EXTENDED REPORT
Inflammation assessment in patients with arthritis using a novel in vivo fluorescence optical imaging technology

Stephanie G Werner,1 Hans-Eckhard Langer,1 Sarah Ohndorf,2 Malte Bahner,3 Peter Schott,4 Carsten Schwenke,5 Michael Schirner,3 Hans Bastian,2 Gudrun Lind-Albrecht,1 Bernward Kurtz,4 Gerd R Burmester,2 Marina Backhaus2

ABSTRACT
Background Indocyanine green (ICG)-enhanced fluorescence optical imaging (FOI) is an established technology for imaging of inflammation in animal models. In experimental models of arthritis, FOI findings corresponded to histologically proven synovitis. This is the first comparative study of FOI with other imaging modalities in humans with arthritis.
Methods 252 FOI examinations (Xiralite system, mivenion GmbH, Berlin, Germany; ICG bolus of 0.1 mg/kg/body weight, sequence of 360 images, one image per second) were compared with clinical examination (CE), ultrasonography (US) and MRI of patients with arthritis of the hands.
Results In an FOI sequence, three phases could be distinguished (P1–P3). With MRI as reference, FOI had a sensitivity of 76% and a specificity of 54%, while the specificity of phase 1 was 94%. FOI had agreement rates up to 88% versus CE, 64% versus greyscale US, 88% versus power Doppler US and 83% versus MRI, depending on the compared phase and parameter. FOI showed a higher rate of positive results compared to CE, US and MRI. In individual patients, FOI correlated significantly (p<0.05) with disease activity (Disease Activity Score 28, r=0.41), US (r=0.40) and RAMRIS (Rheumatoid Arthritis MRI Score) (r=0.56). FOI was normal in 97.8% of joints of controls.
Conclusion ICG-enhanced FOI is a new technology offering sensitive imaging detection of inflammatory changes in subjects with arthritis. FOI was more sensitive than CE and had good agreement with CE, US in power Doppler mode and MRI, while showing more positive results than these. An adequate interpretation of an FOI sequence requires a separate evaluation of all phases. For the detection of synovitis and tenosynovitis, FOI appears to be as informative as 1.5 T MRI and US.

INTRODUCTION
With recent advances in the management of rheumatic diseases, imaging plays a major role in early diagnosis, estimation of prognosis and evaluation of therapeutic outcome. In rheumatoid arthritis (RA), treat-to-target strategies1 and the adequate use of disease-modifying drugs2 require sensitive instruments that allow a valid detection of affected joints.

Careful clinical examination (CE) is a prerequisite but may miss subclinical inflammation in early disease as well as in clinical remission under treatment.3–5 Conventional radiography is commonly used as an indicator of prognosis and represents the standard outcome measure of disease progression in clinical studies but is displaying the result of previous inflammatory processes rather than presenting current disease activity. MRI is considered the gold standard for imaging of synovitis, and MRI bone marrow oedema has been shown to be the strongest independent predictor of radiographic progression in RA.6 7 However, broader usage of MRI in clinical routine settings may be restricted by workflow considerations, cost and limited availability.

Fluorescence optical imaging (FOI) is an established technology that has been evaluated for imaging of inflammation in a variety of animal models.8 In experimental models of arthritis, indocyanine green (ICG)-enhanced FOI findings corresponded to histologically proven synovitis,14 15 The feasibility of this approach in humans was tested,16 17 and an FOI system with fixed optical geometry was developed (Xiralite X4; mivenion GmbH, Berlin, Germany).

We report the results of the first comparative study of this commercially available FOI system with CE, US and contrast-enhanced MRI in two major cohorts of patients with arthritis and allied conditions and controls.

PATIENTS AND METHODS
Patients
Two hundred and fifty-two subjects with arthritis and allied conditions were recruited in two centres. One hundred and fifty-three consecutive FOI examinations were evaluated in centre 1. Ninety-nine outpatients were recruited randomly in centre 2. Inclusion criteria were symptoms in the hands and agreement for participation in the study. Two patients did not want to participate in the study.
after detailed information. Six healthy individuals and six subjects with arthralgia without any sign of an inflammatory rheumatic disease served as the control group.

The study was performed in compliance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Charité University Clinic Berlin. All study participants had signed consent forms after receiving written and oral information.

