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**Par**

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## MALADIES INFLAMMATOIRES CHRONIQUES DE L'INTESTIN CHEZ LE TRANSPLANTÉ RÉNAL : UNE ÉTUDE FRANÇAISE RÉTROSPECTIVE MULTICENTRIQUE

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# Résumé

## Introduction

Les corticoïdes et immunosuppresseurs sont utilisés dans le traitement des maladies inflammatoires chroniques de l'intestin (MICI) (maladie de Crohn et rectocolite hémorragique). Pourtant, les MICI peuvent récidiver ou apparaître après greffe d'organe. Souvent étudiées en greffe hépatique, il n'existe que très peu de cas publiés en transplantation rénale. Notre but était de rassembler une série significative de cas de MICI chez des transplantés rénaux afin d'en déterminer les caractéristiques, de rechercher les facteurs associés à la récurrence, et d'évaluer l'évolution des MICI après la greffe.

## Patients et méthode

Il s'agit d'une étude multicentrique rétrospective basée sur un questionnaire envoyé à 12 centres français. Les critères d'inclusion étaient: tous les patients transplantés rénaux ayant eu un diagnostic de MICI avant ou après la greffe. Nous avons recensé les caractéristiques démographiques des patients, les antécédents de maladies auto-immunes, l'évolution de la MICI avant et après la greffe, le statut CMV, la survenue d'une infection/maladie à CMV, et le traitement immunosuppresseur.

## Résultats

40 patients transplantés rénaux entre 1989 et 2011 ont été inclus. 28 avaient une MICI connue avant la greffe. 11 ont récidivé et 12 ont développé une MICI de novo après la greffe. Le délai médian de poussée après la greffe a été de 17 (1-167) mois pour les récurrences et de 91 (3-139) mois pour les MICI de novo. Une infection ou maladie à CMV était significativement corrélée à la survenue d'une récurrence, et 6 des 7 infections ou maladies à CMV recensées sont survenues chez des patients développant une MICI post-greffe. L'évolution post-greffe était favorable puisque 67,9% des patients étaient considérés sévères avant la greffe contre 28,6% après la greffe.

## Conclusion

Il s'agit de la plus grande cohorte de transplantés rénaux atteints d'une MICI. La prévention de ces maladies après la greffe reste à déterminer.

**INFLAMMATORY BOWEL DISEASES IN RENAL TRANSPLANT RECIPIENT: A FRENCH RETROSPECTIVE MULTICENTRIC STUDY**


## Abstract

### Background

Corticoids and immunosuppressants are used for to treat inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis). Nevertheless IBD can recur or ocur after transplantation. These cases are most frequently studied after liver transplantation and only a few cases are published after kidney transplantation. We wanted to collect a cohort of IBD cases in renal transplant recipients to provide an overview of the characteristics of these patients, to determine the associated factors with the recurrence, and to assess the evolution of IBD after transplantation.

### Materials and methods

This is a retrospective multicentric study based on a questionnaire send to 12 french centers. The inclusion criteria were: all renal transplanted patients with a diagnosis of IBD before or after transplantation. Demographic characteristics, history of auto-immune disease, IBD evolution before and after transplantation, CMV status, occurrence of a CMV infection/disease and immunosuppressive treatment were recorded.

### Results

Fourty kidney recipients transplanted between 1989 and 2011 were included. 28 had an IBD known before transplantation. 11 recurred and 12 developed an IBD de novo after transplantation. The median delay of flare-up after transplantation was 17 (1-167) months for the recurrences and 91 (3-139) months for the de novo IBD. A CMV infection/disease was significantly correlated to the recurrence and 6 of the 7 CMV infections or diseases occurred in patients who developed post-transplant IBD. Post-transplant evolution was favorable as 67,9% of the patients were considered severe before transplantation against 28,6% after transplantation.

### Conclusion

We report the most extensive cohort of IBD in renal transplant recipients. Prevention of such diseases after transplantation needs to be determined.

## Mots-clés

- maladie inflammatoire chronique de l'intestin
- transplantation rénale

## Key-words

- inflammatory bowel disease
- renal transplantation

**Cette thèse a été rédigée en anglais en vue d'une publication dans une revue internationale.**

## Table des matières

## Abbreviations

**AID :** Auto-Immune Disease

**AIH** : Auto-Immune Hepatitis

**ALS** : Antilymphocyte Serum

**CD** : Crohn's Disease

**CMV** : Cytomegalovirus

**CT :** Corticosteroids

**HLA** : Human Leukocyte Antigen

**IBD :** Inflammatory Bowel Disease

**IHC :** Immunohistochemistry

**IL2R** : Interleukine 2 Receptor

**IS** : Immunosuppressive

**MMF** : Mycophenolate Mofetil

**MPS** : Mycophenolate Sodium

**mTORI** : mammalian Target Of Rapamycin Inhibitor

**OLT** : Orthotopic Liver Transplantation

**PCR** : Polymerase Chain Reaction

**PSC :** Primary Sclerosing Cholangitis

**UC** : Ulcerative Colitis

**5-ASA** : 5-Aminosalicylates

## Introduction

Inflammatory bowel diseases (IBD) are characterised by an intestinal mucosal inflammation due to a mucosal immune system dysregulation. Crohn's disease (CD) and ulcerative colitis (UC) are the two major IBD. They are associated with specific and nonspecific gene variants, some shared by the two diseases, and environnemental factors which remain currently unidentified.

In France, the incidence of IBD is about 8,2 cases per 100000 inhabitants for CD with a North-South gradient and a peak of frequency between 20 and 24 years, and 7,2 cases per 100000 inhabitants for UC with a homogeneous geographical distribution and a peak of frequency between 30 and 34 years [1].

The main treatments of IBD include 5-aminosalicylates (5-ASA) and steroids, but immunosuppressants and TNF-alpha inhibitors are used in refractory or severe forms to avoid surgery.

Appearance or recurrence of IBD after solid organ transplantation which occur despite the immunosuppressant and steroid treatments have already been described, but mostly after liver transplantation because of the association between primary sclerosing cholangitis (PSC) or auto-immune hepatitis (AIH) and IBD. Thus some have reported an incidence of de novo IBD after liver transplantation of 206 cases per 100000 per year [2, 3].

Only a few cases of IBD recurrence or occurring de novo have been reported after kidney transplantation.

We here report a multicentric retrospective series of patients who underwent renal transplantation and who had a diagnosis of IBD before or after transplantation. Our aim was to provide an overview of the characteristics of these patients, to determine the associated factors with the recurrence and to assess the evolution of these diseases after transplantation.

## Materials and methods

This is a retrospective multicenter observational study based on a questionnaire send to 12 French renal transplantation departments by mail during 2011 (Bretonneau Hospital, Tours ; Necker-Enfants Malades Hospital, AP-HP, Paris ; Georges Pompidou European Hospital, AP-HP, Paris ; La Cavale Blanche Hospital, Brest ; Caen Hospital, Caen ; Gabriel Montpied Hospital, Clermont-Ferrand ; Dupuytren Hospital, Limoges ; La

Milétrie Hospital, Poitiers ; Maison Blanche Hospital, Reims ; Pontchaillou Hospital, Rennes ; Bois-Guillaume Hospital, Rouen ; Nouvel Hôpital Civil, Strasbourg).

