Service de radiodiagnostic
et radiologie interventionnelle
Prof. Reto MEULI, Chef de Service
Rue du Bugnon 46, CH-1011 Lausanne

Protocol Title: Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis, a comparative study

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
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Sponsor/Project Leader:	Dre Sabine Schmidt Kobbe Médecin cheffe, PD, MER Service de radiodiagnostic et radiologie interventionnelle Centre hospitalier universitaire Vaudois - CHUV Sabine.schmidt@chuv.ch
Secondary Investigators :	Fabio Ramos Poroes (FRP) Médecin assistant Service de radiodiagnostic et radiologie interventionnelle Centre hospitalier universitaire Vaudois - CHUV Fabio.Ramos-Poroes@chuv.ch Naik Vietti Violi (NVV) Cheffe de clinique Service de radiodiagnostic et radiologie interventionnelle Centre hospitalier universitaire Vaudois - CHUV Naik.Vietti-Violi@chuv.ch Tobias Zingg (TZ) Médecin associé Service de chirurgie viscérale Tobias.Zingg@chuv.ch Emilie Uldry (EU) Médecin associée Service de chirurgie viscérale Emilie.Uldry@chuv.ch Frédéric Schütz (FS) Maître d'enseignement et de recherche Plate-forme de biostatistiques, faculté de biologie et médecine Université de Lausanne Frederic.schutz@unil.ch
Investigated Intervention:	Initial MRI assessment in acute pancreatitis
Version and Date:	Version 4 (03/10/2021)

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CONFIDENTIALITY STATEMENT

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PROTOCOL SIGNATURE FORM

Study Title	Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis, a comparative study

The Sponsor-Investigator has approved the protocol version 4 (03.10.2021) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor:

Name: *Sabine Schmidt Kobbe*

Date: 4/10/21 Signature: S. Schmidt Kobbe

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ANOVA	*Analysis Of Variance*
AP	*Acute Pancreatitis*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CHUV	*Lausanne University Hospital*
CRF	*Case Report Form*
CT	*Computed Tomography*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTSI	*Computed Tomography Severity Index*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GBCA	*Gadolinium-Based Contrast Agent*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
MRI	*Magnetic Resonance Imaging*
MRSI	*Magnetic Resonance Severity Index*
NSF	*Nephrogenic Systemic Fibrosis*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
PACS	*Picture Archiving and Communication System Workstation*
ROI	*Region Of Interest*
SAE	*Serious Adverse Event*
SD	*Standard Deviation*
SI	*Severity Index*

1 BACKGROUND AND RATIONALE

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas resulting from the inappropriate intracellular activation of proteolytic pancreatic enzymes, which leads to autodigestive injury of the pancreatic gland (1). The incidence of acute pancreatitis varies across Europe with highest incidence, >40 per 100 000 person per year, reported from eastern or northern regions (2). There are multiple aetiologies of AP. The most common causes are alcohol abuse and gallstones (3). According to the 2012 revision of the Atlanta classification, AP is diagnosed by any two of the following criteria : (a) sudden onset of epigastric pain radiating to the back, (b) serum amylase and/or lipase levels three times superior than the upper limit of the normal values, and/or (c) characteristic findings of AP on imaging (4). The latter is mostly performed with computed tomography (CT) or, rarely, with Magnetic Resonance Imaging (MRI). Although AP often runs a mild clinical course, up to 20% of the patients develop severe disease (5). In this context, patients are subject to a long lasting hospital stay and are at high risk of complications such as infected necrosis or organ failure with mortality rates of 30% (6). Regarding treatment, mild AP responds to conservative management, whereas severe AP requires a more aggressive, sometimes surgical approach. Consequently, it is of major importance to distinguish between the 2 forms.

Clinically, the severity of AP is defined by the presence or absence of organ failure, local complications, or both. Several clinical and laboratory scoring systems, like the Ranson criteria, have been designed to accurately correlate the complications like organ failure and mortality in AP (7). In imaging , the Computed Tomography severity index (CTSI), developed by Balthazar et al. (8) is the most widely adopted scoring system for clinical and research settings. The CTSI allows the staging of the severity of the inflammatory process, the evaluation of the pancreatic necrosis and the definition of the local complications, by differentiating mild (interstitial/oedematous) AP from severe (necrotizing) AP and, thus, enabling the correct patient management. It also correlates well with morbidity, mortality and length of hospital stay (9,10).

