

● INVITED REVIEW

Sigma-1 receptor: a new player in neuroprotection against chemotherapy-induced peripheral neuropathy

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Abstract

Chemotherapy-induced peripheral neuropathy is a very frequent neurological complication in cancer. Oxaliplatin (OXA) is a platinum analogue used as a first-line agent in the treatment of colorectal cancer. OXA induced peripheral neuropathy (OIN) is the main toxicity both during and after the completion of chemotherapy that presents as two distinct syndromes: acute and chronic neuropathy. None of the neuroprotective agents previously tested had prevented or limited the acute and/or chronic OIN. MR309 (previously developed as E-52862) is a novel selective sigma-1 receptor (S1R) antagonist with preclinical analgesic activity in OXA-induced neuropathic pain in animal models. This review analyzes the results of the recently published phase II, randomized, double-blind, placebo-controlled clinical trial including 124 patients with colorectal cancer (CRC) treated with MR309. This study shows encouraging findings in the setting of neuroprotection against OIN with an acceptable safety profile. The study demonstrated MR309 usefulness in decreasing acute OIN, by reducing cold hypersensitivity experienced by patients, and pointed to the amelioration of chronic OIN by lowering the proportion of patients who developed severe chronic OIN. In addition, we provide a summary and discussion on the pathways that can be modulated by the S1R to explain the observed clinical benefits in the OIN.

Key Words: oxaliplatin; chemotherapy-induced peripheral neuropathy; sigma-1 receptor; neurotoxicity; MR309; E-52862

Introduction

Chemotherapy-induced peripheral neuropathy is probably the most prevalent neurological complication in cancer treatment and the most common toxic neuropathy in our environment (Argyriou et al., 2012). Among neurotoxic chemotherapy drugs, platinum compounds are one of the most widely used. Specifically, oxaliplatin (OXA) is a platinum analogue administered as a first-line agent in the treatment of colorectal cancer (CRC), the third most common cancer worldwide. Moreover, OXA is the most neurotoxic platinum agent at conventional doses and is increasingly used to treat other malignancies. Peripheral neurotoxicity secondary to OXA usually presents itself as two distinct clinical syndromes: acute and chronic neuropathy (Argyriou et al., 2012; Velasco et al., 2014).

Acute OXA-Induced Neuropathy (OIN)

The acute peripheral syndrome usually occurs soon after the first administration in nearly all patients, and is characterized by reversible acral, perioral or pharyngolaryngeal dysesthesias, typically induced or exacerbated by cold. Patients may also present a neuromyotonia-like syndrome, with hyperexcitability motor symptoms (Argyriou et al., 2012; Velasco et al., 2014). The mechanism involved is a transient channelopathy due to the abnormal functioning of sodium and potassium channels. After being administered, OXA rapidly undergoes non-enzymatic biotransformation into the active metabolite (dach-platinum (Pt(DACH)Cl₂)) by losing the oxalate chain, which is considered responsible for the acute syndrome. Oxalate is a known dianion metal chelator, and Ca²⁺ and/or Mg²⁺ chelation has been suggested as a putative mechanism underlying acute

OIN. Physiologically, the binding of extracellular calcium within the pore of Na⁺ channels is required for channels to close. Their release from the pore may be necessary for the activation gates to open. Oxalate interferes with channel deactivation rate by increasing neuronal hyperexcitability and predisposition to ectopic activity which are mechanisms of paresthesia and cramps generation (Grolleau et al., 2001; Park et al., 2011). Furthermore, OXA exacerbates cold perception in sensory neurons by modulating the transcription of distinct ionic channels. These changes lead to a lowered expression of distinct potassium channels (TREK1, TRAAK) and the increased expression of pro-excitatory channels such as the hyperpolarization-activated channels, promoting over-excitability (Descoeur et al., 2011). These acute neurotoxic effects of OXA on small A_δ and C nerve sensory fibres can be objectively measured in patients through a thermal Quantitative Sensory Test (QST), by detecting variation in cold, cold pain thresholds (allodynia) and the intensity of pain evoked by suprathreshold cold stimuli (hyperalgesia) (Velasco et al., 2015). To date, pain management strategies have failed to alleviate these symptoms and avoiding cold stimuli and wearing gloves are recommended to patients as strategies to reduce the acute cold sensory hypersensitivity induced by OXA. Noteworthy, several clinical and neurophysiologic studies have demonstrated a close association between acute and chronic OIN, and the usefulness of acute syndrome assessment in predicting the severity of development of the chronic form (Park et al., 2009; Velasco et al., 2014).