Clinical and laboratory assessment

CE and laboratory tests (erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)) were performed. Clinical swollen and tender joints (including distal interphalangeal joint (DIP) 2–5) were scored for presence and absence (0–1). The Disease Activity Score 28 (DAS28) was used to assess disease activity in patients with RA, psoriatic arthritis (PsA) and undifferentiated arthritis (uA).

Ultrasoundography

Seventy-four subjects from centre 2 were examined by GSUS and PDUS (Mylab 70 XVG, Esaote, Genova, Italy). Nine hundred and sixty-two joints (wrist, metacarpophalangeal joint (MCP) 2–5, proximal interphalangeal joint (PIP) 2–5 and DIP 2–5 of the clinically dominant hand) were evaluated semiquantitatively (grades 0–3) for synovitis and synovial/tenosynovial vascularity in a standardised manner. Tenosynovitis was scored for presence and absence (0–1). For individual patients, a US sum score over the evaluated joints was calculated.

Magnetic resonance imaging

Fat-saturated coronal proton-density (FS-PD-TSE), non-enhanced and enhanced T1-TSE with subtraction, coronal and axial fat-saturated postintra venous gadolinium (Dotarem, 0.2 ml/kg/ body weight) (FS-T1-TSE) sequences of the clinically dominant hand were performed in 25 patients (1.5 T MRI; Siemens Magnetom Symphony, Erlangen, Germany). MRI findings (MCP 1–5, interphalangeal joint finger 1 (IP), PIP 2–5, DIP 5 and wrist as a whole) were scored according to the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) criteria. Tenosynovitis was scored for presence and absence (0–1). The RAMRI score was calculated.

Fluorescence optical imaging

Background of the technology and details of the Xiralite system (figure 1) are described in a supplementary text (only online available). The FOI examination follows a standardised procedure: both hands are placed on a preformed hand rest. Ten seconds after starting the examination, an ICG bolus is injected (ICG-Pulsion, body weight) (FS-T1-TSE) may be distinguished as defined in table 1.

RESULTS

Patients’ characteristics

The main clinical, laboratory, MRI and US characteristics are detailed in table 1.

Morphological FOI findings

Analysing a single FOI sequence, we found that, within each image stack, three phases (P1–P3) may be distinguished as defined by the different time points’ increased signal intensities in the fingertips. Figure 2 shows a typical FOI image of highly active RA, displaying focal increased signal intensity in all three phases. Inflammatory activity in a variety of affected structures was also detected in PsA (figure 3). A triangular, slightly arcuate enhancement from nail bed into DIP was observed in 60 out of 64 (94%) subjects with PsA compared with 8 out of 38 (21%) in patients with definite RA (sensitivity 94%, specificity 79%, positive predictive value 0.88, negative predictive value 0.88; subjects with both RA and psoriasis have been excluded from the calculation).
Correlations of FOI with assessments of disease activity
FOI scores correlated significantly and relevantly with the Rheumatoid Arthritis MRI Score (RAMRIS) \(r = 0.66, p < 0.0001\) and RAMRIS synovitis \(r = 0.56, p < 0.0001\), weakly correlated with DAS28 \(r = 0.32, p < 0.0001\) and did not correlate with laboratory parameters of systemic inflammation (ESR and CRP).

Agreement rates
ARs of CE and GSUS ranged from 56% to 60%, ARs of CE and PDUS ranged from 76% to 84%, ARs of CE and FOI ranged from 44% to 88% and ARs of MRI and FOI ranged from 48% to 88%, depending on the parameter and subgroup (tables 3, 4, S1 and S2). The disagreement mainly resulted from the higher rate of positive findings in FOI. The highest agreement was found for P1, and the lowest was found for phase 2 (P2).

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Safety
In all subjects, the procedure was well tolerated. Adverse events were not observed.

DISCUSSION
ICG-enhanced FOI with the Xiralite system is a new imaging technology. To our knowledge, this is the first study to evaluate the application in patients with arthritis and to compare it with CE, US and MRI.

We found that FOI agreed well with CE, MRI and US. FOI was more sensitive for detecting synovitis and tenosynovitis than CE. FOI showed a higher rate of positive findings than the other compared modalities. In an FOI sequence, three phases could be distinguished, with different sensitivity and specificity as well with different AR. FOI scores correlated significantly with assessment of disease activity (DAS28, US score, RAMRIS). In healthy subjects, FOI was negative in almost all joints.

