CKD-ASSOCIATED PRURITUS

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Divisions of Nephrology and Palliative Medicine
DISCLOSURES

• Cara Therapeutics Nephrology Advisory Board
OBJECTIVES

• Describe CKD-associated pruritus (CKD-aP)

• Review current available treatments and data supporting them

• Present new treatments for CKD-aP in the pipeline

• Summarize an approach to therapy
CASE: MR. MARTINEZ

• Mr. Martinez is a 49-year-old man with ESRD on in-center HD for 9 years. He finds you in nephrology clinic one day and tells you he’s in crisis because he can’t stop itching. He’s driving his wife crazy because he can’t sleep and is constantly scratching himself. The itching is so bad that he is unable to sit through an entire 4-hour dialysis session.

• He looks at you with a serious face and tells you that things are so bad that he is considering “giving up.”

• What is your approach to this patient?
Symptom Prevalence: ESRD on dialysis and conservative management


Brennan, *Progress Pall Care* 2015.
CKD-aP

- Also known as uremic pruritus
- Common (30-70% of patients)
- Associated with decreased quality of life and worsening symptoms of depression
- Independently associated with increased mortality
- Amplifies other symptoms that impair quality of life
  - e.g., poor sleep
- Research into treatment strategies for pruritus is a high priority for patients

Weisborg, CJASN 2007; Weissshar, NDT 2009; Manns, CJASN 2014; Mettang, KI 2014.
International Comparisons of Prevalence, Awareness and Treatment of Pruritus in People on Hemodialysis

**METHODS**
Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) Between 2012 and 2015

**OUTCOMES**
- 18% of patients were very much or extremely bothered by itchy skin.
- 69% of medical directors underestimated the prevalence of pruritus in their facility.
- Among patients nearly always or always bothered by itching, 18% used no treatment for pruritus.

**CONCLUSION**
Many patients' lives could be improved by increased awareness and treatment of CKD-associated pruritus.

PREVALENCE OF MODERATE-TO-SEVERE CKD-aP IN HEMODIALYSIS PATIENTS

Dialysis Outcomes and Practice Patterns Study (DOPPS), 2012-2015

Rayner, CJASN 2017.

GCC = Gulf Cooperation Council; ANZ = Australia and New Zealand
ANATOMICAL DISTRIBUTION OF CKD-aP

- Severe itching typically bilateral, symmetrical, persistent, and generalized
- Back, abdomen, arms, and legs
CKD-aP

Scratch marks with excoriations

Hyperkeratotic partly excoriated nodules (prurigo nodularis)

Deep scars and prurigo nodules

NON-UREMIC CAUSES OF ITCH

Primary Dermatologic Conditions
- Drug-induced hypersensitivity and other allergies
- Contact dermatitis
- Psoriasis
- Dermatophytosis (tinea cruris, tinea pedis, tinea corporis)
- Bullous pemphigoid
- Infestations
  - Bed bugs
  - Scabies
  - Lice

Systemic Conditions
- Cholestasis
- Viral hepatitis
- Primary biliary cirrhosis
- Hematologic malignancy
- Hodgkin’s lymphoma
- Cutaneous T-cell lymphoma
- Polycythemia vera
- Post-herpetic neuralgia
- HIV
<table>
<thead>
<tr>
<th>Pathogenetic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism (elevated PTH, Phos, Ca)</td>
</tr>
<tr>
<td>Histaminergic reaction</td>
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<tr>
<td>Structural Skin Alterations</td>
</tr>
<tr>
<td>Systematic Inflammation</td>
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<tr>
<td>Alterations in nociceptive sensory pathways</td>
</tr>
<tr>
<td>Opioid Receptor Dysfunction</td>
</tr>
</tbody>
</table>
CKD-aP: PATHOGENESIS

Hyperparathyroidism (elevated PTH, Phos, Ca)
Histaminergic reaction
Structural Skin Alterations
Systematic Inflammation
Alterations in nociceptive sensory pathways
Opioid Receptor Dysfunction
CKD-aP: Pathogenesis

