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TOPIC PAPER

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Preliminary experience with a terpene mixture versus ibuprofen for treatment of category III chronic prostatitis/chronic pelvic pain syndrome

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Abstract To evaluate the efficacy of a terpene mixture (rowatinex) compared to ibuprofen, patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) were randomly selected to either receive rowatinex 200 mg t.i.d. or ibuprofen 600 mg t.i.d. After a 6-week treatment, the decrease in the mean total NIH-CPSI score was significant in both groups from 21.4 to 15.3, (6.1 ($p < 0.01$) and from 21.2 to 16.8, (4.4 ($p = 0.04$) in the rowatinex and ibuprofen group, respectively. The rate of definite improvement as defined as 25% improvement in the total score was superior ($p = 0.04$) in the rowatinex group (68%) versus the ibuprofen group (40%). Judging from these results, rowatinex gave significant symptomatic relief and may be of benefit for many men diagnosed with CP/CPPS. Further, including the placebo-controlled studies are necessary to define its role in the management of this difficult to treat disease.

Keywords Chronic prostatitis · Terpenes

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a fairly common and poorly understood clinical entity that causes significant discomfort for patients, and it can be extremely difficult to treat this disease [11]. The quality of life for a patient with chronic prostatitis is similar to the difficulties experienced by patients with acute myocardial infarction, unstable angina or active Crohn's disease [12]. Despite its prevalence and significant impact on quality of life, our understanding of the pathophysiology and treatment of prostatitis has not advanced.

The suggested management of CP/CPPS includes antibiotic therapy, anti-inflammatory drugs, α-blocker therapy, repetitive prostate massage, lifestyle changes and supportive therapy [9, 21]. However, given the lack of proven efficacy and patient dissatisfaction with the above management, it is not surprising that patients have frequently turned to phytotherapy and other alternative treatments. Although the alternative therapies are plentiful, few have been subjected to rigorous scientific investigation and clinical trials.

Phytotherapy, the use of plant-derived or "herbal" products, is gaining popularity in North America, and this is already the treatment of choice for many chronic conditions in both Europe and Asia. In treating prostatitis, phytotherapeutic agents have been used with variable results. These medicines include such agents as cernitin pollen extract (extract of bee pollen), quercetin (a polyphenolic bioflavonoid) and saw palmetto, an herbal lipid-extract from the American dwarf palm tree. Cernilton and quercetin have documented anti-inflammatory effects and both medicines have demonstrated symptomatic improvements in CP/CPPS [22].

Rowatinex is a terpenic mixture composed of pinene (31%), camphene (15%), anethol (4%), borneol (10%), cineol (3%) and fenchone (4%) in olive oil, and it is mainly used to control the pain of urolithiasis. Up to now, the documented properties of rowatinex include anti-inflammatory, anti-spasmodic, anti-bacterial, analgesic effects. Among the reported properties of rowatinex, the anti-inflammatory effect is achieved by the suppression of arachidonic acid metabolism and cytokine production. The rationale of using rowatinex in prostatitis is the medicine's potential anti-inflammatory

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effect, which may have positive influences on the inflammatory process seen in chronic prostatitis.

This prospective study was designed and conducted to evaluate the efficacy of rowatinex, compared to ibuprofen, for the treatment of patients with CP/CPPS.

Patients and methods

Study design

We conducted a 6-week, randomized, single blind study from October 2003 to April 2004 to investigate the symptomatic improvement for men with CP/CPPS who received either rowatinex or ibuprofen. After written informed consent was obtained from the them, the patients were sequentially randomized to receive either rowatinex 200 mg or ibuprofen 600 mg orally three times daily for 6 weeks (days 1–43) after a 2-week washout period (days (14–(1), during which time the patients had to discontinue all previous analgesic medications for 2 weeks before they started taking the newly prescribed drug.

