EMA Moves Toward Approval of ^{177}Lu-Oxodotreotide

Advanced Accelerator Applications SA (AAA; Saint-Genis-Pouilly, France) announced on July 21 that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) had issued a positive opinion recommending marketing authorization of ^{177}Lu-oxodotreotide (Lutathera) for treatment of unresectable or metastatic, progressive, well-differentiated, somatostatin receptor (SSTR)–positive gastroenteropancreatic neuroendocrine tumors (NETs) in adults. The European Commission, which has the authority to approve medicines for the European Union, Iceland, Norway, and Liechtenstein, will review the CHMP recommendation. Stefano Buono, CEO of AAA, said, "We are proud to achieve this important milestone. We look forward to collaborating with the European health authorities to make ^{177}Lu-oxodotreotide widely available as soon as possible. To date, more than 1,700 NET patients across 10 European countries have already received the treatment under compassionate use and named patient programs."

The CHMP adopted its opinion based on the results of a randomized pivotal phase 3 study (NETTER-1) that compared treatment using ^{177}Lu-oxodotreotide with a double dose of octreotide long-acting release (LAR) in 229 patients with inoperable midgut NETs progressive under standard octreotide LAR treatment and overexpressing SSTRs. Efficacy and safety data also came from an Erasmus University Medical Center phase 1/2 trial conducted in more than 1,200 patients with a wide range of NET involvement. The NETTER-1 study met its primary endpoint by demonstrating that treatment with ^{177}Lu-oxodotreotide was associated with a statistically significant and clinically meaningful risk reduction of 79% in disease progression or death versus treatment with a double dose of octreotide LAR. ^{177}Lu-oxodotreotide, when administered concomitantly with a renal-protective agent, had low rates of grade 3 or 4 hematologic toxicity and no evidence of nephrotoxicity over the median study follow-up of 14 mo.

Advanced Accelerator Applications SA

FROM THE LITERATURE

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

MR vs PET/CT Imaging in Multiple Myeloma

Moreau and colleagues from University Hospital Nantes (France) and a consortium of French and U.S. researchers representing the Imagerie Jeune Myélome study reported on July 7 ahead of print in the *Journal of Clinical Oncology* on a prospective comparison of MR and ^{18}F-FDG PET/CT imaging in initial diagnostic detection of bone lesions and in assessment of prognostic value after chemotherapy but before maintenance therapy in symptomatic patients with multiple myeloma. The study included 134 patients who received a combination of lenalidomide, bortezomib, and dexamethasone (RVD) chemotherapy with or without autologous stem cell transplantation, followed by lenalidomide maintenance. Patients underwent PET and MR imaging at diagnosis, after 3 cycles of RVD, and before maintenance therapy. At diagnosis, MR and PET/CT results were positive in 127 (95%) and 122 (91%) patients, respectively. Normalization of MR at the second and third imaging timepoints was not predictive of progression-free nor overall survival (PFS and OS, respectively). PET/CT normalized after 3 cycles of RVD in 32% of patients with positive PET results at diagnosis, and 30-mo PFS was improved in this group. PET/CT normalized before maintenance in 62% of patients who were positive at diagnosis, and this group had better PFS and OS over the duration of the study. Extramedullary disease at diagnosis was determined to be an independent prognostic factor for both PFS and OS, and PET/CT normalization before maintenance was an independent prognostic factor for PFS. The authors concluded that although no difference between MR and PET/CT was noted in detection of bone lesions at diagnosis, PET/CT "is a powerful tool to evaluate the prognosis of de novo myeloma."

