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Safety and Efficacy of Vedolizumab in Kidney Transplant Recipients With Crohn's Disease

Marco Busutti[1], Olga Baraldi[1], Clara Valentina Porcu[2], Gianluca Samele[2], Anita Campus[2], Valeria Grandinetti[1], Claudia Bini[1], Michele Provenzano[2], Nikolas Dussias[3], Fernando Rizzello[3,4], Paolo Gionchetti[3,4], Gaetano La Manna[1,2] and Giorgia Comai[1]

[1]Nephrology, Dialysis and Renal Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; [2]Nephrology Unit, Department of Medical and Surgical Science (DIMEC), Alma Mater Studiorum University of Bologna, Bologna, Italy; [3]Gastroenterology Unit, Department of Medical and Surgical Science (DIMEC), Alma Mater Studiorum University of Bologna, Bologna, Italy; and [4]IBD Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Correspondence: Gaetano La Manna, Nephrology, Dialysis and Renal Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, via Massarenti, 9, 40137, Bologna, Italy. E-mail: gaetano.lamanna@unibo.it

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis are chronic and idiopathic inflammatory bowel diseases, characterized by gastrointestinal symptoms such as abdominal pain, fecal urgency, and diarrhea[1,2]; and extra intestinal manifestations that may involve almost any organ including the kidney. The most common renal extra intestinal manifestations are nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis. In addition, kidney damage in patients with CD may result from dehydration, long-term malnutrition, anemia, and side-effects of medical therapy.[3]

The management of kidney transplant (KT) recipients with CD is extremely challenging and complex; traditional treatments such as mesalazine, azathioprine, and steroids are burdened by significant side effects[4] and newer biological drugs such as anti-tumor necrosis factor-alpha inhibitors are possibly correlated with increased risk of infectious complications and malignancy.[5,6]

Vedolizumab is an antibody against α4β7 integrin, selectively blocking lymphocyte homing in the gut. It is approved for moderately to severely active ulcerative colitis and CD not responsive to standard therapy or tumor necrosis factor-alpha inhibitors.[7] Several studies in the literature show the efficacy and safety of vedolizumab in patients with CD; nevertheless, data on KT recipients with CD (KTCD) has not been reported so far. We describe our monocentric experience with the use of vedolizumab in 3 KTCD patients.

CASE PRESENTATION

Case 1

A 50-year-old male diagnosed with CD in 1997 was treated with multiple therapeutic lines, including azathioprine and mesalazine, with limited clinical benefits. In 2016, he underwent a KT from a deceased donor for end-stage renal disease caused by focal segmental glomerulosclerosis. Maintenance immunosuppressive therapy was based on prednisone 2.5 mg/d, new prolonged release tacrolimus 2.25 mg/d (trough level 5–7 ng/ml) and azathioprine 75 mg/d. At the beginning of 2017, azathioprine was replaced by mycophenolic acid 540 mg/d after a cellular borderline rejection. Over the years, he had frequent reactivation of CD with subsequent prerenal acute kidney injury (AKI), often requiring hospitalization.

After developing steroid-dependent bowel disease, in July 2021 he was started on vedolizumab treatment. Intravenously vedolizumab 300 mg was administered for the first 2 times every 2 weeks as induction therapy (as per Center protocol) then bimonthly as CD maintenance therapy associated with budesonide 3 mg every other day (is ongoing tapering to completely suspend steroids).

