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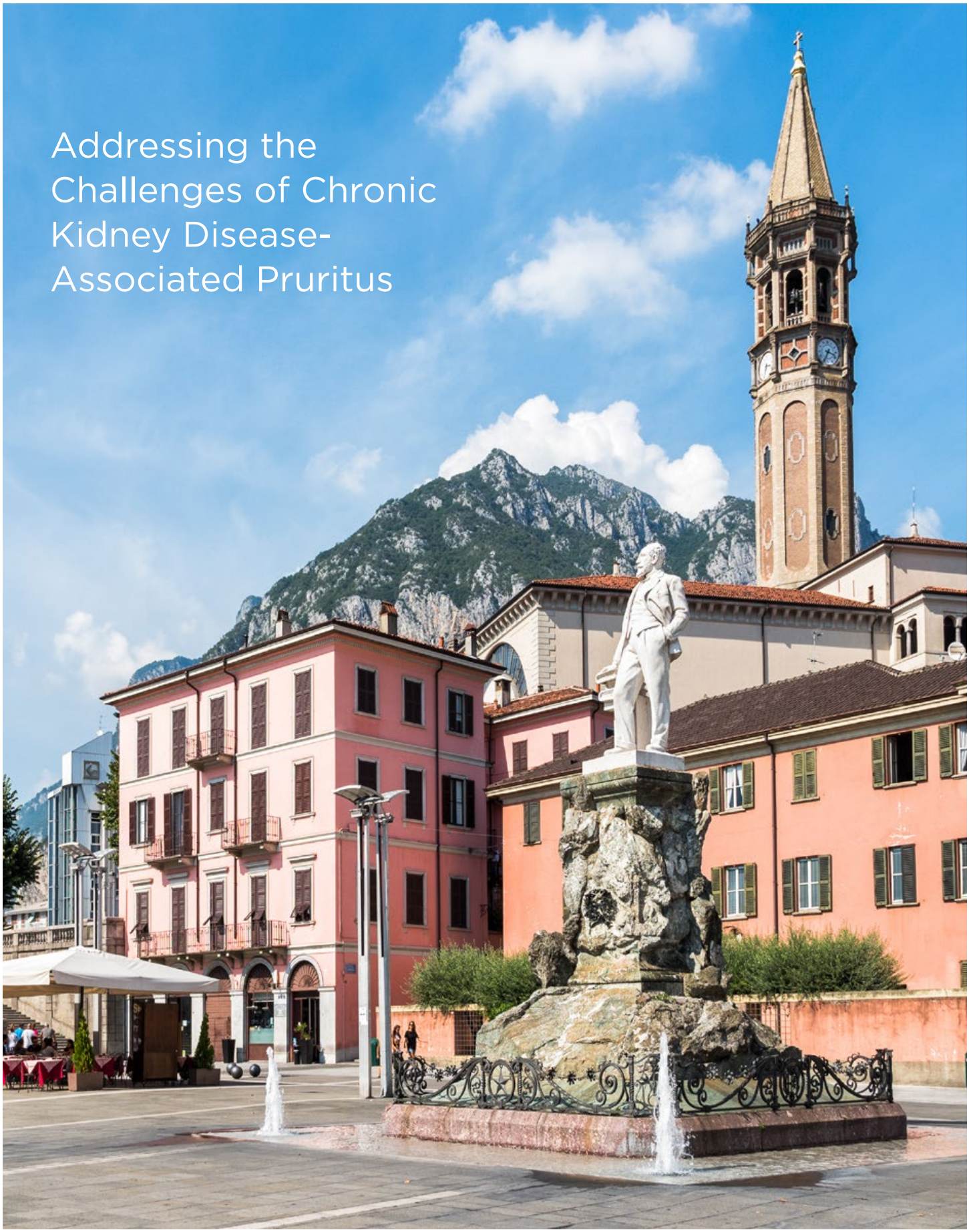

