Année 2018/2019 N°

# Thèse

Pour le

**DOCTORAT EN MEDECINE**

Diplôme d'État

par


## Nicolas GOIN

Né le 19 septembre 1990 à Amiens (80)


---

**TITRE**

**Induction chez les patients transplantés rénaux à partir de donneurs Maastricht III : Sérum antilymphocytaire versus Anticorps anti-IL2-récepteur**

---

Présentée et soutenue publiquement le **14 octobre 2019** devant un jury composé de :

Président du Jury : Professeur Jean-Michel HALIMI, Néphrologie, Faculté de Médecine – Tours

Membres du Jury :

Professeur Jacques DANTAL, Néphrologie, Faculté de Médecine – Nantes

Professeur Antoine THIERRY, Néphrologie, Faculté de Médecine – Poitiers

Docteur Philippe GATAULT, Néphrologie, MCU-PH, Faculté de Médecine – Tours

Docteur Jean-Christophe VENHARD, Anesthésie-Réanimation, PH, CHU – Tours

***Directeur de thèse : Professeur Matthias BUCHLER, Néphrologie, Faculté de Médecine – Tours***

UNIVERSITE DE TOURS
**FACULTE DE MEDECINE DE TOURS**

**DOYEN**
**Pr Patrice DIOT**

**VICE-DOYEN**
Pr Henri MARRET

**ASSESSEURS**
Pr Denis ANGOULVANT, *Pédagogie*
Pr Mathias BUCHLER, *Relations internationales* Pr Theodora BEJAN-ANGOULVANT, *Moyens – relations avec l'Université* Pr Clarisse DIBAO-DINA, *Médecine générale* Pr François MAILLOT, *Formation Médicale Continue*

Pr Patrick VOURC'H, *Recherche*

**RESPONSABLE ADMINISTRATIVE**
Mme Fanny BOBLETER

********

## DOYENS HONORAIRES

Pr Emile ARON (†) – *1962-1966*
*Directeur de l'Ecole de Médecine - 1947-1962*
Pr Georges DESBUQUOIS (†) - *1966-1972*
Pr André GOUAZE - *1972-1994*
Pr Jean-Claude ROLLAND – *1994-2004*
Pr Dominique PERROTIN – *2004-2014*

## PROFESSEURS EMERITES

Pr Daniel ALISON
Pr Philippe ARBEILLE
Pr Catherine BARTHELEMY
Pr Gilles BODY
Pr Jacques CHANDENIER
Pr Alain CHANTEPIE
Pr Pierre COSNAY
Pr Etienne DANQUECHIN-DORVAL
Pr. Dominique GOGA
Pr Alain GOUDEAU
Pr Anne-Marie LEHR-DRYLEWICZ
Pr Gérard LORETTE
Pr Roland QUENTIN
Pr Elie SALIBA

## PROFESSEURS HONORAIRES

P. ANTHONIOZ – A. AUDURIER – A. AUTRET – P. BAGROS – P.BARDOS – J.L. BAULIEU – C. BERGER – JC. BESNARD – P. BEUTTER – C. BONNARD – P. BONNET – P. BOUGNOUX – P. BURDIN – L. CASTELLANI – B. CHARBONNIER – P. CHOUTET – T. CONSTANS – C. COUET – L. DE LA LANDE DE CALAN – J.P. FAUCHIER – F. FETISSOF – J. FUSCIARDI – P. GAILLARD – G. GINIES – A. GOUAZE – J.L. GUILMOT – N. HUTEN – M. JAN – J.P. LAMAGNERE – F. LAMISSE – Y. LANSON – O. LE FLOCH – Y. LEBRANCHU – E. LECA – P. LECOMTE – E. LEMARIE – G. LEROY – M. MARCHAND – C. MAURAGE – C. MERCIER – J. MOLINE – C. MORAINE – J.P. MUH – J. MURAT – H. NIVET – L. POURCELOT – P. RAYNAUD – D. RICHARD-LENOBLE – A. ROBIER – J.C. ROLLAND – D. ROYERE - A. SAINDELLE – J.J. SANTINI – D. SAUVAGE – D. SIRINELLI – B. TOUMIEUX – J. WEILL

## PROFESSEURS DES UNIVERSITES - PRATICIENS HOSPITALIERS

ANDRES Christian ..... Biochimie et biologie moléculaire
ANGOULVANT Denis ..... Cardiologie
AUPART Michel ..... Chirurgie thoracique et cardiovasculaire
BABUTY Dominique ..... Cardiologie
BAKHOS David ..... Oto-rhino-laryngologie
BALLON Nicolas ..... Psychiatrie ; addictologie
BARILLOT Isabelle ..... Cancérologie ; radiothérapie
BARON Christophe ..... Immunologie
BEJAN-ANGOULVANT Théodora ..... Pharmacologie clinique
BERNARD Anne ..... Cardiologie
BERNARD Louis ..... Maladies infectieuses et maladies tropicales
BLANCHARD-LAUMONNIER Emmanuelle .... Biologie cellulaire
BLASCO Hélène ..... Biochimie et biologie moléculaire
BONNET-BRILHAULT Frédérique ..... Physiologie
BRILHAULT Jean ..... Chirurgie orthopédique et traumatologique
BRUNEREAU Laurent ..... Radiologie et imagerie médicale
BRUYERE Franck ..... Urologie
BUCHLER Matthias ..... Néphrologie
CALAIS Gilles ..... Cancérologie, radiothérapie
CAMUS Vincent ..... Psychiatrie d'adultes
COLOMBAT Philippe ..... Hématologie, transfusion
CORCIA Philippe ..... Neurologie
COTTIER Jean-Philippe ..... Radiologie et imagerie médicale
DE TOFFOL Bertrand ..... Neurologie
DEQUIN Pierre-François..... Thérapeutique
DESOUBEAUX Guillaume..... Parasitologie et mycologie
DESTRIEUX Christophe ..... Anatomie
DIOT Patrice ..... Pneumologie
DU BOUEXIC de PINIEUX Gonzague ..... Anatomie & cytologie pathologiques
DUCLUZEAU Pierre-Henri ..... Endocrinologie, diabétologie, et nutrition
DUMONT Pascal ..... Chirurgie thoracique et cardiovasculaire
EL HAGE Wissam ..... Psychiatrie adultes
EHRMANN Stephan ..... Réanimation
FAUCHIER Laurent ..... Cardiologie
FAVARD Luc ..... Chirurgie orthopédique et traumatologique
FOUGERE Bertrand ..... Gériatrie
FOUQUET Bernard ..... Médecine physique et de réadaptation
FRANCOIS Patrick ..... Neurochirurgie
FROMONT-HANKARD Gaëlle ..... Anatomie & cytologie pathologiques
GAUDY-GRAFFIN Catherine ..... Bactériologie-virologie, hygiène hospitalière
GOUPILLE Philippe ..... Rhumatologie
GRUEL Yves ..... Hématologie, transfusion
GUERIF Fabrice ..... Biologie et médecine du développement et de la reproduction
GUYETANT Serge ..... Anatomie et cytologie pathologiques
GYAN Emmanuel ..... Hématologie, transfusion
HAILLOT Olivier ..... Urologie
HALIMI Jean-Michel ..... Thérapeutique
HANKARD Régis..... Pédiatrie
HERAULT Olivier ..... Hématologie, transfusion
HERBRETEAU Denis ..... Radiologie et imagerie médicale
HOURIOUX Christophe ..... Biologie cellulaire
LABARTHE François ..... Pédiatrie
LAFFON Marc ..... Anesthésiologie et réanimation chirurgicale, médecine d'urgence
LARDY Hubert ..... Chirurgie infantile
LARIBI Saïd ..... Médecine d'urgence
LARTIGUE Marie-Frédérique ..... Bactériologie-virologie
LAURE Boris ..... Chirurgie maxillo-faciale et stomatologie
LECOMTE Thierry ..... Gastroentérologie, hépatologie
LESCANNE Emmanuel ..... Oto-rhino-laryngologie
LINASSIER Claude ..... Cancérologie, radiothérapie
MACHET Laurent ..... Dermato-vénéréologie
MAILLOT François ..... Médecine interne
MARCHAND-ADAM Sylvain ..... Pneumologie
MARRET Henri ..... Gynécologie-obstétrique

