REVIEW

Mirogabalin and emerging therapies for diabetic neuropathy

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Abstract: There are currently no approved disease-modifying therapies for diabetic neuropathy, and there are only 3 US Food and Drug Administration-approved therapies (pregabalin, duloxetine, and tapentadol) for painful diabetic neuropathy. They each have moderate efficacy with adverse effects limiting optimal dose titration. There is a considerable need for new therapies for the management of painful diabetic neuropathy. We reviewed the potential role of mirogabalin, which like gabapentin and pregabalin modulates the alpha-2/delta-1 subunit of the voltage-gated calcium channel, allowing the influx of calcium and release of neurotransmitters at the synaptic cleft in the central nervous system and spinal cord. It has shown efficacy and good tolerability in a Phase II study in diabetic painful neuropathy and based on the results of two Phase III clinical trials in diabetic painful neuropathy and post-herpetic neuralgia, Daiichi Sankyo submitted a marketing application for neuropathic pain in Japan in February 2018. We have also reviewed potential new therapies, currently in Phase II clinical trials that may modify disease and/or relieve neuropathic pain through novel modes of action.

Keywords: diabetic neuropathy, painful diabetic neuropathy, treatment, mirogabalin

Introduction

Diabetic peripheral neuropathy (DPN) is among the most frequently encountered long-term complications of diabetes and has a prevalence of at least 50%.[1,2] It is characterized by small and large fiber dysfunction and damage as a consequence of metabolic and vascular risk factors. DPN remains an unmet need for both patients and physicians and is a primary driver of physical and psychological comorbidity. Indeed, both quality of life and economic burden associated with DPN are significant and moreover, it is strongly associated with mortality.[3–5] Several phenotypic variants of diabetic neuropathy have been recognized, but the most common is distal symmetrical polyneuropathy, an ascending neuropathy occurring in a glove and stocking distribution accounting for ~75% of diabetic neuropathies.[6] The symptoms in DPN are often related to small nerve fiber dysfunction and manifest as pain and dysesthesia, classically described as an unpleasant "burning", "shooting", "prickly", and "excruciating" pain, typical of neuropathic pain.[7,8] Painful DPN is particularly difficult to manage and although a number of agents are available, optimal pain control is inadequate.[5,9]

Current therapies

There are no FDA-approved disease-modifying therapies for DPN. Optimizing glycemic control remains the most broadly accepted approach to prevent the progression

of neuropathy with moderate benefit in patients with Type 1 diabetes,[10] but with limited benefit in Type 2 diabetes.[11] Simultaneous pancreas and kidney transplantation restores normoglycemia and renal function and may reverse DPN.[12]

Controlling pain in diabetic neuropathy

Neuropathic pain is a debilitating feature of DPN resulting in significant morbidity.[5,13] Although tight glycemic control may prevent the progression of diabetic neuropathy, there is a paucity of data suggesting that improved glycemic control improves pain in DPN.[14] Moderate improvements in pain are considered to be ~30%–50% pain relief, whereas >50% pain relief is considered a good outcome.[15] Unfortunately, painful DPN responds poorly to conventional analgesics, but tend to be frequently used especially in primary care settings.[16] Guidelines do not recommend nonsteroidal anti-inflammatories due to their lack of efficacy and propensity to deteriorate renal function.[9] Currently, five professional organizations have produced expert guidance on the management of painful diabetic neuropathy.[8,17–21] Medications recommended include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or γ-aminobutyric acid (GABA) analogs (gabapentin or pregabalin) as first-line agents followed by opioids and topical treatments. The only two medications with both FDA and European Medicines Agency (EMA) approval for the treatment of painful DPN are pregabalin and duloxetine. Recently, the COMBO-DN study has shown the effectiveness of a combination of duloxetine and pregabalin in painful DPN.[22]

Tricyclic antidepressants

Developed initially for depression, TCAs are commonly used as analgesics for neuropathic pain in contemporary clinical practice. The exact mechanism promoting analgesia in painful DPN is still not precisely known, but they are known to act through a number of pathways, with antagonistic actions at the N-methyl-D-aspartate, 5-HT, histamine, muscarinic, and α-adrenergic receptors while also blocking the reuptake of noradrenaline and serotonin from synaptic clefts[23] as well as indirect modulation of the opioid system in the brain.[24–26] The use of TCAs is limited by their adverse effect profile.[27]

