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Letter

Gastrointestinal AEs seen in the POP trial due to SOD mimetic activity of calmangafodipir?

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As the main inventor of calmangafodipir (together with Karl Reineke, US 9,1187,509 B2), I have with great enthusiasm read the results of the POP trial published in EBioMedicine [1]. This is a well planned and executed Phase 1 study. With the limitations, as meritoriously discussed by the authors, the results are indeed promising. However, when it comes to the most common adverse events (AEs), namely gastrointestinal (GI) AEs, I have not been able to find any further specification of the types of GI AEs and how these distributed in the various groups. Although the distribution of GI AEs across the treatment groups is given in Supplementary Table 2 [1], by definition these AEs may include several different kinds of side effects with various etiologies, e.g., nausea, vomiting, dyspepsia and diarrhea. From a mechanistic point of view, these AEs may well be due to superoxide dismutase (SOD) mimetic activity of calmangafodipir [2] in a similar manner as rapid administration of mangafodipir (Teslascan™) causes nitroglycerin-like cardiovascular AEs [3].

In May 1992 I started working for Nycomed Imaging AS in Oslo. My first undertaken was to investigate whether the nitroglycerin-like cardiovascular side effects (mainly facial flushing and reflexively increase in heart rate and blood pressure) seen upon rapid intravenous administration of mangafodipir (an MRI contrast agent under development) were of any safety concern. By applying a classic pharmacological approach, we were able to show that mangafodipir protected endogenous NO from being destroyed by superoxide anions, apparently by its SOD mimetic activity and consequently caused vasodilation upon rapid administration [3]. By lowering the injection rate of mangafodipir, the cardiovascular side effects were significantly reduced and were of little or no safety concern.

In our first feasibility study with mangafodipir in colon cancer patients [4], there were eight events (in four patients) of mild (grade 1) diarrhea in the mangafodipir group *but* none in the placebo group. When mangafodipir is used as an MRI contrast agent, mild diarrhea has been reported to occur. Interestingly, a phase III randomized trial of adding topical nitroglycerin to first-line carboplatin chemotherapy for advanced non–small cell lung cancer showed a statistical higher frequency of diarrhea in the nitroglycerin group compared to the placebo group, 23% versus 14% [5]. Heat stable enterotoxins are well known to bind and activate membrane-bound guanylate cyclase, which leads to intracellular accumulation of cyclic GMP and downstream effects on several signaling pathways causing increased intestinal secretion and diarrhea [6]. Both mangafodipir and nitroglycerin increase the intracellular content of cyclic GMP through an NO-mediated activation of soluble guanylate cyclase, which may similar to heat stable enterotoxins increase intestinal secretion and hence cause diarrhea.

From both a mechanistic and safety point of view it is essential to know the frequency of diarrhea and other GI AEs in the various groups, not at least for the planning of the upcoming phase II/III studies.

Disclosure

Dr. Karlsson is co-founder and owns shares in PledPharma AB and the main inventor on two granted patent families (e.g., US8377969, US8633174, and US9187509) owned by PledPharma AB, and has royalty agreement with PledPharma AB. Dr. Karlsson is a main inventor on a pending patent application PCT/EP2017/078982 (in international phase) owned by Karlsson-Tuner Invest AS (KTAS), with a royalty agreement with KTAS. Dr. Karlsson is founder and main owner of Karlsson-Tuner Invest AS, Norway, the sponsor of ongoing research and patenting activities (PCT/EP2017/078982).

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