MARUANI Annabel ..... Dermatologie-vénéréologie
MEREGHETTI Laurent ..... Bactériologie-virologie ; hygiène hospitalière
MITANCHEZ Delphine ..... Pédiatrie
MORINIERE Sylvain ..... Oto-rhino-laryngologie
MOUSSATA Driffa ..... Gastro-entérologie
MULLEMAN Denis ..... Rhumatologie
ODENT Thierry ..... Chirurgie infantile
OUAISSI Mehdi ..... Chirurgie digestive
OULDAMER Lobna ..... Gynécologie-obstétrique
PAINTAUD Gilles ..... Pharmacologie fondamentale, pharmacologie clinique
PATAT Frédéric ..... Biophysique et médecine nucléaire
PERROTIN Dominique ..... Réanimation médicale, médecine d'urgence
PERROTIN Franck ..... Gynécologie-obstétrique
PISELLA Pierre-Jean ..... Ophtalmologie
PLANTIER Laurent ..... Physiologie
REMERAND Francis ..... Anesthésiologie et réanimation, médecine d'urgence
ROINGEARD Philippe ..... Biologie cellulaire
ROSSET Philippe ..... Chirurgie orthopédique et traumatologique
RUSCH Emmanuel ..... Epidémiologie, économie de la santé et prévention
SAINT-MARTIN Pauline ..... Médecine légale et droit de la santé
SALAME Ephrem ..... Chirurgie digestive
SAMIMI Mahtab ..... Dermatologie-vénéréologie
SANTIAGO-RIBEIRO Maria ..... Biophysique et médecine nucléaire
THOMAS-CASTELNAU Pierre ..... Pédiatrie
TOUTAIN Annick ..... Génétique
VAILLANT Loïc ..... Dermato-vénéréologie
VELUT Stéphane ..... Anatomie
VOURC'H Patrick ..... Biochimie et biologie moléculaire
WATIER Hervé ..... Immunologie

## PROFESSEUR DES UNIVERSITES DE MEDECINE GENERALE

DIBAO-DINA Clarisse
LEBEAU Jean-Pierre

## PROFESSEURS ASSOCIES

MALLET Donatien ..... Soins palliatifs
POTIER Alain ..... Médecine Générale
ROBERT Jean ..... Médecine Générale

## MAITRES DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS

BARBIER Louise..... Chirurgie digestive
BERHOUET Julien ..... Chirurgie orthopédique et traumatologique
BRUNAULT Paul ..... Psychiatrie d'adultes, addictologie
CAILLE Agnès ..... Biostat., informatique médical et technologies de communication
CLEMENTY Nicolas ..... Cardiologie
DENIS Frédéric ..... Odontologie
DOMELIER Anne-Sophie ..... Bactériologie-virologie, hygiène hospitalière
DUFOUR Diane ..... Biophysique et médecine nucléaire
ELKRIEF Laure ..... Hépatologie – gastroentérologie
FAVRAIS Géraldine ..... Pédiatrie
FOUQUET-BERGEMER Anne-Marie ..... Anatomie et cytologie pathologiques
GATAULT Philippe ..... Néphrologie
GOUILLEUX Valérie..... Immunologie
GUILLON Antoine ..... Réanimation
GUILLON-GRAMMATICO Leslie ..... Epidémiologie, économie de la santé et prévention
HOARAU Cyrille ..... Immunologie
IVANES Fabrice ..... Physiologie
LE GUELLEC Chantal ..... Pharmacologie fondamentale, pharmacologie clinique
LEFORT Bruno ..... Pédiatrie
LEMAIGNEN Adrien ..... Maladies infectieuses
MACHET Marie-Christine ..... Anatomie et cytologie pathologiques

MOREL Baptiste ..... Radiologie pédiatrique
PIVER Éric ..... Biochimie et biologie moléculaire
REROLLE Camille ..... Médecine légale
ROUMY Jérôme ..... Biophysique et médecine nucléaire
SAUTENET Bénédicte ..... Thérapeutique
TERNANT David ..... Pharmacologie fondamentale, pharmacologie clinique
VUILLAUME-WINTER Marie-Laure ..... Génétique
ZEMMOURA Ilyess ..... Neurochirurgie

## MAITRES DE CONFERENCES DES UNIVERSITES

AGUILLON-HERNANDEZ Nadia ..... Neurosciences
BOREL Stéphanie ..... Orthophonie
MONJAUZE Cécile ..... Sciences du langage – orthophonie
NICOGLOU Antonine ..... Philosophie – histoire des sciences et des techniques
PATIENT Romuald..... Biologie cellulaire
RENOUX-JACQUET Cécile ..... Médecine Générale

## MAITRES DE CONFERENCES ASSOCIES

RUIZ Christophe ..... Médecine Générale
SAMKO Boris ..... Médecine Générale

## CHERCHEURS INSERM - CNRS - INRA

BOUAKAZ Ayache ..... Directeur de Recherche INSERM – UMR INSERM 1253
CHALON Sylvie ..... Directeur de Recherche INSERM – UMR INSERM 1253
COURTY Yves ..... Chargé de Recherche CNRS – UMR INSERM 1100
DE ROCQUIGNY Hugues ..... Chargé de Recherche INSERM – UMR INSERM 1259
ESCOFFRE Jean-Michel ..... Chargé de Recherche INSERM – UMR INSERM 1253
GILOT Philippe ..... Chargé de Recherche INRA – UMR INRA 1282
GOUILLEUX Fabrice ..... Directeur de Recherche CNRS – UMR CNRS 7001
GOMOT Marie ..... Chargée de Recherche INSERM – UMR INSERM 1253
HEUZE-VOURCH Nathalie ..... Chargée de Recherche INSERM – UMR INSERM 1100
KORKMAZ Brice ..... Chargé de Recherche INSERM – UMR INSERM 1100
LAUMONNIER Frédéric ..... Chargé de Recherche INSERM - UMR INSERM 1253
MAZURIER Frédéric ..... Directeur de Recherche INSERM – UMR CNRS 7001
MEUNIER Jean-Christophe ..... Chargé de Recherche INSERM – UMR INSERM 1259
PAGET Christophe ..... Chargé de Recherche INSERM – UMR INSERM 1100
RAOUL William ..... Chargé de Recherche INSERM – UMR CNRS 7001
SI TAHAR Mustapha ..... Directeur de Recherche INSERM – UMR INSERM 1100
WARDAK Claire ..... Chargée de Recherche INSERM – UMR INSERM 1253

## CHARGES D'ENSEIGNEMENT

***Pour l'Ecole d'Orthophonie***
DELORE Claire ..... Orthophoniste
GOUIN Jean-Marie ..... Praticien Hospitalier

***Pour l'Ecole d'Orthoptie***
MAJZOUB Samuel..... Praticien Hospitalier

***Pour l'Ethique Médicale***
BIRMELE Béatrice ..... Praticien Hospitalier

# SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate, je promets et je jure
d'être fidèle aux lois de l'honneur et de la probité dans
l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle
à mes promesses. Que je sois couvert d'opprobre et
méprisé de mes confrères si j'y manque.

# Résumé

**Introduction :** Nous avons analysé l'évolution de la fonction des greffons issus d'un même donneur décédé après arrêt cardiocirculatoire contrôlé (DDACc) lorsque l'un des deux receveurs a reçu une induction par anticorps anti-IL2-récepteur (anti-IL2R) et l'autre par sérum antilymphocytaire (SAL), induction actuellement recommandée en raison de la crainte de reprise retardée de fonction du greffon (RRF).

**Matériel et Méthodes :** Cette étude rétrospective a été menée aux centres hospitalo-universitaires de Tours, Nantes et Poitiers de novembre 2015 à décembre 2018. Nous avons comparé 23 receveurs de greffons issus de DDACc induits par anti-IL2R aux 23 receveurs du rein adelphe ayant reçu une induction par SAL. Nous avons analysé dans ces deux groupes la survenue de RRF, le débit de filtration glomérulaire (DFG) et la protéinurie à 3, 6 et 12 mois post-transplantation ainsi que la survenue d'infections sévères à 1 an.

**Résultats :** Nous avons observé 20% (4/20) de RRF dans le groupe anti-IL2R *vs* 11% (2/18) dans le groupe SAL (ns). La fonction rénale à 3 et 6 mois n'était pas significativement différente selon l'induction. Elle était meilleure dans le groupe anti-IL2R que dans le groupe SAL à 12 mois (DFG à 58 ± 18 *vs* 46 ± 20 mL/min/1,73 $m^2$, $p < 0,05$). La protéinurie n'était pas significativement différente à 3, 6 et 12 mois. Le taux d'infections nécessitant une hospitalisation à 1 an était inférieur dans le groupe anti-IL2R comparé au groupe SAL : 17% (4/23) *vs* 48% (11/23), $p < 0,05$.

**Conclusion :** Nous n'avons pas observé de différence d'évolution de fonction du greffon chez des patients transplantés rénaux à partir d'un DDACc induits par anti-IL2R comparés aux receveurs du rein adelphe induits par SAL. Cela et le surrisque infectieux associé au SAL pourraient inciter à un changement des recommandations.

Mots clé : Transplantation rénale, Donneur décédé après arrêt cardiocirculatoire contrôlé, Anticorps anti-IL2-récepteur, Sérum antilymphocytaire

# Abstract

**Introduction:** We analyzed the graft function evolution in kidney transplant recipients from controlled deceased donors after cardiocirculatory death (cDCD) when one of the two recipients received an induction by anti-IL2-receptor antibodies (anti-IL2R) and the other an induction by antithymocyte globulin (ATG) which is currently recommended due to fear of delayed graft function (DGF).

**Material and Methods:** This retrospective study was carried out at the university hospital centers of Tours, Nantes and Poitiers from November 2015 to December 2018. We compared 23 recipients from cDCD induced by anti-IL2R to the 23 contralateral kidney recipients who received an induction by ATG. We analyzed in both groups the occurrence of DGF, the glomerular filtration rate (GFR) and the proteinuria at 3-, 6- and 12-months post-transplantation, as well as the occurrence of severe infections at 1 year.

