Apremilast in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Pilot Study

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Objective: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a disease with an uncertain cause and limited effective treatments. Apremilast (Celgene Corporation, Summit, NJ, USA) is a selective phosphodiesterase type 4 (PDE4) inhibitor that modulates the immune system. An open-label, one-arm, pilot study was conducted to explore its potential for improving CP/CPPS symptoms.

Methods: Males ≥ 18 years of age were treated with 20 mg oral apremilast twice daily for up to 12 weeks. Outcomes were measured with Global Response Assessment (GRA), pain visual analog scale (VAS), Chronic Prostatitis Symptom Index (CPSI), Pittsburgh Sleep Quality Index (PSQI), SF-12 mental (MCS) and physical (PCS) health-related quality of life subscales, and voiding diaries. Repeated measures and paired t-tests evaluated changes from baseline to end of treatment, and at a final visit 4 weeks off the drug.

Results: Seventeen men (94% Caucasian; mean age 48.2 ± 10 years) were treated (mean 115.8 ± 56.1 doses). Mean VAS (3.4 ± 2.0 vs 1.8 ± 1.7; P = 0.0011), PSQI (9.4 ± 4.4 vs 7.4 ± 4.2; P = 0.037) and CPSI (26.1 ± 5.0 vs 17.2 ± 8.3; P = 0.0016) scores improved from baseline to end of treatment. Incontinence episodes per day improved slightly (P = 0.042). When only those completing at least 8 weeks of treatment were examined (n = 9), significant changes in CPSI, VAS, and PSQI were still observed. At the final visit, 8/9 (88.9%) men also reported some improvement in pain related to sex. Side-effects were generally mild and well tolerated.

Conclusion: These results suggest that apremilast may improve CP/CPPS symptoms with only mild side-effects. However, placebo controlled studies are necessary to determine efficacy.

Key words apremilast, chronic prostatitis/chronic pelvic pain syndrome, pelvic pain, prostatitis, treatment

INTRODUCTION

It is estimated that between 2 and 14% of men worldwide may have symptoms of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).1 CPPS accounts for approximately 8% of visits to urologists and poses a substantial cost, both to the healthcare system and to the patient’s quality of life.2 A wide variety of pharmacological therapies has been utilized to treat CP/CPPS, including alpha-blockers, antibiotics, anti-inflammatory medications and other agents such as finasteride. The efficacy of these treatments remains controversial.

The National Institutes of Health classification recognizes four categories of prostatitis, underscoring a general lack of consensus regarding the pathological basis of CP/CPPS.3,4 Even though there is no infecting organism in CP/CPPS, cytokines and other inflammatory mediators have been implicated. In the expressed prostatic secretions of men with clinically diagnosed CP/CPPS versus those with either no urological disease or benign prostatic hypertrophy (BPH), Nadler et al. found that interleukin-1B was measurable in 90% of those with CP/CPPS IIIA, the pro-inflammatory but non-bacterial form of prostatitis. It was rarely detected in controls, men with BPH, or non-bacterial, non-inflammatory CP/CPPS (IIB). Tumor necrosis factor (TNF)-alpha was also measurable in all groups, but levels were the highest in CP/CPPS IIIA patients.5

Apremilast (Celgene Corporation, Summit, NJ, USA) is an orally available small molecule that selectively inhibits phosphodiesterase type 4 (PDE4), and thus modulates a network of pro- and anti-inflammatory modifiers. Inhibitors of PDE4 cause accumulation of intracellular cyclic adenosine monophosphate (cAMP), which activates protein kinase A and other downstream effectors, resulting in inhibition of transcription of pro-inflammatory cytokines.6 Apremilast is under clinical development...
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2. METHODS

After institutional review board approval was obtained, an open-label, one-arm study was conducted. Inclusion criteria were men aged 18 years or older with greater than 3 months of pain in the perineum, scrotum or penis, a Chronic Prostatitis Symptom Index (CPSI) score > 15/24, negative urine culture for greater than 3 months, and who were refractory to other forms of treatment (e.g. non-steroidal anti-inflammatories, alpha antagonists, antibiotics). Patients with history of active or prior genitourinary cancer, including prostate cancer, genital infections, ureteral or bladder calculi, or prior abdominal or pelvic radiation were excluded. Patients were treated with 20 mg of oral apremilast twice daily for up to 12 weeks, in similar fashion to current ongoing clinical trials for the treatment of psoriatic arthritis. Study visits included a pre-treatment screening and visits at 0 weeks (start of drug), 1, 2, 4, 6, 8, 10, and 12 weeks, with a final visit at 16 weeks (after 4 weeks off the drug). In patients who did not complete 12 weeks of treatment, the last week during which the last dose of drug was taken was considered end of treatment. Changes in pre-treatment to end of treatment, then end of treatment to 4 weeks off the drug were evaluated. The primary efficacy measure was a Global Response Assessment (GRA) that measures improvement in overall symptoms on a 7-point scale (markedly worse to markedly improved). Those who are moderately or markedly improved are generally considered responders to treatment. Secondary efficacy measures included a pelvic pain visual analog scale (VAS) describing pain on a scale of 0 to 10 (none to severe), Chronic Prostatitis Symptom Index (CPSI), SF-12 mental (MCS) and physical (PCS) health-related quality of life subscales, 2-day voiding diary, Pittsburgh Sleep Quality Index (PSQI), and an end of study GRA measuring overall improvement in pain related to sex. Side-effects were monitored closely. Patient dosage was titrated based on the tolerability of side-effects.

