Efficacy and Safety of a Novel κ-Agonist for Managing Intractable Pruritus in Dialysis Patients

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Key Words
Hemodialysis · κ-Receptor agonist · Long-term efficacy and safety · Nalfurafine hydrochloride · Pruritus

Abstract
Background: Our previous placebo-controlled, prospective, double-blind study demonstrated that a new opioid κ-receptor agonist, nalfurafine hydrochloride, effectively reduced treatment-resistant pruritus in 337 hemodialysis patients. Thus, we designed this study to evaluate prospectively the efficacy, safety, addiction liability, and pharmacokinetics of nalfurafine given orally for 1 year. Methods: This open-label study examined the effects and adverse drug reactions (ADRs) of 52-week oral administration of nalfurafine hydrochloride (5 μg/day) in 211 hemodialysis patients with a treatment-resistant itch. Results: Of 211 patients, 145 completed the study as scheduled. The mean pruritus value assessed by the visual analogue scale was 75.2 mm during the pre-observation period, which decreased significantly to 50.9 and 30.9 mm in week 2 and 52, respectively, indicating a long-lasting efficacy. ADRs occurred in 103 patients (48.8%). Frequent ADRs were insomnia (sleep disturbance, 19.4%), constipation (7.1%) and increased blood prolactin (3.3%), similar to previous reports. Regarding addiction liability, it appeared unlikely that nalfurafine hydrochloride was abused. After the start of treatment, plasma drug levels reached a steady state in week 2 with no apparent tendency of systemic accumulation. Conclusions: Nalfurafine hydrochloride, orally administered at 5 μg/day for 52 weeks to hemodialysis patients, produced a long-term suppression of pruritus without significant safety problems.

Introduction
Pruritus is an uncomfortable perception which makes the individual scratch the affected regions [1]. Diseases associated with pruritus include dermatological, liver, and endocrine diseases, malignancy, and chronic kidney diseases. Treatments suppressing pruritus include anti-
histamines, topical steroids, phototherapy, skin moisturization, and so on. However, these treatments are often ineffective in hemodialysis patients who suffer from severe pruritus [2–5].

Pruritus in hemodialysis patients is systemic and persistent, causing marked mental and physical stress. The Dialysis Outcomes and Practice Pattern Study (DOPPS) demonstrated that moderate to more severe pruritus develops in 42% of hemodialysis patients [6]. This study and an extensive study from Niigata University revealed a high prevalence of depression and sleep disorder and an increased risk of death in patients complaining of severe pruritus [6, 7]. Thus, a clear breakthrough is needed in the management of treatment-resistant pruritus.

In a previous clinical study [8], we showed that the opioid μ-system is upregulated and the κ-system is suppressed in hemodialysis patients with severe itching. We therefore hypothesized that treatment-resistant pruritus would be attributable to an imbalance of the endogenous opioid peptides in the central nervous system [8]. The involvement of the opioids in pruritus has been indicated by morphine, a μ-receptor agonist, which induces a severe itch [1, 3] and by intranasal butorphanol, a κ-receptor agonist, which is effective for intractable systemic pruritus [9].

Nalfurafine hydrochloride is a novel κ-receptor agonist created by Toray Industries, Inc., Japan, based on a new concept pertaining to opioid receptor affinity and selectivity [10, 11]. In studies using animal models, nalfurafine exerted antipruritic activity not only for antihistamine-sensitive but also for antihistamine-resistant itch [12–15]. Three reviews described this new κ-receptor agonist as a promising treatment for uremic pruritus [3–5]. In a randomized comparative study, Wikström et al. [16] demonstrated pruritus severity to be reduced in 144 patients when nalfurafine was intravenously given after hemodialysis 3 times weekly.

We performed a prospective, randomized, double-blind comparative study for 2 weeks, to compare the antipruritic effect of oral nalfurafine (2.5 and 5.0 μg) and a placebo in 337 patients, and demonstrated that nalfurafine significantly reduced the pruritus [17]. There were few serious adverse drug reactions (ADRs).