Case 2

A 64-year-old female with autosomal dominant polycystic kidney disease underwent KT from a deceased donor in 2014. At the time of CD diagnosis, the patient was on maintenance immunosuppressive therapy with

Table 1. Clinical and demographical characteristics

Characteristic	Case 1	Case 2	Case 3
Age	50	64	56
Sex	Male	Female	Male
Nephropathy	FSGS	ADPKD	IgA nephropathy
Kidney transplant year	2016	2014	2003
Maintenance immunosuppressive therapy at time of starting vedolizumab	Prednisone 2.5 mg/d	Prednisone 5 mg/d	Prednisone 2.5 mg/d Tacrolimus ER 7.5 mg/d
	Tacrolimus LCPT 2.25 mg/d	Tacrolimus ER 4 mg/d	
	Mycophenolic acid 540 mg/d		
Therapy Crohn's disease	-1997–2017 azathioprine 75 mg/d and mesalazine	-azathioprine 50 mg/d from 2020–2021	-2021 vedolizumab
	-2017–2021 budesonide	-2021 vedolizumab	
	-2021 vedolizumab + budesonide		
Time of start Vedolizumab after transplant	5 yr	7 yr	19 yr
Time of start vedolizumab from Crohn's disease diagnosis	25 yr	2 yr	0 yr

ADPKD, autosomal dominant polycystic kidney disease; ER, extended release; FSGS, secondary to segmentary focal glomerulosclerosis; LCPT, new prolonged release tacrolimus.

prednisone 5 mg/d, tacrolimus extended release 4 mg/d (trough level 5–7 ng/ml) and mycophenolic acid 720 mg/d.

In 2020, after seeking a specialist for diarrhea and abdominal pain, a diagnosis of CD was made, mycophenolic acid was suspended, and the patient was started on azathioprine 50 mg/d. One year later, due to limited clinical response, treatment with vedolizumab was prescribed. Vedolizumab was given 300 mg intravenously as induction treatment and every 2 months thereafter as unique maintenance therapy for CD.

Case 3

A 56-year-old male underwent KT from a deceased donor in 2003 due to end-stage renal disease for an IgA nephropathy. In 2016, following new onset of chronic diarrhea, therapy with mycophenolic acid was discontinued with no clinical benefits. In 2021, he was diagnosed with CD during maintenance immunosuppressive therapy with prednisone 2.5 mg/d and tacrolimus extended release 7.5 mg/d (trough level 5–7 ng/ml). Treatment with vedolizumab was started as first line therapy, at 300 mg intravenously every 2 weeks for first and second administration (as per Center protocol), then every 2 months as unique maintenance therapy.

Main clinical characteristics of the 3 patients are summarized in Table 1. We followed the patients for at least 12 months after the start of vedolizumab treatment. Maintenance immunosuppressive therapy was maintained, unchanged after vedolizumab start in all 3 patients. No adverse events and no infectious complications have been reported so far.

All 3 patients showed an improvement of gastrointestinal symptoms. Specifically, all patients achieved clinical remission, defined as a Harvey Bradshaw Index score ≤ 4; 1 patient required a course of oral budesonide due to disease flare during the follow-up period, the other 2o patients maintained remission without the need for CD-related oral steroids (all patients maintained antirejection medication with low dose prednisone). On endoscopic evaluation after 1 year of treatment, 2 of the 3 patients exhibited complete mucosal healing (SES-CD score 0); the third patient had not yet achieved endoscopic remission. The 2 patients achieving endoscopic remission also had a normalization of C-reactive protein levels.

From a nephrological perspective, all 3 patients showed a stabilization of estimated glomerular filtration rate and tacrolimus trough level and also a decrease in AKI events and hospitalization; after starting treatment with vedolizumab, none of the patients required hospitalization, as reported in Supplementary Table S1.

We evaluated the Coefficient of Variation[8] in trend of estimated glomerular filtration rate and tacrolimus trough levels, comparing the 24 months before the start of vedolizumab and the 12 months after, obtaining significant results both for estimated glomerular filtration rate and tacrolimus (respectively, 25.5% vs. 4.3% and 55.04% vs. 7.28%). Data are depicted in Figure 1.

