

CHAPTER 9

Discussion

Future perspectives

DISCUSSION

As described in *chapter 2*, feasibility studies have shown that clinical arthritis can be visualized using positron emission tomography (PET). Most likely though, PET will have no place in the diagnosis of clinically accessible arthritis, because of its high cost and radiation burden. However, early diagnostics and intensive monitoring of disease activity are becoming increasingly important in rheumatoid arthritis (RA) management. PET could address these clinical needs by sensitive and specific detection, and quantification of subclinical synovitis. This requires a specific tracer that targets binding sites in developing and persisting arthritis during treatment.

So far, most of the PET studies in RA have been performed using the rather nonspecific tracer [^{18}F]FDG, that targets all metabolically active cells (1). Elzinga *et al.* reported [^{18}F]FDG uptake in a larger number of joints in RA compared to osteoarthritis patients (2), but, as confirmed by others, absolute uptake was not significantly different (3-5). Therefore, investigation of other PET tracers – that target inflammation more specifically – is warranted. Van der Laken *et al.* previously demonstrated that (*R*)-[^{11}C]PK11195 PET could visualize knee arthritis in RA patients (6). Moreover, initial results pointed to the ability of (*R*)-[^{11}C]PK11195 PET to detect subclinical synovitis.

Building on these results, the next step was to investigate the potential of (*R*)-[^{11}C]PK11195 PET in early diagnostics and treatment monitoring of RA. In the first part of this thesis, we demonstrated that PET with macrophage targeting is a novel and promising approach to visualize subclinical arthritis activity. This was shown in different patient populations: patients at risk for RA, patients with minimal disease activity (MDA) or even in remission, both with longstanding RA duration or with early RA. Our results indicated that macrophage-targeted PET could predict development of RA in patients at risk. Furthermore, our results strengthened the case for additional imaging in the prediction of future flaring in RA patients in clinical remission (7)/MDA.

Signs of subclinical synovitis have also been found with other imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI), but these techniques lack specificity for detection of subclinical disease as high levels of scan positivity were found in joints without a correlation with clinical outcome (8-11). In contrast, PET seems to add in particular in view of specificity, with demonstrated correlations between scan and clinical outcome. Previously performed scintigraphy with radiolabeled IgG already showed the potential of nuclear imaging to predict development of clinical disease activity (12). With the introduction of PET the sensitivity level was increased significantly. However, in contrast to US and MRI, PET poses radiation-related risks to patients, which should be weighed against the benefits of the scan(s) and should be kept within the safety limits defined by guidelines of radiation safety for patients. An advantage of MRI is the anatomical information that is provided and its lower costs compared to PET. But, since the introduction of hybrid PET/MRI technology (13), the strengths of both imaging techniques could be

combined. Future studies should investigate the advantage of dual scanning in the detection of subclinical synovitis. Furthermore, although PET is currently an expensive technique, it is to be expected that with increasing use of PET scanning in routine clinical practice (in various medical disciplines such as oncology, hematology, cardiology, neurology/psychiatry), as well as increasing number of scanners installed in hospitals, costs will decrease with time. This has also happened for CT in the past.

One of the strengths of PET, compared to other imaging techniques, is the versatility of PET tracers that can be used to investigate the target of interest. This was demonstrated in part 2 of this thesis, in which we investigated three novel macrophage-targeted PET tracers – [¹¹C]DPA-713, [¹⁸F]DPA-714 and [¹⁸F]fluoro-PEG-folate – for arthritis imaging. Improved target-to-background characteristics compared to those of (*R*)-[¹¹C]PK11195 were found. Previously, studies in neuro-inflammation already proved the superior binding affinities and specific-to-nonspecific binding of [¹¹C]DPA-713, [¹⁸F]DPA-714 compared to (*R*)-[¹¹C]PK11195 (14-16). Furthermore, FR-targeted single-photon emission computed tomography (SPECT) has been successfully exploited for imaging of arthritis in RA in previous studies (17;18). Clinical studies should prove whether our results can be translated to the human situation.