***Inclusion criteria***

The inclusion criteria were: all kidney graft recipients who had a diagnosis of IBD (CD or UC) diagnosed before or after transplantation. Diagnosis of IBD was established using standard clinical, radiologic, endoscopic and histological criteria.

***Study groups***

We determined 3 study groups: 1. the « no recurrent IBD » group: patients with an IBD diagnosed before transplantation with no recurrence after transplantation, 2. the « recurrent IBD » group: patients with an IBD diagnosed before transplantation and recurrence after transplantation, 3. the « de novo IBD » group: patients with an IBD diagnosed after transplantation.

***Recorded parameters***

Patients medical charts and demographics were recorded, including initial nephropathy, age at transplantation, age at the diagnosis of IBD, gender, history of auto-immune disease (AID) (including PSC, AIH, periodic disease, systemic lupus erythematosus, sarcoidosis, Sjögren's syndrome), history of IBD before transplantation, HLA type, cytomegalovirus (CMV) status, and post-operative immunosuppressive treatment.

The outcome were recorded, including patient and graft survival, occurrence of IBD post-transplantation and the diagnostic means used, treatment of IBD, occurrence of IBD associated complications, immunosuppressive therapy three months after transplantation, at the time of diagnosis or recurrence of IBD after transplantation and at the end of the follow-up, acute rejection episodes, CMV infection or disease. CMV infection was monitored using pp65 antigenaemia and/or serum polymerase chain reaction (PCR) and/or CMV inclusion on the biopsies at the time of the first flare-up after the graft.

For the comparison of « no recurrent IBD » group and « recurrent IBD » group, we used the immunosuppressive therapy at 3 months after transplantation because we believe that is the most representative and comparable treatment.

***Severity of the IBD***

For the patients who had an IBD known before the graft, we defined the severity of the IBD as followed:

- severity before transplantation: the IBD was considered « not severe » if the patient never received anti-TNF therapy or azathioprine and if he never underwent surgery and had no treatment for his IBD at the time of transplantation; the IBD was considered « severe » if the patient received during his IBD history anti-TNF and/or azathioprine and/or underwent a surgery and/or had a treatment for his IBD at time of transplantation.
- severity after transplantation: the IBD was considered « not severe » if the patient had 0 or 1 flare-up after transplantation and no complication of the IBD ; it was considered « severe » if he had more than 1 flare-up after transplantation and/or a complication of the IBD.

***Statistical analysis***

Quantitative data are presented as means (±standard deviation) or medians (range). Qualitative data are expressed in n (%). Because of the weak number of events, we only analysed the risk factor of recurrence of IBD after transplantation through an univariate analysis using Cox proportional hazards regression model performed using StatView software (SAS Institute, Cary, NC, USA). A value of $p<0,05$ was considered as significant.

## Results

***Characteristics of renal transplant patients with IBD***

We collected the data of 46 patients who were diagnosed with IBD. We finally included 40 patients to our study (6 patients excluded because of important missing data): 24 CD, 13 UC, 3 indeterminate colitis. 28 had an IBD known before transplantation: 17 in the « no recurrent IBD » group, 11 in the « recurrent IBD » group. 12 developed an IBD after transplantation and were classified in the « de novo IBD » group.

These 40 patients (26 men, 14 women) underwent kidney transplantation between June 1989 and July 2011 for chronic tubulointerstitial nephropathy (11), malformative uropathy or hypoplasia (7), polycystic kidney disease (4), IgA nephropathy (4), membranoproliferative glomerulonephritis (2), AA amyloidosis (2), focal segmental glomerulosclerosis (1), malignant hypertension (1), IgM nephropathy (1), Alport

syndrome (1), chronic glomerulonephritis (1), hemolytic and uremic syndrome (1), or indeterminate nephropathy (4). Baseline characteristics are shown in table 1.

Concerning the CMV status: seronegative patients with seronegative donor didn't receive any CMV prophylaxis and didn't have any CMV infection or disease; 2/13 seropositive patients with seronegative donor received CMV prophylaxis and one of these two developed a CMV infection; 8/10 seronegative recipients of seropositive donors received a CMV prophylaxis and 2 of them developed a CMV infection or disease; 2/4 seropositive recipients of seropositive donors received CMV prophylaxis and all developed a CMV infection or disease.

All patients received an induction therapy except one who received corticoïds, cyclosporine and FTY-720.

10 rejection episodes occurred: 7 acute cellular rejections, 1 acute humoral rejection, 2 chronic rejections.

The median duration of the post-transplantation follow-up was 95,5 (5-265) months. 2 patients had lost their graft during this follow-up at 5 and 11 years after transplantation and 1 died because of a digestive amyloidosis.

**Table 1.** Characteristics of patients with IBD at the time of and/or after renal transplantation

| | Overall population |
|---|---|
| **Number of patients** | |
| - Brest | 2 |
| - Caen | 6 |
| - Clermont | 1 |
| - Limoges | 2 |
| - Necker | 1 |
| - Poitiers | 1 |
| - Pompidou | 1 |
| - Rennes | 1 |
| - Reims | 9 |
| - Rouen | 7 |
| - Strasbourg | 2 |
| - Tours | 7 |
| Total (%) | 40 |
| **Demographic characteristics :** | |
| - male gender (%) | 26 (65) |
| - mean age at transplantation (years) | 40,6 (±12,7) |
| - mean age at the diagnosis of IBD (years) | 32,8 (±13,6) |
| **Type of IBD :** | |
| - Crohn's disease (%) | 24 (60) |
| - Ulcerative colitis (%) | 13 (32,5) |
| - Indeterminate colitis (%) | 3 (7,5) |
| **CMV status (D/R)** (%) | |
| - neg/neg | 13(32,5) |
| - neg/pos | 13(32,5) |
| - pos/neg | 10(25) |
| - pos/pos | 4(10) |
| **IS therapy at time of transplantation** | |
| - induction with ALS | 19 |
| Anti-IL2R | 20 |
| - Tacro/MMF/CT | 7 |
| - Tacro/Aza/CT | 1 |
| - Cyclo/MMF/CT | 18 |
| - Cyclo/MMF | 2 |
| - Cyclo/Aza/CT | 8 |
| - Cyclo/CT | 3 |
| - mTORI/MMF/CT | 1 |

*Qualitative data are expressed in n (%), quantitative data in mean (±SD) or median (range) as appropriate.*
*IBD, inflammatory bowel disease ; CMV, cytomegalovirus ; D/R, donnor/recipient ; IS, immunosuppressive ; ALS, antilymphocyte serum ; IL2R, interleukine 2 receptor; Tacro, tacrolimus ; MMF, mycophenolate mofetil ; CT, corticosteroids ; mTORI, mammalian target of rapamycin inhibitor ; Cyclo, cyclosporine ; Aza, azathioprine.*

***Risk factors of recurrence of IBD after transplantation***

Among the 28 patients with an IBD known before transplantation, 11 (39,3%) had a recurrence after transplantation (table 2).