Journal of Clinical Oncology

Biomarkers and Early AD Diagnosis

In an article in the August issue of *The Lancet. Neurology* (2017;16:661–676) Frisoni and colleagues from University Hospitals/University of Geneva (Switzerland) and a consortium of researchers from Switzerland, Italy, Sweden, The Netherlands, the UK, the United States, Spain, and Germany reported on a strategic 5-phase "roadmap" to foster clinical validation of biomarkers in Alzheimer disease (AD), adapted from approaches

currently used with cancer biomarkers. The authors noted that although diagnosis of AD can clearly be improved by assessing biomarkers of functional impairment, neuronal loss, and protein deposition with PET and MR neuroimaging or cerebrospinal fluid analysis, widespread implementation of and reimbursement for these techniques are hampered by the absence of evidence-based validation of clinical usefulness. Phase 1 of the roadmap includes preclinical exploratory studies to aggregate sufficient evidence of analytic validity, much of which is already available for AD biomarkers. However, evidence of clinical validity (phases 2 and 3) and clinical utility (phases 4 and 5) is not yet sufficient. Phase 2 targets clinical assay development for AD pathology, and phase 3 calls for retrospective studies using longitudinal data available in repositories. Phase 4 should include prospective diagnostic accuracy studies, with phase 5 addressing disease burden reduction investigations. The authors identify research priorities to complete these phases, including standardization of neuroimaging and assay readouts and thresholds for normal/abnormal, evaluation of performance of these techniques in detecting early disease, development of diagnostic algorithms that include combinations of biomarkers, and development of clinical guidelines for use of biomarkers in qualified clinics.

The Lancet. Neurology

^{18}F-FDG PET In Vitro Imaging of Bacteria

Heuker et al. from the University of Groningen/University Medical Center Groningen (The Netherlands) and the University of Twente (Enschede, The Netherlands) reported in the July 10 issue of *Scientific Reports* (2017;7:4973) on a study designed to determine to what extent bacterial pathogens contribute to PET signal in ^{18}F-FDG imaging of infection. In an in vitro study of clinical isolates of 22 common gram-negative and -positive bacterial pathogens, they looked at ^{18}F-FDG uptake and investigated whether FDG inhibits bacterial growth. After incubation with ^{18}F-FDG, uptake in the bacteria was assessed by gamma-counting and micro-PET imaging. Growth inhibition by the tracer was assayed with Staphylococcus aureus and the gram-positive model bacterium Bacillus subtilis. All tested isolates actively accumulated ^{18}F-FDG. ^{18}F-FDG uptake was lower in B. subtilis phosphotransferase system mutants that exhibit glucose uptake impairment. FDG inhibited growth of S. aureus and B. subtilis to only a minor extent, an effect not seen in the B. subtilis phosphotransferase system mutants. The authors concluded that "these observations imply that bacteria may contribute to the signals observed in FDG PET infection imaging in vivo" and that "active bacterial FDG uptake is corroborated by the fact that the B. subtilis phosphotransferase system is needed for ^{18}F-FDG uptake, while phosphotransferase system mutations protect against growth inhibition by FDG."

Scientific Reports

Differentiating Radiation Necrosis from Recurrence in GBM

In an article e-published on July 18 ahead of print in the *Journal of Neuroimaging*, Hojjati et al. from University Hospitals Cleveland Medical Center (OH), Case Western Reserve University (Cleveland, OH), and the University of Connecticut School of Medicine (Farmington) reported on a study comparing the utility of quantitative PET/MR, dynamic susceptibility contrast (DSC) perfusion MR, and PET/CT imaging in differentiating radiation necrosis from tumor recurrence in patients with treated glioblastoma multiforme (GBM). Twenty-four patients who had been treated with surgery, radiation, and temozolomide and who showed progression on imaging follow-up underwent PET/MR and perfusion MR imaging. Nineteen of these patients also underwent PET/CT on the same day. Conclusive diagnosis was by pathology in 17 and clinical/radiologic consensus in 7 patients. A total of 28 lesions were identified for the cohort. After analysis, a relative mean of lesion-to-contralateral white matter for quantitative PET/MR $\geq$1.31 resulted in an area under the curve of .94, with sensitivity and negative predictive value both at 100%. For perfusion MR, cerebral blood volume max $\geq$3.32 yielded an area under the curve of .94, with sensitivity and negative predictive value measuring 100%. Joint modeling with the 2 modalities resulted in an area under the curve of 1.0. The authors concluded that "quantitative PET/MRI parameters in combination with DSC perfusion MRI provide the best diagnostic utility in distinguishing radiation necrosis from tumor recurrence in treated GBMs."

