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Anti-TNF α therapy for chronic inflammatory disease in kidney transplant recipients

Clinical outcomes

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Abstract

Anti-tumor necrosis factor- α (TNF α) therapy has improved the prognosis of many chronic inflammatory diseases. It appears to be well-tolerated by liver-transplant patients. However, their use and their safety in kidney-transplant patients have yet to be determined.

In this retrospective study, we identified 16 adult kidney-transplant patients aged 46.5 years (34–51.8) who received anti-TNF α therapy from 7 kidney transplantation centers. The indications for this treatment included: chronic inflammatory bowel disease (n=8), inflammatory arthritis (n=5), AA amyloidosis (n=1), psoriasis (n=1), and microscopic polyangiitis (n=1).

Anti-TNF α therapies resulted in a clinical response in 13/16 patients (81%). Estimated glomerular filtration rates (MDRD-4) were similar on day 0 and at 24 months (M24) after anti-TNF α treatment had been initiated (41 [12–55] and 40 [21–53] mL/min/1.73 m², respectively). Two allograft losses were observed. The 1st case was due to antibody-mediated rejection (M18), while the 2nd was the result of AA amyloidosis recurrence (M20). There were several complications: 8 patients (50%) developed 23 serious infections (18 bacterial, 4 viral, and 1 fungal) and 4 developed cancer. Five patients died (infection n=2, cardiac AA amyloidosis n=1, intraalveolar hemorrhage following microscopic polyangiitis n=1, and acute respiratory distress syndrome n=1). On univariate analysis, recipient age associated with death ($P=0.009$) and infection development ($P=0.06$).

Using anti-TNF α therapies, remission can be achieved in chronic inflammatory diseases in kidney-transplant patients. However, concomitant anti-TNF α and immunosuppressive therapies must be used with caution due to the high risk of infection, particularly after the age of 50.

Abbreviations: GFR = glomerular filtration rate, TNF α = tumor necrosis factor- α .

Keywords: anti-TNF α therapy, chronic inflammatory disease, inflammatory arthritis, inflammatory bowel disease, kidney transplantation

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1. Introduction

The advent of tumor necrosis factor- α (TNF α) inhibitors (anti-TNF α therapies) within the past decade has resulted in a revolution in the management of severe chronic rheumatoid (psoriatic arthritis, ankylosing spondylitis, or rheumatoid arthritis), gastrointestinal (Crohn disease and ulcerative colitis), and dermatologic (psoriasis) inflammatory diseases.

TNF α is a pleiotropic cytokine produced by immune cells (macrophages, dendritic cells, and T lymphocytes).^[1] TNF α binds to 2 surface receptors, namely, TNFR1 and TNFR2, and activates different signaling pathways associated with cell proliferation; inflammation induction, immune modulation, and proinflammatory cytokine production; and cell apoptosis.^[1,2]

Very few studies regarding the use of anti-TNF α therapy in kidney transplant patients have been conducted. Organ transplant patients have been excluded from anti-TNF α drug safety studies due to the increased risks of infection^[3] and cancer specific to this population.^[4,5] Anti-TNF α treatment is associated with an increased incidence of severe bacterial,^[6,7] viral (i.e., herpesvirus),^[8] and opportunistic (i.e., tuberculosis)^[9,10] infections and may cause certain cancers.^[11] Anti-TNF α drugs also cause hypersensitivity reactions, which may contribute to autoimmune disease development, particularly drug-induced lupus.^[4] To date, the literature includes only case series regarding organ transplant patients treated with anti-TNF α drugs.^[12–18]

We retrospectively evaluated 16 kidney transplant patients treated with anti-TNF α drugs for chronic inflammatory diseases. Our study objectives were to describe the indications for anti-TNF α treatment, the responses to treatment, and the safety of these drugs in this population of immunocompromised patients.

2. Patients and methods

2.1. Methods

This multicenter retrospective observational study was conducted in 7 French kidney transplant centers. We identified 16 patients (11 male) aged 46.5 years (34–51.8) from the ASTRE prospective database of the Spiesser Kidney Transplantation Group (Angers, Caen, Clermont-Ferrand, Reims, and Strasbourg University Hospitals) and the DIVAT prospective database (Necker and Toulouse University Hospitals). Patients aged at least 18 years who had undergone kidney transplantation and received anti-TNF α treatment were included in this study. The ethical committee of the institution approved the extraction of data from the patient charts.

Patient medical charts and demographics were retrieved from the hospital registries, and the following data were recorded: age, gender, nephropathy, past history of infection or malignancy, date of transplantation, and postoperative immunosuppressive regimen. We examined the kidney transplantation outcomes of these patients, including patient and graft survival, occurrence of acute rejection episodes, infections, cancer, adverse event with TNF therapy, causes of graft loss, and patient death. The glomerular filtration rate (GFR) was estimated (eGFR) using the Modification of Diet in Renal Disease 4 (MDRD4) formula. Failing data were retrospectively found in the patient record.