**Results:** We observed 20% (4/20) of DGF in the anti-IL2R group *vs* 11% (2/18) in the ATG group (ns). Graft function at 3 and 6 months was not significantly different according to the induction. It was better in the anti-IL2R group than in the ATG group at 12 months (GFR at 58 ± 18 *vs* 46 ± 20 ml/min/1.73m2, $p < 0.05$). Proteinuria was not significantly different at 3, 6 and 12 months. The rate of infections requiring hospitalization at 1 year was lower in the anti-IL2R group compared to the ATG group: 17% (4/23) *vs* 48% (11/23), $p < 0.05$.

**Conclusion:** We did not observe any graft function difference in kidney transplant recipients from cDCD donors induced by anti-IL2R compared to the contralateral kidney recipients induced by ATG. Given the increased infectious risk associated with ATG, this could lead to a change in recommendations.



Keywords: Kidney transplantation, Controlled donation after cardiocirculatory death, Anti-IL2-receptor antibodies, Antithymocyte globulin

## Remerciements

A monsieur le Professeur Jean-Michel Halimi, pour me faire l'honneur de présider le jury de ma thèse et m'avoir appris l'exercice de la néphrologie au lit du patient.

A monsieur le Professeur Matthias Büchler, pour avoir dirigé ce travail et pour m'avoir enseigné une médecine humaine avant tout.

A monsieur le Professeur Jacques Dantal, pour avoir accepté de juger la qualité de ma thèse et pour avoir rendu possible ce travail collaboratif.

A monsieur le Professeur Antoine Thierry, pour avoir accepté de faire partie du jury de ma thèse et pour avoir facilité la coopération de nos centres sur ce travail.

A monsieur le Docteur Philippe Gatault, pour avoir accepté d'évaluer ma thèse et pour ses qualités médicales et scientifiques transmises dans la bonne humeur.

A monsieur le Docteur Jean-Christophe Venhard, pour avoir accepté de juger ce travail et pour son concours à celui-ci d'une autre fenêtre que celle de la néphrologie.

Au Docteur Elodie Bailly pour l'initiative de ce projet, nos échanges et ses précieux conseils tout au long de mon internat.

Aux équipes de transplantation rénale, de coordination de greffe et de prélèvement d'organes des centres de Tours, Nantes, Poitiers et La Roche-Sur-Yon pour leur participation à ce travail.

Aux docteurs Barbet, Benoit, Cloarec, Davourie-Salandre, Dumont, El Khoury, François, Ganea, Golea, Grezard, Kaysi, Longuet, Merieau, Pierre, Prat, Rabot, Sautenet et Valentin, pour leurs conseils et leur encadrement bienveillant au cours de ma formation de néphrologue.

Aux secrétaires et à l'ensemble de l'équipe paramédicale du service pour ce travail collectif agréable et enrichissant au quotidien.

A tous les médecins et soignants d'autres horizons qui ont bien voulu me transmettre leur savoir pour le bien des patients.

A monsieur le Professeur Christophe Baron, au Docteur Roxane Lemoine, à l'ensemble de l'équipe du laboratoire T2I et à mes camarades de Master 2 pour leur goût de la recherche et leur accompagnement dans cette année des plus enrichissantes.

A tous ceux qui ont partagé cette aventure de l'internat avec moi : Charlotte D, Johan N, Alexandre E, Mélanie B, Thibault M, Charlotte J, Eloi C, Annabelle G, Claire G, Florent VT, Jean-Baptiste DF, Léa M, Léa L, Alexandre F, Valentin M, Paul D, Piotr S, Hélène C, Adeline B, Anne-Laure P, Martin E, Misylias B, Charlotte C, Germain D, Maxime D, Chloé L, Hélène M, Joffrey M, et Mathias B pour nos échanges et pour tous les excellents moments passés ensemble comme pour leur solidarité dans ceux plus difficiles.

A Xavier S, Sabrina C, Corentin A, Pierre-Louis B, Aurélien L, Lucile B, Clément B, Simon D, Lucie D, Olivier I, Stéphanie L, Audrey L, Andréa P, Fanny P, Armand V : pour cette précieuse amitié qui traverse les années.

A mes grands-parents, pour leurs encouragements depuis le tout début.

A mes parents, pour leur soutien inconditionnel et leurs valeurs transmises qui font de moi celui que je suis aujourd'hui et qui continueront à guider mes pas.

A Paul et Anne-Laure, pour cette belle vie partagée où que l'on soit, quoique l'on fasse.

A Coralie, pour avoir accepté de cheminer et de tout partager avec moi hier, aujourd'hui et demain.

## Table des matières

## Liste des abréviations

Anti-IL2R : anticorps anti-IL2-récepteur
CRN : circulation régionale normothermique,
DDME : donneur décédé en état de mort encéphalique
DDAC : donneur décédé après arrêt cardiocirculatoire
DDACc : donneur décédé après arrêt cardiocirculatoire contrôlé
DDACnc : donneur décédé après arrêt cardiocirculatoire non contrôlé
DFG : débit de filtration glomérulaire
ICN : inhibiteurs de la calcineurine
LAT : limitation ou arrêt programmé des thérapeutiques actives
LIR : lésions d'ischémie reperfusion
RRF : reprise retardée de fonction du greffon
SAL : sérum antilymphocytaire

## Abbreviations list

Anti-IL2R: anti-IL2-receptor antibodies
ATG: antithymocyte globulin
BMI: body mass index
cDCD: controlled donation after cardiocirculatory death
CD: cluster of differentiation
CMV: cytomegalovirus
CNI: calcineurin inhibitors
DBD: donation after brain death
DCD: donation after cardiocirculatory death
DGF: delayed graft function
EBV: Epstein Barr virus
GFR: glomerular filtration rate
HLA: human leukocyte antigen
IRI: ischemia-reperfusion injury
LAT: limitation or programmed withdrawal of active treatments
MAP: mean arterial pressure
NRP: normothermic regional perfusion
SGF: slow graft function
uDCD: uncontrolled donation after cardiocirculatory death

## Introduction

La transplantation rénale est le meilleur traitement de l'insuffisance rénale terminale en termes de survie, de qualité de vie et de coût[1,2]. Toutefois, le nombre de patients inscrits sur la liste d'attente de transplantation rénale augmente alors que le taux de transplantations réalisées reste stable, limité par la pénurie d'organes disponibles[3]. Les prélèvements d'organes sont réalisés à partir de donneurs vivants ou à partir de donneurs décédés, majoritairement en état de mort encéphalique (DDME). Afin d'accroître le don d'organes, le recours à des donneurs décédés après arrêt cardiocirculatoire (DDAC) s'est développé au cours des dernières décennies, permettant d'améliorer l'accès à la greffe des patients sur la liste d'attente[3–6].

On distingue différentes catégories de DDAC, définies par la classification de Maastricht (révisée en 2016), selon que l'arrêt cardiocirculatoire est non contrôlé (DDACnc) ou contrôlé (DDACc) dans le cas où il s'agit de patients hospitalisés en service de réanimation pour lesquels une décision de limitation ou d'arrêt programmé des thérapeutiques (LAT) est prise en raison du pronostic des pathologies ayant amené la prise en charge en réanimation[7].

Bien que leur pronostic à moyen et long terme soit similaire à celui des transplantations réalisées à partir de DDME[4,8,9], les transplantations réalisées à partir de DDAC sont associées à plus de reprise retardée de fonction du greffon (RRF) et à plus de lésions d'ischémie reperfusion (LIR) du greffon, en particulier en cas de DDACnc[6,8]. Les techniques de préservation d'organe *in situ* chez les DDAC avant le prélèvement permettent de limiter ces lésions, les meilleurs résultats étant associés à l'utilisation de la circulation régionale normothermique (CRN)[10,11].

Pour limiter les complications des LIR en post-transplantation immédiat chez les receveurs de greffons issus de DDAC (toutes catégories confondues), il est

recommandé de différer l'usage des inhibiteurs de la calcineurine (ICN) vasoconstricteurs et néphrotoxiques[12]. Bien qu'associée à un surrisque de complications infectieuses, une induction par sérum antilymphocytaire (SAL) déplétant les lymphocytes T est recommandée chez ces receveurs pour limiter les LIR et différer l'introduction des ICN sans les surexposer à la survenue d'un rejet aigu[12,13].

Toutefois, ces recommandations sont de faible niveau de preuve et il y a peu de travaux bien conduits étudiant l'immunosuppression d'induction chez les receveurs de greffons rénaux issus de DDACc.

Une induction non-déplétante par anticorps anti-IL2-récepteur (anti-IL2R) et l'introduction précoce des ICN sont habituellement recommandées en cas de faible risque immunologique et en l'absence de risque de RRF[14]. Cette stratégie n'est que peu étudiée chez les receveurs de reins issus d'un DDACc[15,16] . Elle pourrait être une alternative au SAL compte tenu du moindre risque de LIR auquel sont exposés ces greffons comparés aux DDACnc et du faible impact des dons issus de DDAC sur le pronostic à long terme comparés aux DDME, malgré un taux de RRF plus élevé.