Journal of Neuroimaging

^{68}Ga-DOTANOC PET/CT and SSTRs in Lymphoma

Ruuska et al. from the University of Turku/Turku University Hospital (Finland) and La Paz University Hospital (Madrid, Spain) reported on July 7 ahead of print in *Acta Oncologica* on a study designed to use ^{68}Ga-DOTANOC PET/CT and immunohistochemistry to analyze somatostatin receptor (SSTR) subtype status in patients with lymphoma. The study included 21 patients with newly diagnosed lymphoma who underwent ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT before treatment. Among factors analyzed were visually evaluated tracer uptake, SUV_{max} in each patient, Deauville scores on ^{18}F-FDG PET/CT, Krenning scores on ^{68}Ga-DOTANOC PET/CT, and $SSTR_{2,3,5}$ status by biopsy/excision immunohistochemistry. Twenty patients had ^{18}F-FDG–positive lesions (Deauville score $\geq$3). Thirteen patients had ^{68}Ga-DOTANOC–positive lymphomas (Krenning score $\geq$2). ^{68}Ga-DOTANOC uptake was highest in a patient with Hodgkin lymphoma of nodular sclerosis subtype and a patient with diffuse large B-cell lymphoma (median SUV_{max} of 9.8 and 9.7, respectively). Immunohistochemistry showed strong $SSTR_2$ immunopositivity in tumor cells from both patients. Some patients in the study showed $SSTR_2$ immunopositivity mainly in endothelial and dendritic cells and follicular centers of lymph nodes con-

tributing to a positive PET/CT but low tumor-specific uptake. $SSTR_3$ and $SSTR_5$ were negative in most lymphoma subtypes. The authors concluded that because ^{68}Ga-DOTANOC PET/CT is positive in some lymphoma subtypes that express SSTRs, "these tumors present a potential risk of being misinterpreted as neuroendocrine tumors if a representative tumor sample is not available." In addition, lymphomas with high expression of SSTRs may be more amenable to treatments targeting these receptors.

Acta Oncologica

^{18}F-FDG PET vs CT in Early ALCL Staging

In an article e-published on July 19 ahead of print in the *European Journal of Dermatology*, Ram-Wolff et al. from the Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris (France) reported on a study comparing the utility of ^{18}F-FDG PET and CT in initial staging of anaplastic large-cell lymphoma first presenting in the skin. The study included 11 such patients (6 men, 5 women; mean age, 59.7 y) who underwent imaging with both modalities. Imaging results were compared with biopsy findings. In 7 patients (64%), imaging showed extracutaneous disease. ^{18}F-FDG PET agreed with CT results in 5 patients (45%; 4 with negative findings and 1 with both cutaneous and extracutaneous lesions). The 2 modalities were discordant in 6 patients (55%). ^{18}F-FDG PET showed extracutaneous lesions undetected on CT in these patients. For 5 (45%) in this group therapeutic management was changed or influenced on the basis of PET findings. For all patients imaged, the sensitivities of CT and ^{18}F-FDG PET for detection of lesions were 18% and 64%, respectively.

European Journal of Dermatology

Propranolol Before PET in Young Patients

George et al. from the University of Kentucky (Lexington) reported on July 20 ahead of print in *Pediatric Hematology and Oncology* on a study investigating the effectiveness and safety of a single 20-mg dose of propranolol in adolescent and young adult patients to reduce physiologic uptake of ^{18}F-FDG in brown adipose tissue in PET scanning. The study included 10 patients (median age, 18 y; range, 14–24 y), each of whom received the single dose before undergoing PET imaging. Five of the patients had undergone earlier PET imaging in which adipose tissue uptake was identified. After propranolol premedication, only 1 patient had persistent adipose uptake. No adverse effects or significant changes in serum glucose, heart rate, or blood pressure were observed. The authors concluded that these preliminary data suggest that propranolol is "convenient and safe in fasting adolescent and young adult oncology patients undergoing PET scans," but added that larger studies are needed.