Descriptive statistics were examined for all patients. Changes from pre-treatment to end of treatment were examined using paired t-tests for the VAS score. Repeated measures analyses were used to examine the changes from pre-treatment to end of treatment for the voiding diary variables, CPSI, SF-12® and PSQI. Repeated measures analyses were also used to examine the changes from end of treatment to the final follow-up 4 weeks later. SAS for Windows version 9.2 (Cary, NC, USA) was used for all analyses.

3. RESULTS

A total of 21 male subjects meeting inclusion criteria were recruited from the offices of private urologists. Of these, two patients failed screening for the study, one patient was lost to follow-up, and one patient withdrew before starting therapy. The remaining 17 men, 94% Caucasian and average age of 48.2 ± 10 years underwent treatment with apremilast (mean 115.8 ± 56.1 doses) as described in the Methods section.

At the end of treatment, patients demonstrated a significant improvement in mean CPSI scores from 26.1 ± 5.0 to 17.2 ± 8.3 (P = 0.0016). On the primary efficacy measure (GRA), 2 of the 17 men (11.8%) reported marked improvement in symptoms since starting therapy. An additional 6 of the 17 men (35.3%), however, were slightly improved. Mean pelvic pain VAS scores also significantly improved from 3.4 ± 2.0 to 1.8 ± 1.7 (P = 0.0011). PSQI showed a small but significant improvement from 9.4 ± 4.7 to 7.4 ± 4.2 (P = 0.037). No difference in SF-12 PCS and MCS scores were observed at end of treatment (Table 1). Even though some small improvements were seen in voiding diary variables, changes were not statistically significant for urgency episodes per day, episodes of nocturia, and number of voids per day. However, there was a small but statistically significant improvement in episodes of incontinence per day (1.2 ± 2.6 vs 0.5 ± 1.9, P = 0.042) (Table 2).

Of 17 patients who began the study, only 13 completed surveys at week 16, which was 4 weeks off apremilast. Even after 4 weeks off the drug, 6 of 13 men were treatment responders (moderately or markedly improved) on the final GRA. This was an increased number of men from the end of treatment. Mean CPSI scores had significantly improved again from the end of treatment to 16 weeks (17.2 ± 8.3 vs 12.5 ± 6.4, P = 0.034). The SF-12 PCS also showed a small significant improvement (48.3 ± 8.4 vs 53.3 ± 5.2, P = 0.0049). The PSQI, VAS, and SF-12 MCS showed no significant change in symptom

### TABLE 1. Responses on symptom measures

<table>
<thead>
<tr>
<th>Survey responses</th>
<th>End of treatment (n = 17)</th>
<th>4 weeks off drug (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survey</strong></td>
<td><strong>Pre-treatment score</strong></td>
<td><strong>Treatment end score</strong></td>
</tr>
<tr>
<td>CPSI</td>
<td>26.1 ± 5.0</td>
<td>17.2 ± 8.3</td>
</tr>
<tr>
<td>PSQI</td>
<td>9.4 ± 4.4</td>
<td>7.4 ± 4.2</td>
</tr>
<tr>
<td>VAS</td>
<td>3.4 ± 2.0</td>
<td>1.8 ± 1.7</td>
</tr>
<tr>
<td>SF-12 MCS</td>
<td>43.1 ± 11.2</td>
<td>45.5 ± 11.9</td>
</tr>
<tr>
<td>SF-12 PCS</td>
<td>48.7 ± 7.5</td>
<td>48.3 ± 8.4</td>
</tr>
</tbody>
</table>

*Statistically significant. CPSI, Chronic Prostatitis Symptom Index; PSQI, Pittsburgh Sleep Quality Index; SF-12 MCS, SF-12 mental component summary; SF-12 PCS, SF-12 physical component summary; VAS, visual analog scale.
scores suggesting that symptom improvements achieved during treatment did not rebound.

