World Journal of Transplantation

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DOI: 10.5500/wjt.v6.i1.174

World J Transplant 2016 March 24; 6(1): 174-182
ISSN 2220-3230 (online)

MINIREVIEWS

Imaging-based diagnosis of acute renal allograft rejection

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Author contributions: Thölking G wrote the paper; Schuette-Nuetgen K performed research and wrote the paper; Kentrup D performed research, analyzed data and wrote the paper; Pawelski H performed research and analyzed data; Reuter S designed research and wrote the paper.

Supported by The Collaborative Research Centre 656 (Deutsche Forschungsgemeinschaft, SFB656, Projects C7 and PM12 and 21); and Innovative Medizinische Forschung, Medical Faculty, University of Münster, No. IRE121102.

Conflict-of-interest statement: The authors have declared that no competing interests exist.

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Received: June 22, 2015
Peer-review started: June 23, 2015
First decision: August 14, 2015
Revised: November 13, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: March 24, 2016

Abstract

Kidney transplantation is the best available treatment for patients with end stage renal disease. Despite the introduction of effective immunosuppressant drugs, episodes of acute allograft rejection still endanger graft survival. Since efficient treatment of acute rejection is available, rapid diagnosis of this reversible graft injury is essential. For diagnosis of rejection, invasive core needle biopsy of the graft is the "gold-standard". However, biopsy carries the risk of significant graft injury and is not immediately feasible in patients taking anticoagulants. Therefore, a non-invasive tool assessing the whole organ for specific and fast detection of acute allograft rejection is desirable. We herein review current imaging-based state of the art approaches for non-invasive diagnostics of acute renal transplant rejection. We especially focus on new positron emission tomography-based as well as targeted ultrasound-based methods.

Key words: Acute allograft rejection; Imaging; Positron emission tomography; Ultrasound; Magnetic resonance imaging; Single photon emission computed tomography; Kidney transplantation; Renal

Core tip: Kidney transplantation is the best available treatment for patients with end stage renal disease. For diagnosis of rejection, invasive core needle biopsy of the graft is currently considered as the "gold-standard". As biopsies carry the risk of significant graft injury, a non-invasive, specific and fast tool screening the whole graft for acute rejection is desirable. We herein review current imaging-based state of the art approaches for non-invasive diagnosis of acute kidney allograft rejection, focussing particularly on new positron emission tomography-based as well as targeted ultrasound-based methods.

Thölking G, Schuette-Nuetgen K, Kentrup D, Pawelski H, Reuter S. Imaging-based diagnosis of acute renal allograft rejection. *World J Transplant* 2016; 6(1): 174-182 Available from: URL: http://www.wjgnet.com/2220-3230/full/v6/i1/174.htm DOI: http://dx.doi.org/10.5500/wjt.v6.i1.174

INTRODUCTION

Kidney transplantation (KTx) is the favorable treatment for patients suffering from end stage renal disease (ESRD)[1]. Although modern immunosuppressive regimens offer good patient and graft survival rates, acute rejection (AR) after KTx remains a serious problem significantly limiting both graft and patient survival[2,3].

Therefore, early detection and treatment of AR is necessary. To date, renal biopsy is the "gold-standard" to diagnose AR, but might jeopardize allograft recipients due to its invasive character.

Thus, non-invasive techniques for detection of AR are desired. During the last decades, medical imaging techniques have improved tremendously. Novel methods do not only focus on structural details, but also visualize functional processes.

This review focuses on the current non-invasive imaging techniques to detect AR which might replace renal biopsies in the future.

ULTRASOUND

Sonographic allograft examination is part of the standard care of transplanted patients. This procedure detects allograft swelling, morphological changes, abatement of corticomedullary differentiation, alterations of echogenicity and distinctive structures such as medullary pyramids; renal blood circulation can be analyzed by means of Doppler ultrasound and contrast-enhanced ultrasound examination. While the method is cost-effective and widely available, it still has considerable limitations in sensitivity and specificity for the diagnosis of AR.

New approaches might overcome these caveats. The resistive index (RI) is a noninvasive method using the vascular resistance and elastic compliance to evaluate the function of the allograft. Unfortunately, the RI measured in the allograft is influenced by systemic parameters like the vascular compliance, pulse pressure, heart rate and rhythm. Due to progressing arteriosclerotic processes of the vascular system, older recipient age is the strongest determinant for a higher RI[4]. Higher RIs are also associated with antibody-mediated rejection and acute tubular necrosis in index biopsies[4], and RIs of 0.8 or higher are associated with decreased patient survival[4,5]. However, data on the correlation between RI and allograft outcome are unequivocal[4-6].