Pediatric Hematology and Oncology

^{18}F-FDG and ^{11}C-PiB PET in AD Risk Prediction

In a study e-published on June 24 ahead of print in the *Journal of Alzheimer's Disease*, Iaccarino et al. from San Raffaele University and Hospital/San Raffaele Scientific Institute (Milan, Italy), the Karolinska Institutet (Stockholm, Sweden), Uppsala University/Uppsala University Hospital (Sweden), and Stockholm University (Sweden) used optimized data analysis methods to look at the separate and combined values of ^{18}F-FDG PET for brain glucose metabolism and ^{11}C-PiB PET for cerebral amyloid burden in predicting conversion from mild cognitive impairment (MCI) to Alzheimer disease (AD). The study included 30 individuals (63.57 ± 7.78 y) with MCI, 14 of whom converted to AD during a median follow-up of 26.5 mo. Using a statistical parametric (SPM) mapping approach for ^{18}F-FDG PET and SUV ratio semiquantification for ^{11}C-PiB PET, receiver operating characteristic analyses showed areas under the curve of 0.89 and 0.81. ^{18}F-FDG PET showed higher specificity but lower sensitivity than ^{11}C-PiB PET. Combining the 2 improved classification accuracy. Over the course of the study's follow-up period, all patients positive on both imaging techniques converted to AD and all who were negative on both remained stable. Both ^{18}F-FDG PET and ^{11}C-PiB PET imaging showed strong utility in predicting conversion from MCI to AD, with ^{18}F-FDG PET showing optimal performance based on the SPM assessment. The authors concluded that "measures of brain glucose metabolism and amyloid load represent extremely powerful diagnostic and prognostic biomarkers with complementary roles in prodromal dementia phase, particularly when tailored to individual cases in clinical settings."

Journal of Alzheimer's Disease

^{11}C-Methionine PET and Glioma Recurrence

Xu et al. from Zhejiang University (Hangzhou, China) reported on July 5 ahead of print in *Oncotarget* on a meta-analysis intended to assess the accuracy of ^{11}C-methionine PET in identifying recurrent glioma in patients who had undergone prior therapy. The authors conducted a search of the PubMed, Embase, and Chinese Biomedical databases. A total of 23 articles met the inclusion criteria, representing 29 studies and 891 patients. In addition to surveying the methodologic approaches and quality of the studies, the authors pooled the data to determine a summary measure of the diagnostic accuracy of ^{11}C-methionine PET in identifying recurrent glioma. The pooled sensitivity and specificity were 88% and 85%, respectively, with an area under the curve for the summary receiver-operating characteristic curve of 0.9352. They concluded that the literature suggests that "^{11}C-methionine PET has excellent diagnostic performance for differentiating glioma recurrence from treatment effect."

Oncotarget

Early ^{18}F-Sodium Fluoride PET Response in mCRPC

In an article e-published on June 27 ahead of print in the *Journal of Clinical Oncology*, Harmon et al. from

the University of Wisconsin–Madison, the Prostate Cancer Clinical Trials Consortium (Madison, WI, and New York, NY), the National Cancer Institute (Bethesda, MD), and Memorial Sloan Kettering Cancer Center (New York, NY) described changes in early ^{18}F-sodium fluoride PET/CT response measures in metastatic prostate cancer and their correlation with clinical outcomes. The study included 56 patients with metastatic castration-resistant prostate cancer (mCRPC) with osseous metastases. Each patient underwent PET/CT at baseline and after 3 cycles of either chemotherapy (n = 16) or androgen receptor pathway inhibitors (n = 40). The reseachers used Quantitative Total Bone Imaging, a previously reported tool, to extract a broad range of functional information and to assess response. Among the metrics assessed were SUV_{max} and SUV_{total}, which were compared with data on progression-free survival (PFS). Functional disease burden, expressed as SUV_{total}, as measured after 3 cycles of therapy was the strongest univariate predictor of PFS, and changes in functional burden showed a stronger correlation to PFS than did changes in number of lesions. No differences in imaging response or PFS were identified for the 2 types of treatment in the study. The authors concluded that these data support "ongoing development of NaF PET/CT–based imaging biomarkers in mCRPC to bone."

