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Prévention de la tuberculose chez les transplantés rénaux : rôle clé de la consultation maladie infectieuse avant la transplantation

Prevention of tuberculosis among kidney transplant patients: key role of the infectious disease consultation prior to the transplantation

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Abréviations françaises

IDR : Intradermo réaction

IGRA : Interferon-gamma release assay

ITL : Infection tuberculeuse latente

OMS : Organisation Mondiale de la Santé

TB : Tuberculose

Abbreviations

BCG: Bacille Calmette-Guerin

BMI: Body Mass Index

CMV: Cytomegalovirus

EBV: Epstein-Barr virus

HBC: High burden countries

HHV6: Human Herpes Virus 6

HSV: Herpes simplex virus

HTLV1: Human T cell leukemia/lymphoma virus type 1

IGRA: Interferon-gamma release assay

IQR: Interquartile range

LTBI: Latent tuberculosis infection

Med: Median

TB: Tuberculosis

TST: Tuberculin skin-test

SOT: Solid organ transplant

VZV: Varicella-zoster virus

WHO: World Health Organization

Introduction (français)

La tuberculose (TB) est une maladie reconnue pour sa contagiosité et son fort taux de mortalité avant le développement de la quadrithérapie appropriée. La maladie est due à l'infection par un bacille acido-alcoolo résistant, *Mycobacterium tuberculosis,* capable de persister en intra-cellulaire et ainsi d'échapper aux défenses immunitaires (1). La TB reste la première cause de mortalité d'origine infectieuse dans le monde et est à ce titre l'une des priorités de l'Organisation Mondiale pour la Santé (OMS) (2). Après contact avec un individu contagieux, deux scénarios peuvent survenir : la vaste majorité (90%) des individus vont développer une infection tuberculeuse latente (ITL) tandis que 10% ne seront pas infectés (3). L'ITL est définie par l'OMS comme un état d'activation immunitaire persistant en réponse à la stimulation antigénique maintenue par *Mycobacterium tuberculosis* sans argument pour une TB active (4). Parmi les individus atteints d'ITL, 10% vont développer une TB maladie en population générale. Cette proportion est plus forte chez les sujets immunodéprimés, pour lesquels la maladie est plus grave. Les facteurs de risque de la TB se distinguent entre les aspects environnementaux, liés aux problématiques sociales et à la pauvreté, qui vont prédominer dans les pays à forte prévalence, et la susceptibilité de l'hôte, telle que l'immunodépression, qui prédomine dans les pays à faible prévalence. L'OMS définit les pays fortement touchés par la TB comme ceux réunissant plus de 80% des cas mondiaux. Ces pays à forte prévalence s'opposent aux pays à faible incidence, dont les taux sont inférieurs à 10/100 000 personne/année (2). Avec l'augmentation des patients immunodéprimés, partiellement due au développement des activités de greffe, il est devenu indispensable de détecter les patients avec ITL afin de prévenir la survenue d'une TB post transplantation, même dans les pays à faible incidence.

Les recommandations pour le dépistage de l'ITL sont basées sur la prévalence de la TB. Dans les zones à forte prévalence, il est recommandé de prescrire une prophylaxie pour tout candidat à la transplantation d'un organe solide (5). A l'inverse dans les pays à faible prévalence, les indications de prophylaxie varient selon une appréciation individuelle du risque (5–9). Il est à noter l'absence de standardisation des pratiques autour du dépistage de l'ITL et de la prophylaxie de la TB pour les candidats à la transplantation dans les pays à faible incidence.

Le but de cette étude rétrospective monocentrique est de décrire la population des patients candidats à une transplantation rénale en termes de risque de TB et de définir ceux éligibles à la prophylaxie. Les objectifs secondaires sont la comparaison des patients avec et sans indication à traitement de l'ITL et de décrire les pratiques autour de la prévention de la TB chez les candidats à une transplantation rénale dans notre centre.

Abstract

Introduction: Tuberculosis (TB) remains a burden in low prevalence countries, especially for immunocompromised patients such as solid organ transplant (SOT) recipients with an overall incidence of 0.8% and 0.7 to 5% in kidney transplant recipients. However, practices concerning TB screening and treatment for latent tuberculosis infection (LTBI) in SOT recipients are not standardized between centers.

Objectives: This monocentric retrospective cohort study aims at describing the risk of TB in a population of candidates for kidney transplantation and defining those eligible for chemoprophylaxis.

Results: From January 2020 to June 2021, 136 patients were evaluated by an infectious disease specialist before transplantation. Out of 136 patients, 27 (20%) were eligible for LTBI treatment, 10 (37%) of whom were treated for LTBI on the sole basis of a positive IGRA and had no other known risk factors of TB. Apart from the known risk factors of TB, patients with LTBI were significantly older (P = 0.026) and more immune to Hepatitis A (P = 0.016) and HHV6 (P = 0.013) than the general population of kidney transplant recipients. Twenty (74%) patients were treated exclusively with isoniazid whereas 7 (26%) were treated with a combination of rifampin and isoniazid. Three (12.5%) patients reported side effects including 1 hepatic cytolysis. No interactions with immunosuppressant treatment were described.

Conclusion: TB prevention requires a dedicated evaluation for a better care of SOT recipients.

Introduction

Tuberculosis (TB) is a disease well-known for its high contagiousness and mortality rate before the development of appropriate therapeutic combinations. The pathogenic agent of TB is *Mycobacterium tuberculosis*, an acid-alcohol-resistant bacteria whose particularity is to persist intracellularly by evading immune defenses (1). TB is still the leading cause of mortality from infectious disease worldwide and remains a priority for the World Health Organization (WHO) (2). After having been in contact with a contagious individual, two possible scenarios can occur: first, the vast majority (90%) of patients will develop an asymptomatic latent tuberculosis infection (LTBI). Second, approximately 10 % of cases will not be infected (3). LTBI is defined by the WHO as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB (4). Among the individuals with LTBI, 10% will develop a TB disease, with a higher probability for immunocompromised patients (10). Risk factors of tuberculosis can be divided into 2 categories : environmental exposure, linked to social issues and poverty in high prevalence countries, and host factors, such as immunosuppression. The latter is the most prominent factor in low prevalence countries. The WHO defined high-burden countries (HBC) as the top 30 countries with the most prevalence of TB (2). They account for 86% of the cases of tuberculosis. Those HBC differ from low-prevalence countries whereby a typical incidence of less than 10 per 100 000 population per year (2). With the surge of immunocompromised patients, partially due to the increasing transplantation activity, it became essential to screen patients with LTBI to prevent the occurrence of TB disease after transplantation.

