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Review

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging of macrophages in large vessel vasculitis: Current status and future prospects

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ABSTRACT

Macrophages are key players in the pathogenesis of large-vessel vasculitis (LVV) and may serve as a target for diagnostic imaging of LVV. The radiotracer, ^{18}F-FDG has proven to be useful in the diagnosis of giant cell arteritis (GCA), a form of LVV. Although uptake of ^{18}F-FDG is high in activated macrophages, it is not a specific radiotracer as its uptake is high in any proliferating cell and other activated immune cells resulting in high non-specific background radioactivity especially in aging and atherosclerotic vessels which dramatically lowers the diagnostic accuracy. Evidence also exists that the sensitivity of ^{18}F-FDG PET drops in patients upon glucocorticoid treatment. Therefore, there is a clinical need for more specific radiotracers in imaging GCA to improve diagnostic accuracy. Numerous clinically established and newly developed macrophage targeted radiotracers for oncological and inflammatory diseases can potentially be utilized for LVV imaging. These tracers are more target specific and therefore may provide lower background radioactivity, higher diagnostic accuracy and the ability to assess treatment effectiveness. However, current knowledge regarding macrophage subsets in LVV lesions is limited. Further understanding regarding macrophage subsets in vasculitis lesion is needed for better selection of tracers and new targets for tracer development. This review summarizes the development of macrophage targeted tracers in the last decade and the potential application of macrophage targeted tracers currently used in other inflammatory diseases in imaging LVV.

Contents

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1. Introduction

The human blood vessel system is one of the largest organ systems in the human body [1,2]. As part of the cardiovascular system, the blood vessel system functions by distributing blood cells, oxygen and nutrients to, as well as expelling waste such as carbon dioxide from, all organs and tissues. Separately, in the lymphoid system, blood vessels act as the transit site of lymphoid and myeloid cells of the immune system. Given the importance of blood vessels, inflammation of the vessels (vasculitis) can have major health consequences. The Chapel Hill Consensus Conference in 2012 revised the nomenclature of the primary vasculitides and classified vasculitis based on the size of the vessels involved into small-vessel vasculitis (SVV), medium-vessel vasculitis (MVV), large-vessel vasculitis (LVV) and variable-vessel vasculitis (VVV) [3]. LVV is a disease marked by inflammation of the vessel wall that progresses to vascular remodeling and thickening of the vessel wall causing stenosis, occlusion or dilatation of the vessels which may result in ischemic complications such as sight loss, stroke and aneurysms. Therefore, early recognition of LVV is crucial.

Nuclear imaging is currently gaining importance as a non-invasive tool for the diagnosis and monitoring of vascular inflammation. The application of nuclear imaging in the detection of LVV was initially a serendipitous discovery by Blockmans et al. [4]. In their study, the authors compared ^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and Gallium-68 scintigraphy in patients with fever of unknown origin (FUO) and found vascular uptake in patients with underlying vasculitis. Given the limited resolution of nuclear imaging cameras, these techniques are more efficient in the assessment of LVV but not MVV or SVV [5]. However, recent studies have also indicated the potential role of new PET camera systems (up to 2 mm resolution) in the detection of organ involvement in MVV and SVV [6–9].

Macrophages have been recognized as key cellular players in the pathogenesis of LVV. Circulating monocytes are recruited to vasculitic lesions where they are activated and differentiate into macrophages. These activated macrophages produce pro-inflammatory cytokines and chemokines which amplify the inflammatory response and induce vascular remodeling [2,10]. ^{18}F-FDG PET as a tool for imaging inflammation has already proven to be useful for early diagnosis of LVV (within 3 days of glucocorticoid treatment – sensitivity and specificity may drop afterwards). However, ^{18}F-FDG is less useful for monitoring disease progression and evaluating therapy responses due to a dramatic drop in diagnostic accuracy in patients undergoing glucocorticoid treatment and inability to differentiate long lasting vessel wall remodelling with active vasculitis. Better and more specific macrophage targeted radiotracers are therefore needed to improve diagnostic accuracy and treatment monitoring especially in patients with ongoing glucocorticoid treatment. Following a brief overview of LVV pathogenesis, this review summarises the development of macrophage targeted tracers in the last decade using two different nuclear imaging approaches – positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging. Moreover, the potential application of tracers currently used in other inflammatory diseases in imaging macrophages in LVV is discussed as well.

2. Large-vessel vasculitis (LVV)

LVV includes two pathological conditions: giant cell arteritis (GCA) and Takayasu arteritis (TAK). The pathogenesis of both GCA and TAK involves inflammation, often granulomatous, of large to medium size arteries (aorta and its major branches). GCA generally occurs in older Caucasian female individuals (≥50 years old) of Scandinavian descent in Europe and Minnesota. The disease usually affects the aorta and its major branches with a predilection towards carotid and vertebral arteries although other types of arteries can also be affected. GCA belongs to a clinical disease spectrum which includes cranial GCA (C-GCA) and large-vessel GCA (LV-GCA) [3,11,12]. LV-GCA often overlaps with polymyalgia rheumatica (PMR), another inflammatory disorder of the elderly, affecting muscles marked by pain and stiffness in the neck, shoulder and hip region. Studies have shown that 40–60% GCA patients may have PMR and according to the literature, up to 21% of PMR patients may develop GCA [11,17]. TAK, on the other hand, is more common in younger Asian females (≤50 years old) [3,13,14]. GCA and TAK have a similar clinical presentation including fever of unknown origin (FUO), headache, malaise, anorexia, weight loss and in the progressive phase of the disease, symptoms of occlusion and aneurysm. Histopathological features in the affected vessels of GCA and TAK are overlapping and thus the only factor distinguishing GCA and TAK is geographical distribution and the age of onset [11,14–17].

2.1. Pathogenic model of large-vessel vasculitis

The etiology of LVV is unknown. However, based on clinical and experimental investigations, a pathogenic model for disease development and progression has been proposed which includes four phases.

2.1.1. Vascular dendritic cell (vasDC) activation

Vascular dendritic cells (vasDC) are sentinel immune surveillance cells located in the adventitia of the artery. When no inflammation occurs, resting vasDc are CD83-MHC-II[low]. In the event of vasculitis, vasDC are activated through the stimulation of toll-like receptors (TLRs) by a factor yet to be identified. Studies have shown increased expression of TLR 2 and TLR 4 on vasDC of vasculitis patients. Activation of vasDC by TLR 4 ligands changes the phenotype of vasDc into CD83^{+}MHC-II^{high} and induces the production of chemokines such as CCL18, CCL19, CCL20, CCL21 and cytokines such as IL-1β, IL-6, IL-18, IL-23 and IL-33. These chemokines and cytokines are responsible for the recruitment and polarisation of CD4^{+} T-cells in addition to promoting angiogenesis [2,18–20].