Addressing the Challenges of Chronic Kidney Disease-Associated Pruritus

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Summary

Chronic kidney disease-associated pruritus (CKD-aP) is a systemic condition with a nondermatological cause, diagnosed once other potential aetiologies have been examined, addressed, and discounted. CKD-aP occurs in around two-thirds of patients with CKD receiving dialysis and can be extremely bothersome for some. The exact cause of CKD-aP may be at least partially related to uraemic toxin accumulation, the calcium–phosphate–parathyroid hormone axis and upregulation of the immune system, and skin-based cells producing itch-exacerbating factors. Opioid and opioid-receptor imbalance may also lead to increased pruritus. It is important to recognise, assess, and attempt to treat CKD-aP as the condition is associated with overall poor quality of life (QoL), poor sleep, depression, missed haemodialysis sessions, and increased mortality. Treatment for CKD-aP begins by addressing potential problems with xerosis, which may provide some relief. There is only one CKD-aP-specific medication, the κ-opioid agonist nalfurafine hydrochloride; however, this is currently only approved in Japan. While gabapentin and mu-opioid antagonists are used for CKD-aP, they are off-label and have side-effect profiles that may limit use without proper titration. Clinical trials are investigating a few new CKD-aP treatments such as the κ-opioid receptor agonist difelikefalin, currently in Phase III studies. Given the nephrological and dermatological components of CKD-aP, and studies of such, EMJ brought together nephrologist Prof Francesco Locatelli and dermatologist Prof Franz J. Legat to help gain insight into the current understanding of CKD-aP diagnosis, issues affecting QoL, and treatment.

INTRODUCTION

CKD-aP is characterised by itching for at least 6 weeks without primary skin lesions. It develops due to a systemic condition related to renal insufficiency. As aetiology, persistence over time, severity, and body location can change, both between patients and within a patient, there are few established diagnostic criteria beyond renal insufficiency and exclusion of other causes.[1]

The most recent Dialysis Outcomes and Practice Patterns Study (DOPPS), which included 23,264 patients with CKD receiving haemodialysis, found that 67% of those surveyed were experiencing CKD-aP. While for many this was rated as 'somewhat' or 'moderately' bothersome, nearly 20% reported they were 'very much' or 'extremely' bothered by pruritus.[2] As such, CKD-aP is a problem that needs to be considered and assessed in all people with CKD.

To gain insight into the current understanding of CKD-aP, discuss how it is diagnosed, and review current and potential future treatments, EMJ brought together Prof Locatelli, a nephrologist and expert on CKD, and Prof Legat, a dermatologist with expertise in chronic pruritus.

AETIOLOGY OF CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

CKD-aP pathophysiology is not fully understood and is often multifactorial. At its base, CKD-aP may be related to the xerosis often found in people with CKD. However, even after treatment, pruritus may persist.[3] It was initially thought that CKD-aP was due to an accumulation of uraemic toxins caused by progressive renal function decline and, where relevant, poor-quality haemodialysis. High phosphorus, calcium, and parathyroid hormone levels may also be major factors involved in pruritus and, to a lesser extent, aluminium accumulation and vitamin A deficiency.[1,3]

Systemic inflammation and/or skin microinflammation may also lead to CKD-aP. Prof Locatelli noted that "inflammation associated with CKD, an important factor in deteriorating renal function and in aggravating CKD-related anaemia, is possibly involved in causing itch." Indeed, in CKD there are increased levels of inflammatory and immune system components such as the cytokines IL-6 and IL-2, T-lymphocytes, and mast cells.[1]

An increase in compounds associated with itching ('pruritogens') in the circulation, such as histamine and IL-31, potentially leads to neurogenic pruritus. Pruritogens can also be released by immune system cells and skin keratinocytes and are capable of stimulating pruriceptive peripheral sensory nerve fibres. The itch signal is transferred via the dorsal root ganglia and dorsal horn of the spinal cord to the thalamus and then to several brain regions, where it is perceived as itch and scratching is induced. Thus, a combination of neurogenic itch and pruriceptive itch may play a role in CKD-aP. Furthermore, central nervous system itch signalling may become disproportionate to or disassociated from a causative factor, leading to peripheral neuropathy manifesting as pruritus.[1,4]