Screening guidelines of LTBI are based on the prevalence of tuberculosis. In areas of high prevalence, such as HBC, chemotherapy is recommended for all solid organ transplant (SOT) recipients (5). In low-incidence regions, chemotherapy indications are subjected to

an individual risk assessment (5–9). It should be noted that, practices concerning TB screening and chemoprophylaxis for SOT recipients are not standardized among centers.

This monocentric retrospective cohort study aims at describing the risk of TB in a population of candidates for kidney transplantation and defining those eligible for chemoprophylaxis. The secondary objectives are to compare patients with LTBI and without LBTI within the collected data and to describe practices toward TB-related risk management for kidney transplantation candidates in our center.

Material & Methods

Patient's inclusion and eligibility criteria

Data were collected from a prospective cohort of patients seen in infectious disease consultation before transplantation from January 2020 to June 2021. Eligible patients were at least 18 years old and were not under juridic protection. The exclusion criterion was defined by patients who opposed to being involved in the study.

The following data were retrospectively collected: age, sex, body mass index, country of birth, familial origins, dialysis, primary diagnosis leading to transplantation, previous renal transplantation, immunosuppressant treatment before transplantation, prior medical history of non-TB infectious disease, long-term (> 3 months) stay in countries of high TB-endemicity, contact with infected individuals from TB, prior medical history of TB, interferon-gamma release assay (IGRA), thoracic imaging prior consultation, serological assessment of CMV, EBV, Toxoplasmosis, HIV, HSV, HTLV1, HHV6, VZV, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, Syphilis. Every patient had an IGRA and there was no tuberculin skin test (TST) performed.

Statistical analysis

Categorical variables are expressed in terms of frequency and percentage. Quantitative variables with normal distribution are expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR) otherwise. The normality of distributions was checked graphically and using the Shapiro-Wilk test ($n \leq 50$) or Kolmogorov-Smirnov test ($n > 50$). Comparisons between patients with indication to chemoprophylaxis and patients without indication were performed using the Chi-square test (or Fisher's exact test in case of expected value < 5) for categorical variables and Student's t-test for quantitative variables.

Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

Ethical considerations

Each patient received an informative letter requesting opposition. Collected data were anonymized. The data collection complies with the « Commission National de l'Informatique et des Libertés » guidelines.

Results

Patients' characteristics

From December 2019 to October 2020, 258 patients were evaluated in nephrology consultation to assess their eligibility for transplantation. Among them, 138 patients had had a consultation with an infectious disease specialist in a period extending from January 2020 to June 2021. 2 patients were excluded due to their reported opposition. The process of inclusion is summarized in the flow chart (Fig. 1). Baseline characteristics are shown in table 1.

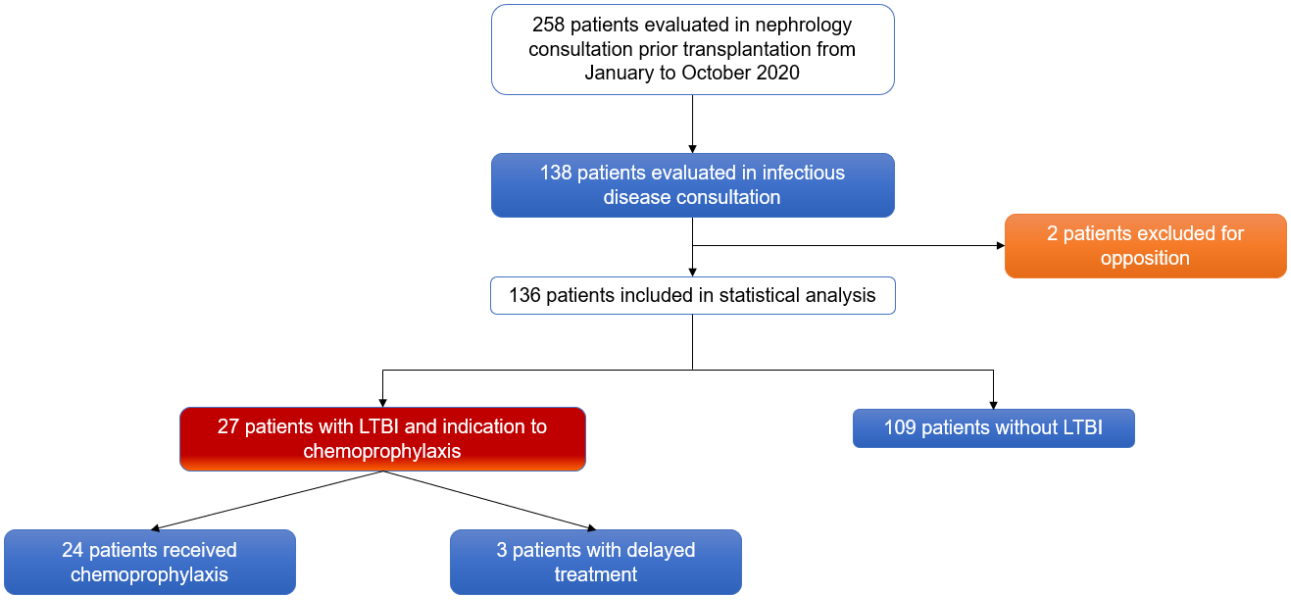

Figure 1. Flow chart

The cohort included a majority of men with a sex ratio of 1.83, and a majority (75%) of patients on dialysis. The first causes of nephropathy leading to transplantation were undetermined, followed by diabetes and hypertension. Thirty-five (26%) patients had at least one factor of immunosuppression prior to transplantation. The median duration of follow-up was 1 year (IQR 1).

