Milestone in the treatment of men's disease with regenerative medicine

MukoCell, a tissue-engineered mucosa, is about to confirm the therapeutic efficacy in the plastic reconstruction of urethra in a prospective randomised clinical trial

Tissue engineering combines the field of cell biology with material science in order to generate tissues and organs that may be used for regeneration, replacement or reconstruction of human bodies. In the past 10 years there has been an exponential growth in these therapies, with great optimism and excitement about the potential effects or implications.

Since the end of the 20th century, cultured urethral mucosa cells have been used for repair of hypospadias, a congenital malformation of the urinary tract. In a survey published in 2019[1], tissue-engineered grafts showed even better results when used in children for primary hypospadias repair than in adults for urethral stricture repair.

Treating urethral stricture

Recently, a breakthrough in the surgical treatment of male urethral stricture was reported[2] when a total of 65 patients with urethral strictures successfully were treated with MukoCell, a tissue-engineered oral mucosa transplant. With a mean follow-up of 12.1 months, recurrence was observed in only 12 patients. This corresponds to a success rate of 81.5%.

About 1% of the male population suffers from strictures of the urethra. Patients are chronically ill, with severely diminished quality of life, suffering from low urinary flow, pain, chronic urinary infections, urinary stones, urinary reflux, and damage to and failure of the urinary system. If left untreated, life-threatening urinary retention can occur.

Complications of treatment

The gold standard for urethral reconstruction is represented by the use of oral mucosa graft, with success rates reported in literature of around 80%. However, due to the complication rate at the mucosa harvest site, only a minority of operative urologists carry out this procedure. It requires the excision of large segments of mucosa from the mouth of the patients. This severe damage to healthy tissue frequently is accompanied by multiple injuries with a significant impact on patients' quality of life – intraoral pain, bleeding, swelling, sensory loss and oral numbness – which in many cases are persistent. Other long term consequences include compromised oral health, scarring, chronic ulcers due to repeated bites on scar bulges, impaired lip mobility, permanent salivation, oral stenosis, facial deformities, diminished facial expressions, impaired mouth opening and impaired drinking, eating and speaking, periodontal disease; and loss of teeth and implants. One of the late consequences resulting from chronic irritation and inflammation is the increased risk of oral cancer.

Because of these risks and complications many doctors and patients refuse this operation. Moreover, in certain situations this operation cannot be performed, such as where the patient only has a small oral cavity or limited mouth opening capacity, meaning access to the oral cavity is limited and excision of larger pieces of oral mucosa is not possible. A significant proportion of patients are not willing to undergo the excision of oral grafts, including patients with tendency to increased scar formation, where the excision of oral mucosa is associated with risks of parafunctional bites, chronic irritation and inflammation; or patients with dentures, where the excision may lead to poorly fitting dentures or loss of dental implants. This counts even more if there is pre-existing oral mucosal damage, for example after previous removal of oral mucosa.

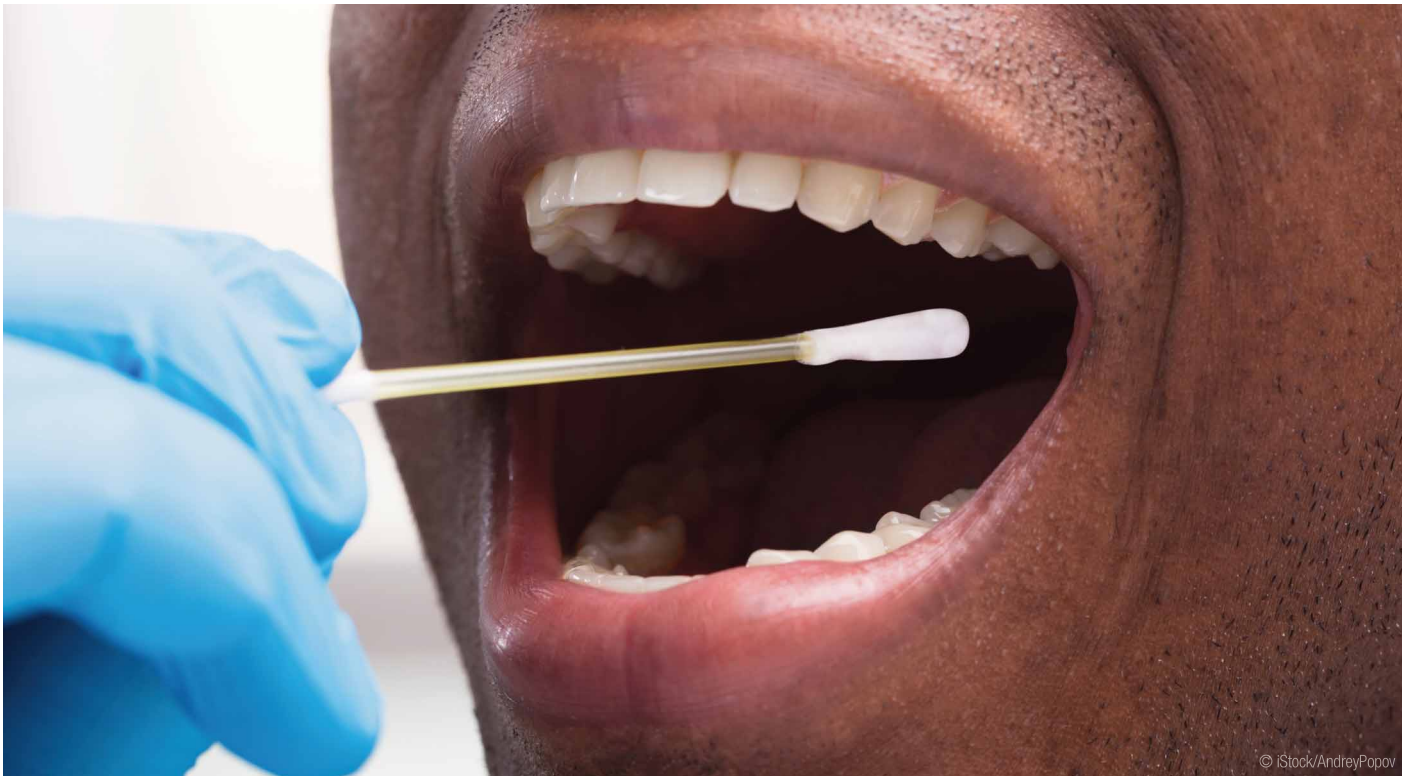
For other patients the oral complications cannot be tolerated because impairment of physiognomy, oral anatomy or gustatory sensation impacts their job or social function; such as teachers, singers, politicians, actors, speakers, salespeople, cooks and musicians who play wind or brass instruments.

