Modulation of the Mu and Kappa Opioid Axis for the Treatment of Chronic Pruritus

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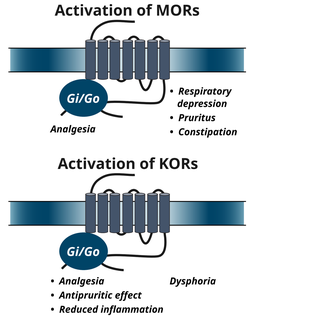
Introduction

- Conditions such as uremic pruritus (UP) and prurigo nodularis are characterized by chronic pruritus, which negatively impacts quality of life (QoL), sleep, and mood[1-7]
- Opioid receptors and their endogenous ligands are involved in the regulation of itch, with activation of mu (μ) opioid receptors (MORs) causing itchy skin and activation of kappa (κ) opioid receptors (KORs) reducing itch (**Figure 1**)[8-10]
  - Unlike MOR agonists, MOR antagonists and KOR agonists are not associated with addictive potential[11-13]
- Imbalances in the MOR and KOR systems in the skin or central nervous system are thought to contribute to the pathophysiology of severe chronic pruritus[14-18]
- Accordingly, targeting MORs and KORs represents an active area of research for novel treatments[14,16]

Figure 1. Different Consequences of Activation of MORs and KORs[8,10]



Gi/Go, Gi/Go protein; KOR, kappa (κ) opioid receptor; MOR, mu (μ) opioid receptor.

Objective

- To provide a narrative overview of studies supporting opioid receptor agonists and/or antagonists in chronic pruritus

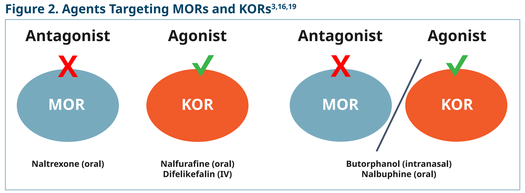
Methods

- The PubMed database was searched to identify English-language literature on the role of opioid receptor agonists and/or antagonists in chronic pruritus in the past decade
  - Search terms included (*pruritus OR itch*), *opioid*, (*kappa OR mu*), and (*agonist OR antagonist*)
  - Select references cited within identified publications were noted as well
- Findings from relevant publications were summarized as a narrative review

Results

- In the United States, opioid receptor–targeting agents have been used off-label to treat chronic itch[19]
- Several agents that target MORs and KORs are being used off-label or are in clinical development for the treatment of chronic itch associated with various disease states (**Figure 2**)

Figure 2. Agents Targeting MORs and KORs[3,16,19]



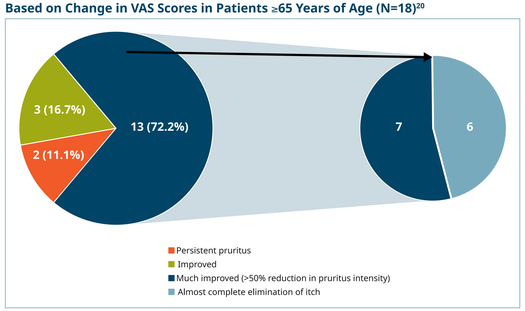
IV, intravenous; KOR, kappa (κ) opioid receptor; MOR, mu (μ) opioid receptor.

MOR Antagonist

Naltrexone

- An observational study (N=18) of the MOR antagonist naltrexone (50 mg/d), used off-label for the treatment of severe itch of varying etiologies, including prurigo nodularis, demonstrated efficacy based on change in visual analog scale (VAS) scores (**Figure 3**)[20]
  - 16 patients (88.9%) experienced symptomatic improvement
  - 5 patients (27.8%) reported adverse events (AEs), including insomnia, fatigue, constipation, and anorexia

Figure 3. Effects of MOR Antagonist Naltrexone on Pruritus (Varying Etiologies) Based on Change in VAS Scores in Patients ≥65 Years of Age (N=18)[20]



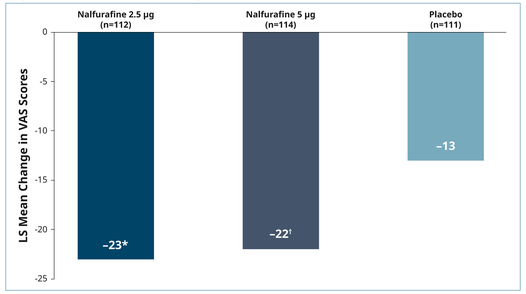
MOR, mu (μ) opioid receptor; VAS, visual analog scale.