L'objectif de cette étude est de comparer la survenue de RRF et l'évolution de la fonction rénale à un an des deux greffons issus d'un même DDACc lorsque l'un des receveurs reçoit une induction par anti-IL2R et l'autre par SAL.

Nous avons décidé de mener ce travail aux centres hospitalo-universitaires de Tours, Nantes et Poitiers où le prélèvement d'organe à partir de DDACc est pratiqué depuis 2015, ces centres ayant été parmi les premiers centres français à le développer.

Nous présentons notre travail sous forme d'article.

# Induction in kidney transplant recipients from controlled deceased donors after cardiocirculatory death:

# Antithymocyte globulin

# versus

# Anti-IL2-receptor antibodies

## Introduction

Renal transplantation is the best treatment for end-stage renal disease in terms of survival, quality of life and cost[1,2]. However, the number of patients on renal transplant waiting list is increasing while the rate of transplantations performed remains stable, limited by the shortage of available organs[3]. Organ harvesting is performed from living donors or from deceased donors, mostly donation after brain death (DBD). In order to increase the number of available organs, the use of deceased donors after cardiocirculatory death (DCD) has been developed in recent decades, improving the patients on waiting list access to transplantation[3–6].

There are different categories of DCD donors, defined by the Maastricht classification (revised in 2016), depending on whether the cardiocirculatory arrest is uncontrolled (uDCD) or controlled (cDCD) in the case of patients hospitalized in intensive care units for whom a decision of limitation or programmed withdrawal of active treatments (LAT) is taken because of the prognosis of the pathologies which led the patient to intensive care unit[7].

Although their medium- and long-term prognosis is similar to transplantations from DBD donors[4,8,9], transplantations from DCD donors are associated with more delayed graft function (DGF) ant more graft ischemia-reperfusion injury (IRI), especially in case of uDCD[6,8]. *In situ* organ preservation techniques in DCD donors prior to harvesting limit these lesions, the best results being associated with the use of normothermic regional perfusion (NRP)[10,11].

To limit IRI complications during the immediate post-transplantation period in transplant recipients from DCD donors (all categories combined), it is recommended to postpone the use of calcineurin inhibitors (CNI) known for their vasoconstrictor effect and their nephrotoxicity[12]. Although associated with an increased risk of

infectious complications, a T lymphocyte-depleting induction by antithymocyte globulin (ATG) is recommended in these recipients to limit IRI and to delay CNI introduction without overexposing them to the risk of acute rejection[12,13].

However, these recommendations are of low level of evidence and there are few well conducted studies regarding immunosuppressive induction in transplant recipients from cDCD donors.

Non-depleting anti-IL2-receptor antibodies (anti-IL2R) induction and early introduction of CNI are usually recommended in DBD kidney recipients with low-immunological risk and when there is a low risk of DGF[14]. This strategy is poorly studied in kidney recipients from cDCD donors[15,16] . It could be an alternative to ATG given the lower risk of IRI to which these grafts are exposed compared to uDCD and the low impact of DCD on long-term prognosis compared to DBD, despite a higher DGF rate.

Our study objective is to compare the occurrence of DGF and the one-year function evolution of grafts from the same cDCD donor when one of the two recipients receives an induction by anti-IL2R and the other by ATG.

## Material and Methods

### 1- Study design

We carried out a multicenter retrospective study in the university hospital centers of Tours, Poitiers and Nantes. Inclusions were conducted between November 1, 2015 and December 31, 2018. The end-point date was September 1, 2019.

### 2- Donors

We studied all cDCD kidney donors from Tours, Poitiers, Nantes and La Roche-Sur-Yon (belonging to Nantes harvesting network) during the inclusion period. We selected all cDCD donors for whom both recipients had undergone a kidney transplantation in Tours, Poitiers or Nantes. Among them we included all donors and their paired kidney recipients when one recipient received an induction by anti-IL2R and the other by ATG.

The harvesting procedure followed the French Biomedicine Agency recommendations with the placement of arterial and venous femoral accesses before the LAT implementation leading to cardiac arrest. After the occurrence of cardiac arrest and 5 minutes of observation without any intervention, the intensive care unit team installs the cannulas that will be used for NRP, using the accesses already in place. NRP functions until kidneys are explanted. Then, grafts must be placed into perfusion machines, as recommended.

Different phases are described during this procedure: the agonic phase between the implementation of the LAT and the occurrence of cardiac arrest, the circulatory arrest phase between the cardiac arrest and the NRP onset (corresponding to the no flow duration), the functional warm ischemia time between the fall of mean arterial pressure (MAP) below 45 mmHg during the agonic phase and the NRP onset

(includes low flow and no flow periods) and the cold ischemia time between the explantation of the kidneys and their transplantation.

Time constraints frame these different phases: the duration between the LAT and the circulatory arrest must not exceed 180 min, that between the MAP < 45 mmHg and the circulatory arrest 100 min. The setup of cannulas should not exceed 20 minutes. The operating time of the NRP must not exceed 4 hours, and the cold ischemia duration is limited to a maximum of 18 hours.

We collected the following donor characteristics: age, gender, weight, height, body mass index (BMI), reason for admission to intensive care unit, serum creatinine (in µmol/L) at the arrival in intensive care unit and before harvesting, cytomegalovirus (CMV) and Epstein Barr virus (EBV) serological status (positive or negative), the durations of asystolic and agonic phases and the functional warm ischemia time. We also noted the cold ischemia time for each of the grafts.

**3- Attribution rules to reduce the risk of DGF and IRI**

In France, cDCD donor grafts cannot be assigned to recipients in the super-emergency category, or as part of the national hyperimmunized or regional immunized priorities. They are allocated at the local, interregional and national levels according to the kidney REIN score which takes into account the time spent on the waiting list, the waiting time on dialysis, the number of HLA mismatches between donor and recipient, the age difference between donor and recipient, the distance from harvesting center to transplantation site and an indicator of access to transplantation difficulty. Distance plays an important role insofar as it correlates with the cold ischemia time. One of the two kidneys is allocated locally and the other at the interregional or national level.

**4- Recipients**

The included recipients were divided into 2 groups according to the induction therapy received, by anti-IL2R or by ATG.

According to the French Biomedicine Agency recommendations, patients eligible to kidney transplantation from a cDCD donor must be over 18 years old, must be waiting for a first kidney transplant, have a low-immunological risk and have their anti-human leukocyte antigen (HLA) immunization status up to date. The collection of their consent after information is mandatory.

In the anti-IL2R group, patients received an induction by basiliximab (Simulect, Novartis™) in 2 injections of 20 mg at day 0 pre-transplantation and day 4 post-transplantation, with introduction of CNI (0.1 mg/kg twice a day) at day 0 post-transplantation. In the ATG group, patients received an ATG (Thymoglobulin, Sanofi™) induction at the 1.5 mg/kg dose for the first infusion with delayed introduction of CNI between day 2 and day 4 post-transplantation. Further ATG doses were adapted to peripheral lymphocytes and/or CD3+ T cells count. In both groups immunosuppression regimen also included corticosteroid therapy and mycophenolate mofetil treatment from day 0.

Initial characteristics: Regarding the recipients we noted their demographic characteristics (age, sex, weight, height, BMI), the duration of hemodialysis treatment, the pre-emptive or not nature of the transplantation, their initial nephropathy, their CMV and EBV serological status (positive or negative), the number of HLA mismatches relative to their donor (for HLA A, B, DR and DQ), and their initial hospital stay duration.

Post-transplant renal graft recovery: We collected the following graft recovery parameters during the immediate post-transplantation period: DGF defined by the

need for hemodialysis within 7 days after transplantation (the reason for which hemodialysis was needed and the number of sessions were also reported) and slow graft function (SGF) defined by a serum creatinine greater than 250 µmol/L at day 5 post transplantation in the absence of DGF.

Renal function: Proteinuria in g/g of creatininuria, serum creatinine in µmol/L and glomerular filtration rate (GFR) in mL/min/1.73m$^2$ of body surface according to the MDRD formula were analyzed at 3, 6, and 12 months. All those parameters were measured in routine follow-up consultations or during hospitalizations at the times of interest.

Histology: Systematic graft biopsies, performed at 3-months post-transplantation in two centers (Tours and Nantes), were analyzed according to the Banff International Classification. The occurrence of an acute cellular rejection or a borderline acute cellular rejection defined by the Banff criteria was reported during the first-year post-transplantation.

Patient and graft survival: One-year patient and graft survivals were also studied.

Safety: We also focused on the occurrence of post-transplantation complications. We collected data about infectious complications: occurrence of CMV infection (defined by the positivity of the viral load measured in the blood by polymerase chain reaction during the systematic follow-up of each center) or CMV disease (defined as an influenza-like illness or an organ injuries related to CMV), positivity of BK virus viral load measured in the blood by polymerase chain reaction during the systematic follow-up of each center, occurrence of BK virus nephropathy diagnosed after graft biopsy and occurrence of any other infection requiring hospitalization.