DISCUSSION

CD is a heterogeneous disease and extra intestinal manifestations can affect almost every organ, including the kidney. In particular, patients with CD are 5 times more likely to suffer from end-stage renal disease and require replacement therapy during their life.[9] There is a lack of data in the literature about KTCD recipients, but the few studies suggest that patients with CD undergoing KT have shorter overall graft survival rates compared to controls without CD. Particularly, in one of the mentioned study, the shorter graft survival was related to higher infection rate, in the other one (conducted in an extremely selected population) to the recurrence of amyloidosis.[S1] Despite the absence of strong evidence, KTCD patients are suggested to

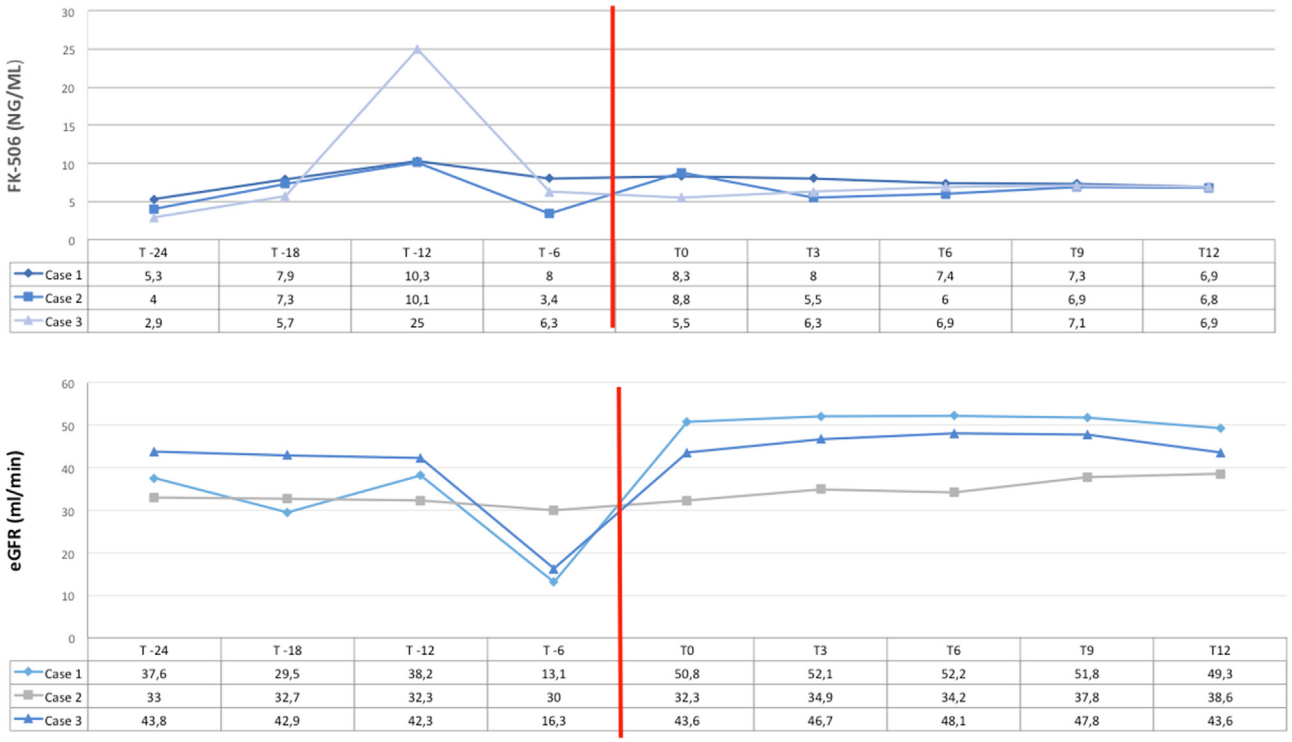

Figure 1. Serum level of eGFR and tacrolimus trough levels 24 months before and 12 months after the start of Vedolizumab. eGFR, estimated glomerular filtration rate.

receive low dose steroids in the immunosuppressive regimen, as we did in the 3 patients we report on.

Renal damage in patients with inflammatory bowel diseases can occur on different pathophysiological playgrounds; prerenal AKI results from kidney hypoperfusion due to diarrhea episodes, dehydration, and/or anemia.

