



# Utilisation du ruxolitinib dans la GVH aigüe cortico-résistante de l'enfant, une étude multicentrique du groupe pédiatrique de la SFGM-TC

Louise Laisné

## ► To cite this version:

Louise Laisné. Utilisation du ruxolitinib dans la GVH aigüe cortico-résistante de l'enfant, une étude multicentrique du groupe pédiatrique de la SFGM-TC. Sciences du Vivant [q-bio]. 2019. dumas-03276929

**HAL Id: dumas-03276929**

**<https://dumas.ccsd.cnrs.fr/dumas-03276929>**

Submitted on 2 Jul 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1**  
*sous le sceau de l'Université Bretagne Loire*

Thèse en vue du  
**DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE**

présentée par

**Louise LAISNÉ**

Née le 28-05-1990 à Aix en Provence

---

**Utilisation du  
ruxolitinib dans la  
GVH aigüe cortico-  
résistante de  
l'enfant, une étude  
multicentrique du  
groupe pédiatrique  
de la SFGM-TC**

**Thèse soutenue à Rennes**

**Le 17-04-2019**

devant le jury composé de :

**Thierry LAMY DE LA CHAPELLE**

PU-PH, Hématologie, Hôpital Pontchaillou, Rennes,  
*Président du jury*

**Virginie GANDEMER**

PU-PH, Onco-hématologie pédiatrique, Hôpital Sud,  
Rennes, *Directrice de thèse*

**Patrick PLADYS**

PU-PH, Néonatalogie, Hôpital Sud, Rennes,  
*examineur*

**Guillaume ROBERT**

PH, équipe ressource régionale de SPP, Pédiatrie,  
CHU Rennes, *examineur*

## Professeurs des Universités - Praticiens Hospitaliers

| Nom Prénom                                                   | Sous-section CNU                                                       |
|--------------------------------------------------------------|------------------------------------------------------------------------|
| ANNE-GALIBERT Marie-Dominique                                | Biochimie et biologie moléculaire                                      |
| BARDOU-JACQUET Edouard                                       | Gastroentérologie; hépatologie; addictologie                           |
| BELAUD-ROTUREAU Marc-Antoine                                 | Histologie; embryologie et cytogénétique                               |
| BELLISSANT Eric                                              | Pharmacologie fondamentale; pharmacologie clinique; addictologie       |
| BELOEIL Hélène                                               | Anesthésiologie-réanimation; médecine d'urgence                        |
| BENDAVID Claude                                              | Biochimie et biologie moléculaire                                      |
| BENSALAH Karim                                               | Urologie                                                               |
| BEUCHEE Alain                                                | Pédiatrie                                                              |
| BONAN Isabelle                                               | Médecine physique et de réadaptation                                   |
| BONNET Fabrice                                               | Endocrinologie, diabète et maladies métaboliques; gynécologie médicale |
| BOUDJEMA Karim                                               | Chirurgie générale                                                     |
| BOUGET Jacques<br>Professeur des Universités en surnombre    | Thérapeutique; médecine d'urgence; addictologie                        |
| BOUGUEN Guillaume                                            | Gastroentérologie; hépatologie; addictologie                           |
| BOURGUET Patrick<br>Professeur des Universités Emérite       | Biophysique et médecine nucléaire                                      |
| BRASSIER Gilles                                              | Neurochirurgie                                                         |
| BRETAGNE Jean-François<br>Professeur des Universités Emérite | Gastroentérologie; hépatologie; addictologie                           |
| BRISOT Pierre<br>Professeur des Universités Emérite          | Gastroentérologie; hépatologie; addictologie                           |
| CARRE François                                               | Physiologie                                                            |
| CATROS Véronique                                             | Biologie cellulaire                                                    |
| CATTOIR Vincent                                              | Bactériologie-virologie; hygiène hospitalière                          |
| CHALES Gérard<br>Professeur des Universités Emérite          | Rhumatologie                                                           |
| CORBINEAU Hervé                                              | Chirurgie thoracique et cardiovasculaire                               |

|                                                                        |                                                                         |
|------------------------------------------------------------------------|-------------------------------------------------------------------------|
| CUGGIA Marc                                                            | Biostatistiques, informatique médicale et technologies de communication |
| DARNAULT Pierre                                                        | Anatomie                                                                |
| DAUBERT Jean-Claude<br>Professeur des Universités Emérite              | Cardiologie                                                             |
| DAVID Véronique                                                        | Biochimie et biologie moléculaire                                       |
| DAYAN Jacques<br>(Professeur associé)                                  | Pédopsychiatrie; addictologie                                           |
| DE CREVOISIER Renaud                                                   | Cancérologie; radiothérapie                                             |
| DECAUX Olivier                                                         | Médecine interne; gériatrie et biologie du vieillissement; addictologie |
| DESRUES Benoît                                                         | Pneumologie; addictologie                                               |
| DEUGNIER Yves<br>Professeur des Universités en surnombre + Consultanat | Gastroentérologie; hépatologie; addictologie                            |
| DONAL Erwan                                                            | Cardiologie                                                             |
| DRAPIER Dominique                                                      | Psychiatrie d'adultes; addictologie                                     |
| DUPUY Alain                                                            | Dermato-vénéréologie                                                    |
| ECOFFEY Claude                                                         | Anesthésiologie-réanimation; médecine d'urgence                         |
| EDAN Gilles                                                            | Neurologie                                                              |
| FERRE Jean Christophe                                                  | Radiologie et imagerie Médecine                                         |
| FEST Thierry                                                           | Hématologie; transfusion                                                |
| FLECHER Erwan                                                          | Chirurgie thoracique et cardiovasculaire                                |
| FREMOND Benjamin                                                       | Chirurgie infantile                                                     |
| GANDEMER Virginie                                                      | Pédiatrie                                                               |
| GANDON Yves                                                            | Radiologie et imagerie Médecine                                         |
| GANGNEUX Jean-Pierre                                                   | Parasitologie et mycologie                                              |
| GARIN Etienne                                                          | Biophysique et médecine nucléaire                                       |
| GAUVRIT Jean-Yves                                                      | Radiologie et imagerie Médecine                                         |
| GODEY Benoît                                                           | Oto-rhino-laryngologie                                                  |

|                                                                              |                                                                         |
|------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| GUGGENBUHL Pascal                                                            | Rhumatologie                                                            |
| GUIGUEN Claude<br>Professeur des Universités Emérite                         | Parasitologie et mycologie                                              |
| GUILLÉ François                                                              | Urologie                                                                |
| GUYADER Dominique                                                            | Gastroentérologie; hépatologie; addictologie                            |
| HAEGELEN Claire                                                              | Anatomie                                                                |
| HOUOT Roch                                                                   | Hématologie; transfusion                                                |
| HUSSON Jean-Louis<br>Professeur des Universités Emérite                      | Chirurgie orthopédique et traumatologique                               |
| HUTEN Denis<br>Professeur des Universités Emérite                            | Chirurgie orthopédique et traumatologique                               |
| JEGO Patrick                                                                 | Médecine interne; gériatrie et biologie du vieillissement; addictologie |
| JEGOUX Franck                                                                | Oto-rhino-laryngologie                                                  |
| JOUNEAU Stéphane                                                             | Pneumologie; addictologie                                               |
| KAYAL Samer                                                                  | Bactériologie-virologie; hygiène hospitalière                           |
| KERBRAT Pierre, RETRAITE                                                     | Cancérologie; radiothérapie                                             |
| LAMY DE LA CHAPELLE Thierry                                                  | Hématologie; transfusion                                                |
| LAVIOLE Bruno                                                                | Pharmacologie fondamentale; pharmacologie clinique; addictologie        |
| LAVOUE Vincent                                                               | Gynécologie-obstétrique; gynécologie médicale                           |
| LE BRETON Hervé                                                              | Cardiologie                                                             |
| LE GUEUT Mariannick<br>Professeur des Universités en surnombre + consultanat | Médecine légale et droit de la santé                                    |
| LE TULZO Yves                                                                | Réanimation; médecine d'urgence                                         |
| LECLERCQ Christophe                                                          | Cardiologie                                                             |
| LEDERLIN Mathieu                                                             | Radiologie et imagerie Médecine                                         |
| LEGUERRIER Alain<br>Professeur des Universités Emérite                       | Chirurgie thoracique et cardiovasculaire                                |
| LEJEUNE Florence                                                             | Biophysique et médecine nucléaire                                       |
| LEVEQUE Jean                                                                 | Gynécologie-obstétrique; gynécologie médicale                           |