Another potential CKD-aP aetiology is opioid imbalance. Opioids, with receptors located in both the brain and skin, can cause itching and so may have a role in itch pathophysiology.[5] In CKD-aP, it is suggested that brain-located mu-opioid receptors may be overstimulated and periphery- and skin-located κ-opioid receptors may be antagonised.[1] This is of particular relevance as drugs targeting these receptors are in use and in trials for CKD-aP alleviation.

DIAGNOSIS OF CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

Diagnosis of CKD-aP starts with exclusion of other factors that could cause or contribute to chronic pruritus. Skin examination, in consultation with a dermatologist if needed, can confirm or exclude many dermatological conditions. Basic laboratory investigations help determine other potential causes. Diabetes, for example, is prevalent in people with end-stage CKD, and may be a major source of chronic itching.[2] Diverse underlying medical conditions such as anaemia, and psychiatric conditions such as depression, should be investigated and treated if present. Patients may also be taking a wide range of medications, many of which have pruritus as a possible side effect. However, Prof Legat commented: "if you talk to the nephrologist to find out which of these you could stop, there aren't any."

There is no 'typical' patient with CKD-aP, but Prof Legat said that he sees it more often in people around and over 50 years of age. "The itch is typical only in that it is chronic," Prof Legat explained. "It could be on different sides at different times. Maybe at Time 0, the patient has the most intense itch on their back; 2 weeks later, it could be on the arms. It's not known why this happens despite everything else staying the same: dialysis three times per week, same food, same drugs, but still, the itch location may change." Prof Locatelli noted, however, that some conditions can change without the patient or healthcare professional being aware, such as the sterilisation modality of dialysis filters, the type of heparin for anticoagulation during haemodialysis, or the treatment and quality of the water and bath concentrate used for the haemodialysis. Each of these potential factors need to be investigated, which is not an easy task. CKD-aP may also be exacerbated by exposure to extreme temperatures, water, and physical activity, so lifestyle questions are key.[1]

In general, people with CKD have more extreme xerosis and skin that may typically be a slightly yellow-grey colour.[6,7] Prof Legat pointed out that while these are not defining criteria for CKD-aP, for the dermatologist encountering a patient with chronic pruritus they can indicate that CKD may be the cause. In those with xerosis, he explained, "usually, when a patient takes off their clothes, they start to scratch when the air hits the skin." However, he continued, while white streaks may be observed from scratching dry skin, "typically the patient doesn't have many scratch lesions, except for those who have had pruritus for a long time; however, these patients can develop chronic prurigo with intensely itching nodules or umbilicated skin lesions."

While CKD-aP may be reported more often by those on haemodialysis, in part as they are regularly questioned about their health, Prof Legat cautioned that it should not be assumed that haemodialysis is causing the problem. "In my pruritus clinic, there are also patients not on dialysis. Sometimes they are newly diagnosed with either considerable kidney problems or significantly reduced glomerular filtration index and no other problems, so there is a definite link between chronic pruritus and CKD other than just haemodialysis."

UNDER-RECOGNITION OF CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS AS A PROBLEM

Both professors confirmed that pruritus is not commonly assessed on a regular basis in patients with CKD. Part of the reason for this, explained Prof Locatelli, is that it is only with the advent of life-extending CKD treatments that QoL issues are being increasingly considered. Patients with CKD have so many other problems that previously the initial priority was survival. But, he confessed, "CKD-aP is still not considered a very important symptom for the doctor. Nowadays, when the nephrology situation is stable [...] and the patient is doing well, only then do other problems arise, and for the patient, pruritus is very important." Prof Legat confirmed this: "pruritus can be much more disturbing and annoying than haemodialysis as it is constant, 24 hours, 7 days per week, often exacerbates at night [...] and significantly interferes with sleep."