Chronic OIN

In chronic OIN, patients typically develop sensory symmetrical

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symptoms in a 'stocking/glove' distribution during treatment, which despite not always being painful, can cause discomfort and may compromise simple daily activities such as writing or buttoning clothes. This negatively impacts their quality of life (Mols et al., 2013; Argyriou, 2015). This pattern reflects the selective sensory neuron damage on the dorsal root ganglia neurons due to several mechanisms, not fully elucidated, that include the formation of DNA intrastrand adducts and interstrand crosslinks, mitochondrial dysfunction and oxidative stress as the main triggers to neuronal apoptosis and consequent axonal degeneration (Argyriou et al., 2012). Chronic OIN is of major concern owing to its high prevalence, which can reach up to 80% of patients (Velasco et al., 2014), and its long-term duration, with often incomplete recovery becoming an irreversible sequel of oncologic therapy in many patients for decades (Briani et al., 2014). Because it is well-recognized as a cumulative dose-related adverse event the only ways to prevent its progression towards a severe and disabling neuropathy are early detection recognition and initial management indicating dose-delay, dose-reduction, or treatment discontinuation. However, these interventions can negatively interfere in patients outcome and therefore are unfortunately implemented late, when the nerve damage is already ongoing. When established, treatment of chronic OIN aims to relieve disturbing symptoms such as neuropathic pain, numbness, and tingling. The types of drugs usually recommended include topical analgesics, antidepressants, and anticonvulsants (Hershman et al., 2014; Cavaletti and Marmiroli, 2018). Currently evidence-based treatment only supports duloxetine as a demonstrated agent against pain due to OIN, which only displays a very modest and limited effect on pain relief (Smith et al., 2013; Cavaletti and Marmiroli, 2018). Therefore, chronic OIN remains a clinically-relevant unsolved issue in daily medical practice.

Neuroprotection by Sigma-1 Receptor Ligand MR309 in OIN

Several neuroprotective therapies against OIN, including drugs, dietary supplements, and physical or behavioral interventions have been and are currently being investigated (Cavaletti and Marmiroli, 2018). However, up to now, and despite extensive efforts, none of the neuroprotective agents previously tested in humans have prevented or limited either acute or chronic OIN (Hershman et al., 2014; Cavaletti and Marmiroli, 2018).

MR309 (CAS registry number 1265917-14-3), previously developed as E-52862, is a novel selective sigma-1 receptor (S1R) antagonist, that has demonstrated analgesic activity in several models of neuropathic pain in animals. These models include OXA and taxane-induced neuropathy (Nieto et al., 2014; Gris et al., 2016). Moreover, MR309 presents good safety and tolerability profiles after single and multiple doses in healthy human volunteers in phase I clinical trials (Díaz et al., 2012). We tested the efficacy of MR309 in ameliorating OIN in 124 chemotherapy-naïve patients in a proof-of-concept, explorative, phase II, randomized (1:1), double-blind, placebo-controlled clinical trial (Bruna et al., 2018). CRC patients from 5 institutions scheduled to receive OXA as one component of their chemotherapy regimen were randomized to either 1 daily oral dose of 400 mg of the study drug (MR309) or placebo for the first 5 days of each chemotherapy cycle, up to a maximum of 12 cycles. This inter-

mittent schedule, rather than a continuous dosing regimen, was decided on despite being potentially suboptimal in assessing the effect on cumulated OIN, because at the time of the trial development, there was no safety data available for continuous and prolonged administrations. Outcome measures included: changes in thermal sensitivity by QST, the Total Neuropathy Score, nerve-conduction studies, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale, and health-related quality of life tests (Cavaletti et al., 2013; Velasco et al., 2014). Specifically, acute OIN syndrome was quantitatively assessed by changes of cold pain perception versus baseline, providing the cold pain threshold (CPT) and the intensity of pain evoked by suprathreshold cold stimuli on the skin covering the thenar eminence. Evoked pain was measured by the 11-point numerical pain rating scale (Velasco et al., 2015). Patients were periodically evaluated before and after OXA administration, and up to 6 weeks after finishing OXA treatment. A synopsis of the protocol and the major results of the trial are available at EU Clinical Trials Register (EudraCT Number: 2012-000398-21) (2012).