Hyperparathyroidism
(elevated PTH, Phos, Ca)

Histaminergic reaction

MBD parameters are *not* associated with pruritus in the highest quality observational data available

Optimal “goals” for treating phosphorous or PTH in patients with pruritus are unknown

Antihistamines are not effective

Antihistamines are sedating

Antihistamines have anticholinergic side effects
CKD-aP: PATHOGENESIS

Hyperparathyroidism (elevated PTH, Phos, Ca)

Histaminergic reaction

Antihistamines are not effective
Antihistamines are sedating
Antihistamines have anticholinergic side effects

MBD parameters are not associated with pruritus in the highest quality observational data available

Optimal "goals" for treating phosphorous or PTH in patients with pruritus are unknown.
Xerosis (dry skin)
• Xerosis prevalent in patients with CKD
• Emollients are successful in some patients, but not all
• Role of structural skin changes in pruritus unclear

Systemic Inflammation
• Increased inflammatory markers and decreased albumin associated with worse pruritic symptoms
• Transplant patients have decreased prevalence of pruritus as graft failure occurs compared to non-transplant CKD patients
# Adjusted Odds of Being Affected by Moderate-to-Extremely Itchy Skin

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Adjusted Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.06 [1.02-1.10]</td>
</tr>
<tr>
<td>Hepatitis B/C</td>
<td>1.26 [1.06-1.50]</td>
</tr>
<tr>
<td>Albumin &gt;4</td>
<td>0.87 [0.80-0.95]</td>
</tr>
<tr>
<td>Albumin &lt;3.5</td>
<td>1.14 [1.04-1.25]</td>
</tr>
<tr>
<td>CRP 10 – 15</td>
<td>1.39 [1.06-1.83]</td>
</tr>
<tr>
<td>CRP 15 or higher</td>
<td>1.31 [1.05-1.64]</td>
</tr>
<tr>
<td>Phosphorus 5.5 - &lt;6.7</td>
<td>1.01 [0.91-1.13]</td>
</tr>
<tr>
<td>Phosphorus ≥ 6.7</td>
<td>1.07 [0.95-1.21]</td>
</tr>
</tbody>
</table>

**no association was observed with serum phosphorus, calcium, calcium-phosphorus product, PTH, or Kt/V.**

Rayner, CJASN 2017.
CKD-aP: PATHOGENESIS

Nociceptive sensory pathway alterations
• Symmetric pattern; “burning, tingling” description of pruritus
• Success with gabapentinoids

Opioid receptor dysfunction
• mu receptor agonists cause pruritus
• Success with opioid modulators in treating uremic pruritus
Brain

Skin

Itch Signal

Pain Signal

Cutaneous Itch Input

Cutaneous Pain Input

Descending Inhibitory Pathways

Substance P

Spinal Cord

mu receptor

kappa receptor
TREATMENT

KDIGO
Treatment of Uremic Pruritus: A Systematic Review

Elizabeth Simonsen, BSc,1 Paul Komenda, MD, MHA,1,2,3,4 Blake Lerner, BSc,1 Nicole Askin, MLIS,5 Clara Bohm, MD,1,2,3 James Shaw, MD,1,2 Navdeep Tangri, MD, PhD,1,2,3,4 and Claudio Rigatto, MD, MSc1,2,3,4