FOI relies on the fluorescence optical detection of vascularity in inflamed tissues by the means of ICG as a fluorophor. Angiogenesis is an early event and is highly dysregulated in inflammatory disorders such as arthritis or psoriasis. In RA, hypervascularisation and angiogenesis of the synovial membrane are considered to be primary pathogenic mechanisms responsible for the aggressiveness of the rheumatoid pannus on the joint and are suggested as the link to bone destruction. Synovial vascularisation correlated with the disease activity of a given joint, with radiographic progression and with the therapeutic response in patients with RA.

Correlation of FOI with assessments of disease activity
FOI scores correlated significantly and relevantly with DAS28 (r=0.41, p<0.0001) and US (r=0.40, p=0.0008) but not with laboratory parameters (ESR and CRP).

Subgroup analysis
Generally, the AR did not differ significantly in RA, PsA or uA. Exceptions were the AR for FOI versus CE (s+t) in RA and uA (p=0.0309) and the AR of FOI and GSUS in RA compared to uA (p=0.0013) and PsA (p=0.0017, tables S2 and S3).

Control group
In 12 controls (6 healthy and 6 with arthralgia without any sign of inflammatory rheumatic disease; median age 30 years, range 21–56 years, 3 women), 360 joints were evaluated. FOI did not detect any positive findings in 97.8–100% of joints (figure S1), depending on the evaluated image or phase. FOI displayed positive findings in 1 out of 360 joints (0.3%) in CI, 6 out of 360 joints (2.2%, grade 1 changes) in P2 and none in P1 and P3. MRI was available in five controls. While MRI was normal, FOI showed minimal changes in CI and P2 (1 out of 60 joints, 1.2%, and 2 out of 60 joints, 3.3%) and none in P1 and P3.

from 35% to 88%, ARs of GSUS and FOI ranged from 53% to 72% and ARs of PDUS and FOI ranged from 46% to 82%, depending on the parameter and subgroup (tables 3, 4, S1 and S3). The disagreement mainly resulted from the higher rate of positive findings in FOI. The highest agreement was found for P1, and the lowest was found for P2.
In animal models, FOI has been shown as an appropriate method to identify inflammatory changes in arthritic joints.\textsuperscript{15, 29} The histopathological findings of these studies showed early inflammatory changes in FOI-positive joints.

In the present study, FOI was compared to CE, MRI and US in two larger cohorts of patients with arthritis and in healthy controls. The major findings were comparable in both centres.

**FOI versus CE**

FOI agreed well with clinically swollen and tender joints. Disagreement of FOI and CE mainly resulted from the higher rate of positive findings in FOI. The highest agreement was seen for FOI P1 and swollen and tender joints, indicating that P1 displays joints with high clinical activity. With MRI or US as reference, FOI was more sensitive than CE.

**FOI versus MRI**

FOI agreed well with MRI synovitis and tenosynovitis. Taking MRI as reference, FOI had a sensitivity of 76% and a specificity of 54%, with a higher specificity (94% and 89%) and a lower sensitivity (27% and 47%) for P1 and P3, respectively. AR was up to 88%. Thus, FOI is able to detect MRI synovitis and tenosynovitis reliably. Disagreement of FOI and MRI mainly resulted from the higher rate of positive findings in FOI. A possible explanation is that the different imaging modalities display distinct aspects of the underlying inflammatory pathology. This hypothesis can be proven only by histological examinations.

**FOI versus US**

FOI agreed well with US. With GSUS or PDUS as reference, we found a sensitivity of 70% and 74% and a specificity of 48% and 42%, respectively. A higher specificity and a lower sensitivity were seen for P1 (GSUS 95% and 22%; PDUS 90% and 33%) and P3 (GSUS 78% and 51%; PDUS 69% and 60%). AR was up to 82% with PDUS. Thus, FOI displayed US synovitis and tenosynovitis reliably. Similar to MRI, the disagreement of FOI and US mainly resulted from the higher rate of positive findings in FOI. FOI agreed in a higher range with PDUS, which also displays vascularity.

In a comparative study\textsuperscript{30} with MRI as reference, US revealed a sensitivity of 40–70% for synovitis and an agreement (73–100%) comparable to our findings for FOI. Especially for the inflammatory changes compared to morphological changes, the sensitivity and agreement of US were lower than those for destructive changes. Similar results were obtained in other studies.\textsuperscript{31, 32} US and MRI display both morphological changes (eg, pannus, erosions) and dynamic changes (eg, hyperaemia, hypervascularity, hyperperfusion). FOI only displays the dynamic changes. Because of the broader range of dynamic changes compared to morphological changes, we strongly believe that interpretation of findings is more difficult and this may have an influence on sensitivity and AR.