KOR Agonists

Nalfurafine

- Nalfurafine is a KOR agonist approved in Japan for the treatment of UP[3]
  - A phase 3, randomized, placebo-controlled, double-blind study of oral nalfurafine (2.5 μg, 5 μg) in hemodialysis patients with UP (N=337) demonstrated significant differences vs placebo on the primary endpoint of VAS scores (**Figure 4**)[21]
  - The most frequent AE was insomnia

Figure 4. Change in VAS Scores From Baseline (Preobservation Period) to Last 7 Days of Treatment With KOR Agonist Nalfurafine vs Placebo for Uremic Pruritus[21]



KOR, kappa (κ) opioid receptor; LS, least squares; VAS, visual analog scale.
*P=0.0001 vs placebo. †P=0.0002 vs placebo.

Difelikefalin

- Two randomized, double-blind, placebo-controlled trials evaluated the peripherally acting KOR agonist difelikefalin in hemodialysis patients with moderate-to-severe UP[22,23]
  - Phase 2 study (NCT02858726): In 174 patients with UP randomly assigned to receive IV difelikefalin 0.5, 1.0, or 1.5 μg/kg or placebo 3 times a week, difelikefalin (all doses combined) significantly reduced itch intensity (Worst Itching Intensity Numeric Rating Scale [WI-NRS]) scores from baseline to week 8 compared with placebo (primary outcome; P=0.002)[22]
  - Phase 3 study (NCT03422653): Compared with placebo, a significantly greater proportion of patients treated with IV difelikefalin 0.5 μg/kg 3 times a week achieved the primary endpoint of ≥3-point improvement in WI-NRS scores from baseline to week 12[23]
  - Itch-related QoL was improved in both trials, and the most common AEs were diarrhea, dizziness, and nausea/vomiting, with most being mild or moderate

Combination MOR Antagonists/KOR Agonists

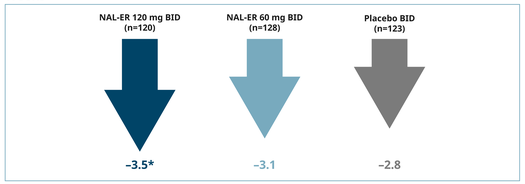
Butorphanol

- A case series (N=16) demonstrated efficacy of intranasal MOR antagonist/KOR agonist butorphanol (10 mg/mL as needed up to every 4 hours) used off-label for the treatment of chronic refractory pruritus[24]
  - Most patients (13/16; 81.3%) improved on the basis of WI-NRS scores and/or patient reports, with a ≥4-point decrease in itch scores among 6 patients (1 patient had no improvement, and 2 were lost to follow-up)
  - Significant improvements on measures of QoL (Dermatology Life Quality Index, Skindex-10 survey) and depressive symptoms (Beck Depression Inventory) were observed
  - 3 patients reported AEs (insomnia, lightheadedness, lethargy)

Nalbuphine

- A phase 2/3, randomized, placebo-controlled, double-blind study (NCT02143648) included 373 hemodialysis patients with moderate-to-severe UP; 120/373 received the oral MOR antagonist/KOR agonist nalbuphine (NAL) 120 mg (dose based on molecular weight, including active drug and salts) extended-release (NAL-ER) tablets twice daily (BID) and demonstrated significant and durable itch-intensity reductions (primary endpoint) vs placebo (**Figure 5**)[25]
  - In a patient subgroup with severe UP (n=179), sleep disruption attributed to itching improved significantly vs placebo (P=0.006)
  - The most common reason for discontinuing treatment was gastrointestinal side effects (eg, nausea, vomiting) during titration

