New transrectal prostate biopsy approach:

May improve tolerability and safety

Dr. Marcin Sieczkowski
Gdansk (PL)

sieczkowski@gmail.com

Histopathological examination is the essential basis in the diagnosis of prostate cancer. Most likely, it will be a long time before prostate biopsy will be replaced by the new biochemical tests or imaging-based solutions. That is why it is highly important to determine what is the best approach concerning this procedure. The Guidelines of the European Association of Urology (EAU) clarify much on the matter, but there are still many issues that remain uncertain [1].

For years, transrectal prostate biopsy with antimicrobial prophylaxis, usually based on fluoroquinolones, remained the standard. Due to the increasing bacterial resistance to fluoroquinolones, their side effects and rising rate of infectious complications, changes in approach to prostate biopsy have been necessary. In line with the European Commission's final decision (EMEA/H/A-31/1452), fluoroquinolones have been banned to be used for all perioperative prophylaxis [2]. This recommendation has been also confirmed by the EAU Guidelines panel as in regards to prostate biopsy [1]. This decision is just one of many strategies that can contribute to patient safety during prostate biopsy.

Non-antibiotic strategies

Among different non-antibiotic strategies tested for this purpose, the beneficial effect has been achieved by use of a rectal povidone-iodine preparation. Meta-analysis by Pradere et al. showed the reduction of infectious complications rate (RR 0.50, 95% CI 0.38-0.65, p <0.000001, I2=27%, 1,686 participants, 8 eight studies) as well as re-hospitalisation (RR 0.38, 95% CI 0.21-0.69, p=0.002, I2=0%, 620 participants, 4 four studies) following the application of this method [3]. However, this proved to be an insufficient measure.

Up until now, the best results so far in reducing infectious complications related to prostate biopsy have been obtained by changing from transrectal to transperineal route. The same meta-analysis demonstrated that transperineal biopsy was associated with significantly reduced infectious complications as compared to transrectal one (RR 0.55, 95% CI 0.33-0.92, p=0.02, I2=0%, 1,330 participants, 7 seven studies) [3]. This insight is also supported by the large population-based study from England where patients undergoing transperineal biopsy were less likely to be readmitted because of sepsis (1.0% vs 1.4%; aRD -0.4%, CI -0.6 to -0.2) [4].

The above results seem to fully justify the EAU Guidelines stating that transperineal biopsy should be a primary choice and transrectal approach should be abandoned despite any possible logistical challenges [1]. Unfortunately, these challenges are not the only problems associated with transperineal route.

The previously mentioned population study from England demonstrated that patients undergoing transperineal biopsy were more likely to have an overnight hospital stay (12.3% vs 2.4%; aRD 9.7%, 95% confidence interval [CI] 7.1-12.3) and were more likely to be readmitted with urinary retention (1.9% vs 1.0%; aRD 1.1%, CI 0.7-1.4) than those undergoing a transrectal procedure [4]. The authors concluded that this means that use of the transperineal route would prevent one readmission for sepsis in 278 patients at the cost of three additional patients readmitted for urinary retention [4].

Despite advances in performing transperineal prostate biopsy under local anaesthesia, it may also be associated with more discomfort. The systematic review by Xiang et al. revealed that the transperineal approach significantly increased patient pain (RR = 1.83, 95% CI 1.27–2.65) [5]. Furthermore, the issue of an increased risk of erectile dysfunction after transperineal biopsy remains unclear. It is known that up to 25% of males undergoing this procedure have been reported to experience deficits in sexual function [6]. Tan et al. have postulated that transperineal access may induce erectile dysfunction through neuropraxia at a higher rate than the transrectal approach given passage of multiple punctures through the prostatic apex where the neurovascular bundles are converging [6].

Systemic antibiotic strategies

Finding a simple antibiotic strategy to reduce infectious complications after transrectal prostate biopsy in the post-quinolones era is difficult. Targeted prophylaxis based on the rectal swab may reduce infective complications and prove to be more cost-effective in the long term. However, it is unclear whether there is sufficient evidence to recommend its use in pre-biopsy screening programmes as no randomised controlled trials (RCTs) are available on non-fluoroquinolones. An additional limitation of rectal swab cultures is that they must be taken preferably one week prior to the biopsy which complicates practicalities [7, 8].

