Pruritis: A Vexing Problem With a Promising New Therapy

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As anyone who provides care in a dialysis clinic is aware, pruritis is a common and debilitating symptom for patients receiving maintenance dialysis. In a recent survey from the Dialysis Outcomes and Practice Patterns Study group encompassing 17 countries, nearly 1 in 5 patients (18%) were “extremely” or “very much” troubled by “itchy skin,” a total that rose to nearly 3 in 8 (37%) when moderate symptoms were included.1 As would be expected, chronic itching impairs quality of life.2 Unfortunately, physicians do not fully appreciate the burden of pruritis, with dialysis unit medical directors underestimating the prevalence in 69% of units. This may be because 1 in 6 patients reports not having alerting facility staff to the symptoms.1

For at least 3 reasons, nephrologists and other providers should take pruritis very seriously. First, from among myriad challenges in the care of dialysis patients, pruritis has been identified as 1 of the top 10 areas of research priority by a multidisciplinary group consisting of patients and their caregivers, physicians and nurses, and other key dialysis unit personnel such as dieticians, social workers, and pharmacists.3 Thus, across the many symptoms that trouble dialysis patients, pruritis is clearly one of the most important. Second, pruritis is associated with mortality in dialysis patients.4,5 Although epidemiologic studies reporting such associations cannot prove causality, there are plausible mechanistic hypotheses for this relationship. One possibility is that infection risk can increase from skin excoriation; another is that patients who experience burdensome symptoms (such as pruritis, cramping, restless legs, or others) seem, in general, to be more likely to skip, shorten, or otherwise compromise their dialysis treatment sessions. Third, concerns about pruritis may be easily lost in the complex milieu of care for dialysis patients, an environment in which there is often miscommunication between patients and their physicians about patient priorities, diagnoses, and treatment plans.6 When rounding in the dialysis clinic, nephrologists and other providers must address many domains of care, including adequacy of dialysis, hyper- and hypotension, ultrafiltration and volume control, management of anemia and mineral metabolism, optimization of vascular access, and others, all of which much be addressed quickly, efficiently, and with appropriate concern for the regulatory, documentation, and compliance aspects of care. It is therefore understandable (although of course not desirable) that concerns about pruritis might be consigned to the bottom of the list of competing priorities.

The mechanisms of pruritus are, disappointingly, far from well understood. As recently reviewed by Arzhan et al.,7 possible causes include buildup of pruritogens, dysregulation of mineral metabolism, increased inflammation, neuroregulatory changes, and propensity for abnormally dry skin (xerosis cutis). Pruritogens might include as-yet poorly understood uremic toxins, which may be poorly cleared via dialysis. Metastatic microcalcifications, presumably due to secondary hyperparathyroidism, seem to be likely contributors. Elevations in markers of inflammation, such as C-reactive protein, interleukin-6, and interleukin-31, have been invoked as potential mediators of the problem, yet identification of increased levels of these markers does not, in itself, help explain the underlying cause of the inflammatory state. Upregulation of the neural pathways that mediate pruritis has also been invoked, such as an increase in neurotropin-4 that appears correlated with

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pruritis. Stimulation of μ-opioid receptors by endorphins has also been invoked, supported by findings that the μ-opioid antagonist naltrexone might reduce the sensation of itching. These proposed mechanisms likely work in concert to cause pruritis.\(^7\) For example, although parathyroidectomy appears to help relieve symptoms in some patients with advanced secondary hyperparathyroidism, others who suffer from pruritis do not seem to have particularly advanced secondary hyperparathyroidism, or striking elevations in serum phosphate.

Traditionally, treatment options for pruritis have been suboptimal. A comprehensive review of treatment options was recently undertaken by Simonsen et al.\(^8\) This review of 44 studies examined the broad range of medications used for pruritis, encompassing oral agents, topical agents, and other interventions. Oral agents included gabapentin and pregabalin, mast cell stabilizers (e.g., cromolyn sodium, nicotinamide, zinc sulfate), the leukotriene inhibitor montelukast, ondansetron, cromolyn sodium, nicotinamide, naltrexone, and nalfurafine hydrochloride (a κ-opioid receptor agonist). The authors concluded that only gabapentin/pregabalin showed convincing evidence of effectiveness, based on 6 trials comparing the agents with placebo. Unfortunately, when these agents were compared with active comparators in a small number of short-term (≤12 weeks) trials, they did not demonstrate relative effectiveness. Concern has also been raised about a potential association of gabapentin with increased mortality in epidemiologic studies,\(^9\) although, as in all observational studies, confounding is a possibility in this study because patients with the most severe itching, and therefore risk of adverse outcomes, might be those preferentially treated with gabapentin. Nonetheless, questioning whether gabapentin might directly confer harm to dialysis patients is still appropriate. Evidence for topical agents is modest at best. Regarding nonpharmacologic interventions, the effects of phototherapy and of dialysis modality changes have been studied. For the former, 4 trials of phototherapy (encompassing only 112 patients in total) did not appear to show robust benefits of either ultraviolet or far-infrared light. For the latter, very modest evidence suggests that hemodialfiltration, hemoperfusion, and high-permeability hemodialysis may be beneficial, requiring further trials.

