

原 著

「レンヌ事件」について — フランスにおける 第 I 相試験死亡事故の教訓

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Puzzling out the tragedy of Rennes: The death of a healthy volunteer in the first-in-human trial in France

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Abstract

Background : In January 2016 in Rennes, France, unexpected acute neurotoxic reactions, including a cerebral stroke resulting in brain death, occurred in 5 of 6 healthy volunteers in the first-in-human (FIH) trial of BIA 10-2474, fatty acid amide hydrolase (FAAH) inhibitor, to treat several neurological disorders with enhancing the function of the endocannabinoid system. That was in the fifth cohort of a multiple ascending dose (MAD) study, following single ascending dose (SAD) studies, after completion of 84 volunteers without serious adverse reactions.

Objective : To analyze the mechanism of this still inexplicable phenomenon.

Method : Narrative, non-systematic review of literature concerning this case.

Findings : Immediately after the event, the French regulatory authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé; ANSM) set up a committee (Comité Scientifique Spécialisé Temporaire: CSST) to investigate this issue; and another agency (Inspection Général des Affaires Sociales: IGAS) conducted an independent inspection. The reports of these investigations and related literature regarding this event indicate: (1) regardless of the serious reaction (later resulting in death) in the first volunteer of the cohort, the candidate drug had been administered to the other succeeding volunteers on consecutive days; (2) although the SAD studies showed problematic PK (pharmacokinetics)/PD (pharmacodynamics) results, the MAD studies were continued; (3) the question of neurotoxicity of the agent was begged without clear logic. With the data and clinical symptoms written in the literature mentioned above, we newly found the possible pathophysiology of the tragic phenomenon: the candidate drug might provoke cerebral microbleeds by either platelet dysfunction or aggressive angiitis of the central nervous system through the endocannabinoid system.

Discussion and conclusion : Though the intended mechanism of action of the candidate drug held lesser importance in the literature we overviewed, we found it the most explainable pathophysiology for the tragedy. Clinical symptoms and data indicate a simple and straight forward mechanism behind this puzzling phenomenon.

Key words

biphasic action of endocannabinoids, drug-induced hemorrhagic tendency, early phase clinical trial, regulatory science, adverse drug reaction

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