2.1.2. Recruitment, activation and polarisation of CD4^{+} T-cells

The chemokines produced by activated vasDC (CCL18, CCL19, CCL20, CCL21) recruit CD4^{+} T-cells, which enter the adventitia through the *vasa vasorum*. Recruited CD4^{+} T-cells are then activated through

docking of T-cell receptors (TCRs) to MHC-II on vasDC – presenting a still unknown antigen. Upon activation, T-cells differentiate into different subtypes depending on the presence of specific cytokines in the micro-environment. The cytokines IL-12 and IL-l8 polarise the T-cells into T helper 1 (Th1) subtype. Th1 cells produce interferon-γ (IFN-γ), a very powerful pro-inflammatory cytokine that is important for macrophage activation, production of pro-inflammatory cytokines and chemokines, and production of vascular endothelial growth factor (VEGF). VEGF then activates vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) promoting vascular remodeling, neoangiogenesis, production of chemokines (CCL2, CX3CL1 CXCL9, CXCL10 and CXCL11) for recruitment of monocytes and T-cells, and T-cell activation via the NOTCH-NOTCH ligand activation pathway [2,18–21]. On the other hand, cytokines like IL-1β, IL-6, IL-21 and IL-23 polarise T-cells into T helper 17 (Th17) subtype, which produce pro-inflammatory cytokines and chemokines such as IL-17, IL-21, IL-22, IL-26 and CCL20. IL-17 is a potent pro-inflammatory cytokine that exerts its effect by activating VSMCs and ECs inducing production of chemokines (CCL2, CCL20, CXCL1, CXCL2, CXCL5 and CXCL8) that subsequently promote the recruitment of T-cells, monocytes and neutrophils. IL-17 also induces the production of cytokines such as IL-1β, IL-6, IL-21 and IL-23 by macrophages and vasDCs, thus stabilizing the Th17 lineage. IL-21 induces activation of natural killer cells (NK cells), the differentiation of cytotoxic CD8$^+$ T-cells and the differentiation of Th17 cells. IL-22 is responsible for induction of an acute phase reaction while the chemokine CCL20 facilitates the recruitment of CD4$^+$ T-cells and dendritic cells. The IL-6-IL-17 Th17 pathway is sensitive to glucocorticoid (GC) treatment. However, in the chronic phase of LVV, the IFN-γ Th1 pathway is dominant and is unaffected by GC treatment [2,18–20].

2.1.3. Recruitment and activation of monocyte

Monocytes are divided into three subtypes namely the classical monocytes (marked by CD14^{bright}CD16$^-$), intermediate monocytes (marked by CD14^{bright}CD16$^+$) and non-classical monocytes (marked by CD14^{dim}CD16$^+$). Classical monocytes express CCR2, which is the receptor for CCL2 while the CD16$^+$ intermediate and non-classical subsets express CX3CR1, a receptor for CX3CL1 [23]. Activation of ECs and VSMCs by IFN-γ and IL-17 lead to the production of CCL2 and CX3CL1, which in turn promote the recruitment of circulating monocytes to the vasculitic lesions [19,23]. Due to the presence of various cytokines in the microenvironment, recruited monocytes become activated and differentiate into macrophages. These macrophages, some of which merge into multi-nucleated giant cells, produce a wide range of pro-inflammatory cytokines and growth factors that activate the VSMCs, ECs and T-cells and thus amplify the inflammatory response. Growth factors produced by activated macrophages are also responsible for vascular remodeling and angiogenesis. Moreover, activated macrophages also produce reactive oxygen species and matrix metalloproteinases (MMPs), which are responsible for tissue destruction [18,19,22,24,25].

2.1.4. Vascular remodeling

Macrophages activated by IFN-γ produce VEGF and platelet derived growth factors (PDGF). PDGF activates VSMCs by promoting their migration towards the intima of the vessels and inducing their proliferation leading to intimal hyperplasia, occlusion and ischemic complications. Activated macrophages and VSMCs also produce MMPs namely MMP-9 and MMP-2, which digest elastin in the internal elastic lamina leading to destruction of the media. VEGF and IL-33 produced by activated DCs and macrophages are the main effectors of neoangiogenesis. In LVV, the *vasa vasorum* is reported to infiltrate the media and intima promoting the migration and recruitment of inflammatory cells. Taken together, these processes initiate an inflammatory amplification loop that enhances tissue destruction and vascular remodeling which ultimately results in ischemic complications [18,19,24].

2.2. Macrophages in vasculitis

Macrophages are generally divided into two major subtypes: classically activated macrophages (M1) and alternatively activated macrophages (M2). Depending on the cytokines in the microenvironment, macrophages are polarised into these distinct subtypes. M1 macrophages are considered pro-inflammatory that are generated through Th1 responses. This subtype is activated by IFN-γ and produces pro-inflammatory cytokines such as IL-1β, IL-6, IL-12 and IL-23; growth factors such as VEGF and PDGF; MMPs; and reactive oxygen species whose functions are clearly important in the pathogenesis of LVV [24,26,27].

M2 macrophages, known as the anti-inflammatory and tissue repairing subtype, are divided into four subsets: M2a, M2b, M2c and M2d macrophages. IL-4 and IL-13 polarise macrophages into M2a subsets, immune complexes, TLR and IL-1R ligands polarise macrophages into M2b subsets while IL-10, TGF-β and glucocorticoids polarise macrophages to M2c subsets. These three subsets are marked by production of IL-10 and upregulation of the macrophage mannose receptor (MMRs/CD206) [24,26–28]. The M2d subset is induced by IL-6 and produces high levels of VEGF, IL-10, IL-12, TNF-α and TGF-β. This subset might be important in the pathogenesis of LVV corresponding to high levels of IL-6 in GCA patients. Recently, another subset activated by IL-17 was identified. Similar to M1 macrophages, this subset produces pro-inflammatory cytokines but also showed upregulation of the scavenger receptor CD163, a marker for M2 polarisation [28,29]. Important to note is that the classification of macrophages into M1/M2 subsets is based on *in vitro* models under specific and controlled conditions that may not mirror macrophage behavior *in vivo*. It is well known that macrophages are remarkably plastic and can easily change phenotypes depending on the signals they receive in their microenvironment [24,28,30]. Reports also indicate that macrophages in pathological conditions may show an intermediate phenotype with mixed M1 and M2 characteristics [31].

