CHAPTER 10

Summary

SUMMARY

In rheumatoid arthritis (RA), early therapeutic intervention and optimal suppression of disease activity are essential in the prevention of (progression of) erosive damage. Positron emission tomography (PET) may be useful for early diagnostics and therapy monitoring in RA.

Part I: Visualization of subclinical synovitis in RA

In *chapter 2*, a systematic overview is presented of the current literature on PET as a diagnostic and monitoring tool for peripheral inflammatory arthritis. The majority of available studies (n=18) proved the feasibility of PET imaging in patients with clinically active arthritis using the PET tracer [^{18}F]FDG, that targets all metabolically active cells. In addition, six studies (including *chapter 3* of this thesis), reported visualization by PET of subclinical synovitis, defined as synovitis that cannot be detected by clinical examination. Presence of subclinical synovitis may predict the development of RA in patients at risk. In addition, in RA patients in clinical remission, presence of subclinical synovitis may predict flaring of arthritis activity and associated risk of ongoing joint damage.

More selective imaging of RA could be achieved by targeting of synovial macrophages. In the subsequent chapters of part I, macrophage PET imaging of subclinical synovitis in patients at risk of developing RA (i.e. anti-citrullinated antibody protein (ACPA)-positive, arthralgia patients) (early diagnostics, *chapter 3*) and in RA patients in clinical remission/ minimal disease activity (MDA) during/after treatment was further explored (therapy monitoring, *chapters 5 and 6*). To put the PET performance for early diagnostics into perspective, MRI was investigated in the same patients at risk of developing RA in *chapter 4*. MRI was also included as a comparative imaging modality for PET in *chapters 5 and 6*.

Exploring the application of macrophage PET for early diagnostics of RA, the results in *chapter 3* demonstrated that *(R)*-[^{11}C]PK11195 PET could detect subclinical synovitis in 4/29 ACPA-positive, arthralgia patients. These patients all developed active arthritis in the hands/wrists within 14 months. These results showed the potential of *(R)*-[^{11}C]PK11195 PET in the prediction of RA. In the same patients we performed MRI of hand/wrist joints. In contrast to the relatively low number of abnormalities found with *(R)*-[^{11}C]PK11195 PET, MRI abnormalities were found in up to 93% of patients (*chapter 4*). However, the presence of MRI-detected subclinical synovitis and/or bone marrow edema was not related to development of clinical arthritis. In addition, MRI of four healthy controls also showed mild signs of synovitis on MRI, suggesting a low specificity of MRI for the assessment of arthritis. In addition, aging was identified as a factor contributing to the frequency of MRI-detected inflammation, pointing to a link with degenerative joint disease. From this study, we conclude that abnormal signs on MRI are poorly related to clinical signs and outcome.

Altogether, these results show that *(R)*-[^{11}C]PK11195 PET is a promising technique for the assessment and monitoring of arthritis and/or remission in RA.

In the next chapters, the value of PET in therapy monitoring was investigated. In a cohort of longstanding RA patients in clinical remission/MDA (n=29, mean disease duration 9 years) a positive relation was described between cumulative PET scores and the development of flare during three year follow-up (*chapter 5*). In contrast, median cumulative MRI scores were not significantly different between patients with and without a flare during follow-up. Similar results were found in a cohort of early RA patients in a treat-to-target design aiming at clinical remission *(chapter 6)***.** Median cumulative PET scores – in contrast to MRI scores – could distinguish between patients with and without short-term flare in hands and/or wrists (1.5 [IQR 0.8-5.3] vs 0.0 [IQR 0.0-1.0], p= 0.04).

Part II: novel macrophage targeting PET tracers

The second part of this thesis investigated whether three novel macrophage-targeted PET tracers, [^{11}C]DPA-713, [^{18}F]DPA-714 and [^{18}F]fluoro-PEG-folate could improve the fairly unfavourable target-to-background ratios of *(R)*-[^{11}C]PK11195.

In *chapter 7*, it was demonstrated *in vitro* that the relative binding of DPA-713 and DPA-714 was 7-fold and 25-fold higher, respectively, than that of PK11195. In addition, in an *in vivo* rat model of arthritis, arthritic knee-to-bone ratios of [^{11}C]DPA-713 (1.6 ± 0.31) and [^{18}F]DPA-714 (1.55 ± 0.10) were significantly improved compared to *(R)*-[^{11}C]PK11195 (1.14 ± 0.19).

In *chapter 8*, an alternative molecular target present on macrophages was explored in arthritis PET imaging: the folate receptor (FR)-beta. We described the synthesis of a novel FR-targeted radioligand: [^{18}F]fluoro-PEG-Folate. Specific accumulation of [^{18}F]fluoro-PEG-folate was shown *in vivo* in arthritic rat knees and, compared to *(R)*-[^{11}C]PK11195, favourable arthritic knee-to-bone ratios were shown (1.64 ± 0.15 vs 1.14 ± 0.19, respectively).

In conclusion, these studies show that the macrophage tracers [^{11}C]DPA-713, [^{18}F]DPA-714 and [^{18}F]fluoro-PEG-Folate could improve arthritis imaging compared to the established tracer *(R)*-[^{11}C]PK11195 by providing better contrast.