CT is the gold-standard imaging technique for confirming clinically suspected AP, staging the disease's severity and assessing for complications (8). CT features that can confirm AP include parenchymal enlargement, ill-defined pancreatic margins, changes in density, inhomogeneity of the pancreatic parenchyma, and increased density of the peripancreatic adipose tissue with fat stranding and fluid collections (11). However, CT imaging is invariably associated with radiation exposure and requires intravenous injection of iodinated contrast medium which is linked with nephrotoxicity and may trigger allergic reactions in some cases (12,13). For these reasons, an imaging procedure that involves less side effects should be considered as a safer alternative.

Magnetic resonance imaging (MRI) is considered as an alternative imaging modality to CT and may even offer more exact information in the assessment of AP because of the inherent higher contrast resolution compared with CT(14). MRI provides better characterization of the content of collections and may even identify the aetiology of AP, such as bile duct gallstones or ductal anomalies, only rarely detected by means of CT (14). Moreover, it should be emphasized that MRI is a non-ionizing cross sectional imaging method and the intravenously injected contrast medium gadolinium has a safer intravenous contrast profile in comparison to the iodinated contrast medium intravenously injected before CT examinations(14,15). MRI offers the opportunity to go beyond visual assessment by means of a recently developed quantitative imaging sequence, called T2 mapping. The latter can quantify signal changes reflective of underlying tissue properties, and thus quantify parenchymal oedema that typically occurs in acute pancreatitis. Quantification of T2 signal using T2 mapping in AP has not been reported to date, but preliminary studies showed that the typically increased pancreatic/peripancreatic signal detected on T2-weighted MR sequences has the potential to provide diagnostic and classification of AP (16–20). In particular, a study conducted at the CHUV by Vietti Violi et al. showed that the presence of pancreatic disease was associated with increased T2 relaxation times compared to healthy pancreas (20). This evaluation offers several advantages, including increased reproducibility and sensitivity than the visual assessment of T2-weighted MR images for

identifying minor parenchymal changes and thus may offer a means of objective staging (18,20).

Generally, the initial exploration of AP is quite rarely performed with MR, mainly because of the still lower availability and the longer data acquisition of this technique compared with CT. In fact, at most radiological emergency units there is no MR scanner available for urgent body examinations. However, two years ago, a MR scanner has been implemented at the emergency unit of the CHUV which runs 24h/24h and recent technological developments, especially the increasing speed of image acquisition, have facilitated the use of MRI in patients with AP. This gives us the unique opportunity to perform a comparative study by directly comparing CT with MRI for the initial assessment of AP and, hopefully, validating MRI as the imaging modality of choice for the assessment of AP. We will compare both imaging modalities by performing CT and MRI within a delay of 24hours. We will also then compare MR and CT- findings in view of the patients' clinical outcome, which we define as the duration of the hospital stay.

Two previous publications have already compared MRI with CT for the initial assessment of AP(13,21). Arvanitakis et al included 35 patients with AP and compared contrast-enhanced CT (CECT) with contrast-enhanced MRI, while Stimac et al included 101 patients and compared CECT with nonenhanced MRI. Arvanitakis et al performed two MR examinations in each patient with AP, the first one on the 7th day and the second one on the 30th day after admission (13), while Stimac et al performed MRI between the 3rd and the 5th day after patients' admission to the hospital (21).

Both working groups agreed on the equal diagnostic and prognostic value of MRI to CT. Moreover, Arvanitakis et al showed a statistically significant correlation between MR features of AP and the length of patients' hospitalization (13). Finally, according to Stimac et al, the haemorrhagic type of AP, that can only be detected by MRI, but not by CT, was equally significantly correlated with the length of patient's hospital stay (21).

Thus, we think that thanks to the recent technical advances in MRI, especially the recent development of a prototype T2-mapping MR sequence, MRI may now be superior to CT so that we should use it in the clinical routine for the initial assessment in patients with AP.

By validating MRI as initial imaging modality of choice in AP, we may avoid potential side effects of CT examinations in the future, especially radiation exposure invariably associated with CT. In fact, MRI is free of radiation exposure and the MRI contrast agent gadolinium has definitely fewer side effects, in particular less nephrotoxicity than the iodinated contrast agents necessary for CT imaging (14,15). Furthermore, MRI may provide the disease's aetiology and enables more accurate staging of the inflammation because of oedema quantification.

