Examination of the Significant Placebo Effect in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome

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OBJECTIVE To examine the significant "placebo effect" in a randomized, double-blind, placebo-controlled interstitial cystitis/bladder pain syndrome trial. Randomized clinical trials are the reference standard for therapeutic impact assessment. However, proving efficacy of treatments for interstitial cystitis/bladder pain syndrome with rigorous placebo-controlled trials is difficult due to a significant effect of the placebo intervention.

METHODS Interstitial cystitis/bladder pain syndrome patients were randomized to receive subcutaneous adalimumab or subcutaneous placebo every 2 weeks for 12 weeks and outcome measures were assessed.

RESULTS Of the 43 patients, 21 received adalimumab and 22 received placebo. Of the patients who received placebo, there was a statistically significant improvement demonstrated in the O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes of −8.1 (95% confidence interval [CI], 3.0-13.2), Interstitial Cystitis Symptom Index of −3.7 (95% CI, 0.9-6.5), Interstitial Cystitis Problem Index of −4.4 (95% CI, 2.0-6.8), and Pelvic Pain, Urgency, Frequency scale of −6.9 (95% CI, 2.8-11.0) at week 12 compared with baseline. Most of the significantly improved placebo patients felt their improvement was because they were more conscientious about following physician advice and feeling less stress while in the study.

CONCLUSION Patients with moderate to severe interstitial cystitis/bladder pain syndrome had significant improvement after receiving only advice and support. This intervention is risk free and inexpensive. Physicians should review standard advice with all interstitial cystitis/bladder pain syndrome patients before starting medical therapy. UROLOGY 84: 321−326, 2014. © 2014 Elsevier Inc.

Interstitial cystitis (IC), including painful bladder syndrome or bladder pain syndrome (BPS), is a chronic and disabling disease. The large number and variety of treatments for IC/BPS reflect the absence of effective treatment.[1] The etiology and pathophysiology of IC/BPS is uncertain and there is no optimal treatment. Many patients have persistent symptoms despite a variety of medical treatments. A well-designed, randomized clinical trial is the reference standard for evaluating treatment efficacy in IC/BPS and should include a placebo arm.[2]

A significant effect has been repeatedly observed in patients who only received placebo intervention in randomized, double-blind, placebo-controlled IC/BPS trials. In past studies, the placebo global response assessment (GRA) overall response ranged from 12% to 20%.[3-5] As previously reported in our study evaluating the efficacy of adalimumab for the treatment of IC/BPS, a confounding result demonstrated 50% of the placebo patients had a ≥50% statistical overall improvement in GRA.[6] An initial query of the placebo patients who improved reported that they felt their improvement was due to physician advice and support they received during the study. These results were comparable with those of Foster et al[7] who observed a higher overall GRA response rate of 45% for subjects randomized to placebo who received an education and behavior modification program. This significant improvement with only advice and support is higher than many commonly used medications for the treatment of IC/BPS. The purpose of this article is to examine this significant "placebo effect" in the treatment of IC/BPS.

MATERIALS AND METHODS

This was a phase III, randomized, double-blind, placebo-controlled, and proof of concept study (ClinicalTrials.gov Identifier NCT01295814) conducted in Escondido, California between March 2011 and March 2013. The study protocol was reviewed, approved, and monitored by a local institutional review board. Each patient provided written informed consent before participation.

Study Participants

Men and women aged between 18 and 65 years, previously diagnosed with moderate or severe IC/BPS, were recruited.