## 5- Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego California USA) and R Statistical Software version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). The Mann-Witney test or the Wilcoxon rank sum test with continuity correction were used to compare quantitative variables. The binary variables were compared using the Chi-2 test (with Yates correction if needed) or the Fisher exact test. Survival analysis were performed using the Log Rank test. The differences between variables were considered statistically significant for a p value $< 0.05$.

## 6- Ethical approval

This study received the agreement from ethics committees of the three centers where it was performed. Patients received a consent form after oral information from the nephrologist during a routine consultation.

# Results

## 1- Donors

Between November 01, 2015 and December 31, 2018, we identified 97 cDCD donors for whom kidney harvesting was performed in the French university hospital centers of Tours, Nantes and Poitiers and in La Roche-Sur-Yon departmental hospital. For 62 of these donors, both kidneys were grafted in one of those three university hospital centers. Among them, we identified 23 donors for whom one of the two kidney graft recipients received an induction by anti-IL2R and the contralateral kidney graft recipient received an induction by ATG (**Figure 1**).

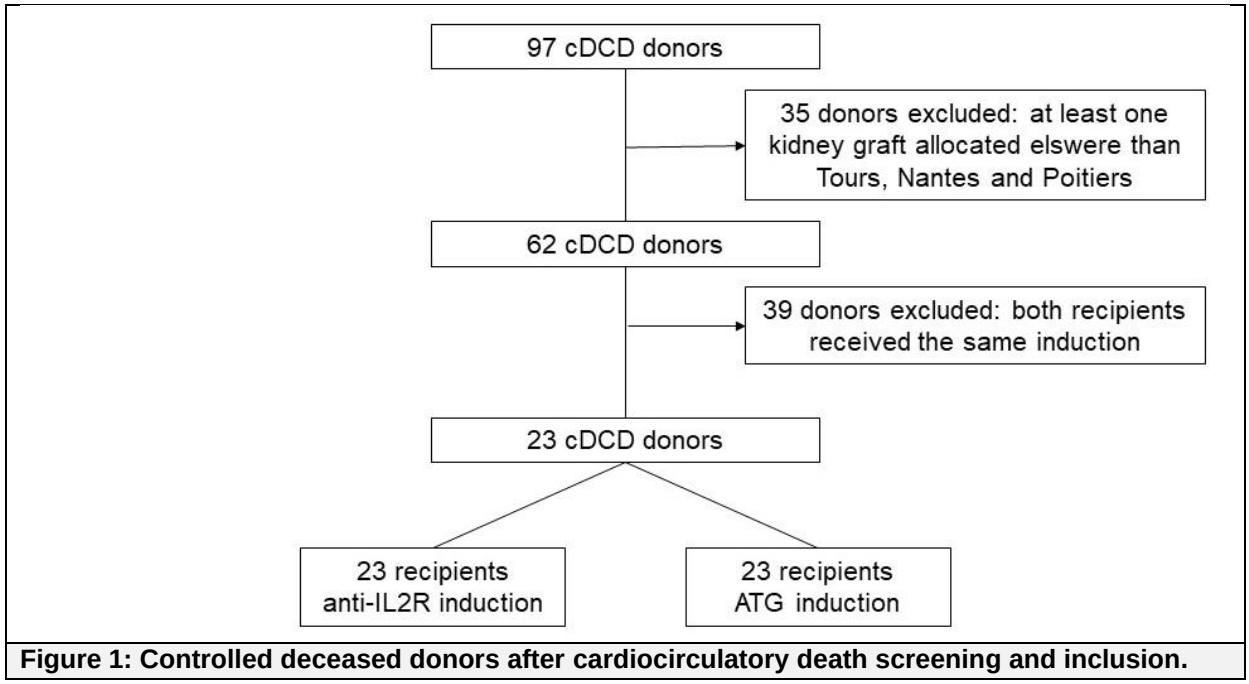


**Figure 1: Controlled deceased donors after cardiocirculatory death screening and inclusion.**

*cDCD: controlled deceased donation after cardiocirculatory death, ATG: antithymocyte globulin, anti-IL2R: anti-IL2R-receptor antibodies*

As summarized in **Table 1**, cDCD donors included were mainly men (18/23) and their reasons for admission to intensive care units were homogeneously distributed between trauma (7/23), vascular cause (8/23) and cardiac arrest (8/23).

| **Table 1: Included controlled deceased donors after cardiocirculatory death characteristics (n = 23).** | |
|---|---|
| Age (years) | 50.2 ± 13.2 |
| Sex Ratio (M/F) | 19/4 |
| BMI (kg/m$^2$) | 25.9 ± 5.3 |
| Reason of admission to intensive care unit (%) | |
| Trauma | 7 (30) |
| Vascular | 8 (35) |
| Cardiac arrest | 8 (35) |
| Serum creatinine at arrival in the intensive care unit (µmol/L) | 77 ± 23 |
| Serum creatinine before harvesting (µmol/L) | 65 ± 22 |
| Duration of agonic phase (min) | 26 ± 29 |
| Duration of asystolic phase (min) | 25 ± 9 |
| Warm Ischemia Time (min) | 30 ± 11 |

*M: male, F: female, BMI: Body Mass Index*

## 2- Recipients

A total of 46 recipients who received a kidney graft from these cDCD donors were distributed between the anti-IL2R group (n = 23) and the ATG group (n = 23) depending on the induction they received. The reason for which recipients received anti-IL2R was mainly low-immunological risk (for 21/23 patients), except for one patient with no central venous access and another patient with a positive donor / negative recipient EBV mismatch. Anti-IL2R induction was mostly performed in the university hospital center of Tours (for 20/23 patients).

All recipient characteristics are summarized in **Table 2**. The two groups were comparable, except for the number of HLA mismatches that was lower in the anti-IL2R group than in the ATG one (3.7 ± 1.4 *vs* 5.3 ± 1.8 respectively, $p < 0.05$).

| Table 2: Recipients initial characteristics depending on immunosuppressive induction. | | | |
|---|---|---|---|
| | anti-IL2R (n=23) | ATG (n=23) | p |
| Age at transplantation (years) | 59.1 ± 7.6 | 58.2 ± 9.4 | ns |
| Sex Ratio (M/F) | 18/5 | 18/5 | ns |
| BMI | 27.6 ± 6.0 | 25.0 ± 3.8 | ns |
| Duration of hemodialysis treatment (months) | 22.8 ± 15.0 | 27.7 ± 22.6 | ns |
| Pre-emptive transplantation (%) | 3 (13) | 5 (22) | ns |
| Origin of initial nephropathy (%) | | | |
| Glomerular | 6 (26) | 9 (39) | ns |
| Vascular | 2 (9) | 5 (22) | ns |
| Genetic | 7 (30) | 3 (13) | ns |
| Tubulo-interstitial | 2 (9) | 2 (9) | ns |
| Other | 6 (26) | 5 (22) | ns |
| CMV matching between donor and recipient (%) | | | |
| D+/R- | 2 (9) | 5 (22) | ns |
| D+/R+ | 6 (26) | 3 (13) | ns |
| D-/R+ | 6 (26) | 7 (30) | ns |
| D-/R- | 9 (39) | 8 (35) | ns |
| EBV matching between donor and recipient (%) | | | |
| D+/R- | 5 (22) | 1 (4) | ns |
| D+/R+ | 18 (78) | 22 (96) | ns |
| D-/R+ | 0 (0) | 0 (0) | ns |
| D-/R- | 0 (0) | 0 (0) | ns |
| Number of HLA mismatches between donor and recipient (for HLA A, B, DR and DQ) | 3.7 ± 1.4 | 5.3 ± 1.8 | P < 0.05 |
| Cold ischemia time (min) | 639 ± 269 | 486 ± 176 | ns |

*cDCD: controlled deceased donation after cardiocirculatory death, ATG: antithymocyte globulin, anti-IL2R: anti-IL2R-receptor antibodies, M: male, F: female, BMI: body mass index, CMV: cytomegalovirus, EBV: Epstein Barr virus, D+ and D-: donor positive and negative serological status respectively, R+ and R-: recipient positive and negative serological status respectively, HLA: Human Leukocyte Antigen, ns: non-significant.*

One patient death occurred at day 100 in the ATG group and the 12-month follow-up was not available for 2 patients in both groups at the end-point date. Though, data at 6 and 12 months were available for 23 and 21 patients in the anti-IL2R group and for 22 and 20 patients in the ATG group respectively.

i- Post-transplant renal graft recovery

Excluding preemptive transplantations, 20% (4/20) of patients in the anti-IL2R group had a DGF compared to 11% (2/18) in the ATG group, this difference was not significant. The need for hemodialysis was explained by hyperkalemia for the four patients in the anti-IL2R group and for one patient in the ATG group, and the occurrence of an acute pulmonary edema for another patient in the ATG group. Only one hemodialysis session was required in most patients, except in one patient for whom 5 sessions were performed. Slow graft function (preemptive transplantations included and DGF excluded) was observed in 37% (7/19) of patients in the anti-IL2R *vs* 43% (9/21) in the ATG group (non-significant).

ii- Graft function

The estimated GFR was 49 ± 19 ml/min/1.73m$^2$ *vs* 50 ± 19 ml/min/1.73m$^2$ at 3 months, 53 ± 19 ml/min/1.73m$^2$ *vs* 49 ± 18 ml/min/1.73m$^2$ at 6 months and 58 ± 18 ml/min/1.73m$^2$ *vs* 46 ± 20 ml/min/1.73m$^2$ at 12 months in the anti-IL2R and ATG groups respectively. The difference between the two groups was only significant at 12 months ($p < 0.05$).

