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Summary of Mechanism of Hepatic Adverse Reactions with Pexidartinib
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Assessment of Pexidartinib Hepatic Adverse Reactions

Pexidartinib is associated with two clinically distinct types of hepatic adverse reactions. The first type is aminotransferase elevations, which occur in the absence of significant bilirubin and alkaline phosphatase (ALP) elevations, are frequent, dose dependent, and generally low-grade. The second hepatic adverse reaction is mixed or cholestatic hepatotoxicity, defined as aminotransferase increase with concurrent increase in ALP with or without increase in bilirubin. This second type of hepatic adverse reactions is uncommon, and while they are rarely serious, they can be life threatening. The mechanisms of these two types of hepatic adverse reactions are not fully understood, and the mechanisms are likely different. Hence, they are discussed separately below.

Mechanism of Aminotransferase Elevations

The increase of aminotransferases is attributed to pexidartinib's inhibition of colony-stimulating factor-1 receptor (CSF1R). Frequent, clinically nonsignificant, dose-dependent increases of these serum enzymes have been reported for several other agents targeting the colony-stimulating factor-1 (CSF-1)/CSF1R pathway.[1-5] These agents include receptor kinase inhibitors as well as monoclonal antibodies to CSF1R or its ligand, CSF-1. For example, dose-dependent and reversible increases in serum enzymes were reported following intravenous administration of the anti-CSF1R monoclonal antibody FPA008.[1] In addition, patients (n=63) with rheumatoid arthritis experienced mean increases in aspartate aminotransferase (AST) of 33% and alanine aminotransferase (ALT) of 24% during treatment with the CSF-1 receptor kinase inhibitor JNJ-40346527.[2] Four of these patients experienced ALT increases >3× upper limit of normal, whereas no patient experienced increased bilirubin. The biological mechanism for these enzyme increases has been attributed to reduced clearance of these enzymes from the circulation possibly related to reduction in the number of Kupffer cells in the liver.[1-5]

Increases in ALT and AST during pexidartinib treatment are also dose-dependent and reversible. In the toxicology program, increases in ALT and AST were more frequent and greater in magnitude with increasing pexidartinib doses (Table 1). In the Phase 1 dose-escalation study, AST increase was a dose-limiting toxicity at 1200 mg/day. Maximum observed AST levels were highly correlated with pexidartinib exposure, whereas the correlations between ALT and pexidartinib exposure were less robust. Exposure-response analyses across several pexidartinib clinical studies also showed exposure-related increases in serum CSF-1 concentrations and ALT and AST increases. Acute hepatocellular hepatotoxicity with increases in ALT and AST, in the absence of ALP and bilirubin increases, are dose-dependent and reversible. In all patients with full follow-up, the majority of patients recovered within 1 month and all patients recovered within 2 months. Although the specific molecular and cellular mechanisms for pexidartinib-related increases in aminotransferases have not been defined, these data indicate that aminotransferase elevations result from dose-dependent inhibition of CSF1R.

Table 1. Aminotransferase Levels in Rats After 4 Weeks of Pexidartinib Treatment

	Dose (mg/kg/day) and Margin of Exposure[a]			
	0	**20 (0.4×)**	**60 (1.5×)**	**200 (5×)**
ALT (U/L) mean (SD)	37 (4.6)	61 (13.6)	96 (22.6)	159 (30.2)
AST (U/L) mean (SD)	83 (13.0)	134 (10.9)	185 (39.1)	223 (26.4)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; BID = twice daily; popPK = population pharmacokinetics; SD = standard deviation.
[a]Margin of exposure is the mean AUC in rats as a multiple (×) of the mean AUC (popPK analysis) in patients at 800 mg/day (400 mg BID).

Mechanism of Mixed or Cholestatic Hepatotoxicity

The mechanism by which pexidartinib causes mixed or cholestatic hepatotoxicity remains unknown, and there is no evidence that it relates to pexidartinib's inhibition of CSF1R pathway inhibition. Mixed or cholestatic hepatotoxicity has not been reported with other agents targeting the CSF-1/CSF1R pathway. Toxicology and other nonclinical studies, including in vitro evaluation of hepatotoxicity and population exposure simulation analyses by DILIsym®, did not identify a toxicity of pexidartinib and its major metabolite, ZAAD-1008, that was comparable with the mixed or cholestatic hepatotoxicity observed in patients. Review of cases of mixed or cholestatic hepatotoxicity across the pexidartinib clinical program included evaluation of concomitant medications, but did not identify a dose-response relationship or any risk factors. Because there is no relationship with pexidartinib dose or exposure, no predictive risk factors, and the mechanism for the toxicity is unknown, pexidartinib's mixed or cholestatic hepatotoxicity is considered idiosyncratic, which is the case for many other agents that have been associated with cholestatic hepatotoxicity.

Summary

Pexidartinib is associated with two types of hepatotoxicity. Aminotransferase elevations are closely related to pexidartinib's dose-dependent inhibition of CSF1R. In contrast, the mixed or cholestatic hepatotoxicity associated with pexidartinib is idiosyncratic. Daiichi Sankyo will continue to work with the FDA to define a Risk Evaluation and Mitigation Strategy (REMS) with a patient registry that will further characterize the risk of hepatotoxicity and better inform risk-mitigation strategies for pexidartinib.

References

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