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BLADDER

Predicting outcomes after intradetrusor onabotulinumtoxina for non-neurogenic urgency incontinence in women

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Develop models to predict outcomes after intradetrusor injection of 100 or 200 units of onabotulinumtoxinA in women with non-neurogenic urgency urinary incontinence (UUI). Models were developed using 307 women from two randomized trials assessing efficacy of onabotulinumtoxinA for non-neurogenic UUI. Cox, linear and logistic regression models were fit using: (1) time to recurrence over 12 months, (2) change from baseline daily UUI episodes (UUIE) at 6 months, and (3) need for self-catheterization over 6 months. Model discrimination of Cox and logistic regression models was calculated using c-index. Mean absolute error determined accuracy of the linear model. Calibration was demonstrated using calibration curves. All models were internally validated using bootstrapping. Median time to recurrence was 6 (interquartile range [IQR]: 2-12) months. Increasing age, 200 units of onabotulinumtoxinA, higher body mass index (BMI) and baseline UUIE were associated with decreased time to recurrence. The c-index was 0.63 (95% confidence interval [CI]: 0.59, 0.67). Median change in daily UUIE from baseline at 6 months was -3.5 (IQR: -5.0, -2.3). Increasing age, lower baseline UUIE, 200 units of onabotulinumtoxinA, higher BMI and IIQ-SF were associated with less improvement in UUIE. The mean absolute error predicting change in UUIE was accurate to 1.6 (95% CI: 1.5, 1.7) UUI episodes. The overall rate of self-catheterization was 17.6% (95% CI: 13.6%-22.4%). Lower BMI, 200 units of onabotulinumtoxinA, increased baseline postvoid residual and maximum capacity were associated with higher risk of self-catheterization. The c-index was 0.66 (95% CI: 0.61, 0.76). The three calculators are available at http://riskcalc.duke.edu. After external validation, these models will assist clinicians in providing more accurate estimates of expected treatment outcomes after onabotulinumtoxinA for non-neurogenic UUI in women.

PROSTATE

5-alpha reductase inhibitors induce a prostate luminal to club cell transition in human benign prostatic hyperplasia

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Benign prostatic hyperplasia (BPH) is a progressive expansion of peri-urethral prostate tissue common in aging men. Patients with enlarged prostates are treated with 5-alpha reductase inhibitors (5ARIs) to shrink prostate volume by blocking the conversion of testosterone to dihydrotestosterone (DHT). A reduction in DHT levels can elicit atrophy and apoptosis of prostate secretory luminal cells, which results in a favorable clinical response characterized by improved lower urinary tract symptoms. However, the histologic response to 5ARI treatment is often heterogeneous across prostate acini and lower urinary tract symptoms can persist to require surgical intervention. We used two spatial profiling approaches to characterize gene expression changes across histologically normal and atrophied regions in prostates from 5ARI-treated men. Objective transcriptomic profiling using the Visium spatial gene expression platform showed that 5ARI-induced atrophy of prostate luminal cells correlated with reduced androgen receptor signaling and increased expression of urethral club cell genes including LTF, PIGR, OLFM4, SCGB1A1 and SCGB3A1. Prostate luminal cells within atrophied acini adapted to decreased DHT conditions by increasing NF-κB signaling and anti-apoptotic BCL2 expression, which may explain their survival. Using GeoMx digital spatial profiling with a probe set to assess ~18,000 RNA targets, we confirmed that atrophied acini expressing SCGB3A1 displayed higher levels of club cell markers compared to histologically normal acini with NKX3-1 expression. In addition, club-like cells within regions of 5ARI-induced atrophy closely resembled true club cells from the prostatic urethra. A comparison of histologically normal regions from 5ARI-treated men and histologically normal regions from untreated men revealed few transcriptional differences. Taken together, our results describe a heterogeneous response to 5ARI treatment where cells in atrophied acini undergo an adaptation from a prostate secretory luminal to a club cell-like state in response to 5ARI treatment.

Assessment of Frailty and Association With Progression of Benign Prostatic Hyperplasia Symptoms and Serious Adverse Events Among Men Using Drug Therapy