|                                                               |                                                                  |
|---------------------------------------------------------------|------------------------------------------------------------------|
| LIEVRE Astrid                                                 | Gastroentérologie; hépatologie; addictologie                     |
| MABO Philippe                                                 | Cardiologie                                                      |
| MAHE Guillaume                                                | Chirurgie vasculaire ; médecine vasculaire                       |
| MALLEDANT Yannick<br>Professeur des Universités Emérite       | Anesthésiologie-réanimation; médecine d'urgence                  |
| MENER Eric<br>(Professeur associé)                            | Médecine générale                                                |
| MEUNIER Bernard                                               | Chirurgie digestive                                              |
| MICHELET Christian<br>Professeur des Universités en surnombre | Maladies infectieuses; maladies tropicales                       |
| MOIRAND Romain                                                | Gastroentérologie; hépatologie; addictologie                     |
| MORANDI Xavier                                                | Anatomie                                                         |
| MOREL Vincent<br>(Professeur associé)                         | Epistémologie clinique                                           |
| MOSSER Jean                                                   | Biochimie et biologie moléculaire                                |
| MOURIAUX Frédéric                                             | Ophtalmologie                                                    |
| MYHIE Didier<br>(Professeur associé )                         | Médecine générale                                                |
| ODENT Sylvie                                                  | Génétique                                                        |
| OGER Emmanuel                                                 | Pharmacologie fondamentale; pharmacologie clinique; addictologie |
| PARIS Christophe                                              | Médecine et santé au travail                                     |
| PERDRIGER Aleth                                               | Rhumatologie                                                     |
| PLADYS Patrick                                                | Pédiatrie                                                        |
| RAVEL Célia                                                   | Histologie; embryologie et cytogénétique                         |
| REVEST Matthieu                                               | Maladies infectieuses; maladies tropicales                       |
| RICHARD de LATOUR Bertrand<br>(Professeur associé)            | Chirurgie thoracique et cardiovasculaire                         |
| RIFFAUD Laurent                                               | Neurochirurgie                                                   |
| RIOUX-LECLERCQ Nathalie                                       | Anatomie et cytologie pathologiques                              |
| ROBERT-GANGNEUX Florence                                      | Parasitologie et mycologie                                       |

|                                                   |                                                                         |
|---------------------------------------------------|-------------------------------------------------------------------------|
| ROPARS Mickaël                                    | Chirurgie orthopédique et traumatologique                               |
| SAINT-JALMES Hervé                                | Biophysique et médecine nucléaire                                       |
| SAULEAU Paul                                      | Physiologie                                                             |
| SEGUIN Philippe                                   | Anesthésiologie-réanimation; médecine d'urgence                         |
| SEMANA Gilbert                                    | Immunologie                                                             |
| SIPROUDHIS Laurent                                | Gastroentérologie; hépatologie; addictologie                            |
| SOMME Dominique                                   | Médecine interne; gériatrie et biologie du vieillissement; addictologie |
| SOULAT Louis<br>(Professeur associé)              | Thérapeutique; médecine d'urgence; addictologie                         |
| SULPICE Laurent                                   | Chirurgie générale                                                      |
| TADIÉ Jean Marc                                   | Réanimation; médecine d'urgence                                         |
| TARTE Karin                                       | Immunologie                                                             |
| TATTEVIN Pierre                                   | Maladies infectieuses; maladies tropicales                              |
| TATTEVIN-FABLET Françoise<br>(Professeur associé) | Médecine générale                                                       |
| THIBAUT Ronan                                     | Nutrition                                                               |
| THIBAUT Vincent                                   | Bactériologie-virologie; hygiène hospitalière                           |
| THOMAZEAU Hervé                                   | Chirurgie orthopédique et traumatologique                               |
| TORDJMAN Sylvie                                   | Pédopsychiatrie; addictologie                                           |
| VERHOYE Jean-Philippe                             | Chirurgie thoracique et cardiovasculaire                                |
| VERIN Marc                                        | Neurologie                                                              |
| VIEL Jean-François                                | Epidémiologie, économie de la santé et prévention                       |
| VIGNEAU Cécile                                    | Néphrologie                                                             |
| VIOLAS Philippe                                   | Chirurgie infantile                                                     |
| WATIER Eric                                       | Chirurgie plastique, reconstructrice et esthétique; brûlologie          |
| WODEY Eric                                        | Anesthésiologie-réanimation; médecine d'urgence                         |

## Maîtres de Conférence des Universités - Praticiens Hospitaliers

| Nom Prénom                                                                     | Sous-section CNU                                                |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------|
| ALLORY Emmanuel<br>(Maître de conférence associé des universités de MG)        | Médecine générale                                               |
| AME-THOMAS Patricia                                                            | Immunologie                                                     |
| AMIOT Laurence (Baruch)                                                        | Hématologie; transfusion                                        |
| ANSELMi Amédéo                                                                 | Chirurgie thoracique et cardiovasculaire                        |
| BEGUE Jean-Marc                                                                | Physiologie                                                     |
| BERTHEUIL Nicolas                                                              | Chirurgie plastique, reconstructrice et esthétique ; brûlologie |
| BOUSSEMART Lise                                                                | Dermato-vénéréologie                                            |
| CABILLIC Florian                                                               | Biologie cellulaire                                             |
| CAUBET Alain                                                                   | Médecine et santé au travail                                    |
| CHHOR-QUENIART Sidonie<br>(Maître de conférence associé des universités de MG) | Médecine générale                                               |
| DAMERON Olivier                                                                | Informatique                                                    |
| DE TAYRAC Marie                                                                | Biochimie et biologie moléculaire                               |
| DEGEILH Brigitte                                                               | Parasitologie et mycologie                                      |
| DROITCOURT Catherine                                                           | Dermato-vénéréologie                                            |
| DUBOURG Christèle                                                              | Biochimie et biologie moléculaire                               |
| DUGAY Frédéric                                                                 | Histologie; embryologie et cytogénétique                        |
| EDELINE Julien                                                                 | Cancérologie; radiothérapie                                     |
| FIQUET Laure<br>(Maître de conférence associé des universités de MG)           | Médecine générale                                               |

| Nom Prénom                                                              | Sous-section CNU                                                 |
|-------------------------------------------------------------------------|------------------------------------------------------------------|
| GARLANTEZEC Ronan                                                       | Epidémiologie, économie de la santé et prévention                |
| GOUIN Isabelle épouse THIBAUT                                           | Hématologie; transfusion                                         |
| GUILLET Benoit                                                          | Hématologie; transfusion                                         |
| JAILLARD Sylvie                                                         | Histologie; embryologie et cytogénétique                         |
| KALADJI Adrien                                                          | Chirurgie vasculaire; médecine vasculaire                        |
| LAVENU Audrey                                                           | Sciences physico-chimiques et technologies pharmaceutiques       |
| LE GALL François                                                        | Anatomie et cytologie pathologiques                              |
| LEMAITRE Florian                                                        | Pharmacologie fondamentale; pharmacologie clinique; addictologie |
| MARTINS Pedro Raphaël                                                   | Cardiologie                                                      |
| MATHIEU-SANQUER Romain                                                  | Urologie                                                         |
| MENARD Cédric                                                           | Immunologie                                                      |
| MOREAU Caroline                                                         | Biochimie et biologie moléculaire                                |
| MOUSSOUNI Fouzia                                                        | Informatique                                                     |
| NAUDET Florian                                                          | Thérapeutique ; médecine d'urgence ; addictologie                |
| PANGAULT Céline                                                         | Hématologie; transfusion                                         |
| RENAUT Pierrick<br>(maître de conférence associé des universités de MG) | Médecine générale                                                |
| ROBERT Gabriel                                                          | Psychiatrie d'adultes; addictologie                              |
| SCHNELL Frédéric                                                        | Physiologie                                                      |

**Nom Prénom****Sous-section CNU**

THEAUDIN Marie épouse SALIOU

Neurologie

TURLIN Bruno

Anatomie et cytologie pathologiques

VERDIER Marie-Clémence  
(Lorne)Pharmacologie fondamentale; pharmacologie clinique;  
addictologie

ZIELINSKI Agata

## REMERCIEMENTS

### **À Monsieur le Professeur Thierry LAMY DE LA CHAPELLE**

Vous me faites l'honneur et le plaisir de présider ce jury de thèse. Veuillez recevoir par ce travail ma profonde et sincère reconnaissance.