Parenchymal damage can be the result of prolonged or close prerenal AKI events, but also from other kidney manifestations related to CD such as glomerulonephritis, tubulointerstitial nephritis, or amyloidosis, and may correlate with the activity of the disease. Moreover, some CD medications' side-effects can lead to kidney damage.

Postrenal causes of kidney injury are less common, mainly related to obstructive nephrolithiasis.

Therefore, effective management of CD symptoms is essential to improve renal outcomes of these patients.[3]

The management of CD in KT recipients is very challenging and is encumbered by a lack of studies in the literature. The "traditional" CD medical therapies are burdened by significant side-effects. Mesalazine is nephrotoxic and may lead to interstitial fibrosis and papillary necrosis.[3,4] In addition, more recent CD medical therapy, such as tumor necrosis factor-alpha inhibitors, in KT recipients are associated with an enhanced risk of malignancy and infectious complications.[5,6]

Vedolizumab is a monoclonal antibody against $\alpha 4\beta 7$ integrin, which acts by preventing the infiltration of leukocytes selectively in the gastrointestinal submucosa. Due to its gut selectivity, vedolizumab is not associated with a higher risk of systemic infections and malignancy.[S2] The side-effects of vedolizumab reported in GEMINI 1 and 2 trials do not include nephrotoxicity, although in the literature there are 2 case reports of acute interstitial nephritis after administration.[S3]

Table 2. Teaching points

CD and UC are chronic and idiopathic IBDs, characterized by gastrointestinal symptoms and EIMs.
The most common renal EIMs are nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis, and amyloidosis. In addition, kidney damage in patients with CD may result from dehydration, long-term malnutrition, anemia, and side-effects of medical therapy.[3]
The "traditional" CD medical therapies are burdened by significant side effects: mesalazine is nephrotoxic and may lead to interstitial fibrosis and papillary necrosis. Calcineurin inhibitors cause the vasoconstriction of the afferent arterioles thereby increasing risk of AKI and leading to renal damage. TNF alpha inhibitors in KT recipients are associated with an enhanced risk of malignancy and infectious complications.
KTCD patients treated with vedolizumab showed improvements in gastrointestinal symptoms that lead to more stable eGFR value and tacrolimus through levels, and less AKI and hospitalization events.

AKI, acute kidney injury; CD, Crohn's disease; eGFR, estimated glomerular filtration rate; EIMs, extra intestinal manifestations; ER, extended release; IBDs, inflammatory bowel diseases; KT, kidney transplant; KTCD, KT recipients with CD; UC, ulcerative colitis.

Few studies in the literature, although limited to a small sample of patients, have shown the efficacy and safety of vedolizumab in liver transplant recipients with CD[S4,S5]; nevertheless, no data on KT recipients has been reported so far. A recently published review on the use of nontransplant biologics in solid organ transplant recipient, albeit the lack of data, suggests the possibility to use vedolizumab in solid organ transplant recipients without the need for adjustment in immunosuppressive therapy and/or specific infection prophylaxis.[S6]

To our knowledge, this is the first experience with the use of vedolizumab in KTCD patients. In our experience, no adverse events, no infectious complications, and no nephrotoxicity has been observed after 12 months of treatment. We compared the clinical course of the same 3 patient in the 12 months before the start of vedolizumab, observing improvements in gastrointestinal symptoms that lead to more stable estimated glomerular filtration rate value and tacrolimus trough levels, and less AKI and hospitalization.

This experience is limited by the low number of patients, the retrospective observation, and the absence of a control group, not allowing any finishing conclusion. Nevertheless, these encouraging results can lay the groundwork to design clinical studies to further investigate the safety and efficacy of vedolizumab in KTCD patients.

Teaching points are resumed in Table 2.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary References.

Table S1. Incidence of hospitalization and AKI 12 months before and after the administration of Vedolizumab.

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