Journal of Clinical Oncology

^{18}F-Florbetapir PET Imaging in CAA Hemorrhage

Raposo et al. from the Hôpital Pierre-Paul Riquet, the Centre Hospitalier Universitaire de Toulouse, the Toulouse NeuroImaging Center, and the Université de Toulouse (France) reported on July 19 ahead of print in *Neurology* on a study assessing the extent to which ^{18}F-florbetapir could bind vascular amyloid in cerebral amyloid angiopathy (CAA) by comparing cortical tracer retention during the acute phase in patients with CAA-related lobar intracerebral hemorrhage (ICH) and patients with hypertension-related deep ICH. The study included 15 patients (mean age, 67 ± 12 y) with CAA-related acute lobar ICH and 18 patients with acute deep ICH (mean age, 63 ± 11 y) who underwent ^{18}F-florbetapir PET and brain MR imaging as well as *APOE* genotyping. SUV ratios were calculated with the whole cerebellum as a reference and compared between the 2 groups of patients. The mean global cortical SUV ratio was significantly higher in patients with CAA-related ICH and was able to differentiated patients with CAA ICH from those with deep ICH with a sensitivity of 73.3% and specificity of 83.3%. The authors concluded, however, that "although ^{18}F-florbetapir PET can label vascular β-amyloid and might serve as an outcome marker in future clinical trials, its diagnostic value in acute CAA-related ICH seems limited in clinical practice."

Neurology

Trends in SPECT for CAD

In an article e-published in July ahead of print in *Circulation. Cardiovascular Imaging,* Jouni et al. from the Mayo Clinic (Rochester, MN) looked at temporal trends in SPECT myocardial perfusion imaging in patients with coronary artery disease (CAD) over more than 2 decades at the Mayo clinic. The study included patients who underwent stress SPECT studies from 1991 to 2012 and who had histories of CAD, defined as previous myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass grafting. The authors divided the study into 5 time periods: 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2012. A total of 19,373 patients (mean age, 66.2 ± 10.9 y; 75.4% men, 24.6% women) were included. An average of 495 tests per year were documented for the 1991–1995 time period, a figure that rose to 1,425 in 2003 but decreased to 552 by 2012, with no accompanying evidence of substitution of other stress modalities. Tests in asymptomatic patients increased until 2006 and then decreased. Examinations in patients with typical angina decreased over the overall time period, whereas those in patients with dyspnea and atypical angina increased. Almost 80% of all tests performed in 2012 had a low-risk summed stress score compared with 29% in 1991. The authors concluded that these results suggest that "among patients with a history of CAD, SPECT was being increasingly utilized in patients with milder CAD," a trend paralleling "reduced utilization of other stress modalities, coronary angiography, reduced smoking, and greater utilization of optimal medical therapy for prevention and treatment of CAD."

Circulation. Cardiovascular Imaging

^{11}C-Acetate PET and Multiparametric MR in Prostate Cancer

Polanec et al. from the Medical University of Vienna (Austria) reported on July 18 online in *PLoS One* (2017; 12:e0180790) on a study designed to determine whether multiparametric ^{11}C-acetate PET added to MR imaging facilitates differentiation between benign and malignant prostate tumors and can improve local and distant staging. The study included 56 patients with elevated prostate-specific antigen levels or suspicious findings at digital rectal examination or transrectal ultrasonography, with histopathologic confirmation. All patients underwent separate ^{11}C-acetate PET and 3T multiparametric MR imaging. Two MR parameters (T2W and diffusion-weighted imaging) were found to yield the highest sensitivity, specificity, and diagnostic accuracy (95%, 68.8%, and 88%, respectively), for detection of primary prostate cancer. No assessment with a single parameter or any other combinations of up to 5 parameters yielded similar results. The addition of ^{11}C-acetate PET data to the MR results improved local staging with sensitivity, specificity, and diagnostic accuracy of 100%, 96%, and 97%, respectively, compared to MR alone with 72.2%, 100%, and 95.5%. The PET-MR combined data

correctly detected osseous and liver metastases in 5 patients. The authors concluded that ^{11}C-acetate PET and multiparametric MR imaging facilitate "improved local and distant staging, providing 'one-stop' staging in patients with primary prostate cancer, and therefore has the potential to improve therapy."