This report describes results of a prospective, open-label study using daily oral treatment with nalfurafine (5 μg) for 52 weeks in 211 hemodialysis patients with severe pruritus. We evaluated the efficacy, safety, addiction liability, and pharmacokinetics of this drug.

Patients and Methods

Patients
Patients with chronic renal failure who satisfied all of the following requirements were eligible for the study: (1) receiving hemodialysis at least twice weekly; (2) having given written informed consent to participate in this study, carried out in compliance with the principles of the Declaration of Helsinki and other relevant statutes; (3) complaining of pruritus resistant to conventional treatment (unresponsive to treatment during the 1-year period before consent, that is responding inadequately to any of the following treatments for at least 2 consecutive weeks: systemic therapy (oral administration or injection of antihistamines or antiallergic drugs indicated for pruritus) and topical treatment [ointments (steroids, etc.), moisturizing agents indicated for pruritus and prescribed by doctors], and (4) age over 20 years at the time of consent.

Of the eligible patients, those satisfying the following requirements during the latter half (7 days) of the pre-observation period (14 days in total) were finally enrolled: (1) visual analogue scale (VAS) value was obtained both morning and evening for ≥5 days, and the mean morning or evening VAS value (whichever was larger) was ≥50 mm; (2) either the morning or the evening VAS value (whichever was larger) was ≥20 mm on at least 5 days, and (3) during the latter half of the pre-observation period, daytime and nighttime pruritus scores were rated on at least 2 days using the Shiratori severity score (patient self-assessment, table 1) and the larger score, either daytime or nighttime, was ≥3 (moderate) on at least 2 days.

Study Design
This study was designed as an open-label, single-arm, prospective trial which was composed of a 14-day pre-observation period, a 2- to 25-day formal registration period, a 52-week drug treatment period, and a 4-week post-observation period.

Each patient took nalfurafine 5 μg orally (two 2.5-μg capsules) once daily (after supper, as a rule) for 52 weeks. If the doctor judged that it was impossible to continue treatment at the 5-μg dose due to adverse events (AEs), a dose reduction to 2.5 μg/day was permitted.

During the pre-observation and each treatment period (1, 2, 4, 12, 24, 36 and 52 weeks after starting treatment, and 4 weeks after treatment completion), conventional anti-itch drugs which had been started before this study were continuously administered as baseline therapy, without changing mode or dosage of the drugs.

Evaluation of Pruritus
We evaluated the pruritus in 3 ways. First, pruritus severity was primarily assessed with VAS value [18]. The VAS was a 100-mm horizontal line without notch or gradation. The left end (0 mm) corresponded to no pruritus and the right end (100 mm) to maximal pruritus severity. Each patient was instructed to mark the point on the scale corresponding to his/her itch severity in the absence of doctors and nurses.

During each treatment period, patients recorded the highest severity experienced during the 12-hour period before each recording point. VAS values were recorded twice daily (morning and evening) during the pre-observation period, and 1, 2, 4, 12, 24, 36 and 52 weeks after starting treatment, and 4 weeks after treatment completion (the post-observation period).
One-Year Effects of Nalfurafine in HD Patients

Table 1. Shiratori severity score

| Score (severity) | Daytime symptoms                                      | Nighttime symptoms                              |
|------------------|-------------------------------------------------------|-------------------------------------------------|
| 4 (severe)       | Intolerable itch, not relieved by scratching but instead worsens. Cannot focus on work or study | Can hardly sleep because of itch. Scratching all the time, but itch intensifies with scratching |
| 3 (moderate)     | Scratching even in the presence of others. Irritation as a result of itch, continuous scratching | Wake up because of itch. Can fall asleep again after scratching, but continue to scratch unconsciously while sleeping |
| 2 (mild)         | Itch sensation is relieved by light, occasional scratching. Not too disturbing | Feel somewhat itchy, but can obtain relief by scratching. Do not wake up because of itch sensations |
| 1 (slight)       | Feel itchy sometimes, but tolerable without scratching | Feel slightly itchy when going to sleep, but do not need to scratch. Sleeping well |
| 0 (no symptoms)  | Hardly feel itchy or do not feel itchy at all          | Hardly feel itchy or do not feel itchy at all    |

Second, each patient was instructed to remember the pruritus severity during the period between the morning of the previous and current dialysis sessions and to assess it using the Shiratori severity score (patient self-assessment) [19]. In this assessment, pruritus was scored from 0 (absent) to 4 (intense) (table 1).