### **À Madame le Professeur Virginie GANDEMER**

Vous m'avez fait l'honneur de diriger ce travail de thèse. Je vous remercie pour votre disponibilité et vos précieux conseils tout au long de ce travail. Je vous suis profondément reconnaissante pour votre encadrement ponctué de beaucoup de patience. Votre rigueur et pertinence ont suscité toute ma considération. Veuillez trouver dans ce travail toute ma gratitude ainsi que l'expression sincère de mon estime et ma reconnaissance.

### **À Monsieur le Professeur Patrick PLADYS**

Vous me faites l'honneur de juger ce travail. Je vous remercie de votre accueil et suis très honorée d'intégrer très prochainement votre équipe. Veuillez croire en l'assurance de ma respectueuse considération.

### **À Monsieur le Docteur Guillaume ROBERT**

Tu me fais l'honneur de juger ce travail. Je te remercie d'avoir accepté de faire partie de ce jury de thèse. Ta rigueur, ta grande capacité de réflexion (quelle que soit l'heure du jour ou de la nuit), ton enthousiasme et ta bonne humeur m'ont beaucoup apporté tout au long de mon internat. Merci également pour les moments de détente autour d'un tarot ou d'un brunch. Soit assuré de ma grande reconnaissance et de mon profond respect

### **Aux équipes de néonatalogie et de pédiatrie du CHU de Rennes**

Merci pour la richesse de l'enseignement que vous m'avez fourni. Merci pour ces quatre années d'internat à vos côtés, qui ont été on ne peut plus à la hauteur de mes attentes.

À l'équipe de néonatalogie soins intensifs pour m'avoir soutenue dans mes premiers pas d'interne.

À l'équipe d'onco-hématologie, pour les 6 mois sans aucun doute les plus intenses de mon internat. Merci pour tout ce que vous m'avez apporté médicalement et humainement. À Jacinthe pour ta spontanéité, ta curiosité et ton soutien. Merci à Rico pour les instants musicaux.

À l'équipe de réanimation néonatale, pour m'avoir permis de confirmer une passion pour la néonatalogie. À Nadia pour son écoute, pour les cours de pose KT sur cuisses de dinde, pour les soirées escalades (bonne excuse pour papoter). À Stéphanie pour tous les petits moments passés dans ton bureau, pour les restos indiens et toutes les soirées passées ensemble.

À l'équipe des nourrissons, pour m'avoir fait découvrir la grande polyvalence possible dans notre métier.

À l'équipe des grands enfants, une grande famille ! Je n'aurais jamais imaginé tant apprécier le travail auprès des ados, et c'est bien grâce à la belle énergie que vous y mettez . À Véro (maman) pour ta rigueur et ta douceur. À David (papa) pour ton soutien dans nos projets de réaménagement. À Morgane pour avoir été une confidente hors pair ! À Evelyne pour ta patience.

À l'équipe des urgences pédiatriques, pour la confiance qu'ils m'accordent dans ses derniers pas d'interne, sans jamais manquer de répondre à toutes les questions que je peux encore poser.

À l'équipe de le CASED, à Martine, pour le boulot difficile qu'ils font avec une grande bienveillance.

**À l'équipe de pédiatrie du CH de Lorient**, avec qui j'ai fait mes débuts en pédiatrie générale, et avec laquelle je travaillerai avec grand plaisir dans le futur.

**Aux pédiatres libéraux de St Brieuc**, Jean-François, Gilles et Joseph. Merci de m'avoir ouvert les yeux sur une toute autre façon d'exercer notre beau métier. Merci de m'avoir fait découvrir la richesse du travail en équipe auprès des familles que vous suivez.

**À mes co-internes et amis**. À Simon avec qui j'ai partagé une grande partie de mon internat, pour le meilleur et pour le pire, merci pour ton soutien informatique sans faille ! Valentine (Tite Chaiiise), superbe rencontre venue de Besançon, pour le congrès en jumpy et les beaux voyages, j'espère bien te voir en Bretagne prochainement. Mais aussi à Nico, Flora, Emmanuelle, Blandine, Mathilde (mon ptit Chénin) et Valentin, avec qui j'ai partagé cet internat de pédiatrie et bien d'autres bons moments. À Timothée, Lauriane, Hélène, Yasmine, que pour les bons moments !

**À mes amis de longue date**. Eulalie pour ton soutien depuis presque toujours. Sandrine pour les moments de rires, les voyages en Pompi, pour ton écoute et ton expérience. Les amis du groupe gastronomique, Noëlie, Florie (BBD), Mathieu, Mickaël et Julia pour les 6 ans d'externat passés avec vous et notre amitié qui dure malgré la distance. Bastien, mon ostéopathe préféré.

**À ma Famille**. Papa, pour m'avoir transmis cette belle vocation. Maman pour m'avoir toujours soutenue dans mes choix. Mes frères, Simon, Colin et Hugo que j'aime fort. Mes grands-parents pour leur amour et les belles valeurs qu'ils m'ont transmises. Marion pour être comme ma sœur. « Jacqueline » qui va bientôt agrandir la famille pour mon plus grand bonheur de future tata.

À Jean Yves et Capucine pour avoir répondu à mes questions les plus farfelues, pour m'avoir accueillie et soutenue dans les moments les plus durs de ces longues études. À Claude et Chantal pour être des supers tontons et tata.

À Léo...

## TABLE DES MATIÈRES

|                                                                                |           |
|--------------------------------------------------------------------------------|-----------|
| <b>Professeurs des Universités - Praticiens Hospitaliers .....</b>             | <b>2</b>  |
| <b>Maîtres de Conférence des Universités - Praticiens Hospitaliers.....</b>    | <b>7</b>  |
| <b>REMERCIEMENTS.....</b>                                                      | <b>10</b> |
| <b>TABLE DES MATIÈRES.....</b>                                                 | <b>13</b> |
| <b>TITRE .....</b>                                                             | <b>15</b> |
| <b>ABSTRACT .....</b>                                                          | <b>16</b> |
| <b>INTRODUCTION.....</b>                                                       | <b>16</b> |
| <b>PATIENTS AND METHODS .....</b>                                              | <b>17</b> |
| Patients.....                                                                  | 18        |
| <i>Diagnosis of Steroid-Refractory Acute GVHD and use of ruxolitinib .....</i> | <i>18</i> |
| <i>Treatment response .....</i>                                                | <i>18</i> |
| <i>Toxicity and tolerance assesement .....</i>                                 | <i>19</i> |
| <i>Statistics .....</i>                                                        | <i>19</i> |
| <b>RESULTS .....</b>                                                           | <b>19</b> |
| Patients.....                                                                  | 19        |
| <i>Organs involved .....</i>                                                   | <i>19</i> |
| <i>GVHD characteristics .....</i>                                              | <i>20</i> |
| <i>Prior management.....</i>                                                   | <i>20</i> |
| <i>Response.....</i>                                                           | <i>20</i> |
| Ruxolitinib dosing .....                                                       | 21        |
| Adverse effects .....                                                          | 22        |
| <b>DISCUSSION.....</b>                                                         | <b>22</b> |
| <b>REFERENCES .....</b>                                                        | <b>25</b> |

## LISTE DES ILLUSTRATIONS

|                                   |           |
|-----------------------------------|-----------|
| <b>FIGURE LEGENDS .....</b>       | <b>27</b> |
| <b>Table 1. ....</b>              | <b>28</b> |
| <b>Table 2. ....</b>              | <b>29</b> |
| <b>Table 3. ....</b>              | <b>30</b> |
| <b>Figure 1.....</b>              | <b>31</b> |
| <b>Figure 2.....</b>              | <b>32</b> |
| <b>Figure 3.....</b>              | <b>33</b> |
| <b>Supplemental Table 1. ....</b> | <b>34</b> |

# **RUXOLITINIB IN CHILDREN WITH STEROID REFRACTORY ACUTE GRAFT VERSUS HOST DISEASE: A MULTICENTER STUDY OF THE PEDIATRIC GROUP OF SFGM-TC**

SHORT TITLE: RUXOLITINIB IN PEDIATRIC GRAFT VERSUS HOST DISEASE.