2.2. Statistics

All analyses were performed using Stata software (version 13, StataCorp, College Station, TX) and were performed for a 2-sided type I error of α 5%. Baseline characteristics are presented as the mean \pm standard deviation (SD) or the median (interquartile range) for continuous data (assumption of normality assessed via the Shapiro–Wilk test) and as numbers and percentages for categorical data. Quantitative variables were compared between independent groups (infection yes/no and death yes/no) by Student *t* test or the Mann–Whitney *U* test if the conditions of the *t* test were not met (normality and homoscedasticity were analyzed using the Fisher–Snedecor test). When appropriate, comparisons between independent groups were analyzed using a Chi-squared test or Fischer exact test for categorical variables. The relationships between quantitative outcomes were analyzed using correlation coefficients (Pearson or Spearman, according to the statistical distribution). Regarding the evolution of the eGFR (longitudinal repeated data), random-effects models were used to account for between- and within-patient variability. Finally, due to the design of this study (meta-analysis of individual data), these analyses were completed using generalized linear mixed models (logistic regression for dichotomous dependent variables: infection yes/no and death yes/no) to study the fixed effects described previously, and the study was considered a random effect (to measure between- and within-study variability). Given the sample size, no meta-regression analysis was performed based on the results of the multivariate analysis. Last, sensitivity analysis was performed to measure the impact of missing data.

Table 1

Characteristics of kidney transplant recipients treated with anti-TNF α therapy.

	Patients (n=16)
Male, n, %	11 (68.8)
Cause of end-stage renal disease, n, %	
Chronic interstitial nephritis	5 (31.2)
IgA nephropathy	1 (6.2)
Autosomal dominant polycystic kidney disease	1 (6.2)
Chronic glomerulopathy	3 (18.8)
Malformative uropathy	2 (12.4)
Primary hyperoxaluria	1 (6.2)
Unknown	3 (18.8)
Age at transplantation, median (IQR), year	46.5 [34–51.8]
Cardiovascular event before KT, n, %	4 (25)
Cancer before KT, n, year	
Breast cancer	1 (-6 year)
Basocellular carcinoma	1 (-9 year)
Infection before KT, n, %	3 (18.75)
Previous kidney transplantation, n, %	2 (12.5)
Anti-TNF α before kidney transplantation, n, %	5 (31.2)
Induction immunosuppressive regimen, n, %	13 (81.3)
Rabbit antithymocyte globulin, n, %	4 (25)
Anti-IL-2 receptor antibody, n, %	9 (56.3)
Maintenance immunosuppressive regimen at onset of anti-TNF α therapy, n, %	
Cyclosporine/tacrolimus	9 (56.3)/6 (37.6)
Mycophenolic acid/azathioprine	8 (50)/8 (50)
Everolimus	1 (6.2)
Steroids	15 (93.8)
Steroids \geq 10 mg/day at onset of anti-TNF α therapy, n, %	8 (50)
Steroids \geq 10 mg/day 3 months after anti-TNF α initiation, n, %	10 (62.4)
Prophylaxis for cytomegalovirus in D+/R– or R+, n, %	4/8 (50)
Trimethoprim-sulfamethoxazole prophylaxis, n, %	7 (44)

D = donor, IQR = inter-quartile range, KT = kidney transplantation, R = recipient, TNF α = tumor necrosis factor- α .

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. Prior to kidney transplantation, 2 patients developed neoplasms (breast adenocarcinoma and basal-cell carcinoma), and 3 patients developed serious infections requiring hospitalization. The 1st patient (P#14) developed 3 bacterial infections (urinary tract, gastrointestinal, and cutaneous) during his 1st kidney transplantation, the 2nd patient (P#7) developed eye shingles, and the 3rd patient (P#10) developed dialysis catheter-related staphylococcal septicemia.

Five patients began anti-TNF α treatment before kidney transplantation (Table 1). Three patients (P#4, P#5, and P#15) discontinued treatment following transplantation before resuming it at 4, 6, and 22 months, respectively, after transplantation (Table 2). Patients P#9 and P#14 continued their treatments, which they had initiated at 15 and 42 months, respectively, prior to transplantation (Table 2).

Cytomegalovirus prophylaxis was administered to 4/8 patients (50%) at risk for viral reactivation or primary graft infection upon anti-TNF α treatment initiation. Seven patients (44%) received *Pneumocystis* pneumonia prophylaxis (trimethoprim/sulfamethoxazole) upon anti-TNF α treatment initiation.

Table 2
Anti-TNF α treatment indications, tolerance and outcomes in 16 kidney transplant recipients.

