General Medicine Open

Commentary

ISSN: 2515-4737

Topical NaV1.7 channel blocker failed in postherpetic Neuralgia (PHN): lessons to learn

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Xenon Pharmaceuticals and Teva Pharmaceuticals both worked on the development of TV-45070, previously known as XEN402, characterized by Teva as a potent Nav1.7 inhibitor [1,3]. Inherited erythromelalgia (IEM) is a rare disorder, based on a range of gain-of-function mutations, located in domains I to IV of NaV1.7. TV-45070 orally administered was reported to decrease pain in a first pilot study in IEM patients [2]. For the further development, TEVA decided to also develop a topical formulation based on an ointment, and its physicochemical and pharmaceutical properties were not further specified. The rationale for this new development was given as: "*To maximize inhibition of Navs locally in skin and subcutaneous tissue and minimize systemic adverse events, topical TV-45070 was developed to depot in the skin and underlying tissue while maintaining low plasma concentrations* (pp310-311) [3]."

Results of a new proof of principle study in postherpetic neuralgia (PHN) was reported last year (2017), based on an elegant cross-over design in 70 patients, randomized to receive twice daily active or placebo ointment. Patients with mean daily pain scores equal or greater than 4 (using an 11-point Numerical Rating Scale) for at least 4 days during the initial placebo 7-day run-in period were randomized. The dose administered was dependent on the area treated, and varied between 60 and 240 mg. The concentration of TV-45070 in the ointment was 4% and 8%, as mentioned by TEVA at its website [4]. Due to drop-outs during the study in both arms and during both cross-over periods, the efficacy analysis was based on 57 patients only. There was no difference between analgesia as measured via the primary outcome variable in both treatment groups, and the reduction compared to baseline was only around 0,95 points on the NRS. Plasma concentrations detected were reported to be low in comparison to plasma levels earlier measured after oral dosing. After oral dosing plasma levels were higher and were related to the induction of some adverse events. However, the base ointment selected, frequently induced local skin reactions in both arms, although reported to be mild in 66%, they were occasional moderate in 28%, suggesting a suboptimal vehicle.

Now there may be various reasons why topical TV-45070 did not reach significance in this study, as measured via the first outcome variable. One possible reason was that the mean duration of pain in this cohort was much longer than normal (longer than 5 years), and thus the cohort might be more treatment refractory than normal.

In the explored population 8 patients were heterozygous carriers of the Nav1.7 R1150W polymorphism, and in this small subpopulation the carriers of the mutation responded better compared to the placebo-response. The authors also conducted a 50% responder analysis, where TV-45070 did significantly better compared to placebo. In the discussion they pointed out that this positive responder rate: "*suggests that a subpopulation of PHN patients exists that is more likely to have an analgesic effect and, further suggests the possibility exists that this response to topical TV-45070 could be mechanism based* (p.317 [3]". This is a very important remark, because recent data support their suggestion, and although there is uniformity in etiology, currently at least 3 different pathogenetic and symptomatic subgroups defined in PHN, that are differentiated from each other [5].

1. patients with irritable nociceptors presenting stimulus-evoked symptoms of mechanical allodynia and thermal hyperalgesia;
2. patients with deafferentation presenting spontaneous pain and partial sensory deficits;
3. and patients with central reorganization presenting mechanical allodynia and sensory deficits.

Clearly the presence of various phenotypes related to sodium channels may add to the complexity. If this differentiation is followed, topical Nav1.7 blockers will especially be effective in group 1 and most probably not in group 3! However, we do not have sufficient tools at the moment to differentiate sufficiently between the 3 groups. Quantitative sensory testing was suggested to bring clarity, but recently it appeared that such testing correlates with neuropathy only, and not with pain [6].

Another problem is related to the fact that we are not totally sure about what Nav channels play a pathogenetic role in the nociceptors of patients with PHN. 6 of 9 channels are most probably relevant in the epidermis, not only on nociceptor, but also on non-neuronal targets cross-talking with the nociceptors, the keratinocyte or immune-competent cells [7]. Moreover, NaV1.7 is expressed in free nerve terminals of peptidergic and non-peptidergic intraepidermal small nerve fibers, all up to the terminal boutons. NaV1.7 ion channels are co-localized in the small fibers, together with NaV1.6, NaV1.8 and NaV1.9 [8-9]. Recently three fundamental and unanswered questions related to NaV1.7 were put forward:

1. where in nociceptive pathways Nav1.7 needs to be inhibited,
2. what level of functional inhibition is required to effect analgesia, and
3. which pathological pain conditions will respond favorably to highly selective Nav1.7 inhibitors? [10].

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Received: March 07, 2018; **Accepted:** March 21, 2018; **Published:** March 23, 2018

Therefore, a less selective sodium channel blocker might cover more of the disturbed channel functions and might lead to better topical analgesia. This is the approach we selected some years ago, when we started evaluating the safety and the efficacy of the archetype of the unselective sodium channel blockers, phenytoin, compounded in a topical cream in the concentration range 5-20%. Our vehicle did not result in relevant adverse events, to date only 2 patients from more than 100 entered in a data pool, reported transient redness and burning. Moreover, we developed a single-blind placebo-controlled response test, to differentiate responders from non-responders within 30 minutes. Enriching subsequent studies with such a response-phase might select out non-responders in a more effective way than following the stratification in 3 subgroups mentioned and try to identify subgroup number one. Absence of detectable phenytoin levels in 16 patients treated with 10% phenytoin cream in our center, together with the fast action of onset suggests an intra-epidermal mechanism of action.

Sodium channels play a major role in peripheral neuropathies, and we need to explore whether PHN is the best indication for topical treatments, given the complexity of its pathogenesis. Currently our thinking is, that painful diabetic neuropathy and small fiber neuropathy are more likely to respond, given the importance of their intra-epidermal pathology. This is recently supported by findings of NaV1.7 channelopathies in SFN and in PDN [11,12].

Conflict of interest

The author is a patent holder of two patents related to the topical formulations of phenytoin in the treatment of pain: 1) Topical phenytoin for the use in the treatment of peripheral neuropathic pain and 2) Topical pharmaceutical composition containing phenytoin and a (co-) analgesic for the treatment of chronic pain.

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