FUTURE PERSPECTIVES

PET with macrophage targeting showed high potential for imaging of subclinical synovitis with clinical value for early diagnostics and therapy monitoring. To further develop this technique as a predictive tool for development of clinical disease activity, sensitivity of should be further optimized. In the pre-clinical RA group specificity and predictive values of PET were high (100%, 100% (PPV) and 80% (NPV)), but sensitivity was moderate (44% for clinical arthritis development in whole body and 67% if limited to the hands/wrists (field of view of PET scan). In the remission/MDA populations, results indicated a relationship between cumulative PET score and development of flare. However, there was overlap, in particular for the lower cumulative PET scores, between the flare and no flare group. This may also be optimized if the sensitivity of the scan can be increased. The most likely explanations of moderate sensitivity were 1) limitation of the field of view of the applied PET scans to hands/wrists while clinical arthritis could develop anywhere (*e.g.* sensitivity of macrophage PET improved from 45% to 67% in pre-clinical RA when the clinical outcome was limited to arthritis development in hands/wrists) and 2) application of a macrophage tracer ((*R*)-[¹¹C]PK11195) with high background uptake in peri-articular tissue. The high background uptake limited the detection of more subtle arthritis, which is essential when depicting subclinical synovitis. To improve these factors, we will extend the scanning area in future studies to whole body imaging, including feet (where RA activity frequently starts). Secondly, we have developed a panel of three alternative novel

macrophage tracers. These tracers showed a potentially lower background uptake in our preclinical studies. Two of these tracers ($[^{18}\text{F}]\text{DPA714}$ and $[^{18}\text{F}]\text{fluoro-PEG-folate}$) are labelled to F-18, which is commercially attractive as F-18 has a longer half-life than C-11 (110 versus 20 minutes), which makes F-18 tracers suitable for central synthesis and distribution to other medical centers farther away. Future studies will explore the applicability of the new macrophage tracers in clinical studies for both early diagnostics and therapy monitoring. Finally, in addition to improvement of sensitivity of the macrophage PET scan for detection of subclinical arthritis, larger patient populations need to be investigated to define cut-off values of (cumulative) PET scores of significance for optimal prediction of disease development and exacerbation of disease activity.

It is to be expected that macrophage PET imaging will not stand on itself as a tool for prediction of development of clinical disease activity. Both for prediction of development of RA in the very early phase and in remission states of disease, to guide treatment in these patients (who can taper/stop medication and who needs to continue or intensify treatment), imaging will most likely become part of a prediction algorithm using multiple tests. For instance in early developing disease, selection of high risk patients will start with cheaper and easier to apply tests such as clinical picture (*e.g.* symmetric inflammatory arthralgia in small joints) and a positive ACPA test, including the titer. ACPA-positive arthralgia patients currently have a risk of 30-50% to develop clinical RA within one year. Currently, treatment strategies are investigated to prevent development of (progression of) RA. Based on group discussions with RA patients, we felt that it is justified to subject individuals to such preventive treatment in clinical care settings if their risk of developing RA is $\geq 80\%$. Macrophage PET imaging may add to the above-mentioned risk factors in the predictive algorithm by increasing the positive predictive value to $\geq 80\%$. Such studies are currently being prepared in a multicentre design. If the outcome is positive in pre-selected risk patients, the predictive value of macrophage PET may also be explored in patients with lower risk profiles based on clinical and serological findings. Similar explorations also need to be undertaken in remission/MDA RA patients, where imaging, clinical and serological data need to be integrated and incorporated in the development of predictive algorithms in order to guide treatment decisions. Subsequently, randomised studies need to be designed where imaging-based treatment decisions are compared to non-imaging-steered decisions. Long-term clinical follow-up should be included. This step is important to prove that the tool is not only predictive but can also improve therapeutic outcome.

Apart from assessment of persisting arthritis activity in clinical quiescent disease during or after treatment, PET has also been investigated as a tool to predict therapeutic outcome very early after initiation of the treatment (19). The predictive ability of the tool can potentially be further optimized by replacement of the aspecific inflammation tracer $[^{18}\text{F}]\text{FDG}$, applied in above-mentioned study, by our novel and more specific macrophage tracers.

Another issue that needs to be addressed is the investigation of healthy controls. As the spectrum of detection of arthritis is shifting towards subtle, subclinical inflammatory activity, the differentiation between normal and abnormal is crucial. MRI of hand/wrists of healthy controls also shows signs of mild inflammation (20), and not all MRI findings in RA patients are clinically important. The development of clinically relevant cut-off values of imaging outcome may therefore be necessary (21). Although macrophage PET seems to perform superiorly with regard to specificity as compared to MRI in the studies described in this thesis, it is also relevant to validate these findings with inclusion of larger healthy control populations in future studies.

To date, a PET scanner is usually equipped with an integrated computed tomography (CT) scanner. The (low-dose) CT scan provides anatomical delineation of the PET signals. With the introduction of hybrid PET-MRI scanners on the market, new options for sensitive and specific arthritis detection may rise. MRI can provide detailed anatomical information of the soft tissues including synovial tissue which can add to the molecular information provided by PET. Moreover, the radiation burden of the PET tool will be decreased if PET-CT can be replaced by PET-MRI due to lack of radiation of low-dose CT (which may in particular add up with whole body scanning and scanning at multiple time points).

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