Arguably, M1 macrophages would be expected to be the dominant subset in vasculitic lesions given their role in the inflammatory amplification loop in LVV. However, Ciccia et al. reported that both M1 and M2 macrophages are significantly expanded in the inflamed arteries of GCA patients [32]. The roles of M2 subsets in vasculitis have yet to be investigated but it has been suggested that M2 macrophages may contribute to giant cell formation, angiogenesis and vascular remodeling [24]. Currently, there is a lack of knowledge regarding the detailed phenotypes and subset distribution of macrophages in vasculitic lesions in LVV. A more detailed knowledge of macrophage subsets/phenotypes in early and chronic vasculitic lesions may shed light on their specific role in LVV pathogenesis.

2.3. The importance of macrophage targeted imaging in the diagnosis of LVV

Currently, diagnosis of GCA and TAK relies heavily on the assessment of clinical symptoms, laboratory assessment of acute phase reaction protein levels [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] and levels of serum IL-6 [11,15–17]. In 1990, the American College of Rheumatology (ACR) developed criteria for the classification of GCA and TAK to discriminate GCA and TAK from other types of vasculitis [12,13]. While these criteria were not intended for the diagnosis of the diseases, they have been widely misused as a diagnostic tool. To date, the golden standard for GCA diagnosis is a positive temporal artery biopsy (TAB). However, inflammatory lesions in GCA arteries often are patchy and focal in nature which may lead to a false negative result if the biopsy was taken from a non-inflamed region. TAB is also not useful in LV-GCA without temporal artery involvement. The use of color Doppler ultrasonography (CDUS) in the diagnosis of GCA has also been applied. CDUS of inflamed artery produces a "halo" sign at regions with thickening of the vessel wall. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are likewise useful in the assessment of artery involvement, disease extent and assessment

of vascular damage particularly in patients with an established diagnosis of GCA [33,34,37]. In the case of TAK, diagnosis is usually carried out via arteriographies such as CDUS, CTA and MRA [35,36].

Given that macrophages dominate the cellular infiltrate in vasculitic lesions, imaging macrophages *in vivo* may prove to be very useful in the diagnosis and tracking of disease activity and progression in LVV. Biopsies may yield a false negative diagnosis as a result of the focal nature of GCA lesions. Ultrasonography and angiography by means of CDUS, MRA or CTA can only detect GCA lesions after morphological changes (later phase). PET on the other hand, has proven to be more useful in detecting early inflammatory stages of vasculitis [37–39]. ^{18}F-FDG PET signal intensity has been found to be strongly associated with macrophage density [40–42]. Activated macrophages and lymphocytes overexpress glucose transporters (Glut-1 and Glut-5) and undergo a switch to glycolysis. Based on this principle, ^{18}F-FDG, a radiolabelled glucose analog, is highly taken up by infiltrating immune cells (including macrophages) in active vasculitic lesions. In the past decade, ^{18}F-FDG PET has proven to be an efficient method for the diagnosis of GCA, TAK and large-vessel involvement in PMR patients. However, ^{18}F-FDG is not specific as it is also taken up by other proliferating cells. Reports have also indicated higher ^{18}F-FDG uptake in aging vessels due to changes of metabolic activity, persistent vessel wall remodeling and atherosclerotic calcifications which may further affect diagnostic accuracy [43,44]. Therefore, more specific radiotracers are needed. With extensive research currently being done on developing new radiotracers specifically targeting macrophages, nuclear imaging may not only provide a non-invasive tool for the diagnosis of LVV but may also be useful in assessing disease progression and effectiveness of treatment in reducing vessel wall inflammation.

3. Positron emission tomography (PET) and single photon emission computed tomography (SPECT)

PET and SPECT are nuclear imaging techniques based on detection of gamma rays [45,46]. Of all existing *in vivo* imaging techniques, PET and SPECT have the highest sensitivity – up to picomolar level for PET and nanomolar level for SPECT – while other techniques such as MRI can only achieve milli to micromolar sensitivity. Despite their superior sensitivity, spatial resolution of PET and SPECT is limited and anatomical information is poor when compared to other techniques making PET/SPECT less useful for imaging medium to small vessels (<4 mm) [45,47,48]. However, the ability of PET and SPECT to visualize functional information *in vivo* is important for early diagnosis and disease assessment. Since MR or CT can provide morphological information and better spatial resolution, these modalities are often combined in a single PET/CT, PET/MR or SPECT/CT camera system, referred to as hybrid imaging. These combinations provide an improvement to the limited spatial resolution of PET and SPECT [46,49]. Using combined PET/CT, Gaemperli et al. successfully detected temporal artery inflammation in GCA patients [50]. The combination of these modalities is also important to obtain accurate molecular and anatomical image co-registration, including soft tissue attenuation correction, for accurate quantification of radiotracers in target tissues [49].

Besides the similarities between PET and SPECT, each modality also offers specific advantages. The main advantage of PET over SPECT is its higher sensitivity, spatial resolution and the ability of absolute quantification. Another advantage of PET is that the radiotracers are identical to the non-radioactive counterparts (*i.e.* substitution of C^{12} with C^{11}) [45,51]. With regard to background noise, Takahashi et al. compared PET and SPECT by using ^{90}Y, a radionuclide that can be used for both PET and SPECT, and showed that PET produced superior images compared to SPECT due to lower background noise [52]. However, SPECT also offers some advantages over PET. SPECT radionuclides generally have longer half-lives compared to PET radionuclides making them more suitable for labelling larger biomolecules such as peptides and antibodies. As larger biomolecules have a slower rate of tissue penetration

– translating to a longer time for the radiotracers to reach target tissues – the longer half-lives of SPECT radiotracers allow the measurement of slow kinetic processes that might take hours or days to achieve [45,53] Nevertheless, emerging PET radionuclides such as ^{64}Cu and ^{89}Zr have longer half-lives, comparable to SPECT radionuclides, and are gaining popularity for antibody tagging (immuno-PET). Despite the multiple advantages of PET over SPECT, PET should not be assumed to be the preferred method of nuclear imaging. This is because SPECT scanners are more widely available, SPECT scans are relatively inexpensive and production of SPECT radiotracers is independent of a cyclotron. Additionally, recent advances in gamma cameras have improved the resolution and sensitivity of SPECT although spatial resolution of PET is still comparatively higher [46,54]. In daily practice, the design of radiotracers to be used for nuclear imaging between these two modalities is mainly based on the availability of the machines, cost and the target molecule to be tagged.