Serotonin-norepinephrine reuptake inhibitors

The SNRIs exert their analgesic effects by altering the balance of neurotransmitters centrally and through stimulation of descending inhibitory pathways by selectively antagonizing the effects of both serotonin and norepinephrine.[28]

Duloxetine was the first agent to be approved by the FDA for the treatment of diabetic painful neuropathy based on data from several large randomized controlled trials.[29–33] Goldstein et al demonstrated that doses of 60 and 120 mg of duloxetine were associated with an improvement in average daily pain scores in a randomized, placebo-controlled trial in 457 patients.[31] More recently, Lunn et al conducted a Cochrane review, analyzing data from eight different studies (n=2,728), comparing duloxetine to placebo.[29] They reported that doses of 60 and 120 mg of duloxetine were associated with a significant improvement in neuropathic pain in DPN. The adverse effect profile of duloxetine is more favorable compared with TCAs, with fewer anti-muscarinic adverse effects.[34,35] Patients treated with duloxetine were found to have slight weight gain and raised fasting glucose levels, although to a lesser extent than with pregabalin.[36] Duloxetine is considered to be more cost-effective than pregabalin and was approved for the treatment of diabetic painful neuropathy by National Institute for Clinical Excellence.

GABA$_A$ α$_2$δ subunit

The α$_2$δ subunit (α$_2$δ-1 and α$_2$δ-2) of voltage-sensitive calcium channels in the central nervous system (CNS) has been utilized as the molecular target for pain relief in neuropathic pain. The FDA and EMA have approved pregabalin as first-line treatment for painful DPN.[19,37,38] Both pregabalin and gabapentin act as a nonselective ligand at the α2δ-1 and α2δ-2 subunits. The structure of these channels is composed of a central pore-forming alpha-1 subunit, a disulfide-linked glycoprotein consisting of α2δ subunits and intracellular beta subunits. Enhanced understanding of the α2δ subunits has suggested that α2δ-1 and α2δ-2 may in fact have different clinical effects.[39,40] Binding to α$_2$δ-1 may contribute to analgesic effects, whereas binding to α$_2$δ-2 appears to contribute to undesirable CNS effects such as somnolence.[37,41,42] Additional experimental studies have shown that GABA$_A$ receptors containing α2δ-2 and α2δ-3 subunits are crucial components of spinal pain control. Defining the precise role of GABA$_A$ receptor subtypes remains a key area for therapeutic advancement to ensure that novel GABA modulators are developed as a potential new therapeutic area for chronic neuropathic pain.[39,40] More recently, it has been suggested that GABA$_A$ α5 receptors play a role in the loss of GABAergic inhibition and contribute to long-lasting secondary allodynia and hyperalgesia,[43] and antagonism of GABA$_A$ α2δ-5 leads to reversal of impaired rate-dependent depression of the Hofmann reflex, a potential biomarker for spinally mediated pain secondary to loss of GABAergic

inhibition in diabetes.[44,45] AZD7325 is a novel partial α2δ-2,3 subtype-selective $GABA_A$ receptor modulator with minimal in vitro efficacy at the α2δ-1 and α2δ-5 receptor subtypes and produces anxiolytic effects in humans associated with selective $GABA_A$ α2δ-2,3 agonism.[46] There was increased expression of $GABA_A$ α2δ-1 mRNA and α2δ-1 protein in the dorsal root ganglion and dorsal horn of rat models of neuropathic pain.[47] Transgenic mice with elevated neuronal expression of the α2δ-1 subunit exhibited hypersensitivity to both tactile allodynia and thermal hyperalgesia and electrophysiological hyperexcitability in the dorsal root ganglion and spinal cord.[48] Gabapentin blocked voltage-gated calcium channel currents in a concentration-dependent manner in these transgenic mice.[48] The role of $GABA_A$ subtypes in promoting analgesia is complex and requires further study.

