

Re: A Randomized, Double-blind, Placebo-controlled Trial of Certolizumab Pegol in Women with Refractory Interstitial Cystitis/Bladder Pain Syndrome

Bosch, PC

Eur Urol 2018;74:623–30

Experts' summary:

Interstitial cystitis/bladder pain syndrome (IC/BPS) remains a disease with no cure, and treatment can only provide symptomatic relief. Certolizumab pegol, a new anti-TNF- α agent, was evaluated in a pilot study in a group of 42 female patients with moderate to severe IC/BPS for whom previous therapies had been unsuccessful [1]. The primary endpoint was the difference in global response assessment (GRA) between certolizumab pegol and placebo at week 2, which did not significantly differ between the study groups. However, there was a significant difference in GRA pain ($p = 0.002$), GRA urgency ($p = 0.02$), and GRA overall symptoms ($p = 0.006$) by week 18. In terms of secondary endpoints at week 18, there was a significant difference of -3.6 ($p = 0.03$) for the Interstitial Cystitis Symptom Index, -3.0 ($p = 0.042$) for the Interstitial Cystitis Problem Index, -2.0 ($p = 0.02$) for the pain scale, and -1.7 ($p = 0.03$) for the urgency scale, as well as a $>30\%$ reduction in pain ($p = 0.02$).

Experts' comments:

The etiology of IC/BPS is described as multifactorial, with genetic and environmental factors, which is the main obstacle in clinical trials. However, the presence of serum and urinary antibodies specific to the bladder epithelium in IC/BPS patients is consistent with autoimmune involvement. Thus, immunotherapy, specifically human monoclonal antibodies inhibiting NGF and TNF- α , have shown high efficacy in pain control for PBS/IC [2,3]. However, one study failed to prove the efficacy of adalimumab as a result of a significant placebo effect [4]. The present study therefore included a 1-mo washout period, which decreased the placebo effect on overall GRA from 50% in the previous study [4] to an average of 14%.

The time to obtain significant improvement in each individual autoimmune disease varies for anti-TNF- α agents. As the underlying mechanism could be similar, the primary endpoint was chosen at 2 wk because some authors observed a positive effect on rheumatoid arthritis by this time, while others reported improvement in psoriatic arthritis at 24 wk [1]. However, the time period

for a significant improvement for women with moderate to severe IC/BPS appears to be longer (ie, 10–18 wk) as IC/BPS represents a longstanding disease. There was a similar GRA treatment response rate obtained when treating IC/BPS patients with adalimumab, so a head-to-head comparison would be interesting [4], as well as combinations with other immunopathway-modulating agents. Some limitations of the study were the small sample size and the fact that neither cystoscopy nor cytology was performed, so tuberculosis or carcinoma in situ could possibly have been missed and it was not possible to rule out Hunner's ulcers.

The debate concerning PBS/IC diagnostic criteria continues, leading to high heterogeneity of patients enrolled in treatment studies. The small number of randomized clinical trials is a major limitation that must be addressed in the future.

Conflicts of interest: The authors have nothing to disclose.

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Re: Are We Improving Erectile Function Recovery After Radical Prostatectomy? Analysis of Patients Treated over the Last Decade

Capogrosso P, Vertosick EA, Benfante NE, et al

Eur Urol 2019;75:221–8

The devil's in the Details?

Experts' summary:

A retrospective analysis delivered recently by Capogrosso et al. [1] was intended to answer whether advances in

radical prostatectomy (RP) technique and post-RP care brought any improvement in functional outcomes. The authors identified 2364 patients treated with RP at a single academic center during 2008–2015. To remove surgical experience as a confounder, individuals treated by a surgeon who performed <100 procedures were excluded. The endpoint was established as erectile function (EF) assessed by International Index of Erectile Function (IIEF)-6, with recovery defined as IIEF-6 ≥ 24 . The analysis was conducted in patients in whom bilateral nerve-sparing (NS) surgery was performed and who obtained no adjuvant or salvage treatment.

Experts' comments:

Although sparing of neurovascular bundles should intuitively be associated with better EF and continence recovery rates, it is still not clear which part of the NS procedure plays a crucial role and to what extent [2]. This uncertainty constitutes an important rationale for the analysis performed by Capogrosso et al. [1]. The functional outcomes of NS achieved after 10-yr experience are at first disturbingly poor. Recovery rates not only have not improved over the analyzed period, but also have decreased significantly ($p = 0.01$). A possible explanation of this phenomenon lies in a multivariable analysis—after accounting for the stabilization of the clinical and pathological covariate declining trend. Baseline factors have repeatedly been stressed as crucial for functional outcome—recently also of robot-assisted RP (RARP) [3]. It is however obvious that an absolute lack of change in recovery rates is unexpected given the surgical technique refinements and postoperative care improvements. Since functional benefits of RARP are already supported by a small meta-analysis, increasing use of this approach is to be at least signaled [4]. Results of Capogrosso et al. [1] correspond with the aforementioned systematic review—a multivariate analysis revealing the advantage of RARP. Therefore, if adjustment for positive and negative predictors of EF recovery brings no changes, what is the cause of stagnancy?

The recent understanding of NS includes awareness of nerve structures extending into the entire circumference of the periprostatic fascia, and not only neurovascular bundles. Since the high anterior release technique is not always feasible, “preserveness” of NS can be categorized using a dedicated score [5]. Reliable data regarding the extent of sparing cannot be collected retrospectively. It should also be assumed that each surgeon has his or her own “sparing score.” Moreover, despite the exclusion of surgeons who performed <100 procedures, there might have been some who started to operate with a new surgical approach after gaining certain experience with another. Experience is thus not the only confounder. Although the use of phosphodiesterase type 5 seems not to be an issue, more extensive use of other erectile

aids could be missed or unrecorded. Finally, the complex etiology of erectile dysfunction warrants that prevalence of post-RP erectile dysfunction can be in synergy with raising rates of depression. The conclusion that the authors arrived at is therefore fully justified—there is much to be done.

Conflicts of interest: The authors have nothing to disclose.

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Re: Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial

Parker CC, James ND, Brawley CD, et al

Lancet 2018;392:2353–66

Experts' summary:

In this randomised trial, Parker et al. [1] studied the effect of radiotherapy to the prostate on overall survival (OS) in 2061 men with metastatic prostate cancer (PCa), of whom 1029 were randomised to standard of care (SOC; androgen deprivation therapy [ADT] ± docetaxel) and 1032 were randomised to SOC plus prostate radiotherapy between 2013 and 2016. In unselected newly diagnosed metastatic patients, radiotherapy to the prostate did not improve OS (0.92, 0.80–1.06; $p = 0.266$). In the prespecified subgroup

analysis by baseline metastatic burden (a high metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both), OS was improved in patients with a low metastatic burden who were randomised to radiotherapy (hazard ratio 0.68, 95% confidence interval 0.52–0.90; $p = 0.007$). The authors conclude that prostate radiotherapy should be a standard treatment option for men with a low metastatic burden.

Experts' comments:

Several retrospective analyses have noted a survival benefit in men with metastatic PCa who underwent local treatment [2], while a few were not able to confirm these findings [3,4].

Recently, Boeve et al. [5] published data from the HORRAD trial, which randomised 432 patients with