Inclusion/exclusion criteria

Men 18 years or older diagnosed with CP/CPPS and with culture-negative urine tests, expressed prostatic secretions and semen cultures at the screening were eligible for our study. A pain score of four or greater on the national institutes of health chronic prostatitis symptom index (NIH-CPSI) average pain score (question 4), a total urination score of three or less on the NIH-CPSI urination domain (questions 5 and 6) at the time of screening and baseline, and reported pain in the pelvic region for at least three or more months were required for inclusion into our study. The exclusion criteria were acute or chronic bacterial prostatitis, bacteriuria within 3 months of screening, a history of cancer, neurological disorders, previous urological surgery, diabetes, abnormal digital rectal examination (DRE) except for benign enlargement, urological stones, a history of urinary retention and an abnormal peak urinary flow (Qmax). Medications that could interfere with the study drug or influence the symptoms of CP/CPPS were discontinued for at least 4 weeks before and during the study (such as antibiotics, α-blockers, α-adrenergic agents, anti-cholinergics, anti-spasmodics or muscle relaxants, cimetidine, warfarin and herbal medications).

Evaluations

The patients were screened on day 14. The screening procedures including a focused medical history, NIH-CPSI scoring, physical examination, serum prostate-specific antigen (PSA), DRE and the classic ''four-glass test'' [8] were performed to determine whether the patient met the criteria for category III CP/CPPS (culture-negative prostatic secretion and urine after prostatic massage with or without increased number of WBC). Baseline measurements were obtained on day 0 that included a repeated NIH-CPSI scoring, a complete blood count, blood chemistry and peak urinary flow rate (Qmax).

The efficacy of rowatinex and ibuprofen was evaluated by measuring changes in the NIH-CPSI on days (14, 0, 15 and 43. The NIH-CPSI is a validated scoring system that assesses pain, urinary symptoms and quality of life [4]. The NIH-CPSI contains nine questions covering the three domains of pain, urinary symptoms and quality of life. Patient symptoms in each domain are assigned points for a total of 43 points (pain 21, urinary symptoms 10 and quality of life 12). The questionnaire was completed by the patient and scored by the examiner. Based on the NIH-CPSI score, the severity of CP/CPPS can be classified as mild (0–14 points), moderate (15–29) or severe (30 points or more).

Data analysis

The efficacy of rowatinex and ibuprofen was evaluated by the change in NIH-CPSI scores during the washout period and the 6-week treatment period using matched paired *t*-tests. Statistical comparison of the efficacy between the rowatinex and ibuprofen groups was performed with an unpaired *t*-test. During the course of this study, definite improvement was defined as a 25% decrease over the baseline in the total NIH-CPSI score. To compare the response in the two treatment groups, Pearson chi-square analysis was used. All the analysis was performed using statistical analysis system Version 6.12 (SAS Institute Inc., Cary, NC, USA) with $p < 0.05$ considered as statistically significant.

Results

A total of 50 patients were enrolled in the study with 25 participants in the rowatinex- and ibuprofen-treatment groups, respectively. Table 1 describes the baseline patient characteristics by the treatment group. The mean patient age was 43.2 years (range 22–58) and it was similar between the treatment groups (rowatinex 44.2 years and ibuprofen 42.7 years). The mean total NIH-CPSI score at baseline was 21.3 (range 16–33). The total and domain NIH-CPSI of initial and baseline scores were similar between the treatment groups. For any other parameters, the rowatinex and ibuprofen groups had very similar clinical and demographic characteristics. Table 2 describes the subscores comparing the initial score with the baseline scores (which was named the washout period), the subscores

Table 1 Baseline demographics of rowatinex and ibuprofen treatment group

	Mean (SD)	
	Rowatinex	Ibuprofen
Patient age	44.2 (2.1)	42.7 (2.9)
Ml/s Qmax	18.1 (9.2)	19.2 (10.2)
Serum PSA	1.21 (0.7)	1.51 (1.1)
Mean NIH-CPSI score		
Total 0–43	21.62 (4.2)	22.12 (6.0)
Pain domain score 0–21	11.7 (3.1)	11.9 (2.4)
Urinary score 0–10	1.8 (0.7)	1.6 (0.9)
Quality of life score 0–12	7.9 (1.8)	7.7 (1.9)

There were no significant differences between the two groups *SD* standard deviation, *NIH-CPSI* national institutes of health chronic prostatitis symptom index