Gabapentin
Widely prescribed for diabetic neuropathy, gabapentin inhibits the presynaptic calcium channel at the α2δ ligand.[49] Backonja et al randomized patients in a ratio of 1:1 to receive either gabapentin or placebo and reported a number needed to treat (NNT) of 3.7 to achieve 50% pain relief after 8 weeks of treatment.[50] Since then several studies have confirmed the efficacy of gabapentin for neuropathic pain.[51–57] Several systematic reviews have found a significant analgesic effect of gabapentin in neuropathic pain[27,58] and a Cochrane Collaboration review on gabapentin reported an NNT of 5.9 for the relief of neuropathic pain.[59] Rudroju et al compared the efficacy and safety of a number of drugs in painful DPN and concluded that gabapentin offered the most favorable balance of safety and efficacy.[27]

Pregabalin
Pregabalin has higher reported potency due to higher absorption and affinity for the α2δ1 subunit. The efficacy of pregabalin in painful diabetic neuropathy has been established in four double-blind placebo-controlled trials,[60–63] and a recent meta-analysis found that pregabalin was the most efficacious agent for the management of painful DPN when patients were asked to grade their level of pain on a visual analog scale.[64] It exhibits a dose-dependent response, with 600 mg being associated with the greatest analgesic effect, improved mood, and less sleep interference. Sicras et al also reported that pregabalin was associated with reduced healthcare costs in a cost-comparative analysis of patients treated with pregabalin and gabapentin.[65] Weight gain can be an issue with pregabalin, and in a pooled analysis of 41 trials (n=3,187) while the majority of patients treated with

pregabalin (150–600 mg/day) for 1 year maintained weight within ±7% of their baseline weight, one in six patients gained ≥7% weight from baseline within 2–12 months of commencing treatment.[36] Patients should also be warned against abrupt discontinuation of pregabalin, as this has been associated with encephalopathy and cerebral edema, and there is the issue of recreational abuse amongst illicit drug users.[66,67]

Combination therapy
The COMBO-DN study was designed to compare the efficacy and tolerability of high-dose monotherapy (duloxetine 120 mg daily or pregabalin 600 mg daily) to standard dose combination therapy (duloxetine 60 mg and pregabalin 300 mg daily) in patients with painful DPN who were resistant to standard dose monotherapy.[22] There was no significant difference between standard dose combination therapy and high-dose monotherapy.[22] In a secondary analysis, duloxetine 60 mg/day was superior to pregabalin 300 mg/day in the initial 8-week run-in phase, and this remains the only head-to-head trial of pregabalin and duloxetine.

Other anticonvulsants
Other anticonvulsants such as lamotrigine and topiramate have been studied in painful diabetic neuropathy. A Cochrane review analyzed four trials of lamotrigine in painful DPN and found no evidence of its efficacy.[68,69] Trials evaluating topiramate have reported similar conflicting findings.[64,70,71] Although Raskin et al reported that topiramate was efficacious in the management of painful diabetic neuropathy, Thienel et al reported that a number of smaller studies had not shown any benefit.[70,71] It is evident that achieving adequate pain relief in painful DPN remains difficult for many patients and adequate analgesia may require combination therapy. The need for new more effective agents is apparent.

The case for mirogabalin
Mirogabalin and pregabalin were recently compared in partial sciatic nerve ligation and streptozotocin-induced diabetes.[47] Mirogabalin showed more selective binding affinity for the human and rat $α_2δ$ subunits, with a slower dissociation for the $α_2δ$-1 subunit compared with the $α_2δ$-2 subunit and hence potent analgesia with less CNS side effects.

Pharmacokinetics
The pharmacokinetics of mirogabalin has been studied extensively in healthy subjects with doses ranging from 3 to 75 mg (data on file, Daiichi Sankyo).[72] Following oral administration, maximum plasma concentration of mirogabalin is

achieved at ~1 hour.[72] The area under the plasma concentration-time curve and maximum plasma concentration are proportional with higher doses.[72] The plasma protein binding of mirogabalin is relatively low at ~25% in humans.[72] The drug is largely renally excreted and undergoes minimal in vivo metabolism.[72] A multicenter open-label study assessed the pharmacokinetics and safety of a single dose of 5 mg mirogabalin in 30 participants with normal, mild, moderate, or severe renal impairment.[73] The plasma concentration-time curve increased with severity of renal impairment.[73] A statistical model detailing the population pharmacokinetics of mirogabalin in relation to varying degrees of renal impairment has been developed and identified an effect on renal and nonrenal clearances of mirogabalin.[72] The simulation suggested reducing the dose of mirogabalin by 50% in people with moderate renal impairment and by 75% in people with severe renal impairment.[72] A recent randomized, placebo-controlled, double-blind, sequential, ascending-dose study evaluated single (10–40 mg) and repeated (10, 15 mg twice a day) doses of mirogabalin in Japanese, Korean, Chinese and White subjects and demonstrated comparable pharmacokinetic parameters.[74]