Case	Age KT	Sex	Date after KT, months	Indication	Anti-TNF α molecule	Response to anti-TNF α	Infection (n)	Tumor	Others	Anti-TNF α discontinuation (cause, month)	Last F/U patient outcome and current KT α status, μ mol/L
1	51	M	8	AS	Eta	CR	2	0	0	0	220 (M24)
2	25	M	80	AS	Eta	CR	0	Hodgkin M32	0	Hodgkin M32	167 (M34)
3	48	M	61	Rheum psoriatic	Inf	PR	1	0	0	Infection M5	Death (infection)/94 (M10)
4*	74	M	6	AS	Eta	NR	0	0	0	Death M1	Death (ADRS) (M1)
5*	44	M	21	AS	Eta Ada M18	PR	0	0	0	0	142 (M60)
6	54	F	72	UC	Inf	PR	1	M12 Lung adenocarcinoma	0	Cancer M14	200 (M20)
7	35	M	122	Crohn	Ada	CR	0	0	0	0	133 (M22)
8	31	M	168	Crohn	Ada	CR	0	0	0	0	114 (M17)
9	45	F	-15	UC	Inf	CR	0	0	0	CR M33	122 (M56)
10	18	M	68	Crohn	Inf	RC	0	0	0	0	120 (M17)
11	19	F	40	Crohn	Inf Ada M1, 5	PR	0	0	TCMR M3 ABMR M7	INF (allergy) M1, 5 Ada: AMR M7	HD (M18)
12	39	F	160	Crohn	Inf	NR	9	Cutaneous M46+48 Renal carcinoma M23	Psoriasis M17	0	193 (M85)
13	56	M	61	AS+ Crohn	Eta	CR	5	0	0	Infection M26	Death (M29)
14*	49	M	-42	Psoriasis	Ada	CR	1	0	0	CR M48	169 (M48)
15	61	F	4	Rheumatoid arthritis	Cert	NR	2	0	0	Infection M1	HD M20+ death (M28) (heart amyloidosis AA)
16	51	M	1	ANCA vasculitis	Inf	CR	2	0	0	Infection M11	Death (alveolar hemorrhage)/507 (M71)

ABMR=acute antibody-mediated rejection, Ada=adalimumab, ADRS=acute respiratory distress syndrome, AS=ankylosing spondylitis, Cert=certolizumab, CR=complete remission, d=day, Eta=etanercept, F/U=follow-up, HD=hemodialysis, Inf=infliximab, KT=kidney transplant recipients, M=month, TCMR=acute T cell-mediated rejection, TNF α =tumor necrosis factor- α , UC=ulcerative colitis.
 *Anti-TNF α therapy introduced and stopped before kidney transplantation.

The indications for anti-TNF α treatment were rheumatoid (n=5, 31%), gastrointestinal (n=8, 50%), and dermatologic (n=1, 6%) disease, as well as microscopic polyangiitis (n=1, 6%) and familial Mediterranean fever (n=1, 6%) (Table 2).

3.2. Clinical response to anti-TNF α treatment

Overall, clinical responses were observed by clinicians in 13/16 cases. A complete response was observed in 9 cases (56%), and a partial response was observed in 4 cases (25%) (Table 2). Two complete responses (40%) and 2 partial responses (40%) were noted in patients with chronic rheumatoid disease (n=5); 5 complete responses (62.5%) and 2 partial responses (25%) were noted in patients with chronic inflammatory bowel disease (n=8); 1 complete response was noted in a patient with pustular psoriasis, resulting in adalimumab discontinuation at M48; and 1 complete response was noted in a patient being treated for microscopic polyangiitis. One patient (P#15) with AA amyloidosis discontinued treatment at M1 due to a urinary tract infection; thus, anti-TNF α treatment effectiveness could not be determined in this patient.

Table 3
Description of severe infectious complications that occurred during anti-TNF α therapy.

Infections	Patient (no. flares)
Bacterial infection, N	
Pyelonephritis	6 (11)
Acute cholecystitis	3 (3)
Bacterial dermohypodermatitis	1 (2)
Bacteremia	1 (2)
Viral infection, N	
Cutaneous herpes zoster	1 (2)
BK viremia	1 (1)
CMV enteritis	1 (1)
Fungal infection, N	
Candidemia	1 (1)

CMV=cytomegalovirus, TNF α =tumor necrosis factor- α .

3.3. Infectious complications

Eight patients (50%) developed 23 serious infections while receiving anti-TNF α treatment (1.43 infections per patient) (Tables 3 and 4). These patients mainly developed bacterial infections (n=16) (primarily upper urinary tract infections and acute cholecystitis), although viral infections (n=4) (varicella-zoster virus [VZV], cytomegalovirus, and BK viremia) and a fungal infection were also noted. On univariate analysis, the mean ages of the patients who did and did not develop infection were 51.1 \pm 6.4 and 36.8 \pm 18.3 years, respectively, P=0.06 (Table 4). Induction therapy, corticosteroid doses \geq 10 mg, and

Table 4
Infectious complications in our 16 kidney transplant recipients treated with anti-TNF α therapy: univariate analysis.

