Condition

- Joint disorders

Synonym
ankylosing spondylitis, axial spondyloarthritis

Research involving
Human

Sponsors and support

Primary sponsor: Zuyderland Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,AbbVie,Galapagos,Novartis,Pfizer,UCB

Intervention

Keyword: measurement instrument, outcome, spondyloarthritis, structural damage

Outcome measures

Primary outcome

Validation of the CTSS and CTFASSS in an independent cohort, following the Outcome OMERACT filter (truth, discrimination, feasibility)

Secondary outcome

8.1.2. Secondary study parameters/endpoints (if applicable)

- Comparison of the psychometric properties (e.g. discrimination) between ldCT and CR in the assessment of progression of structural damage;
- Comparison between an ldCT-score including syndesmophyte formation and facet joint ankylosis (CTFASSS, under development) and a score that only includes syndesmophytes (CTSS);
- Estimation of the potential reduction in the sample size required in controlled trials when using an ldCT score instead of CR to assess progression of structural damage;
- Reliability of structural progression on ldCT at 1 year;
- Psychometric properties of structural progression on ldCT limited to the thoracic spine, with reduced radiation exposure compared to an ldCT score of the whole spine, compared to CR.

8.1.3. Other study parameters (if applicable)

Beyond the main research questions of the study, additional questions can be addressed in AXIOMA. Examples are:

- Assessment of the relationship between bone mineral densities using ldCT (Hounsfield units) and progression of structural damage;
- Assessment of whether a syndesmophyte captured by ldCT is predictive of a syndesmophyte later visible on CR;
- Assessment of whether progression of spinal damage in ldCT is associated with progression of damage at the sacro-iliac joints also assessed with ldCT;
- Investigation of the relationship with major outcomes over time, e.g. longitudinal association of structural damage and spinal mobility or functional impairment, relationship between disease activity and structural progression as measured by ldCT.

New objectives related to the 4-year extension of AXIOMA:

- To gain insight into spinal and SIJ structural damage progression over time, as measured by ldCT, in patients with axSpA;
- To analyse the predictive validity of MRI spinal and SIJ structural lesions (erosions, fatty lesions, ankylosis) using the ldCT structural lesions as the gold standard;
- To investigate whether a change in inflammation, as measured on MRI, is associated with a change in structural damage, as measured on ldCT, both in the spine and SIJ;
- To investigate the longitudinal relationship between spinal and SIJ structural damage and spinal mobility, including individual spinal mobility measures and also including an assessment of the relationship between the structural damage in each spinal segment structural damage and spinal mobility;
- To investigate the longitudinal relationship between spinal and SIJ

structural damage and functional impairment;

- To investigate the longitudinal relationship between spinal and SIJ structural damage and overall functioning and health, and also health-related quality of life;

- To investigate the longitudinal relationship between disease activity and spinal and SIJ structural damage progression;

- To investigate the role of physical activity as a proxy for mechanical stress on structural damage progression;

- To investigate the impact of different coping strategies on structural damage progression, as well as on clinical outcomes such as functional impairment, global functioning and HRQoL;

- To investigate whether a change in MRI spinal and SIJ structural lesions is associated with a change in clinical outcomes, such as functional impairment, spinal mobility and overall functioning and HRQoL;

Study description

Background summary

In spite of its popularity as a research field, it is not known whether biological drugs such as TNF-inhibitors and IL-17 inhibitors slow the progression of structural damage in axial spondyloarthritis (axSpA) and can thus be declared *disease modifying*. Lack of clarity here may either imply the absence of a true pathophysiological effect or a metrological artifact (or in theory a combination of both). The current gold standard for the assessment of structural damage is conventional radiography (CR); however, it has several limitations: only the anterior vertebral corners are assessed, the thoracic spine cannot be reliably assessed due to overprojection of soft tissues and bones, it only allows a 2 dimensional assessment, sensitivity to change is limited, damage progression cannot be reliably captured at 1 year and therefore can only be measured at 2 years, among others. Nevertheless, a better