**Controls**

In the control group, FOI was normal in 97.8% joints. None of the 360 joints was FOI positive in P1 or P3. Positive findings were in low grade. This observation supports the interpretation that the disagreement of FOI with MRI and US in the majority of cases did not result from false-positive findings.

**Subgroups**

AR did not differ significantly between patients with RA, PsA and uA in most scenarios. Thus, this finding suggests that FOI is able to detect inflammatory changes independently of the underlying disease.

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### Table 3  ARs of fluorescence optical imaging with CE, MRI and US

<table>
<thead>
<tr>
<th>CE s (%)</th>
<th>CE t (%)</th>
<th>CE s + t (%)</th>
<th>MRI S (%)</th>
<th>MRI T (%)</th>
<th>MRI S/T (%)</th>
<th>GSUS (%)</th>
<th>PDUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
<td>C1</td>
<td>C2</td>
</tr>
<tr>
<td>FOI C1</td>
<td>72</td>
<td>46</td>
<td>71</td>
<td>44</td>
<td>73</td>
<td>44</td>
<td>73</td>
</tr>
<tr>
<td>FOI P1</td>
<td>79</td>
<td>82</td>
<td>80</td>
<td>80</td>
<td>84</td>
<td>88</td>
<td>78</td>
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<tr>
<td>FOI P2</td>
<td>58</td>
<td>48</td>
<td>58</td>
<td>46</td>
<td>56</td>
<td>46</td>
<td>59</td>
</tr>
<tr>
<td>FOI P3</td>
<td>78</td>
<td>70</td>
<td>77</td>
<td>66</td>
<td>81</td>
<td>70</td>
<td>79</td>
</tr>
</tbody>
</table>

More detailed tables S1, S2 and S3 including 95% CI are only available online.

AR, agreement rate; c1, centre 1; c2, centre 2; CE, clinical examination; CI, composite image; FOI, fluorescence optical imaging; GSUS, ultrasonography in greyscale mode; MRI, magnetic resonance imaging; PDUS, ultrasonography in power Doppler mode; s, swollen joints; s, synovitis; t, tender joints; T, tenosynovitis.

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### Table 2  Sensitivity and specificity of FOI and CE versus PDUS, GSUS and MRI (synovitis or tenosynovitis) as standards of reference along with 95% confidence intervals

<table>
<thead>
<tr>
<th>FOI</th>
<th>MRI S or T (%)</th>
<th>PDUS (%)</th>
<th>GSUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>FOI C1</td>
<td>51% (38/75)</td>
<td>81% (182/225)</td>
<td>67% (88/132)</td>
</tr>
<tr>
<td></td>
<td>41%</td>
<td>72%</td>
<td>58%</td>
</tr>
<tr>
<td>FOI P1</td>
<td>27% (20/75)</td>
<td>94% (209/223)</td>
<td>33% (49/148)</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>43%</td>
<td>21%</td>
</tr>
<tr>
<td>FOI P2</td>
<td>72% (54/75)</td>
<td>56% (127/225)</td>
<td>72% (106/148)</td>
</tr>
<tr>
<td></td>
<td>63%</td>
<td>81%</td>
<td>62%</td>
</tr>
<tr>
<td>FOI P3</td>
<td>47% (35/75)</td>
<td>69% (201/225)</td>
<td>60% (89/148)</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>58%</td>
<td>50%</td>
</tr>
<tr>
<td>Any phase (P1–P3)</td>
<td>76% (57/75)</td>
<td>54% (122/225)</td>
<td>74% (110/148)</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>85%</td>
<td>66%</td>
</tr>
<tr>
<td>CE</td>
<td>53% (38/75)</td>
<td>81% (182/225)</td>
<td>43% (31/75)</td>
</tr>
<tr>
<td></td>
<td>41%; 60%</td>
<td>72%; 89%</td>
<td>44%; 58%</td>
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</table>

Any phase, positive in any phase; CE, clinical examination (swollen joints); CI, composite image; FOI, fluorescence optical imaging; GSUS, ultrasonography in greyscale mode; MRI, magnetic resonance imaging; PDUS, ultrasonography in power Doppler mode; S, synovitis; T, tenosynovitis.
Table 4 ARs of CE with MRI, US and fluorescence optical imaging

