Discussion & Future perspectives
DISCUSSION

This thesis outlines different potential aspects in which positron emission tomography (PET) could have additional value in the field of inflammatory rheumatic diseases. From the year 1995 onwards, an increasing number of PET studies have been published. The review presented in chapter 2 was the base for further research presented in this thesis. To image arthritis, most of these studies used the tracer $[^{18}\text{F}]$FDG, which is a glucose analog that accumulates in metabolically active cells. Although fairly non-specific, $[^{18}\text{F}]$FDG PET revealed a good sensitivity in different studies to visualize arthritic joints, with an estimated sensitivity of 56-77\% (1). With regard to specificity, $[^{18}\text{F}]$FDG showed more PET-positive joints in rheumatoid arthritis (RA) patients than in the control group with osteoarthritis (OA) (29\% and 6\%, respectively). However, PET outcome measures were not able to distinguish reliably between RA and osteoarthritis (2). To improve specificity in PET imaging, tracers targeting more specific molecular pathways are needed and should be investigated in future studies, as presented in this thesis.

One of these potential new pathways for RA is targeting macrophages to their translocator protein (TSPO; formerly known as benzodiazepine receptor). Macrophages infiltrate in synovium as RA develops and continue to be a good biomarker during treatment in later phases of the disease, regardless of the choice of therapy (3). Previous studies (4, 5, 6) suggested that new generation TSPO tracers with lower levels of background binding may be useful in arthritis, as was also observed in neurology brain studies targeting cerebral inflammation (7-11). Therefore, the next step in macrophage-targeted PET imaging was to investigate these new generation TSPO tracers in an animal arthritis model. In this preclinical arthritis setting the new TSPO tracers indeed revealed better imaging characteristics than $(R)-[^{11}\text{C}]PK11195$ (12). Building on these results, two new generation TSPO PET tracers $[^{11}\text{C}]$DPA-713 and $[^{18}\text{F}]$DPA-714 were investigated in RA patients (chapter 4). These new TSPO tracers did show joint targeting in clinically active RA patients, and both tracers performed well with lower background compared to the previously investigated macrophage tracer $(R)-[^{11}\text{C}]PK11195$. Highest target uptake was obtained with $[^{11}\text{C}]$DPA-713. The new generation TSPO tracers, therefore, provide new opportunities for early diagnosis and therapy monitoring of RA disease activity.

In search of potential tracers for imaging AS, three different radioactive tracers were explored in a stepwise approach (chapter 3). The previously mentioned $[^{18}\text{F}]$FDG and $(R)-[^{11}\text{C}]PK11195$, which perform well in RA, seem less favorable for imaging sites of disease activity in AS. $(R)-[^{11}\text{C}]PK11195$ imaging did not reveal inflammatory sites, which may in part be explained by high background uptake in vertebral column and pelvis. $[^{18}\text{F}]$FDG performed better with a few sites with
enhanced tracer accumulation. Most optimal imaging results were obtained with \(^{18}\text{F}\)Fluoride PET scans of the spine, imaging sites of new bone formation which is a hallmark of AS. \(^{18}\text{F}\)Fluoride PET demonstrated more AS-like lesions than \(^{18}\text{F}\)FDG (glucose metabolism) and also more than magnetic resonance imaging (MRI) (total AS-like lesions 17 vs. 3 vs. 9, respectively). A potential confounder for detection of AS lesions by \(^{18}\text{F}\)Fluoride imaging may be the co-presence of OA, since degenerative changes may also cause a positive \(^{18}\text{F}\)Fluoride signal (13-15). Nevertheless, the findings in PET-positive lesions at anatomical locations corresponding to typical AS lesions suggest that AS activity was better reflected by bone formation on PET than by inflammation. This idea was strengthened by the finding of bone formation at the junction of enthesis and bone in histological evaluations of PET-positive lesions in the spine (chapter 6). The results of this study show the potential value of \(^{18}\text{F}\)Fluoride PET in AS by imaging bone formation as expression of disease activity.