assessment method has been lacking.
Recently, low-dose computed tomography (ldCT), which is the radiation-poor so more acceptable alternative to conventional CT, has entered the field of axSpA. Major advantages of CT are the lack of overprojection, giving the possibility to assess the whole spine; the ability to scroll through the slices and the 3-dimensionality of the images allowing to assess syndesmophytes from different planes, namely coronal and sagittal, and thereby assessing eight quadrants per vertebral unit instead of two corners. Our team has released the CT-Syndesmophyte-Score (CTSS) and has proved its validity.[1] ldCT, covering the whole spine, detects 5 times more progression in the form of new and growing syndesmophytes, within a 2-year interval than CR, which is limited to the cervical and lumbar spine. Most progression was found to take place in the thoracic spine, which can only reliably be assessed with ldCT. ldCT allows a more detailed assessment of the growth of syndesmophytes, which in turn resulted in a more pronounced difference in the detection of grown syndesmophytes as compared to CR: ldCT detected 8 times more grown syndesmophytes than CR. These findings allow the application of ldCT in axSpA-trials and observational studies while limiting sample-size (in provisional sample size calculations we estimated a possible reduction of 40%).[2] Currently, our team is running another project involving ldCT. As in early axSpA CR is very limited in detecting structural damage,[3] we are assessing whether ldCT can already in the early disease capture some measurable damage. This study is ongoing as part of the follow-up of the Spondyloarthritis Caught Early (SPACE) cohort.[4]
In comparison with CR ldCT has interesting additional research options. It provides access to facet joints and may shed light on initial processes leading to ankylosis. We have already shown that the assessment of facet joint ankylosis is feasible, reliable and sensitive to change.[5] One of our hypotheses awaiting further testing is that an ldCT score that combines syndesmophytes and facet joint ankylosis may not only outperform the modified Stoke in Ankylosing Spondylitis Spine Score (mSASSS, the most adequate scoring method for CR) but also the CTSS (e.g. more discriminative), and thus better reflects irreversible (bone) changes and their consequences in patients with axSpA. A CT facet ankylosis syndesmophytes spine score (CTFASSS) is being developed in our Sensitive Imaging of Axial Spondyloarthritis (SIAS) cohort in which the CTSS and the facet joint ankylosis score had been developed.[1] The new scoring method will combine both syndesmophytes (development and growth) and facet joint ankylosis into one outcome. Both the CTSS and CTFASSS require further validation before they (or one of them) can eventually be used for instance in clinical trials and that is one of the aims of this project.
Another option for further research is to limit the field of view to only the thoracic spine, thus further reducing the already acceptably low radiation level. Based on previous data we hypothesize that such a focused ldCT-scan will not jeopardize discrimination too much, while preserving many of the methodological advantages of ldCT.
A last - but urgently required - additional option for research is to reduce the minimum time-interval for detecting real progression of damage from two

years to one year. We hypothesize that ldCT-scanning of the spine and scoring with an appropriate method will give resolution here. In summary, this project aims at developing and defining the role of ldCT in the assessment of structural damage in axSpA. The main outcome of this project is an appropriately validated ldCT-scoring method for structural damage in patients with axSpA. Such a method should be ready for application in clinical trials.
As ldCT is gaining popularity in the field of axSpA, it becomes important to get insight into the course of structural damage progression over time. So far, progression of structural damage as measured with ldCT has only been investigated over a period of 2 years. Having identified a cohort of patients with baseline structural damage and thus at risk for the development of more damage, creates an opportunity to get insight into the progression of damage over time in axSpA, as measured with ldCT, and both at the spinal and SIJ level. Having a longer follow-up with both clinical outcomes and a complete imaging assessment, including conventional radiographs, ldCT, as well as spinal and SIJ MRI, allows to investigate the relationships between outcomes over time, including shedding light on the longitudinal relationship between several outcomes.
By adding a complete axial MRI to the assessments performed will allow to investigate a current hot topic in field of axSpA, which are the structural lesions as assessed on MRI and their validity and predictive validity. As CT is the gold standard technique to assess bone damage, we can investigate whether structural lesions seen on MRI, e.g. erosions, are also seen on ldCT, or whether MRI-structural lesions can predict the development of CT-detected structural lesions. If so, MRI-structural lesions could be used as surrogate markers of structural damage. But if not, the field of axSpA also gets clarity in that assessing the effect of interventions on MRI structural lesions is not the way to go. The doubts around MRI structural lesions have led to not include them in the most recent update of the ASAS Core Set for axSpA.[6] At the same time, the need to measure structural damage in a more sensitive way calls for more research in this area.