AJKD 2017
# Treatment Regimens Evaluated

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Topical</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Mast cell stabilizers</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Emollients</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
<td>Tacrolimus</td>
<td>Dialysis Modification</td>
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<tr>
<td>Montelukast</td>
<td>Capsaicin</td>
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<tr>
<td>Nalfurafine</td>
<td>Sarna</td>
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<tr>
<td>Naltrexone</td>
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<td>Primrose Oil</td>
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<td>Thalidomide</td>
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<td>Cholestyramine</td>
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<tr>
<td>Ondansetron</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
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<tr>
<td>Foroutan (2017)</td>
<td>IR</td>
<td>Parallel arm</td>
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<tr>
<td>Amirkhanlou (2016)</td>
<td>IR</td>
<td>Parallel arm</td>
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<tr>
<td>Nofal (2016)</td>
<td>EG</td>
<td>Parallel arm</td>
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<tr>
<td>Yue (2015)</td>
<td>CN</td>
<td>Parallel arm</td>
</tr>
<tr>
<td>Solak (2012)</td>
<td>TR</td>
<td>Crossover</td>
</tr>
<tr>
<td>Tol (2010)</td>
<td>TR</td>
<td>Crossover</td>
</tr>
<tr>
<td>Wu (2010)</td>
<td>CN</td>
<td>Parallel arm</td>
</tr>
<tr>
<td>Naini (2007)</td>
<td>IR</td>
<td>Parallel arm</td>
</tr>
</tbody>
</table>

Simonsen, AJKD 2017.
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Dose and Duration</th>
<th>Comparator Dose and Duration</th>
<th>Pruritus Measurement</th>
<th>Outcome Measurement</th>
<th>Results</th>
<th>Statistically Significant Difference Between Treatments?</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forouzan et al. (2017)</td>
<td>Gabapentin 50 mg 3×/wk post-HD (titrated up to 50 mg 1×/d) for 4 wk</td>
<td>Dextromethorphan 10 mg 2×/d for 4 wk</td>
<td>Mean VAS scores at BL &amp; post</td>
<td>Gabapentin: 7.5 ± 1.2 BL</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence (16.2%), edema (8.1%), drowsiness (6.1%), imbalance (8.2%)</td>
<td></td>
</tr>
<tr>
<td>Aminian et al. (2016)</td>
<td>Gabapentin 100 mg 1×/d for 2 wk</td>
<td>Ketotifen 1 mg 2×/d for 2 wk</td>
<td>% Responders</td>
<td>Gabapentin: 88.4%; ketotifen: 76.9%</td>
<td>No</td>
<td>Gabapentin: drowsiness (15.4%), dizziness (3.8%), ketotifen: drowsiness (15.4%), dizziness (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Neve et al. (2016)</td>
<td>Gabapentin 100 mg 1×/d for 2 wk</td>
<td>Placebo 3×/wk post-HD for 1 mo</td>
<td>10-cm VAS, 5-D pruritus scale</td>
<td>Gabapentin: 88.8%</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence (11.5%), fatigue (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Yasuda et al. (2015)</td>
<td>Gabapentin 75 mg 2×/wk for 6 wk</td>
<td>Placebo 0.5 mg 1×/d</td>
<td>10-cm VAS, 5-D pruritus scale</td>
<td>Gabapentin: 77.9%</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence (4.3%), dizziness (1.5%), loss of balance (1.5%), constipation (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Solak et al. (2012)</td>
<td>Gabapentin 300 mg 3×/wk post-HD for 6 wk</td>
<td>Placebo for 6 wk</td>
<td>10-cm VAS, 5-D pruritus scale</td>
<td>Gabapentin: 7.5 ± 1.4 BL</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence (11.1%), weakness (11.1%)</td>
<td></td>
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<tr>
<td>Tsai et al. (2010)</td>
<td>Gabapentin 300 mg 3×/wk post-HD for 6 wk</td>
<td>Placebo for 8 wk</td>
<td>10-cm VAS</td>
<td>Gabapentin: 7.5 ± 1.4 post</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al. (2010)</td>
<td>Gabapentin 100 mg 1×/d for 2 wk</td>
<td>Standard treatment</td>
<td>% of patients with symptom improvement</td>
<td>Gabapentin: 89%; control: 25%</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: dizziness (16.6%), drowsiness (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Naini et al. (2007)</td>
<td>Gabapentin 400 mg 2×/wk post-HD for 4 wk</td>
<td>Placebo 2×/wk for 10-cm VAS</td>
<td>Mean decrease from BL VAS</td>
<td>Gabapentin: 6.7 ± 2.6; placebo 1.5 ± 1.8</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence, dizziness, &amp; nausea (subsidized after 5-10 d)</td>
<td></td>
</tr>
<tr>
<td>Gunai et al. (2004)</td>
<td>Gabapentin 300 mg 3×/wk post-HD for 4 wk</td>
<td>Placebo 3×/wk post-HD for 4 wk</td>
<td>Mean VAS scores at BL &amp; post</td>
<td>Gabapentin: 8.4 ± 0.94; placebo: 7.6 ± 2.6 post</td>
<td>Yes, in favor of gabapentin</td>
<td>Gabapentin: somnolence, dizziness, fatigue (subsidized after 7 d)</td>
<td></td>
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</tbody>
</table>