Recently, another non-invasive index for the prediction of AR has been developed on the base of contrast-enhanced ultrasonography (CEUS). It includes CEUS factors such as rising time, time to peak and delta-time among regions of interest[7].

Acoustic radiation force impulse imaging (ARFI) assesses tissue elasticity and was utilized to identify AR in a small series of 8 patients. ARFI-values were elevated by more than 15% in patients undergoing AR, when compared to other causes of allograft damage[8]. However, the method has not been evaluated by others and is not used in clinical routine yet.

An experimental but promising procedure is the use of microbubbles targeting T-lymphocytes. The accumulation of T cells during AR can be visualized *via* microbubbles coupled to anti-CD3 antibodies (Figure 1)[9]. The method allows differential diagnosis of AR with high specificity.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) is another non-invasive method to evaluate kidney allograft function. MRI is based on the detection of signals from hydrogen nuclei or protons changing their magnetic behaviour in response to altered magnetic fields in the MRI system, and can reveal various tissue characteristics, including intrinsic MR properties like the relaxation times T_1 and T_2[10]. An important advantage of MRI is the high spatiotemporal resolution, which allows the precise visualization of anatomical structures as well as functional assessment of the graft. MRI allows the detection of distinctive features of vascular and interstitial structures, there by discriminating between different mechanisms of renal allograft injury such as AR or acute tubular necrosis (ATN)[11]. In the field of nephrology, various MRI techniques can be used to visualize different pathophysiological processes[10].

Dynamic contrast enhanced MRI (DCE MRI) is a common MRI method involving the use of a contrast agent. DCE MRI using gadolinium-based contrast agents is also termed MR renography (MRR). The contrast agents are freely filtered at the glomeruli but are not secreted or reabsorbed in the tubules. Therefore they can optimally be used to quantify renal perfusion, glomerular filtration rate (GFR) and tubular function, which helps to distinguish between AR and ATN[11]. The assessment involves the measurement of cortical and medullary blood flow within the graft after administration of contrast agent. In contrast to normal grafts, the cortical and medullary blood flow is significantly reduced in grafts experiencing AR. The predominantly reduced medullary blood flow seems to be characteristic for AR and helps to differentiate between AR and ATN[12].

Identification of and discrimination between various mechanisms of allograft damage is also possible by using a tracer kinetic renal model which determines the mean transit time (MTT) of a tracer through the

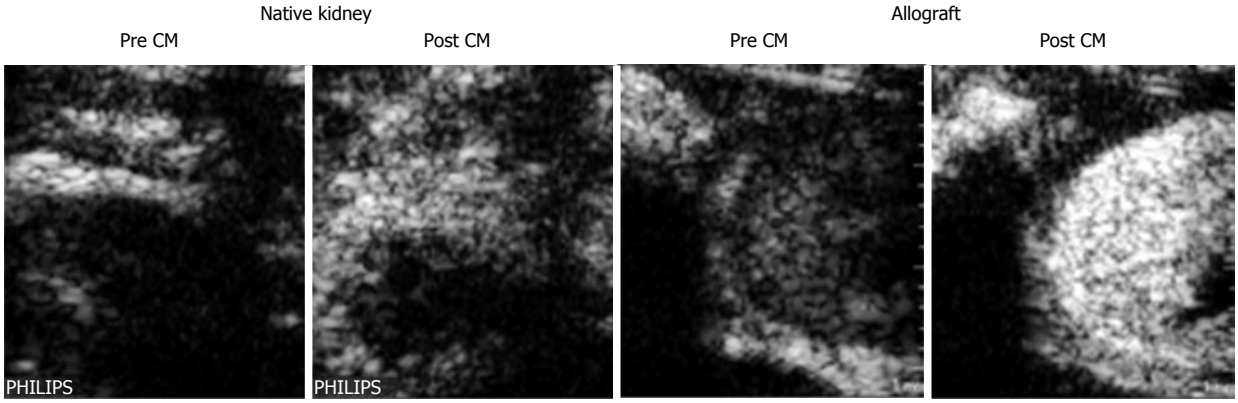

Figure 1 Representative ultrasound images of an allogeneically transplanted (aTX) rat kidney (graft) and its native control kidney (native) on day 4 post surgery. Depicted are examples of transversal images taken before (pre CM) and 15 min after (post CM) tail vein injection of anti-CD3-antibody labeled microbubbles. CM: Contrast media/microbubbles conjugated to anti CD3 antibody.

different compartments of the kidney[13]. However, although differences in the fractional MTT values between normal grafts or grafts undergoing AR or ATN have been observed, substantial overlaps among these groups and with healthy control kidneys exist. Moreover, the rare but characteristic risk of gadolinium-induced nephrogenic systemic fibrosis needs to be considered[14].