Louise Laisne<sup>1</sup>, Benedicte Neven MD PhD<sup>2</sup>, Jean-Hugues Dalle MD PhD<sup>3</sup>, Claire Galambrun MD<sup>4</sup>, Maxime Esvan<sup>5</sup>, Cecile Renard MD<sup>6</sup>, Fanny Rialland MD<sup>7</sup>, Anne Sirvent MD<sup>8</sup>, Virginie Gandemer MD PhD<sup>1</sup> on behalf of the pediatric group of SFGM-TC.

1: Department of Pediatric Hematology and Oncology, University Hospital of Rennes, France.

2: Department of Pediatric Hematology-Immunology, Hospital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, INSERM, Paris, France.

3: Hemato-Immunology Department, Robert Debre Hospital, and Paris-Diderot University, Paris, France

4: Department of Pediatric Hematology and Oncology, Timone Enfants Hospital and Aix-Marseille University, Marseille, France

5: Clinical Investigation Center of Rennes, National Institute of Health and Scientific Research (CIC-INSERM 0203), Rennes, France.

6: Institute of Pediatric Hematology and Oncology, Hospices Civils de Lyon, Lyon, France.

7: Pediatric Hematology and Oncology Department, University Hospital, Nantes, France.

8: Pediatric Hematology and Oncology Department, University Hospital, Montpellier, France.

## ABSTRACT

We conducted a national multicenter retrospective study in France to evaluate efficacy and tolerance of ruxolitinib in children with steroid-refractory acute graft-versus-host disease (aGVHD) after allogeneic hematopoietic stem cell transplant. Patients were recruited from the 15 pediatric transplantation centers in France. Transplanted patients were eligible if they met the following criteria: aged  $\leq 18$  years at transplantation, receiving a myeloablative allogeneic haematopoietic stem cell transplant irrespective of the stem cell source, having an acute GVHD of grade  $\geq 2$  and treated with ruxolitinib for steroid refractory acute GVHD. Treatment failure was defined by the absence of improvement of aGVHD, deterioration of aGVHD in any organ by at least one stage, the development of acute GVHD manifestations in a previously unaffected organ, and the use of any additional agents to control the disease. Twenty-nine patients received ruxolitinib for steroid-refractory aGVHD. Six patients achieved a complete response at day 28 after the start of treatment but finally 19 patients (65.5%) achieved a CR with a median delay of 41 days (5 to 93 days). Two patients had a partial response. All patients who achieved CR or PR discontinued corticosteroid treatment. Eight patients showed treatment failure. Overall response rate was 72.4%. Twenty three of 29 patients were alive at a median follow-up of 685 days (177 to 1042 days) after the HSCT. Viral replication (including CMV, EBV and ADV) was observed in 51.7% of cases. We did not observe severe hematological adverse events and cytopenia requiring a modification of ruxolitinib doses always resolved. The median initial dose of ruxolitinib was 12.6 mg/m<sup>2</sup>/day with a huge range (6.3 to 28.7 mg/m<sup>2</sup>/d). We could not demonstrate any relationship between initial dose and effectiveness. Ruxolitinib may constitute a promising second line treatment for children with steroid-refractory aGVHD that should be validated in prospective large-scale pharmacokinetic and efficacy trial.

## INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment in a number of pediatric hematological pathologies despite acute and long term toxicities. Acute graft-versus-host disease (aGVHD) is an important cause of morbidity and mortality in patients receiving HSCT. Its incidence is estimated about 30%, leading to death in 10 to 20% of aGVHD cases [1,2].

The prognosis of patients with aGVHD depends mainly on the response to steroid treatment, which is known to be effective in approximately 50% of cases [3]. Indeed the mortality rate of steroid refractory or recurrent aGVHD remains as high as 50 to 70% [4].

There is currently no standardized second line strategy for steroid-resistant aGVHD. Several immunosuppressive therapies are used in this indication with variable response rates in childhood. Monoclonal anti-TNF $\alpha$  (infliximab) have been shown to have response rates between 30% and 60%, however relapse at discontinuation was very common (approximately 80%)[5,6]. Alemtuzumab shows similar response rates (50 to 70%) but mainly effective in cutaneous GVHD [7]. Response rates are similar for the other molecules commonly used with 53% for basilizumab [8], 46% for daclizumab [9] and 57% for sirolimus [3]. On the other hand, extracorporeal photopheresis has also been used, particularly in cutaneous aGVHD with a response rate of 30 to 85% (depending on the severity of the initial GVHD) but remains difficult to perform in young children [3].

Recently, JAK signaling has been shown to be instrumental in multiple steps leading to inflammation and tissue damage in GVHD [10]. Thus, JAK 1 is involved in the signal transmission of several cytokines, in particular IL-2, IL-6 and INF- $\gamma$  [11]. First use of ruxolitinib, a selective JAK 1/2 inhibitor, in the treatment of adult steroid-refractory aGVHD, has been reported in 2015 by R Zeizer [12]. A response rate of 81% in aGVHD was achieved in this study leading to promises.

Few data on the efficacy of ruxolitinib in pediatric steroid-refractory aGVHD have also been reported but concerned only a small number of patients from a single center [13].

Prospective trials are underway but results are not known to date [14]. Furthermore, most of these studies planned to include mainly adult patients and only children over 12 years-old. The pediatric use of ruxolitinib in steroid refractory aGVHD remains therefore poorly documented to date.

We conducted a national multicenter retrospective study in France to evaluate efficacy and tolerance of ruxolitinib in children with steroid-refractory aGVHD.

## **PATIENTS AND METHODS**

We retrospectively analyzed all children treated by ruxolitinib for steroid-refractory aGVHD between March 2014 and January 2017. Patients were recruited from the 15 pediatric transplantation centers in France.

## **Patients**

Transplanted patients were eligible if they met the following criteria: aged  $\leq 18$  years at transplantation, receiving a myeloablative allogeneic haematopoietic stem cell transplant irrespective of the stem cell source, having an aGVHD of grade  $\geq 2$ , occurred before day 100 after HSCT and treated with ruxolitinib for steroid refractory aGVHD.

This study was approved by the ethics committee of the CHU of Rennes, France

### ***Diagnosis of Steroid-Refractory Acute GVHD and use of ruxolitinib***

GVHD was staged according to Glucksberg-scale .

GVHD was defined steroid-refractory when GVHD symptoms were resistant to treatment with methylprednisolone ( $\geq 1$  mg/kg/day) given for at least 7 days .

The majority of patients were treated with ruxolitinib as an add-on immunosuppression therapy. As pediatric dosing of ruxolitinib in aGVHD is unknown (no marketing authorization in this indication), starting dose for the youngest was 5 mg/day but doses were variable according to centers and tolerance. Ruxolitinib was given orally BID. As a general rule according to dosing recommendations, gradual tapering of the dose of ruxolitinib was considered (decrease or spacing daily dosage) [11].