Study objective

HYPOTHESES
i. An ldCT-score that includes syndesmophyte formation and facet joint ankylosis will outperform a score that only includes syndesmophytes (CTSS).
ii. ldCT has superior *psychometric properties* to CR in the assessment of progression of structural damage and may lead to 40% reduction of required sample size in controlled trials.
iii. In contrast to CR, ldCT has the ability to capture structural progression reliably already within 1 year.
iv. Limiting ldCT*s field of view to the thoracic spine only will reduce radiation exposure while preserving superior *psychometric properties*.

2. OBJECTIVES

Primary Objective: To validate the CTSS and CTFASSS in an independent cohort according to the OMERACT filter (truth, discrimination and feasibility);

Secondary Objectives:
i. To investigate whether ldCT has superior psychometric properties (e.g. discrimination) to CR in the assessment of progression of structural damage;
ii. To investigate whether an ldCT-score including syndesmophyte formation and facet joint analysis (CTFASSS, under development) performs better than a score that only includes syndesmophytes (CTSS);
iii. To estimate a potential reduction in the sample size required in controlled trials when using an ldCT score instead of CR to assess progression of structural damage;
iv. To determine whether ldCT can capture structural progression reliably at 1 year;
v. To investigate whether an ldCT score limited to the thoracic spine has superior psychometric properties compared to CR with reduced radiation exposure compared to an ldCT score of the whole spine.
vi. Beyond the main research questions of the study, additional questions can be addressed in AXIOMA. Examples are: comparing bone mineral densities using ldCT (Hounsfield units) with progression of structural damage; whether a syndesmophyte captured by ldCT is predictive of a syndesmophyte later visible on CR; assessing whether progression of spinal damage in ldCT is associated with progression of damage at the sacro-iliac joints also assessed with ldCT; relationship with major outcomes over time, e.g. longitudinal association of structural damage and spinal mobility or functional impairment, relationship between disease activity and structural progression as measured by ldCT.
vii. New objectives related to the extension of AXIOMA:
a. To gain insight into spinal and SIJ structural damage progression over time, as measured by ldCT, in patients with axSpA;
b. To analyse the predictive validity of MRI spinal and SIJ structural lesions (erosions, fatty lesions, ankylosis) using the ldCT structural lesions as the gold standard;
c. To investigate whether a change in inflammation, as measured on MRI, is associated with a change in structural damage, as measured on ldCT, both in the spine and SIJ;
d. To investigate the longitudinal relationship between spinal and SIJ structural damage and spinal mobility, including individual spinal mobility measures and also including an assessment of the relationship between the structural damage in each spinal segment structural damage and spinal mobility;
e. To investigate the longitudinal relationship between spinal and SIJ structural damage and functional impairment;
f. To investigate the longitudinal relationship between spinal and SIJ structural damage and overall functioning and health, and also health-related quality of life;
g. To investigate the longitudinal relationship between disease activity and spinal and SIJ structural damage progression;
h. To investigate the role of physical activity as a proxy for mechanical

stress on structural damage progression;
i. To investigate the impact of different coping strategies on structural damage progression, as well as on clinical outcomes such as functional impairment, global functioning and HRQoL;
j. To investigate whether a change in MRI spinal and SIJ structural lesions is associated with a change in clinical outcomes, such as functional impairment, spinal mobility and overall functioning and HRQoL;

Study design

Study design: The Axial Spondyloarthritis International Outcome Assessment (AXIOMA) Cohort is a prospective multicenter observational study.
Duration: 48 months of follow-up for each patient (for the whole study a recruitment period of 12 months is expected). Patients will be invited to a visit at baseline, 1 year, 2 years and 4 years. At 6 and 18 and 36 months they will be invited to fill in a questionnaire online/on paper.
Setting: Patients will be recruited and observed in the rheumatology outpatient clinic.

