1. Study Title

Fluorescence optical imaging in patients with juvenile rheumatic diseases

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Clinical trial protocol

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2. Synopsis

Title of the study: Assessment of inflammation in patients with juvenile rheumatic diseases using the fluorescence optical imaging Xiralite® in comparison to sonography and low-field strength magnetic resonance imaging

Study design: Observational study

Study duration: 2 years, starting 1st of May 2012

Study phase: Not applicable, non-interventional, observational study solely for diagnostic purpose

Indication: Juvenile inflammatory and non-inflammatory rheumatic diseases

Study objectives: To assess inflammation in children and adolescents with juvenile rheumatic diseases affecting the hands and/or fingers by clinical evaluation, in comparison to in vivo fluorescence optical imaging [FOI] technology using Xiralite®, ultrasonography (in grey scale mode [GSUS] and power Doppler mode [PDUS]), and low-field strength magnetic resonance imaging (MRI).

Patients/subjects

- Children and adolescents aging 6 to 18 years affected by an inflammatory rheumatic disease (i.e., juvenile idiopathic arthritis [JIA]) or a non-inflammatory rheumatic disease (i.e., pain syndromes) affecting the hands and fingers.
- Eligibility for fluorescence imaging technology, ultrasound, and low-field strength MRI.

No of study centers: 3 centers

No of patients: 50 with juvenile inflammatory and 50 with non-inflammatory rheumatic disease

Methodology: Clinical assessment

- Pediatric total joint assessment, including swollen joint count (SJC), tender joint count (TJC), and no of joints with limitation of passive motion
- Physicians' global assessment of disease activity
- Parents' global assessment of the child's overall wellbeing
- Childhood health assessment questionnaire (CHAQ)
- Laboratory values (ESR, CrP)
- Juvenile arthritis disease activity score

Ultrasound (GSUS, PDUS)
Fluorescence optical imaging by Xiralite®
Low-field strength MRI

Adverse events: With regards to the usage of the Xiralite® diagnostic imaging, sonography imaging and MRI will be documented.

Analysis schedule:

- One-time clinical evaluation of 50 patients with juvenile idiopathic arthritis at any time point in the course of disease regardless of the therapy used to treat the arthritis and of 50 patients with non-inflammatory juvenile rheumatic diseases with current clinical hand and/or finger involvement
- The patients with non-inflammatory juvenile rheumatic diseases serve as control subjects in view of inflammation assessment by the different methods.

3. Introduction

Juvenile idiopathic arthritis (JIA) is a term describing children and adolescents with chronic inflammatory joint disease. JIA may lead to cartilage and joint destruction (1). Patients with inflammatory joint disease are usually classified according to the International League of Associations for Rheumatology criteria which were published as a second revision in 2004 (2). Arthritis goes along with swelling, pain and limitation of motion of affected joints. The clinical detection of swelling and pain and/or limitation of the range of motion in a joint are required for the diagnosis of arthritis. However, clinical assessment requires particular expertise in the assessment of joint inflammation. Patients may be difficult to evaluate when they report joint pain, but do not have relevant joint effusion. The clinical judgement about the presence or absence of arthritis decides on the diagnosis, and the determined number of joints with arthritis decides on the allocation to a certain JIA category. Moreover, the presence of polyarticular joint affection requires a consequent anti-inflammatory treatment with disease modifying antirheumatic drugs in order to prevent joint damage and disability. It has been repeatedly shown that imaging measures may be very helpful with regard to provide additional information to the clinical judgement.

Conventional radiography is well defined in analyzing long term sequels of inflammation by defining bone erosions and destruction. However, sequential performance is not recommended. Moreover, standard X-ray does not detect synovitis or effusions, its sensitivity with regards to inflammation especially early in the course of disease, is limited.

In contrast to this, ultrasonography is a technique which is particularly helpful in the assessment of joint inflammation in children. Especially joints of the extremities can be analysed with regards to synovitis, effusion and bone destruction. The technique can be performed on site and it does not have any known side effects. In addition, power Doppler ultrasound (PDUS) can be applied together with grey scale ultrasound (GSUS) by measuring the extent of perfusion of the inflamed tissue. Recently it could be shown that ultrasound is more sensitive in showing arthritis than the clinical evaluation (3). Magni-Manzoni et al. described a standardized procedure to assess joints in children. They described the usefulness of this method in view of detecting subclinical arthritis (4). Particularly they were able to show that residual joint inflammation can be present even if an experienced examiner has considered the joint to be in remission.