Third, the doctor in charge assessed the severities of daytime and nighttime pruritus based on self-assessment data using the Shiratori score and information collected by interviewing the patients. Improvement during the period from the day following the last day of the pre-observation period to the day following the last day of each treatment period was evaluated, using the Shiratori score: markedly improved (disappearance of symptoms or improvement by more than 3 grades of the Shiratori score), moderately improved (improvement by more than 2 grades), slightly improved (improvement by more than 1 grade), unchanged (no change), or worsened (exacerbation of the Shiratori score).

Safety Assessment
Safety was evaluated by determining AEs and ADRs after starting treatment with nalfurafine, using subjective and objective symptoms, vital signs (body temperature, blood pressure, and heart rate), hematological and biochemical data, and electrocardiography. ADRs were tabulated in accordance with, and preferred terms of, the Medical Dictionary for Regulatory Activities/J (MedDRA/J, Ver. 9.0) developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals. Furthermore, AEs and ADRs were classified according to severity (mild, moderate, and severe) and causal relationship to the drug. Severity was defined as mild (easily tolerable, not interfering with normal everyday activities), moderate (interfering with normal everyday activities), and severe (preventing normal everyday activities).

Addiction Liability
Addiction liability was monitored by doctors interviewing each patient at 5 time points (week 4, 12, 52 during drug administration, and 1 and 4 weeks after treatment completion), using a questionnaire for assessing addiction liability of drugs in the field of psychiatry (table 2) [20]. The questionnaire data were analyzed by the Addiction Evaluation Committee composed of 6 doctors, who were experts in drug addiction and experienced in assessing addiction liability.

Plasma levels of nalfurafine were measured during the pre-observation period, 1, 2, 4, 12, 24, 36 and 52 weeks after starting treatment, and 1 week after treatment completion.

Statistical Analysis
The mean VAS value for each treatment period was calculated. The magnitude of change from the VAS value in the latter 7 days of the preobservation and its 95% confidence interval (CI, two-tailed) were determined regarding VAS values and the Shiratori severity score (assessed by patients). Intergroup comparisons were performed using paired t tests. Regarding the degree of improvement based on the Shiratori score (assessed by doctors), the percentage of patients rated as ‘markedly improved’ and ‘moderately improved’ and its 95% CI (two-tailed) were determined. Improvement was scored as follows: ‘markedly improved’ was 3, ‘moderately improved’ was 2, ‘slightly improved’ was 1, ‘unchanged’ was 0, or ‘worsened’ was −1. To perform intergroup comparison with the Wilcoxon signed rank test, we changed the scores to ranks and tested the sum of the ranks.

Results

Patients Studied
This study was carried out at 50 dialysis hospitals across Japan, with preliminary registration of 234 patients. After we excluded 23 patients who withdrew or did not satisfy the formal registration requirements, the drug was taken by 211 formally registered patients. Table 3 summarizes the patients’ background.

Completion of Study and Exposure to the Drug
The study was completed by 145 patients and discontinued prematurely by 66 patients. The dose was reduced from 5 to 2.5 μg/day in 29 cases. As to the drug exposure level, the mean and median dosing periods were 41.2 ± 18.0 weeks (mean ± SD) and 52 weeks, respectively, though the planned dosing period was 52 weeks.

In 26 of the 66 patients, the reason for the premature discontinuation was an AE. The number of patients in...
whom ADRs was the reason was only 12 of those 26 patients; 3 patients suffered from mild ADRs, 8 patients moderate ADRs, and 1 patient reported constipation as a severe ADR. The other reasons for discontinuation were the patient’s decision in 25 cases, and a change of hospital in 15 cases.