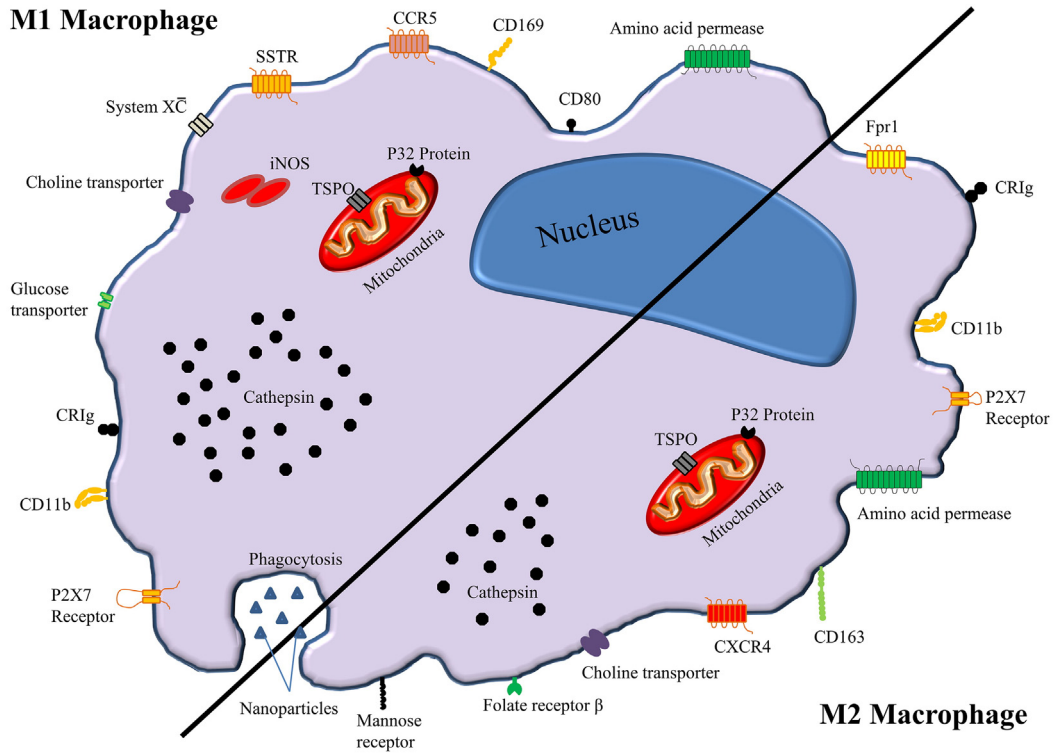## 4. Macrophage targeted PET and SPECT radio-tracers

Since macrophages are key players of various inflammatory disorders and oncological conditions, they are considered an important target for nuclear imaging both for diagnosis and assessment of treatment effectiveness. The importance of macrophage targeting is also emphasized by the recent increase in research and development of new radiotracers targeting various biological pathways and markers on macrophages for LVV and other related inflammatory diseases (Fig. 1).

4.1. Clinically investigated macrophage targeted tracers for large vessel vasculitis

To date, the only radiotracer used in clinics for diagnosis of LVV is ^{18}F-FDG. Macrophage targeted radiotracers targeting translocator protein (TSPO) have also been tested in LVV imaging showing promising results emphasizing the suitability of macrophage targeted radiotracers for imaging LVV.

4.1.1. Glucose metabolism targeted ^{18}F-FDG PET

Since the discovery of the usefulness of ^{18}F-FDG PET in diagnosis of LVV by Blockmans et al., this radiotracer has been widely employed for diagnosing GCA and TAK. However, consensus guidelines for the interpretation of scan results are currently lacking. Table 1 summarises the methods currently used for interpretation of ^{18}F-FDG PET scan results in LVV. In a recent study by Stellingwerf et al., different scoring methods for ^{18}F-FDG PET scans in GCA patients were compared [59]. The group concluded that the visual grading system with grade 3 uptake (higher than liver uptake) yielded the highest diagnostic accuracy for qualitative method (sensitivity of 83% and specificity of 91%) while standardized uptake value (SUVmax) aorta to liver ratio was the superior semi-quantitative method (cut-off value of 1.03, sensitivity of 72% and specificity of 92%). However, diagnostic accuracy dropped dramatically in patients undergoing glucocorticoid treatment. A recent study by Clifford et al. indicated a sensitivity and specificity of only 71.4% and 64.3% respectively in GCA patients after only 12 days of glucocorticoid treatment [60]. Thus, although ^{18}F-FDG PET has been proven a useful tool for diagnosis of LVV, more specific radiotracers are needed to improve diagnostic accuracy especially in patients undergoing glucocorticoid treatment. Additionally, in regards to disease monitoring, Blockmans et al. also published their findings on repetitive ^{18}F-FDG PET scan on GCA patients undergoing glucocorticoid treatment where lower ^{18}F-FDG uptake was shown compared to baseline and 3 months after treatment but no further reduction was shown after 6 months of treatment in patients with and without a disease flare [61]. However, these results appear inconsistent with recent observations by Malezewski et al. in repeat temporal artery biopsies demonstrating a time-dependent decrease of macrophage rich granulomatous

Fig. 1. Distribution of macrophage specific radiotracers targets. These biomarkers are generally expressed in all activated macrophages. However, some markers are highly upregulated on M1 macrophage while the others are expressed more on M2 macrophages. This figure showed the expression of the markers based on dominant expression on M1 and M2 subset.

inflammation in GCA patients upon glucocorticoid treatment of 50% and 25% after 9 and 12 months respectively [62]. This inconsistency might be caused by ^{18}F-FDG uptake by other persistent infiltrating lymphocytes in the vessels despite reduction in inflammation. In addition, higher ^{18}F-FDG uptake has also been reported in aging vessels due to changes in metabolic activity, vessel wall remodeling and atherosclerosis [43,44]. Therefore, more specific macrophage targeted radiotracers are also needed for better visualisation of reduced inflammation and treatment monitoring.

4.1.2. Translocator protein (TSPO) targeted imaging

For over 20 years, macrophage targeted radiotracers targeting translocator protein (TSPO; also known as PBR or peripheral benzodiazepine receptor) have been used in PET imaging for neuroinflammatory diseases (Table 3). TSPO is a 18 kDa protein expressed on the outer membrane of mitochondria. Although TSPO is expressed in both M1 and M2 subsets, some reports have shown higher expression in M2 macrophages [63,64]. In more recent studies, targeting TSPO receptors

Table 1
Summary of ^{18}F-FDG PET scoring methods in LVV diagnosis.