In addition to application studies of PET for diagnostics of RA and AS, there is a clinical need to increase the therapeutic efficacy of expensive biologic agents in both RA and AS. Earlier studies showed that PET might be able to predict treatment early in the course of treatment, potentially even at baseline. In RA for instance, two studies comparing \(^{18}\text{F}\)FDG PET data of RA patients at baseline and a few weeks after treatment found significant correlations between early changes of \(^{18}\text{F}\)FDG uptake in the arthritic joints and DAS28 score up to 22 weeks (19, 20). In this thesis another novel approach was investigated, using the radioactive labeled drug \((^{89}\text{Zr})\) rituximab, which targets B-cells, and using PET to predict clinical response to rituximab after 24 weeks already at baseline (chapter 5). Clinical responders at 24 weeks had significantly higher \(^{89}\text{Zr}\)-rituximab uptake in PET-positive hand joints than non-responders. In addition, in an exploratory analysis, the positive predictive and negative predictive value for clinical response was 90% and 75% respectively, at a specific T/B ratio cut-off value of 4.0. In contrast, clinical and laboratory parameters at baseline were not able to differentiate potential responders from non-responders. Therefore, quantitative PET imaging could add to treatment efficacy by selecting potential responders to a (new) rituximab therapy. This may also apply to other therapies.

In addition, in AS about 70% of patients respond to anti-TNF \(\alpha\) therapy and data on the effects of anti-TNF on inhibition of bone formation are controversial (16). In this thesis we presented the ability of \(^{18}\text{F}\)Fluoride PET to monitor anti-TNF treatment effects on bone formation in AS patients over 12 weeks (chapter 6). Clinical responders at 24 weeks already showed significantly reduced \(^{18}\text{F}\)Fluoride uptake in costovertebral lesions and SI joints after 12 weeks of anti-TNF treatment. The potential application of PET in therapy monitoring has also been addressed by our group (6, 17, 18), and others in several RA studies (chapter 2) (19). These studies
discovered a decline of tracer uptake in arthritic joints after drug interventions and PET outcome was in agreement with changes in disease activity scores or C-reactive protein (CRP) for instance after 4 weeks and 12 weeks of treatment (1). Therefore, PET may also hold promise for monitoring therapies in AS and RA.

One of the strengths of PET compared to other imaging techniques is the ability to provide unique whole-body molecular information in a relatively small amount of time (~45 minutes). The collection of whole body information can be valuable for new drug development. For example, in oncology whole body “immuno-PET” studies with labeled monoclonal antibodies (mAbs) have successfully been applied in combination with $^{89}$Zr-labeled rituximab for imaging and radioimmunotherapy of CD20 positive B-cell lymphomas (21). Interestingly, in these studies, it was observed that the spleen might serve as “sink” for mAbs during first passage in circulation causing lower tracer availability in target tissue (21, 22). In line with this, chapter 7 of this thesis whole-body PET revealed that the iodine labeled drug called F8-IL10 accumulated unexpectedly high in the liver and spleen. Accordingly, blood analyses showed fast blood clearance of $^{[124]}$I-F8-IL10. Subsequent animal experiments revealed increased expression of fibronectin in liver and spleen in arthritic rats compared to control healthy rats. In addition, a possible dose-targeting relation also played a role suggesting a potential “sink like” effect. This translational study demonstrated the value of in-vivo biodistribution imaging of new and potentially new anti-rheumatic drugs by PET-CT.

**FUTURE PERSPECTIVES**

The unique characteristics of PET imaging like quantification, sensitive whole-body imaging and potentially high specificity by using tissue-specific tracers opens multiple opportunities within the field of rheumatology. Potential (pre-)clinical applications are visualization of (subclinical) disease activity for early diagnostics and disease monitoring in clinical remission, treatment monitoring or prediction of therapeutic outcome, PET-guided research of disease pathways and/or PET-guided drug development in RA and AS. Although promising data have already been published and described in this thesis, more steps need to be taken to implement PET in clinical practice of rheumatology.

The possibility of imaging IA with PET was first demonstrated as a coincidental finding in oncology patients with arthritic joints on whole body $^{[18]}$F-FDG PET. After that multiple studies strengthened the potential of PET in arthritic diseases. However, results to date are preliminary with small groups of study subjects and heterogeneous outcome parameters. Additionally, the rheumatologic field exhibits
multiple disease entities and almost certainly there is not one single covering tracer that performs optimally in all these different disease entities. Therefore, the search for and development of optimal tracer(s) to address specific clinical needs is ongoing and a different clinical question may request a different tracer. An optimal tracer binds specifically to a cell or part of the pathogenesis and shows no or low uptake in normal physiological processes, thus obtaining high target-to-background ratios. For RA we showed that macrophage targeting by either \((R)-[^{11}C]PK11195\) or the new generation of TSPO tracers \([^{18}F]DPA-714 /[^{11}C]DPA-713\) has promise and warrants further investigation. The latter tracers performed well in an explorative setting in RA patients as presented in this thesis. Future larger studies have to prove their value in RA. In AS however, we showed that \([^{18}F]FDG\) or targeting macrophages is most likely not successful for monitoring AS disease activity and that the \([^{18}F]Fluoride\) tracer has more potential for AS imaging. More therapy monitoring (also in comparison with other imaging modalities) and image-guided biopsy studies are needed to further determine the role of \([^{18}F]Fluoride\) PET in AS.