	Infections (n=8)	No infections (n=8)	P
Male	5	6	NS
Age at transplant (years), median (IQR)	51 (48.5–55)	33 (22–44.5)	0.06
Anti-TNF α before KT	2	3	NS
Inflammatory disease			NS
IBD	3	0	
Rheumatic disease	2	5	
Others	3	3	
Rabbit antithymocyte globulin induction	5 (62.5)	5 (62.5)	NS
Tacrolimus vs Cyclosporin	4/4	2/5	NS
Steroids at anti-TNF α initiation	8	7	NS
Steroids >10 mg at anti-TNF α initiation	5 (62.5)	3 (37.5)	NS
Anti-TNF α , n, %			NS
Infliximab	4 (57.1)	3 (42.9)	
Other anti-TNF α	4 (44.4)	5 (55.6)	

IBD=inflammatory bowel disease, IQR=inter-quantile range, KT=kidney transplantation, NS=not significant, TNF α =tumor necrosis factor- α .

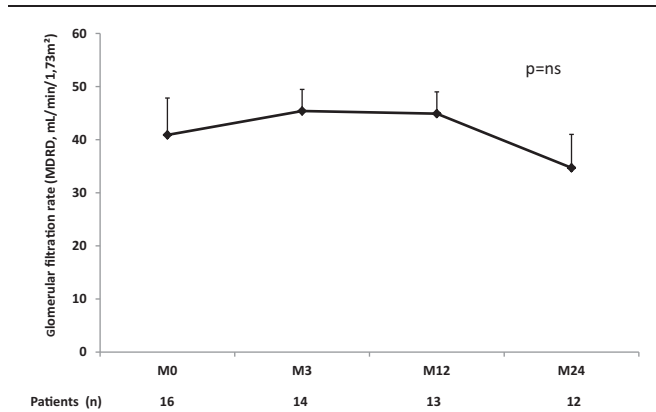


Figure 1. Evolution of estimated glomerular filtration rates (MDRD, mL/min/1.73m²) of kidney transplant recipients treated with anti-TNF α therapy. MDRD=Modification of Diet in Renal Disease 4, TNF α =tumor necrosis factor- α

pretransplant anti-TNF α treatment were not associated with infection risk (Table 4).

3.4. Cancer

Four patients (25%) developed cancer while receiving anti-TNF α treatment (Table 2). Three patients with chronic inflammatory bowel disease developed a solid tumor or multiple solid tumors after biological therapy initiation. These included 1 case of lung adenocarcinoma at M12, which resulted in infliximab discontinuation at M14 (P#6 was still alive at the last follow-up at M20); 2 basal-cell carcinomas at M46 and M48 (P#12); and a papillary adenoma of the kidney at M23 (P#13 died of septicemia at M26). P#2 developed Hodgkin lymphoma at M32, which resulted in anti-TNF α treatment discontinuation.

3.5. Changes in the glomerular filtration rate and graft survival

The estimated GFR remained stable over time during anti-TNF α treatment as follows: 41 (12–55) mL/min/1.73m² at D0, 44.5 (33–56) mL/min/1.73m² at M3, 41 (34–57) mL/min/1.73m² at M12, and 40 (21–53) mL/min/1.73m² at M24 (Fig. 1, Table 2).

Two patients (12.5%) lost their grafts. The 1st, P#15, developed AA amyloidosis recurrence in the graft at M29 of anti-TNF α treatment despite certolizumab treatment. The 2nd, P#11, who exhibited donor-specific antibodies before anti-TNF α treatment, lost the graft (Table 2) at M18 (58 months after transplantation) due to antibody-mediated rejection. The patient had been receiving adalimumab for Crohn disease and developed a cutaneous rash while receiving infliximab treatment (M1.5), which resulted in the initiation of adalimumab treatment. A graft biopsy performed at M3 due to increased blood creatinine levels revealed an inflammatory infiltrate occupying 25% to 30% of the biopsy and signs of t1 tubulitis consistent with either borderline rejection (Banff 2007)^[19] or acute tubulointerstitial nephritis. High-dose corticosteroid therapy and anti-TNF α treatment discontinuation improved graft function. Adalimumab was subsequently resumed at M6. A biopsy conducted at M8 due to further graft function deterioration and increased Luminex preexisting donor-specific antihuman leukocyte antigen antibody (DQ7) mean fluorescence intensity showed acute antibody-mediated rejection (g1+ptc2).^[19] No treatment reduction was observed (cyclosporin A, azathioprine, and steroids) after

anti-TNF α treatment initiation, nor was treatment reduction observed during the preceding 3 months.

3.6. Patient survival

Overall, 5 patients died a median of 28 months (1–71) after anti-TNF α therapy initiation (Table 2). Two patients died of bacterial infections. One of them (P#3) died of septic shock of gastrointestinal origin at M10 of anti-TNF α treatment despite treatment discontinuation at M5 due to gangrenous cholecystitis accompanied by biliary peritonitis. The 2nd developed multiple infections, including 2 bacterial infections, 1 BK viral infection, and 1 candidal infection. He died of a bacterial infection at M29. Two patients died after anti-TNF α treatment was discontinued. P#15 lost the renal graft at M20 due to AA amyloidosis recurrence and died at M28 of cardiac AA amyloidosis. Patient P#16, who had microscopic polyangiitis, died of intraalveolar hemorrhage at M71 despite treatment discontinuation at M11 following 2 VZV infections, the 1st of which involved the thorax, and the 2nd of which involved the eyes. Another patient (P#4) died of acute respiratory distress syndrome of unknown cause at M1 after anti-TNF α treatment (10 months after transplantation). On univariate analysis, the patients who died were significantly older (58.0 ± 10.2 vs 37.3 ± 12.7 years; $P=0.009$) than their surviving counterparts.