Our project should be considered a clinical study with risk category B, since MRI examinations will be performed with the intravenous injection of a contrast medium. However MRI has a safer intravenous contrast profile in comparison to CT(14,15). Hypersensitivity reactions to gadolinium-based contrast agents (GBCA) rate is 0.04-1% (including mild reactions such as nausea) of which only 6-20% are severe including anaphylaxis (22,23). Furthermore, patients will be enquired about allergies before MRI examinations. The intravenous injection of gadolinium, such as Dotarem® we use at the CHUV, will be done only under medical supervision. Adverse reactions will be managed according to European Society of Urogenital Radiology guidelines(15). Nephrogenic systemic fibrosis is a serious late adverse reaction associated with exposure to GBCAs that can occur in patients with severe renal impairment (24). The degree of renal insufficiency is an important risk factor for the development of nephrogenic systemic fibrosis. Previous studies demonstrated a far greater incidence of NSF in patients with stage 5 chronic kidney disease than the milder degrees of severe renal impairment and negligible risk in patients with a GFR above 30 mL/min/1.73 m2 (24,25). For this reason, only patients with a GFR above 30 mL/min/1.73 m2 will be included in this study.

2 STUDY OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Our hypothesis is that MRI is a valid alternative to CT and even offers more detailed information than CT in the initial assessment of AP thanks to the recently developed MR sequence T2-mapping:

I. MRI is at least as effective as CT in assessing AP.
II. MR findings (i.e. quantitative values obtained by T2-mapping) correlate with the length of the patients' hospital stay.

Primary objective: We are aiming to validate MRI as the imaging modality of choice for the initial assessment of AP at our institution by performing a comparative study.

2.2 Primary and secondary endpoints

Primary endpoint:

AP severity assessment will be graded according to the severity index (SI), originally developed at CT (8) and shown on the table 1 below. Depending on the imaging modality, we determine the CTSI (CT severity index) or MRSI (MR severity index).

Table 1

Severity index (SI)	
Characteristics	Score
I. Grading of pancreatitis	
Grade A: normal pancreas	0
Grade B: focal or diffuse enlargement of pancreas	1
Grade C: peripancreatic inflammation	2
Grade D: single acute fluid collection	3
Grade E: two or more acute fluid collections	4
II. Pancreatic parenchymal necrosis	
None	0
Less than 30%	2
Between 30% and 50%	4
More than 50%	6
SI = Grading of pancratitis + Pancreatic parenchymal necrosis	0-10

The SI will be assessed on CT (CTSI) and similarly on MRI (MRSI) performed at 48-72 hours after admission. We will then compare the findings obtained with the two modalities.

Secondary endpoint:

Comparing MRI findings to the clinical stage of AP, including severity parameters, in particular the Ranson score, shown below (Table 2), laboratory values and the further clinical evolution of their pancreatitis, listed below (Table 3). For each laboratory parameter, the highest value during the whole hospital stay of each patient will be selected.

Table 2

Ranson criteria		
At admission	Age	> 55 years
	WBC count	> 16000 cells/mm3
	Blood glucose	> 200mg/dl
	Serum AST	>250 IU/L
	Serum LDH	>350 IU/L
After 48 hours	Corrected serum calcium	< 2 mmol/l
	Hematocrit fall	> 10%
	PaO2	< 60mmHg
	BUN increase	> 1.8 mmol/l
	Sequestration of fluids	> 6l
	Base deficit	> 4 mEq/L
Total (each item worth 1 point)		0-11

WBC : white blood cell, AST : aspartate transaminase, LDH : D-lactate dehydrogenase , PaO2 : partial pressure of arterial oxygen, BUN : blood urea nitrogen

Table 3

Severity parameters of AP		
Clinical parameters	Laboratory parameters	Radiological parameters
Age	Ranson criteria	Computed Tomography severity index
Intensive care unit length of stay	White blood cell	"Magnetic resonance imaging severity index"
Hospital length of stay	Aspartate aminotransferase	T2 transverse relaxation time on axial cross-section (head, body, and tail)
Lung failure	Lactate dehydrogenase	
Kidney failure	Glucose	Radiological complications[3]
Septic shock	Calcium	
Surgical interventions[1]	Lipase	
Minimally-invasive Interventions[2]	Amylase	
Death	Alanine aminotransferase	
	Total bilirubin	
	Alkaline phosphatase	
	Gamma-glutamyl transferase	
	C-reactive protein	
	Creatinine	

