Journal of Pharmacological and Toxicological Methods 85 (2017) 82–86

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

The northeast regional SPS meeting update: Safety pharmacology innovations and applications

Malar Pannirselvam [a,*], Tiffini Brabham [b], Alfred W. Botchway [c], Donald B. Hodges [a], Martin Traebert [d], Michael K Pugsley [e]

[a] Vertex Pharmaceuticals Incorporated, Boston, MA, United States
[b] Global Safety Pharmacology, Pfizer, Andover, MA, United States
[c] Xenometrics LLC., Kansas City, KS, United States
[d] Safety Pharmacology, Novartis Pharma AG, Basel, Switzerland
[e] Department of Toxicology & PKDM, Purdue Pharma LP, Cranbury, NJ, United States

ARTICLE INFO

Article history:
Received 6 November 2016
Received in revised form 22 November 2016
Accepted 23 November 2016
Available online 30 November 2016

Keywords:
Fatty acid acyl hydrolase (FAAH)
Stem cell
Cardiomyocyte
EEG
Hearing loss
BIA 10-2474
CGF166
hERG (I_{Kr})
I_{Ks}
Organs on chip
Rat telemetry
Suicidal ideation and behavior

ABSTRACT

The Safety Pharmacology Society (SPS) held a Northeast (NE) regional meeting in Boston, MA on May 13, 2016 at the Vertex Pharmaceuticals Incorporated site. There were 103 attendees from the pharmaceutical industry, contract research organizations (CROs), academia, and global regulatory agencies. An assortment of scientific topics were presented by 7 speakers that included broad topics in the cardiovascular (organ on chip, statistical power and translation of rat cardiovascular telemetry data and dual inhibition of I_{Kr} and I_{Ks} on QT interval prolongation) and central nervous system (in vitro platform for neurotoxicity, an integrated risk assessment of suicidal ideation and behavior, and EEG advances in safety pharmacology) and a novel topic discussing preclinical challenges faced in the development of a novel gene therapy. A highlight of the meeting was an in-depth discussion on the fatty acid acyl hydrolase (FAAH) inhibitor BIA 10-2474 which involved a comprehensive overview of the biology and pharmacology of FAAH followed by a presentation from the Biotrial (Rennes, France) team that conducted the clinical trial. An additional poster session was held that included 13 fascinating posters on cutting edge safety pharmacology topics.

Contents

* Corresponding author at: Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, United States.
E-mail address: malar_pannirselvam@vrtx.com (M. Pannirselvam).

http://dx.doi.org/10.1016/j.vascn.2016.11.005
1056-8719/

1. An introduction to the meeting content

The principles that define the fundamentals of the safety pharmacology society lie, in part, on the basis of a celebrated quote by the famous toxicologist Dr. Gerhard Zbinden "…adverse drug reactions which the standard toxicological test procedures do not aspire to recognize include most of the functional side-effects. Clinical experience indicates, however, that these are much more frequent than the toxic reactions due to morphological and biochemical lesions…" (Zbinden, 1979; Hock, 2013). The Safety Pharmacology Society (SPS), incorporated in 2001, evolved from the General Pharmacology/Safety Pharmacology Discussion Group. SPS has continued to grow since ratification of the ICH S7A guidelines (Bass, Hombo, Kasai, Kinter, & Valentin, 2015). SPS made an enormous effort in leading education and methodological advancement in all major (core battery) physiological systems including cardiovascular, central nervous system and respiratory as well as the gastrointestinal and renal systems in support of new drug discovery and development and drug safety. The society has one global meeting each year, alternating the location between North America and Europe. Annual meetings are well attended by representatives from the pharmaceutical and biotechnology industries, academia, CRO's, and global regulatory agencies. The annual SPS meeting is the main opportunity for the discipline to promote the science of safety pharmacology and advance knowledge globally; however, a local (or regional) meeting, particularly in places like the greater Boston area, has the advantage to appeal to numerous startup companies, mid-sized biopharmaceutical companies as well as giants in the pharmaceutical industry. Such a local meeting places the society in a better position to showcase SPS to colleagues in other areas of nonclinical (as well as clinical) drug safety assessment. As well, regional meetings are cost-effective ways for graduate students and postdoctoral fellows from academia within the region to attend and explore the rapidly evolving aspects of safety pharmacology. With this in mind, the first Northeast Regional SPS Meeting was organized at Vertex Pharmaceuticals Incorporated in Boston, MA.