Clinical studies

Vinik et al conducted a multicenter, randomized, double-blind, placebo- and active comparator-controlled, proof-of-concept Phase II study.[42] In this study, adults with diabetic painful neuropathy of 6 months or greater were randomized (2:1:1:1:1:1:1) to receive placebo, increasing doses of mirogabalin (5, 10, 15, 20, and 30 mg daily), and pregabalin 300 mg daily for 5 weeks.[42] The severity of pain was measured over 5 weeks with a meaningful effect described as a 1-point or greater change in average daily pain score (rated on a numerical scale of 0–10). A dose of 30 mg mirogabalin caused a reduction in average daily pain scores of 1 or greater, whereas 15 and 20 mg doses caused a statistically significant reduction in pain scores; this was not considered to be clinically meaningful. Median time to meaningful pain relief was 30, 16, 20, and 16 days in the mirogabalin 10, 15, 20, and 30 mg/day groups, compared with 36 days in the placebo group ($P<0.05$ for all comparisons).

There were statistically significant differences in the change in the average daily pain score between pregabalin 300 mg and mirogabalin 15 and 30 mg. However, subjects in the pregabalin arm received 300 mg in divided doses and it remains unknown whether higher single doses would have affected efficacy. Second, the placebo response rate was higher than expected in this study as Freeman et al previously showed a placebo

response of –1.47, whereas in the present study, it was –1.86.[75] This single study suggests that mirogabalin may have a role in the management of painful diabetic neuropathy. However, the unique design of the trial necessitates caution when comparing these data with other published trials.

In addition to efficacy, this Phase II trial assessed the safety of mirogabalin using adverse event (AE) data, clinical laboratory tests, and electrocardiograms. Most frequent AEs (n=277) were mild to moderate dizziness (9.4%), somnolence (6.1%), and headache (6.1%); otherwise, mirogabalin was well tolerated. Hutmacher et al carried out exposure-response modeling for mirogabalin with respect to pain scores and adverse effects and showed that the incidence of dizziness and somnolence decreased over time and twice-daily dosing of mirogabalin was predicted to yield a lower incidence of dizziness compared with once-daily dosing.[76] Taken together, these findings suggest that the doses of mirogabalin can be titrated to achieve equivalent analgesic effect to pregabalin but with less adverse effects, particularly dizziness.[76] While, mirogabalin was well tolerated in Japanese subjects with normal and mild to severe renal impairment, dizziness, somnolence, and vomiting were reported with greater frequency in those with end-stage renal disease. It is therefore likely that the dose of mirogabalin will need dose adjustment in patients with moderate to severe renal impairment. However, of note only 5 mg of mirogabalin was used, and as reported previously this dose is unlikely to demonstrate a clinically meaningful analgesic effect in painful DPN.[42]

Efficacy of mirogabalin compared with pregabalin, gabapentin, and duloxetine

In the absence of direct head-to-head trials and given the paucity of efficacy data on mirogabalin, any comparisons between agents must be made with caution. Vinik et al reported that the percentage of subjects who reported a ≥50% reduction in average daily pain scores were 20%, 29%, 39%, 43%, and 44% after 5 weeks for 5, 10, 15, 20, and 30 mg of mirogabalin, respectively.[42] In a Cochrane review by Moore et al, a ≥50% reduction in average daily pain scores was achieved in 41% of patients receiving 600 mg of pregabalin.[77] For gabapentin[78] and duloxetine,[29] a ≥50% reduction in pain was found in 38% and 40%, respectively (Table 1).

AEs of mirogabalin compared with pregabalin, gabapentin, and duloxetine

The frequency of CNS adverse effects was 14% in the mirogabalin group compared with 12% in the pregabalin group (39). Seven percent of patients in the mirogabalin group

were unable to continue with treatment compared with 4% in the placebo group. This compares favorably to duloxetine, where a Cochrane review of 18 trials (n=6,407) reported that ~12.5% of patients had to discontinue duloxetine due to adverse effects.[29] A similar 12% rate of discontinuation due to AEs has been reported for gabapentin.[59] A Cochrane review of pregabalin reported treatment discontinuation due to AEs in 18%–28% of subjects, though most trials utilized 600 mg of pregabalin.[42,77]

Mirogabalin has equivalent efficacy but may be a more tolerable therapeutic option for painful diabetic neuropathy based on a comparison of efficacy and AEs (Table 1).