Method	Description	Reference
Qualitative	First impression visual method based on expert opinion	[55]
Qualitative	Visual grading system based on four point scale (grade 0 = no vascular uptake, grade 1 = lower than liver uptake, grade 2 = similar to liver uptake, grade 3 = higher than liver uptake).	[56]
Semi quantitative	Ratio between the aortic wall standardized uptake value (SUVmax aorta) and liver uptake (SUVmax liver).	[57]
Semi quantitative	Ratio between the aortic wall standardized uptake value (SUVmax aorta) and lung uptake (SUVmax lung) or venous blood pool background (SUVmean venous blood pool).	[58]

has shown promising results in imaging non-neuronal inflammatory diseases such as rheumatoid arthritis, atherosclerosis, GCA, TAK and systemic lupus erythematosus [65–67,69,72,77]. Pugliese et al. first tested ^{11}C-PK11195, a TSPO targeted radiotracer, for LVV imaging in a small study involving fifteen patients with a systemic inflammatory disorder with a high suspicion of LVV [67]. Visual analysis showed focal vascular uptake in all six symptomatic patients as compared to no uptake in asymptomatic patients. Semi-quantitative analysis comparing the SUVmax aorta to the SUVmax venous blood pool revealed that all six symptomatic patients had individual target to background ratios (TBR) of >1.20 (2.41 ± 1.59, p = 0.001) while all asymptomatic patients had TBR of <1.20. A PET/CT scan was repeated for one symptomatic

patient after 20 weeks of glucocorticoid treatment and the result indicated a reduction of vascular ^{11}C-PK11195 uptake in parallel with a reduction of serum inflammatory markers and clinical improvement. Furthermore, Lamare et al. tested ^{11}C-(R)-PK11195 in individuals with systemic inflammation suspected of LVV (symptomatic, n = 3; asymptomatic, n = 4) [72] demonstrating a two-fold increase of vascular ^{11}C-(R)-PK11195 uptake in symptomatic patients as compared to asymptomatic patients. These studies suggest the potential of targeting TSPO for LVV imaging and support the contention that targeting (M2) macrophages is feasible for imaging LVV. However, there is a disadvantage in targeting TSPO. Owen et al. found that in some patients, TSPO tracers were less efficient in binding to the target receptor [97,98]. Older generation TSPO targeted radiotracers such as PK11195 based tracers also have high background blood-pool accumulation which affects their accuracy. Nevertheless, new TSPO targeted radiotracers with improved binding characteristics compared to classic TSPO radiotracers have been developed and are currently being evaluated in pre-clinical studies although these new tracers exert various binding capability depending on TSPO polymorphism (Table 2).

4.2. Macrophage targeted tracers investigated in other inflammatory diseases

To date, a number of macrophage targeted tracers are already available clinically or are being evaluated in clinical studies for oncological and other inflammatory diseases. In addition, many newly developed macrophage targeted tracers are currently emerging and are undergoing preclinical testing. Although these tracers have yet to be tested for

Table 2
List of TSPO targeted radiotracers in inflammatory disorders.

Radiotracer	Modality	Clinical/preclinical	Disease	Reference
^{11}C-PK11195	PET	Clinical	Multiple sclerosis	[65]
	PET	Preclinical	Neuro-inflammation	[66]
	PET/CT	Clinical	Systemic inflammation (predominantly GCA)	[67]
	PET	Preclinical	Neuro-inflammation	[68]
	PET/CT	Clinical	Atherosclerosis	[69]
	PET	Preclinical	Cerebral ischemia	[70]
^{11}C-(R)-PK11195	PET	Clinical	Rheumatoid arthritis	[71]
	PET/CT	Clinical	Systemic inflammation (predominantly GCA)	[72]
	PET	Preclinical	Traumatic brain injury	[73]
	PET	Clinical	Multiple sclerosis	[74]
	PET	Preclinical	Lung inflammation	[75]
	PET	Preclinical	Liver damage	[76]
	PET	Clinical	Rheumatoid arthritis	[77]
	PET	Preclinical	Cerebral ischemia	[78]
^{18}F-DPA714	PET	Preclinical	Neuro-inflammation	[66]
	PET	Preclinical	Abdominal aortic aneurysm	[79]
	PET	Preclinical	Multiple sclerosis	[80]
	PET	Preclinical	Cerebral ischemia	[70]
	PET	Preclinical	Peripheral tissue inflammation	[81]
	PET/CT	Preclinical	Rheumatoid arthritis	[82]
	PET/CT	Preclinical	Allograft rejection	[83]
	PET	Preclinical	Traumatic brain injury	[84]
^{11}C-PBR28	PET	Clinical	Multiple sclerosis	[85]
	PET	Preclinical	Acute inflammation and adjuvant arthritis	[86]
^{11}C-PBR111	PET	Preclinical	Epilepsy	[87]
	PET	Preclinical	Multiple sclerosis	[88]
	PET	Clinical	Multiple sclerosis	[89]
^{18}F-PBR06	PET	Clinical	Quantification of brain TSPO expression	[90]
^{18}F-FEDAC	PET	Preclinical	Lung inflammation	[75]
	PET	Preclinical	Liver damage	[76]
^{18}F-FEDAA1106	PET	Clinical	Multiple sclerosis	[91]
	PET	Preclinical	Atherosclerosis	[92]
^{11}C-DPA713	PET	Preclinical	Neuro-inflammation	[66]
^{11}C-vinpocentine	PET	Clinical	Multiple sclerosis	[65]
^{11}C-SSR180575	PET	Preclinical	Neuro-inflammation	[68]
^{11}C-DAC	PET	Preclinical	Multiple sclerosis	[93]
^{18}F-GE-180	PET	Preclinical	Cerebral ischemia	[78]
^{125}I-Iodo-DPA-713	SPECT/CT	Preclinical	Tuberculosis associated inflammation	[94]
	SPECT/CT	Preclinical	Atherosclerosis	[95]
	SPECT/CT	Preclinical	Chronic pancreatitis	[96]

vasculitis, such radiotracers have potential to be used for macrophage imaging in LVV as well.

4.2.1. Macrophage targeted radiotracers in clinical studies

Besides targeting glucose metabolism and TSPO, macrophage targeted radiotracers targeting other biological pathways and receptors are already available for diagnosis and assessment of many other diseases (Table 3). These tracer targets are generally expressed in all activated macrophages. However, some target receptors or metabolic activities are higher in certain subsets of macrophages depending on the polarisation stimulus in the microenvironment. Therefore, some of these tracers are more suitable to target M1 macrophage while others preferentially target M2 macrophages. As mentioned earlier, macrophages are incredibly plastic and switch phenotypes governed by factors in the microenvironment. Therefore, although these radiotracers have potential to be utilized for LVV imaging, their suitability needs to be further investigated as macrophages in LVV lesion might express different targets compared to other diseases.