The median duration of the post-graft follow-up was 76 (5-265) months in the « no recurrent IBD » group, 129 (36-210) months in the « recurrent IBD » group (p=0,344).

In the « no recurrent IBD » group, 5 patients were treated at time of transplantation with 5-ASA, 4 with corticosteroids and 2 with azathioprine for the IBD. Except the 5-ASA, that treatment was restored after transplantation. In the « recurrent IBD » group, 2 were receiving 5-aminosalicylates, 1 corticosteroids and 1 azathioprine at time of transplantation for the IBD. All these treatments were restored after transplantation.

CMV infection or disease was significantly more frequent in patients with recurrence (1 in the « no recurrent IBD » group, 3 in the « recurrent IBD » group, p=0,007).

We found no difference in these two groups concerning gender, age, associated AID, CMV status, immunosuppressive therapy at 3 months after transplantation, IBD severity before transplantation, resumption of IBD treatment after transplantation or occurrence of a rejection (table 2).

The mean age at the diagnosis of IBD was significantly lower in those who didn't recur (27,5 versus 31,3 years, p=0,036) and the median delay between the diagnosis of the IBD and transplantation tended to be longer in the « not recurrent IBD » group (158 versus 97 months, p=0,086).

**Table 2.** Univariate analysis for recurrence of pre-transplant IBD (n=28)

| | **No recurrent IBD** | **Recurrent IBD** | **p** |
|---|---|---|---|
| **Number of patients** (%) | 17 (60,7) | 11 (39,3) | |
| **Demographic characteristics :** | | | |
| - male gender (%) | 13 (76,5) | 6 (54,5) | 0,577 |
| - mean age at the diagnosis of IBD (years) | 27,5±10,7 | 31,3±13,4 | 0,036 |
| - mean age at transplantation (years) | 42,5±11,3 | 42,5±13,2 | 0,930 |
| - associated AID (%) | 2 (11,8) | 1 (9) | 0,448 |
| **Type of IBD :** | | | |
| - Crohn's disease (%) | 10 (58,8) | 7 (63,6) | |
| - Ulcerative colitis (%) | 6 (35,3) | 4 (36,4) | |
| - Indeterminate colitis (%) | 1 (5,9) | 0 | |
| **IBD severity before transplantation** | | | |
| - not severe | 5 (29,4) | 4 (36,4) | |
| - severe | 12 (70,6) | 7 (63,6) | 0,469 |
| **Median delay between IBD diagnosis and transplantation** (months) | 158 (16-383) | 97 (10-321) | 0,086 |
| **CMV :** | | | |
| - D+/R- CMV status (%) | 4 (23,5) | 2 (18,2) | 0,921 |
| - CMV infection/disease (%) | 1 (5,9) | 3 (27,3) | 0,007 |
| **IS therapy :** Induction | | | |
| - IL2R | 9 (52,9) | 7 (63,6) | 0,214 |
| - ALS | 7 (41,2) | 4 (36,4) | 0,354 |
| At 3 months post-transplantation n (%) | | | |
| - Tacrolimus | 3 (17,6) | 1 (9,1) | 0,694 |
| - Cyclosporine | 11 (64,8) | 10 (90,9) | 0,423 |
| - MMF | 13 (76,5) | 6 (54,5) | 0,788 |
| - Azathioprine | 3 (17,6) | 5 (45,4) | 0,517 |
| - Corticosteroids | 15 (88,2) | 9 (81,8) | 0,669 |
| **Resumption of IBD treatment after transplantation :** | | | |
| - 5-ASA/CT/Aza | 0/4/2 | 2/1/1 | 0,974 |
| **Rejection** (%) | 4 (23,5) | 3 (27,3) | 0,701 |

*Qualitative data are expressed in n (%), quantitative data in mean (±SD) or median (range) as appropriate.*
*AID, auto-immune disease ; D+/R-, seropositive donor and seronegative recipient ; CMV, cytomegalovirus ; ALS, antilymphocyte serum ; IL2R, interleukine 2 receptor ; IS, immunosuppressive ; MMF, mycophenolate mofetil ; 5-ASA, 5-aminosalicylates ; CT, corticosteroids ; Aza, azathioprine*.

***Evolution of pre-transplant IBD***

We wanted to assess the behaviour of the IBD before and after transplantation (Figure 1). 19/28 (67,8%, 11CD, 7 UC, 1 indeterminate colitis) patients received an anti-TNF therapy and/or azathioprine and/or underwent a surgery for their IBD before transplantation and/or received a treatment for their IBD at the moment of transplantation and were considered as severe. The 9 others (6 CD, 3 UC) without any treatment for their IBD at transplantation and who never received anti-TNF therapy or azathioprine or had surgery were considered as not severe.

After transplantation, among the 11 who recurred 8 patients (5 CD, 3 UC) had another flare-up and 4 of them had a complication (1 uveitis, 1 occlusion, 1 amyloidosis, 1 digestive fistula with abscess). Five of these eight patients were considered severe before transplantation.

Finally, 19/28 (67,9%) were severe before transplantation, whereas only 8/28 (28,6%) were severe after transplantation.

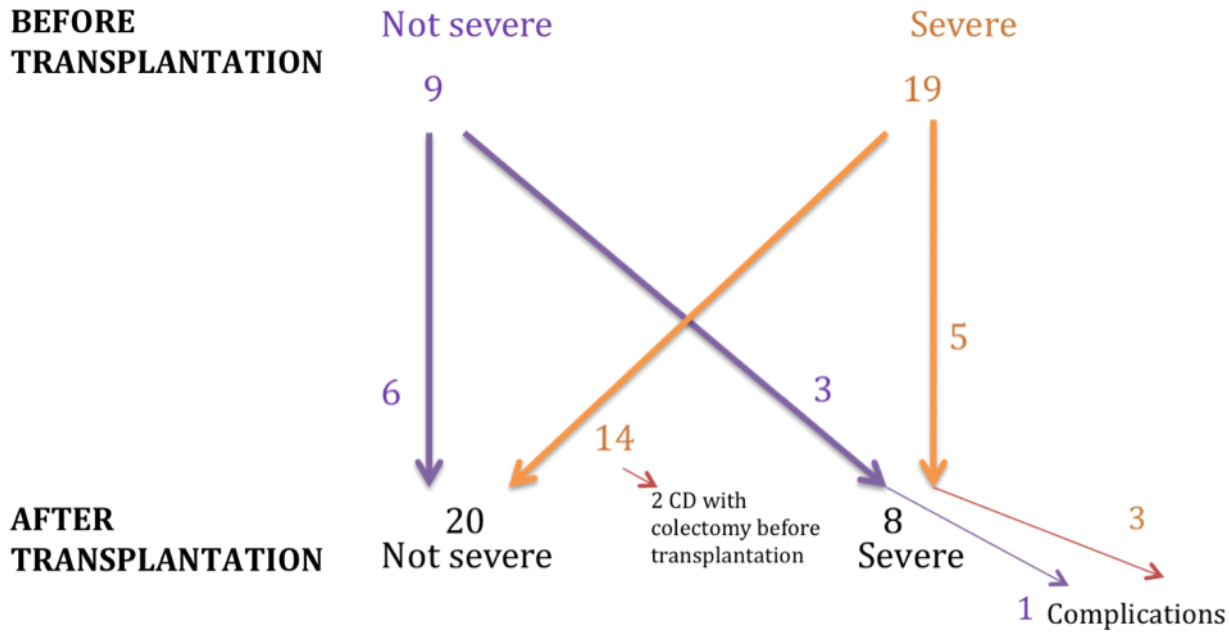


**Figure 1.** Evolution of pre-transplant IBD

*Before transplantation:*
*- not severe IBD: patients who never received anti-TNF therapy, azathioprine, never underwent surgery and had no treatment for their IBD at the time of transplantation*
*- severe IBD: patients who received during their IBD history anti-TNF and/or azathioprine and/or underwent a surgery and/or had a treatment for their IBD at transplantation.*