1Surgical interventions: necrosectomy, intestinal resection
2Minimally-invasive interventions: percutaneous abdominal punctures, percutaneous abdominal and endoscopic drainages, endoscopy, embolization, venous/biliary stent placement
3Radiological complications are complications detected on CT or MRI images: gastrointestinal-perforation, gastrointestinal-bleeding, pseudo-aneurysm

2.3 Study design

This is a prospective, non-randomized, single arm, monocentric study.

2.4. Study intervention

Using the MR scanner T (3 T, VIDA, Siemens Healthcare, Erlangen, Germany) implemented in our emergency department, a single MR examination of the pancreas will be performed according to the technical parameters used in our daily routine. All patients will be scanned in a supine position using an 18-channel body array coil and a 32-channel spine coil. MR parameters include axial (3mm) and coronal (3mm) Half-Fourier Acquisition Single-shot Turbo Spin Echo (HASTE) MR sequences, an axial (6mm) diffusion-weighted MR sequence (DWI), axial T1-weighted MR sequences VIBE) (3mm) before and after the intravenous injection of 0,2cc/kg of gadoteric acid, Dotarem®, and a heavily T2-weighted sequence in the coronal oblique plane centered on the

main pancreatic duct (MR-Wirsungography). with Relaxation Enhancement (RARE) centered on the head and tail of the pancreas).

Finally, a recently developed, T2 mapping prototype sequence will be acquired in the axial plane as follows: A multiecho spin-echo (MESE)(26) prototype sequence will be used to acquire a 10-fold undersampled k-space using prospective acquisition correction (PACE)(27) with external triggering (15 slices, 0.8 × 0.8 × 5 mm resolution, ΔTE/TR/TA 10.6 msec/2.2 sec/2:39 min). According to the individual trigger efficiency of a patient, the MR technician will choose either a phase scout or a 1D navigator at the liver dome to trigger the acquisition on end-expiration, thus allowing free breathing for the patients. For the reconstruction of T2 maps, a combination of generalized auto-calibrating partially parallel acquisition (GRAPPA)(28) and model-based accelerated relaxometry by iterative nonlinear inversion (MARTINI)(29), termed GRAPPATINI(30), will be employed. Furthermore, synthetic T2-weighted images with different simulated echo times (TE = 40/100/150 msec) will be generated by applying the forward signal model onto the quantitative maps.

3 STUDY POPULATION AND STUDY PROCEDURES

3.1 Inclusion and exclusion criteria, justification of study population

Inclusion criteria will be the following:

I. Patients diagnosed with AP in the visceral surgery department at the Lausanne University Hospital (CHUV), Switzerland, during the period between December 2020 and November 2022. According to the guidelines, AP is defined as two or more of the following characteristics: abdominal pain, and serum amylase or lipase levels three or more times the upper limit of normal (> 210 U/L and > 180 U/L, respectively) (4).
II. Patients undergoing a contrast-enhanced CT during their hospital stay about 48-72 hours after admission.

Exclusion criteria will be the following:

I. intubation and/or ventilation
II. renal failure with estimated glomerular filtration rate (GFR) less than 30 ml/min/1.73 m^2),
III. history of allergic reactions to any contrast media,
IV. proven or suspected pregnancy,
V. age under 18 years,
VI. general exclusion criteria for MRI:
    a. Patients with non-MRI compatible metallic or electronic implants, devices or metallic foreign bodies (shrapnel, cochlea implants, neurostimulator, or other non-MRI compatible implants),
    b. Non-MRI compatible cardiac pacemaker,
VII. previous diagnosis of chronic pancreatitis,
VIII. inability to cooperate because of claustrophobia,
IX. inability to cognitively and/or linguistically understand the patient consent sheet,
X. patients with missing clinical or radiological data.