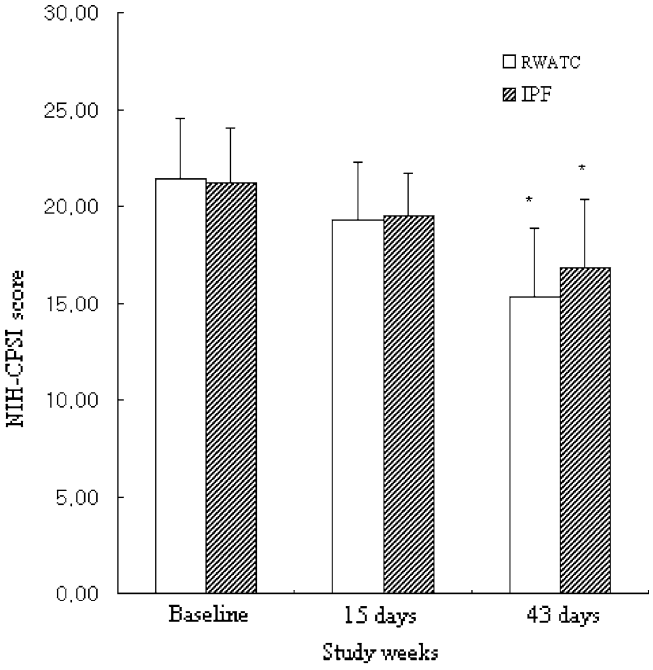

Fig. 1 Mean changes from the baseline in the total NIH-CPSI score (0–43 scale). After 6 weeks of treatment, changes in the rowatinex (*RWATC*) and ibuprofen (*IPF*) groups are statistically significant compared to the baseline. *$p < 0.05$, compared to baseline

comparing the baseline with the ending score after 6 weeks of treatment in each group, and the comparison between the rowatinex and ibuprofen groups. Although the changes during washout period was not significant in total and any domain NIH-CPSI score, after the 6-week treatment, the decrease in the mean total NIH-CPSI score was significant in both the groups (from 21.4 to 15.3, (6.1 $p < 0.01$ and from 21.2 to 16.8, (4.4 $p = 0.04$ in the rowatinex, and ibuprofen groups, respectively) (Figs. 1, 2). The mean changes from baseline to 6 weeks in the pain domains of the NIH-CPSI for the rowatinex and ibuprofen groups were (3.6 ($p = 0.02$) and (2.7 ($p = 0.04$), respectively (Fig. 3). The mean changes from baseline to 6 weeks in the quality of life/impact domains of the NIH-CPSI for the rowatinex and ibuprofen groups were (2.2 ($p = 0.03$) and (1.7 ($p = 0.03$), respectively (Fig. 4). In both the treatment groups, the pain and quality of life/impact domains were significantly improved from the baseline to 6 weeks ($p < 0.05$).

There was similar improvement in the specific NIH-CPSI pain and quality of life/impact domain score in both groups compared to the baseline values. Although there was more improvement in the numerical value for the rowatinex group compared to ibuprofen group, this difference was not statistically significant at 6 weeks (Table 2).

However, there was a significantly greater percentage of patients in the rowatinex—treatment group who demonstrated a definite improvement (a 25% decrease in the NIH-CPSI total score) compared to the ibuprofen group (68.0% vs. 40.0%, respectively, $p = 0.04$).

Rowatinex was generally well tolerated, and only three patients of the rowatinex group complained of a mild degree of heart burn or nausea that did not require discontinuation of treatment.

Table 2 The assessments of the washout period and the 6-week treatment period within groups and comparison of efficacy between rowatinex and ibuprofen groups after 6 weeks of treatment

	RWATC (p-value)*		IPF (p-value)*		RWATC versus IPF
	Washout	43 days	Washout	43 days	43 days
Mean NIH-CPSI change					
Total	−1.5 (>0.05)	−6.1 (<0.01)	−1.4 (>0.05)	−4.4 (0.03)	0.06**
Pain domain	−0.8 (>0.05)	−3.6 (0.02)	−0.7 (>0.05)	−2.7 (0.04)	0.11**
Urination domain	−0.3 (>0.05)	−0.3 (0.18)	−0.2 (>0.05)	−0.1 (0.57)	0.06**
QoL domain	−0.4 (>0.05)	−2.2 (0.03)	−0.5 (>0.05)	−1.7 (0.03)	0.12**
Definite improvement[a]		68 (17/25)		40 (10/25)	0.04***