Another potential reason for under-recognition of CKD-aP is that because of multifactorial aetiology, assessment and diagnosis take a long time and, more importantly, are not undertaken because there are currently few effective treatments. "Interest is concentrated on a disease where there is a clinical solution," stated Prof Locatelli. Prof Legat, who runs one of the only specialist clinics for chronic pruritus in Austria, discussed how "even in dermatology, patients with chronic pruritus cost you a lot of time." An initial consultation of a patient with chronic CKD-aP can take 30 minutes or more simply to ascertain when the chronic pruritus started, where the problem is located, what the comorbidities are, and which medications the patient is taking.

Compounding the problem of under-recognition is the fact that, according to Prof Locatelli, "dermatologists know that CKD-aP exists but the interaction between nephrologists and dermatologists is not as it should be, possibly because nephrologists realise that dermatologists themselves are usually unable to resolve the problem." Similarly, Prof Legat highlighted that as nephrologists focus only on the kidneys and haemodialysis or internal medicine problems, they are also not able to solve patients' CKD-aP problems. Prof Locatelli, in agreement with

Prof Legat, highlighted that "this situation has to be improved for the sake of patients. The two disciplines have to work more closely together in the clinic and particularly in studies so that we can learn from each other about the internal medicine and dermatology problems and better focus our research efforts on the needs of patients with CKD-aP."

A final factor in under-recognition of CKD-aP is that patients themselves may not be aware that the pruritus they are experiencing is related to their kidney problems.[8] As such, many may not report their symptoms or report them only to their primary care provider.[9] "It would be an important step forward to obtain feedback from these patients and actively ask them about pruritus and QoL," said Prof Legat.

THE IMPACT OF UNRECOGNISED AND UNTREATED CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

Currently, the major problem according to Prof Locatelli is that "we are usually looking at pruritus without the consequences related to it." Not only is CKD-aP in itself sometimes a highly bothersome issue for the patient,[2,7] it is associated with sequalae such as reduced QoL, poor sleep, depression, missed dialysis sessions, and risk of increased mortality.[2,10] This last risk is borne out by the DOPPS data that showed an adjusted associated mortality hazard index of 1.24 for patients with CKD-aP who were extremely bothered by pruritus,[2] which highlights the importance of addressing CKD-aP. "If you know that cardiovascular disease problems give you an associated mortality rate that is 15% higher," postulated Prof Legat, "would you not treat the cardiovascular disease? However, CKD-aP studies show an associated higher mortality yet it is not considered a problem."

A major difficulty with CKD-aP is its impact on sleep. DOPPS study data showed the overall prevalence of poor sleep (≥3 nights/week of restless sleep) was 32.1%, with a strong relationship between increased prevalence and how much a person was bothered by pruritus.[2] "Patients are unable to sleep at night and have restorative sleep," said Prof Locatelli. This is important not only because poor sleep is annoying but also because it is associated with cardiovascular mortality.[11] "If the itch decreases," said Prof Legat, "sleep improves, which has an important effect on how the patient performs overall, in their haemodialysis, and on other comorbidities."

Depression is also not simply an adverse clinical condition related to how bothered someone is by their CKD-aP,[2] but also, according to Prof Locatelli, "a factor associated with survival. If you don't have itch anymore and you sleep well, you feel better, you need fewer antidepressants, fewer other additional medications. This is a very important aspect that we think about [...] as reducing the itch directly improves not only how the patient feels but their health; it is absolutely linked. Unfortunately, at present we do not have effective and well-tolerated treatments."

RECOGNITION OF CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS AS A PROBLEM: PATIENT-RELATED OUTCOME MEASURES

One way to improve recognition of the impact of CKD-aP is to have the patient keep a daily diary of their symptoms, on paper or by using an app, to record details of the itch. A good record, suggested Prof Legat, would note pruritus intensity, how much it bothers a person, and how much it interferes with daily life and sleep. They can, he continued, "record itch on a visual analogue, numeric rating scale, or on a verbal rating scale." The key is to have an understanding of the itch on a daily basis. "If you record repeatedly, you can graph to see if it goes up, down, or is stable."