4. Discussion

To our knowledge, our study reports the largest case series of kidney transplant patients treated with anti-TNF α drugs. The clinical response rate noted in our study (13/16; 81.3%) is similar to that noted among all solid-organ transplant patients in the literature who received anti-TNF α treatment (29/36; 80.6%) (Tables 5 and 6).

However, in our series, we observed a particularly high rate of severe infections (8/16, 50% of patients). Most of these infections were bacterial and resulted in permanent treatment discontinuation in 4 patients (Table 2) and death in 2 patients. These outcomes have rarely been reported in previous series. Only 1 study, which evaluated liver transplant patients who received anti-TNF α treatment for inflammatory bowel disease, observed a similar infection rate (3/8, 37.5%).^[17] Combining the results of our series with those of previously reported series (Table 5) showed that 12/52 patients (23.2%) developed infections while receiving anti-TNF α treatment. Anti-TNF α therapy administration in patients who have not undergone organ transplantation is associated with an increased risk of bacterial infection,^[6,7] viral reactivation (particularly herpesviruses),^[8] and opportunistic infections, especially tuberculosis.^[8] This risk seems to be heightened: during the first 3 months after anti-TNF α therapy initiation,^[27] is also increased by the presence of underlying disease, and the combination of immunosuppressive treatment and corticosteroids >10mg/day.^[10] This was not observed in our series (Table 4). In addition to being more frequent among immunocompromised patients receiving anti-TNF α therapy, infections seem to be particularly severe in these patients. We noted a relationship between infection occurrence in patients receiving anti-TNF α therapy and patient death (4 of 5 patients died, $P=0.04$). International guidelines^[28] underscore the importance of detecting and treating tuberculosis. It may be necessary: to place kidney transplant patients on antiinfection prophylaxis upon anti-TNF α therapy initiation, in addition to surveilling these patients closely; and to decrease immunosuppressive regimen dose (i.e., steroids).

Table 5
Anti-TNF α treatment for inflammatory bowel disease in solid organ recipients, a review of the literature.

Reference	Organ transplanted year (IQ)	Immunosuppressive regimen	Biologic	Clinical response	Complications
Inflammatory bowel disease					
Lal et al 2007 ^[20]	Liver n=1	Tac	Infliximab	Remission clinic and endoscopic	None
Page et al 2008 ^[21]	Liver n=1	CsA/Aza	Infliximab for 2 years, followed by Ada	1/1	Lupus-like syndrome
El-Nachef et al 2010 ^[13]	Liver n=2; kidney=1; 6 [6–23]	NC	Infliximab n=3	3/3	Pyelonephritis n=1
Temme et al 2010 ^[15]	Kidney n=2	Tac n=1/CsA n=1; MMF n=2; steroids n=2	Infliximab n=2	2/2	None
Mohabat et al 2012 ^[17]	Liver n=8; 3.5 [1–14]	Tac n=6/CsA n=2; Aza n=3; MMF n=1; steroids n=5/8	Infliximab n=4; infliximab then Ada n=4	Clinical 6/8; endoscopic 4/3%	Cryptosporidiosis; clostridium difficile colitis; bacterial pneumonia; EBV-PTLD n=1 and 1 death
Sandhu et al 2012 ^[12]	Liver n=6; 7 [6–10]	Tac n=5/CsA n=1; Aza n=1; MMF n=0; steroids n=3 (50%)	11 CR (65%); 2 PR (12%)	4/6	Systemic lupus erythematosus (n=1); colorectal cancer n=1
Indriolo et al 2013 ^[22]	Liver n=3; kidney n=1	Tac/Aza/steroids n=1; Tac n=1; CsA n=1; Tac/SRL n=1	Infliximab n=4	Clinical 3/4; endoscopic 1/3	Moluscum contagiosum n=1
Schnitzler et al 2015 ^[14]	Liver n=3; heart n=1	Tac n=2; Tac/steroids n=1; Tac/MMF/steroids n=1	Infliximab n=3; Ada n=1	Clinical 3/4; endoscopic 3/4	None at M81, M82, M140, M157

Ada = adalimumab, Aza = azathioprine, CR = complete remission, CsA = cyclosporin A, EBV = Epstein–Barr virus, M = month, MMF = mycophenolate mofetil, PR = partial remission, PTLTD = posttransplantation lymphoma disease, Tac = tacrolimus, TNF α = tumor necrosis factor- α .