3.2 Recruitment, screening and informed consent procedure

Prospectively and consecutively, one of the associated surgeons (TZ, EU) will identify all the patients with AP addressed in emergency to the visceral surgery department at the Lausanne University Hospital (CHUV), Switzerland, during the period between December 2020 and November 2022. Immediately after their arrival the patients that respond to our inclusion criteria will be invited to be part of the study.

The physician in charge of the enrolment will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Patients will then have a delay of 24 hours to ask questions and sign the general consent.

According to the clinical routine, each patient with AP will have a clinical assessment and laboratory workup on admission and 48 hours later to measure the Ranson score. As clinically

indicated and corresponding to our daily routine, a CT examination with intravenous iodinated contrast medium administration will be performed at about 48-72 hours of admission to assess the severity of AP.

Patients who signed the formal consent, using the approved consent form, will then undergo an additional MRI including MR sequences necessitating the intravenous injection of gadolinium, Dotarem®. The surgeon in charge of recruitment will notify FRP who will plan a MRI examination in the radiological emergency department and make sure that the CT scan will not be analyzed by SaS and NVV. Hereby, the time delay between the two imaging procedures will not exceed 24 hours.

The consent form will be signed and dated by the surgeon (TZ, EU) in charge of the enrolment at the same time as the study participant will sign. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process will be documented in the patient file and any discrepancy to the process described in the protocol will be explained.

Project participants will not be monetarily compensated.

3.3 Study procedures

According to the clinical routine, all patients will have a clinical assessment and laboratory workup at admission and 48 hours later to define the Ranson score (Table 3). For each laboratory parameter included in table 2, the highest value of the hospital stay will be selected and registered.

Equally according to our clinical routine, each patient will undergo a CT examination with intravenously injected contrast medium administration within 48-72 hours of admission to assess the severity of AP. The CT images will immediately analysed by the radiologists routinely in charge followed by their written report available in SOARIAN within 2-3 hours after data acquisition, which corresponds to our clinical routine.

Patients who signed our consent form will undergo an additional MR examination with the intravenous injection of the contrast agent Dotarem® (see under 2.4). The imaging data will be stored on the server of the CHUV and will be assessed using the picture archiving and communication system workstation (PACS; Carestream Vue, v. 11.4; Carestream Health, Rochester, NY) radiology tool of the CHUV.

The radiologists NV or SaS with 5 and 15 years of experience in abdominal MRIs, respectively, will analyse the MR images within the 6 hours following the data acquisition, blinded to the CT examination. AP severity assessment will be graded according to the severity index (MRSI) (table 1) and possible bile duct stones or other significant MR findings will be searched. Furthermore, in order to quantify acute edema of the pancreatic gland (reflecting the degree of pancreatitis) NVV or SaS will determine the T2 values (median and SD) of the pancreatic parenchyma by manually drawing one region of interest (ROI) in each head, body, and tail. They will draw the largest possible ROI in each area, while avoiding the pancreatic duct, vessels, focal lesions, and zones showing clear partial volume effects.

After the MR image analysis, the MR findings will be compared with the CT results. Findings detected on the MR images that were not visible on the previously performed CT examination and considered important for further patients' management will be immediately transmitted to our surgical colleagues.

Table 4

Overview of study procedures

Time (hours)	Admission	0-24 h after admission	24-48 h after admission	48-72 h after admission	Further hospital stay
oral and written Information		+			
Written consent			+		
check inclusion/exclusion criteria	+	+	+		
laboratory workup	+		+		+
CT examination				+	
MRI examination				+	
Clinical outcome[1]					+
Radiological outcome[2]					+

1Clinical outcome: primary clinical outcome : hospital length of stay; secondary clinical outcome: intensive care unit length of stay, lung failure, kidney failure, septic shock, surgical interventions (necrosectomy, intestinal resection), minimally-invase interventions (percutaneous abdominal punctures, percutaneous abdominal and endoscopic drainages, endoscopy, embolization, venous/biliary stent placement), death.

2Radiological outcome: radiological complications detected on CT or MRI images at admission or on follow up CT examination if necessary (gastrointestinal-perforation, gastrointestinal-bleeding, pseudo-aneurysm.

