PREVENTION OF COMPLICATED UTIS WITH BIOCOMPATIBLE HYALURONIC ACID COPOLYMER (DEFLUX®) TREATMENT OF THE KIDNEY TRANSPLANTED VESICOURETERAL REFLUX. A SINGLE CENTRE EXPERIENCE

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ABSTRACT

Introduction: *Urinary tract infections (UTI) are the most frequent early and late infectious complications in renal transplant patients. Vesicoureteral reflux (VUR) occurs in more than 86% of renal transplants. It is considered as a possible cause of the onset of complicated urinary tract infections although its actual impact remains uncertain. A therapeutic option in the treatment of VUR, successfully used in particular in pediatric patients, is represented by the injection in the ureter of hyaluronic acid/dextranomer polymers (Dx/HA, Deflux®) performed through the endoscopy procedure. In this study the experience of the Nephrology Unit at the University of Padova is reported.*

Methods: *Six renal transplanted female patients (mean age 45.6 years) who presented a history of recurrent complicated UTIs (more than 3/year), were considered. In these patients a retrograde and voiding cystography documented the presence of VUR at the transplanted kidney. Between February 2016 and July 2018 all these patients underwent endoscopic treatment with Dx/HA.*

Results: *Five patients, after endoscopic treatment with Dx/HA, did not show at the follow up until present any episode of complicated UTIs, confirming the successful of this therapeutic option for the UTI due to VUR in renal transplanted patients.*

Conclusions: *Although based on a limited number of patients, the endoscopic treatment of VUR with hyaluronic acid copolymer Deflux® in kidney transplanted patients is safe, non-invasive, repeatable if necessary, and the results in our patients are favorable. Although considering a period of observation of two years, it might be too short to demonstrate the effectiveness of the treatment in the long-term. However, being able to successfully correct the VUR in kidney transplanted patients represents a very important chance to reduce complicated UTIs in kidney transplanted patients thus increasing the chance for the transplanted organ's survival.*

Keywords: *Renal Transplant, vesicoureteral reflux, urinary tract infections, renal transplant complications, biocompatible hyaluronic acid copolymer.*

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Background

Urinary tract infections (UTI) are the most frequent early and late infectious complications in renal transplant patients. They have an incidence of more than 75%, are more common in female patients and approximately 25% of patients are affected within the first year of transplantation[1,2].

Clinical pictures of UTI in renal transplanted patients include asymptomatic bacteriuria (more than 100.000 CFU/ml for urine culture in absence of local/systemic symptomatology), uncomplicated UTI (more than 100.000 CFU/ml for urine culture and local symptomatology) and complicated UTI (more than 100.000 CFU/ml for urine culture and fever plus one of the following: pain in the transplanted kidney, chills, bacteremia, pyelonephritis documented by an instrumental examination), which are present in 45%, 30% and 25% of the cases, respectively.

Several predisposing factors for UTI complicating renal transplanted patients are considered important such as female gender, age, diabetes mellitus, history of recurrent UTIs prior to renal transplantation, deceased donor, re-transplantation, immunosuppressive regimen and urinary tract abnormalities.

Vesicoureteral reflux (VUR) occurs in more than 86% of renal transplants. It is considered as a possible cause of the onset of complicated urinary tract infections although its actual impact remains uncertain and debated[3, 4].

VUR is commonly defined as the retrograde, non-physiological flow of urine from the bladder to the high excretory pathways during urination or during bladder filling and can be determined by both anatomical and functional disorders. Five degrees of VUR have been classified by the International Reflux Grading System, depending on the retrograde filling level and the dilatation of the excretory pathway.

This classification is based on the radiographic appearance of cystourethrography. A therapeutic option in the treatment of VUR, which has been successfully used in particular in pediatric patients, is represented by the injection in the ureter of hyaluronic acid/dextranomer polymers (Dx/HA, Deflux®) performed through the endoscopy procedure.

Methods

Six renal transplanted female patients (mean age 45.6 years) at the Kidney and Pancreas Transplant Unit at the University of Padova, with a clinical follow-up by the Nephrology, Dialysis and Transplant Unit at the University of Padova, who presented a history of recurrent complicated UTIs (more than 3/year), were considered. In these patients a retrograde and voiding cystography documented the presence of VUR at the transplanted kidney.

Between February 2016 and July 2018 all these patients underwent endoscopic treatment with Dx/HA in the Urology Department of our University Hospital. Three patients had a direct implant of the ureteral ostium of the transplanted kidney at the level of the right lateral wall of the bladder as described at cystourethroscopy performed during treatment. In one patient it was in a lateralized position almost on the right side wall of the bladder and in two cases the new ostium was on the bladder dome.

The postoperative program included the execution of a lower abdomen ultrasound at a distance of about 40 days, with evaluation of the bladder pre- and post-urinary residuals. Patients were informed regarding the procedure, which being an established surgical procedure does not need to be submitted to the ethics committee. Informed consent was however obtained by all the patients.

Results

Five patients, after endoscopic treatment with Dx/HA, did not show at the follow up until present any episode of complicated UTIs, confirming the successful of this therapeutic option for the UTI due to VUR in renal transplanted patients.