Demographic characteristics and comorbidities	n = 136
Age (years) [mean +/- SD]	**56 +/- 14**
[Min-Max] years	[20-78]
Sex ratio M/F [n (%)]	**88 (65) / 48 (35)**
Body Mass Index (BMI) (kg/m²) [mean +/- SD]	**27 +/- 7**
Dialysis [n (%)]	**102 (75)**
Hemodialysis / Peritoneal Dialysis / Modality	80 (63) / 12 (10)
Non available [n (%)]	*10 (7)*
Time on dialysis (years) [med (IQR)]	3 (2.25)
Nephropathy leading to transplantation	
Diabetes [n (%)]	20 (15)
Hypertension [n (%)]	10 (7)
Polycystic kidney disease [n (%)]	16 (12)
Renal agenesis [n (%)]	3 (2)
Toxicity due to previous treatment [n (%)]	3 (2)
Immunological	
IgA nephropathy [n (%)]	15 (11)
ANCA glomerulonephritis [n (%)]	2 (1.5)
Membranous glomerulonephritis [n (%)]	4 (3)
Membrano-proliferative glomerulonephritis [n (%)]	4 (3)
Others [n (%)]	14 (10)
Undetermined [n (%)]	31 (23)
Immunosuppression prior to transplantation	
Previous kidney transplantation [n (%)]	18 (13)
Ongoing immunosuppressant treatment [n (%)]	14 (10)

HIV [n (%)]	2 (1)
Asplenia [n (%)]	1 (1)
Hypogammaglobulinemia [n (%)]	1 (1)

Table 1. Baseline characteristics of 136 patient candidates to kidney transplantation

The infectious disease specialist's reports show that the majority of the patient cohort (60/136, 44%) were born in France. However, for 55 (41%) patients, the country of birth was not specifically reported. This could suggests that they were born in France or Europe. Patients from Maghreb (10/136, 7%) and Sub-Saharan Africa (9/136, 7%) were the most numerous immigrants from the population in this study population (Fig. 2 A). Among TB endemic areas, travels were more frequent to the countries of origin of the patients, namely in the Maghreb and Sub-Saharan Africa (Fig. 2 B).

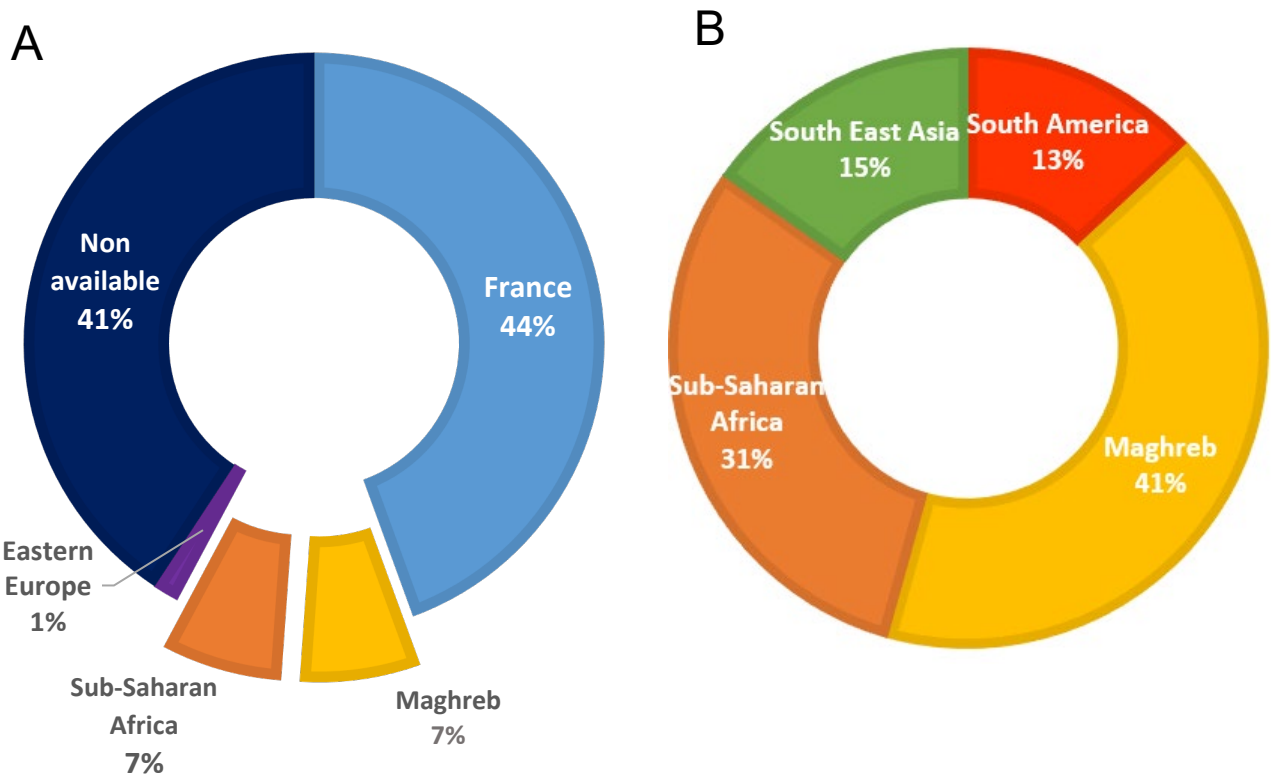

Figure 2. Country of birth (A) of the patients and travel history in high endemicity areas (all length of stay (B)

Past immunization

The highest seroprevalence in this cohort were VZV (99%), EBV (96%), Measles (95%) and Rubella (94%). Two (1%) patients were HIV positive and had a controlled infection with a negative viral load. Eighty-four patients (62%) and 86 (65%) were CMV and toxoplasmosis positive respectively (table 2).