Another option is an augmented prophylaxis with two (or more) antibiotics of different classes. Meta-analysis of 10 RCTs by Pilatz et al. confirmed the benefit of this strategy. However, no established standard combination exists to date. Most importantly, the systemic use of two antibiotics for antimicrobial prophylaxis contradicts the principles of antibiotic stewardship [9].

New approach

Facing the above problems mentioned above, Drug-Eluting Biopsy Needle (DEBN) may be another alternative for reducing post-biopsy infectious complications rate. DEBN may limit the systemic prophylaxis to only one systemic antibiotic supported by local release of another antibiotic of different class; therefore, reducing the risks of side effects as well as changes of the microbiome.

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DEBN is a patented (PCT/PL2016/000006) medical device which is a novel approach to the problem of transrectal ultrasound prostate biopsy (TRUS-Bx) related infectious complications. It consists of a polymer coated biopsy needle and anaesthesia needle containing an antibiotic that is released directly to the prostate during the biopsy procedure. This solution may allow the co-administration of various antibiotics, thereby broadening their spectrum of activity and potentially reducing the number of infectious complications.

DEBN is the first medical device to enable simultaneous organ-targeted delivery of antibiotics during prostate biopsy procedure. The presented model of DEBN contains poly(vinyl alcohol) and amikacin sulphate.

DEBN clinical trial

After numerous preclinical tests including studies on different formulations, microbiological and animal models, validation of production, packaging, sterilisation, biocompatibility, and ageing tests, the clinical trial was planned to assess the suitability of DEBN. This clinical investigation will be performed as a multicentre, double-blind, and non-inferiority trial in the eight clinical sites in Poland and Hungary specialised in the prostate biopsy procedure. The aim of this study is to assess whether safety and efficacy of transrectal biopsy performed with DEBN are non-inferior to standard transrectal biopsy combined with augmented prophylaxis. The main observation will focus on the rate of infectious complications in the study arms. Primary hypothesis of the investigation states that transrectal prostate biopsy performed with DEBN is non-inferior to standard transrectal prostate biopsy combined with augmented prophylaxis (fosfomycin trometamol 3 g p.o. + amikacin 15 mg/kg i.m.).

This clinical investigation aims to enrol approximately 123 subjects, including a potential 20% drop-out. The patient population of this study will be male aged ≥45 and < 80 years with an indication to transrectal prostate biopsy. Patient participation will last up to 44 days and will require five visits [Fig. 1]. The first four visits are on-site visits, and the last visit (visit 5) will be performed as a telephone visit, unless any safety concerns or any other reasons occur that in the investigators opinion require the visit to be performed on-site. Additionally, in case of any safety concerns, an unscheduled visit may be performed (telephone or on-site) at any time between Visit 3 and Visit 5, at the discretion of the investigator.