Several macrophage surface receptors are gaining importance in imaging inflammatory diseases. One of the target surface receptors for macrophage targeted imaging is the somatostatin receptor (SSTR). SSTRs are G-protein coupled receptors expressed throughout various tissues and by cells of the immune system. Recently, Tarkin et al. assessed the expression of SSTR2 on macrophages subsets and found higher expression on M1 macrophages [103]. In recent studies by Gormsen et al. and Tarkin et al., ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE displayed superior specificity, sensitivity and accuracy in imaging cardiac sarcoidosis and atherosclerosis in patients compared to ^{18}F-FDG due to lower background noise [102,103]. Another surface receptor, the macrophage mannose receptor (MMR/CD206), is considered a hallmark of M2 macrophages is also utilized as tracer target. In an attempt to understand HIV associated vascular inflammation, research by Zanni et al. revealed a higher uptake of the MMR specific SPECT tracer ^{99m}Tc-Tilmanocept in the aorta of HIV patients compared to non-HIV controls and demonstrated co-localisation of ^{99m}Tc-Tilmanocept with CD206^{+} macrophages [104]. Recently, a CXCR4 specific PET radioligand, ^{68}Ga-Pentixafor, has been developed for cancer imaging. CXCR4 is chemokine receptor belonging to the family of G-protein coupled receptors that are expressed on immune cells and is upregulated in various oncological conditions [105–107]. Hyafil et al. used this radioligand to successfully image atherosclerosis in atherosclerosis patients [107]. They found that there was focal uptake of ^{68}Ga-Pentixafor in atherosclerotic lesions and no uptake in asymptomatic controls. Another receptor, namely the folate receptor, is also currently emerging as a potential target for imaging tumours and inflammatory diseases. Physiologically, folate is an important compound that is critical for DNA and RNA synthesis. There are three different Folate receptors subtypes namely FR-α, FR-β and FR-γ. While these folate receptors are expressed in various tissues, the active form of the FR-β is exclusively expressed on all activated macrophages, and association has been described with the M2 subtype [108–110]. Matteson et al. successfully imaged inflamed joints in rheumatoid arthritis patients with FolateScan™ (^{99m}Tc-EC20) albeit with low sensitivity (40%) [112].

Apart from surface receptors, some tracers target biological pathways. Similar to imaging glucose uptake in ^{18}F-FDG PET, radiolabelled choline has been used to target macrophages and tumours. Choline is a precursor of phosphatidylcholine, a major constituent of the cell membrane with increased choline uptake by tumours and activated macrophages at inflammatory sites having been previously reported [111]. Vöö and colleagues imaged atherosclerotic patients with ^{18}F-FCH (fluorocholine) revealing a higher uptake in symptomatic plaques compared to asymptomatic plaques that were highly correlated with macrophage infiltration [108].

Another pathway utilized in macrophage targeting involves system X$\bar{\text{C}}$. System X$\bar{\text{C}}$ is a cell membrane transporter that functions in cysteine/glutamate uptake and its expression is reported to be upregulated in LPS and IFN-γ induced M1 macrophages [113,114]. Chae et al. imaged a ^{18}F labelled glutamate derivative, ^{18}F-FSPG, that is specifically taken up by system X$\bar{\text{C}}$, in sarcoidosis patients [115]. Their findings showed a higher radiotracer uptake in sarcoidosis patients than in non-sarcoidosis patients. Additionally, compared to ^{18}F-FDG, ^{18}F-FSPG demonstrated significantly lower background uptake. Another radiotracer, ^{11}C-Methionine (^{11}C-MET), a well-established radiotracer for neuro-oncological diseases is also rising in imaging inflammatory diseases. The principle behind ^{11}C-MET PET is that proliferating cells have elevated amino acid uptake and studies have reported that infiltrating macrophages in tumour lesions showed increased methionine uptake [116]. The first report of ^{11}C-MET in inflammatory disease was reported by Morooka et al. where the group imaged nine patients with myocardial infarction and found ^{11}C-MET uptake in infarct regions [117]. Recent reports also showed a 7 fold increase of ^{11}C-MET in M1 macrophages in comparison to M2 macrophages and lower background uptake compared to ^{18}F-FDG [118,119].

Upon activation, certain enzymes are upregulated in macrophages which can therefore be utilized as tracer targets. Two of such enzymes are inducible nitric oxide synthase (iNOS) and cathepsin. The enzyme iNOS synthesizes Nitric oxide (NO) that is highly upregulated in M1 macrophages and has been widely used as a marker for M1 macrophages [120–122]. Huang et al. synthesized a novel iNOS specific radiotracer for PET imaging referred to as ^{18}F-NOS and tested the tracer in a human model of lung inflammation (endotoxin instillation) [123]. It was found that there was a 30% increased radiotracer uptake after endotoxin-induced lung inflammation compared to baseline. On the other hand, cathepsins are cysteine proteases that are highly expressed in macrophages. While cathepsins are expressed in both M1 and M2 macrophages, studies have shown that expression levels are higher in

Table 3
Macrophage targeted radiotracers in clinical studies.

Tracer target	Dominant macrophage subset	Radiotracer	Type	Modality	Disease	Reference
Somatostatin receptor (SSTR)	M1	^{68}Ga-DOTATATE	Chemical	PET/CT	Atherosclerosis	[99]
		^{64}Cu-DOTATATE	Chemical	PET/MR	Atherosclerosis	[100]
		^{68}Ga-DOTATOC	Chemical	PET/MR	Atherosclerosis	[100]
		^{64}Cu-DOTATATE	Chemical	PET/CT	Atherosclerosis	[101]
		^{68}Ga-DOTANOC	Chemical	PET/CT	Cardiac sarcoidosis	[102]
		^{68}Ga-DOTATATE	Chemical	PET/CT	Atherosclerosis	[103]
Macrophage mannose receptor (MMR/CD206)	M2	^{99m}Tc-Tilmanocept	Chemical	SPECT/CT	Arterial inflammation	[104]
CXCR4 (CD184)	M2	^{68}Ga-pentixafor	Chemical	PET/MR	Atherosclerosis	[107]
Choline metabolism	M1/M2	^{18}F-FCH	Chemical	PET/CT	Atherosclerosis	[111]
Folate receptor beta (FR-β)	M2	^{99m}Tc-EC20	Chemical	SPECT	Rheumatoid arthritis	[112]
System X$\bar{\text{C}}$ (cysteine/glutamate antiporter)	M1	^{18}F-FSPG	Chemical	PET/CT	Sarcoidosis	[115]
Amino acid metabolism	M1	^{11}C-methionine	Amino acid	PET	Myocardial infarction	[117]
Inducible nitric oxide synthase (iNOS)	M1	^{18}F-NOS	Chemical	PET/CT	Lung inflammation	[123]
Cathepsin	M1/M2	^{68}Ga-BMV101	Chemical	PET/CT	Pulmonary fibrosis	[127]

M1 macrophages [124–126]. Withana and colleagues generated a ^{64}Cu labelled probe (BMV101) for targeting cysteine cathepsins for fibrosis PET imaging in pulmonary fibrosis patients demonstrating a three-fold greater radiotracer uptake in the patients' lungs compared to healthy controls [127].