In our study, 4 patients (25%) developed either solid tumors (n=3) or hematologic malignancies (n=1) (Table 2). No patients died as a direct result of these cancers following a median follow-up of 7 months (2–47). Two other cases of neoplasms following anti-TNF α therapy (6/52 organ transplant patients overall, 11.5%) have been reported in liver transplant patients, 1 case of Epstein–Barr-virus-associated lymphoma and 1 case of colorectal adenocarcinoma (Table 4). The risk of lymphoma and solid tumors (particularly tumors of the skin) is heightened after kidney transplantation, as well as in the setting of inflammatory bowel disease^[11,29–33] and rheumatoid arthritis.^[34–36] However, patients with spondyloarthritis do not appear to have an increased cancer risk.^[37] The relationship between anti-TNF α therapy and cancer is unclear.^[38] In patients with inflammatory bowel disease, anti-TNF α therapy may increase the risk of nonmelanoma skin cancer, although this risk is mainly related to thiopurine use,^[39] as well as the risk of melanoma,^[29] and reduce the incidence of colorectal adenocarcinoma by controlling bowel inflammation.^[40] Patients with rheumatoid arthritis receiving anti-TNF α therapy seem to be at greater risk for nonmelanoma skin cancer^[41] and melanoma,^[42] whereas patients being treated for spondyloarthritis do not seem to have an increased cancer risk.^[37] In our study, 2 patients developed breast cancer

(–6 years) and basal-cell carcinoma (–9 years), respectively, before receiving anti-TNF α therapy. Neither of these patients relapsed after transplantation. Following kidney transplantation, the risk of cancer recurrence may reach 20% depending on the type of cancer.^[43] Therefore, based on the cancer history of the patient, a waiting period may be necessary before kidney transplantation is authorized.^[5] Initiating anti-TNF α therapy does not seem to contribute to subsequent cancer recurrence.^[44,45]

We observed 1 case of a kidney graft loss (P#11, Table 2) at M18 secondary to antibody-mediated rejection in a patient treated with adalimumab for Crohn disease. No cases of organ rejection have been reported in the literature (Tables 5 and 6). TNF α and its receptors, TNFR1 and TNFR2, play important roles in kidney transplant rejection.^[11] In animals, anti-TNF α therapy may prolong kidney graft survival in the event of rejection.^[46] Thus, the abovementioned antibody-mediated rejection was probably unrelated to the use of this drug; thus, we cannot rule out autoimmune adalimumab-induced acute interstitial nephritis at M3.^[47,48] Other autoimmune phenomena with renal manifestations have been reported in the setting of anti-TNF α therapy, namely, lupus^[49–51] and glomerulonephritis.^[52] In the literature, two cases of cutaneous lupus have been

Table 6
Anti-TNF α treatment for psoriasis or other indications in solid organ recipients, a review of the literature.

Reference	Organ transplanted year (IQ)	Immunosuppressive regimen	Biologic	Clinical response	Complications
Psoriasis					
Brokalaki et al 2012 ^[23]	Pancreas-renal n=18	Tac/MMF/steroids	Etanercept	1/1	None at 2 years
Hoover et al 2007 ^[16]	Liver n=16	Tac/sirolimus	Etanercept	1/1	None at 6 months
Collazo al 2008 ^[24]	Liver n=11	Tac/MMF/steroids	Etanercept	1/1	None at 5 months
Madankumar et al 2015 ^[25]	Liver n=15	Tac/everolimus/steroids	Etanercept	1/1	Multiple angiocholitis
Others					
Leroy et al 2009 ^[18]	Kidney n=1	CsA/MMF/steroids	Infliximab	1/1	None at 8 years
Meytas et al 2007 ^[26]	Heart n=2	NC	Infliximab	2/2	None

CsA = cyclosporin A, MMF = mycophenolate mofetil, ND = no data, Tac = tacrolimus, TNF α = tumor necrosis factor- α .

Table 7**Univariate analysis of infections in solid organ recipients treated with anti-TNF α therapy in the literature and in our study.**

	Infections	No infections	P
Male, n	6	24	NS
Female, n	5	8	
Age at transplant, median (IQR), year	32.5 (27–51.5)	31 (27–39)	NS
Organ recipient			NS
Kidney, n, %	8 (38.1)	13 (61.9)	
Other, n, %	6 (20)	24 (80)	
Inflammatory disease, n, %	14 (27.4)	37 (72.5)	NS
IBD	8 (22.2)	28 (87.8)	
Rheumatic disease	2 (28.6)	5 (71.4)	
Others	4 (50)	4 (50)	
Induction regimen, n, %			NS
Steroids			
Yes	9 (32.1)	19 (67.9)	
No	1 (10)	9 (90)	
Azathioprine/MMF			NS
Yes	7 (28.2)	19 (71.8)	
No	4 (30.8)	9 (69.2)	
Treatment numbers, n, %			NS
1	1 (12.5)	7 (87.5)	
2	4 (40)	6 (60)	
3	6 (27.3)	16 (72.7)	
Anti-TNF α , n, %			NS
Infliximab	6 (33.3)	18 (66.7)	
Other anti-TNF α	8 (29.6)	19 (70.4)	
Death, n, %	4 (28.5)/10 (71.4)	1 (2.8)/36 (97.3)	0.046

IBD = inflammatory bowel disease, IQR = inter-quartile range, MMF = mycophenolate mofetil, NS = not significant, TNF α = tumor necrosis factor- α .

reported in liver transplant patients who received infliximab and adalimumab, respectively (Table 5), although neither patient presented with kidney involvement.