Our study can be thought of as positive as it reveals promising encouraging findings in the neuroprotection setting against acute, and potentially, chronic OIN. Firstly, MR309 significantly reduced cold hypersensitivity and allodynia (preserving and reducing the cold pain and cold-evoked pain temperature thresholds, respectively) as well as the hyperexcitability motor symptoms and signs in active patients. This demonstrates its usefulness in decreasing acute OIN, considered one of the first steps to developing chronic OIN. Secondly, MR309 significantly reduced the proportion of patients who developed severe (grade ≥ 3) chronic OIN compared with the placebo group (3.0% vs. 18.2%) assessed by the NCI-CTCAE scale. Thirdly, patients randomized to the active treatment arm were able to receive significantly more OXA than placebo-treated patients, augmenting the OXA exposure, although this was based on raw dose and not on body surface area-adjusted dose. Interestingly, premature withdrawal due to cancer progression was less frequent in the MR309 group (7.4% vs. 25.0% in the placebo group; $P = 0.054$). In conjunction with the good tolerability adverse events report, MR309 showed a safety profile of being apt for use in oncological patients. However, MR309 usefulness on the neuroprotective effect against chronic OIN remains to be clarified. Despite the positive effects found using the NCI-CTCAE scale, the lack of differences observed between active and placebo groups in nerve conduction studies and the neurological scores measured by the Total Neuropathy Score, might potentially be overtaken by using more appropriate continuous dosing regimens. Moreover, the implicit limitations in the nature of the exploratory design of the trial cannot be overlooked.

Modulation of S1R in OIN

S1R is a ligand-regulated non-ATP-binding membrane bound chaperone protein located in mitochondrial-associated endoplasmic reticulum (ER) membranes (MAM), forming a complex with BiP in resting states. At this location, its action contributes to sustaining the correct conformation of the inositol triphosphate receptor type 3 (IP3R3) to ensure proper Ca^{2+} signaling from the ER into mitochondria to facilitate the production of ATP, to modulate the ER stressor sensors inositol-requiring enzyme 1 (IRE-1), and also to attenuate the formation

of reactive oxygen species. Moreover, S1R can translocate to the plasmatic membrane to interact with a wide spectrum of ion channels, receptors, and kinases. Similarly, it can also be translocated to the nucleus, thus playing a role in the regulation of gene transcription (Su et al., 2016). These pleiotropic modulating actions and their expression throughout the entire nervous system have converted this receptor into a target of high interest in the treatment of a wide variety of neurodegenerative diseases and neuropathic pain disorders (Su et al., 2016; Weng et al., 2017). However, the endogenous ligands for this receptor have not been fully identified, and can include steroid hormones and sphingolipid-derived amines. In addition, although the S1R function is altered by ligands, it can also be active even in absence of ligands (Aydar et al., 2002), thereby the classical notion of agonist and antagonist might not be fully applicable to compounds that interact with S1R.

MR309 has been defined as an antagonist of S1R due to its inhibitory tonic action over opioid receptors of this receptor, where agonists inhibit the antinociception induced by morphine and antagonists enhance the antinociceptive effect (Chien and Pasternak, 1994). However, MR309 actions over other intracellular S1R and voltage gated channels have not been investigated. To date, MR309 has shown high affinity for the S1R ($K_i = 17$ nM), excellent S1R/S2R selectivity (> 550) without significant direct activity on another 170 receptors, including ion channels and enzymes (Romero et al., 2012).

The positive results of MR309 in preventing acute OIN obtained in the clinical trial reported by our group (Bruna et al., 2018) could be related to the capacity of S1R to modulate the voltage-gated sodium (Nav) and potassium (Kv) channels. The alteration in the current kinetics of these ions is under the suspected mechanism to induce the neuromyotonia-like symptoms and the axonal hyperactivity in A δ and C nerve fibers. This causes the paresthesia and the disturbing sensations triggered by cold. It has been reported that S1R agonist can modulate Nav 1.2 and Nav 1.4 (Su et al., 2016), and polymorphisms in the latter have also been involved in the risk of developing acute and chronic OIN (Argyriou et al., 2013). Conversely, it also has been observed that S1R antagonists can also modulate the Nav activity (Balasuriya et al., 2012), highlighting the current unclear nomenclature used to refer the S1R ligands. In addition, S1R also regulate Kv 1.2, Kv 1.3, and Kv1.4 channels, altering their kinetics. These interactions may take two forms. In absence of S1R agonist, the sigma receptor accelerates Kv channel inactivation, but in presence of S1R agonist, the interaction between the S1R and the Kv channel reduces the peak current flow (Aydar et al., 2002). This MR309 action on S1R on Kv modulation could therefore contribute to reverting the axonal hyperexcitability phenomenon, both in motor and sensory neurons responsible for the acute neurotoxicity syndrome associated with OXA administration.