Another MRI technique which is independent from contrast agent usage is diffusion-weighted MRI (DWI MRI). DWI MRI depends on the signal decay that is induced by the relative diffusion-based displacement of water molecules, which can be quantified by calculating the so called apparent diffusion coefficient (ADC). The ADC is influenced by the tissue microstructure and does not account for directionality of molecular motion. To address this issue of anisotropic diffusion properties due to the radial orientation of main anatomic structures like vessels and tubules, the more sensitive diffusion tensor imaging (DTI) has been applied[15]. DTI allows the assessment of the fractional anisotropy (FA) of tissues, thereby considering the directionality of diffusion. Recently, the role of diffusion-weighted MRI for differentiation between AR and ATN was discussed, and new automated segmentation protocols might be helpful[16].

The differentiation between AR and ATN might also be possible by applying blood-oxygen level-dependent (BOLD) MR[17-19]. This method utilizes the paramagnetic effects of deoxyhemoglobin. Deoxyhemoglobin is increased in tissues with lower oxygen concentration and shortens the transverse relaxation time constant T2*. Inversely, the apparent relaxation rate, R2* (= 1/T2*), is elevated. Therefore, BOLD MR can serve as a non-invasive technique to evaluate the renal parenchymal oxygenation concentration. In kidneys displaying AR, a significantly lower medullary R2*, corresponding to a higher oxygenation, was observed compared to ATN[18,20].

Arterial spin labeling (ASL) MRI is another approach to assess allograft function especially for longitudinal perfusion evaluation. ASL MR utilizes arterial blood as an endogenous contrast agent. Inflowing blood is selectively labeled by altering its longitudinal magnetization to have an opposite magnetization compared to the destination tissue. The difference between a labeled image (tag) and a non-labeled image (control) can be used to determine tissue perfusion. ASL MR has successfully been applied to examine native and transplant kidneys. ASL studies using a flow sensitive alternating inversion recovery (FAIR-ASL) scheme (for details see[21]) revealed a significant lower overall or medullary perfusion in allografts when compared to healthy kidneys for subjects with eGFR > 60 mL/min per 1.73 m^2 or with eGFR < 60 mL/min per 1.73 m^2 respectively[22]. Also, a significant lower cortical perfusion in renal grafts with acute decrease in renal function was observed when compared to allografts with good postoperative and long-term function[23].

Given the need for non-invasive diagnosis of renal inflammation, several studies used nanoparticles to detect specific immune cells or immune proteins in the kidney (for review see[24]). In the context of renal transplantation, Hauger *et al*[25] and Chae *et al*[26] reported successful usage of super magnetic iron oxide (SPIO) particle-loaded macrophages to differentiate between various causes of graft failure. Accumulation of iron particles in the kidney during AR was shown 3 and 5 d after application, respectively. Unfortunately, non-phagocytic cells such as T-cells generally have a low labeling efficiency and poor contrast agent incorporation, which limits cellular MR imaging *in vivo*. Recently, Liu *et al*[27] reported a new synthesized class of MRI contrast agent, IOPC-NH2 particles, for labeling of T-cells in allograft rejection in a rat model of heart-lung transplantation. This technique might represent an approach for potential clinical translation of MRI-based tracking of non-phagocytic cells, such as T- and B-lymphocytes.

Various MRI techniques including BOLD, DWI and ASL have been combined in several longitudinal