4.2.2. Macrophage targeted radiotracers in preclinical studies

As described above, numerous macrophage targeted tracers are already clinically available, but the specificity of the tracers can still be improved for better diagnostic accuracy. Better and more specific radiotracers targeting for example SSTR, MMR and folate receptors are being developed and extensive research is currently focused on developing new macrophage targeted tracers targeting various other receptors and biological pathways (Table 4). A particularly interesting newly developed ^{18}F-PEG-folate targeting FR-β has been reported to be more sensitive compared to ^{18}F-FDG. It has also been shown to have a lower blood-pool radioactivity and 1.5 times improved target to background ratio compared to [11]C-(R)-PK11195 [141,142]. Since [11]C-(R)-PK11195 was already proven to be superior to ^{18}F-FDG in LVV imaging, the new ^{18}F-PEG-folate might prove to be useful in LVV imaging. Additionally, a shift towards peptide and antibody based radiotracers can be observed in current radiotracer developments with multiple studies showing promising results. Short peptides such as cinnamoyl-F-(D)L-F-(D)L-F (cFLFLF) and D-Ala1-peptide T-amide (DAPTA), formyl peptide receptor 1 (Fpr1) and chemokine receptor CCR5 antagonists were recently labelled with radioligands for macrophage imaging in murine models [145,146,149]. Radiotracers based on antibodies that bind to macrophage surface receptors such as CD163, CD11b, CD169 and CRIg have also been developed and studied in murine models of atherosclerosis, host versus graft disease and rheumatoid arthritis [145,147,148,151,152]. These peptide and antibody based radiotracers might exhibit higher specificity for macrophages compared to chemical radiotracers utilizing metabolic activity such as ^{18}F-FDG, however they are large in size and therefore have poor tissue penetration ability and slow blood clearance.

Macrophages are phagocytic cells. Based on this principle, radiolabelled nanoparticles have been developed to target macrophages based on their ability to phagocytose these nanoparticles. Recently, Park et al. developed [89]Zr-oxalate for PET imaging of rheumatoid arthritis in mouse models [156]. Small animal PET showed higher [89]Zr-oxalate uptake compared to ^{18}F-FDG in RA induced joints. Nahrendorf et al. developed a ^{64}Cu labelled dextran-coated magnetic nanoparticle, ^{64}Cu-TNP, which can be used for PET imaging as well as a contrast-enhancing agent for MRI [154]. In an atherosclerotic mouse model, ^{64}Cu-TNP showed higher signals in atherosclerotic plaques when compared with ^{18}F-FDG whereas histological examination revealed a direct correlation between ^{64}Cu-TNP uptake and CD68^{+} macrophages. This study illustrates the potential of macrophage specific radiotracers for the application of hybrid PET/MR imaging.

5. Future directions and theranostic applications

Good radiotracers should have a high affinity to its target, be highly specific, have rapid plasma clearance, possess a low radiation dose, and exhibit low toxicity [157–159]. Hence, designing a radiotracer requires thorough consideration of selecting target biomarkers or biological pathways, the ligand or molecule for radiolabelling, the target tissue, and also in determining suitable radionuclides. However, not all molecules are suitable for tagging with any readily available radionuclide. For example, tagging an antibody with the short half-life [11]C

Table 4
Macrophage targeted radiotracers in preclinical studies.

Tracer target	Dominant macrophage subset	Radiotracer	Type	Modality	Disease	Reference
Macrophage mannose receptor (MMR/CD206)	M2	^{64}Cu-MAN-LIPs	Coated liposome	PET/MR	Tumour (TAMS imaging)	[128]
		^{99m}Tc-anti MMR	Nanobody	SPECT/CT	Rheumatoid arthritis	[129]
		^{18}F-FB-anti-MMR	Antibody fragment	PET	Tumour (TAMS imaging)	[130]
		^{68}Ga-NOTA-MSA	Chemical	PET/CT	Atherosclerosis	[131]
		^{18}F-FDM	Chemical	PET	Atherosclerosis	[132]
		^{18}F-FDM	Chemical	PET/CT	Atherosclerosis	[133]
		^{111}In-Tilmanocept	Chemical	SPECT	Atherosclerosis	[134]
Somatostatin receptor (SSTR)	M1	^{18}F-FDR-NOC	Chemical	PET/CT	Atherosclerosis	[135]
Folate receptor beta (FR-β)	M2	^{99m}Tc-his-folate	Chemical	SPECT/CT	Tumour (TAMS imaging)	[136]
		^{67}Ga-DOTA-Bz-folate	Chemical	SPECT/CT	Tumour (TAMS imaging)	[137]
		^{111}In-DTPA-folate	Chemical	SPECT/CT	Rheumatoid arthritis	[138]
		^{99m}Tc-folate	Chemical	SPECT	Atherosclerosis	[139]
		3′-aza-2′-^{18}F-fluorofolicacid	Chemical	PET/CT	Tumour (TAMS imaging)	[140]
		^{18}F-fluoro-PEG-folate	Chemical	PET	Rheumatoid arthritis	[141]
		^{18}F-fluoro-PEG-folate	Chemical	PET/CT	Rheumatoid arthritis	[142]
CD80	M1	^{11}C-AM7	Chemical	PET/CT	Atherosclerosis	[133]
		^{11}C-AM7	Chemical	PET/CT	Atherosclerosis	[143]
CD163	M2	^{68}Ga-ED2	Antibody	PET	Rheumatoid arthritis	[144]
Formyl peptide receptor 1 (Fpr1)	M2	cFLFLF-PEG-DOTA-[64]Cu	Peptide	PET	Macrophage infiltration in diabetes	[145]
		cFLFLF-PEG -[64]Cu	Peptide	PET/CT	Osteoarthritis	[146]
CD11b	M1	^{99m}Tc-MAG3-anti-CD11b	Antibody	SPECT/CT	Atherosclerosis	[147]
Siloadhesin (CD169)	M1	^{99m}Tc-SER-4	Antibody	SPECT/CT	Allograft rejection	[148]
CCR5	M1	^{64}Cu-DOTA-DAPTA	Peptide	PET/CT	Vascular injury	[149]
		^{64}Cu-DOTA-DAPTA-comb	Peptide conjugated nanoparticles	PET/CT	Vascular injury	[149]
P32 protein	M1/M2	^{64}Cu-LyP-1-dendrimer	Peptide labelled dendrimer	PET/CT	Atherosclerosis	[150]
CRIg (VSIG4)	M1/M2	^{99m}Tc-anti-Vsig4-nanobody	Nanobody	SPECT/CT	Rheumatoid arthritis	[151]
		^{99m}Tc-anti-Vsig4-nanobody	Nanobody	SPECT/CT	Hepatitis	[152]
P2X7 receptor	M1/M2	^{11}C-GSK1482160	Chemical	PET/CT	Neuro-inflammation	[153]
Macrophage phagocytosis	M1/M2	^{64}Cu-TNP	Nanoparticle	PET/CT	Atherosclerosis	[154]
		[89]Zr-PL-HDL	Nanoparticle	PET	Tumour (TAMS imaging)	[155]
		[89]Zr-AI-HDL	Nanoparticle	PET	Tumour (TAMS imaging)	[155]
		[89]Zr-oxalate	Nanoparticle	PET	Tumour (TAMS imaging), tissue inflammation and rheumatoid arthritis	[156]