Simonsen, AJKD 2017.
With the exception of gabapentin, the current evidence for the available treatments of uremic pruritus is weak.

“Despite many published studies, the combination of flawed methodology, high risk of bias, small sample size, and study heterogeneity prevent generation of robust treatment guidelines”

“High-quality studies are urgently needed to bridge this major gap between research output and identified patient priorities”
Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care


“Current evidence is sufficient to support the development of clinical guidelines to aid in the stepwise approach to uremic pruritus, sleep disturbances, restless legs, pain, and depression in CKD”
GABAPENTINOIDS: ARE WE OVERPRESCRIBING?

Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern?

Christopher W. Goodman, M.D., and Allan S. Brett, M.D.

Treatment of chronic noncancer pain during the opioid epidemic has become challenging. Gabapentinoids for the treatment of postherpetic neuralgia (gabapentin and pregabalin) fibromyalgia.

N ENGL J MED 377;5 NEJM.ORG AUGUST 3, 2017

Abuse and Misuse of Pregabalin and Gabapentin

Kirk E. Evey1,2 · Megan D. Morrison1 · Stephen R. Saklad1

Doctors sound the alarm on "opioid alternative" gabapentin

CBS/AP · April 2, 2018, 12:58 PM
NEW CONCERNS WITH GABAPENTINOIDS

• In setting of opioid crisis, doctors are looking for alternatives
• In 2016, gabapentin was the 10th most prescribed medication in the US
• 64 million prescriptions dispensed (up from 39 million in 2012)
• In 2016, pregabalin ranked 8th in drug spending in the US

INCREASED MISUSE AND ABUSE OF GABAPENTINOIDS

• Increasing numbers of patients are taking higher-than-recommended amounts to achieve euphoric highs
• 1.6% prevalence of gabapentinoid abuse in general population
• 3-68% prevalence of gabapentinoid abuse among opioid abusers
• Risk factors for abuse
  • Substance abuse (opioids), psychiatric comorbidities
• Gabapentinoids are increasingly being identified in post-mortem toxicology analyses
Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients

METHODS

National cohort study of US hemodialysis patients
n=140,899

USRDS

UNITED STATES RENAL DATA SYSTEM

19% and 4% used gabapentin and pregabalin, respectively, in 2011

OUTCOME: Adjusted Hazard Ratio (95% CI)