_Antipruritus Efficacy_

Figure 1 shows the time course of mean VAS values. The mean VAS value was 75.2 mm (95% CI, 73.5–76.9) in the pre-observation period. At week 2, the VAS value (50.9 mm, 47.6–54.3) was significantly reduced compared with that in the pre-observation period. At week 24, the VAS value (33.6 mm, 29.3–37.9) was also significantly smaller than that in the pre-observation period. VAS values fell continuously through the 24-week treatment (p < 0.01, paired t test) and remained around 31 mm through 52 weeks. These results suggest that this drug has a prolonged efficacy to suppress itch. The postobservation VAS value (47.9 mm, 43.7–52.1) was significantly larger than

| Table 2. Evaluation of addiction liability: questionnaire on the drug |
|---------------------------------------------------------------|
| Response | Very much | Considerably | Slightly | Not at all |
|----------|-----------|--------------|----------|-----------|
| **Questionnaire on the drug (dosing period)** | | | | |
| A1 | Do you feel your head is clearer and your mind is functioning more smoothly after taking this drug? | | | | |
| A2 | Do you feel less concerned with persons or matters you don’t like after taking this drug? | | | | |
| A3 | Do you speak more or move more actively after taking this drug? | | | | |
| A4 | Do you feel more confident in yourself after taking this drug? | | | | |
| A5 | Do you feel like you are floating as if intoxicated after taking this drug? | | | | |
| A6 | Do you feel irritated or lonely when the effects of this drug disappear? | | | | |
| A7 | Do you want to continue taking this drug? | | | | |
| A8 | Do you feel this drug is gradually becoming less effective? | | | | |
| A9 | Do you want to take this drug in larger amounts? | | | | |
| A10 | Do you feel nausea or trembling of the hands or feet when the effects of this drug disappear? | | | | |
| **Questions on the drug (post-observation period)** | | | | |
| B1 | Have you become irritated and unstable since discontinuing the drug? | | | | |
| B2 | Have you been sleeping worse since discontinuing the drug? | | | | |
| B3 | Have you experienced nausea, vomiting, trembling or numbness of the hands or feet, sweating and so on since discontinuing the drug? | | | | |
| B4 | Are you eager to resume taking the drug? | | | | |
| B5 | Have you experienced any convulsions since discontinuing the drug? | | | | |
| B6 | Have you experienced clouding of consciousness, seeing something strange or hearing strange sounds since discontinuing the drug? | | | | |
that (30.9 mm, 26.6–35.1) at week 52, indicating a clear anti-itch effect of nalfurafine and an intensification of the itch after the treatment cessation.

Time course of the magnitude in nighttime pruritus scores was assessed by the Shiratori severity score (patient assessment, fig. 2). The decrease in the score started at week 2 and continued until week 52 (p < 0.01, paired t test). The mean decrease was 0.97 (0.86–1.07), 1.55 (1.40–1.70) and 1.57 (1.41–1.73) at weeks 2, 24 and 52, respectively. Thus, the antipruritic effect was maintained for 52 weeks. The Shiratori score in the post-observation period (1.04, 0.90–1.19) was significantly higher than that of week 52 (p < 0.01, Wilcoxon signed rank test).

Figure 3 shows the time course of the degree of improvement based on the Shiratori score (assessment by doctors). The sum of the percentage of ‘markedly improved’ plus ‘moderately improved’ was 18.1% (CI, 13.1–24.1) at week 2, rose markedly reaching 49.4% (41.4–57.3) at week 24, and remained high until week 52. In all treatment periods, the improvement was significantly greater than that of the pre-observation period (p < 0.01, Wilcoxon signed rank test). The percentage at 4 weeks after treatment completion (post-observation period) was 24.3% (18.3–31.2), which was lower than the percentage at week 52 (p < 0.01, Wilcoxon signed rank test).