*After transplantation:*
*- not severe IBD: ≤ 1 flare-up after transplantation and no complication of the IBD*
*- severe IBD: > 1 flare-up after transplantation and/or a complication of the IBD*

***Post-transplant IBD: IBD de novo and recurrences***

23 patients have had a flare-up of IBD after transplantation (table 3).

12 patients developed an IBD de novo post-transplant while they had no history of IBD before. A colonoscopy with biopsies was performed in all of them for the diagnosis. 7 (58,3%) were men and the median delay between transplantation and the diagnosis of IBD was 91 (3-139) months. CMV testing was negative either with antigenaemia, serum PCR or CMV inclusion in the biopsies at the time of the flare-up.

6/12 have had at least another flare-up (1 CD with multiple complications: esophagitis, digestive fistula, abscess). 3/6 didn't have any immunosuppressive therapy modification after the first flare-up (2 with MMF and cyclosporine, 1 with azathioprine, cyclosporine and corticosteroids), 1 had a temporary withdrawal of MMF and 2 switched from MMF to mycophenolate sodium (MPS). After the second flare-up all 6 patients switched from MMF or MPS to azathioprine and were still under azathioprine after a median duration of 155,5 (38-246) months of follow-up.

11 patients with an IBD pre-transplant recurred after the graft. The median delay between the graft and the first flare-up after the graft was 17 (1-167) months.

Treatments given for the flare-up are described in the table 3.

Among the 7 CMV infections or diseases occurred in the total population during the follow-up, 6 occured in patients with a post-transplant IBD (recurrences and de novo). 4 occurred before the recurrence (date for 2 patients not known).

Among the 10 rejection episodes, 6 occurred in patients with a post-transplant IBD.

**Table 3.** Patients with post-tranplant IBD

| | Recurrence | IBD de novo |
|---|---|---|
| **Number of patients** | 11 | 12 |
| **Demographic characteristics :** | | |
| - male gender (%) | 6 (54,5) | 7 (58,3) |
| - mean age at transplantation (years) | 42,5 (±13,2) | 36,1 (±13,2) |
| - mean age at the diagnosis of IBD (years) | 31,3 (±13,4) | 41,8(±12,9) |
| - median delay between transplantation and the 1rst flare-up after transplantation (months) | 17 (1-167) | 91 (3-139) |
| **Type of IBD :** | | |
| - Crohn's disease (%) | 7 (63,6) | 7 (58,3) |
| - Ulcerative colitis (%) | 4 (36,4) | 3 (25) |
| - Indeterminate colitis (%) | 0 | 2 (16,7) |
| **CMV :** | | |
| CMV status (D/R) (%) | | |
| - neg/neg | 3(27,3) | 4(33,3) |
| - neg/pos | 4(36,3) | 3(25) |
| - pos/neg | 2(18,2) | 4(33,3) |
| - pos/pos | 2(18,2) | 1(8,4) |
| CMV disease/infection (%) | 3 (27,3) | 3 (25) |
| **IS treatment at the 1rst flare-up after transplantation** | | |
| - Tacro/MMF/CT | 0 | 3 |
| - Tacro/mTORI/CT | 1 | 0 |
| - Tacro/MMF | 0 | 1 |
| - Cyclo/MMF/CT | 3 | 2 |
| - Cyclo/Aza/CT | 3 | 1 |
| - Cyclo/MMF | 1 | 4 |
| - Cyclo/Aza | 2 | 0 |
| - Cyclo | 1 | 1 |
| **Therapy started for IBD after transplantation** | | |
| - none | 0 | 3 |
| - 5-ASA | 5 | 0 |
| - 5-ASA + topical CT | 1 | 0 |
| - 5-ASA + per os CT | 0 | 1 |
| - CT alone per os/topical | 3/1 | 4/2 |
| - Azathioprine + per os CT | 0 | 1 |
| - Azathioprime + topical CT | 0 | 1 |
| - anti-TNF | 1 | 0 |
| **Rejection** (%) | 3 (27,3) | 3 (25) |

*Qualitative data are expressed in n (%), quantitative data in mean (±SD) or median (range) as appropriate.*
*CMV, cytomegalovirus ; IS, mmunosuppressive ; Tacro, tacrolimus ; MMF, mycophenolate mofetil ; CT, corticosteroids ; mTORI, mammalian target of rapamycin inhibitor ; Cyclo, cyclosporine ; Aza, azathioprine ; 5-ASA, 5-aminosalicylates.*

## Discussion

### *IBD in renal transplantation versus in liver transplantation*

We report, to our knowledge, the most important series of IBD in kidney transplant recipients. Post-transplant IBD is mostly described after liver orthotopic transplantation (OLT) (Table 4) [2-18] because the incidence of IBD is increased in patients with PSC or AIH which are causes of terminal liver failure: 55-75% of PSC and 4% of AIH develop IBD [8].

We observed a recurrence rate of IBD after transplantation of 39,3% in a median follow-up of 95,5 (5-265) months. The recurrence occurred in 17 (1-167) months in median after transplantation. In liver transplanted patients for AIH or PSC, the recurrence rate is higher with a cumulative risk for recurrence of 63% at 5 years and 72% at 10 years [13]. Interestingly the first flare-up after OLT occurs with a similar median delay of 14 (1,2-103,2) months than in our cohort [8, 13, 18]. After renal transplantation, the cases of recurrence of IBD are rarely reported [19, 20].

We report 12 cases of IBD de novo. In OLT, the cumulative risk for IBD de novo is of 10% at 5 years and 30% at 10 years [13]. In renal transplantation, we only reviewed 11 cases, which are shown on table 5 [2, 21-29]. The majority of these cases and those after OLT were UC, whereas we had a majority of CD in our population, maybe because of the North-South gradient of CD existing in France (our centers were rather located in the North) [1]. They occured at a similar age as our patients. The delay of occurrence was pretty variable: 91 (3-139) months in our serie, 42 (9-132) months in the cases after kidney transplantation described in the literature, 30 (2-168) months after OLT. Most of the flare-up improved with 5-aminosalicylates and/or corticosteroids like in our population.