Our study had several limitations. First, the retrospective nature of our study may have resulted in an underestimation of the number of kidney transplant patients who received anti-TNF α therapy. Second, because of the small size of our series, the number of indications (chronic inflammatory bowel disease, chronic rheumatoid diseases, or others) for anti-TNF α therapy and the variety of drugs used, only patient age was identified as a risk factor for infection and death (Table 4). In the literature, age is an independent risk factor for infection and death in patients with chronic inflammatory diseases, regardless of whether or not these patients have been treated with biological therapy,^[53] as well as in patients who have undergone kidney transplantation.^[54] On univariate analysis, no other risk factors for infection (i.e., organs transplanted, indications, numbers of concomitant immunosuppressive treatments, or corticosteroid doses) were identified after reviewing all solid-organ transplant patients reported in the literature (Table 7).

In conclusion, anti-TNF α therapies are effective for treating chronic inflammatory diseases in kidney transplant patients and do not lead to graft function deterioration. However, infection and cancer rates are particularly high among these immunocompromised patients. Regular screening for infection and cancer may thus be recommended for this at-risk population, in addition to antiinfection prophylaxis. Tailoring concomitant immunosuppressive therapy must be investigated in further studies to ensure that anti-TNF α therapy is safe in kidney transplant patients.

References

- Al-Lamki RS, Mayadas TN. TNF receptors: signaling pathways and contribution to renal dysfunction. *Kidney Int* 2015;87:281–96.
- Palladino MA, Bahjat FR, Theodorakis EA, et al. Anti-TNF-alpha therapies: the next generation. *Nat Rev Drug Discov* 2003;2:736–46.
- Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357:2601–14.
- Nanau RM, Neuman MG. Safety of anti-tumor necrosis factor therapies in arthritis patients. *J Pharm Pharm Sci* 2014;17:324–61.
- AlBugami M, Kiberd B. Malignancies: pre and post transplantation strategies. *Transplant Rev (Orlando)* 2014;28:76–83.
- Pena-Sagredo JL, Hernandez MV, Fernandez-Llanio N, et al. Listeria monocytogenes infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience. *Clin Exp Rheumatol* 2008;26:854–9.
- Lanternier F, Tubach F, Ravaud P, et al. Incidence and risk factors of Legionella pneumophila pneumonia during anti-tumor necrosis factor therapy: a prospective French study. *Chest* 2013;144:990–8.
- Winthrop KL, Baddley JW, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA* 2013;309:887–95.
- Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumor necrosis factor therapy in USA. *Ann Rheum Dis* 2013;72:37–42.
- Salmon-Ceron D, Tubach F, Lortholary O, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.
- Lebrec H, Ponce R, Preston BD, et al. Tumor necrosis factor, tumor necrosis factor inhibition, and cancer risk. *Curr Med Res Opin* 2015;31:557–74.
- Sandhu A, Alameel T, Dale CH, et al. The safety and efficacy of antitumour necrosis factor-alpha therapy for inflammatory bowel disease in patients post liver transplantation: a case series. *Aliment Pharmacol Ther* 2012;36:159–65.
- El-Nachef N, Terdiman J, Mahadevan U. Anti-tumor necrosis factor therapy for inflammatory bowel disease in the setting of immunosuppression for solid organ transplantation. *Am J Gastroenterol* 2010;105:1210–1.
- Schnitzler F, Friedrich M, Stallhofer J, et al. Solid organ transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity in a large single center cohort. *PLoS One* 2015;10:e0135807.
- Temme J, Koziolk M, Bramlage C, et al. Infliximab as therapeutic option in steroid-refractory ulcerative colitis after kidney transplantation: case report. *Transplant Proc* 2010;42:3880–2.
- Hoover WD. Etanercept therapy for severe plaque psoriasis in a patient who underwent a liver transplant. *Cutis* 2007;80:211–4.
- Mohabbat AB, Sandborn WJ, Loftus EV Jr, et al. Anti-tumour necrosis factor treatment of inflammatory bowel disease in liver transplant recipients. *Aliment Pharmacol Ther* 2012;36:569–74.
- Leroy S, Guignon V, Bruckner D, et al. Successful anti-TNFalpha treatment in a child with posttransplant recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2009;9:858–61.
- Solez K, Colvin RB, Racusen LC, et al. Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant* 2008;8:753–60.
- Lal S, Steinhart AH. Infliximab for ulcerative colitis following liver transplantation. *Eur J Gastroenterol Hepatol* 2007;19:277–80.
- Page AV, Liles WC. Tumor necrosis factor-alpha inhibitor-induced lupus-like syndrome presenting as fever of unknown origin in a liver transplant recipient: case report and concise review of the literature. *Transplant Proc* 2008;40:1768–70.
- Indriolo A, Fagioli S, Pasulo L, et al. Letter: infliximab therapy in inflammatory bowel disease patients after liver transplantation. *Aliment Pharmacol Ther* 2013;37:840–2.
- Brokalaki EI, Voshege N, Witzke O, et al. Treatment of severe psoriasis with etanercept in a pancreas-kidney transplant recipient. *Transplant Proc* 2012;44:2776–7.
- Collazo MH, Gonzalez JR, Torres EA. Etanercept therapy for psoriasis in a patient with concomitant hepatitis C and liver transplant. *P R Health Sci J* 2008;27:346–7.
- Madankumar R, Teperman LW, Stein JA. Use of etanercept for psoriasis in a liver transplant recipient. *JAAD Case Rep* 2015;1:536–7.
- Metyas S, La D, Arkfeld DG. The use of the tumour necrosis factor antagonist infliximab in heart transplant recipients: two case reports. *Ann Rheum Dis* 2007;66:1544–5.