3.4 Withdrawal and discontinuation

In case of patient withdrawal before the MR examination, patient data will not be collected. In case of patient withdrawal after completing the MR examination, patient data will remain registered on the PACS of our hospital and the data collected until withdrawal from the study will be used to ensure the quality of the study.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan and sample size calculation

According to our surgical colleagues about 1-2 patients with AP are admitted to the visceral surgery unit per week. Since, the project duration will be 24 months from December 2020 to November 2022, we will be able to include approximately 104-208-patients in our study considering a refusal to participate of about 20-30% (which is an estimated value based on former experiences with prospective clinical studies). The project duration for each patient will correspond to hospital length of stay for AP.

In order to show that MRI is at least as effective as CT in assessing AP (non-inferiority; primary endpoint), we will compare the MRSI and CTSI values; we consider that the values are similar if the average of the absolute differences between the two values is less than 0.5.

In order to determine the number of patients required to show that the average difference is below this value, we used data from Arvanitakis et al (13) in order to estimate the expected differences between the MRSI and the CTSI values. Based on this data, a minimum of 13 patients is required to show, using a confidence interval for the differences between MRSI and CTSI values, that MRI is at least as effective as CT.

However, in the data from Arvanitakis et al (13), most of the patients show lower values of both MRSI and CTSI (85% have values of 4 or lower for both measurements). In order to show that the effectiveness is the same not only for the lower range of the measurements but also for the higher range, we need a sample containing enough patients with higher (≥ 5) values. This requires a minimum of 91 patients.

We do not have preliminary data allowing us to calculate the number of samples needed to show a correlation between the quantitative values obtained by T2-mapping and the length of the patients' hospital stay.

All statistical analyses will be performed by a statistician using the commercially available software R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r-project.org/.). The data will be represented graphically using scatterplots and analysed as indicated above (by calculating differences between MRSI and CTSI for the primary endpoint, and by calculating correlations for the secondary endpoint).

4.2. Handling of missing data and drop-outs

Not applicable. Patients with missing data will be excluded.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

5.2 (Serious) Adverse Events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigators and Sponsor-Investigator make a causality assessment of the event to the trial invervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigators and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow up of (Serious) Adverse Events

Not applicable. No serious adverse events are expected. MRI is a safe examination. Adverse allergic reactions will be managed according to European Society of Urogenital Radiology guidelines during hospitalization (28). Allergic reaction will be documented in patients' medical records. There will be no participants terminating the study with reported ongoing (S)AEs and all (S)AEs will be followed up until resolution.
Health hazards that require measures will be reported to Swissmedic and to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

5.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

5.4 Radiation

Not applicable.

5.5 Pregnancy

Patient will be inquired about any possible pregnancy when getting enrolled in the study and during the established safety procedures routinely performed by means of a questionnaire before MR examinations at the CHUV. Patients with proven or suspected pregnancy will be excluded.

5.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

5.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment (n<30),
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

MR images will remain registered in the PACS at CHUV for at least 10 years. All the collected data will be stored at a safe location on a server at CHUV with access only to to FRP, SAS and NVV.

5.8 Insurance

In the event of study-related damage or injuries, the liability of the institution CHUV provides compensation, except for claims that arise from misconduct or gross negligence. Our study being considered category B, the CHUV provides a separate study insurance. The « Commission cantonale d'éthique de la recherche sur l'être humain du canton de Vaud » is in possession of a guarantee of liability.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Our results may help to validate MRI as the imaging modality of choice for the assessment of AP at our institution. This might have considerable impact on the management of AP patients since MRI provides a better characterization of the content of inflammatory collections than CT and also more often identifies the aetiology of AP, such as gallstones or ductal anomalies (14). This can be of direct benefit for some patients participating in our study. Moreover, it should be emphasized that MRI is a non-ionizing cross sectional imaging method and has a safer intravenous contrast profile in comparison to CT(14,15). Thus, by validating MRI as the imaging modality of choice for the assessment of AP at our institution, we will limit the cancer risk associated with low-dose radiation exposure (31), nephrotoxicity and allergic reactions linked to iodinated contrast medium (12,13).