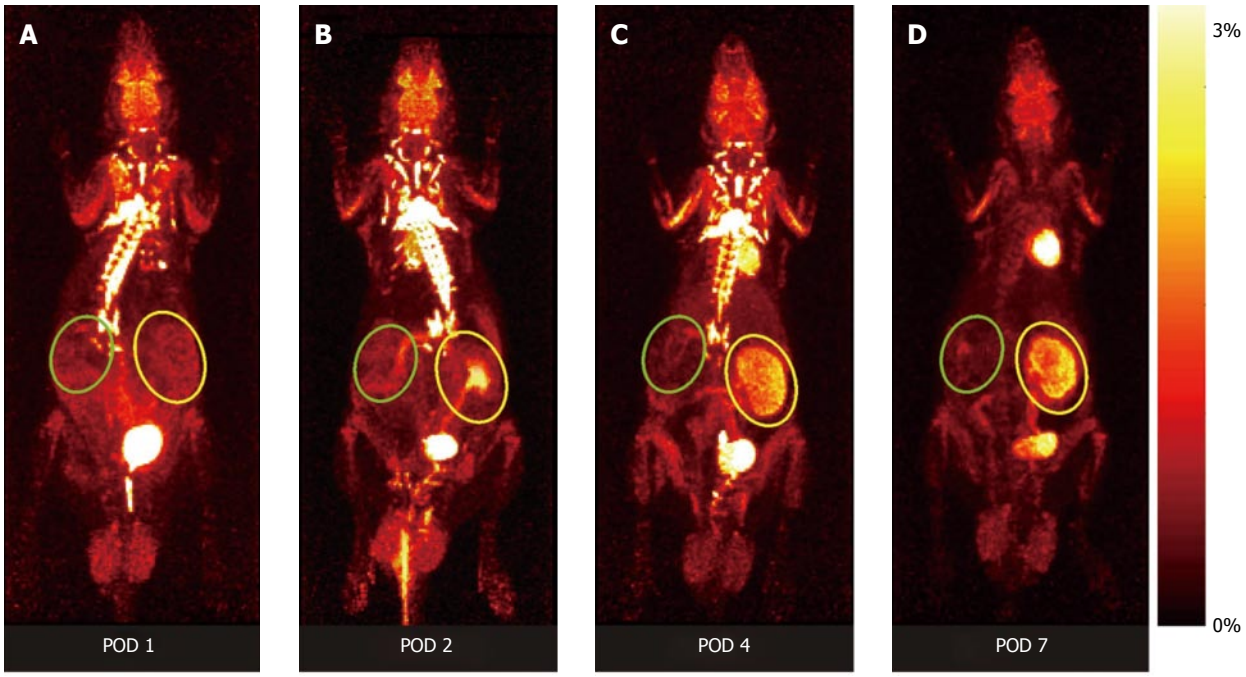

Figure 2 Representative positron emission tomography-images of dynamic whole body acquisitions of a series of an allogeneically transplanted rat [postoperative day 1 (A), 2 (B), 4 (C), and 7 (D)], after tail vein injection of 30 MBq ^{18}F-fluordeoxyglucose (maximum a posterior projection, 180 min pi). While the allograft undergoing rejection shows distinct enhancement of ^{18}F-FDG (yellow circle) the native control kidney without rejection does not (green circles). Figure taken from[44]. POD: Postoperative day; FDG: Fluordeoxyglucose.

studies, but case numbers were low and results were contradictory[28,29]. Further longitudinal studies with larger sample sizes are needed to determine the value of the different MR techniques for the evaluation of long-term allograft function.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is an imaging procedure based on the detection of internal radiation. After administration of an intravenous radioactive tracer, gamma rays emitted by the tracer are recorded by an external detector system called gamma camera. PET enables whole body visualization with high intrinsic sensitivity and provides high specificity although only very low concentrations of the tracer are needed[30,31]. The method offers a spatial resolution of 3-5 mm and generates 3D images[32]. Metabolic and cellular processes like pH-changes, apoptosis, inflammation and infection can be visualized[33].

The use of ^{18}F-fluordeoxyglucose (FDG) for scintigraphic detection of glucose metabolism was published in 1978[34] and became the mainly used radionuclide in PET. After injection of the tracer, ^{18}F-FDG enters the cell using glucose transporters like GLUT1. ^{18}F-FDG acts like a glucose analogue and correlates with the metabolic activity of the cell. After phosphorylation of ^{18}F-FDG, it cannot be further metabolized and is entrapped in cells with a high metabolism. The biodistribution of ^{18}F-FDG can be assessed by PET[35]. ^{18}F-FDG-PET is a well-established method used in clinical diagnostic. However, PET with glucose-based radionuclides is not specific for a particular disease and needs to be evaluated in the clinical context. For example, the uptake of ^{18}F-FDG depends on the presence of glucose transporters which are upregulated under several conditions, like inflammation and tumor genesis. The application field of PET has extended over the last years, and ^{18}F-FDG-PET has successfully been used in many pathological processes like cancer[36-38], vasculitis[39], fever of unknown origin[40], asthma[41], cystic fibrosis[42], and organ transplantation[43-46].