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Altered mental status</th>
<th>Fall</th>
<th>Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0-100 mg</td>
<td>1.10 (1.07-1.24)</td>
<td>1.26 (1.07-1.48)</td>
<td>1.04 (0.82-1.32)</td>
</tr>
<tr>
<td>&gt;100-200 mg</td>
<td>1.31 (1.17-1.46)</td>
<td>1.35 (1.15-1.57)</td>
<td>1.20 (0.96-1.49)</td>
</tr>
<tr>
<td>&gt;200-300 mg</td>
<td>1.41 (1.30-1.54)</td>
<td>1.30 (1.14-1.48)</td>
<td>1.08 (0.89-1.31)</td>
</tr>
<tr>
<td>&gt;300 mg</td>
<td>1.50 (1.39-1.63)</td>
<td>1.55 (1.39-1.72)</td>
<td>1.38 (1.18-1.61)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0-100 mg</td>
<td>1.51 (1.32-1.74)</td>
<td>1.24 (1.00-1.54)</td>
<td>1.20 (0.87-1.66)</td>
</tr>
<tr>
<td>&gt;100 mg</td>
<td>1.46 (1.24-1.71)</td>
<td>1.68 (1.36-2.08)</td>
<td>1.38 (1.00-1.92)</td>
</tr>
</tbody>
</table>

*Compared to reference of no use.

CONCLUSION Gabapentin and pregabalin should be used judiciously in patients on hemodialysis, and research to identify the most optimal dosing is warranted.

doi: 10.1681/ASN.2018010096
GABAPENTIN/PREGABALIN: RECOMMENDATIONS

• Caution patients about risks of gabapentinoids; perhaps avoid in very frail patients at high risk of falls

• Important to dose gabapentinoids appropriately for renal function

• Caution patients about risks of using gabapentin in ways other than prescribed
  • Many patients taking “prn”

• Be cautious about prescribing to patients at high risk for abuse and/or who are prescribed opiates or benzodiazepines
## Gabapentinoids: Dosing in Renal Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>100-300 mg PO thrice weekly after HD; 100-300 mg PO qHS in PD†; 100 mg PO every other night to 300 mg PO qHS in CKD5-CKM</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>25-75 mg PO thrice weekly after HD; 25-75 mg PO qHS in PD†; 25 mg every other night to 75 mg qHS in CKD5-CKM</td>
</tr>
</tbody>
</table>
## Emerging Treatment Options for CKD-aP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Current Status</th>
<th>Efficacy</th>
<th>Most Common AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nalfurafine</strong></td>
<td>Approved in Japan and Korea for the improvement of pruritus in hemodialysis patients</td>
<td>Significant decreases in VAS scores with oral nalfurafine vs placebo administered for 14 days</td>
<td>Insomnia, constipation, somnolence, dizziness, and nausea</td>
</tr>
<tr>
<td>Selective κ-opioid receptor agonist(^1)</td>
<td></td>
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<tr>
<td><strong>Difelikefalin</strong></td>
<td>Phase III for use in moderate to severe pruritus in patients undergoing hemodialysis</td>
<td>Significant reductions in itch intensity and improvements in QOL with difelikefalin IV vs placebo for 12 weeks</td>
<td>Diarrhea, dizziness, and nausea</td>
</tr>
<tr>
<td>Selective, peripherally restricted, κ-opioid receptor agonist(^3)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
CR845 Effects Mediated by Peripheral κ-Opioid Receptors

Novel Chemical Class – "hydrophilic" tetrapeptide

KOR in the brain: dysphoria and hallucinations

CR845 acts at KOR on:

- Immune cells: anti-inflammatory
- DRG: anti-nociceptive
- Sensory nerves: anti-nociceptive and anti-pruritic

DRG=dorsal root ganglion
**Phase 3 Study Design**

**Screen**

1-1 Randomization

- **KORSUVA 0.5 mcg/kg after each hemodialysis session**
- **Placebo after each hemodialysis session**

**Endpoints: Week 12**

**Primary**
- Proportion of subjects achieving ≥3 point improvement from baseline in weekly mean of daily worst itching intensity NRS (WI-NRS)

**Secondary**
- Proportion of subjects achieving ≥4 point improvement from baseline in weekly mean of daily WI-NRS
- Change from baseline in itch-related Quality of Life as measured by 5-D Itch and Skindex-10 questionnaires

52 Week Open-Label Extension Ongoing
**Improvement in Worst Itch-NRS (Week 12)**

- **KORSUVA subjects >2.5 times more likely to experience ≥3-point improvement**
  - KORSUVA (N = 189)
  - Placebo (N = 189)
  - Odds Ratio: 2.72
  - P = .000019