radionuclide would yield an incompetent radiotracer since a viable antibody requires a longer period of distribution and tissue penetration time. The choice of radionuclide is also important in consideration of the target tissue. In general, sufficient time for blood clearance is preferred to lower the background blood-pool radioactivity. Depending on the molecule's blood clearance rate, some molecules with slower clearance rate are more suitable to be tagged with longer half-life radionuclides such as ^{18}F while molecules with rapid blood clearance can be tagged with short half-life radionuclides such as ^{11}C. In LVV imaging especially, rapid blood-pool clearance is a particularly important aspect to be taken into consideration in designing new radiotracers.

All radiotracers listed in Tables 2–4 are potentially applicable in LVV imaging. Theoretically, radiotracers targeting specific markers are better choices than radiotracers targeting metabolic activity. An example is the high background ^{18}F-FDG uptake in other proliferating cells. Targeting TSPO has been proven to work in LVV imaging. Therefore, newly developed ^{18}F-PBR06, ^{18}F-FEDAC, ^{18}F-FEDAA1106 and ^{18}F-GE-180 may have a great potential for LVV imaging. Other clinically established radiotracers targeting SSTR such as ^{64}Cu-DOTATATE and newly developed ^{18}F-FDR-NOC may also prove to be useful in LVV imaging. ^{18}F-PEG-folate which has been shown to be superior compared to first generation TSPO imaging tracers because of better target-to-background signal and might also be an interesting option for LVV imaging. However, although these tracer targets are highly expressed on activated macrophages, they are also expressed on other cells. Newer radiotracers such as ^{18}F-NOS and ^{68}Ga-pentixafor are more specific and may prove to be better macrophage targeted radiotracers although their suitability in imaging LVV has yet to be investigated. Antibody based radiotracers such as ^{68}Ga-ED2 (anti CD163), ^{99m}Tc-MAG3-anti-CD11b and ^{99m}Tc-anti-Vsig4-nanobody could be superior to chemical based radiotracers because of their high specificity for macrophages. However, these radiotracers are large (150 kD) and will have problems penetrating the tissue and have yet to undergo clinical trials. Additionally, there is currently no available data showing the capability of these radiotracers in discriminating atherosclerosis and vasculitis. Since both of these diseases are characterized by the influx of macrophages and T-cells, it is important for future studies to distinguish the macrophage subsets and the difference in biomarker expression between the macrophages in atherosclerotic lesions and vasculitic lesions. It is also important to compare these radiotracers in both diseases to discover radiotracers capable of distinguishing vasculitic lesions and atherosclerotic lesions.

Radiolabelled antibodies may also shed new light in theranostic applications. Theranostics is a newly coined term that refers to a molecule that can act as both a diagnostic and therapeutic tool. Various theranostic radiopharmaceuticals have been developed for cancer therapy (for a comprehensive review see [160]). A possible theranostic approach in LVV may be to radiolabel specific therapeutic antibodies or drugs with radionuclides – thereby providing imaging capability and hence identification of the potential therapeutic target, followed by higher targeted, unlabelled therapeutic dose. This may support development of precision medicine. With regard to macrophages, macrophage targeted therapy has been proven to be effective in several inflammatory disorders with several newly developed macrophage targeted therapeutic antibodies and immunotoxins [161,162]. Radiolabelling these therapeutic agents may be an interesting prospective development in the theranostic field. However, it is currently unknown whether or not macrophage targeted therapy is beneficial in LVV. Further studies involving this modality in vasculitis should be carried out before theranostic applications can be considered.

6. Concluding remarks

Macrophages are important effector cells in the pathogenesis of large- and medium-vessel vasculitis and hence imaging macrophages is considered an effective tool in the diagnosis and monitoring of these diseases. Over the past decade, ^{18}F-FDG PET has been proven to be a valuable modality in the early diagnosis of large vessel vasculitis but quickly loses its diagnostic accuracy following glucocorticoid treatment and less useful in monitoring long-term treatment follow-up of patients. As the main principle behind ^{18}F-FDG PET is to image activated macrophages and lymphocytes, numerous well-established and newly emerging macrophage targeted radiotracers may prove to generate more favorable results than ^{18}F-FDG PET in imaging LVV. Newer radiotracers such as ^{18}F-PBR06, ^{64}Cu-DOTATATE, ^{18}F-PEG-FOLATE, ^{18}F-NOS and ^{68}Ga-pentixafor are more macrophage specific than ^{18}F-FDG. Moreover, antibody based radiotracers such as ^{68}Ga-ED2 (anti CD163) and ^{99m}Tc-MAG3-anti-CD11b could even be better compared to chemical based radiotracers because of their high specificity. A drawback however, is that antibodies are large molecules which impairs tissue penetration. With regard to macrophage-targeted tracers, knowledge on macrophage subset distribution and their marker expression in LVV is currently limited. Therefore, future studies identifying macrophage phenotypes is required in order to cast a better understanding on the underlying pathogenesis of LVV and subsequently provide the necessary insight for better selection of tracers as well as new targets for tracer development.

Take-home messages

- Macrophages as key players in the pathogenesis of LVV can be utilized as a diagnostic imaging target.
- ^{18}F-FDG PET has proven to be useful in diagnostic imaging of LVV. However, this radiotracer is not specific and its diagnostic accuracy drops dramatically in patients undergoing glucocorticoid treatment.
- Macrophage targeted imaging utilizing radiotracers that target the TSPO receptor has proven to be valuable for LVV imaging.
- Macrophage targeted radiotracers developed for imaging cancer and inflammatory diseases can potentially be used for imaging LVV.

Conflict of interest

The authors declare no conflict of interest.

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