- [27] Arnott ID, Watts D, Satsangi J. Azathioprine and anti-TNF alpha therapies in Crohn's disease: a review of pharmacology, clinical efficacy and safety. *Pharmacol Res* 2003;47:1-0.
- [28] Schreiber S, Campieri M, Colombel JF, et al. Use of anti-tumour necrosis factor agents in inflammatory bowel disease. European guidelines for 2001-2003. *Int J Colorectal Dis* 2001;16:1-1. discussion 2-3.
- [29] Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology* 2012;143:390.e1-9.e1.
- [30] Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617-25.
- [31] Magro F, Peyrin-Biroulet L, Sokol H, et al. Extra-intestinal malignancies in inflammatory bowel disease: results of the 3rd ECCO Pathogenesis Scientific Workshop (III). *J Crohns Colitis* 2014;8:31-44.
- [32] Soderlund S, Brandt L, Lapidus A, et al. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;136:1561-7. quiz 818-9.
- [33] Castano-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. *Aliment Pharmacol Ther* 2014;39:645-59.
- [34] Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;54:692-701.
- [35] Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275-85.
- [36] Amari W, Zeringue AL, McDonald JR, et al. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. *Rheumatology (Oxford)* 2011;50:1431-9.
- [37] Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. *Ann Rheum Dis* 2016;May 4. pii: annrheumdis-2016-209270. doi: 10.1136/annrheumdis-2016-209270. [Epub ahead of print].
- [38] Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;39:447-58.
- [39] Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011;141:1621.e1-5-8. e1-5.
- [40] Baars JE, Looman CW, Steyerberg EW, et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *Am J Gastroenterol* 2011;106:319-28.
- [41] Scott FI, Mamtani R, Brensinger CM, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. *JAMA Dermatol* 2016;152:164-72.
- [42] Raaschou P, Simard JF, Holmqvist M, et al. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ* 2013;346:f1939.
- [43] Penn I. The effect of immunosuppression on pre-existing cancers. *Transplantation* 1993;55:742-7.
- [44] Bernheim O, Axelrad J, Itzkowitz SH, et al. Previous cancer/lymphoma and refractory inflammatory bowel disease. *Dig Dis* 2015;33(Suppl 1):44-9.
- [45] Axelrad J, Bernheim O, Colombel JF, et al. Risk of new or recurrent cancer in patients with inflammatory bowel disease and previous cancer exposed to immunosuppressive and anti-tumor necrosis factor agents. *Clin Gastroenterol Hepatol* 2016;14:58-64.
- [46] Imagawa DK, Millis JM, Seu P, et al. The role of tumor necrosis factor in allograft rejection. III. Evidence that anti-TNF antibody therapy prolongs allograft survival in rats with acute rejection. *Transplantation* 1991;51:57-62.
- [47] Korsten P, Sweiss NJ, Nagorsnik U, et al. Drug-induced granulomatous interstitial nephritis in a patient with ankylosing spondylitis during therapy with adalimumab. *Am J Kidney Dis* 2010;56:e17-21.
- [48] Yoshioka T, Yamakawa T, Yamaguchi M, et al. [Granulomatous interstitial nephritis in a patient with Behcet's disease treated with infliximab]. *Nihon Jinzo Gakkai Shi* 2013;55:1412-7.
- [49] Williams VL, Cohen PR. TNF alpha antagonist-induced lupus-like syndrome: report and review of the literature with implications for treatment with alternative TNF alpha antagonists. *Int J Dermatol* 2011;50:619-25.
- [50] Shakoor N, Michalska M, Harris CA, et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002;359:579-80.
- [51] Williams EL, Gadola S, Edwards CJ. Anti-TNF-induced lupus. *Rheumatology (Oxford)* 2009;48:716-20.
- [52] Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. *Nephrol Dial Transplant* 2005;20:1400-6.
- [53] Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2015;29:290-305.
- [54] Knoll GA. Kidney transplantation in the older adult. *Am J Kidney Dis* 2013;61:790-7.