Proteinuria was 0.23 ± 0.28 g/g of creatininuria *vs* 0.58 ± 1.14 g/g at 3 months, 0.26 ± 0.29 g/g *vs* 0.42 ± 0.55 g/g at 6 months and 0.15 ± 0.17 g/g *vs* 0.69 ± 2.00 g/g at 12 months in the two groups respectively, without any significant difference.

The evolution of renal function and proteinuria is presented in **Figure 2**.

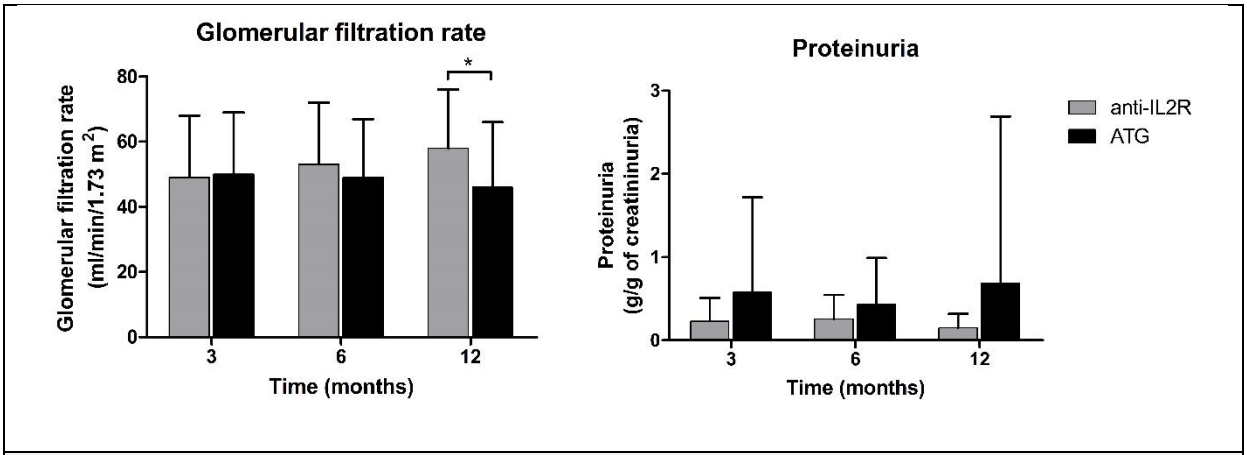


**Figure 2: One-year evolution of glomerular filtration rate and proteinuria in recipients from cDCD donors depending on immunosuppressive induction.**
Estimated glomerular filtration rate was signicantly higher in the anti-IL2R group at 12 months compared to the ATG group ($p < 0.05$).

*cDCD: controlled deceased donation after cardiocirculatory death, anti-IL2R: anti-IL2R-receptor antibodies, ATG: antithymocyte globulin, * $p < 0.05$*

iii- Rejection

Two acute rejections (9%, 2/23) occurred in both groups. We did not observe any acute cellular rejection in the anti-IL2R group *vs* 4% (1/23) in the ATG group and 9% (2/23) *vs* 4% (1/23) of borderline acute rejection respectively, these differences were not significant.

iv- Histology

Histological analysis (according to the Banff classification) of graft biopsies performed at 3 months was available for 20 recipients in the anti-IL2R group and 13 recipients in the ATG group, as these biopsies are routinely performed in only two of the three inclusion centers (Tours and Nantes). There was no significant difference between the two groups in terms of microvascular acute or chronical injuries. Indeed, the g score was at 0.30 ± 0.47 *vs* 0.15 ± 0.38, the v score at 0.05 ± 0.22 *vs* 0.00 ± 0.00, the cpt score at 0.20 ± 0.52 *vs*. 0.00 ± 0.00, the cv score at 1.05 ± 0.89 *vs* 0.70 ± 0.82 and the ah score at 0.95 ± 1.08 *vs* 0.77 ± 1.01 respectively. The cg score was null in

all biopsies. Regarding tubulo-interstitial injuries, the tubulitis (t) score was significantly higher in the anti-IL2R group (0.50 ± 0.89) *vs* the ATG group (0.00 ± 0.00), $p < 0.05$. Other markers of tubulo-interstitial injuries in the anti-IL2R group (i score at 0.26 ± 0.56, ci score at 0.60 ± 0.68 and ct score at 0.60± 0.68) did not significantly differ from the ATG group (i score at 0.08 ± 0.28, ci score at 0.31 ± 0.48 and ct score at 0.54 ± 0.52). The mesangial matrix increase was not different in the two groups (mm score at 0.31 ± 0.48 in the anti-IL2R group *vs* 0.23 ± 0.60 in the ATG group). C4d deposition was detected in none of the biopsies. Results are shown in **Table 3**.

**Table 3: Histological analysis of biopsies performed at 3-months post-transplantation in recipients from cDCD donors depending on the induction they received.**
Biopsies were performed in 20 recipients of the anti-IL2R group and 13 recipients of the ATG group. t score was significantly higher in the anti-IL2R group compared to ATG group ($p < 0.05$).

| Biopsy performed at 3 months Banff Score | anti-IL2R (n=20) | ATG (n=13) | p |
|---|---|---|---|
| g | 0.30 ± 0.47 | 0.15 ± 0.38 | ns |
| i | 0.26 ± 0.56 | 0.08 ± 0.28 | ns |
| t | 0.50 ± 0.89 | 0.00 ± 0.00 | <0.05 |
| v | 0.05 ± 0.22 | 0.00 ± 0.00 | ns |
| cpt | 0.20 ± 0.52 | 0.00 ± 0.00 | ns |
| cg | 0.00 ± 0.00 | 0.00 ± 0.00 | ns |
| ci | 0.60 ± 0.68 | 0.31 ± 0.48 | ns |
| ct | 0.60 ± 0.68 | 0.54 ± 0.52 | ns |
| cv | 1.05 ± 0.89 | 0.70 ± 0.82 | ns |
| ah | 0.95 ± 1.08 | 0.77 ± 1.01 | ns |
| mm | 0.31 ± 0.48 | 0.23 ± 0.60 | ns |
| C4d | 0.00 ± 0.00 | 0.00 ± 0.00 | ns |

*cDCD: controlled deceased donation after cardiocirculatory death, anti-IL2R: anti-IL2R-receptor antibodies, ATG: antithymocyte globulin, ns: non-significant.*

v- Survival

The only graft loss being due to the only death observed at day 100 in the ATG group, the survival of patients and grafts were identical: 100% at 1 year in the anti-IL2R group *vs* 95.7% in the ATG group, without significant difference as shown in **Figure 3**. The only patient death occurred after the occurrence of a multimestastatic adenocarcinoma.

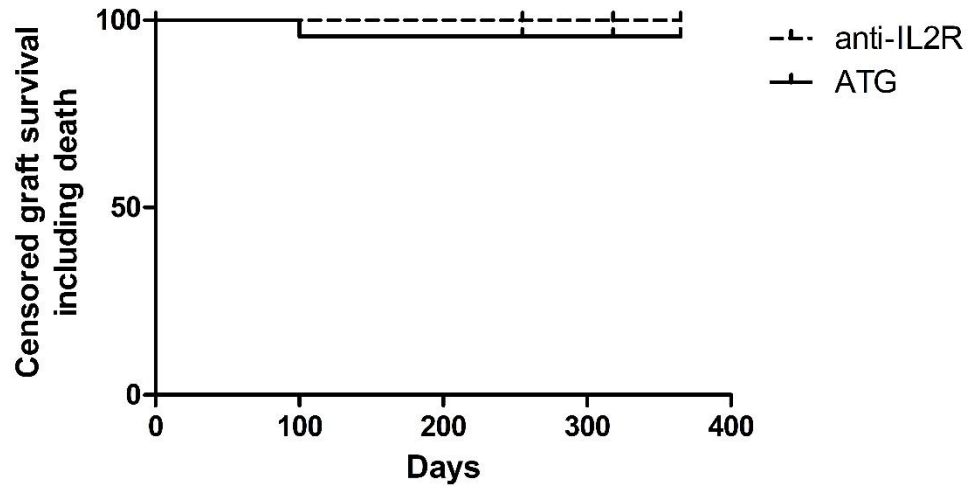


**Figure 3: One-year censored graft survival (including death) of recipients from cDCD donors depending on induction therapy.**
The only graft loss during the first-year post-transplantation was due to the death of a patient at day 100 in the ATG group. The survival was not statistically different between the two groups.