Positive serological assessment	[n (%)]
CMV	**84 (62)**
EBV	**130 (96)**
Toxoplasmosis	**86 (65)**

Non-available data	*4 (3)*
HIV	**2 (1)**
HTLV1	**2 (2)**
HSV	**91 (81)**
Non-available data	*23 (17)*
VZV	**132 (99)**
HHV6	**62 (55)**
Borderline	*1 (1)*
Non-available data	*24 (18)*
Hepatitis A	**73 (55)**
Non-available data	*4 (3)*
Hepatitis B	**7 (5)**
Hepatitis C	**4 (3)**
Hepatitis E	**1 (1)**
Borderline	*3 (2)*
Non-available data	*10 (7)*
Rubella	**121 (94)**
Borderline	*2 (2)*
Non-available data	*7 (5)*
Measles	**126 (95)**
Non-available data	*4 (3)*
Mumps	**113 (89)**
Borderline	*4 (3)*
Non-available data	*9 (7)*
Syphilis	**2 (1)**

Table 2. Positive serological assessment among 136 patient candidates for kidney transplantation If note mentioned all data were available

Risk of LTBI in the studied population

No signs of acute TB (such as fever, weight loss, fatigue, cough, sputum, dyspnea and night sweats) were described during the examination of this population. Chest imaging was reported for 64 patients (47%), which was systematically a thoracic computed tomography (CT) scan. No cavitation nor mediastinal adenopathy were found on thoracic imaging.

Risk factors of LTBI in our patient cohort are listed in table 3. Approximately a fourth (26%) of the patients originated from a high endemicity country. A few of them had a previous personal history of TB (4%) or active TB among relatives (4%). Six patients (9%) had radiological evidences compatible with post-TB sequelae including calcifications (n = 1) and micronodules (n = 5). Nine patients had undetermined IGRA. Among those 9, 3 patients had a control of the assay. For the 6 remaining patients, the test was not repeated but they had no other known risk factors of TB.

Patients who were diagnosed with LTBI by the infectious disease specialist had an indication to receive TB chemoprophylaxis or LTBI's treatment. "Diagnosed with LTBI" or "with an indication for TB chemoprophylaxis" are terms used conversely in the text from this point.

Characteristics of the population in terms of risk of LTBI	n = 136
Country of birth and/or familial origin from a TB-endemic-country [n (%)]	**21 (26)**
Non-available data [n (%)]	*55 (68)*
Travel history	
Maghreb (n)	25
Sub-Saharan Africa (n)	18
South America (n)	7
South East Asia (n)	9
Non available data [n (%)]	*9 (7)*

Past medical history of TB [n (%)]	**5 (4)**
TB among relatives *Non-available data [n (%)]*	**3 (4)** *52 (38)*
Stay of 3 months or more in a TB-endemic-country [n (%)] *Non-available data (n,%)*	**21 (17)** *13 (10)*
Radiological evidence compatible with post-TB sequelae [n (%)] *Non-available data [n (%)]*	**6 (9)** *72 (53)*
IGRA	
Positive [n (%)] *Limit of positivity threshold [n (%)]*	**24 (19)** *2 (2)*
Negative [n (%)]	**93 (73)**
Undetermined [n (%)]	**9 (7)**
Non-available [n (%)]	**8 (6)**

Table 3. Distribution of risk factors of LTBI in the cohort of 136 patients
If note mentioned all data were available

Characterization of patients with LTBI

According to the infectious disease specialist evaluation, 27 (20%) patients had LTBI and required TB chemoprophylaxis. The table 4 summarized their characteristics in terms of risk factors. All IGRA positive patients were considered for treatment except for 2 patients. One of whom, who apart from showing an IGRA being at the test's positivity limit showed no other known risk factors. The other patient had an IGRA performed after the infectious disease evaluation and the positivity was not reported to the infectious disease specialist.

Among those 27 LTBI patients, 10 (37%) were treated for LTBI on the sole basis of a positive IGRA and had no other known risk factors of TB. On the other side, 4 (15%) patients were treated despite a negative, borderline or unavailable IGRA. All of them had at least 2 risk factors. More details concerning those 4 patients are listed below :

- 2 patients with a negative IGRA had a past medical history of TB (pulmonary and undetailed site) with no appropriate treatment mentioned. Those patients were born and stayed for more than 3 months in a high-endemicity TB country,
- 1 patient, whose IGRA result was not available, came from a high-endemicity country with a history of stayed for longer than 3 months in the country
- 1 patient, whose IGRA was at the threshold of positivity, had a prior exposure of TB (pulmonary) from the relatives and stayed longer than 3 months in a high-endemicity TB country.

Of the whole cohort, 8 patients had no available IGRA result. However, only one had additional risk factors for LTBI (as described above). Hence, only 1 on 8 patients with non-available IGRA was treated for LTBI.

Characteristics and distribution of risk factors among patients with LTBI	n = 27
Sex Ratio M/F [n (% out of 27)]	**19 (70) / 8 (30)**
Dialysis [n (% out of 27)]	**20 (74)**
Country of birth and/or familial origin from a TB-endemic-country [n (% out of 27)] *Non-available data [n (%)]*	**16 (72)** *5 (19)*
Travel history	
Maghreb (n)	11
Sub-Saharan Africa (n)	7
South America (n)	2
South East Asia (n)	3
Past medical history of TB [n (% out of 27)]	**3 (11)**
TB among relatives [n (% out of 27)]	**1 (8)**

Non-available data [n (%)]	*14 (52)*
Stay of 3 months or more in a TB-endemic-country [n (% out of 27)] Non-available data [n (%)]	**12 (46)** *1* (4)
Radiological evidence compatible with post-TB sequelae [n (% out of 27)] *Non-available data [n (%)]*	**5 (26)** *8 (30)*
Positive IGRA [n (% out of 27)] **Borderline IGRA [n (% out of 27)]**	23 (85) 1 (4)

Table 4. Characteristics of patients with indication to chemoprophylaxis
If not mentioned all data were available

Patients with risk factors in spite of a negative IGRA

Seventeen (12.5%) patients had risk factors of LTBI in spite of a negative IGRA. They were not diagnosed with LTBI nor considered for chemoprophylaxis by the infectious disease specialist. Among those 17 patients, the risk-factor number reached two for 7 patients and the remaining 10 had a single factor that could contribute to developing LTBI. Hereunder are additional details concerning the patients:

- 10 patients were born and/or raised by a family originating from a high endemicity country,
- 2 patients had a prior history of TB (1 LTBI, 1 pulmonary TB) well treated,
- 2 patients had a history of exposition to TB from a close relative (pulmonary TB),
- 9 patients had a history of staying for longer than 3 months in a high endemicity country,
- 2 patients had a lesion on chest imaging potentially compatible with post-TB sequelae (micronodule and ground glass opacity) but non-specific,

- 7 patients had two risk factors: they were born or raised by a family originating from a high endemicity country and stayed more than 3 months in those countries. One of them had aspecific ground glass opacity at thoracic imaging in addition to the previous risk factors.