Recently, our group was able to non-invasively assess renal function by ^{18}F-fluoride clearance and to monitor graft inflammation by ^{18}F-FDG[43,47]. This PET method allows the visualization of molecular and cellular processes characteristic for AR, *e.g.*, the assessment of metabolic activity of recruited leucocytes, hypoxia cell death, as well as allograft function. The pattern of the ^{18}F-FDG-uptake during AR indicates a state of increased metabolism, driven by inflammatory cells (Figure 2). The specific distribution pattern of cell activity allows the discrimination of AR from other pathological conditions in both a rat renal transplantation model and in transplanted patients[44,48]. Despite specific signals in kidney allografts undergoing AR, the clearance of ^{18}F-FDG has to be taken into account. ^{18}F-FDG signals derived from urinary tracer remnants within the urinary pelvis can be avoided by extending the time between the application of the tracer and the PET procedure, or by simply using ^{18}F-FDG labelled T-cells[44,49]. As ^{18}F-FDG uptake by renal allografts immediately decreases after

successful treatment of AR, the method might also be used to monitor treatment efficacy[43].

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Single photon emission computed tomography (SPECT) is another nuclear imaging-based method for the detection of AR in kidney allografts. Similar to PET, SPECT provides functional rather than morphological data, but while PET captures an indirect signal (pairs of gamma rays resulting from annihilation of the emitted positrons with electrons) SPECT directly measures gamma radiation from the deployed radioisotopes. Although PET provides higher spatial resolution[32], better sensitivity and better quantification, SPECT is still the most commonly used technique. Beside its high availability and the wide range of adequate radionuclides, the cost-effectiveness is a noteworthy advantage of SPECT[50]. Regarding the available tracers used to visualize metabolic processes as well as cellular and molecular events, the generally longer half-lives of SPECT radionuclides are of additional advantage, as they better correspond to the duration of the investigated biological processes. Common markers in SPECT are ^{111}In, ^{67}Ga, ^{123}I and ^{99m}Tc, the latter offering the broadest application spectrum because of its relatively simple production, availability and optimal decay characteristics compared to the rather unstable and short-lived PET tracers[51]. However, the more complex incorporation process of ^{99m}Tc into a molecule which is impeded by involvement of chelating moieties and possible steric hindrance needs to be mentioned. Thus, thorough definition and characterization of the respective processes to be examined is necessary in order to choose the appropriate tracer.

The broad application field of SPECT imaging in numerous diseases has continuously expanded during the last years. Existing technologies have been optimized and new, more sophisticated approaches have been evolved. Particular in oncology, lots of different strategies have been introduced facilitating SPECT-based diagnosis and therapeutic monitoring in oncological patients[52-54]. Moreover, processes like tissue injury, cell death or angiogenesis in cardiac and pulmonary diseases[55-57], as well as specific bacterial infections[58], inflammation severity in rheumatoid arthritis[59] and neurological disorders[60-62] can be detected and monitored with increasing precision.

According to the various pathophysiological mechanisms involved in AR after kidney transplantation, different markers for SPECT imaging have been developed during the last decades. The general principles of detecting the diverse pathophysiological processes and their implementation in PET-based diagnosis have already been discussed above. Many of these processes can be assessed by SPECT as well.

As early as in 1976, George *et al*[63] were able to visualize kidney allograft rejection using ^{99m}Tc-sulfur colloid, which accumulates in areas of fibrin thrombi in acute and chronic rejecting allografts.

As leukocyte recruitment plays a crucial role in allograft rejection, many attempts to label various cell lines *ex vivo* and *in vivo* have been made. Common markers used for radiolabelling white blood cells in SPECT are ^{99m}TC-HMPAO or ^{111}In-oxine[64-66]. Compared to ^{18}F-FDG, these markers are more stable, have a longer half-life time and therefore should be used for sustained biological processes[67]. Labeling efficiency and viability of the marked cells are additional concerns. Whereas the labeling rate of ^{18}F-FDG is only about 60%, ^{111}In-oxine and the PET marker ^{64}Cu exhibit are more efficient and have labeling rates of approximately 80%. Viability of the cells was shown to be comparable within the first four hours for ^{111}In-oxine, ^{99m}Tc-HMPAO, ^{64}Cu and ^{18}F-FDG, while a significant decline of cell survival was observed after 24 h[68]. Regarding kidney transplantation, the use of ^{99m}Tc-HMPAO-labeled mononuclear cells has been shown to differentiate between rejection and ATN[69].