Another valuable method to detect joint inflammation is magnetic resonance imaging (MRI). Especially strong T2-weighted images using fat suppression have been shown to be very sensitive in analysing joint effusion, synovitis and bone oedema in adults (5-7) and children (8;9). It can therefore be used to guide the decision to change in therapeutic management. The recently developed paediatric MRI score seems to be a reliable and valid method for assessing disease activity and damage in JIA (10).
Since the 1990s open, dedicated low-field strength MRI are at disposal as a new MRI examination in rheumatology (11). The low-field strength MRI has several advantages over the conventional MRI. They are smaller devices with lower acquisition costs. As open devices they are much more convenient to the patients (12). In patients with RA conventional high-field-strength MRI and low-field-strength MRI showed similar results in the detection and grading of bone erosions, joint-space narrowing, and synovitis in the hand and wrists (13). It can be assumed that low-field MRI is applicable in children and adolescents just as in adults. To our knowledge there are no studies with low-field strength MRI in patients with JIA. Our study will provide detailed data on low-field MRI in children with rheumatic diseases.

Indocyanine green-enhanced (ICG) fluorescence optical imaging (FOI) is another promising imaging device to detect joint inflammation. It was recently evaluated in adult rheumatoid arthritis patients. It has been found to be sensitive in the detection of inflammatory changes of the wrist and fingers (14). In experimental models of arthritis FOI has been correlated to histologically proven synovitis (15). Mivenion GmbH, Berlin, Germany, has constructed and

patented the optical system Xiralite X4®, which can be used to measure indocyanine green enhanced fluorescence of the hands and fingers. ICG is a well-known fluorescent dye used in ophthalmology and surgical disciplines. ICG-Pulsion® is licensed for the diagnostic analysis of microcirculation including the eye. The dosage of ICG used is 0.1 mg per kg body weight intravenously as bolus injection. Images using the Xiralite® camera system are then acquired throughout 6 minutes. The provided software (XiraView 3.6) is semi-automatically analysing 3 phases of the diagnostic test with regards to the signal intensity measured. The early phase, the intermediate and the late phase have been described to correspond with local perfusion and the presence of synovitis/arthritis.
In one study, the Xiralite system was used in comparison with B-mode sonography and MRI and has been shown to be comparably sensitive to these techniques in 252 adult patients with arthritis. The authors described even a higher sensitivity of the Xiralite system in comparison to PDUS and MRI especially in the early detection of inflammation (16). In this study, inflammatory changes were found independently of the underlying disease (14).
Experience using this ICG diagnostic imaging in children affected by juvenile rheumatic diseases is very limited. To our knowledge there is just one pilot study with patients with JIA (17;18). According to the preliminary data the Xiralite system seems to be very valuable in detecting inflammation in joints also in children. Its diagnostic value shall therefore be evaluated in more detail in this study. In addition, it shall be looked at specific imaging features which characterize different categories of juvenile arthritis.
This shall be done by comparing the new technique of fluorescence optical imaging with the clinical judgement, ultrasound (GSUS, PDUS) and low-field MRI. Since all of the applied methods are not involving exposure to ionizing radiation, all of these techniques can be considered safe in the usage with children.

4. Study objective

Experience in using FOI and low field MRI are very limited. This large study will provide first data on different imaging measures in children with juvenile idiopathic arthritis and other chronic rheumatic diseases.

- To compare different methods, i.e. i) clinical assessment (joint count), ii) FOI using the Xiralite system®, iii) standardised ultrasonography (GSUS and PDUS), iv) low-field MRI in the assessment of joint inflammation in children and adolescents with juvenile inflammatory and non-inflammatory rheumatic diseases.

- To evaluate the value of FOI using the Xiralite system in discriminating patients with juvenile inflammatory versus non-inflammatory rheumatic disease

- To describe FOI patterns in children with different categories of juvenile idiopathic arthritis

5. Investigational plan

5.1 Overall study design and plan description

The study design is completely observational and not-interventional. In this regard all patients exhibiting arthritis of hands and fingers or complaining about pain in the hands and fingers are subject of the study. Fifty patients will be evaluated by either one of the investigators in addition to standardized ultrasonography (GSUS and PDUS) and FOI by the Xiralite®. Both imaging modes will be performed by a blinded assessor. Picture analysis will be done by all investigators including co-investigators Stefanie Werner, MD and Marina

Backhaus, MD, both from the Department of Rheumatology and Clinical Immunology, Charité-University Medicine Berlin, Charitéplatz 1, 10117 Berlin.