### ***Treatment response***

Response was evaluated according to previously defined diagnostic criteria for aGVHD.

Treatment responses were categorized as complete response (CR), partial response (PR) or treatment failure. A CR to ruxolitinib was defined as the absence of any symptoms related to GVHD. A PR was defined as the improvement of at least one stage in the severity of aGVHD in one organ without deterioration in any other organ. A response had to last for at least 3 weeks. Treatment failure was defined by the absence of improvement of aGVHD, deterioration of aGVHD in any organ by at least one stage, the development of aGVHD manifestations in a previously unaffected organ, and the use of any additional agents to control the disease.

Patients were scored at day 28 for their best response and for their best overall response at any time after starting treatment with ruxolitinib, with follow-up censored at the onset of any subsequent systemic immunosuppressive therapy.

***Toxicity and tolerance assesement***

In this retrospective study, we only focused on hematological and infectious toxicities because they are the most frequently described in previous reports and because other adverse events were very challenging to report in such a retrospective study.

Hematological toxicity was considered as significant when thrombocytopenia an/or neutropenia lead to a dose adjustment of ruxolitinib.

Blood cytomegalovirus, Epstein-Barr virus and adenovirus PCRs were performed twice weekly per routine and any positive value was considered to indicate viremia. Any grade III or IV infectious complication was also collected as a significant infectious complication.

***Statistics***

Univariate logistic regressions were conducted to model the response (complete versus no complete response either partial response or failure). Factors with a significance of  $p < 0.20$  during univariate analyzes were included in a multivariate model, then a step-by-step selection was performed to obtain a final multivariate model. Significance was defined as  $p < 0.05$ .

**RESULTS*****Patients***

Twenty-nine patients of median age 4.3 years (range 0.6 to 14.5) received ruxolitinib for steroid-refractory aGVHD, of which 16/29 (55.2 %) were under 6 years old (median age: 2.4 years and median weight: 13.2 kg).

Table 1 shows patients and transplants characteristics.

***Organs involved***

14 out of 29 patients (48.3%) have multiple organ involvement. Organs involved included gastrointestinal tract (GI) (n=7); skin (n=7); liver (n=1); GI and liver (n=3); skin and GI (n=5), and other skin aGVHD combined (n=6). Few patients gathered typical acute GVHD organ involvement and further developed chronic GVHD organ lesions.

### ***GVHD characteristics***

Acute GVHD was diagnosed at a median of 21 days (range, 10 to 100) after HSCT and ruxolitinib was started at a median of 91 days (range, 17 to 518) after HSCT.

Table 2 shows GVHD characteristics.

### ***Prior management***

The median number of immune suppressive agents received before initiation of ruxolitinib, with exclusion of agents used for acute GVHD prophylaxis was 2 (range, 1 to 6) for the overall cohort. Two periods could be divided. Patients who received a HSCT from 2014 to 2015 (n=18) started ruxolitinib in third line (range, 1 to 6) and those who received a HSCT from 2016 to 2017 (n=9) in second line (range, 1 to 4). The various treatment used were reported in table 2. Only three patients (all with skin aGVHD) started ruxolitinib in second line at a median of 37 days (28-55) after transplant.

Details of ruxolitinib (mg/m<sup>2</sup>/day) administration according to body weight, age, involved organs are listed in supplemental table 1.

### ***Response***

We evaluated 29 patients for response to ruxolitinib.

#### ***Complete response***

Only 6 patients achieved a CR at day 28 after the start of treatment with ruxolitinib but finally 19 patients (65.5%) achieved a CR with a median delay of 41 days (5 to 93).

Out of the 19 patients who achieved CR, 17 discontinued ruxolitinib after a median time of 216 days (range, 70 to 575) and 2 are still treated at the date of the latest news. The median follow-up time for these 17 patients was 685 days (range, 177 to 1042). Best response was lasting after stopping ruxolitinib because only 1/17 relapsed.

Interestingly, the response rate in the population less than 6 years old (16/29) tended to be higher with 81.3% overall response (75% CR and 6.3% PR) (p = 0.2453). Complete response was also obtained for the three patients who benefited from ruxolitinib in second line treatment, in a delay of 18 days (5-42).

*Partial response*

Two patients showed a partial response to ruxolitinib, with the best response observed for one after 34 days and the other after 101 days. One of these patients died under ruxolitinib and the other one is always treated on the last follow-up date (04-18).

*Management of corticosteroids after introduction of ruxolitinib*

All patients who achieved CR (except 2 missing data) discontinued corticosteroid treatment after a median time since the introduction of ruxolitinib of 82 days (22 to 464 days).

Among the 2 patients who achieved PR, 1 discontinued corticosteroid treatment prior to the introduction of ruxolitinib, the other one after 15 days.

*Treatment failure*

Eight patients were deemed to be treatment failures. Ruxolitinib was stopped in each. The median duration of treatment with ruxolitinib was recorded for 4/8 and ranged from 43 to 236 days with a median duration of 183 days.

The causes of treatment failure are progression of GVHD under ruxolitinib requiring introduction of an additional immunosuppressive treatment for 7 patients and death under ruxolitinib for 1 patient (multi-visceral failure and graft rejection).

*Overall survival*

Twenty three of 29 patients were alive at a median follow-up of 685 days (177 to 1042 days) after the HSCT and 480 days (93 to 829 days) after the start of treatment with ruxolitinib. Causes of death in 6 children included 1 relapses of the initial pathology, 2 infections (1 adenovirus infection, 1 refractory sepsis with pseudomonas aeruginosa), 2 worsening of GVH and 1 graft rejection.

We could not find any association of baseline characteristics and CR/PR to ruxolitinib (Table 3).

**Ruxolitinib dosing**

All patients started treatment in 2 doses per day.

The median initial dose of ruxolitinib was 12,6 mg/m<sup>2</sup>/day with a huge range (6.3 mg/m<sup>2</sup>/d to 28.7 mg/m<sup>2</sup>/d) especially for the 16 children (55.2%) under 6 years old (Figure 1). The median initial dose was comparable for children over or under 6 years old, respectively 12,6 and 12,8 mg/m<sup>2</sup>/day.

We could not demonstrate any relationship between initial dose and effectiveness (Figure 2). The delay to reach the best response was not either influenced by dosage.(Figure 3)

## Adverse effects

### *Viral replication*

Fifteen patients (51.7%) did not present any viremia. Viral replication has been reported in 12 patients (41.4 %) including cytomegalovirus (n=5, 17.2 %), Epstein-Barr virus (n=3, 10.3 %), adenovirus (n=2, 6.9 %) and combined replication (n=2, 6.9 %). Data were not available for 2 patients. Except for one patient who died of adenovirus infection, appropriate antimicrobial agents could treat all patients successfully, without stopping ruxolitinib.

### *Hematological toxicities*

We did not find any neutropenia or anemia requiring adjustment of the dose of ruxolitinib. Three patients (10.3%) having pronounced thrombocytopenia required dose reduction of ruxolitinib. Two of these presented a CR despite dose reduction.

## DISCUSSION

The management of steroid refractory or recurrent aGVHD after HSCT is challenging and there is no standardized second line strategy.

We conducted a retrospective national study to evaluate efficacy and safety of ruxolitinib in children with steroid refractory aGVHD. We showed that the overall response rate was 72.4% (21/29) with complete response in 65.5% of cases. The response rate even reached 81.3% for the 16 children less than 6 years old. Our results in a series of severe GVHD (75.9 % grade 3 and 4) are comparable with those published by Zeiser *et al* in adulthood [12], and promising. Indeed, other second line agents used for steroid refractory aGVHD in children such as infliximab, basiliximab, daclizumab or alemtuzumab, inconstantly reach 50% of complete response [5-7-8-9]. Nevertheless our response rate at the time point “day 28” is poorer than in the childhood study of Khandelwal *et al* [13]. As in a second or more line setting, therapy that benefits most patients is the crucial point, we have chosen not to consider this time point as the principal endpoint but the response rate at any time. Thus, we showed that response could be obtained in less than one week and frequently in about 1.5 months. In all children with CR or PR, corticosteroids could have been stopped and common adverse effects related to prolonged use have been saved.