### *Role of CMV*

We have observed a significative correlation between recurrence and CMV infection or disease (p=0,007). In the same way, active IBD-free survival after OLT was significantly higher in patient without CMV infection, and de novo IBD developed only in patients who experienced CMV infection (diagnosed using pp65-antigenemia) in the population studied by Verdonk et al. [12]. They found no relation with primary versus secondary CMV infection. A significative correlation between a CMV mismatch (seronegative

recipients of a seropositive donor) and occurrence of de novo IBD after OLT was also shown [13]. We know these patients are more prone to develop CMV infection but we didn't find this correlation.

In fact, CMV plays a role in IBD out of the context of transplantation. CMV reactivation is rare in patients with mild to moderate IBD. But in severe steroid refractory IBD, the prevalence of CMV in the colonic biopsies is between 30 and 40% [30, 31].

Some think that CMV, attracted and reactivated by the many cytokines that are produced in active IBD, is a marker of severity without impact on the evolution [32]. But CMV increases intestinal permeability [33] and facilitates exposure of the mucosal immune system to the luminal flora. CMV-infected cells can stimulate pro-inflammatory cytokines production and the proliferation of T lymphocytes [12, 34]. For Roblin et al., there is a correlation between the presence of CMV in the colon and a resistance of IBD to the immunosuppressive therapy and antiviral treatment can restore this sensitivity [35].

If CMV is the trigger or just exacerbates the mucosal inflammation is yet unknown but it should be considered, especially in transplanted patients, and the European Crohn's and Colitis Organisation (ECCO) recommends to exclude CMV colitis by tissue PCR or IHC in immunomodulatory refractory cases of IBD before increasing immunomodulator therapy [36]. In our study 6/7 CMV infections or diseases were found in patients with a post-transplant IBD and we can hypothetise that a latent infection may have facilitate the colitis. Of note, blood CMV antigenaemia or PCR do not reflect CMV reactivation in colonic mucosa. Thus it is necessary to document the presence of CMV in the tissue [37].

***Other risk factors of post-transplant IBD***

A longer interval between the diagnosis of IBD and transplantation tended to be associated to an asymptomatic IBD after transplantation (158 months in the "no recurrent IBD" group versus 97 months in the "recurrent IBD" group, p=0,086). This may explain the mean age at the diagnosis of IBD, which was significantly lower in those who didn't recur (27,5 versus 31,3 years, p=0,036). In OLT, a longer delay between the diagnosis of IBD and transplantation significantly decrease the risk of recurrence [13].

We didn't find any correlation between the resumption of the treatment taken before transplantation for the IBD and the risk for recurrence. The two patients who took over

5-ASA after transplantation recurred IBD. Verdonk et al. recommended initiation of a 5-ASA, which may significantly decreased the risk of recurrence of IBD [13].
The use of azathioprine has been associated with less post-transplant IBD [5, 8]. We didn't observe this correlation, but azathioprine is often used at a lower dose than in IBD (1,5mg/kg/j versus 2-2,5mg/kg/j) and it could be not sufficient to prevent IBD flare-up. Even though some studies have shown that MMF could be an alternative therapy for active CD or UC with intolerance to azathioprine [38-41], it is less effective [41] and not recommended. We found no influence of MMF on post-transplant IBD.

We didn't find any correlation between the use of cyclosporine or tacrolimus with the recurrence of IBD. However tacrolimus was found to be an independent factor for IBD post-OLT in multivariate analysis [8, 13].

***Evolution of the IBD after transplantation***

In our population, the evolution of the IBD was quite mild after transplantation (67,9% were severe before transplantation, instead of 28,6% after transplantation).
IBD evolution after transplantation is controversial: for some it is not affected by OLT [9, 42], for others, IBD activity increases after transplantation for PSC or AIH [4, 13, 43, 44]. A short duration of the steroids treatment has been associated with a more severe course post transplantation [18].

***Physiopathologic hypothesis***

Anticalcineurin inhibitors can be used in refractory IBD to avoid surgery. Their efficacy is related to the transcription inhibition of pro-inflammatory cytokines in T cells.
Several studies have shown that IV cyclosporine [45-47] and tacrolimus [48-51], could be effective for induction of a remission in active steroids refractory UC. But it is not effective for the maintenance of the remission [47, 52, 53].
So why, under that treatment for the graft, some patient recur or develop IBD?
Anticalcineurin inhibitors exacerbate some mucosal and immunological abnormalities associated with IBD. They reduce the mucosal barrier function already deficient in IBD [54], increase the intestinal permeability [55] and lead to an inappropriate activation of the mucosal immune system by commensal bacteria. They also reduce the regulatory T cells generation, which are crucial for immunological homeostasis in the intestine and down-regulate the apoptosis of T lymphocytes. Thus, when used for a long term in

predisposed patients, anticalcineurin inhibitors, and especially tacrolimus that is a stronger inhibitor than cyclosporine, could promote IBD [13].

Another hypothesis proposed by Ramji et al. is that a low-level anti-interleukine 2 inhibition obtained with per os anticalcineurin inhibitor in transplantation allows a certain degree of graft tolerance but is not sufficient to avoid AID in predisposed patients [7].

***Limits***

Our study has several limits. Its retrospective nature limits its exhaustivity while the determination of the patients was dependant of the medical team's memory.

Diagnosis of IBD after transplantation is quite difficult and needs to have eliminated infectious disease, toxic reaction and intestinal cancer. Whereas a colonoscopy was always performed in the « IBD de novo » group, it was the case in 6/11 patients in the « recurrent IBD group » and one had an entero-IRM.

Even though the difference is not significative, the median duration of the post-transplant follow-up was shorter in the « no recurrent IBD » group than in the « recurrent IBD » group: would they have had a recurrence if the follow-up were longer?

Finally, the small number of patients limits the statistical power.

**Conclusion**

We describe the most extensive cohort, to our knowledge, of 23 cases of IBD after renal transplantation. We found that the recurrence of the IBD is associated with the occurrence of a CMV infection or disease.

Even though the evolution seems to be mild after transplantation in our population, this fact is discussed in liver transplanted patients and means of prevention have yet to be determined with randomised studies: should we prefer azathioprine or MMF? Should we use systematic preventive treatment with 5-aminosalicylates? Finally, CMV colonic infection should be searched not only with blood investigations but also with colonic biopsies in case of severe refractory flare-up of IBD.