In addition, MRI investigations of one hand (the clinically more dominant one) will be acquired using a dedicated MRI machine capable to image the finger and wrist joint with increased patient comfort. MRI examinations will be performed by the Department of Radiology, Charité Medical School, under the supervision of Kay G. Hermann, MD. Image analysis will be performed independently from the results of FOI and US results.

5.2 Selection of study population / Inclusion criteria

Subjects will be female and male children and adolescents of any race or ethnicity, affected by JIA or chronic arthralgia meeting the following inclusion criteria:

- Children and adolescents aging 6 to 18 years.
- Parents/legal guardian and patients are willing to participate in the study and have signed the informed consent for the study voluntarily.
- Patients and parents/legal guardians agreed to comply with the diagnostic protocol and are willing to perform at least the clinical examination, the sonography and the Xiralite® examination. The performance of an MRI is not mandatory but optional.
- JIA according to the International League of Associations for rheumatology (ILAR criteria) and involvement of at least one finger or wrist joint with pain and/or limitation of motion and/or swelling ever in the disease course, or
  Juvenile non-inflammatory rheumatic disease (e.g., patients with complex regional pain syndrome Type I/II, diffuse idiopathic pain or localized idiopathic pain, patients with psoriasis and joint pain) with at least one finger or wrist joint with pain and/or limitation of motion within the previous three months.

Exclusion criteria:

- Any chronic and/or active infection predominantly affecting the hands and wrists.
- Pregnant or breast-feeding females.
- Patients having a history of any other severe chronic disease than juvenile idiopathic arthritis may be excluded.
- Patients with thyreoid disease.
- Patients who are hypersensitive (allergic) to indocyanine green, sodium iodide or iodine.
- Patients hypersensitive (allergic) to gadolinium DTPA contrast media may be excluded with regards to the performance of the MRI analysis, however may be eligible for sonography and Xiralite® diagnosis.

5.3 Clinical investigation

5.3.1 Physicians' assessment

The physician assessment will include patient characteristics (age, gender, body height and weight). The duration of clinical symptoms will be documented in addition to the current modes of treatment including medication. Any disease in the last 6 months affecting the hands and fingers like fracture, trauma, surgery etc. will be documented. Further items to be recorded are diagnoses and laboratory values (ESR: erythrocyte sedimentation rate, mm/h; CPR: C- reactive protein, mg/l)

- **Physician global assessment of disease activity** (on 21-point numeric rating scale)

- **JADAS-10 (20)**
  The JADAS-10 (Disease Activity Score for juvenile idiopathic arthritis) includes 4 measures: physician global assessment of disease activity (21-point numeric rating scale, range 0 – 10), parents/patient global assessment of well-being (21-point numeric rating scale, range 0 – 10), active joint count (based on the count of any involved joint, irrespective of its type, up to a maximum of 10 joints), and erythrocyte sedimentation rate (normalizes to a 0-10 scale according the following formula: ESR (mm/h) – 20 /10, before making the calculation, ESR values <20mm/hour are converted to 0 and ESR values >120mm/h are convert to 120. The JADAS is calculated as the similar linear sum of the scores of its 4 components, which yields a global score of 0-40.

- **Joint assessment**

  - **Swollen joint count**
    all joints including the fingers and the wrists on both sides will be examined for swelling. Swelling will be classified as present ("1") or absent ("0").

  - **Tender joint count**
    all joints including the fingers and the wrists on both sides will be assessed for tenderness by applying moderate pressure and during passive joint movement. Joint tenderness will be classified as either present ("1") or absent ("0").

  - **Limitation of passive motion**
    all joints including the fingers and the wrists on both sides will be assessed for limitation of motion (LOM). LOM will be classified as present ("1") or absent ("0").