**Table 3. Patients’ background**

|                                | 211          |
|--------------------------------|--------------|
| Number of patients             | 211          |
| Gender                         |              |
| Male                           | 166 (78.7%)  |
| Female                         | 45 (21.3%)   |
| Age, years                     | 61.4 ± 11.4  |
| Body weight, kg                | 57.82 ± 10.08|
| Underlying disease             |              |
| Glomerulonephritis             | 91 (43.1%)   |
| Diabetic nephropathy           | 55 (26.1%)   |
| Others                         | 65 (30.8%)   |
| Duration of hemodialysis, years| 8.33 ± 6.98  |
| Duration of pruritus, years    | 5.23 ± 4.58  |
| Shiratori severity score       |              |
| (patient assessment)           |              |
| (latter 7 days)                | 3.22 ± 0.41  |
| Drugs for treatment of pruritus|              |
| Present                        | 203 (96.2%)  |
| Absent                         | 8 (3.8%)     |
| Baseline treatment, systemic therapy |         |
| Antihistamine alone            | 41 (19.4%)   |
| Antiallergic drug alone        | 129 (61.1%)  |
| Both                           | 41 (19.4%)   |
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| Steroids                       | 152 (72.0%)  |

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1 Mean ± SD.
Treatment was discontinued due to ADRs was 6.2% at week 24 and remained constant afterward, and there was no marked elevation in this percentage with prolonged treatment.

The incidence of ADRs which exceeded 1% is shown in Table 4, in which all ADRs are classified based on whether they occurred within 2 weeks or between 3 and 52 weeks of the current 1-year open-label study. ADRs which occurred in 2 weeks of our earlier prospective double-blind study [17] are also presented in Table 4. Insomnia, constipation, and somnolence occurred within the first 2 weeks in 32 of 41 patients, 7 of 15 patients, and 4 of 5 patients, respectively, whereas anemia occurred between 3 and 52 weeks. Thus, like the cumulative incidence tendency for total ADRs, these ADRs appeared soon after the start of the treatment.

When the ADRs which occurred within 2 weeks in this 1-year study and in the 2-week double-blind study are compared, the incidence of insomnia is similar. In contrast, the incidence of constipation, somnolence, and pruritus is lower in the current 1-year study.

No severe ADRs were seen except constipation in 1 patient. As serious ADRs, vertigo occurred in 2 patients (0.9%), and anemia, disorientation and acute pancreatitis in 1 each (0.5%). No clinically significant delayed ADRs which required prolonged (week 24 or longer) treatment were reported. There were no clinically significant changes in the vital signs or electrocardiographic findings.
Addiction Liability and Tolerance
In all patients, the addiction liability of nalfurafine was assessed at 5 times. None showed symptoms attributable to psychological dependence on the drug. In the analysis of physical dependence, mild hypnagogic hallucination when falling asleep was noted in 1 patient. However, since this is occasionally seen even in healthy individuals [21], it seemed to be attributable to the psychotropic effects of the drug rather than withdrawal symptoms. Thus, there was no evidence of physical dependence.

Development of tolerance to the drug (attenuation of the effect with time) was noted in 5 of the 211 patients. However, analysis of the efficacy data from the entire study population revealed no tendency for tolerance development.

Pharmacokinetics
When the hemodialysis patients were orally given this drug at daily doses of 2.5–5 μg (primarily 5 μg), the plasma level of nalfurafine reached 6.19 ± 3.43 pg/ml (blood was sampled 16 ± 4 h after oral administration) at week 2, without showing a further rise. This is because the drug is removed by the dialyzer. In 172 of 180 patients, the plasma level of the drug was below the detection limit approximately 1 week after treatment completion. These results indicate that nalfurafine is unlikely to accumulate systemically in hemodialysis patients or to raise the risk of ADRs when administered repeatedly for 52 weeks.

Discussion
Regarding the antipruritic effects of nalfurafine, the decrease in VAS values at week 2 was 24.4 mm, followed by further decreases in VAS values until week 24 (fig. 1). The low VAS values remained stable until week 52. Interestingly, the decrease in the VAS value was comparable to that (23.4 mm) recorded at 2 weeks at the 5-μg dose in our previous placebo-controlled, double-blind study [17]. Therefore, we think that despite an open-label study, these VAS values are as reliable as those obtained in the double-blind study.

