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Platinum Opinion

# Clinical Experience with Urethral Reconstruction Using Tissue-engineered Oral Mucosa: A Quiet Revolution

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The ready availability of tissues and organs to replace and repair those that have been damaged is an important clinical need. The field of tissue engineering might offer an innovative solution. For three decades we have been hearing promises of the utility of tissue engineering. Hyperbole has become routine, leading us to believe that by combining cells and degradable materials, ex vivo organs can be developed to replace or repair diseased tissues The number of publications referring to stem cells increased from 4402 in 1996 to 21 193 in 2012, representing an annual growth rate of 7.0% [1]. Tissue engineering solutions have been suggested in the field of urology for many decades, but despite technical success in the laboratory, clinical application has been modest. In addition, education and training are required for the introduction of new technology within health systems and for optimisation of patient outcomes following the use of new technology [2]. To reach their full potential, developing technologies, in addition to science and engineering, require commercial upscaling of production in a safe and regulated framework for clinical use [2,3]. The gap between technical success in the laboratory or animal experiments and clinical application of tissue-engineered materials for the human bladder has been reported in the literature, with the authors honestly reporting "Reality or myth?" and "When will we get there?" [4–7].

The same gap between investigative in vitro studies and clinical use of tissue-engineered materials in patients is evident for urethral reconstruction. The literature contains myriad reports regarding different experimental tissue-engineered products, but only three reports on the use of these materials in patients with urethral strictures [8–10]. In 2008, Bhargava et al [8] reported clinical outcomes for autologous tissue-engineered buccal mucosa (TEMB) in five patients with penile strictures due to lichen sclerosus using a one-stage ($n = 2$) or two-stage ($n = 3$) technique. The authors concluded that in patients with a lichen sclerosus stricture, TEMB use was not without complications, namely fibrosis and contraction [8]. In 2011, Raya-Rivera et al [9] reported on the clinical use of tissue-engineered autologous tubularised urethra in five boys with traumatic posterior strictures during extended follow-up (median 6 yr) [9]. Of the five patients, only one required a transurethral incision for an early recurrent stricture at the proximal anastomotic site; the procedure was deemed a success for all patients, with a median maximum flow rate of 27.1 ml/s at the last follow-up [9]. These two articles represent the most important reports on the clinical use of tissue-engineered materials for urethral reconstruction, having used the material as a tube in complex traumatic posterior strictures or as an onlay in patients with genital lichen sclerosus [8,9]. Ram-Liebig et al [3] recently reported on the largest series of patients ($n = 21$) to undergo urethroplasty using tissue-engineered oral mucosa for anterior urethral strictures. During a median follow up of 18 mo (range 13–22) the success rate was 80.9%. This study represents the most important step in the clinical use of tissue-engineered material for urethral reconstruction. The authors showed that by following strict protocol criteria, it is possible to move tissue-engineering technology from the laboratory bench to the bedside [3].

However, realisation of this aim represents a very difficult challenge and we must take care not to deceive patients into thinking that this "quiet revolution" in urethral reconstruction will be available soon for all urethral conditions (congenital or acquired) requiring surgery.

There are two important questions regarding tissue-engineered material and urethral reconstruction according

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to evidence available in the literature that should be shared with readers.

(1) How should tissue-engineered material for urethral reconstruction be used on a large scale in different countries?

This point is important when considering the differing economic resources in each country for project investment and the bureaucratic steps required for product registration [3]. The documents required for a centralised European marketing authorisation must be presented in a dossier comprising the following five modules [3]:

- Module 1: regional administrative data;
- Module 2: summaries of quality, nonclinical, and clinical data;
- Module 3: manufacturing and quality information with specific consideration of chemical, pharmaceutical, and biological substances;
- Module 4: nonclinical study data; and
- Module 5: clinical study data.

The development and subsequent approval of a tissue-engineered product (TEP) require significant financial and human resources [3]. There is one exception that differs greatly from the general requirements for a centralised marketing authorisation for advanced therapy medical products (ATMPs) that allows medical practitioners in a hospital to provide ATMPs to their patients [8]. This exception is limited to custom-made products prepared on a nonroutine basis for individual patients within the same member state. Traceability, quality, and pharmacologic vigilance standards for these products must be equivalent to standards for centrally authorised products. The manufacture of these products must be authorised by the competent authority of the member state to ensure their quality [3,8].

To summarise, limited economic resources and bureaucratic steps for product registration are involved for the development of tissue-engineered material for a clinician's own patients to be used only within the same country. By contrast, a marketable product that can be used in any European country will require considerable financial, laboratory, and human resources, and several years of development before it can be registered with the Committee for Advanced Therapies at the European Medicines Agency [3]. Finally, considering the steady increase in the incidence of urethral strictures, especially post-traumatic stenosis, in developing countries (China, India, Africa), the World Health Organisation should develop a new investment framework to achieve dramatic worldwide health gains in the management of tissue-engineered urethral reconstruction in the near future.

(2) How should tissue-engineered material for urethral reconstruction be used on a large scale for different urethral conditions (simple vs complex)?

The ultimate goal in the use of engineered material for urethral reconstruction should be to provide a wide range of products that differ in dimension (from 3 to 15 cm in length) and shape (rectangular vs tubular) for adaptation in different types of urethroplasty. This would require a prospective, multicentre, randomised, double-blind, and placebo-controlled/comparative design for a phase 3 study in a large series of patients. Randomisation and control groups require an appropriate comparison or justified placebo. However, these steps are generally difficult to implement for TEPs, in particular because these products are often developed for conditions for which an adequate alternative treatment or standard of care is currently not available [3]. We are thus still far from this step.

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