Details on TB chemoprophylaxis

Among the 27 patients with LTBI, 20 (74%) patients were prescribed only isoniazid q.d. in contrast to 7 (26%) patients who were prescribed a combination of isoniazid and rifampin q.d.. Twenty-four patients out of 27 started the LTBI treatment. Three patients had their treatment delayed until confirmation of the indication for transplantation. Even when the treatment was delayed, the infectious disease specialist mentioned which option of LTBI treatment he chose for the patient. The median duration of treatment was 9 months (IQR 3) for isoniazid alone therapy and 3 months for each rifampin and isoniazid combination. Seventeen (70%) patients were on dialysis when starting the treatment. Rifampin was always administered at 600 mg q.d. and isoniazid median dose was 200 mg q.d. (IQR 100). Nine patients had 300 mg q.d of isoniazid. All of them were on dialysis.

Three (12.5%) patients showed side effects associated with TB chemoprophylaxis. The 3 patients were on dialysis. Side effects included minor headaches, nausea and hepatic cytolysis. Headaches and nausea occurred for 2 patients treated with 200 mg q.d. of isoniazid alone. For 1 of the patients treated with a combined 300 mg q.d. of isoniazid and rifampin, a hepatic cytolysis of more than 3 times values the upper limit of normal aminotransferase occurred. The hepatic disorders resolved after rifampin discontinuation.

Details on transplantation

In March 2022, 36 out of 136 patients underwent kidney transplantation. Among them, 5 patients were diagnosed with LTBI and received chemoprophylaxis with no known

interference with the immunosuppressant treatment. They were all on dialysis before transplantation and each of them received isoniazid alone at doses between 200 and 300 mg q.d.. Four of them had a complete LTBI treatment before transplantation. Induction protocol included anti-thymocyte globulin or basiliximab and corticosteroids followed by mycophenolate mofetil and tacrolimus as mainstay treatment.

Comparison between patients with and without LTBI

Table 5 summarizes the comparison data between patients with and without LTBI. Previous personal medical history or among the relatives TB, abnormal chest imaging and EBV, VZV, HIV, HTLV1, Rubella, Measles, Hepatitis B, Hepatitis C, Hepatitis E and Syphilis positive serologies were not analyzed due to non-comparable proportion in each group.

	Patients without LTBI (n=109)	**Patients with LTBI (n=27)**	***P* value**
Age (mean +/- SD)	54.7 +/- 13.9	61.4 +/- 14.3	**0.026**
Male sex [n (%)]	69 (63)	19 (70)	0.49
BMI (mean +/- SD)	26.7 +/- 5	25.7 +/- 4.3	0.33
Familial origin or birth in a high endemicity country [n (%)]	10 (18)	11 (50)	**0.003**
Stay of 3 months or more in high endemic areas [n (%)]	9 (9)	12 (44)	**<0.001**
Positive IGRA [n (%)]	1 (0.9)	23 (92)	**<0.001**
Dialysis [n (%)]	83 (76)	20 (74)	0.82
Previous immunosuppressant [n (%)]	15 (14)	1 (4)	0.19
Prior kidney transplantation [n (%)]	16 (15)	1 (4)	0.19
Past immunization			
CMV [n (%)]	66 (60)	19 (70)	0.33
Toxoplasmosis [n (%)]	66 (63)	20 (74)	0.28
HSV [n (%)]	72 (81)	19 (79)	1.00
Mumps [n (%)]	90 (90)	23 (89)	0.73
HHV6 [n (%)]	44 (49)	18 (78)	**0.013**
Hepatitis A [n (%)]	52 (52)	21 (78)	**0.016**

Table 5. Comparison between patients with LTBI (chemoprophylaxis' indication) and without LTBI

Known risk factors and positive IGRA were closely associated with the diagnosis of LTBI by the infectious disease specialist (familial origin or birth in a high endemicity country [P = 0.003], stay of 3 months or more in a high endemic areas [P < 0.001], positive IGRA [P < 0.001]). The data collected shows that patients with LTBI are significantly older (P = 0.026) and already immune to Hepatitis A (P = 0.016) and HHV6 (P = 0.013) possibly due to higher expositions in endemic countries.

Further depiction of practices

The median delay between nephrology examination and infectious disease evaluation was 5 months (IQR 4.25) with prolonged delay starting from September 2020 (Fig. 3).

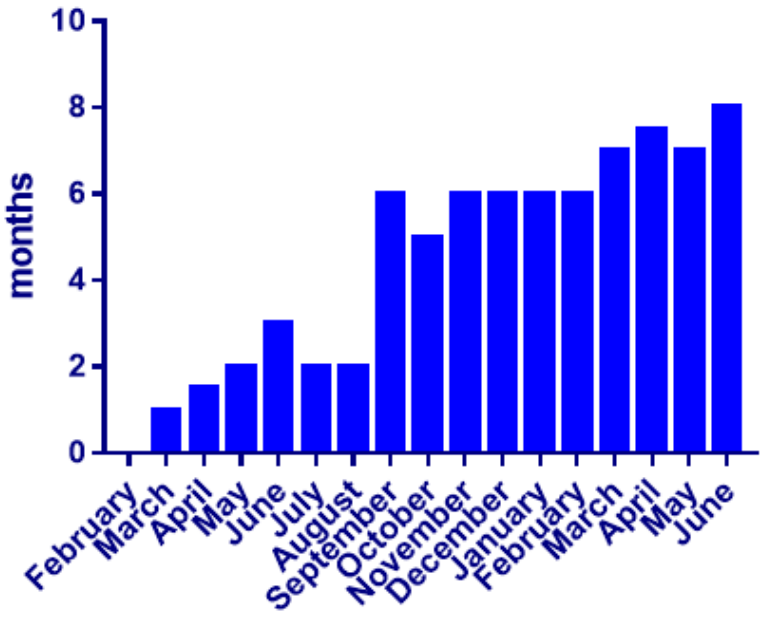

Figure 3. Delay (median) between nephrology appointment and infectious disease evaluation from February 2020 to June 2021

Of all the specific risks factors of LTBI evaluated during the infectious disease consultation, country of birth or familial origins (55 patients, 68%), chest imaging (72 patients, 53%) and prior history of TB among the relatives (52 patients, 38%) were the least notified in the infectious disease specialist's report (table 3). In terms of follow-up, 5 patients out of 27 (19%) had a reevaluation by the infectious disease specialist of their side effects. The other patients were evaluated by the nephrologist.