- **KORSUVA subjects ~3 times more likely to experience ≥4-point improvement**
  - KORSUVA (N = 189)
  - Placebo (N = 189)
  - Odds Ratio: 2.9
  - P = .000032

Estimated percentages & P-values based on a logistic regression model with terms for treatment group, baseline WI-NRS score, and strata. Missing data imputed using multiple imputation (MI) under missing at random (MAR) assumption.
## SUMMARY OF SAFETY

<table>
<thead>
<tr>
<th>Treatment-emergent Adverse Events</th>
<th>Placebo N = 188 n (%)</th>
<th>KORSUVA N = 189 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one treatment-emergent adverse event</td>
<td>117 (62)</td>
<td>130 (69)</td>
</tr>
<tr>
<td>Subjects with at least one serious treatment-emergent adverse event</td>
<td>41 (22)</td>
<td>49 (26)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Non-fatal SAEs</td>
<td>39 (21)</td>
<td>47 (25)</td>
</tr>
<tr>
<td>Treatment-emergent adverse events resulting in discontinuation</td>
<td>9 (4.8)</td>
<td>14 (7.4)</td>
</tr>
</tbody>
</table>

*Most common AEs (≥ 5%) included diarrhea, dizziness, vomiting, nasopharyngitis*
CASE: MR. MARTINEZ

- Mr. Martinez is a 49-year-old man with ESRD on in-center HD for 9 years. He finds you in nephrology clinic one day and tells you he’s in crisis because he can’t stop itching. He’s driving his wife crazy because he can’t sleep and is constantly scratching himself. The itching is so bad that he is unable to sit through an entire 4-hour dialysis session.

- He looks at you with a serious face and tells you that things are so bad that he is considering “giving up.”

- What is your approach to this patient?
History of Pruritus:
- Duration
- Distribution - generalized versus localized, symmetric versus asymmetric
- Exacerbating/ameliorating factors
- Allergy and drug history

Physical Examination:
- Presence of scratch marks
- Rash or skin lesions consistent with dermatologic conditions other than UP
- Signs/systems of other systemic disease (e.g., liver disease)

Non-uremic causes of pruritus
- Treat specific skin condition and/or underlying systemic cause of pruritus

Uremic Pruritus
- Skin Care and Education:
  - Apply emollients two to four times daily, especially after bathing, especially if xerosis present
  - Encourage use of non-drying soap
  - Keep nails short and clean
  - Avoidance of scratching
- Topical Agents:
  - Given minimal risk of toxicity, use prior to systemic therapies
  - e.g., capsaicin (for localized pruritus), pramoxine, gamma-linolenic acid

Dialysis Adequacy (Kt/V)
- If Kt/V < 1.4 or missing treatments, optimize dialysis adequacy
- Consider trial of daily hemodialysis for interested patients

Systemic Medications: gabapentinoids
- Initiate gabapentin at lowest appropriate dose and titrate according to efficacy and side effects
- Good choice for UP concurrent with RLS and/or diabetic neuropathy
- Consider pregabalin if lack of efficacy with or intolerance to gabapentin

Other interventions to consider:
- Kappa-opioid agonists (where available)
- Acupuncture (for interested patients)
- UVB phototherapy
CONCLUSIONS

• CKD-aP is common; prevalence may be slowly decreasing over time
• Symptom severity varies by country
• Generally under-recognized and under-treated
• Some of the most used treatments lack data and are not recommended (i.e., anti-histamines)
• Gabapentin (+/- pregabalin) has the best evidence for efficacy
• Increased concern regarding abuse or misuse of gabapentinoids
• Gabapentinoid use in ESRD associated with increased hazard for AMS, falls, and fracture; the risk appears to dose-dependent
• Phase II/III trials of opioid modulators appear promising
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