The SPS regional meeting was conducted in order to establish several goals. The meeting was conducted to showcase the science of safety pharmacology being conducted across the pharmaceutical industry as well as in academic institutions. It highlighted scientific advances in the field brought about from collaborations with different disciplines, i.e., investigative toxicology, investigative pathology, physiology, pharmacology and many more fundamental areas of medicine and science. It was hoped to enrich the scientific educational experiences amongst junior scientists and students working in the field or related field of drug safety and provided an invitation to colleagues to SPS membership and increased awareness of the benefits of our society.

This meeting report overviews the content discussed and presented at the meeting.

2. Morning chat: FAAH inhibitor clinical trial

2.1. The fundamentals of FAAH inhibition

Dr. Pugsley presented an overview on the fundamentals of FAAH biology, pharmacology of FAAH inhibition and pharmaceutical development of FAAH inhibitors. It has been established that the pharmacological activity of tetrahydrocannabinol ((−)-*trans*-Δ^9THC), the active ingredient of marijuana (derived from the *Cannabis sativa* plant), mediates its primarily psychoactive and related physiological effects by binding to cannabinoid (CB) receptors (Pertwee, 2006). The antinociceptive effect of Δ^9THC has been demonstrated in a variety of non-clinical pharmacological models that includes acute, inflammatory and chronic pain (Robson, 2013).

Two types of CB receptors exist, CB1 and CB2. Pharmacological characterization and determination of localization of the CB receptors in the central and peripheral nervous systems (CB_1) and primarily on immune cells (CB_2) led to the identification of the endogenous ligands *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol to these receptors (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Munro, Thomas, & Abu-Shaar, 1993). Research in the field has primarily focused on the role of anandamide, a fatty acid neurotransmitter which has biological activity comparable to that of Δ^9THC (Pertwee, 2006). However, anandamide is rapidly metabolized by the enzyme, fatty acid acyl hydrolase (FAAH) (Otrubova, Ezzili, & Boger, 2011). The role of the FAAH enzyme in the metabolism of endocannabinoids defined its role as a potential therapeutic target to modulate/amplify the beneficial therapeutic effects ascribed to endogenous anandamide (i.e., physiological analgesia) (Roques, Fournié-Zaluski, & Wurm, 2012). Preclinical studies support a rationale for FAAH as new therapeutic target for the treatment of pain based upon the pattern of expression of CB_1 in the CNS.

2.2. BIA 10-2474, a FAAH inhibitor

In January 2016, BIA 10-2474, a long acting FAAH inhibitor, developed by Bial-Portola & C^a, SA (Portugal) was tested in a phase I clinical trial at Biotrial (a CRO in Rennes, France) when severe clinical adverse events (SAE) developed affecting 6 study participants (Bial News Release, 2016). The first participant dosed in the 5th study cohort of the highest dose tested (50 mg) during conduct of the multiple ascending dose (MAD) phase of the study developed neurological symptoms that preceded coma and brain hemorrhage and death (Eddleston, Cohen, & Webb, 2016; Mallet, Dubray, & Dualé, 2016). Prior to the clinical testing of this FAAH inhibitor several others had advanced into phase I and II clinical trials without development of similar SAE's (Mallet et al., 2016; Roques et al., 2012). The French National Agency for Medicine and Health Products Safety (L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM)) established a Temporary Specialist Scientific Committee (TSSC) to investigate the case. The scientific mission of the TSSC was to analyze the mechanistic and toxicological data of BIA 10-2474 and advance any hypotheses that could possibly explain the clinical toxicity observed (ANSM, 2016a; ANSM, 2016b).

The TSSC report provides only a brief account for the types of nonclinical pharmacology, safety pharmacology and toxicology studies that were conducted to evaluate BIA 10-2474 prior to conduct of the phase I clinical study (ANSM, 2016a). No details beyond general study trends were provided and the report concludes that the safety profile of BIA 10-2474 was much less robust when compared to the development profiles of other FAAH inhibitors (ANSM, 2016a; ANSM, 2016b). The findings from the toxicology studies conducted did not suggest any specific end-organ toxicity that would preclude clinical development. The working hypotheses of the expert group for the observed clinical adverse effects were due to a lack of specificity for the FAAH enzyme, low selectivity (i.e., the drug targets other enzymes/receptors), possible overexposure to high levels of anandamide produced by high doses of enzyme inhibition and a longer half-life of the molecule