Novel therapies in DPN

There has been increasing interest in agents that target the pathophysiology of diabetic neuropathy. Vincent et al recently reviewed a number of cellular targets that could be used to develop novel therapies for DPN.[8,79] Manipulation of the temperature-sensitive transient receptor potential (TRP) channel on nociceptive neurons has been proposed as an attractive strategy in targeting the pain pathway, especially since TRPV1 desensitization by topical agonists such as capsaicin has been used for painful DPN.[80] VEGF-derived peptides may also be utilized as a pathogenetic therapy in diabetic neuropathy.[81,82] Ropper et al investigated VEGF for the treatment of diabetic neuropathy in a double-blind randomized trial but failed to show efficacy.[82] The angiotensin II type 2 receptor (AT2R) axis plays a substantial role in promoting nociceptive signaling by stimulating hyperexcitability and persistent ectopic firing of first-order sensory neurons.[83] Though AT2R antagonists have been long developed, they are now being repositioned as treatments for painful neuropathy.[84] In a Phase IIa study, Rice et al demonstrated the efficacy and safety of EMA401, a small molecular AT2R antagonist, in a cohort of 182 patients with postherpetic neuralgia.[85] Clinical trials are currently suspended following acquisition of the agent by Novartis.[84,86]

Table 1 Comparison of percentage with ≥50% reduction in average daily pain scores, number needed to treat (NNT), and percentage of patients who withdrew due to adverse events (AEs) comparing mirogabalin, pregabalin, gabapentin, and duloxetine

Drug	≥50% pain relief	NNT	% Withdrawal AE
Mirogabalin 30 mg	44%	5.0	7%
Pregabalin 600 mg	41%	5.0	18%–28%
Gabapentin ≥1,200 mg	38%	5.9	12%
Duloxetine 60 mg	40%	5.0	12.5%

Mutations in the Nav1.7 sodium channel have recently been described in a significant proportion of patients with painful diabetic neuropathy.[87] Numerous Nav1.7 antagonists are currently in development. Xenon402, a novel Nav1.7 blocker, was found to be effective in erythromelalgia and it has been suggested that Nav1.7 blockers may be useful in other types of neuropathic pain.[88,89]

Intrathecal drugs can be delivered at high concentration into the cerebrospinal fluid, limiting systemic adverse effects.[90] Whilst intrathecal morphine and ziconotide are approved for intractable pain,[91] they have not been evaluated in DPN. Moreover, one should be cautious in the implantation of intrathecal delivery systems in relation to myelitis and arachnoiditis[92] and impaired wound healing in patients with diabetes.

Produced by cells under stress, erythropoietin (EPO) is known to antagonize the production of proinflammatory molecules and as a consequence promotes tissue regeneration.[93,94] In experimental models, EPO is known to ameliorate DPN, but its use in humans is precluded by tendency to cause thrombosis. ARA290 is a nonhematopoietic peptide synthesized from EPO, which selectively targets the innate repair receptor, downregulating inflammation, without the procoagulant effects of EPO.[95] In a recent Phase II trial of ARA290 in patients with painful DPN, patients receiving ARA290 for 28 days reported a significant improvement in neuropathic symptoms compared with placebo.[95,96] A recent analysis of patients with sarcoidosis and small fiber neuropathy treated with ARA290 using corneal confocal microscopy demonstrated small nerve fiber repair, suggesting a pathogenetic role for ARA290.[97] Moreover, Zhang et al demonstrated that ARA290 can specifically inhibit TRPV1 channel activity and relieve capsaicin-induced hypersensitivity, indicating a dual basis for the efficacy of this drug in diabetic neuropathy.[98]

Conclusion

The rising global burden of diabetes is spurring an increase in the prevalence of diabetic neuropathy and neuropathic pain. At present, there are no FDA-approved pathogenetic therapies for DPN and the efficacy of treatments for painful DPN is limited. Therefore, there is a major need for the development of novel disease-modifying and analgesic therapies for diabetic neuropathy. The promising data on mirogabalin suggests that it may soon be the fourth drug to receive market approval for neuropathic pain.

Disclosure

U Alam has received honoraria for speaking at educational meetings organized by Pfizer. RA Malik has received hono-

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