Different ^{99m}Tc-, ^{111}In- or ^{123}I-labeled antibodies binding to cell surface markers of different immune cells, like CD3, CD4, CD20 or CD25 have been developed for *in vivo* imaging (for review see[31]). Detection of AR in kidney transplantation is possible by using ^{99m}Tc-OKT3, a mouse monoclonal antibody against the CD3 complex, which targets T cells, natural killer cells and natural killer T cells[70]. Side effects of this antibody due to its immunogenicity have been eliminated by using a humanized form, ^{99m}Tc-SHNH-visilizumab[71,72]. Further studies are needed to evaluate its utility in diagnosing AR.

A high-affinity radiolabelled ligand binding to FPR1, a leukocyte receptor which is involved in chemotaxis and inflammatory responses, has recently been reported as a novel method to detect leukocyte accumulation in inflammation. FPR1 is upregulated during inflammation, and the ^{99m}Tc-labeled FPR1 antagonist cFLFLFK-NH_2 has been shown to bind to FPR1 without interfering with the inflammatory processes[73].

Sharif-Paghaleh *et al*[74] published a reporter gene mediated method of radiolabelling regulatory T cells with Techentium-99m pertechnetate ($^{99m}TcO_4^-$) *in vitro* and *in vivo*, enabling the precise visualization of the cells as long as they are vital. This method might become a useful tool in the transplant setting as well.

Besides accumulation of immune cells, complement activation is another mechanism which plays an important role in the pathophysiology of transplantation. Recently Sharif-Paghaleh *et al*[75] successfully demonstrated non-invasive imaging of complement activation following ischemia-reperfusion injury (IRI) in a model of cardiac transplantation, using ^{99m}Tc-recombinant complement receptor 2 (^{99m}Tc-rCR2). As IRI and complement activation *per se* are involved in transplant rejection and complement inhibitors have been developed as a therapeutic option, this principle

could be a useful tool to identify tissue damage after transplantation, to allow patient risk stratification and to monitor the effects of therapeutic interventions.

SPECT imaging can also be applied for monitoring of allograft function. While static imaging using ^{99m}Tc-dimercaptosuccinic acid (DMSA) can visualize functioning kidney tissue and anatomical abnormalities[76,77], dynamic imaging with ^{99m}Tc-diethylenetriaminepentaacetic (DTPA) or ^{99m}Tc-mercaptoacetyltriglycine (MAG3) further allows detection of AR and discrimination from ATN[78-81].

DISCUSSION

Although core needle biopsy of the kidney allograft is still the gold standard to discriminate causes of renal injury, imaging of immunological processes offers promising, novel and non-invasive possibilities. As perfect imaging depends on severity of rejection, imaging-based methods still suffer from low sensibility[82]. Currently, PET and SPECT are able to discriminate ATN from AR. Unfortunately, differentiation between different forms of AR, namely acute antibody mediated rejection (ABMR) and T cell-mediated rejection (TCMR), has not been tested sufficiently in preclinical imaging studies so far. As both entities are treated differently, the discrimination between both is of high clinical relevance. Identification and assessment of discriminating targets like T cells (TCMR) or C4d (ABMR) might support further differential diagnostics. The ultrasound visualization of T-cells by use of microbubbles coupled to anti-CD3 antibodies is a first approach for specific diagnostics of TCMR[9]. MRI-based assessment of IOPC-NH2 labeled T-cells is based on the same principle and has been shown to be useful for the detection of rejection of a heart-lung transplant[27]. New biomarkers, like cell free DNA, microRNA, chemokines, clusters of differentiation or tubular injury markers that correlate with AR, might provide additional information. Unfortunately, most of these markers are time-consuming, expensive and do not distinguish between subclinical tubulitis, BK virus infection and different forms of AR. Nevertheless, some of these approaches, like a combination of monitoring urinary CXCL10:creatinine ratio and donor specific antibodies, might significantly improve the noninvasive diagnosis of ABMR[83]. An approach involving the use of biomarkers as well as non-invasive imaging, might improve sensitivity as well as specificity for the detection of renal allograft AR.

CONCLUSION

Non-invasive methods for specific diagnosis of AR and surveillance monitoring of the allograft are highly desired. Advances in technology and tracer development provide new diagnostic options. At present most of the promising new imaging technologies are still used at a pre-clinical stage, but represent very useful research tools on the way into clinical use. Future studies in human allograft recipients are needed to fully support these methods for clinical routine.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Olaf Boenisch for language editing of the manuscript.

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