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Research Paper

Results of Use of Tissue-Engineered Autologous Oral Mucosa Graft for Urethral Reconstruction: A Multicenter, Prospective, Observational Trial

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ABSTRACT

Background: Harvest of oral mucosa for urethroplasty due to urethral stricture is associated with donor-site-morbidity. We assessed functionality and safety of an authorized tissue-engineered oral mucosa graft (TEOMG) under routine practice in stricture recurrences of any etiology, location, length and severity (real-world data).
Methods: 99 patients from eight centers with heterogenous urethroplasty experience levels were included in this prospective, non-interventional observational study. Primary and secondary outcomes were success rate (SR) and safety at 12 and 24 months.
Findings: All but one patient had ≥1, 77.1% (64 of 83) ≥ 2 and 31.3% (26 of 83) ≥ 4 previous surgical treatments. Pre- and postoperative mean ± SD peak flow rate (Qmax) were 8.3 ± 4.7 mL/s (n = 57) and 25.4 ± 14.7 mL/s (n = 51). SR was 67.3% (95% CI 57.6–77.0) at 12 and 58.2% (95% CI 47.7–68.7) at 24 months (conservative Kaplan Meier assessment). SR ranged between 85.7% and 0% in case of high and low surgical experience. Simple proportions of 12-month and 24-month SR for evaluable patients in all centers were 70.8% (46 of 65) and 76.9% (30 of 39). Except for one patient, no oral adverse event was reported.
Interpretations: TEOMG is safe and efficient in urethroplasty.

1. Introduction

Urethral stricture affects up to 0.6% of the male population with significant disease burden (Alwaal et al., 2014; Liu et al., 2016; Wessells et al., 2017; Latini et al., 2014). Except for the guidelines of the American Urological Association, no therapeutic recommendations exist (Wessells et al., 2017; Latini et al., 2014). These guidelines are mainly based on expert opinions and publications of lower evidence strength grades due to the lack of data obtained from prospective multicenter trials under good clinical practice (GCP) standard (Latini et al., 2014; Mundy, 2006; Tritschler et al., 2013). Consequently, different surgical techniques are applied according to the surgeon's preference and previous experience. Over the last two decades, buccal mucosa became the tissue of choice for urethral reconstruction (Wessells et al., 2017; Ram-Liebig et al., 2015; Markiewicz et al., 2007). However, oral mucosa harvest may lead to donor-site morbidity (Ram-Liebig et al., 2015; Jang et al., 2005; Fasolis et al., 2014; Markiewicz et al., 2008).

Tissue-engineered oral mucosa graft (TEOMG) represents an alternative material for urethroplasty. It helps to avoid morbidities associated with graft harvesting at the oral site and provides substitution tissue for urethral reconstruction in any size required (Ram-Liebig et al., 2015). We conducted an observational study with a TEOMG, with market authorization in Germany (MukoCell®), to expand the knowledge about feasibility, safety, and efficacy when used under routine real-world conditions in non-preselected adult male patients with surgically unsuccessful pretreated urethral stricture. The current data from our observational trial are reported to the Paul-Ehrlich-Institut, the regulatory body in Germany, responsible for marketing authorization of advanced therapy medicinal products (ATMP) - among others - and approval of clinical trials, as well as to the European Medicine Agency (the European Union agency for the evaluation of medicinal products).

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2. Materials and Methods

2.1. Study Design and Patients

The study is a prospective, observational survey conducted at eight German urologic centers, with <10 to >80 urethroplasties/year. This study is registered in Germany at the Paul-Ehrlich-Institut observational trial registry, NIS number 110.

Enrolled were adult male patients with recurrent urethral stricture. Decision for treatment of an individual patient with the autologous TEOMG was met solely by the treating surgeon.

All data captured during the observation were obtained from routine clinical care assessments which were done by the investigators according to their local medical practice (Real-world data), without additional, study-mandated examinations or clinic visits. The study was monitored by an independent licensed German Contract Research Organization.

The trial was designed in accordance with the Declaration of Helsinki with all its amendments. The study was approved by the local ethics committees and the competent national supervisory authority (Paul-Ehrlich-Institut, Langen, Germany). The trial followed GCP guidelines, European guidelines on ATMPs, and German Transplant Act. The patients signed informed consents for biopsy and blood taking, as well as for urethroplasty with TEOMG. The TEOMG implanted in the context of this study (MukoCell®) was provided by UroTiss GmbH, Germany.

