

# Montelukast for Treatment of Refractory Pruritus in Patients on Hemodialysis

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**Introduction.** One of the most common complaints in patients with end-stage renal disease (ESRD) is uremic pruritus. In the recent years, many drugs have been proposed for its treatment which have had paradoxical outcomes. We studied the antipruritus effect of montelukast sodium, a leukotriene receptor antagonist, in patients on hemodialysis.

**Materials and Methods.** The study was conducted as randomized, single-blind, placebo-controlled crossover study in 5 hemodialysis centers. Sixteen patients with refractory pruritus were selected and were divided into 2 groups to receive firstly montelukast and then placebo, or vice versa. Patients were treated by montelukast tablets, 10 mg daily, for 20 days and the washout period was 14 days.

**Results.** Of 16 patients whom were included in the study, 1 died during the placebo period of myocardial infarction and another patient who received montelukast for 20 days faced hemoglobin decrease during the placebo period diagnosed as myelodysplastic syndrome. At the end of the treatment with montelukast, pruritus was reduced by 35% (95% CI, 9.5% to 62.5%), while it was reduced 7% (95% CI, 0.5% to 15.9%) with placebo ( $P = .002$ ). The patients' compliance was assessed satisfactory, except for 1 patient who exited the study due to anemia.

**Conclusions.** Montelukast is more effective than placebo in the treatment of uremic pruritus not responding to the currently available antipruritus drugs, and it can be considered as a new and rather safe and effective treatment option in uremic patients.

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## INTRODUCTION

Uremic pruritus is one of the most common disabling symptoms in patients with end-stage renal disease (ESRD). Sixty percent of patients on dialysis, either hemodialysis or peritoneal dialysis, complain of pruritus, which is often generalized and mostly on the back.<sup>1</sup> In most patients, pruritus begins through the dialysis session and in 25%, it is persistent both along dialysis sessions and between them.<sup>2</sup>

There are different mechanisms that cause

uremic pruritus. The correlation between the mast cells and intensity of pruritus has been studied, and it seems the patients' symptoms are due to histamine release from the mast cells.<sup>3</sup> Nevertheless, the perception of pruritus in the central nervous system is related to opioid receptors which justify the use of opioid antagonists in the management of pruritus.<sup>4</sup> Of the other causes, skin contact to some antigens sensitive to leukotriene B<sub>4</sub> can be mentioned.<sup>5,6</sup>

At present, different treatment options are used

consisting of keeping the optimum adequacy of dialysis ( $Kt/V > 1.2$ ), ultraviolet B radiation, antihistamines, opioid antagonists, erythropoietin, topical capsaicin, evening primrose oil, gabapentin, heparin, cholestyramine, doxepin, thalidomide, charcoal, gamma-linolenic acid, cromolyn sodium, loratadine, ondansetron, nalfurafine, and alternative medicine (acupuncture and massage).<sup>3,4,7-20</sup>

*Montelukast sodium* is a leukotriene receptor antagonist that has been used in the treatment of asthma, atopic dermatitis, allergic rhinitis, and idiopathic urticaria.<sup>21-24</sup> We studied the effect of montelukast in patients on hemodialysis with uremic pruritus lasting more than 3 months, and compared it with placebo effect.