Regulation and standards

Tissue-engineered transplants represent the group of 'advanced tissue-engineered therapies' (ATMPs). These are subject to EU regulation; in order to obtain market access they must receive authorisation from the European Medicines Agency (EMA). In order to obtain this approval, high standards must be met regarding proof of the quality, safety and efficacy of these products. Although tissue-engineered products may have a high impact on patients' health, only a few of them will be approved. Tissue engineering techniques are complex and require a high standard of specialised laboratories.

How MukoCell works

Regarding quality and safety, MukoCell has already received a certificate from the EMA. MukoCell is manufactured in a state of the art cell culture factory, which has been specifically designed for engineering of tissue especially for medical use and complies with GMP guidelines for the production of pharmaceuticals. The manufacturing process starts with a tiny biopsy from the oral mucosa of the patient. Oral mucosa is easily accessible in any patient; and biopsy under simple local anaesthesia is easy, non-invasive and painless for patients. The tissue is sent to the tissue factory where the biopsy is



explanted in cell culture media. Cells are grown out and undergo a standardised aseptic manufacturing process, at the end of which, before the products are used therapeutically, strict quality and safety tests are conducted. Only if the specified quality criteria are met are the products then released for therapeutic application.

The efficacy of MukoCell has been shown in an open non-interventional study. However, to achieve market authorisation, the EMA requests that efficacy be further confirmed in a pivotal clinical study in direct comparison with native oral mucosa. This study will begin shortly and will involve a total of 200 patients, divided into two therapy groups of 100 patients each. Initial results of the study are expected by beginning of 2023. One goal of this clinical study is to show equivalence of the tissue-engineered product with native oral mucosa in urethral stricture treatment; the other goal is to clearly demonstrate the superiority of MukoCell over native oral mucosa as a graft, in terms of the aforementioned frequent and severe intraoral complications and impact on quality of life for patients.

Insurance and cost

The demonstration of MukoCell's superiority is not only important regarding market authorisation, but also in respect to reimbursement by health insurances. The transplantation of native oral mucosa is a procedure developed by hospital surgeons. A critical examination of its safety and effectiveness has never been carried out; and complications are accepted if there is no alternative treatment. Moreover, besides the surgical procedure – which is paid for by the health insurance companies – there are no additional costs associated with using native oral mucosa. In contrast, to justify additional costs arising from the use of a cultivated transplant, the efficacy, safety and superiority to native oral mucosa needs to be proven. Therefore, in the clinical trial it is particularly important that the complications arising from excision of the transplant are recorded and documented as objectively as possible. Since the goal of surgery is to reconstruct the urethra, urologists pay little attention to intraoral complications and commonly play down their severity and importance.

Although the production of MukoCell is very complex and absolute sterility must be maintained during the three-week cultivation period, the costs are acceptable at several thousand euros. What pushes the costs even higher is the need to fulfil the requirements of the EMA in order to obtain marketing authorisation for the product: the planned clinical trial alone will cost around €10m. These costs must also be considered when pricing MukoCell.

The requirements of the regulatory authorities and health insurance companies not only influence the price of the products, but also their availability. MukoCell has been on the market since 2013, but its approval is limited to Germany and only applies in a few individual cases due to the issue of reimbursement.

A real, safe and efficient opportunity

In a 2019 review[2] the opinion was expressed that, due to the specificity of tissue-engineered products and the health benefits they offer, it would be advantageous to reconsider their regulatory requirements. The simplification of these requirements would allow the acceleration of these products into the market, faster availability for the patients and a decrease in the associated costs, making reimbursement less challenging for public health insurances in different countries. Further, it was stated that the use of MukoCell represents a real, safe and efficient opportunity for patients with urethral stricture diseases. However, at present, regulatory, legal and financial issues represent important factors that restrict and slow down the wider use of MukoCell.

References

1 Barbagli G *et al.* 2019, *Asian Journal of Urology*. https://doi.org/10.1016/j.ajur.2018.12.009

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