We could not find any predictive factor for the efficacy of ruxolitinib with respect to the patient, the graft modalities or the GVHD characteristics. Our study also demonstrated that ruxolitinib was effective in gut

aGVHD with a response rate as high as 65% which was an issue because oral administration of ruxolitinib.

These encouraging results have lead during the time period of the study to an earlier use of ruxolitinib (third to second line after steroid failure) in the treatment strategy of steroid refractory aGVHD. We may assume that for the 2 patients who died of aGVHD in our study, the introduction of ruxolitinib was too late to be effective because the time between the HSCT and the introduction of ruxolitinib was longer than the median (from 265 days and 181 days for a median to 110 days). The appropriate time of introduction of ruxolitinib remains to be defined.

Appropriate dosage of ruxolitinib remains also unknown because we could not demonstrate any significant relationship between dosage of ruxolitinib and either rate of efficacy or speed of efficacy on GVHD. Individual blood samples using appropriate model based approaches should be implemented for right dosage adjustment because ruxolitinib interferes with CyP450 (the administration of inhibitors of CyP450 was not recorded in our study). The lack of this pharmacokinetic approach is a limitation of our study. The pharmacokinetic data might be given by REACH studies which are underway to compare ruxolitinib with best available therapy in the treatment of corticosteroid resistant aGVHD (15). Nevertheless, these studies did not still include patients younger than 12 years-old whereas our large pediatric study reported new data about young children.

In the other hand, the safety profile of ruxolitinib was rather favorable. We did not observe severe hematological adverse events and cytopenia requiring a modification of ruxolitinib doses always resolved. Viral replication (including CMV, EBV and ADV) was observed in 54% of cases indicating that viral replications need to be closely monitored. This rate should be interpreted with caution because a comparable frequency of viral replications was reported in children treated with other immunosuppressive drugs including infliximab, alemtuzumab and daclizumab [5-7-9].

In conclusion, ruxolitinib demonstrates high CR rates especially in children less than 6 years old and may be considered as a possible second-line agent for the treatment of corticosteroid resistant aGVHD, including cases of gastrointestinal involvement or severe GVHD. A future prospective large-scale pharmacokinetic and efficacy studies are needed to define the appropriate role of JAK ½ inhibition in steroid refractory aGVHD in pediatric HSCT recipients.

## **ACKNOWLEDGMENTS**

We thank the other members of the pediatric group of SFGM-TC.

## REFERENCES

1. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009;373:1550-1561.
2. Deeg HJ, Henslee-Downey PJ. Management of acute graft-versus-host disease. *Bone Marrow Transplant*. 1990;6:1-8.
3. Deeg HJ. How I treat refractory acute GVHD. *Blood*. 2007;109:4119-4126.
4. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood*. 2015;125:606-615.
5. Sleight BS, Chan KW, Braun TM, Serrano A, Gilman AL. Infliximab for GVHD therapy in children. *Bone Marrow Transplant*. 2007;40:473-480.
6. F. Yalniz, Mehrdad Hefazi, Kristen McCullough , and al. Safety and efficacy of infliximab therapy in the setting of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017; 1478–1484.
7. Khandelwal P, Emoto C, Fukuda T, et al. A prospective study of alemtuzumab as a second-line agent for steroid-refractory acute graft-versus-host disease in pediatric and young adult allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:2220-2225.
8. Massenkeil G, Rackwitz S, Genvresse I, Rosen O, Dorken B, Arnold R. Basiliximab is well tolerated and effective in the treatment of steroid-refractory acute graft-versus-host disease after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2002;30:899-903.
9. Miano M, Cuzzubbo D, Terranova P, et al. Daclizumab as useful treatment in refractory acute GVHD: a paediatric experience. *Bone Marrow Transplant*. 2009;43:423-427.
10. Spoerl S, Mathew NR, Bscheider M, and al. Activity of therapeutic jak 1/2 blockade in graft-versus-host disease. *Blood*. 2014 Jun 12;123(24):3832-42.
11. Takanori Teshima, MD. JAK Inhibition for GVHD Sapporo, JAPAN. 2016 apr 5.
12. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29:2062-2068.
13. Pooja Khandelwal, Ashley Teusink-Cross, Stella M. Davies, et al. Ruxolitinib as Salvage Therapy in Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Hematopoietic Stem Cell Transplant Patients. *Biol Blood Marrow Transplant*. 2017;1122–1127.
14. . Jagasia M, Zeiser R, Arbushites M, Delaite P, Gadbaw B, Bubnoff NV. Ruxolitinib for the treatment of patients with steroid-refractory GVHD: an introduction to the REACH trials. *Immunotherapy*. 2018 Apr;10(5):391-402.

15. REACH2 (NCT02913261): Safety and efficacy of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation. 2017-2021.

**FIGURE LEGENDS**

**Figure 1.** Initial dosage of ruxolitinib. The median initial dose of ruxolitinib was 12.6 mg/m<sup>2</sup>/day given orally BID with a huge range (6.3 mg/m<sup>2</sup>/d to 28.7 mg/m<sup>2</sup>/d) especially for the 16 children (55.2%) under 6 years old

**Figure 2.** Dosage of ruxolitinib according to the response. There is no relationship between initial dosage of ruxolitinib and effectiveness

**Figure 3.** Response time according to the initial dosage of ruxolitinib (inferior or superior at the median initial dose, 12.6 mg/m<sup>2</sup>/day). The time to reach the best response is not influenced by the initial dose of ruxolitinib

**Table 1.** Patient demographics

| Variables                         | absolute number (%) |
|-----------------------------------|---------------------|
| Gender                            |                     |
| Female                            | 8 (27.6)            |
| Male                              | 21 (72.4)           |
| Disease                           |                     |
| Acute leukemias                   | 10 (27.6)           |
| Other hematological malignancies  | 3 (10.3)            |
| Myelosuppression                  | 2 (6.9)             |
| Immune deficits *                 | 10 (27.6)           |
| Metabolic diseases **             | 2 (6.9)             |
| Others ***                        | 2 (6.9)             |
| CMV Status                        |                     |
| R-/D-                             | 9 (31.0)            |
| R-/D+                             | 5 (17.2)            |
| R+/D-                             | 5 (17.2)            |
| R+/D+                             | 10 (27.6)           |
| Source of stem cells              |                     |
| Bone marrow                       | 20 (69.0)           |
| cord blood unit                   | 7 (24.1)            |
| peripheral stem cells             | 1 (3.4)             |
| Bone marrow + cord blood unit**** | 1 (3.4)             |
| Conditioning                      |                     |
| TBI+                              | 6 (20.7)            |
| TBI-                              | 23 (79.3)           |

TBI : total body irradiation

R: recipient

D: donor

\*1 chronic congenital neutropenia , 1 Purtilo syndrome, 2 IPEX syndrome , 1 Wiskott-Aldrich syndrome, 5 severe immunodeficiency

\*\* 1 krabbe disease, 1Hurler disease

\*\*\* 1 Thalassemia, 1 X-linked alveolar proteinosis

\*\*\*\* Cord blood unit from the pregnancy of her sister, bone marrow donor

**Table 2.** GVHD characteristics

| Variables                         | Absolute number (%) |
|-----------------------------------|---------------------|
| Maximum grade of GVH              |                     |
| 1                                 | 0 (0)               |
| 2                                 | 7 (24.1)            |
| <b>3</b>                          | <b>13 (44.8)</b>    |
| <b>4</b>                          | <b>9 (31.0)</b>     |
| Grade of GVH at J1 of ruxolitinib |                     |
| 1                                 | 0 (0)               |
| <b>2</b>                          | <b>11 (37.9)</b>    |
| <b>3</b>                          | <b>13 (44.8)</b>    |
| 4                                 | 3 (10.3)            |
| Not available                     | 2 (6.9)             |
| GVH prophylaxis                   |                     |
| Cyclosporine                      | 4 (13.8)            |
| Cyclosporine + Cellcept           | 13 (44.8)           |
| Cyclosporine + methotrexate       | 4 (13.8)            |
| Other*                            | 8 (27.6)            |
| Curative treatment of GVH         |                     |
| Corticoids**                      | 29 (100)            |
| Infliximab                        | 13 (48.1)           |
| Mycophenolate mofetil             | 11 (40.7)           |
| Extracorporeal photopheresis      | 5 (18.5)            |
| Other***                          | 21 (77.8)           |