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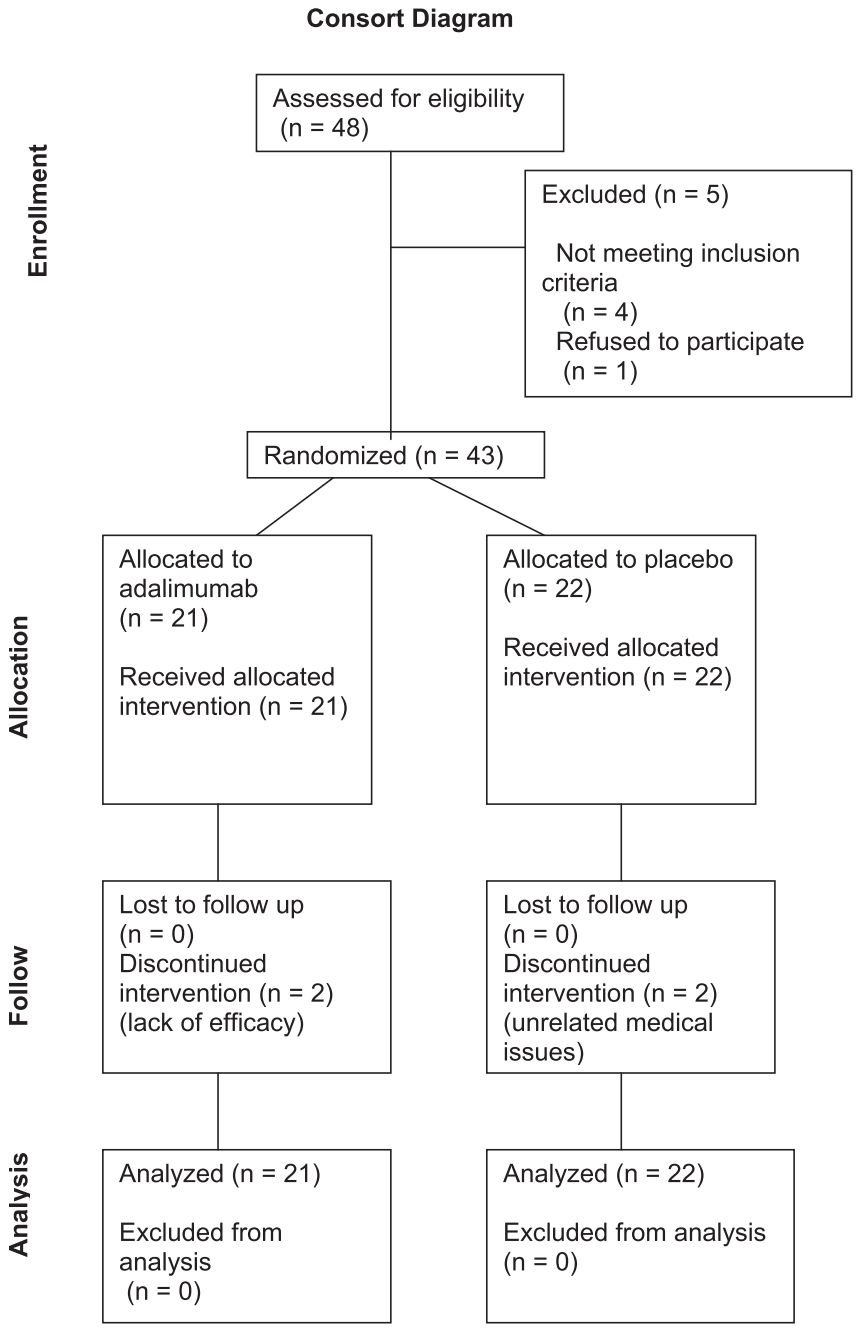

Figure 1. Consort diagram.

Eligibility required fulfillment of certain criteria, including symptoms of urinary urgency, frequency or pain for more than 6 months, urinating at least 7 times/day, a total score of ≥18 on the O'leary-Sant Interstitial Cystitis Symptom Index and Problem Index (OSPI),[8] and a score of ≥15 on the Pelvic Pain and Urgency/Frequency Symptom Scale (PUF).[9] Participants were allowed to continue on current medications.

Study Design

Patients entered a 2-week screening period to access inclusion and exclusion criteria and determine eligibility. Eligible IC/BPS patients were randomized in a blinded fashion to receive a 1:1 ratio subcutaneous adalimumab 80 mg loading dose followed by 40 mg every 2 weeks or subcutaneous placebo for 12 weeks. The study drug and placebo were provided in ready to use unit dose syringes that were identically labeled other than the subject's identification number. Placebo patients who significantly improved were queried after the study as to why they felt they improved.

Outcome Measures

The primary efficacy outcome measure was the change from baseline to week 2, 6, and 12 in the OSPI score. The total OSPI score was also separated into the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) scores. Lubeck et al[10] validated ICSI as a valid measure of change in treatment outcome studies. A change of −4.03 in the ICSI score was the same as a 2-point improvement in GRA.