2.2. Coordination and Schedules

For the manufacture of MukoCell®, a tiny oral biopsy is required. For being authorized to take biopsies, the urologist needs an approval according to German Drug Law from the authority, who granted the Good Manufacturing Practice (GMP) license for the TEOMG. For this, the clinic has first to provide documents to show that it has an appropriate facility. A hygiene plan, complying with the medical standards and suitable for carrying out biopsy procedures and blood collection is also required. The urologist who will have the primary responsibility for biopsy taking and blood collection, as well as the medical staff, who will be involved in the procedures must be trained for biopsy taking and blood collection and their storage as well as documentation of the procedure according to standard operating procedures, in compliance with good professional practice. Once the tissue collection authorization is available, and the patient agrees for the urethroplasty with MukoCell®, the urologist contacts the company by phone or email and informs it about the date, planned for biopsy taking and urethroplasty surgery. Within a few days, or if necessary within hours, he gets a biopsy kit from the Good Manufacturing Practice (GMP) laboratory. The biopsy kits are stable for 6 months. Together with the biopsy kit, the patient gets a unique identification code. This code is the first step of patient recruitment into the study. For tissue collection, a donor record, containing documentation of donor suitability and a patient consent form, should be completed. Once the biopsy is taken, it is put into the specific package, which is picked up at the same day. On the day after, upon arrival in the GMP laboratory, the manufacture begins. For safety reasons, the serologic examination must be negative for specific infectious agents (Human Immunodeficiency Virus, Hepatitis B and C, Treponema Pallidum), to allow release of the tissue for manufacture. Once manufacture begins, the date for urethroplasty is already fixed. According to this date, MukoCell® is placed in a sterile double package, and sent within a qualified transport container to the hospital. It must be used within 48 h.

TEOMG is an industrial product. The manufacturing processes therefore cannot be disclosed in all details. All procedures (identification code, biopsy taking, manufacturing, shipment) are standardized, validated and certified, respectively.

3. Procedures

For manufacture of TEOMG, a tiny oral mucosa biopsy of 0.5 cm^2 (Fig. 1A) was taken from patient's buccal mucosa and sent to the GMP laboratory for aseptic manufacturing of the graft, which has been described elsewhere (Ram-Liebig et al., 2015). In the manufacture site, all culture flasks, materials and documents were identified for each patient with the unique identification code, which was the same, as on the biopsy kit. All manufacture steps took place in an isolator and the culture steps in an incubator (37 °C, 5% CO_2) in the GMP laboratory. After separation from submucosa, the mucosa tissue was used for setting the cell cultures in flasks and their incubation. The expansion of cells took about two weeks. Once the epithelial cells were confluent, primary cultures were detached form the flasks and the non-splitted cells of passage 1 were seeded on a biodegradable membrane. Subsequently, the final TEOMG, consisting of oral epithelial cells from first passage cultured on biodegradable protein containing scaffold, was placed in a sterile container, packaged and pharmaceutically released for therapeutic use, after a final check of properness of quality control results and completeness of documentation. The manufacture of each batch was documented in an according protocol. All remaining materials and wastes were disposed according to specific Standard Operating Procedures. Timing of the whole procedure (3 weeks) was highly reliable, allowing to settle the surgery date as soon as the biopsy is taken from the patient. After release, the TEOMG was sent to the hospital for implantation into the patient's diseased urethra (Ram-Liebig et al., 2015). The shipment of TEOMG is a validated process, ensuring stability and viability of the tissue for 48 h.

Before urethroplasty, information on demographic and medical history was gathered. Pre- and post-operatively, results from physical examination, vital signs measurements, electrocardiogram, serological examinations, concomitant medication, and conventional urological examinations (e.g. urethroscopy, urethrography Fig. 1E, or uroflowmetry) were collected.

The TEOMG was implanted in accordance with the substitution urethroplasty technique routinely applied by the surgeon (Fig. 1B–D) when native buccal mucosa was used. After the operation, an 18 to 20 Ch. Foley silicon catheter was left in the urethra. Suprapubic catheter was placed in the urinary bladder in some cases about 3–6 weeks later, the catheters were removed and the patient underwent voiding urethrography (Fig. 1F).

Routine urological examinations such as uroflowmetry, urethroscopy and/or urethrography were usually repeated every 3 months during the first year and every 6 months during the second year unless there were symptoms of urethral re-stricture (e.g. decreased urinary flow).

4. Outcomes

The primary outcome was the success rate (SR), defined as the absence of stricture recurrence, at 12 months after TEOMG implantation. The prospectively selected definition of stricture recurrence was: evidence of a postoperative peak flow rate (Qmax) < 15 mL/s on uroflowmetry plus the urethra is not passable with a catheter (diameter = 16–18 Ch) or during standard urethroscopy. However, these diagnostic criteria did not correspond to the actual routine diagnostic practice at the participating sites, precluding the use of this definition for stricture recurrence. Therefore, a consolidated assessment of stricture recurrence was made post hoc, based on investigator rating, patient-reported spontaneous micturition after urethroplasty, and uroflow rate following urethroplasty (i.e. Qmax < 15 mL/s). The physician's assessment “treatment successful = yes” was used to exclude stricture recurrence, except in cases where patients reported difficulty of spontaneous micturition, where later re-stricture was detected, where there was need for further instrumental intervention, or where the physician's statement