Discussion

In low-prevalence countries, the overall incidence of TB is estimated at 0.8% for SOT recipients and 0.7 to 5% for kidney transplant recipients (11,12). The majority of TB occurs within the first 6 months post-transplant, except for kidney transplant patients, typically occurring later (median 11.5 months) (12). Extrapulmonary and disseminated TB are more frequent in the SOT recipients and kidney transplant recipients accounting for 67% of cases (13). Notably, the mortality rate associated with TB in SOT recipients is higher compared to other patients (6-22%) (7). TB can be transmitted to transplant patients through 4 different ways: endogenous reactivation, donor-derived reactivation, de novo exposure, or when a patient suffers from an active TB and requires urgent transplantation (6). Identified risk factors for TB in SOT recipients are: diabetes mellitus, immunosuppressive treatment with *OKT3* or anti-T cell antibodies, chronic liver disease in kidney transplant, co-existing infection, lesions on chest radiograph or previous tuberculosis infection (14). Moreover, Hepatitis C was identified as a specific risk factor for kidney transplant recipients (15).

Recommendations agree on routine screening for LTBI before transplantation for all candidates. Since there is no direct microbiologic test for the diagnosis of LTBI, its diagnosis relies on a body of evidence. All recommendations comply with a screening composed of: epidemiologic risk assessment (exposure or history of TB), TST or IGRA. Two categories of IGRA are used in practice: T-SPOT.TB (immunosorbent spot assay) or QuantiFERON-TB (ELISA). Some areas are not systematically evaluated: chest imaging is recommended routinely in most guidelines although one advocates for selective chest evaluation (8). Notably, in this study 53% of the patients had no depiction of thoracic imaging in the infectious disease report. Second testing of TST when negative is recommended by 2 guidelines to avoid false-negative (5,8).

Our study depicts patient candidates for kidney transplantation in terms of infectious risk factors. Twenty-one (26%) patients originated from or were raised by a family coming from a high endemicity country. The vast majority of patients (102/136, 75%) were on dialysis but only 18 % (25/136) were immunocompromised due to a cause other than kidney impairment. The serological assessment for CMV, EBV, HSV, VZV, Hepatitis B, Hepatitis C, Rubella, Measles and Mumps showed similar results to the general population (16–23). Toxoplasmosis seroprevalence appeared higher in our population (65% compared to 30% in French pregnant women population) (24). Hepatitis A immunization was also higher in our study than among young adults in France (55% compared to 11.5%) (25). Nonetheless the compared populations are younger than the population of this study which might explained the differences of data. Among the 27 patients diagnosed with LBTI, a third (37%) showed no other known risk factors for TB and were treated on the sole basis of a positive IGRA. However, we should keep in mind the numerous missing data from our collection. Since all the risk factors were not diligently reported in each observations, it would thus lead to underestimate additional risk factors. This puts the emphasis on a thorough evaluation for all patients, even for those who are not considered at high risk of TB.

Twenty-four (19%) patients in our cohort were IGRA positive. T-SPOT.TB or QuantiFERON-TB were used conversely since no known significant differences in performance were described in the literature (26,27). All patients with positive IGRA were treated except for two: one, whose IGRA positivity was at the threshold of positivity without other risk factors and one whose IGRA positivity was not available at the time of the infectious disease evaluation. The latter and his care providers were informed a later time. However, 17 (12.5%) patients had at least one risk factor (among originating from a high-endemicity country, staying more than 3 months in high-endemicity country, personal history of TB or TB exposure from a relative, having radiological evidence compatible with post-TB sequelae or IGRA positivity) in spite of a negative IGRA and were not diagnosed with LTBI. IGRA,

which is the only objective biological test for LTBI, is among the most important factor for LTBI's diagnosis and treatment according to recommendations (4). A reduced T cell response to antigen stimulation in patients with end-stage kidney could lead to false negative or undetermined IGRA results, suggesting that TST could be the preferred TB-risk assessment test method. However, since IGRA is the favored test for patients vaccinated against the Bacille Calmette-Guerin(BCG), and since the majority of the population fall in the vaccinated category, the choice of IGRA is evermore sustained. Moreover, the reduced lead time to obtain IGRA results as compared to TST made it a more practical choice. Indeed, IGRA results can be obtained within the same day of the test, whereas TST test would require reconvening patients several days after the actual testing. Additionally, T-SPOT.TB and QuantiFERON-TB were both shown to have better performance to diagnose LTBI than TST in immunocompromised and hemodialysis patients (28,29). Considering the importance of IGRA in the LTBI diagnosis, our observations raise multiple questions not clearly answered in the current recommendations. Firstly, how should undetermined or negative IGRA be handled? Some guidelines recommend repeating negative IGRA which was not performed with our patients since the negative ones had no LTBI additional risk factors (5,8). The US guidelines suggest to repeat undetermined IGRA without strong expert recommendation (30). Ultimately, the infectious disease specialist has the final word as to whether or not a test is to be repeated. Secondly, should patients with one risk factor (originating from a high-endemicity country, staying more than 3 months in high-endemicity country, personal history of TB or TB exposure from a relative, radiological evidence compatible with post-TB sequelae) but negative IGRA be treated? In this study, patients with negative, borderline or non-available IGRA were not treated except for 4 patients, who had additional risk factors. Lastly, how to judge the importance of the origin as a risk factor? Some patients were born and raised in a high endemicity country while others were only raised by members settled in a low endemicity country for generations. These unanswered

issues might explain the variability of practices among infectious disease specialists. As this study suggests, risk factors are meant to be stratified so that the strongest precludes in the chemoprophylaxis's indication.