*cDCD: controlled deceased donation after cardiocirculatory death, anti-IL2R: anti-IL2R-receptor antibodies, ATG: antithymocyte globulin*

vi- Infectious complications

There was no significant difference in the occurrence of CMV or BK virus related infectious complications during the first-year post-transplantation with respectively in the anti-IL2R and ATG groups: 4% (1/23) *vs* 17% (4/23) of CMV infection, 4% (1/23) *vs* 0% (0/23) of CMV disease, 26% (6/23) *vs* 35% (8/23) of BK virus viremia and 9% (2/23) *vs* 4% (1/23) of BK virus nephropathy. However, the rate of other infections requiring hospitalization during the first-year post-transplantation was lower in the anti-IL2R group compared to the ATG group: 17% (4/23) *vs* 48% (11/23) respectively, $p < 0.05$.

vii- Initial stay duration

The initial inpatient stay duration did not differ between the two groups: 11.9 ± 5.7 days in case of anti-IL2R induction *vs* 11.0 ± 4.5 days in case of ATG induction.

All main outcomes are summarized in **Table 4**.

**Table 4: Recipients outcomes during the first-year after kidney transplantation from cDCD donors depending on immunosuppressive induction.**

| | anti-IL2R (n=23) | ATG (n=23) | p |
|---|---|---|---|
| Delayed graft function (%) | 4 (20) | 2 (11) | ns |
| Slow graft function (%) | 7 (37) | 9 (43) | ns |
| Glomerular filtration rate (ml/min/1.73m$^2$) | | | |
| at 3 months | 49 ± 19 | 50 ± 19 | ns |
| at 6 months | 53 ± 19 | 49 ± 18 | ns |
| at 12 months | 58 ± 18 | 46 ± 20 | <0.05 |
| Proteinuria (g/g of creatininuria) | | | |
| at 3 months | 0.23 ± 0.28 | 0.58 ± 1.14 | ns |
| at 6 months | 0.26 ± 0.29 | 0.42 ± 0.55 | ns |
| at 12 months | 0.15 ± 0.17 | 0.69 ± 2.00 | ns |
| Proven or suspected acute cellular rejection (%) | 2 (9) | 2 (9) | ns |
| Acute cellular rejection (%) | 0 (0) | 1 (4) | ns |
| Borderline acute cellular rejection (%) | 2 (9) | 1 (4) | ns |
| One-year patient censored survival (%) | 100 | 95.7 | ns |
| One-year graft censored survival including death (%) | 100 | 95.7 | ns |
| Infectious complications | | | |
| CMV infection (%) | 1 (4) | 4 (17) | ns |
| CMV disease (%) | 1 (4) | 0 (0) | ns |
| BK virus viremia (%) | 6 (26) | 8 (35) | ns |
| BK virus nephropathy (%) | 2 (9) | 1 (4) | ns |
| Other infections requiring hospitalization | 4 (17) | 11 (48) | <0.05 |
| Initial inpatient stay (days) | 11.9 ± 5.7 | 11.0 ± 4.5 | ns |

*cDCD: controlled deceased donation after cardiocirculatory death, anti-IL2R: anti-IL2R-receptor antibodies, ATG: antithymocyte globulin, CMV: cytomegalovirus, EBV: Epstein Barr virus, ns: non-significant.*

## Discussion

This is the first French study comparing anti-IL2R *vs* ATG immunosuppressive induction in kidney transplantation after cDCD. Characteristics of the 23 donors included in our study are similar to those of donors from other European cohorts[4,9,17].

In our work, the DGF rate was not different depending on whether their recipients were induced by anti-IL2R (20%) or by ATG (11%), suggesting that anti-IL2R induction with early CNI introduction has little impact on graft function recovery after cDCD. These results are consistent with the work of Ruiz-Martínez *et al.* who compared grafts from different cDCD donors[16]. The DGF rate that we report, lower than those reported by other European teams[4,9,16,17] and the absence of graft primary non-function in our study could have several explanations. On the one hand the use of NRP and perfusion machines has been systematic as recommended by the French Biomedicine Agency and it has been shown that these techniques limit the occurrence of IRI which are responsible for DGF in case of DCD[8,18]. On the other hand, mean cold ischemia time that we report is short and its duration has been reported as a DGF predictive factor[17]. The cold ischemia time minimization and the use of paired kidneys from the same donor strengthen our results by limiting potential confounding bias related to donor pre-treatment or to harvesting or transport conditions. For the relevance of this analysis we excluded pre-emptive transplantations. However, when we study the occurrence of SGF as a criterion for graft function recovery, including these patients, the lack of difference persists between the two groups (37% in the anti-IL2R group *vs* 43% in the ATG group), suggesting again a weak impact of early CNI introduction associated with anti-IL2R on the graft function recovery.

Graft function was not different between anti-IL2R and ATG groups during the first-year post-transplantation, whether it was measured by GFR or proteinuria. There was also no one-year graft survival difference. Anti-IL2R induction therefore does not appear as being associated in the short and medium term with a poorer graft function in recipients from cDCD donors, as suggested by Ruiz-Martínez *et al.* during a shorter follow-up time[16]. The poorer renal function reported at 12 months in the ATG group may be related to the greater number of HLA mismatches observed in this group, the latter being associated with a poorer renal prognosis and with the appearance of anti-HLA antibodies responsible for later graft failure[19,20]. Furthermore, the excellent one-year graft survival rate that we observe could be related to the systematic use of NRP and perfusion machines. Indeed, those techniques are associated with a better transplantation medium-term prognosis after DCD[10,11,18] and the inhomogeneity of their use in other countries could explain lower graft survivals reported[6].

Occurrence of acute cellular or borderline rejection did not differ at one year in both study groups. This result is consistent with the low-immunological risk of patients likely to receive a cDCD donor graft and could justify an anti-IL2R immunosuppressive induction in these patients, as recommended in case of transplantation after DBD[14].

On graft biopsies performed at 3-months post-transplantation, we did not observe any difference in Banff classification analysis except for a higher tubulitis t-score in the anti-IL2R group. In the absence of interstitial inflammation (i-score), the interpretation of this result should be cautious. Indeed, these 2 scores are most often considered conjointly in the diagnostic categories of the Banff classification[21]. Moreover, they are mainly associated with cellular rejection injuries[21] while we do not

show in our study any difference in the occurrence of acute cellular or borderline rejection between the two groups. Finally, injuries induced by ischemia-reperfusion are mostly fibrosis in the medium term[22]. Therefore, tubulitis that we observe at 3 months seems unlikely to be related to the induction impact on IRI.

Patient one-year survival was similar in both groups. Nevertheless, although there was no difference between the 2 groups regarding BK virus or CMV related infections, the number of other infections requiring hospitalization was significantly lower in the anti-IL2R group than in the ATG group (17% *vs* 48% respectively). The association of ATG with an increased infectious risk is described in other studies[23] and is the basis of recommendations limiting its use as induction in low-immunological-risk patients[14]. ATG induction has also been associated in other studies with a significant rate of neoplasms in the medium term[24]. Moreover, this induction exposes patients to long-lasting immunodepletion, in particular to a $CD4^+$ T cells low count that may persist well beyond the first year, as it has been reported by Longuet *et al.*[25]. This long-term lymphocytopenia has been shown as a risk factor for infectious complications, neoplasms and excess mortality[26]. Based on these observations and our results, this could also be a barrier to ATG use in transplant recipients from cDCD donors.

Our work has some limitations. First, the number of patients analyzed is small. The use of cDCD donors is a relatively recent practice in our inclusion centers and the inclusion of paired kidneys from the same donor that makes the strength of our work was exhaustive, not allowing us to include more patients. Expanding the study to more centers would be necessary to confirm our results. In addition, many confounding factors that were not identified in our work can have an impact on the data recorded at distance from transplantation, especially those related to the

recipient such as doses and modifications of maintenance immunosuppression. Although the two recipient groups are comparable in their initial characteristics, taking those factors into account would allow a better long-term analysis of initial induction consequences. At last, induction was not randomly assigned to patients. The predominance of anti-IL2R induction in one of the three centers (Tours) could be a selection bias. Only a well conducted prospective randomized study would allow to overcome this.

As a conclusion**,** we did not show any graft function difference after cDCD whether the recipients received an induction by anti-IL2R or by ATG, both in terms of immediate graft recovery and one-year graft function evolution. This result and the infectious burden associated with ATG may lead to a change in current induction recommendations in these patients.