We expect only little risk for the patients participating at our study. MRI is a very safe imaging modality. Hypersensitivity reactions to GBCA rate is 0.04-1% (including mild reactions such as nausea) of which only 6-20% are severe, including anaphylaxis (22,23). Nephrogenic systemic fibrosis is a serious late adverse reaction associated with exposure to GBCAs that can occur in patients with severe renal impairment (24). The degree of renal insufficiency is an important risk factor for the development of nephrogenic systemic fibrosis. Studies demonstrated a far greater incidence of NSF in patients with stage 5 chronic kidney disease than the milder degrees of severe renal impairment and negligible risk in patients with a GFR above 30 mL/min/1.73 m2 (24,25). For this reason, only patients with a GFR above 30 mL/min/1.73 m2 will be included in this study.

Incidental findings could arise during the scan procedures. If those findings should prove to be of medical importance the treating physician will immediately be informed by one of the radiologist investigators.

6.2 Risk-benefit assessment

MRI is a safe examination. MRI examination will be performed with the established safety procedures in place at CHUV, i.e. questionnaires concerning allergies, implants, stents, et cetera. The intravenous injection of the contrast agent Dotarem® will be done only under medical supervision. Adverse reactions will be managed according to European Society of Urogenital Radiology guidelines (15).

All acquired data will be stored at the CHUV servers and will be password protected. Unauthorized data access will be excluded by all possible means.

Since the study provides a certain potential benefit to participants (i.e. better characterization of collections contents and possible identification of aetiology) and to future patients (i.e. decreased low-dose radiation exposure, nephrotoxicity and allergic reactions linked to iodinated contrast medium), we believe that the risk-benefit assessment argues in favour of our study.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The MR examination will be performed at the department of radiology of the CHUV and analysed by senior abdominal radiologists to ensure a high diagnostic quality for both interpretations.

For quality assurance, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

7.2 Data recording and source data

The MR and CT images will be stored on the server of the CHUV and will be assessed using the PACS in agreement with our clinical routine. Each examination will be scored on the CRF. For each laboratory parameter included in table 2, the highest value of the hospital stay will be selected and registered in the same file. Patients' radiological and clinical data will be entered in the CRF, created on this purpose, to which only FRP, SAS and NVV will have access. CRF will completed by handwriting to ensure traceability. Security copies on PDF from this file will be made and stored on a password protected folder. The CRF will be kept in a locked safe to which only authorized persons will have access.

7.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number (i.e. 00001,00002,00003,…). FRP will store the participant identification list. Further details are given in chapter 7.2.

7.4 Retention and destruction of study data and biological material

All study data are archived electronically for 10 years after study termination or premature termination of the study.

8 MONITORING AND REGISTRATION

The monitoring will be carried out by Prof Clarisse Dromain, Médecin cheffe, Service de radiodiagnostic et radiologie interventionnelle in accordance with ICH GCP. She is independent of the research team and will verify that the clinical trial is well conducted, and that the data are generated, documented and reported in accordance with the requirements of the protocol and applicable regulatory requirements. Specifically, she will verify that:

1. The rights and well-being of human subjects are protected
2. The reported trial data are accurate, complete, and verifiable from source documents.
3. The conduct of the trial is in compliance with the currently approved protocol, with Good Clinical Practice, and with the applicable regulatory requirement(s).

An on-site monitoring via a personal visit, before, during, and after the trial will be organised by Prof Clarisse Dromain who is in charge of the monitoring. During these visits, FRP will ensure access to the clinical trial source data and documents to the monitoring person and will answer questions and requests for corrections during the monitoring visits. The monitoring person will :

- verify that all the investigators have adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
- Verify that written informed consent was obtained before each subject's participation in the trial and that these consent forms are well registered..
- Verify that the main investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator, and have not delegated these functions to unauthorized individuals.
- Verify that the investigators are enroling only eligible subjects. Reporting the subject recruitment rate.
- Verify that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- Verify that FRP provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- Verify that the data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
- Verify that adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
- Inform FRP of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by FRP or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented
- Submit a written report to the sponsor after each trial- site visit or trial-related communication. Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted. Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

This clinical trial will be registered in a national language in the Swiss National Clinical trial Portal (SNCTP via BASEC) and in a registry listed in the WHO International Clinical Trials Registry Platform.

9. FUNDING / PUBLICATION / DECLARATION OF INTEREST

In agreement with the head of the department of radiology of the CHUV, Prof. Reto Meuli, the department will cover the MR examination related expenses of the study participants for the purpose of a comparative study during one year. We are aiming to publish our results in a peer-reviewed journal. There is no conflict of interest regarding the performance of this study.

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