## MATERIALS AND METHODS

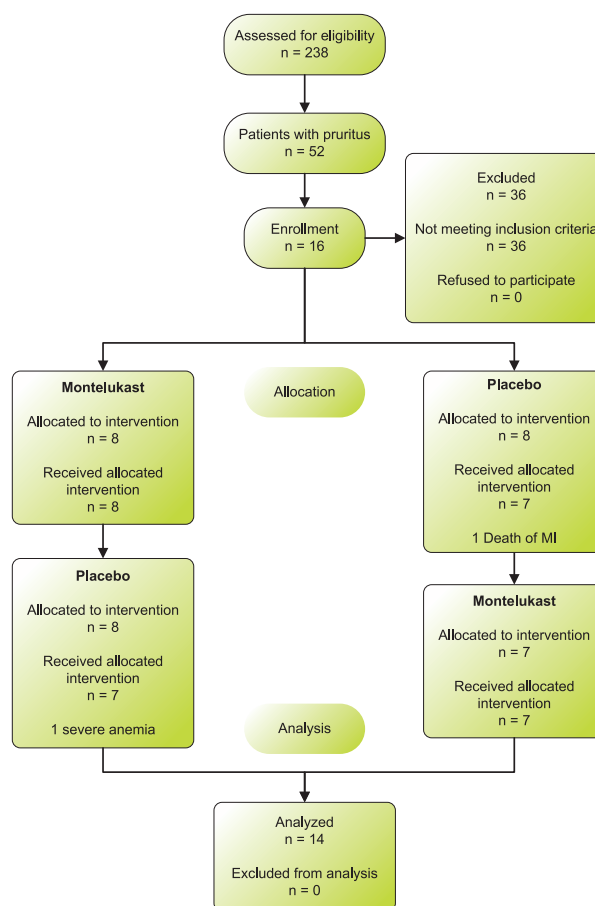
### Patients

We screened 238 patients with ESRD who were on regular thrice weekly hemodialysis for pruritus. They were receiving hemodialysis at 5 centers in Tehran, Iran, including Shohada-e-Tajrish, Shaheed Labbafinejad, Shaheed Chamran, Taleghani, and Tehranpars hospitals. A total of 52 patients complained of pruritus. We enrolled 20 of them who were between 20 to 85 years old and had persistent pruritus for more than 3 months that had led to disturbances during sleep or daily activities. They had experienced at least 1 course of unsuccessful treatment. The exclusion criteria were pruritus for less than 3 months,  $Kt/V$  less than 1.2, and pruritus due to conditions other than ESRD. The latter criterion included skin diseases, malignancies, hepatic cholestasis, hepatitis B and C infections, treatment with steroids, and blood hemoglobin less than 10 g/dL. Accordingly, 32 patients with pruritus for less than 3 months and 4 with pruritus due to other diseases were excluded.

The study protocol and the interventions were instructed to the patients and informed consent was obtained in written form. Eventually, the study was conducted on 16 patients receiving hemodialysis who consented from November 2005 to November 2006. One patient died of myocardial infarction while receiving placebo, and another patient refused to complete the study course (Figure).

### Study Design

The study was designed as a randomized, single-



Flowchart of patients' recruitment and assignment with excluded cases.

blind, placebo-controlled, crossover clinical trial. The patients were randomly divided into groups 1 and 2. The treatment in group 1 was started by montelukast, 10 mg daily, for the first 20 days, washout period for 14 days, and placebo for the last 20 days. In group 2, the treatment was ordered conversely.

The other antipruritic treatment options discontinued 1 week prior to the study. The serum levels of calcium, phosphorus, alanine aminotransferase, aspartate aminotransaminase, alkaline phosphatase, bilirubin, urea, creatinine, and parathyroid hormone, as well as blood hemoglobin and the  $Kt/V$  were measured in all of the patients before the study.

The diet of the patients did not change during the study. The patients' compliance were checked by regular visits during the study. Assessment of pruritus was done using Detailed Pruritus Score introduced by Duo.<sup>25</sup> The scores for sleep disturbances and intensity, area of pruritus were

added and the final score at the beginning and at the end of the study were calculated (maximum score, 45)

### Statistical Analyses

Primary and final scores at the beginning and the end of the study were calculated and the difference was shown as percentage and 95% confidence interval (CI). Data analysis was done by paired *t* test. A *P* value less than .05 was considered significant.

### RESULTS

Of 16 patients whom were included in the study, 10 were men and 6 were women. The mean age of the participants was 65 years and 63 years in the men and the women, respectively. All of the patients were on 4-hour bicarbonate dialysis thrice weekly. The Kt/V was 1.2 or greater. Fourteen patients were receiving antihistamines, naltrexone, or doxepin for pruritus all of which were discontinued a week prior to the study.

One of the patients in group 2, a 58-year-old diabetic woman with ischemic heart disease died during the placebo period of myocardial infarction, and her death was considered as adverse event. Another patient, a 82-year-old man in group 1, who received montelukast for 20 days faced hemoglobin decrease to 6 g/dL during the placebo period that finally diagnosed as myelodysplastic syndrome. Regarding the Good Clinical Practices guidelines in randomized controlled trials,<sup>26</sup> the latter patient was considered as “suspected unexpected serious adverse reaction” and was excluded. Therefore, the study was completed with 14 patients and considering the crossover design of the study, we had 14 patients in each arm.