Additional measures for assessing itch-related QoL include skin-specific tools, including the Dermatology Life Quality Index (DLQI),[12] a validated 10-question measure widely used in clinical practice and investigation; Skindex,[13] which measures the effect of skin disease on QoL; and the 5-D Pruritus Scale, which measures pruritus duration, degree, direction, disability, and distribution.[14] There are also more general QoL measures such as the 36-Item Short Form Health Survey (SF-36) questionnaire.[15]

"It would be good if the nephrology community used the same patient-reported outcome measures," suggested Prof Legat, "so that you

can compare different centres and patients over time." Patients undergoing haemodialysis have several hours available to fill out such questionnaires and Prof Legat suggested that it would be useful "to have a study nurse in every haemodialysis centre so you can obtain additional information on how the patient felt in the last month." However, added Prof Locatelli, while these tools could be relevant, nephrologists, nurses, and patients themselves are frustrated by documenting the disorder without the possibility of improving the clinical situation. "It would be much more rewarding if an efficacious treatment were available," he said.

Both professors discussed that clinical trials also need to have QoL issues as endpoints for treatment success. As an example, Prof Locatelli highlighted how QoL was investigated in trials of erythropoietin in anaemia for people with CKD.

CURRENT TREATMENT FOR CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

The problem for the healthcare professional trying to treat CKD-aP, reported Prof Legat, is that "once you've listened to a patient's problems, you don't have a real solution. You can give them a little bit of relief with our therapeutic armoury but it's very important not to promise too much." Prof Locatelli agreed, saying that "we are very disappointed with the majority of treatments that we've tried to solve CKD-aP [...] some may be useful in the short term, but in the long term it is back at the same intensity as before."

While there are general guidelines for chronic pruritus treatment, such as the S2 Guidelines on Chronic Pruritus and the American Association of Nurse Practitioners (AANP) guidelines,[16,17] there are no specific guidelines for treatment of CKD-aP. There is only one medication approved specifically for CKD-aP, nalfurafine hydrochloride, which activates the κ-opioid receptors that suppress pruritus; however, this is currently only approved in Japan and South Korea.[18]

Antihistamines would usually be the first response to a patient with pruritus but both Profs Legat and Locatelli agreed that these usually do not work for people with CKD-aP. Pruritus may potentially be controlled with dietary modification; improvement of haemodialysis quality; control of phosphorus levels; treatment with vitamin D (if calcium and phosphorus levels are normal); or, for those with high parathyroid hormone, with calciomimetics (in dialysis patients without low calcium levels) or parathyroid gland removal. However, Prof Legat cautioned, in these cases, "CKD-aP may improve for some time, but it comes back again."

Discussing how he would progress through a treatment pathway for a patient with CKD-aP, Prof Legat suggested that xerosis is the first thing that should be addressed and treated. "The basis is always topical treatment with emollients."[1,3] This, he suggested, can include those containing menthol for cooling, and/or polidocanol, a local anaesthetic, both of which can relieve itch to some degree.[17] But, he continued, "if pruritus is severe, this is only a supportive treatment." While for some people with dry skin, keeping hydrated is also a recommendation, the problem with people with CKD, emphasised Prof Locatelli, "is that our patients need to restrict water and salt to avoid hypertension, overhydration, and the risk of pulmonary oedema."

"The third line is gabapentin," detailed Prof Legat, although this is an off-label usage.[1,16] "I have good experience but it is important to start with a very low dose and increase very slowly." This can help to reduce side effects of dizziness and drowsiness. If this does not help, Prof Legat continued, the next step would be a mu-opioid receptor antagonist such as naloxone or naltrexone; again, these are off-label treatments.[1,3,16,17] "You have to use a very low dose or you get problems such as dizziness, drowsiness, vertigo, and bad dreams and you might even have a higher rate of falling." Prof Locatelli emphasised that many patients receiving these treatments complain of such side effects and, because pruritus relief is usually mild, often discontinue the treatment after several weeks.