During the study, three subjects withdrew for side-effects (nausea, diarrhea, nerve-like pain in the lower extremities), two for lack of therapeutic effect, and two for personal issues. Overall, apremilast was well tolerated. Side-effects potentially associated with treatment included lightheadedness, dizziness, headache, facial flushing, nausea, diarrhea, bowel urgency, oral blisters, and a lower leg ulcer resulting from an insect bite. Nausea and diarrhea were the most frequently experienced side-effects (Table 3). Other adverse events considered to have either a remote or non-causal relationship to the study drug (not suspected) included nausea, diarrhea, heartburn, urinary frequency, heart flutter, oral herpes zoster, fatigue, anxiety, nerve-like pain of the lower extremities, and abdominal tenderness.

As treatment duration was variable among the subjects, we also examined the nine patients who completed at least 8 weeks of apremilast and had a final study visit after 4 weeks off the drug. In this group, results were similar to the whole group analysis. Interestingly, although only two of nine men were moderately or markedly improved on the GRA at end of treatment, when reassessed at 16 weeks (off drug), an additional four men reported being moderately or markedly improved. Significant improvements also occurred in CPSI, PSQI, and VAS at end of treatment and the SF-12 scores again were unchanged. Changes in scores were maintained after 4 weeks off the drug, with the exception of a small significant improvement in SF-12 PCS noted from end of treatment to 16 weeks. Five of nine (55.6%) men also reported moderate or marked improvement when asked to rate their pain during sexual activity. Three of nine (33.3%) men reported slight improvement in pain during sexual activity and one patient reported no change.

4. DISCUSSION

Chronic prostatitis is a disease process that is difficult to define and equally as difficult to treat. Infectious, inflammatory, and even more recently, links to cardiovascular disease processes are potential contributing factors. Several studies have examined the utility of alpha-blockers, with Nickel et al. demonstrating in 2008 that 12 weeks of treatment with alfuzosin was only as effective as a placebo in men with CP/CPPS and no prior treatment with alpha-blockers (34.8 vs 33.6%; P = 0.9). In 2004, Alexander et al. studied the efficacy of ciprofloxacin or tamsulosin in men with CP/CPPS versus placebo. The CPSI was found to have decreased in all groups but no statistically significant difference in the primary outcome was seen for ciprofloxacin or tamsulosin treatment compared with placebo.

The modest improvement in symptoms experienced in CP/CPPS patients treated with traditional pharmacological modalities, coupled with the documented role of inflammatory cells and mediators in the suspected pathology of CP/CPPS, has led to a shift in treatment and research to focus on inflammatory pathways. Apremilast is one such immunomodulator that may act on inflammatory pathways to improve CP/CPPS symptoms. In this pilot study, men taking this medication had significant improvements in CPSI, VAS, PSQI, and incontinence. They also reported decreased pain with sexual activity and tolerated the medication well from a side-effect standpoint.

The GRA has been used effectively in studies of vulvodynia and interstitial cystitis, but in this study GRA responses did not exactly mirror the CPSI scores. Interestingly, even though only two men at the end of treatment perceived that symptoms had improved on the GRA, after 4 weeks off therapy several additional patients reported that symptoms had improved since the study started. Perhaps once the drug was stopped, men realized how symptoms had improved since the study started. Responses did not exactly mirror the CPSI scores. Another possible explanation is that the GRA may not have been as sensitive to changes as the other validated instruments used in this study. Further study is needed to assess whether the GRA is sensitive to changes in CP/CPPS symptoms.

The limitations of this study are its small sample size and that it was not a placebo controlled trial. We concede that the placebo affect cannot be ruled out in this study, but recognize that this study was a pilot to determine if further research on apremilast for this disease process is warranted. Also, the voiding diary data did not reflect the other survey results. Based on improvements reported on the validated questionnaires, one would expect voiding diary variables, such as urgency episodes per day, to improve significantly as well. However, as many of the studied variables were normal at the outset of the study, perhaps the potential for improvement in these measures may have been too minimal to detect a significant change.

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The results seen in this proof of concept pilot study, as well as the suggested role of inflammatory mediators in CP/CPPS, provide support for conducting a placebo controlled trial to evaluate apremilast as an effective therapy for CP/CPPS symptoms. Since few treatments exist and are often met with mixed results, exploring apremilast and other agents targeting underlying pathophysiological mechanisms may ultimately provide relief for costly and difficult to treat syndromes such as CP/CPPS.

Acknowledgment
Funding for this study came from the Celgene Corporation, the developers of apremilast.

Disclosure
There are no disclosures from any of the authors.

REFERENCES