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Benign prostatic hyperplasia (BPH) in older men can cause lower urinary tract symptoms (LUTS), which are increasingly managed with medications. Frailty may contribute to both symptom progression and serious adverse events (SAEs), shifting the balance of benefits and harms of drug therapy. To assess the association between a deficit accumulation frailty index and clinical BPH progression or SAE. This cohort study used data from the Medical Therapy of Prostatic Symptoms trial, which compared placebo, doxazosin, finasteride, and combination therapy in men with moderate-to-severe LUTS, reduced urinary flow rate, and no prior BPH interventions, hypotension, or elevated prostate-specific antigen. Enrollment was from 1995 to 1998, and follow-up was through 2001. Data were assessed in February 2021. A frailty index (score range, 0-1) using 68 potential deficits collected at baseline was used to categorized men as robust (score ≤0.1),

prefrail (score 0.1 to <0.25), or frail (score ≥0.25). Among 3047 men (mean [SD] age, 62.6 [7.3] years; range, 50-89 years) in this analysis, 745 (24%) were robust, 1824 (60%) were prefrail, and 478 (16%) were frail at baseline. Compared with robust men, frail men were older (age ≥75 years, 12 men [2%] vs 62 men [13%]), less likely to be White (646 men [87%] vs 344 men [72%]), less likely to be married (599 men [80%] vs 342 men [72%]), and less likely to have 16 years or more of education (471 men [63%] vs 150 men [31%]). During mean (SD) follow-up of 4.0 (1.5) years, the incidence rate of clinical BPH progression was 2.2 events per 100 person-years among robust men, 2.9 events per 100 person-years among prefrail men (AHR, 1.36; 95% CI, 1.02-1.83), and 4.0 events per 100 person-years among frail men (AHR, 1.82; 95% CI, 1.24-2.67; linear P = .005). Larger point estimates were seen among men who received doxazosin or combination therapy, although the test for interaction between frailty index and treatment group did not reach statistical significance (P for interaction = .06). Risk of SAE was higher among prefrail and frail men (prefrail vs robust AHR, 1.81; 95% CI, 1.48-2.23; frail vs robust AHR, 2.86; 95% CI, 2.21-3.69; linear P < .001); this association was similar across treatment groups (P for interaction = .76). These findings suggest that frailty is independently associated with greater risk of both clinical BPH progression and SAEs. Older frail men with BPH considering initiation of drug therapy should be counseled regarding their higher risk of progression despite combination therapy and their likelihood of experiencing SAEs regardless of treatment choice.

Osteopontin Deficiency Ameliorates Prostatic Fibrosis and Inflammation

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Fibrogenic and inflammatory processes in the prostate are linked to the development of lower urinary tract symptoms (LUTS) in men. Our previous studies identified that osteopontin (OPN), a pro-fibrotic cytokine, is abundant in the prostate of men with LUTS, and its secretion is stimulated by inflammatory cytokines potentially to drive fibrosis. This study investigates whether the lack of OPN ameliorates inflammation and fibrosis in the mouse prostate. We instilled uropathogenic E. coli (UTI89) or saline (control) transurethrally to C57BL/6J (WT) or Spp1tm1Blh/J (OPN-KO) mice and collected the prostates one or 8 weeks later. We found that OPN mRNA and protein expression were significantly induced by E. coli-instillation in the dorsal prostate (DP) after one week in WT mice. Deficiency in OPN expression led to decreased inflammation and fibrosis and the prevention of urinary dysfunction after 8 weeks. RNAseq analysis identified that E. coli-instilled WT mice expressed increased levels of inflammatory and fibrotic marker RNAs compared to OPN-KO mice including Col3a1, Dpt, Lum and Mmp3 which were confirmed by RNAscope. Our results indicate that OPN is induced by inflammation and prolongs the inflammatory state; genetic blockade of OPN accelerates recovery after inflammation, including a resolution of prostate fibrosis.

STONES

Early-Onset Kidney Stone Disease-Consequences and Opportunities

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The prevalence of nephrolithiasis in the United States increased from 5% (in 1988 to 1994) to 9% (in 2007 to 2010); among all age groups, the greatest increase in the annual incidence of nephrolithiasis is among adolescents. This earlier age at onset has increased the number of children presenting to the emergency department, admitted to the hospital, and requiring surgery, effects compounded by a 50% recurrence rate of symptomatic stone events within 5 years of diagnosis. The rapid rise of early-onset kidney stone disease suggests that alterations in environmental exposures underlie the shifting epidemiology. Dietary factors, such as low fluid intake, high sodium intake, and low dietary calcium, are associated with an increased risk of incident nephrolithiasis. In addition, there is burgeoning evidence that exposure to potentially modifiable factors, such as oral antibiotic use, contributes to the shift in the epidemiology of nephrolithiasis. Major gaps exist in the evidence base supporting key medical decisions for children with kidney stone disease; these decisions range from diagnostic testing and metabolic assessments to surgical management and secondary prevention. There is great uncertainty about the comparative effectiveness of surgical interventions for children with nephrolithiasis. The Pediatric Kidney Stone Care Improvement Network (PKIDS) is conducting a prospective Patient-Centered Outcomes Research Network (PCORnet)–designated clinical study of 3 existing surgical interventions for kidney stones—ureteroscopy, shockwave lithotripsy, and percutaneous nephrolithotomy—to generate real-world knowledge about the comparative effectiveness of these procedures with respect to stone clearance and patients' lived experiences after surgery (ClinicalTrials.gov Identifier NCT04285658).