Study burden and risks

11.4. Benefits and risks assessment, group relatedness
There are no direct benefits for the patient upon participation in this study. If participating, patients will be contributing to a progress in the knowledge in axSpA and, particularly, in the measurement of structural damage. This knowledge will likely be used in future trials testing the effect of treatment strategies on the inhibition of structural damage. Patients will be informed by the treating rheumatologist in case of unexpected findings important for the patient*s health.
As the study is observational, there are limited risks in participating in the study. Patients will not receive any treatment intervention. Burden and risks associated with participation in the study are related to time spent in the assessments, additional imaging assessments performed particularly ldCT, and radiation associated with imaging. An effective dose of approximately 2.0 mSv is received by a patient for a whole spine ldCT (including SIJ). The dose that was initially theoretically estimated and with the use of a phantom at 4mSV, as earlier published.[1,2] However, the measurement of the radiation dose to which study participants were actually exposed revealed to be substantially lower and to be of 2.0 mSV per ldCT. To compare this with CR, dose values could be derived from the literature. There is a wide variety of reported doses, not always representing current state-of-the art and reported doses may be too high. In 2008, CR of the cervical spine (0.2 mSv), thoracic spine (1.0 mSv), lumbar spine (1.5 mSv) and sacroiliac joints (1.5 mSv) combinedly delivered a radiation dose of 3.4 mSv).[10] A more realistic estimate was made for our SIAS-study radiography protocol, including patients from the Leiden University Medical Center (LUMC) using published methodology.[11] This yielded a total

dose of 0.4 mSv resulting from cervical and lumbar spine and pelvic radiographs. Background radiation in Europe is approximately 2.6 mSv per year.[12] The European Commission for radiation protection has produced guidelines for radiation exposure in medical research for patients under the age of 50 years.[13] The dose delivered by ldCT falls in category 2B, which allows research if it is *aimed directly at the diagnosis, cure or prevention of disease*. Using ldCT, smaller and possibly more syndesmophytes can be seen compared with CR; therefore, it is likely that earlier identification of progression is possible. This would increase the feasibility of, for example, medication trials for the prevention of progression. Therefore, ldCT fulfils the requirement set by the European Commission. Compared with the background radiation and the added value of ldCT over CR, we consider ldCT as a viable method for the assessment of structural damage in the spine. Moreover, the development in software with the capability of reducing the radiation dose further is rapidly growing and lower dosages may be expected in the near future. No other risks are foreseen by the participation in this observational study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

a) Male and female patients of at least 18 years
b) Diagnosis of radiographic axial SpA according to the rheumatologist and fulfilling the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for radiographic axial SpA
c) At least one syndesmophyte (cervical or lumbar) on CR (as assessed by the rheumatologist and local investigator)*
d) Provide a written informed consent
*All local investigators have expertise in the assessment of conventional radiographs and therefore this assessment functions as a type of central reading

Exclusion criteria

a) A history of alcoholism, drug abuse, psychological or other emotional problems, severe co-morbidity that are likely to invalidate informed consent or limit the ability of the subject to comply with the protocol requirements.
b) Pregnancy or an active desire to have children on the short-term
c) Presence of >=18 syndesmophytes (i.e. less than 6 vertebral corners free of syndesmophytes)
d) Spinal surgery with osteosynthesis material present in the spine (foreign material visible on the radiograph)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-09-2021
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	18-01-2021
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	NL75398.096.20