PLoS One

^{18}F-FDG PET/MR and Hepatic Tumor Types

In an article published online on July 3 in *PLoS One* (2017;12:e0180184), Kong et al. from Yeungnam University Medical School and Hospital (Daegu, Republic of Korea) reported on the results of a study using the relationship between metabolism and water diffusivity in hepatic tumors with ^{18}F-FDG PET/MR to look at characteristics of different types of tumors. The study included 41 patients (mean age, 63 ± 13 y; 31 men, 32 women) with hepatic tumors (18 hepatocellular carcinoma [HCC], 6 cholangiocarcinoma [CCC], 10 metastatic tumors, 1 neuroendocrine tumor, and 6 benign lesions). Each patient underwent pretreatment ^{18}F-FDG PET/MR imaging. PET SUV_{max} and apparent diffusion coefficients (ADCs) from diffusion-weighted MR images were analyzed and compared for the different tumor types. Median SUV_{max} values were 3.22 for HCC, 6.99 for CCC, 6.30 for metastatic tumors, and 1.82 for benign lesions. Corresponding ADCs were 1.039×10^{-3} mm/s^2, 1.148×10^{-3} mm/s^2, 0.876×10^{-3} mm/s^2, and 1.323×10^{-3} mm/s^2. SUV_{max} was negatively correlated with ADC and higher in metastatic tumors than in benign lesions. Each group of tumors was found to have different metabolic and water diffusivity characteristics. The authors concluded that "evaluation of hepatic tumors by PET/MRI could be helpful in understanding tumor characteristics."

PLoS One

Scintigraphy vs PET/CT in PCa Bone Mets

In an article published on July 31 ahead of print in *Pharmaceuticals (Basel)*, Thomas et al. from the Universitätsklinikum Bonn (Germany) reported on a study intended to investigate differences between bone scintigraphy and prostate-specific membrane antigen (PMSA) PET/CT in detecting bone metastases in prostate cancer. The study included 30 men with such metastases who underwent both ^{99m}Tc-methylene diphosphonate bone scanning and ^{68}Ga-PSMA PET/CT imaging. Bone scans were analyzed both by experienced readers and with semiautomatic lesion detection software. PET/CT results were analyzed by experienced readers. Results were also compared to serum analysis and standard performance status ratings. The results of visual and semiautomatic detection of lesions were similar in the bone scans, with averages of 19.4 and 17.8 lesions, respectively, detected per patient. ^{68}Ga-PSMA PET/CT findings yielded double the numbers of lesions (average of 40.0 per patient). As expected, the largest differences were found in the thorax and pelvis. The authors noted that despite the better performance of PET/CT in this comparison, "in none of our patients would the difference have led to clinical consequences." They concluded that "for patients undergoing PSMA PET/CT, there is no need to perform additional bone scans if the appropriate PET/CT protocols are applied."

Pharmaceuticals (Basel)

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in June and July. Ceci et al. from the University of Bologna (Italy), the University of California Los Angeles, and Quanta Diagnóstico e Terapia (Curitiba, Brazil) described "New aspects of molecular imaging in prostate cancer" on 13 July ahead of print in *Methods (San Diego, CA).* In an article e-published on June 23 ahead of print in *Minerva Endocrinologica*, Treglia et al. from the Oncology Institute of Southern Switzerland (Bellinzona) and University Hospital Zürich (Switzerland) reported on "Imaging in primary hyperparathyroidism: focus on the evidence-based diagnostic performance of different methods." Le Roux et al. from the Université Européenne de Bretagne and the Université de Brest (France) detailed "New developments and future challenges of nuclear medicine and molecular imaging for pulmonary embolism" on June 27 ahead of print in *Thrombosis Research*.