Comparison between patients diagnosed with LTBI and the others showed that patients with LTBI were older (P = 0.026) and significantly more immune to HHV6 (P = 0.032) and Hepatitis A (P = 0.016) prior to transplantation. This might be linked to a previous exposition in a high endemic country for patients who were from the early generations of immigrants.

All recommendations agree on treating for LTBI TST or IGRA positive patients, patients with a history of previous TB who did not receive appropriate TB therapy and patients with close and prolonged contact with a case of active TB. Other points are not consensual: Two recommendations advocate for treating all individuals originating from a country with a very high incidence (e.g. 100 per 100,000 population per year) (6,9). LTBI's treatment was recently updated in US guidelines which place rifamycin based regimen over a long course of isoniazid monotherapy (6-9 months) (31). Four regimens are considered: 3 months of weekly isoniazid and rifapentine combination, 4 months of daily rifampin, 3 months of daily isoniazid plus rifampin, 6 or 9 months of daily isoniazid. In terms of treatment, the majority of our patients with LTBI (74%) were treated with isoniazid alone for 9 months while 26% had rifampin and isoniazid for 3 months. Thus a small ratio of our treatment complies with the preferred LTBI management according to the US guidelines. However, rifapentine is not available in France and rifamycin-based therapy is more difficult to handle in terms of drugs interactions. Moreover, updated regimens are based on studies that did not target specifically SOT recipients but HIV patients (31). From the study, side effects were reported by 12.5% of the patients. This small occurrence did not allow for a proper cause and effect analysis. No patients received higher than recommended dose of isoniazid or rifampin treatment (32). However, one patient developed hepatic cytolysis with isoniazid posology at the highest authorized for dialysis patient prescribed in combination with rifampin. It reminds

us of the importance of close clinical and biological monitoring and doses adaptation in a population of kidney impaired patients as well as the importance a close follow-up on hepatic repercussions.

A previous study carried out in another French center on kidney transplant recipient patients evaluated by an infectious disease specialist before transplantation found similar results: 17% of patients received LTBI treatment, 6% had a past medical history of TB, 16% had positive IGRA, 11% of patients had side effects with LTBI's treatment. This study differs on the number of patients who stayed in a high endemicity country for more than 3 months (47% from their study *versus* 17% from our study) although it did not increase the number of patients treated for LTBI (33).

The impact of the COVID-19 pandemic on the infectious disease consultations is highlighted by the lengthening of the delay between nephrology and infectious disease appointments. Moreover, kidney transplant operations were stopped for several months at the beginning of the pandemic. This greatly affected the data collection and analysis between LTBI treatment and immunosuppressant post-transplantation.

This study has several limits. Firstly, the retrospective collection and missing data may create a bias towards the interpretation of its analysis. Moreover, the size of the cohort and the lack of statistical power did not enable bivariate analysis to identify a potential confounding variable between LTBI diagnosis and age or positive HHV6 and Hepatitis A positive serology.

Secondly, further comparison among the practices concerning TB's risk prevention before and after the implementation of the infectious disease specialist evaluation prior to kidney transplantation would enhance the analysis. Finally, the small number of patients who underwent kidney transplantation and the short duration of follow-up post-transplantations do not allow us to properly evaluate the impact of the chemoprophylaxis on TB's occurrence

and the possible interactions between chemoprophylaxis and immunosuppressant treatment. The impact of the chemoprophylaxis was previously studied in a literature review of TB occurrence on SOT recipients. 2.6% of patients developed tuberculosis despite chemoprophylaxis. LTBI's treatment was shown to reduce the absolute risk of TB by 8%. Similarly to our study, the incidence of side effects under chemoprophylaxis was 11% (34). Further studies on a larger scale are required to evaluate the impact of a dedicated infectious disease evaluation before transplantation on infectious risk management. Nonetheless, this study highlighted some difficulties that could face the nephrologist and the infectious disease specialist during the management of TB prevention. The overall goal is to stress upon the importance of the infectious disease evaluation and multidisciplinary work for a better care of SOT recipients.

Discussion (français)

L'incidence de la TB dans les pays à faible prévalence est estimée à 0.8% pour les transplantés d'organe solide et oscille entre 0.7 et 5% chez les transplantés rénaux (11,12). La majorité des TB surviennent dans les 6 premiers mois post transplantation, avec un délai allongé pour les transplantés rénaux, atteignant en médiane 11,5 mois. Les formes disséminées et extra-pulmonaires sont plus fréquentes chez les transplantés d'organe solide. De plus les transplantés accusent d'une mortalité accrue face à la TB (6-22%) (7). Ainsi les recommandations s'accordent sur l'indication du dépistage de l'ITL chez tout candidat à la transplantation. Notre étude décrit les patients en attente de transplantation rénale au sein du CHU de Lille en terme de facteurs de risque de TB. Un quart des patients (26%) étaient originaire d'un pays d'endémie tuberculeuse ou d'une famille née en zone d'endémie. La vaste majorité (75%) étaient dialysés au moment du recueil et 18% des patients avaient un facteur d'immunosuppression supplémentaire à l'insuffisance rénale. Parmi les 27 patients diagnostiqués avec une ITL, plus d'un tiers n'avaient pas d'autre facteur de risque de tuberculose à l'interrogatoire et furent traités sur la base d'un test IGRA positif. Ce résultat souligne l'intérêt de réaliser un dépistage exhaustif sans omettre ceux qui ne seraient considérés à haut risque sur la base de l'interrogatoire. Tous les patients IGRA positifs furent traités excepté un dont le test IGRA était à la limite du seuil de positivité et une autre dont le résultat IGRA positif n'était disponible au moment de l'évaluation en maladie infectieuse. Ce dernier ainsi que l'équipe médicale le prenant en charge furent informés dans un second temps. Dix-sept patients (12.5%) avaient un facteur de risque de tuberculose sans test IGRA positif et ne furent pas considérés comme porteurs d'une ITL. L'importance du test IGRA sur la décision de traiter ou non une ITL soulève plusieurs questions non résolues dans les recommandations actuelles. Premièrement comment réagir face à un test IGRA négatif ou indéterminé, faudrait-il répéter le test ? Devrions-nous