5.3.2 Patients Assessment

Patients will be inquired by questionnaires filled out by their parents or themselves. The questionnaire for the parents and the patients contains the global assessment of the child's overall wellbeing (21-point numeric rating scale) (19) and the Childhood Health Assessment Questionnaire(CHAQ) (20)

5.3.3 Imaging

Assessment of inflammation using joint sonography (GSUS and PDUS

Sonography includes B-mode and PDUS. According to Magni-Manzoni (4) the scoring system will define joint effusions, synovitis and hyperperfusion. Effusions and synovitis will be graded from 0 to 3 (0= absent, 1= mild, 2= moderate, 3= marked).

Perfusion will be estimated by 0= absent, 1= the presence of a few colour signals indicating hyperperfusion, 2= perfusion signals in less than half of the synovial/joint area, 3= perfusion signal exceeding more than half of the joint area.

Tab 1: Documentation of Ultrasound and PDUS results

		B-mode ultrasonography				Doppler-ultrasonography	
No.	**Joint**	**Right**		**Left**		**Right**	**Left**
		Joint effusion	**Syno-vitis**	**Joint effusion**	**Syno-vitis**	**Hyperper-fusion**	**Hyperper-fusion**
1	Wrist						
2	MCP 1						
3	MCP 2						
4	MCP 3						
5	MCP 4						
6	MCP 5						
7	PIP 1						
8	PIP 2						
8	PIP 3						
10	PIP 4						
11	PIP 5						
12	DIP 2						
13	DIP 3						
14	DIP 4						
15	DIP 5						

MCP Metacarpophalangeal joint, PIP Proximal interphalangeal joint, DIP Distal interphlangeal joint

Assessment using FOI by Xiralite

The Xiralite/rheumascan imaging sequence will either be analyzed by the automatically generated composite image (PrimaVistaMode) using the integrated software Xiraview 3.6. In addition, as proposed by S. Werner, an early phase (phase 1: time span until strong increased signal intensities appear in the finger tips), an intermediate phase (phase 2: time span from the appearance of the signal in the finger tips till the maximum of the signal), and a late phase of perfusion (phase 3: decreasing signal intensity in the finger tips) will be analyzed.

S. Werner has proposed a score as following:
0 = no signal; 1 = low signal intensity (red dots present in less than 25 % of the joint area); 2 = moderate signal (predominantly red circular signal in more than 25 up to 75 % of the joint area); 3 = high signal (red and white strong signal intensity in more than 75 % of the joint region).

Tab 2: Documentation of Xiralite® rheumascan results

		left				right			
No	**Joint**	**Sum**	**Phase 1**	**Phase 2**	**Phase 3**	**Sum**	**Phase 1**	**Phase 2**	**Phase 3**
1	Wrist								
2	MCP 1								
3	MCP 2								
4	MCP 3								
5	MCP 4								
6	MCP 5								
7	PIP 1								
8	PIP 2								
9	PIP 3								
10	PIP 4								
11	PIP 5								
12	DIP 2								
13	DIP 3								
14	DIP 4								
15	DIP 5								

MCP Metacarpophalangeal joint, PIP Proximal interphalangeal joint, DIP Distal interphlangeal joint

Assessment using MRI

Low- field MRI-analysis will be performed in selected patients by the rheuma imaging research group of Kay G Hermann, MD, Department of Radiology, Charité-University Medicine Berlin, Charitéplatz 1, 10117 Berlin. MRI will be performed on Esaote O-Scan (using a specialized hand coil, with a field of view covering from distal radioulnar joint to metacarpal bases). The imaging protocol consists of T2-weighted images using fat suppression in addition to T1-weighted images before and after contrast media application. Contrast media gadolinium-DTPA is applied intravenously. The drawing of an intravenous line is planned at the time point when a clinically scheduled blood test is needed. Thus, no extra blood draw or venous puncture is planned per se. Thus, invasive diagnostic measures will be limited to a minimum needed for evaluation on standard clinical grounds.