We reported a clinical study regarding 37 hemodialysis patients who reported no itching (n = 19), mild itching (n = 8), and severe itching (n = 10) in which activation of the µ-opioid system in the central nervous system (such as the thalamus and dorsal horn neurons) was implicated in the pathogenesis of uremic pruritus. Furthermore, we demonstrated by a prospective placebo-controlled randomized study that the combination of κ-receptor and its agonist nalfurafine antagonized the µ-receptor-mediated pruritus [17]. Therefore, the results of the present study suggest that nalfurafine is a promising candidate for the treatment of pruritus in hemodialysis patients.

Table 4. Incidence of ADRs (reactions with incidence over 1.0%)

| Severity: | Within 2 weeks of 1-year study, nalfurafine 5 μg (n = 211) | Between week 3 and 52 of 1-year study, nalfurafine 5 μg (n = 211) | Within 2 weeks of double-blind study [17], nalfurafine 5 μg (n = 114) |
|-----------|--------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------|
|           | mild | moderate | severe | total | mild | moderate | severe | total | mild | moderate | severe | total |
| Insomnia  | 21   | (10.0)  | 11     | (5.2)  | 0    | 32     | (15.2) |       | 8    | (3.8)  | 1       | (0.5)  | 0    | 9     | (4.3)  | 13   | (11.4) | 2       | (1.8)  | 1    | (0.9)  | 16     | (14.0) |
| Constipation | 5    | (2.4)   | 1      | (0.5)  | 1    | (0.5)  | 7      | (3.3) | 8    | (3.8)  | 0       | 0      | 8    | (3.8)  | 0    | 8     | (7.0)  | 0    | 8     | (7.0)  |
| Blood prolactin increased | 2    | (0.9)   | 0      | 0      | 2    | (0.9)  |       |       | 5    | (2.4)  | 0       | 0      | 5    | (2.4)  | 0    | 3     | (2.6)  | 0    | 3     | (2.6)  |
| Somnolence | 3     | (1.4)   | 1      | (0.5)  | 0    | 4      | (1.9)  |       | 1    | (0.5)  | 0       | 0      | 1    | (0.5)  | 0    | 4     | (3.3)  | 0    | 4     | (3.3)  |
| Dizziness  | 0    | 2       | (0.9)  | 0      | 2    | (0.9)  |       |       | 1    | (0.5)  | 1      | (0.5)  | 0    | 2      | (0.9)  | 1    | (0.9)  | 0       | 1     | (0.9)  |
| Pruritus   | 1    | (0.5)   | 1      | (0.5)  | 0    | 2      | (0.9)  |       | 2    | (0.9)  | 0       | 0      | 2    | (0.9)  | 0    | 2     | (1.8)  | 1    | (0.9)  | 0       | 3     | (2.6)  |
| Blood TSH decreased | 0    | 0       | 0      | 0      | 4    | (1.9)  | 0      | 0      | 4    | (1.9)  | 0       | 0      | 4    | (1.9)  | 1    | (0.9)  | 1      | (0.9)  | 0    | 2     | (1.8)  |
| Diarrhea  | 1    | (0.5)   | 1      | (0.5)  | 0    | 2      | (0.9)  |       | 1    | (0.5)  | 0       | 0      | 1    | (0.5)  | 0    | 1     | (0.9)  | 0    | 1     | (0.9)  |
| Malaise   | 2    | (0.9)   | 0      | 0      | 2    | (0.9)  |       |       | 1    | (0.5)  | 0       | 0      | 1    | (0.5)  | 0    | 1     | (0.9)  | 0    | 1     | (0.9)  |
| Mood altered | 2    | (0.9)   | 0      | 0      | 2    | (0.9)  |       |       | 1    | (0.5)  | 0       | 0      | 1    | (0.5)  | 0    | 1     | (0.9)  | 0    | 1     | (0.9)  |
| Eczema   | 0    | 1       | (0.5)  | 0      | 1    | (0.5)  |       |       | 2    | (0.9)  | 0       | 0      | 2    | (0.9)  | 0    | 0     | (0.0)  | 0    | 0     | (0.0)  |
| Vomiting | 1    | (0.5)   | 0      | 0      | 1    | (0.5)  |       |       | 2    | (0.9)  | 0       | 0      | 2    | (0.9)  | 0    | 1     | (0.9)  | 0    | 1     | (0.9)  |
| Anemia   | 0    | 0       | 0      | 0      | 2    | (0.9)  | 1      | (0.5)  | 0    | 3      | (1.4)  |       | 0    | 0      | 0    | 2     | (1.8)  | 0    | 0     | (0.0)  |
| Blood TSH increased | 0    | 0       | 0      | 0      | 1    | (0.5)  | 0      | 0      | 1    | (0.5)  | 0       | 0      | 1    | (0.5)  | 0    | 3     | (2.6)  | 0    | 3     | (2.6)  |
| γGTP increased | 0    | 0       | 0      | 0      | 0    | 0      | 0      | 0      | 0    | 2      | (1.8)  | 0       | 0    | 2     | (1.8)  | 0    | 2     | (1.8)  |