traiter les patients avec un seul facteur de risque de tuberculose à l'anamnèse mais un test IGRA négatif ? Comment juger l'importance de l'origine comme facteur de risque ? Certains patients dont la famille est issue d'un pays à forte endémicité sont installés depuis plusieurs générations en France. Sont-ils à mettre au même niveau de risque que les migrants de première génération ? Ces questions non résolues, qui se posent au praticien lors de la consultation pré-transplantation, expliquent en partie la variabilité des pratiques interprofessionnelles dans la décision de considérer ou non un patient à risque de tuberculose. Notre étude suggère la nécessité d'une stratification des facteurs de risque afin de diriger la décision d'initier une prophylaxie ou non.

En comparant les patients diagnostiqués avec une ITL et le reste de la cohorte, une différence significative est mise en évidence en termes d'âge (P = 0.026), d'immunité anti HHV6 (P = 0.013) et Hépatite A (P = 0.016). Les patients avec ITL sont plus âgés et plus immunisés. Ceci est probablement dû à des expositions passées dans les pays à forte endémicité chez des patients migrants de première génération.

Pour ce qui concerne le traitement de l'ITL, la majorité de nos patients (74%) ont eu prescription d'isoniazide seul à la dose 200 mg/jour pendant 9 mois contre 26% d'association rifampicine 600 mg/jour isoniazide 200 mg/jour 3 mois. Une faible proportion de patients ont développés des effets indésirables (12.5%). Tous étaient dialysés avec des posologies d'isoniazide entre 200 et 300 mg/jour, ce qui souligne la nécessité de précautions autour des dosages d'antituberculeux chez cette population insuffisante rénale.

Notre étude a plusieurs limites : 1) le caractère rétrospectif du recueil et le manque de puissance statistique en lien avec un effectif réduit ne permettent de tirer de fermes conclusions quant à nos analyses. 2) Le manque de recul ne permet d'évaluer l'effet de la consultation sur la prévention de la TB post-transplantation. 3) La faible proportion de

patients transplantés et traités pour une ITL ne permet pas d'étudier amplement les interactions entre traitement antirejet et traitement de l'ITL.

L'intérêt de l'étude tient dans sa description des patients candidats à la transplantation en termes de risque de tuberculose ainsi que le détail de l'évaluation infectiologique et les questions qu'elle soulève quant à l'uniformisation des pratiques.

Conclusion

Notre étude réalisée auprès de 136 patients candidats à une transplantation rénale, a permis de mieux décrire cette population en termes de risque de TB, d'identifier une ITL chez 27 (20%) patients dont 10 avec un IGRA positif sans facteur de risque associé et 4 patients avec un IGRA négatif, borderline ou non disponible et au moins un facteur de risque de TB. Le schéma thérapeutique le plus fréquemment prescrit était l'utilisation d'isoniazide seul. Des effets indésirables liés au traitement étaient présents dans 12.5% des cas (3 patients) dont une ayant nécessité interruption et modification de traitement. Cette étude a également permis de souligner la nécessité d'approfondir les modalités diagnostiques de l'ITL, la traçabilité des éléments utiles au diagnostic d'ITL et l'harmonisation des pratiques autour de la prise en charge thérapeutique. Du fait de la pandémie COVID-19 et de la diminution, voire l'interruption de l'activité de transplantation durant quelques mois, il n'a pas été possible d'analyser les suites de la prise en charge après la transplantation rénale.

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Titre de la thèse : Prévention de la tuberculose chez les transplantés rénaux : rôle clé de la consultation maladie infectieuse avant la transplantation

Thèse - Médecine - Lille 2022

Cadre de classement : Maladie infectieuse

DES + FST/option : Médecine interne Maladie infectieuse

Mots-clés : transplantation, rein, tuberculose

Introduction : La tuberculose reste un fardeau dans les pays à faible prévalence, en particulier chez les patients immunodéprimés transplantés d'organe solide. L'incidence est de 0.8% chez les transplantés d'organe et 0.7 à 5% chez les transplantés rénaux. Cependant, les pratiques concernant le dépistage de la tuberculose et la prophylaxie pour l'infection tuberculose latente (ITL) chez le transplanté d'organe solide ne font pas l'objet d'un protocole standardisé entre les centres.

Objectif : Notre étude monocentrique rétrospective sur cohorte prospective a pour objectif de décrire le risque de tuberculose dans une population de patients en attente de transplantation rénale. Elle a également pour but de définir les patients éligibles à une prophylaxie anti-tuberculeuse.

Résultats : De Janvier 2020 à juin 2021, 136 patients ont été évalué en consultation maladie infectieuse. Sur 136, 27 (20%) ont reçu une indication à traitement ITL dont 24 ont débuté le traitement. Parmi ces 27 patients, 10 (37%) ont été diagnostiqué avec une ITL sur la base d'un test IGRA (Interferon Gamma Release Assay) positif isolé et n'avaient pas d'autres facteurs de risque de tuberculose. En dehors des risques connus de tuberculose, les patients diagnostiqués avec ITL étaient significativement plus âgés (P = 0.026) et préalablement immunisés à l'hépatite A (P = 0.016) et au HHV6 (P = 0.013). Vingt (74%) reçurent une indication à être traiter par isoniazide seul tandis que pour 7 (26%) la combinaison rifampicine et isoniazide fut préconisée. Trois (12.5%) des patients traités ont eu des effets indésirables dont une hépatite cytolytique. Il n'y a pas eu d'interactions du traitement anti-tuberculeux avec les traitements immunosuppresseurs décrits dans les courriers post transplantation.

Conclusion : La prévention de la tuberculose requiert une évaluation dédiée pour une meilleure prise en charge des patients transplantés d'organe.

<u>Composition du Jury</u> :

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