<table>
<thead>
<tr>
<th>MRI S (%)</th>
<th>MRI T (%)</th>
<th>MRI S or T (%)</th>
<th>GSUS (%)</th>
<th>PDUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE s</td>
<td>76</td>
<td>76</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>CE t</td>
<td>75</td>
<td>76</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>CE s+t</td>
<td>81</td>
<td>83</td>
<td>77</td>
<td>56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FOI CI (%)</th>
<th>FOI P1 (%)</th>
<th>FOI P2 (%)</th>
<th>FOI P3 (%)</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>72</td>
<td>46</td>
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<td>C2</td>
<td>58</td>
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<td>C1</td>
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<td>46</td>
<td>81</td>
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</tbody>
</table>

More detailed tables S1, S2 and S3 including 95% CI are only available online.

Phases
AR of FOI and CE, MRI and US differed for the CI and the phases. FOI P1 showed the highest agreement with CE and PDUS, which suggests that P1 displays high local disease activity with high vascularity. The specificity of P1 and P3 was high. Thus, findings in these phases seem to be of special interest. The highest sensitivity was seen in P2 and is comparable to the sensitivity of US with MRI as reference reported from other studies.\(^{30,32}\) While the meaning of the phases is still unclear, an adequate interpretation of an FOI exam requires a specific reading of all the phases.

Subclinical inflammation
MRI, GSUS and PDUS showed positive findings in 16%, 58% and 10% of clinically asymptomatic joints, respectively. This is in alignment with results of other studies where MRI and US detected a higher rate of affected joints than CE.\(^{3,30–32}\) In our study, FOI showed positive findings in 45% of clinically asymptomatic joints, indicating that FOI also detects subclinical inflammation.

Differential diagnostic aspects
A characteristic pattern of signal distribution was seen in patients with PsA. The morphological aspect indicates an association with the synovio-entheseal complex.\(^{33}\) This sign may provide additional information for differential diagnosis but has to be validated with a larger number of patients.

Correlations with scores of disease activity
We found that FOI correlated significantly with disease activity scores (DAS28, US score, RAMRIS). Monitoring of disease activity and valid assessment of remission, the special target for RA treatment,\(^{3}\) are a crucial aspect with respect to the rapidly growing armamentarium of disease-modifying drugs. Our data indicate that FOI may be an additional tool for the assessment of disease activity in arthritic conditions.

Limitations
We are aware of some limitations concerning the image interpretation and quantification of pathological changes. While the examination procedure itself has been standardised in detail, consistent standards for image adjustment and interpretation are not yet established. In this study, we have chosen a semi-quantitative evaluation of FOI findings, comparable to US image interpretation. Generally, the digital technology of the Xiralite system allows an automatic image interpretation and quantitative analysis of image sequences, but appropriate software is not yet available. With a substantial\(^{34}\) intrareader (κ=0.75) and inter-reader (κ=0.75) agreement (separate study, data not published), our method of image interpretation seems to be reliable.

In conclusion, ICG-enhanced FOI with the Xiralite system is a new imaging technology that allows a sensitive and valid assessment of inflammation in arthritis. FOI was comparable to 1.5 T MRI and US in detecting synovitis and tenosynovitis. Thereby, it is a fast and safe imaging screening tool for patients with suspected arthritis. Furthermore, FOI is useful for objectifying treatment response and treatment monitoring. FOI was more sensitive than CE. In addition, FOI could be helpful in the differentiation of nail involvement and arthritis of DIPs in patients with psoriasis and/or PsA. However, further investigations are needed for a comprehensive definition of FOI pathologies, advancement of methodical standards and evaluation of sensitivity to change and prognostic value.

Contributors
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. No medical writer was involved in the preparation of the manuscript. SW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: H-EL, MB, SW, SO, MB, MS and GRB. Acquisition of data: SW, SO, H-EL, PS, HB, L-A, BK and MB. Analysis and interpretation of data: SW, H-EL, MB, MB and GRB. Manuscript preparation: H-EL, SW, MB, SO, MB and GRB. Statistical analysis: CS, SW, MB and H-EL.

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Competing interests M. Schirmer and M. Bahner are shareholders of mivenion GmbH.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of the Charité University Clinic Berlin.

Provenance and peer review Not commissioned; externally peer reviewed.

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Clinical and epidemiological research


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Corrections

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