**Table 4.** Studies about recurrence of IBD and de novo IBD after liver transplantation

| | Etiology of liver failure | Number of pre-transplant IBD | Number of recurrence of IBD | De novo IBD | Delay of occurrence (months) | Follow-up after graft (months) | Conclusion |
|---|---|---|---|---|---|---|---|
| **Riley 1997** (USA) [2] | 4 AIH, 5 other hepatitis, 2 PSC, 1 biliary atresia | 0 | 0 | 12 | 48 | | De novo IBD despite IS |
| **Papatheodoridis 1998** (England) [4] | 30 PSC | 16/30 UC | 8 UC | 3 UC | Recurrence : >4<br>De novo : 28,6 (9-32) | 38 (12-92) | Worse course of UC after liver graft without any factor identified.<br>All recurrences after steroids withdrawal |
| **Befeler 1998** (USA) [5] | Including PSC, AIH, PBC | 29 (19 UC, 4 CD) | 7 | 1 UC | ND | 37±6,4 | Better evolution if IBD controlled at graft and Aza post-transplantation |
| **Khan 1999** (USA) [6] | 1 AIH, 1 PSC, 1 ND | 0 | 0 | 3 UC | 12 (6-60) | 11 (6-34) | 3 pediatric cases |
| **Ramji 2002** (Canada) [7] | 1 PBC, 1 HBV | 0 | 0 | 2 CD | 19 and 39 | 115 and ND | Low level of IS : graft tolerance doesn't mean self-tolerance |
| **Haagsma 2003**(Netherlands) [8] | 48 PSC, 30 AIH | 23/48 (18 UC, 4 CD, 1 ind.)<br>2/30 (2 UC) | 9 | 6 (3 UC, 1 CD, 2 ind.) | Recurrences : 12 (3,6-75,6)<br>De novo : 46,8 (13,2-75,6) | 86,4 (13,2-267,6) | More recurrence and de novo IBD if under tacrolimus and not under Aza |
| **Van de Vrie 2003**(Netherlands) [9] | 31 PSC | 18/31 (14 UC, 4 CD) | 10 | 1 | Recurrence : ND<br>De novo : 10 | 62 (15-128) | No influence of IBD on the outcome of the graft. No influence of the graft on the IBD evolution |
| **Papadakis 2004**(USA)[10] | 1 HCV | 0 | 0 | 1 CD | 11 | | Transmission of the donor CD susceptibility ? |
| **Wörns 2006** (Germany) [3] | 2 AIH, 2 cryptogenic cirrhosis, 1 HBV, 1 Wilson | 0 | 0 | 5 UC /314 OLT | 27 (2-30) | | IBD de novo = etiology of diarrhea after transplantation. Aminosalicylates and steroids effective in these patients. |
| **Vu 2006** (Switzerland) [11] | 1 AIH, 1 ethylic cirrhosis, 2 HBV | 0 | 0 | 4 (3 UC, 1 CD) /120 OLT | 54,5 (27-168) | 138 (75-196) | Cyclosporine doesn't prevent occurence of IBD post transplantation |
| **Verdonk 2006**(Netherlands) [12] | 55 PSC, 29 AIH | 28/55 (22 UC, 2 CD, 4 ind.) 3/29 (3 UC) | 12 | 6 (3 UC, 1 CD, 2 ind.) | 16,8 (3,6-75,6) | 76,8 (12-193,2) | Post-transplant IBD (especially de novo IBD) more frequent if CMV infection |
| **Verdonk 2006** (USA) [13] | 60 PSC, 31 AIH | 45/60, 4/31 (44 UC, 4 CD, 1 ind.) | 32 (29 UC, 2 CD, 1 ind.) | 8 (7 UC, 1 CD) | Recurrence : 15,6 (1,2-103,2)<br>De novo : 62,4 (13,2-85,2) | 73,2 (12-139,2) | Risk factors of post-transplant IBD : pre-transplant IBD, use of tacrolimus. Risk factor of de novo IBD : CMV mismatch.<br>Increase in IBD activity after the graft. |
| **Cholongitas 2007** (England) [14] | 56 PSC | 33/56 UC | 17 UC | 3 UC | Recurrence : ND<br>De novo : 9,45 and ND | 34 (12-96) | Disparity in both HLA-DR and DQ associated with stable UC activity after the graft |
| **Barritt 2008** (USA) [15] | 2 PSC, 1 AIH | 0 | 0 | 3 (1 CD, 1 UC, 1 ind.) | 80 (14-108) | | Efficacy of Budesonide in de novo IBD post liver graft. |
| **Hampton 2008** (USA)[16] | 1 AIH | 0 | 0 | 1 CD | 36 | | IBD de novo : some cases of naturally IBD expected, some cases due to altered immunity, role of DAMPs and PAMPs |
| **Dehghani 2009**(Iran)[17] | 1 cryptogenic cirrhosis | 0 | 0 | 1 UC | 5 | | De novo IBD should be condidered as a cause of diarrhea after OLT |
| **Moncrief 2010** (USA)[18] | 49 PSC | 32/49 (32 UC, 8 CD, 2 ind.) | > 13 | 5 | Recurrence : 14,6 (4-47,6)<br>De novo : 57 (2-113) | 68 (33-106) | IBD course more severe after the graft. Protective effect of the steroids duration. |

*PSC, primary sclerosing cholangitis ; IS, immunosuppressant ; AIH, auto-immune hepatitis ; PBC, primary biliary cirrhosis ; UC, ulcerative colitis ; CD, Crohn's disease ; Aza, azathioprine ; ND, non determined ; ind., indeterminate ; HBV, hepatitis B virus ; HCV, hepatitis C virus ; OLT, orthotopic liver transplantation.*

**Table 5.** IBD de novo after renal transplantation in the literature

| | Age (years) | Gender | Initial nephropathy | IS regimen at the diagnosis of IBD | Rejection | CMV informations | Type of IBD | Delay of occurence (months) | Follow-up after the graft (months) | Treatment and evolution |
|---|---|---|---|---|---|---|---|---|---|---|
| Rivera 1990 (Spain) [4] | 27 | M | Unknown | Aza/CT | M3 → IV CT | - | UC | 19 | 72 | PO 5-ASA, topical CT, increase of PO CT→ remission. 4 recurrences. Normal graft function. |
| Passfall 1992 (Germany) [5] | 60 | M | unknown | ciclo | no | IHC biopsy neg | UC | 72 | 87 | 5-ASA and topical CT , then PO CT/PO 5-ASA. Recurrence 12 months later treated with topical 5-ASA. Normal graft function |
| Riley 1997 (USA) [2] | - | - | 1 PKHR 1 Malformative uropathy | Ciclo/CT | - | - | - | - | - | 1 responded to 5-ASA, 1 continued to have flare-up under PO CT |
| Hibbs 2001 (USA) [6] | 6 | M | Goodpasture | Ciclo/Aza/CT | - | IgG+, CMV inclusions on colonic biopsy | UC | 48 | 96 | Pancolectomy after no response to ganciclovir (no evidence of CMV on surgical specimen) |
| Teo 2002 (Australia)[7] | 64 | M | Diabetic nephropathy | Ciclo/Aza | no | IgG+ IgM- | UC | ND | ND | PO CT and 5-ASA → remission |
| Nagai 2005 (Japan) [8] | 31 | F | ND | ND | no | - | UC | 12 | 180 | 2nd graft 1 year later. Severe refractory flare-up of UC 14 years later→ colectomy |
| Halim 2007 (Kuwait) [9] | 40 | M | Chronic glomerulo-nephritis | Basiliximab Tacro/MMF/ CT | Several (noncompliance) | CMV neg in blood | CD | 36 | ND | PO CT and 5-ASA, AB → recovery of IBD. Rapid return in dialysis |
| Halim 2008 (Kuwait) [10] | 39 | M | Nephrosclerosis | ATG Siro/MMF/CT | no | Ag pp65 neg, no signs of CMV on biopsy | CD | 9 | 17 | PO CT and 5-ASA, AB → remission Normal graft function |
| Kourda 2009 (Tunisia) [11] | 42 | F | Unknown | ND | ND | ND | UC | 108 | 132 | Colonic cancer of 6 cm 2 years later, death 1 month after surgery |
| Parames-waran 2011 (India) [12] | 46 | M | Unknown | Aza/CT | no | CMV PCR neg, no signs of CMV on biopsy | UC | 132 | 156 | PO 5-ASA → remission |