GVHD : Graft versus host disease

\* mycophenolate mofetil and methylprednisolone (n=2) ; cyclosporine, methylprednisolone and anti lymphocyte serum (ALS)(n=1) ; cyclosporine and ALS (n=1) ; T depletion (n=1); cyclosporine, mycophenolate mofetil and methylprednisolone (n=1) ; cyclosporine mycophenolate mofetil, methotrexate and rapamycin (n=1) ; cyclosporine and rituximab (n=1)

\*\* 2 mg/kg/day except for 2 (1 mg/kg/day)

\*\*\* inolimomab (n=4), sirolimus (n=4), antithymoglobulines (n=3), tacrolimus (n=3), methotrexate (n=2), cyclosporine (n=2), bolus of corticosteroids (n=2), basiliximab (n=1)

**Table 3.** Univariate analysis for association of baseline characteristics and CR/PR to ruxolitinib

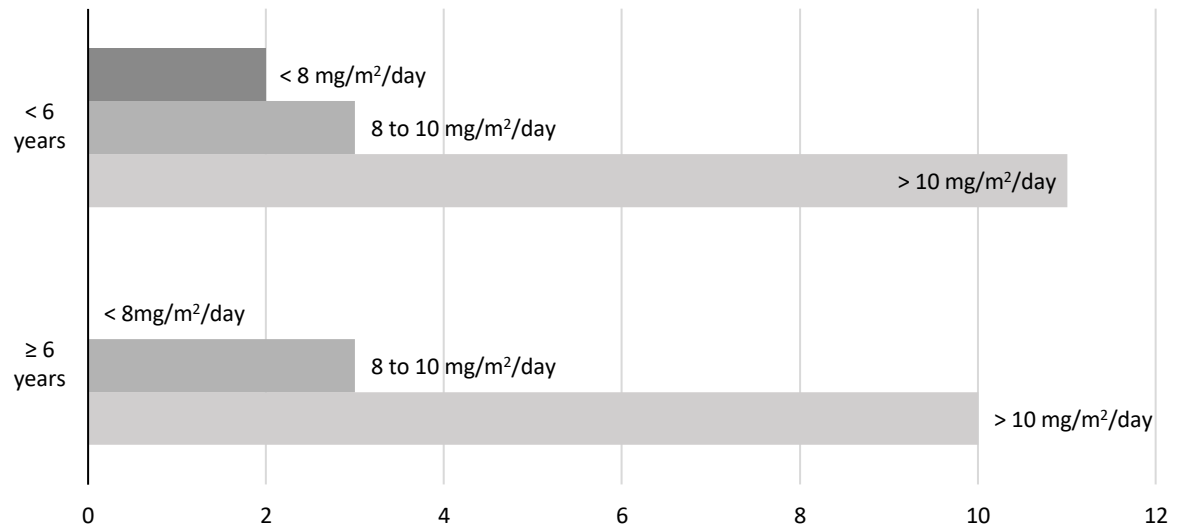
|                                                               | <b>CR/PR</b> | <b>Failure</b> | <b>OR [IC95%]</b>    | <b>P</b>   |
|---------------------------------------------------------------|--------------|----------------|----------------------|------------|
| Number of patients                                            | 21           | 8              |                      |            |
| Age                                                           |              |                |                      | p = 0.2453 |
| < 6 years                                                     | 13           | 3              | 1                    |            |
| > 6 years                                                     | 8            | 5              | 0.37 [0.07-1.98]     |            |
| Weight                                                        |              |                |                      | p = 0.9759 |
| <15 kg                                                        | 7            | 3              | 1                    |            |
| 15-30 kg                                                      | 11           | 4              | 1.18 [0.20 ; 6.93]   |            |
| >30 kg                                                        | 3            | 1              | 1.29 [0.09 ; 17.95]  |            |
| Isolated skin aGVHD                                           |              |                |                      | p = 0.5091 |
| No                                                            | 16           | 7              | 1                    |            |
| Yes                                                           | 5            | 1              | 2.19 [0.21 ; 22.34]  |            |
| GI aGVHD                                                      |              |                |                      | p = 0.6433 |
| No                                                            | 6            | 3              | 1                    |            |
| Yes                                                           | 15           | 5              | 1.50 [0.27 ; 8.34]   |            |
| Source of stem cells                                          |              |                |                      | p = 0.9733 |
| Bone marrow                                                   | 13           | 7              | 1                    |            |
| 2 cord blood units                                            | 1            | 0              | 1.71 [0.02 ; 177.36] |            |
| Peripheral stem cells                                         | 1            | 0              | 1.71 [0.02 ; 177.36] |            |
| Bone marrow + cord blood unit                                 | 1            | 0              | 1.71 [0.02 ; 177.36] |            |
| Cord blood unit                                               | 5            | 1              | 2.04 [0.24 ; 17.56]  |            |
| Gender                                                        |              |                |                      | p = 0.1402 |
| Female                                                        | 8            | 0              | 1                    |            |
| Male                                                          | 13           | 8              | 0.09 [0.00 ; 2.18]   |            |
| Regimen with TBI                                              |              |                |                      | p = 0.7243 |
| No                                                            | 17           | 6              | 1                    |            |
| Yes                                                           | 4            | 2              | 0.71 [0.10 ; 4.89]   |            |
| Number of immune suppressive agents before use of ruxolitinib |              |                |                      | p = 0.5377 |
| 2 or less                                                     | 11           | 3              | 1                    |            |
| 3 or more                                                     | 10           | 3              | 1.82 [0.27 ; 12.17]  |            |
| Grade max of aGVHD                                            |              |                |                      | p = 0.4056 |
| 2                                                             | 5            | 2              | 1                    |            |
| 3                                                             | 11           | 2              | 2.09 [0.25 ; 17.73]  |            |
| 4                                                             | 5            | 4              | 0.56 [0.07 ; 4.40]   |            |