Validation of the Japanese Version of The Wisconsin Stone Quality of Life Questionnaire: Results from SMART Study Group

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The Wisconsin Stone Quality of Life questionnaire (WISQOL) is a health-related quality of life (HRQOL) measure designed for patients with urinary stones. It has been translated and used in several languages. This study aimed to validate the Japanese version of the WISQOL (J-WISQOL). The J-WISQOL was translated and validated using a multistep process proposed by the World Health Organization that involved forward translation, back-translation, and pilot testing with a group of patients. This study enrolled 150 patients with urinary stones who visited three academic hospitals for stone treatment. We assessed convergent validity of

correlation patterns and internal consistency of the J-WISQOL and Short-Form 36-item survey version 2 (SF-36v2). Overall, 150 patients were enrolled. The mean total score of the J-WISQOL was 108.18 ± 20.26 (raw score min-max, 28-140), suggesting that the onset and symptoms of urinary stones reduced the HRQOL in the patients. The J-WISQOL showed good internal consistency (Cronbach's α = 0.96) and interdomain associations (Spearman's correlation coefficient r = 0.67-0.94). The J-WISQOL was correlated with the SF-36v2 in all domains: social, emotional, health, and vitality impact (r = 0.47-0.66). The J-WISQOL is a reliable instrument for evaluating HRQOL measures in patients with urinary stones. It could be a useful quality of life questionnaire for urinary stones in Japan. Clinical Trial 60-20-0047.

PATIENT-CENTERED RESEARCH

Adding Centralized Electronic Patient-Reported Outcome Data Collection to an Established International Clinical Outcomes Registry

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Longitudinal collection of PROs in a registry is recommended for several reasons, yet to date, PROs are not routinely collected from HCT patients to augment clinical registry data. The aim of this study was to determine the feasibility of electronic PRO data collection by a national clinical outcomes registry, by assessing differences between who does and does not report PROs. We conducted a cross-sectional pilot collection of PROs from HCT recipients after treatment using computer-adapted tests from the Patient-Reported Outcome Measurement Information System (PROMIS). We implemented centralized data collection through the Center for International Blood and Marrow Transplant Research (CIBMTR) among patients who underwent HCT for myelodysplastic syndromes (MDS), were at least 6 months post-HCT, and spoke English or Spanish. The main objective was identifying patient, disease, and transplant-related differences associated with completion of electronic PROs. A total of 163 patients were contacted and potentially eligible to participate; of these, 92 (56%) enrolled and 89 (55%) completed the PRO assessment. The most frequent reason for incomplete surveys was inability to contact patients (n = 88), followed by declining to participate in the study (n = 37). There were no sociodemographic or age differences between those who completed the PRO survey (n = 89) and eligible nonresponders (n = 155). Patient scores were within 3 points of the US average of 50 for all symptoms and functioning except physical functioning. Responders and nonresponders did not exhibit meaningfully different sociodemographic characteristics. Difficulty contacting patients posed the greatest barrier and also provided the greatest opportunity for improvement. Once enrolled, survey completion was high. These results support standardizing centralized PRO data collection through the CIBMTR registry.

KIDNEY

Ultrasound-Based Renal Parenchymal Area and Kidney Function Decline in Infants With Congenital Anomalies of the Kidney and Urinary Tract

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Congenital anomalies of the kidney and urinary tract are the leading cause of chronic kidney disease in children. Noninvasive imaging biomarkers that predict chronic kidney disease progression in early infancy are needed. We performed a pilot study nested in the prospective Chronic Kidney Disease in Children cohort study to determine the association between renal parenchymal area (RPA) on first post-natal renal ultrasound and change in estimated glomerular filtration rate (eGFR) in children with congenital anomalies of the kidney and urinary tract. Among 14 participants, 78.6% were males, the median age at the time of the ultrasound was 3.4 months (interquartile range, 1.3-7.9 mo), and the median total RPA z-score at baseline was -1.01 (interquartile range, -2.39 to 0.52). After a median follow-up period of 7.4 years (interquartile range, 6.8-8.2 y), the eGFR decreased from a median of 49.4 mL/min per 1.73 m2 at baseline to 29.4 mL/min per 1.73 m2, an annual eGFR percentage decrease of -4.68%. Lower RPA z-scores were correlated weakly with a higher annual decrease in eGFR (Spearman correlation, 0.35; 95% confidence interval, -0.25 to 0.76). This pilot study shows the feasibility of obtaining RPA from a routine ultrasound and suggests that a lower baseline RPA may be associated with a greater decrease in eGFR over time. Further studies with larger patient cohorts are needed to confirm this association.

- Jennifer Allmaras, MPH, 12/28/2021

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