*Age, age at the diagnosis of the IBD ; IS, immunosuppressive ; ATG, anti-thymocyte globulin ; Tacro, tacrolimus ; Siro, sirolimus ; MMF, mycophenolate mofetil ; CT, corticosteroids ; 5-ASA, 5-aminosalicylates ; AB, antibiotics ; M, masculine ; F, feminine ; IHC, immunohistochemistry.*

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# Annexes

# QUESTIONNAIRE : PATIENTS PRESENTANT UNE MALADIE INFLAMMATOIRE CHRONIQUE DE L'INTESTIN APRES GREFFE RENALE

## A. PATIENT

Initiales : Sexe : M [ ] F [ ] Date de naissance :
Maladie rénale primitive :

**Antécédents :**

- de cholangite sclérosante primitive : oui [ ] non [ ] ND [ ](non déterminé)
- d'hépatite auto-immune : oui [ ] non [ ] ND [ ]
- de maladie périodique : oui [ ] non [ ] ND [ ]
- de lupus érythémateux disséminé : oui [ ] non [ ] ND [ ]
- de sarcoïdose : oui [ ] non [ ] ND [ ]
- de Gougerot : oui [ ] non [ ] ND [ ]
- d'autre maladie inflammatoire : oui [ ] non [ ] ND [ ]
  si oui laquelle :
- si vous avez répondu « oui » à une des questions précédentes :
  année de diagnostic :

Tabagisme : avant greffe : oui [ ] non [ ] ND [ ]
après greffe : oui [ ] non [ ] ND [ ]

## B. GREFFE

Date de greffe :
Poids au moment de la greffe :

**HLA** receveur : A : B : DR : DQ :
donneur : A : B : DR : DQ :

**Statut** CMV : D+/R+ [ ] D+/R- [ ] D-/R+ [ ] D-/R- [ ] ND [ ]
EBV : D+/R+ [ ] D+/R- [ ] D-/R+ [ ] D-/R- [ ] ND [ ]
Toxo : D+/R+ [ ] D+/R- [ ] D-/R+ [ ] D-/R- [ ] ND [ ]
Prophylaxie anti-CMV : oui [ ] non [ ] ND [ ]
Si « oui » laquelle :

**Traitement immunosuppresseur :**

- induction : anti-IL2R [ ] SAL [ ] autre : aucun [ ]
- d'entretient à la sortie d'hospitalisation ou J10 :
  corticoïdes [ ] Cellcept/Myfortic [ ] Azathioprine [ ]
  Tacrolimus [ ] Ciclosporine [ ] Sirolimus [ ]
  Autre :
- d'entretient à M3 :
  corticoïdes [ ] Cellcept/Myfortic [ ] Azathioprine [ ]
  Tacrolimus [ ] Ciclosporine [ ] Sirolimus [ ]
  Autre :

**Evolution** :
- survenue d'un maladie/infection à CMV : oui [ ] non [ ] ND [ ]
Si « oui » date :
traitement :
- survenue d'un rejet :
humoral : oui [ ] non [ ] Si « oui » date :
traitement :
cellulaire : oui [ ] non [ ] Si « oui » date :
traitement : corticoïdes IV [ ] SAL [ ] Autre :

## C 1 . MICI DIAGNOSTIQUEE AVANT GREFFE

- Diagnostic : Crohn [ ] RCH [ ] colite inflammatoire autre [ ]
Date du diagnostic :

- traitements reçus : corticoïdes IV [ ] PO [ ] dérivés du 5-ASA [ ]
ciclosporine [ ] azathioprine [ ]
anti-TNFα [ ] methotrexate [ ]
chirurgie [ ] autre :
- traitement au moment de la greffe :
corticoïdes [ ] dérivés du 5-ASA [ ]
ciclosporine [ ] azathioprine [ ]
anti-TNFα [ ] methotrexate [ ]
aucun [ ] autres :
- reprise de ce traitement après la greffe : oui [ ] non [ ]
- date de la dernière poussée avant greffe :
- MICI considérée : stable [ ] active [ ] au moment de la greffe

**Récurrence après la greffe** : oui [ ] non [ ]

**Si « non »** :
- Autres traitements reçus dans le cadre le la MICI après la greffe:
corticoïdes IV [ ] PO [ ] dérivés du 5-ASA [ ] methotrexate [ ]
ciclosporine [ ] azathioprine [ ] aucun [ ]
anti-TNFα [ ] chirurgie [ ] Autre :

- Modifications du traitement immunosuppresseur : oui [ ] non [ ]
Si « oui » : remplacement du Cellcept par Azathioprine : oui [ ] non [ ]
autre modification :
date :

**Si « oui »** :
Date de la première récurrence :
Traitement immunosuppresseur en cours à ce moment là :
Corticoïdes [ ] dose :
Cellcept [ ]/Myfortic [ ] dose :
Azathioprine [ ] dose :
Ciclosporine [ ] dose :
Tacrolimus [ ] dose :
Sirolimus [ ] dose :
Autre : dose :

Examens complémentaires réalisés au moment du diagnostic :

- biologiques : (photocopie des examens si possible)

Hb : plaquettes : Leucocytes : PNN : Lympho :
Créat : CRP :
IgA : IgG : IgM : dysglobulinémie : oui [ ] non [ ]
Antigénémie CMV : ND [ ]
PCR CMV : ND [ ]
pANCA : oui [ ] non [ ] ND [ ]
xANCA : oui [ ] non [ ] ND [ ]
ASCA (anti-saccharomyces caerevisiae Ab) : oui [ ] non [ ] ND [ ]

- endoscopiques : oui [ ] (photocopie si possible) non [ ] ND [ ]

- biopsie : oui [ ](photocopie si possible) non [ ] ND [ ]
Recherche CMV sur biopsie : positive [ ] négative [ ] ND [ ]

Traitement reçu pour cette récurrence :

- corticoïdes IV [ ] corticoïdes PO [ ] dérivés 5-ASA [ ]
ciclosporine [ ] azathioprine [ ] methotrexate [ ]
anti-TNFα [ ] chirurgie [ ] autre :
- modifications du traitement immunosuppresseur : oui [ ] non [ ]
Si « oui » la(les)quelles :
- traitement anti-infectieux : oui [ ] non [ ]
Si « oui » le(les)quels :

Evolution après cette première récurrence :

- autres poussées : oui [ ] non [ ]