Values represent number with the percentage in parentheses. TSH = Thyroid stimulating hormone.
study strongly suggest that the κ-receptor agonist nalfurafine succeeded in suppressing the endogenous μ-system-induced pruritus for 1 year.

Regarding the Shiratori severity score [19], the decrease in scores assessed by the patients (fig. 2) and the improvement assessed by doctors (fig. 3) show basically similar results. All analyses of efficacy endpoints revealed that the effect of the drug in alleviating pruritus was consistently maintained through 52 weeks. These results suggest that nalfurafine is able to suppress pruritus continuously for 52 weeks without attenuation or any tolerance.

Pruritus treatment is susceptible to a placebo effect. Four weeks after discontinuing the drug, the VAS values increased but only to levels found 2 weeks into the trial. This may be due to some beneficial structural effect in the skin because of prolonged suppression of itching.

Insomnia is one of the most often found ADRs with nalfurafine and attention should be paid to this [17]. The presence/absence of insomnia and other complications in the present study did not markedly affect the time course of the nocturnal VAS values or Shiratori scores (patient assessment), suggesting that insomnia is unlikely to have a major impact on the antipruritic efficacy of this drug at night or on patients’ quality of life.

In the safety evaluation, the incidence of ADRs was 48.8%. In our previous prospective double-blind study conducted in Japan, the ADR incidence was 35.1% in the 5-μg dose group [17]. Considering that the dosing period in the double-blind study was 2 weeks, these results suggest that a 52-week treatment is unlikely to markedly increase ADRs.

Since constipation and somnolence appeared during the first 2 weeks of treatment in half of the affected patients and insomnia occurred during the first 2 weeks in 75% of the affected patients, we think that nalfurafine-mediated ADRs appeared relatively soon after starting the treatment and are easy to be detected. The cumulative percentage of patients whose treatment with this drug was discontinued due to the ADRs was 6.2% at week 24 and remained unchanged until week 52. Thus, the incidence of ADRs requiring drug discontinuation did not rise during prolonged use.

The addiction liability of nalfurafine was strictly assessed 5 times in every patient and evaluated by 3 meetings of the Addiction Evaluation Committee. Results showed there were no patients with psychological or physical dependence. Tolerance to the drug (attenuation of the effect) developed in 5 of 211 patients. However, the efficacy data from the entire study population revealed no tendency for developing tolerance to nalfurafine. Since the addiction is the most serious ADR associated with opioid peptides, the negative possibility of addiction with nalfurafine enables the doctors to give the patients this novel κ-agonist without concern.

**Conclusions**

From this prospective study, nalfurafine hydrochloride orally administered for 52 weeks to hemodialysis patients was effective for treatment-resistant pruritus and safe, showing no possible addiction liability or tendency to accumulate in blood.

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**Disclosure Statement**

H. Kumagai, H. Nakamoto, T. Muramatsu, and H. Suzuki spent some time working as medical consultants on the development of anti-itch agents at Toray Industries, Inc. T. Ebata and K. Takamori occasionally worked as medical consultants in the field of Dermatology at Toray Industries, Inc.

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