Besides the use of different tracers, the first proof-of-concept studies (including studies presented in this thesis) had a limited number of included patients and heterogeneous PET outcome parameters. To proof the value of PET in clinical decision making, validation studies should be performed in larger cohorts. This should be done both in patients that are in an early stage of disease or that are prone for developing definite RA or AS disease, as well as in established patients for the evaluation of various treatments. Healthy/non-IA control groups need to be included and preferably uniform outcome measures should be used. For this purpose, it is needed to develop standardized PET analysis methods especially when (international) multicenter studies will be planned. A practical approach would be to use the already available international standardized guidelines for PET imaging and PET response in oncology.

The major disadvantages of PET are the poor spatial resolution and the use of radioactivity. First, the spatial resolution of a typical PET scanner is \(~4\)mm, which may impede quantitative analysis of small joints, important in arthritis imaging. Because of the limited resolution of PET, partial volume effects, which are defined as the loss of radioactivity in small objects, can occur. As seen in our studies, uptake values in larger joints like wrists or MCP-joints are higher than in PIP joints. To improve the performances of arthritis PET imaging, future PET systems should improve the spatial resolution by optimizing hardware as well as acquisition and reconstruction methods. This could also be achieved by optimizing the PET scanner to specific IA applications like hand/feet scanners. Currently, new total body PET machines are developed encompassing the entire patient, thereby increasing the geometric coverage. This increases the sensitivity of PET images by a factor \(~40\) for
total-body imaging or a factor of approximately 4–5 for imaging a single area (24). The new hybrid imaging technique PET-MRI is another helpful technological evolution which has been introduced recently. PET-MRI combines functional imaging with superior, high-resolution, anatomic details in soft tissue. This is interesting for inflammation in synovial tissue or visualizing bone edema without the additional radiation burden of CT. Preliminary PET-MRI fusion images of RA patients have already been published (25, 26) and although availability is limited, this new hybrid imaging modality might bring PET a major step closer to implementation in daily rheumatologic practice.

Regarding the use of radioactivity, patients are often exposed to effective doses of 7–10 milliSievert (mSv) including a low-dose whole-body attenuation CT. This radiation burden is 4–5 times (e.g., 500 chest radiographs) the yearly natural background dose according to the United Nations (27), and comparable to a diagnostic CT scan of the abdomen (27). In future PET imaging in IA however, radiation exposure can (and will) be diminished due to several (technical) improvements. The availability of radioisotopes with a short half-life, for instance the new TSPO tracer \([^{11}\text{C}]\text{DPA-713}\) (half-life 20 minutes), exposes patients to lower radiation doses and makes repetitive scanning for therapy monitoring possible. Technical improvements as mentioned above will allow use of lower injection doses of tracer, optimization of scanning protocols, post-processing and finally the use of PET-MRI will decrease radiation burden for patients in PET imaging.

Finally, PET will only be interesting for clinical practice if it addresses unmet clinical needs and/or increases cost-effectiveness. Currently, PET imaging is relatively expensive. It is expected though that when clinical application rises PET facilities become more available and radiopharmaceuticals become commercially available at lower costs (e.g., no need for own cyclotron). Cost-effectiveness is already proven in oncology (23). This could also be true in IA when PET aids to achieve tailored treatment in IA patients (e.g., tapering or image-guided treatment intensification) thereby increasing therapeutic efficacy, lowering use of biologic agents and saving costs. Optimally PET is able to prevent the onset of (destructive) IA with less socio-economic costs. Additionally, dynamic and kinetic PET analysis can help in the effective testing of newly developed drugs as seen in chapter 5.

This thesis shows that PET imaging has the potential to become of additional value in the field of rheumatology. Application in most interesting for assessing sub- or preclinical (RA and AS) disease activity, treatment monitoring or even prediction of therapeutic outcome. Combined with the possibility to develop disease-specific PET-tracers and the (recent) technological improvements, PET imaging in IA may finally aid in achieving personalized treatment for RA and AS patients.
REFERENCES


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