- survenue de complications :
perforation colique oui [ ] non [ ]
hémorragie digestive massive oui [ ] non [ ]
septicémie d'origine digestive oui [ ] non [ ]
fistules digestives oui [ ] non [ ]
abcès intestinaux oui [ ] non [ ]
occlusion intestinale oui [ ] non [ ]
cancer colique oui [ ] non [ ]

- Autres traitements reçus :
corticoïdes IV [ ] PO [ ] dérivés du 5-ASA [ ]
ciclosporine [ ] azathioprine [ ] methotrexate [ ]
anti-TNFα [ ] chirurgie [ ]

- Autres modifications du traitement immunosuppresseur : oui [ ] non [ ]
Si « oui » : remplacement du Cellcept par Azathioprine : oui [ ] non [ ]
autre modification :
date :

- Perte du greffon : oui [ ] non [ ]
Si « oui » : date
Si « non » : poids actuel :

Créat actuelle :
Traitement immunosuppresseur actuel :

| | |
|---|---|
| Corticoïdes [ ] | dose : |
| Cellcept [ ]/Myfortic [ ] | dose : |
| Azathioprine [ ] | dose : |
| Ciclosporine [ ] | dose : |
| Tacrolimus [ ] | dose : |
| Sirolimus [ ] | dose : |
| Autre : | dose : |

## C 2. MICI DIAGNOSTIQUEE APRES GREFFE

Diagnostic : Crohn [ ] RCH [ ] colite inflammatoire autre [ ]
Date du diagnostic :

Symptômes digestifs (diarrhée chronique, douleurs abdominales fébriles, rectorragies) sans cause retrouvée survenus avant la greffe : oui [ ] non [ ] ND [ ]

Traitement immunosuppresseur en cours à ce moment là :

| | |
|---|---|
| Corticoïdes [ ] | dose : |
| Cellcept [ ]/Myfortic [ ] | dose : |
| Azathioprine [ ] | dose : |
| Ciclosporine [ ] | dose : |
| Tacrolimus [ ] | dose : |
| Sirolimus [ ] | dose : |
| Autre : | dose : |

Examens complémentaires réalisés au moment du diagnostic :

- biologiques : (photocopie des examens si possible)
  Hb : plaquettes : Leucocytes : PNN : Lympho :
  Créat : CRP :
  IgA : IgG : IgM : dysglobulinémie : oui [ ] non [ ]
  Antigénémie CMV : ND [ ]
  PCR CMV : ND [ ]
  pANCA : oui [ ] non [ ] ND [ ]
  xANCA : oui [ ] non [ ] ND [ ]
  ASCA (anti-saccharomyces caerevisiae Ab) : oui [ ] non [ ] ND [ ]

- endoscopiques : oui [ ] (photocopie si possible) non [ ] ND [ ]

- biopsie : oui [ ](photocopie si possible) non [ ] ND [ ]

  Recherche CMV sur biopsie : positive [ ] négative [ ] ND [ ]

Traitement de la poussée :

- corticoïdes IV [ ] corticoïdes PO [ ] dérivés 5-ASA [ ]
  ciclosporine [ ] azathioprine [ ] methotrexate [ ]
  anti-TNFα [ ] chirurgie [ ] autre :

- modifications du traitement immunosuppresseur : oui [ ] non [ ]

Si « oui » la(les)quelles :

- traitement anti-infectieux : oui [ ] non [ ]

Si « oui » le(les)quels :

Evolution depuis cette première poussée :

- autres poussées : oui [ ] non [ ]
- survenue de complications :
  - perforation colique oui [ ] non [ ]
  - hémorragie digestive massive oui [ ] non [ ]
  - septicémie d'origine digestive oui [ ] non [ ]
  - fistules digestives oui [ ] non [ ]
  - abcès intestinaux oui [ ] non [ ]
  - occlusion intestinale oui [ ] non [ ]
  - cancer colique oui [ ] non [ ]

- Autres traitements reçus :

corticoïdes IV [ ] PO [ ] dérivés du 5-ASA [ ]
ciclosporine [ ] azathioprine [ ] methotrexate [ ]
anti-TNFα [ ] chirurgie [ ]

- Autres modifications du traitement immunosuppresseur : oui [ ] non [ ]
  - Si « oui » : remplacement du Cellcept par Azathioprine : oui [ ] non [ ]
    - autre modification :
    - date :

- Perte du greffon : oui [ ] non [ ]
  - Si « oui » : date
  - Si « non » : poids actuel :
    - Créat actuelle :
    - Traitement immunosuppresseur actuel :
      - Corticoïdes [ ] dose :
      - Cellcept [ ]/Myfortic [ ] dose :
      - Azathioprine [ ] dose :
      - Ciclosporine [ ] dose :
      - Tacrolimus [ ] dose :
      - Sirolimus [ ] dose :
      - Autre : dose :

# 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

Académie d'Orléans – Tours

Université François-Rabelais

**Faculté de Médecine de TOURS**

***FOURNIER Anne*** **Thèse n°**

40 pages – 5 tableaux – 1 figure

**Résumé :**

**Introduction**
Les corticoïdes et immunosuppresseurs sont utilisés dans le traitement des maladies inflammatoires chroniques de l'intestin (MICI) (maladie de Crohn et rectocolite hémorragique). Pourtant, les MICI peuvent récidiver ou apparaître après greffe d'organe. Souvent étudiées en greffe hépatique, il n'existe que très peu de cas publiés en transplantation rénale. Notre but était de rassembler une série significative de cas de MICI chez des transplantés rénaux afin d'en déterminer les caractéristiques, de rechercher les facteurs associés à la récurrence, et d'évaluer l'évolution des MICI après la greffe.

**Patients et méthode**
Il s'agit d'une étude multicentrique rétrospective basée sur un questionnaire envoyé à 12 centres français. Les critères d'inclusion étaient : tous les patients transplantés rénaux ayant eu un diagnostic de MICI avant ou après la greffe. Nous avons recensé les caractéristiques démographiques des patients, les antécédents de maladies auto-immunes, l'évolution de la MICI avant et après la greffe, le statut CMV, la survenue d'une infection/maladie à CMV, et le traitement immunosuppresseur.

**Résultats**
40 patients transplantés rénaux entre 1989 et 2011 ont été inclus. 28 avaient une MICI connue avant la greffe. 11 ont récidivé et 12 ont développé une MICI de novo après la greffe. Le délai médian de poussée après la greffe a été de 17 (1-167) mois pour les récurrences et de 91 (3-139) mois pour les MICI de novo. Une infection ou maladie à CMV était significativement corrélée à la survenue d'une récurrence, et 6 des 7 infections ou maladies à CMV recensées sont survenues chez des patients développant une MICI post-greffe. L'évolution post-greffe était favorable puisque 67,9% des patients étaient considérés sévères avant la greffe contre 28,6% après la greffe.

**Conclusion**
Il s'agit de la plus grande cohorte de transplantés rénaux atteints d'une MICI. La prévention de ces maladies après la greffe reste à déterminer.

**Mots clés :**

- maladie inflammatoire chronique de l'intestin
- transplantation rénale

**Jury** :

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**Date de la soutenance** : 10 avril 2012