After one year one of our patients presented relapse of the reflux and was successfully treated with a new implantation of the biocompatible material Dx/HA, Deflux®. One patient five months after treatment presented with a pyelonephritis, which was treated with i.v antibiotic therapy. It has to be noted, however, that in this case the patient presented the particularly complex picture of grade V VUR in the transplanted kidney and grade III-IV VUR in both native kidneys, which clearly exposed the patient to infective complications of the urinary tract.

Discussion

The endoscopic treatment of VUR was first described in 1984 by Puri and O'Donnell[5]. This procedure provides for the reconstruction of an anti-reflux valve mechanism through an endoscopic ureteral injection of a bulking agent, able to lift the end section of the ureter.

Several types of materials have been used over time for this procedure including PTFE (Teflon), Macroplastique (polydimethylsiloxane), bovine collagen, chondrocytes, autologous fat, coaptite (calcium hydroxyapatite) and silicone with very poor results. These materials, in fact, do not possess the ideal properties to guarantee the success of the procedure and have been abandoned.

The ideal injectable material must, in fact, be sure, easily injectable, stable at the injection site, long lasting, biocompatible, not antigenic and not carcinogenic. In the last 15 years the material mainly used for this treatment has been the hyaluronic acid copolymer (DxHA-Deflux®) approved in 2001 by the Food and Drug Administration (FDA). A meta-analysis that included 5527 patients and 8101 renal units, showed that, after a single injection of the hyaluronic acid copolymer (DxHA-Deflux®), the success of the procedure was 78.5% in the VUR of I-II grade,

72% in the VUR of III grade, 63% in the VUR of IV grade, and 51% in the VUR of V grade and successive injections led to a global success of 85%[6].

Different techniques of endoscopic injection are described, such as STING-Subureteral transurethral injection, HIT-Hydrodistention Implantation Technique, DOUBLE HIT, which do not substantially modify the success rates of the procedure.

Some limits of the endoscopic treatment with Deflux® procedure have to be noted. They are due to the fact that the transplanted ureter is more atonic and rigid compared with the native ureter and it is often in an anomalous anatomical position which make more difficult the insertion of the needle for the injection of the hyaluronic acid copolymer. In addition, there are no studies that valuate the effective duration of the material, and it is only estimated that it could be reabsorbed within the first year of about 20%. Furthermore, there is not much experience between physicians to perform this procedure in adult patients, which still remains a strictly single physician-based method. Finally, the coexistence of urological and/or gynecological problems may strongly complicate the execution of this treatment[7, 8].

In conclusion, the experience of our Centre, although based on a limited number of patients, suggests that indications for the endoscopic treatment of VUR with hyaluronic acid copolymer Deflux® in kidney transplanted patients are essentially clinical and the procedure is safe, non-invasive and repeatable if necessary.

The observational time of our cohort of patients, which includes a total period of two years, could be too short to definitely demonstrate the effectiveness of the treatment in the long-term and although the results of this study are encouraging, the collection of data from longer follow up time are ongoing and the results needed. However, being able to successfully correct the VUR in kidney transplanted patients represents a very important chance to reduce complicated UTIs in these patients thus increasing the chance for the transplanted organ's survival.

References

1) Pichler R, Buttazzoni A, Rehder P, Bartsch G, Steiner H, Oswald J. Endoscopic application of dextranomer/hyaluronic acid copolymer in the treatment of vesico-ureteric reflux after renal transplantation. BJU International 2010; 107: 1967-1972.
2) Ariza-Heredia EJ, Beam EN, Lesnick TG, et al. Impact of urinary tract infection on allograft function after kidney transplantation. Clin Transplant 2014; 28: 683.
3) Jung GO, Chun JM, Park JB, Choi GS, Kwon CH, Joh JW, Lee SK, Kim SJ. Clinical significance of posttransplantation vesicoureteral reflux during short-term period after kidney transplantation. Tranplant Proc. 2008; 40(7): 2339-41.
4) Margreiter M, Györi GP, Böhmig GA, Trubel S, Mühlbacher F, Steininger R. Value of routine voiding cystourethrography after renal transplantation. Am J Transplant 2013; 13(1): 130-5.
5) O'Donnell B, Puri P. Technical Refinements in Endoscopic Correction of Vesicoureteral Reflux. J Urol. 1988; 140: 1101-1102.
6) Elder JS, Diaz M,Caldamone AA, Cendron M, Greenfield S, Hurwtiz R, Kirsch A, Koyle MA, Pope J, Shapiro E. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. Reflux resolution and urinary tract infection. J Urol. 2006; 175: 716-722.
7) Williams MA, Giel WD, Hastings Colleen M. Endoscopic Deflux® injection for pediatric transplant reflux: A feasible alternative to open ureteral reimplant. Journal of Pediatric Urology 2008; 4: 341-344.
8) Castagnetti M, Angelini L, Ghirardo G, Zucchetta P, Gamba PG, Zanon GF, Murer L, Rigamonti W. Ureteral complications after renal transplant in children: Timing of presentation, and their open and endoscopic management. Pediatric Transplantation 2013; 18: 150-154.

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