Prof Legat also mentioned ultraviolet B treatment;[1,3,16] however, although he has had success with it, it is not widely available and, he warned, should not be used on a long-term basis for patients planned for kidney

transplantation as it increases the risk for future nonmelanoma skin cancers with the use of immunosuppressants. Prof Locatelli emphasised that this a critical point, considering the increased frequency of cutaneous neoplasias in transplanted patients.

NEW TREATMENTS FOR CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS

Overall, it was clear from the expert discussion that more clinical trials are needed for CKD-aP-targeting therapies. "We need a drug that has proven effective in clinical trials and been evaluated in real-world conditions to see if this is the right direction," explained Prof Locatelli. Both experts agreed that it is important that these trials are run by, and with input from, both nephrologists and dermatologists.

There are only a handful of drugs currently in clinical studies specifically targeting CKD-aP.[19,20] One such candidate is the κ-opioid receptor agonist, difelikefalin. This is of interest as, according to Prof Legat, "it should penetrate the blood–brain barrier less then nalfurafine so have considerably fewer central nervous system side effects." A recent study showed that difelikefalin administered intravenously three times per week over 12 weeks in patients undergoing haemodialysis led to a significant reduction in itch intensity and improvement of itch-related QoL compared to placebo. While there were some gastrointestinal side effects, these were generally tolerated.[21] As with nalfurafine, Prof Legat pointed out that the advantage of difelikefalin is that it can be administered during haemodialysis. An oral form is also being developed for patients not on haemodialysis or on peritoneal dialysis.

Other molecular targets of consideration are those involved in inflammatory aspects of CKD-aP.[20] For instance, in CKD-aP increased serum IL-31 is correlated with experiencing pruritus.[22] As in clinical trials for atopic dermatitis and prurigo nodularis, the anti-IL-31 receptor blocker nemolizumab has shown significant improvements in pruritus compared to placebo,[23,24] Prof Legat suggested this treatment may also be useful for those with CKD-aP. Additionally, Prof Legat conferred that as the cytokines IL-13 and IL-4 are involved in skin barrier integrity,[25] targeting these may improve CDK-related xerosis.

One key consideration in a clinical trial is which criteria are measured to indicate success. "In studies of biologic drugs for psoriasis, you have to show a drug can reduce pruritus by 4 or more points on a numeric rating scale for itching," said Prof Legat. "In CKD-aP, this is a very high level to reach," however, he continued: "in the difelikefalin study, they showed that even with this high goal, it is possible to obtain a statistically significant result compared to placebo."[21]

This is the start of targeted treatment for CKD-aP, discussed Prof Legat. "We will probably learn about the pathophysiology of CKD-aP from these trials. If one drug succeeds, we have learnt and have something to treat CKD-aP, but if it doesn't succeed, we have also learnt that probably this is not a very important aetiological factor. Thus, besides augmenting basic research into CKD-aP and itch in general, the trial-and-error approach with every bench-to-bedside clinical study will also further improve our understanding of CKD-aP pathophysiology and hopefully find treatments that will help our patients with CKD-aP."

CONCLUSION

From the discussion with Profs Legat and Locatelli it is clear that chronic pruritus is a problem for many patients with advanced CKD. While for some it is mildly bothersome, for others CKD-aP has a major impact on not only QoL but also overall health. Accordingly, CKD-aP should be assessed and acknowledged in all people with advanced CKD, whether or not they are receiving dialysis. Careful diagnosis to ascertain the cause, including recording of symptoms, can help guide how CKD-aP can be most effectively treated for each patient. Although current treatments may not completely alleviate CKD-aP, there is hope as new treatments are in development.

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