The present study\(^5\) provides the most promising evidence to date that practical interventions for dialysis-related pruritis may be within reach. In this phase 2 trial of difelikefalin, an agonist of κ-opioid receptors, investigators randomized 174 hemodialysis patients to 1 of 3 i.v. doses of difelikefalin, versus placebo, in a randomized and blinded trial for 8 weeks. Targeting κ-opioid receptors, activation of which suppresses itching, with difelikefalin is an attractive strategy, as the drug is peripherally restricted (meaning it has no known central nervous system effects), selective (targeting only the κ receptors), and free of known off-target effects.\(^5\) The outcome assessed was change in the weekly mean of the 24-hour Worst Itching Intensity Numerical Rating Score, a scale ranging from 1 to 10 (with 10 representing the worst itching), where a decrease of 3 is likely clinically significant. When all patients randomized to difelikefalin were pooled, the decrease in the Worst Itching Intensity Numerical Rating Score was approximately 1.3 units greater than for placebo patients; the score decreased by approximately 3.2 points in difelikefalin-randomized, and the latter by 1.9 in the placebo patients. The associated \(p\) value was <0.05. The proportion of difelikefalin-randomized patients reaching at least a 4-point decrease in the Worst Itching Intensity Numerical Rating Score was nearly twice as high (44%) as the proportion in the placebo-randomized patients (24%). Sleep disturbance attributable to itching also improved more in the difelikefalin-randomized patients. These results were very similar to results of the phase 3 trial, which were actually published first.\(^3\) One notable finding of the trial was the nontrivial improvement in itching for the patients randomized to placebo, suggesting that when providers merely attend to the problem, some perceived reduction in itching may result.

Difelikefalin calls forth some notes of caution. First, because it is renally cleared, it has been reported to have a relatively long half-life of approximately 24 hours in hemodialysis patients.\(^5\) The manufacturer may have data about dialysis clearance, but, as these are not yet published, the dosing kinetics in maintenance hemodialysis patients may not yet be fully appreciated by the nephrology community. Second, although the drug is not known to cross the blood-brain barrier or to have off-target effects, in both the phase 2 and 3 studies, diarrhea, nausea/vomiting, and dizziness were frequent in patients randomized to difelikefalin, and somnolence occurred more frequently in these patents in the former study. Providers must therefore be alert to these potentially concerning side effects. Reassuringly, in the phase 3 study, there were no signs of dependence in the weeks following cessation of drug. Third, patients...
selected for clinical trials are often “idealized,” in that they are considered suitable for recruitment; as a result, findings from any clinical trial may not be generalizable to the dialysis population as a whole.

A potentially promising avenue of future study relates to inhibitors of the spinal cord receptor natriuretic peptide receptor 1, which is a target of neuropeptide natriuretic peptide B, the latter a major effector of the itch response in mice. A recent report has suggested that inhibition of natriuretic peptide receptor 1 with an appropriate compound (known as JS-11) is associated with halving of the scratch response in mouse models of pruritis. It has therefore been suggested that if this pathway is further defined, and safe inhibitors developed, the result could be therapies that substantially reduce pruritis in dialysis patients.

In summary, pruritis is a common and vexing problem for dialysis patients. The mechanisms underlying it remain to be elucidated; doing so is important because pruritis adversely affects both quality of life and long-term outcomes, including mortality. Difelikefalin is the most promising agent for pruritus to date, based on currently available published trial evidence. As with all agents, its real-world effectiveness, as well as its potential harms, can be assessed only after much wider use outside of the clinical trial environment.

**DISCLOSURE**
The author declared no competing interests.

**SUPPLEMENTARY MATERIAL**
Supplementary File (Word)
Supplementary References.

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