## References


1. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int.* 1996;50(1):235–242.
2. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* 2011;11(10):2093–2109.
3. Rostaing L. [Renal transplantation]. *Nephrol. Ther.* 2017;13(6S):6S25-26S29.
4. Summers DM, Watson CJE, Pettigrew GJ, et al. Kidney donation after cardiocirculatory death (DCD): state of the art. *Kidney Int.* 2015;88(2):241–249.
5. Miñambres E, Rubio JJ, Coll E, Domínguez-Gil B. Donation after cardiocirculatory death and its expansion in Spain. *Curr. Opin. Organ Transplant.* 2018;23(1):120–129.
6. Lomero M, Gardiner D, Coll E, et al. Donation after cardiocirculatory death today: an updated overview of the European landscape. *Transpl. Int.* 2019;tri.13506.
7. Thuong M, Ruiz A, Evrard P, et al. New classification of donation after cardiocirculatory death donors definitions and terminology. *Transpl. Int.* 2016;29(7):749–759.
8. Morrissey PE, Monaco AP. Donation After Circulatory Death: Current Practices, Ongoing Challenges, and Potential Improvements. 2013;97(3):7.
9. Schaapherder A, Wijermars LGM, de Vries DK, et al. Equivalent Long-term Transplantation Outcomes for Kidneys Donated After Brain Death and Cardiac Death: Conclusions From a Nationwide Evaluation. *EClinicalMedicine*. 2018;4–5:25–31.
10. Miñambres E, Rubio JJ, Coll E, Domínguez-Gil B. Donation after cardiocirculatory death and its expansion in Spain. *Curr. Opin. Organ Transplant.* 2018;23(1):120–129.
11. Río F del, Andrés A, Padilla M, et al. Kidney transplantation from donors after uncontrolled cardiocirculatory death: the Spanish experience. *Kidney Int.* 2019;95(2):420–428.
12. van Heurn LWE, Talbot D, Nicholson ML, et al. Recommendations for donation after cardiocirculatory death kidney transplantation in Europe. *Transpl. Int.* 2016;29(7):780–789.
13. Hill P, Cross NB, Barnett ANR, Palmer SC, Webster AC. Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. *Cochrane Database Syst. Rev.* 2017;1:CD004759.
14. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* 2009;9 Suppl 3:S1-155.
15. Yao X, Weng G, Wei J, Gao W. Basiliximab induction in kidney transplantation with donation after cardiac death donors. *Exp. Ther. Med.* 2016;11(6):2541–2546.
16. Ruiz-Martínez L, De-Cos-Gómez M, Valero-San-Cecilio R, et al. Usefulness of Delayed Introduction of Tacrolimus in Kidney Transplants Using Type-III Donors After Circulatory Death. *Transplant. Proc.* 2019;51(2):337–340.
17. Portolés JM, Pérez-Sáez MJ, López-Sánchez P, et al. Kidney transplant from controlled donors following cardiocirculatory death: Results from the GEODAS-3 multicentre study. *Nefrol. Publicacion Of. Soc. Espanola Nefrol.* 2019;39(2):151–159.

18.Moers C, Smits JM, Maathuis M-HJ, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. *N. Engl. J. Med.* 2009;360(1):7–19.
19.Lim WH, Chadban SJ, Clayton P, et al. Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. *Clin. Transplant.* 2012;26(4):E428-437.
20.Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am. J. Transplant. Off. J. Am. Soc. Transplant. Am. Soc. Transpl. Surg.* 2012;12(5):1157–1167.
21.Roufosse C, Simmonds N, Clahsen-van Groningen M, et al. A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology. *Transplantation*. 2018;102(11):1795–1814.
22.Salvadori M, Rosso G, Bertoni E. Update on ischemia-reperfusion injury in kidney transplantation: Pathogenesis and treatment. *World J. Transplant.* 2015;5(2):52–67.
23.Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation. *N. Engl. J. Med.* 2006;355(19):1967–1977.
24.Wang K, Xu X, Fan M. Induction therapy of basiliximab versus antithymocyte globulin in renal allograft: a systematic review and meta-analysis. *Clin. Exp. Nephrol.* 2018;22(3):684–693.
25.Longuet H, Sautenet B, Gatault P, et al. Risk factors for impaired CD4+ T-cell reconstitution following rabbit antithymocyte globulin treatment in kidney transplantation. *Transpl. Int. Off. J. Eur. Soc. Organ Transplant.* 2014;27(3):271–279.
26.Ducloux D, Courivaud C, Bamoulid J, et al. Prolonged CD4 T Cell Lymphopenia Increases Morbidity and Mortality after Renal Transplantation. *J. Am. Soc. Nephrol. JASN*. 2010;21(5):868–875.

## Conclusion

Il s'agit de la première étude française comparant une immunosuppression d'induction par anti-IL2R *vs* SAL chez des receveurs de greffons rénaux issus d'un même donneur DDACc. Les taux de RRF et de reprise lente de fonction du greffon observés n'étaient pas différents selon l'induction reçue, suggérant que l'induction par anti-IL2R avec introduction précoce des ICN n'a que peu d'impact sur la reprise de fonction de ces greffons. Nous n'avons pas non plus constaté de différence majeure de fonction des greffons au cours de la première année post-transplantation selon l'induction reçue, que ce soit en termes de débit de filtration glomérulaire (DFG) ou de protéinurie. De même, il n'y avait pas de différence de survie à 1 an de ces greffons, ni de survenue de rejet aigu cellulaire ou borderline indiquant qu'à court et moyen terme l'induction par anti-IL2R ne semble pas associée à un moins bon pronostic rénal chez ces patients. Le meilleur DFG à 1 an observé dans le groupe anti-IL2R est intéressant mais son interprétation doit rester prudente en l'absence de prise en compte de facteurs liés au receveur tels que les doses ou modifications de l'immunosuppression d'entretien. Sur les biopsies de greffons réalisées à 3 mois post-transplantation, la seule différence observée était un score de tubulite plus important dans le groupe anti-IL2R, peu probablement en rapport avec l'induction. La survie des patients à 1 an était similaire dans les deux groupes. Néanmoins, bien qu'il n'y ait pas de différence entre les deux groupes en termes d'infections liées au BK virus ou au CMV, le nombre d'autres infections ayant nécessité une hospitalisation était significativement plus élevé chez les patients induits par SAL.

En conclusion, nous n'avons pas montré dans cette étude de différence de fonction des greffons issus de DDACc selon que leurs receveurs ont été induits par anti-IL2R ou SAL, tant en termes de reprise immédiate de fonction post-transplantation que

d’évolution à 1 an. Ce résultat et le surrisque infectieux associé au SAL mis en évidence pourraient justifier un changement des recommandations d’induction chez ces patients.

## Perspectives

La pratique en pleine expansion de la transplantation rénale à partir de donneurs DDACc permet de faire face à la pénurie d’organes et d’améliorer l’accès à la greffe de nombreux patients. Le nombre croissant de centres français participant à ce programme et les jalons posés par notre étude ouvrent le champ à de multiples perspectives, notamment à celle d’une étude prospective randomisée comparant les deux inductions de façon plus robuste. Le développement auquel nous travaillons actuellement d’une base de travail collaborative permettant l’analyse des données des receveurs en les confrontant à celles de leurs donneurs nous parait également indispensable à l’évaluation et l’amélioration des pratiques.

**Vu, le Directeur de Thèse**

**Vu, le Doyen**
**De la Faculté de Médecine de Tours**
**Tours, le**

# Goin Nicolas

44 pages – 4 tableaux – 3 figures


**Résumé :**

**Introduction :** Nous avons analysé l'évolution de la fonction des greffons issus d'un même donneur décédé après arrêt cardiocirculatoire contrôlé (DDACc) lorsqu'un des deux receveurs a reçu une induction par anticorps anti-IL2-récepteur (anti-IL2R) et l'autre par sérum antilymphocytaire (SAL), induction actuellement recommandée en raison de la crainte de reprise retardée de fonction du greffon (RRF). **Matériel et Méthodes :** Cette étude rétrospective a été menée aux CHU de Tours, Nantes et Poitiers de novembre 2015 à décembre 2018. Nous avons comparé 23 receveurs de greffons issus de DDACc induits par anti-IL2R aux 23 receveurs du rein adelphe ayant reçu une induction par SAL. Nous avons analysé dans ces deux groupes la survenue de RRF, le débit de filtration glomérulaire (DFG) et la protéinurie à 3, 6 et 12 mois post-transplantation ainsi que la survenue d'infections sévères à 1 an. **Résultats :** Nous avons observé 20% (4/20) de RRF dans le groupe anti-IL2R *vs* 11% (2/18) dans le groupe SAL (ns). La fonction rénale à 3 et 6 mois n'était pas significativement différente selon l'induction. Elle était meilleure dans le groupe anti-IL2R que dans le groupe SAL à 12 mois (DFG à 58 ± 18 *vs* 46 ± 20 mL/min/1,73 $m^2$, $p < 0,05$). La protéinurie n'était pas significativement différente à 3, 6 et 12 mois. Le taux d'infections nécessitant une hospitalisation à 1 an était inférieur dans le groupe anti-IL2R comparé au groupe SAL : 17% (4/23) *vs* 48% (11/23), $p < 0.05$. **Conclusion :** Nous n'avons pas observé de différence d'évolution de fonction du greffon rénal chez des patients transplantés à partir d'un DDACc induits par anti-IL2R comparés aux receveurs du rein adelphe induits par SAL. Cela et le surrisque infectieux associé au SAL pourraient inciter à un changement des recommandations.



**Mots clés :** Transplantation rénale, Donneur décédé après arrêt cardiocirculatoire contrôlé, Anti-IL2-récepteur, Sérum antilymphocytaire


**Jury :**
Président du Jury : Professeur Jean-Michel HALIMI
Directeur de thèse : Professeur Matthias BUCHLER
Membres du Jury :
Professeur Jacques DANTAL
Professeur Antoine THIERRY
Docteur Philippe GATAULT
Docteur Jean-Christophe VENHARD

Date de soutenance : 14 octobre 2014