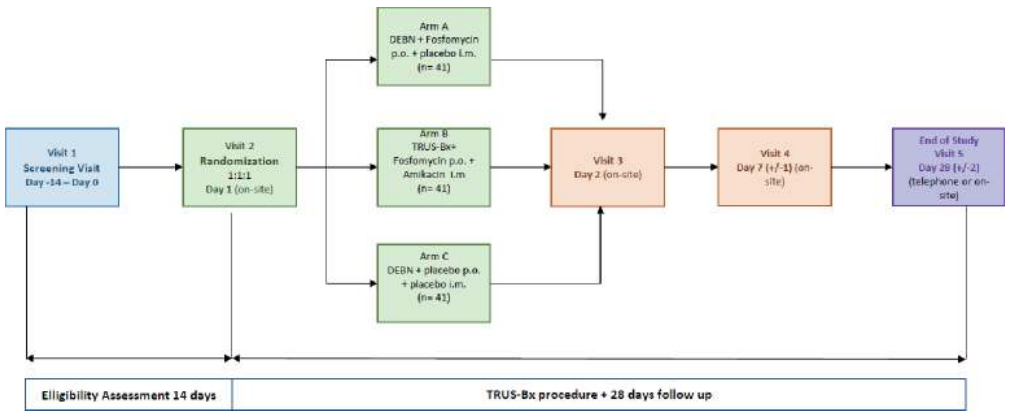

Fig. 1 DEBN trial investigation design scheme

The screening phase begins when written informed consent is obtained from the subject and ends at randomisation. The duration of the screening phase should not exceed 2 two weeks and all examinations must be performed ≤ 14 days prior to planned randomiszation. A patient's eligibility for the study will be finally confirmed during the Baseline Visit (Visit 2) at Study Day, which is the day of randomisation and transrectal prostate biopsy.

Subjects fulfilling the inclusion criteria and not meeting the exclusion criteria will be randomised in a 1:1:1 ratio to one of the three treatment arms:

- Arm A: DEBN transrectal prostate biopsy + fosfomycin 3 g p.o. + placebo i.m.
- Arm B: standard transrectal prostate biopsy + augmented prophylaxis (fosfomycin 3 g p.o. + amikacin 15 mg/kg i.m.)
- Arm C: DEBN transrectal prostate biopsy + placebo p.o. + placebo i.m.
- After the biopsy, the patient will be observed for post-biopsy infectious complications during the follow-up period until day 28. All follow-up visits will be scheduled to occur from the date of transrectal prostate biopsy:
- Visit 3 will be an on-site visit on day 2. Safety assessments will be performed during this visit. At the end of this visit, the second dose of fosfomycin (3 g p.o.) or placebo will be administered.
- Visit 4 on day 7 (+/- 1 day) will be an on-site visit. Safety assessments and success of the biopsy (procedure-related complications) will be performed during this visit.
- Visit 5 on day 28 (+/- 2 days) after the transrectal prostate biopsy will be a telephone visit. This visit will be an End of Study Visit. Safety assessments will be performed.

Patient safety will be monitored by through medical interview and physical examination. Vital signs will be measured, while as well as monitoring the haematology, biochemistry, inflammatory blood parameters, urinalysis, urine culture, and rectal swab will be monitored. Additionally, scales and questionnaires such as I-PSS (International Prostate Symptom Score), IIEF-15 (International Index of Erectile Function), EQ-5D (i.e. EuroQol instrument, a five-dimensional three-level generic measure) will be performed.

The monitoring of adverse events will be performed throughout the study period since the randomisation. Antibiotic prophylaxis will be administered with instructions of not taking any additional systemic antimicrobial treatment. Clinical investigation will be blinded. Placebo will be used for masking amikacin in study arm A and fosfomycin and amikacin in study arm C.

Due to technical reasons, blinding will be executed by introducing blinded and unblinded site teams. The blind team will be responsible for patient recruitment and all study assessments, while the unblinded team will be responsible for transrectal prostate biopsy and antibiotic prophylaxis administration, as well as, medical device and antibiotic prophylaxis management and documentation. These two teams will not contact each other to share the randomisation results.

Non-inferiority study design was chosen as an optimal one, taking into account that superiority of local anti-infectious prophylaxis is not expected to be superior to the systemic one. Non-inferiority design is commonly used to show that there is no difference between the new device or treatment. Active control to supports the conclusion that the new device is not materially worse than the control, which means it is also effective. This design was also chosen also for ethical reasons, as it would not be ethical to use only placebo, or a no-prophylaxis control only.

Non-inferiority margin was chosen as 15% is based on statistical considerations. Primary efficacy criteria is defined as the success rate understood. The rate of biopsies non-complicated by infection (absence of urosepsis or urinary tract infection resulting in the need of systemic antibiotic administration) was chosen as the main area of interest for DEBN, as well as, and to provide the answer for scientific questions on safety and efficacy of transrectal prostate biopsy performed with DEBN.

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