CR : complete response

PR :partial response

aGVHD: acute graft versus host disease

TBI: total body irradiation

**Figure 1.**

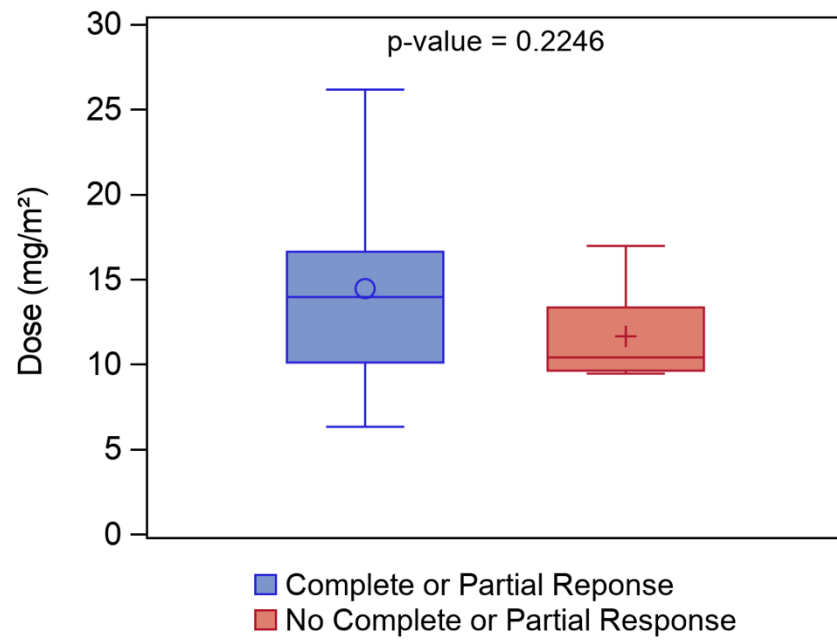
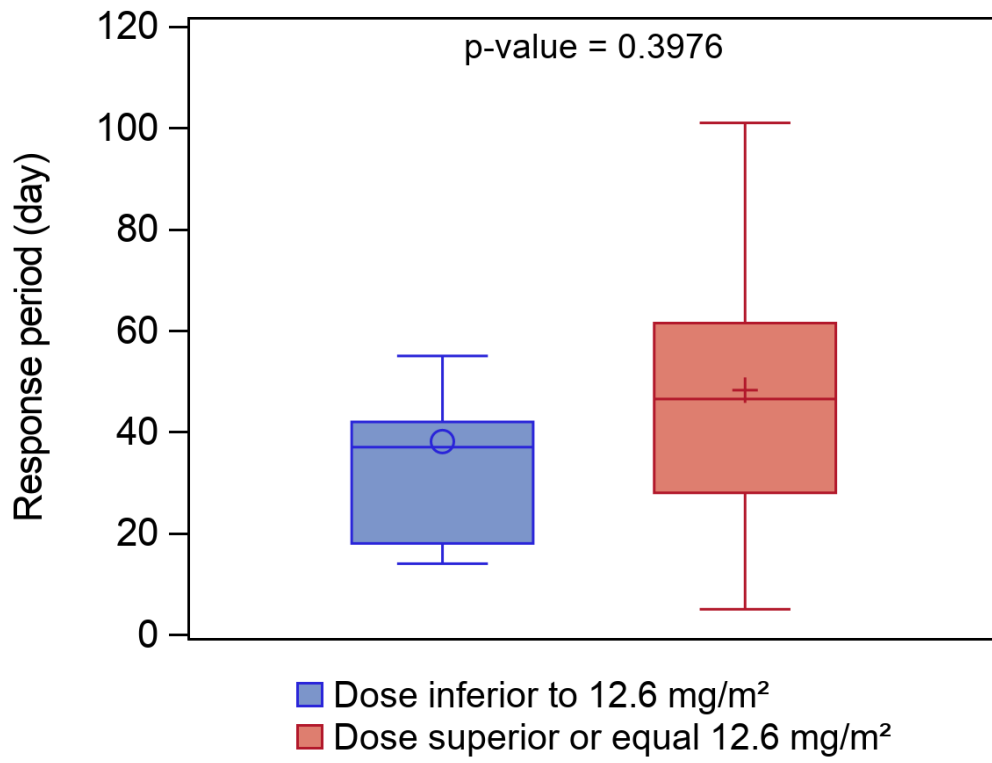
**Figure 2.**

Figure 3.



**Supplemental Table 1.** Details of ruxolitinib (mg/m<sup>2</sup>/day) administration according to body weight, age, involved organs

| Patient | Age at D1 of HSCT (years) | Weight at D1 of HSCT (kg) | Organs involved        | Dosage of ruxo at D1 (mg/day) | Dosage of ruxo at D1 (mg/m <sup>2</sup> /day) |
|---------|---------------------------|---------------------------|------------------------|-------------------------------|-----------------------------------------------|
| 1       | 5.1                       | 16.9                      | Skin, GI               | 20                            | 28.7                                          |
| 2       | 7.6                       | 22.0                      | GI                     | 20                            | 23.6                                          |
| 3       | 2.5                       | 13.5                      | Skin, GI               | 10                            | 17.0                                          |
| 4       | 11.0                      | 36.2                      | GI                     | 20                            | 16.6                                          |
| 5       | 6.8                       | 19.1                      | Skin                   | 20                            | 26.2                                          |
| 6       | 8.4                       | 20.0                      | Skin, GI, BM, Eyes     | 10                            | 12.6                                          |
| 7       | 1.3                       | 9.5                       | Skin                   | 10                            | 22.1                                          |
| 8       | 14.5                      | 73.5                      | GI                     | 20                            | 10.9                                          |
| 9       | 2.8                       | 13.7                      | Skin, GI               | 10                            | 16.8                                          |
| 10      | 14.3                      | 37.8                      | Skin, GI, liver        | 10                            | 8.1                                           |
| 11      | 1.7                       | 12.9                      | GI                     | 5                             | 8.8                                           |
| 12      | 14.4                      | 47.0                      | Liver                  | 20                            | 14.1                                          |
| 13      | 11.8                      | 27.0                      | Liver, GI              | 10                            | 10.2                                          |
| 14      | 6.7                       | 20.0                      | Skin, GI, lung, joints | 10                            | 12.6                                          |
| 15      | 3.8                       | 15.0                      | GI                     | 5                             | 7.8                                           |
| 16      | 1.2                       | 11.2                      | Skin                   | 5                             | 9.8                                           |
| 17      | 1.3                       | 10.0                      | Skin, GI, liver        | 5                             | 10.6                                          |
| 18      | 3.8                       | 16.4                      | Skin, GI               | 10                            | 14.7                                          |
| 19      | 3.8                       | 20.0                      | Skin, kidneys          | 5                             | 6.3                                           |
| 20      | 7.3                       | 29.3                      | Liver, GI              | 10                            | 9.6                                           |
| 21      | 7.8                       | 23.2                      | Skin                   | 10                            | 11.3                                          |
| 22      | 4.3                       | 17.5                      | Liver, GI              | 10                            | 14.0                                          |
| 23      | 0.6                       | 6.8                       | Skin, GI               | 5                             | 14.2                                          |
| 24      | 0.6                       | 6.9                       | Skin                   | 5                             | 14.0                                          |
| 25      | 2.4                       | 11.7                      | Skin                   | 5                             | 9.5                                           |
| 26      | 12.6                      | 29.1                      | Skin, lung             | 10                            | 9.7                                           |
| 27      | 3.7                       | 22.2                      | Skin                   | 10                            | 11.7                                          |
| 28      | 6.4                       | 15.2                      | GI                     | 10                            | 15.5                                          |
| 29      | 1.1                       | 10.7                      | GI                     | 5                             | 10.1                                          |

**LAISNE Louise – Utilisation du ruxolitinib dans la GVH aigue cortico-résistante, une étude multicentrique du groupe pédiatrique de la SFGM-TC**

34 feuilles. 4 tableaux, 3 figures, Thèse : Médecine ; Rennes 1; 2019 ; N° .

**Résumé français**

Nous avons mené une étude rétrospective multicentrique nationale française pour évaluer l'efficacité et la tolérance du ruxolitinib chez les enfants atteints de maladie du greffon contre l'hôte (GVH) aiguë cortico résistante après greffe allogénique de cellules souches hématopoïétiques. Vingt-neuf patients ont été inclus. Dix-neuf patients (65,5%) ont obtenu une réponse complète avec un délai médian de 41 jours (5 à 93). Deux patients ont eu une réponse partielle et 8 patients étaient en échec thérapeutique. Le taux de réponse global était de 72,4%. Vingt-trois des 29 patients étaient en vie après un suivi médian de 685 jours (177 à 1042 jours) après la greffe. Une réplication virale a été observée dans 51,7% des cas. Nous n'avons pas observé d'effets indésirables hématologiques graves. Le ruxolitinib pourrait constituer un traitement de deuxième intention prometteur pour les enfants atteints de GVH cortico résistante.

Rubrique de classement : Étude Clinique Rétrospective

Mots-clés : GVH aigue cortico résistante,  
ruxolitinib,  
pédiatrie

Président : Pr Thierry LAMY LA CHAPELLE

Assesseurs : Pr GANDEMER Virginie

Pr PLADYS Patrick

JURY :

Dr ROBERT Guillaume