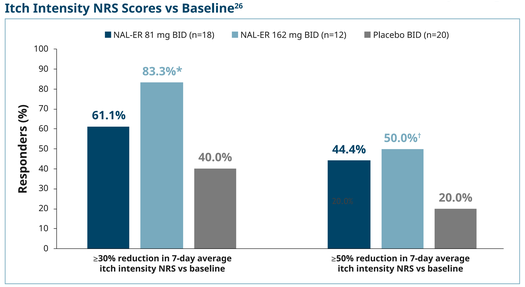
Figure 5. MOR Antagonist/KOR Agonist Nalbuphine in Uremic Pruritus: Change in Worse Itching Intensity (WI-NRS Scores) From Baseline to Last 2 Treatment Weeks[25]



BID, twice daily; NAL-ER, nalbuphine extended-release; WI-NRS, Worst Itching Intensity Numeric Rating Scale.
*P=0.017 vs placebo.

- A phase 2, randomized, double-blind, placebo-controlled trial and open-label extension (NCT02174419) evaluated NAL-ER in patients with moderate-to-severe prurigo nodularis[26]
  - In the modified intent-to-treat population, the proportion of patients with ≥30% response for WI-NRS scores at week 10 was numerically greater with NAL-ER 162 mg BID (44.4%) than with NAL-ER 81 mg BID (27.3%) or placebo (36.4%), although the differences were not statistically significant
  - Patients who received NAL-ER 162 mg BID and completed 10 weeks of double-blind treatment had significant improvements in pruritus symptoms (≥30% and ≥50% reductions in 7-day average itch intensity NRS scores; **Figure 6**), itch-related QoL (P=0.022), and healing of skin lesions
  - Most patients who completed 26 and 50 weeks of open-label treatment experienced improvement in excoriation/crusting and/or healing of skin lesions
  - During the double-blind study, AEs consisted of nausea and dizziness (38.9%, n=7 each) and headache (27.8%, n=5); most AEs were mild or moderate and occurred during titration

Figure 6. MOR Antagonist/KOR Agonist Nalbuphine in Prurigo Nodularis: Proportion of Study Completers With ≥30% and ≥50% Reduction in 7-Day Average Itch Intensity NRS Scores vs Baseline[26]



BID, twice daily; KOR, kappa (κ) opioid receptor; MOR, mu (μ) opioid receptor; NAL-ER, nalbuphine extended-release; NRS, Numeric Rating Scale.
*P=0.008 vs placebo. †P=0.028 vs placebo.

Conclusions

- These data suggest that agents that modulate underlying neurologic components of pruritus through μ-antagonism and/or κ-agonism are effective and safe options for the treatment of chronic pruritus
- These agents have low abuse potential and generally appear well tolerated, with the most commonly reported AEs being insomnia and gastrointestinal effects

Disclosures

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors.

Dr. Elmariah has received honoraria or consulting fees for her participation as an advisory board member, scientific advisor and/or consultant for Trevi Therapeutics, Menlo Therapeutics, RAPT Therapeutics and Sanofi Pharmaceuticals. She is also an investigator for the PRISM trial by Trevi Therapeutics.

Dr. Chisolm has received research and/or consulting support from companies including Trevi Therapeutics, Menlo Therapeutics, Abbvie, Janssen Pharmaceuticals, Kiniksa Pharmaceuticals, and Pfizer. ITCH-E has received support from Sanofi Pharmaceuticals, Pfizer, and Genentech.

Dr. Sciascia is an employee of Trevi Therapeutics and may own stock or stock options.

Dr. Kwatra is an advisory board member/consultant for Abbvie, Galderma, Incyte Corporation, Pfizer Inc., Regeneron Pharmaceuticals, and Kiniksa Pharmaceuticals and has received grant funding from Galderma, Pfizer Inc. and Kiniksa Pharmaceuticals.

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