NIH-CPSI national institutes of health chronic prostatitis symptom index, *RWATC* rowatinex, *IPF* ibuprofen
*matched paired *t*-test for differences over time compared to the baseline value within group
**Unpaired *t*-test for comparison between two groups
***χ^2-test for differences in proportion between two groups
[a]Defined as a 25% decrease over the baseline in the total NIH-CPSI score

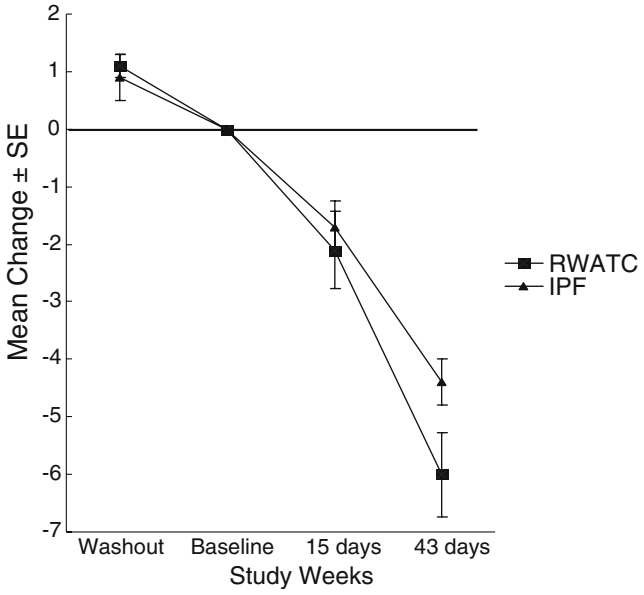

Fig. 2 Mean changes from the baseline in NIH-CPSI total score for the rowatinex and ibuprofen groups. After 6 weeks treatment, the subscore in the rowatinex (*RWATC*) and ibuprofen (*IPF*) groups are statistically significant compared to the baseline. Treatment daily for 6 weeks following 2-weeks washout period

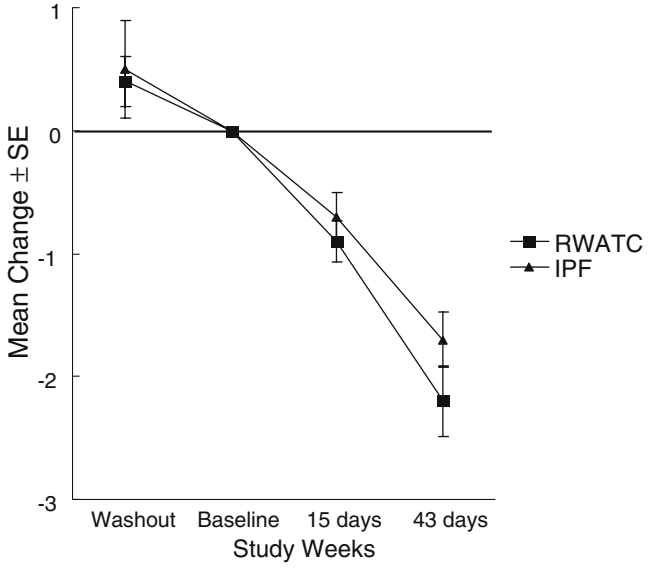

Fig. 4 Mean changes from the baseline in the quality of life/impact domains of the NIH-CPSI for the rowatinex and ibuprofen groups. After 6 weeks of treatment, the subscore in the rowatinex (*RWATC*) and ibuprofen (*IPF*) groups are statistically significant compared to the baseline. Treatment daily for 6 weeks following 2-weeks washout period