MR images will be assessed using the pediatric MRI score (=modified RAMRIS) **(10) in a standardized fashion and blinded to results of other imaging methods** as follows:

- **Synovitis** is assessed in 3 wrist regions (1. the distal radioulnar joint; 2. the radiocarpal joint; 3. the intercarpal and carpometacarpophalangeal, CMC, joints) and in each MCP joint. The 1st CMC joint and the 1st MCP joint are not scored. Using a 0–3 scale. A score of 0 is normal, while scores of 1 to 3 (mild, moderate, severe) increase by thirds of the presumed maximum volume of enhancing tissue in the synovial compartment (21).
- **Bone marrow oedema (BMO)** is assessed using a 0-2 scale (0, no oedema; 1, <50% of the bone involved; 2, ≥50% of the bone involved)
- **Bone erosions** are scored at 15 sites within the carpus (carpal bone, distal radius, distal ulna and metacarpal bases) using a 0-4 scale (0=no erosion; 1=1-25% of the bone eroded; 2=26-50% of the bone eroded; 3=51-75% of the bone eroded; 4=76-100% of the bone eroded)

6. Statistical analysis

Sample size planning is based on the logistic regression model to detect a medium association of inflammation status and the different inflammation assessments with an assumed two-sided alpha level of 5% and a power of 80%. 50 patients with juvenile idiopathic arthritis and 50 patients with non-inflammatory juvenile rheumatic diseases with clinically affected hand and/or finger involvement will be assessed by clinical examination, fluorescence optical imaging, sonography, and magnetic resonance imaging. The patients with non-inflammatory juvenile rheumatic diseases serve as control subjects in view of inflammation assessment by the different methods. Descriptive statistics of the sample are reported by absolute and relative frequency as well as median values with interquartile ranges. The Mann-Whitney test is applied for continuous distributed variables and the chi-square test for categorical variables. The clinical assessment of joint inflammation in children is considered to be the gold standard in the first and second hypothesis. The discriminatory ability of i) fluorescence optical imaging using the Xiralite system®, ii) standardised ultrasonography, and iii) low-field strength magnetic resonance tomography are analyzed by calculating the sensitivity, specificity and the area under curve in reference to the clinical assessment. The area under curve is a well established measure for the discriminatory ability of a method with an appealing clinical interpretation. The areas under curve are compared by the test for correlated receiver operating characteristic curves from DeLong et al. (22). Fluorescence optical imaging patterns in children are investigated by clustering techniques within the categories of juvenile idiopathic arthritis.

7. Ethical considerations

Before any works is begun, necessary approval will be sought from the Ethics committee of the Charité University medicine in Berlin. Patients and parents will be clearly and fully informed about the purpose of the study by the paediatric rheumatologist and a study information handout. Then they are asked for their written consent to take part in the study. Signed informed consent will be obtained from the parents, the patient or the legal guardian before the diagnostic procedures are undertaken. Adolescent patients will be included in all discussions in order to obtain oral or written consent.

8. Personnell requirements

In order to cover the organisational needs for all study centres, employment of a study nurse is necessary. Her/his duties are to make the necessary appointments with patients and their families, be responsible in part for the informed consent of patients and families, prepare medication for each individual patient and perform the particular Xiralite® rheumascan diagnostic tests.
The study nurse will make sure that the documentation is accurate and complete and all the documentation schemes are properly filled out.

Data Management (entry, handling, and analysis) will take place at the German Rheumatism Research Center via a statistician and a student.

The employments will be supported by the financial sponsor.

9. Technical requirements

Sonography

There is a need to perform sonographic diagnostics in parallel in the three different centres. In particular, all centres should use the same sonographic equipment. Since the Charite Campus Mitte is using the most advanced musculoskeletal sonographic technique (Esaoate Inc. equipment) there is a need for comparable equipment at all sites.
There will be a request to the financial sponsor to cover renting of equivalent sonography machines for the time of one year at the study site Charite´Campus Virchow, Berlin Buch and Berlin Friedrichshain. Esaoate Inc. is providing equipment with the same Power Doppler function as currently already available at the Charite Mitte.

Xiralite® rheumascan

Since Xiralite® rheumascan equipment is available at the Charite and Vivantes Friedrichshain, no further equipment is needed. Patients from Helios, Berlin-Buch will be examined at either one of the locations above in cooperation with R. Trauzeddel.

10. Financial requirements

Cost for diagnostic activities

- Travel expenses by families, fees for parking	1,000 €
- Leasing cost for ultrasound devices (650 Euro per month)	6,500 €
- Study assistant (6.8 person months)	14,000 €
- Cost for FOI at Charité Mitte (including scientific evaluation) (50 patients, per patient assessment 250 €)	12,500 €
- Cost for MRI assessments (including scientific evaluation) (45 patients, per patient assessment 350 €)	15,750 €

Consumables

Travel costs to meetings, publication cost, cost for ethical approval	600 €

Total	50,350 €

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