All of the patients received erythropoietin and blood hemoglobin level was higher than 10 g/dL in all of them, with a mean value of  $11.3 \pm 1.2$  g/dL. Serum level of the parathyroid hormone (mean,  $267.0 \pm 239.1$  pg/mL) was higher than 300 pg/mL in 5 patients. Serum phosphorus level (mean,  $4.8 \pm 1.3$  mg/dL) was higher than 5.5 mg/dL in 5 patients. Serum calcium level (mean,  $9.8 \pm 1.0$  mg/dL) was also higher than 9.5 mg/dL in 8 patients that was higher than the ideal level based on the National Kidney Foundation Dialysis Outcomes Quality Initiative Guidelines for patients with ESRD.<sup>27</sup>

Montelukast in comparison with placebo was

more effective in alleviation of uremic pruritus. At the end of the treatment with montelukast, pruritus score was reduced by 35.7% , while it was reduced by 7.1% with placebo (*P* = .002). The mean change in pruritus score was 16.1 (95% CI, 9.5 to 22.5) with montelukast and 7.1 (95% CI, 0.5 to 13.7) with placebo. The patients' compliance was assessed satisfactory, except for 1 patient who exited the study due to anemia.

### DISCUSSION

In 198 patients on hemodialysis who were assessed in our study, 52 (26.3%) had pruritus, while the prevalence of uremic pruritus in other studies was reported to be between 30% to 66%, and even in some population to be 80%.<sup>1,14,28</sup> These differences in prevalence of uremic pruritus are reasonable since multiple factors may have a role in the pathogenesis of pruritus such as dialysis adequacy, anemia, and types of dialysis solution.

There was no significant difference in the frequency of pruritus in the patients from different centers in our study. Since dialysis inadequacy and anemia increase pruritus, these two parameters were considered as exclusive criteria in our study. However, out of the 36 excluded patients with pruritus, none had a Kt/V less than 1.2. This shows dialysis adequacy at the mentioned hemodialysis centers.

The roles of hyperparathyroidism and hyperphosphatemia in uremic pruritus are still controversial,<sup>4,10</sup> so we did not consider these two parameters as exclusive criteria. The results showed hyperparathyroidism in 5 and hyperphosphatemia in 5 patients. All 5 patients with hyperparathyroidism had remarkable response to montelukast and we hypothesized the better effectiveness of montelukast in secondary hyperparathyroidism.

The important finding in this study is that we can say montelukast is effective in the treatment of uremic pruritus when compared with placebo; therefore, montelukast, a leukotriene receptor antagonist, can be included as a new drug to the long list of known antipruritus drugs for uremic pruritus. The main advantages of this drug are: (1) renal adjustment is not necessary; (2) single daily dose is enough; (3) patients show a good compliance; (4) no interaction with other maintenance therapies occurs in patients with ESRD; and (5) there is no known serious side effect for montelukast.

Nonetheless, its disadvantages are its high price and its not being covered by insurance companies at the moment.<sup>29</sup>

In our study, none of the side effects of montelukast, neither common nor rare, were reported. We had faced 1 case of severe anemia that was diagnosed as myelodysplastic syndrome. Anemia has not yet been reported as a side effect of montelukast (even among side effects with less than 1% incidence).<sup>29</sup> Thus, we report it as “suspected unexpected serious adverse reaction.” About 1 patient who did not complete the study because of myocardial infarction and death, it can be inferred that regarding various cardiovascular risk factors in patients with ESRD, this accident can be reported as an adverse event.

## CONCLUSIONS

Montelukast can be considered as a treatment option for uremic pruritus resistant to conventional therapies. In order to confirm the effectiveness of montelukast, we recommend another randomized, double-blind, crossover study in a larger scale and that compare it with the best currently known antipruritus drugs. Moreover, the effectiveness of montelukast enforce the hypothesis of the leukotrienes' effect on uremic pruritus, which suggest more biochemical studies to reveal the relationship between pruritus and leukotriene levels in patients with ESRD. Meanwhile, since patients on peritoneal dialysis were not included in our study, it is recommended that in the future studies, this group of patients be also included.

## CONFLICT OF INTEREST

None declared.

## APPENDIX

### Pruritus Scale Score<sup>25</sup>

1. Severity of pruritus:
  - a. Mild need for scratching (1)
  - b. Need for scratching without excoriation (2)
  - c. Need for scratching with excoriation (4)
  - d. Frustrating pruritus (5)
2. Distribution of pruritus:
  - a. Less than 2 sites (1)
  - b. More than 2 sites (2)
  - c. Generalized (3)
3. Sleep disturbance as a result of pruritus:

- a. Waking up of pruritus (1 score for each time per night, up to 10)
- b. Scratching during night with excoriation (1 score for each time per night, up to 5)

Cumulative score = (severity + sleep disturbance) × distribution

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