Discussion

Chronic prostatitis/chronic pelvic pain syndrome (is a prevalent disorder having a significant impact on the quality of life. Up to now, the exact etiology of CP?/CPPS has not been completely understood and the optimal management of CP/CPPS remains unknown. Clinical and experimental evidence exists to support infective, autoimmune, inflammatory, chemical and neuromuscular theories of disease etiology. The reported management of CP/CPPS includes antibiotics, anti-inflammatory agents, α-blockers, analgesics, finasteride and pentosan polysulfate [7, 10]. Yet most of the prostatitis researchers can agree that patient and physician dissatisfaction concerning the above treatments is high. It is not surprising that patients have turned with increasing frequency to phytotherapy, and they often seek alternative forms of therapy. Phytotherapy has had variable results in the treatment of CP/CPPS. Although CP/CPPS can be divided into two categories, the inflammatory (category IIIA) and non-inflammatory (category IIIB) forms, based on the presence of leukocytes in prostatic fluid, there is no evidence that patients in category IIIA have significantly different responses to the therapy in terms of the treatment compared to those patients in category IIIB. There are two phytotherapeutic agents that have been evaluated in CPPS: quercetin and cernilton [1, 14, 23, 24]. Quercetin, a polyphenolic bioflavonoid, has documented anti-oxidant, nitric-oxide-inhibitor and anti-inflammatory properties that act through interference with nuclear factor-kappa B (NF-κB) [20], and quercetin inhibits the inflammatory cytokines implicated in the pathogenesis of CPPS, such as interleukin-8 [16]. But the exact mechanism of action of this agent is largely unknown. Similarly, the exact mechanism of action of cernilton is also unknown, but cernilton, an extract of bee pollen, has been used in chronic prostatitis for its presumed anti-inflammatory potential associated with cyclo-oxygenase and lipoxygenase inhibiton [1]. Moreover, it was suggested that

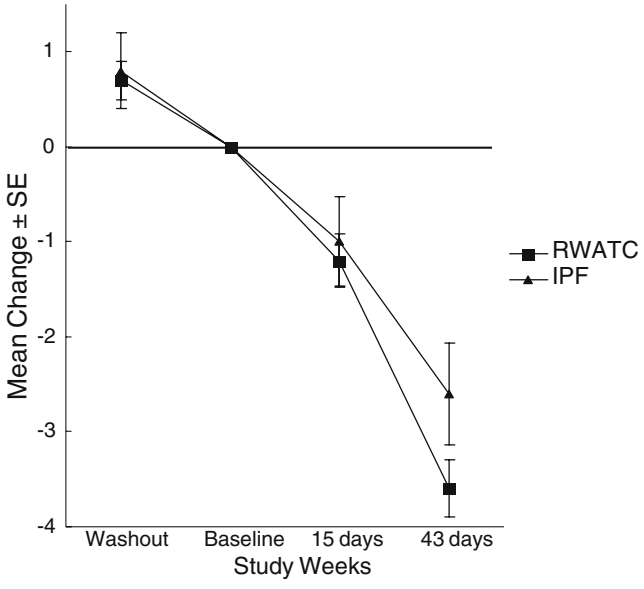

Fig. 3 Mean changes from the baseline in pain domains of the NIH-CPSI for the rowatinex and ibuprofen groups. After 6 weeks of treatment, the subscore in the rowatinex (*RWATC*) and ibuprofen (*IPF*) groups are statistically significant compared to the baseline. Treatment daily for 6 weeks following 2-weeks washout period

cernilton might be a potent smooth muscle relaxant, and this could explain the symptomatic relief obtained in prostadonia that is related to quelling of spasm of the external sphincter [1].

Rowatinex has properties including anti-inflammatory, anti-spasmodic, anti-bacterial and analgesic effects. It is a terpenic complex in an oily solution composed of pinene, camphene, anethol, borneol, cineol and fenchone. Of these components, pinene, a turpentine exuded from many species of pine trees, has anti-bacterial [2], anti-inflammatory [6] and anti-spasmodic activity [15]. Pinene especially inhibits inflammatory mediators including cytokines, NO synthase, cyclooxygenase-2 (COX-2) and inflammatory receptors by modulating the nuclear translocation of NF-κB [25]. Borneol, isolated from the medicinal plant *Fructus amomi*, has been traditionally used to restore consciousness and to relieve pain. Borneol specifically inhibits the nAChR-mediated effects in a non-competitive way, and the inhibitory effect by borneol is more potent than the effect of lidocaine, a commonly used local anesthetic [13]. Cineol, the major constituent of eucalyptus oil, has anti-inflammatory activity that works by the suppression of arachidonic acid metabolism and cytokine production [3].