However, the mechanisms of MR309 to prevent chronic OIN would be more speculative. S1R has been reported as a modulator of several pathways of interest with an alleged role in neuroprotection, such as the regulation of Acid-Sensing proton channels resulting in the inhibition of calcium influx, the activation of tyrosine kinase receptors signaling (as platelet-derived and brain-derived growth factor receptors), the interaction with the integrin β_1 , the upregulation of glutamate receptors GluN2A, GluN2B induced by S1R agonists, the stabilization of

inositol-requiring enzyme 1 (IRE1) signaling to the nucleus to ensure the upregulation of several ER chaperones and antioxidant proteins, and the transcriptional regulation through the interaction with emerin (a nuclear envelope-resident protein that regulates the expression of a large number of genes) (Su et al., 2016). However, all these factors and their signaling pathways have not been specifically assessed in neuropathy-induced by platinum compounds, and only mechanisms involved in reducing the oxidative stress could play a known role. Perhaps more interesting and closely related with the already reported mechanisms involved in the pathogenesis of platinum-induced neuropathies is the regulation of pro-apoptotic pathways by S1R, and the regulation of Ca^{2+} influx between mitochondria and the cellular environment through the relationship with IP3R3 on MAMs. The S1R agonists can induce cell death by activation of the caspase cascades, and the blockade of S1R inhibits the increase of pro-apoptotic proteins (Shen et al., 2016). In addition, one of the well-established functions of the S1R is to regulate Ca^{2+} signaling from the endoplasmic reticulum to the mitochondria by coupling to ankyrin B and IP3R3. Under stress conditions, ER Ca^{2+} depletion, or S1R agonist stimulation, S1R dissociate from BiP to chaperone IP3R3 and release ankyrin from IP3R3, allowing a prolonged Ca^{2+} transfer from ER to mitochondria. At this point, it is tempting to speculate that an excessive mitochondrial Ca^{2+} accumulation induced by an increased need for ATP production due to the hyperexcitability state of neurons in the setting of acute neurotoxicity could favor the mitochondrial permeabilization by the formation of protein transitory pore, facilitating the release of pro-apoptotic factors (Weng et al., 2017). Even if this rise of Ca^{2+} is not toxic in itself, when it occurs synchronously with another toxic event, it has been described that this process can turn into a death stimulus to the cell (Weng et al., 2017). Partial supporting evidence of MR309 action on this mechanism, preventing mitochondrial permeation, is provided in the paclitaxel-induced neuropathy animal model (Nieto et al., 2014), in which the dysfunction of IP3R3 on MAM was reported as one of the key pathogenic processes (Pease-Raissi et al., 2017).

Finally, and not directly related with the OIN modulation, is the increasing interest of the sigma receptors role in drug addiction. Stimulant abuse drugs induce changes in SR activity, establishing redundant and independent reinforcement pathways. However, these changes have been less studied in opioid drugs administration. Drug self-administration induces reinforcing effects of SR agonists due to dopamine transporter actions. Once established, the reinforcing effects of SR agonists are independent of dopaminergic mechanisms traditionally thought to be critical in the reinforcing effects of abused drugs. However, this action can be blocked by SR antagonists, attenuating several manifestations of the addiction (Katz et al., 2016). This effect of SR antagonist, and the enhancing action on opioid receptors (therefore, requiring less analgesic drug dose) increases the interest of MR309 in the management of the painful component of the neuropathy showed by a significant number of patients, at a time when concerns over addiction to painkillers are rising.

Conclusions

S1R, an endoplasmic reticulum-chaperone protein, can modulate cold induced painful response due to OXA ad-

ministration and has therapeutic value for the prevention of OIN. The recently published multicentric trial is the first in demonstrating that MR309, an antagonist of S1R, significantly reduced cold hypersensitivity due to OXA suffered by colorectal cancer patients, and lowered the proportion of patients who developed severe chronic OIN, compared with the placebo group. The promising results obtained by this phase II clinical trial provide clear and novel direction for future studies on the efficacy of modulation of S1R by MR309 to prevent OIN and possibly also CIPN caused by other neurotoxic chemotherapeutic agents.

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