To our knowledge, there have been no reports to date documenting the potential efficacy of rowatinex in patients with CP/CPPS. Generally, placebo-controlled, clinical trial is applied for the evaluation of efficacy of the target drug. Since non-steroidal anti-inflammatory drugs theoretically should improve the inflammatory parameters within the prostate and possibly result in a reduction of symptoms, it is commonly prescribed in clinical aspects. In this study, rowatinex, a multi-action drug with anti-inflammatory, anti-spasmodic, anti-bacterial and analgesic effect was compared to ibuprofen therapy for 6 weeks (following a 2-week wash out period). Treatment with non-steroidal anti-inflammatory ibuprofen proved effective in alleviating symptoms [5]. Although the efficacy of placebo for the patients with CP/CPPS has never been negliginble, this study might be reliable because there was no significant change in NIH-CPSI during the washout period. After a 6-week treatment, improvement in pain, quality of life/impact and total NIH-CPSI score reached significance for both rowatinex and the ibuprofen groups. Although the changes of total and urination domain NIH-CPSI scores for the rowatinex group were superior to those for the ibuprofen groups in numerical value, this difference did not reach a statistical significance, but it has to be mentioned that the washout period was shorter (2 weeks) than the treatment period (6 weeks). However, there was a significantly greater proportion of the patients using rowatinex, who experienced a definitive improvement as defined by a 25% decrease in the total NIH-CPSI score at the baseline compared to the ibuprofen group. Taking this result into consideration, we may expect a significant difference of total NIH-CPSI score between the two groups upon long-term follow-1up. The results of our study may be worthwhile for patients with CP/CPPS and have an important implication for rowatinex application along with other potentially effective therapeutic agents for CP/CPPS. Pain experienced throughout the pelvis is a commonly reported symptom of CP/CPPS. It has been theorized that CP/CPPS may represent an inflammatory dysregulation of the injury response [17], leading to persistent cytokine upregulation, immune cell infiltration, oxidant stress and cellular injury. Therefore, if persistent infection is ruled out either by careful culture testing or failure of appropriate antimicrobial therapy, therapy with agents that block inflammation by modulation of cytokine and arachidonic acid metabolism may improve this condition. As mentioned above, rowatinex is a terpenic complex consisting of elements that have anti-inflammatory and analgesic potential. It is possible that decreased pain after rowatinex treatment is directly due to its anti-inflammatory and analgesic potential.

Although the symptomatic response of patients taking rowatinex was significant, few patients became completely asymptomatic. The etiology of this pain is not fully understood, but the source of the pain may be related to pathology of the bladder, prostate, pelvic side wall, or seminal vesicle [18]. If inflammation within the prostate and seminal vesicle were the only sites of pathology in CP/CPPS, the patients could have been expected to become completely asymptomatic with the treatment of anti-inflammatory agents only. But chronic prostatitis may not be a simple disease that can be defined by a predetermined set of symptoms and a single demonstration of the inflammatory status of the prostate. The NIH chronic prostatitis collaborative research network has recently reported that there is lack of correlation between symptoms and inflammation, which implies that these symptoms may not be of prostatic or seminal vesicle origin, and this emphasizes the importance of considering the role of other organs and systems in the etiology of this syndrome [19].

The limitations of this study include the relatively small number of subjects. As previously mentioned, a total of 50 men were analyzed, of whom 25 received rowatinex. In addition, there was no placebo group. Therefore, we could not find out the precise therapeutic effect of rowatinex as compared to placebo. The need for a placebo group in a future experimental study is apparent.

In conclusion, rowatinex administration allowed the patients to obtain significant symptomatic relief, especially in the pain domain, and it improved the patient's quality of life. Although various modalities have been used in the management of CPPS, no hard and fast treatment guidelines have yet been developed. Rowatinex in combination with the other recommended therapeutic modalities may have significant benefit for many men diagnosed with CP/CPPS, but more research is needed.

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