International Journal of Pharmacy and Analytical Research (IJPAR)

IJPAR |Vol.13 | Issue 4 | Oct - Dec -2024

www.ijpar.com

ISSN: 2320-2831

DOI : https://doi.org/10.61096/ijpar.v13.iss4.2024.510-517

Review

Role Of Post Approval Clinical Trials For Drug Safety

P.Sai Mounika*, Uppula Vennela, Dr.D.Venkata Ramana, Dr.Gadipally Sai Kran

Department of Regulatory, Holy Mary Institute Of Technology & Science, Kondapur, Telangana, India.

*Author for Correspondence: P.Sai Mounika
Email: vennelauppulavennela@gmail.com

Published on: 20 Oct 2024

Published by:
DrSriram Publications

2024| All rights reserved.

Creative Commons Attribution 4.0 International License.

Abstract

Following the drug-approval process, concerns remain regarding the safety of new drugs that are introduced into the marketplace. In the case of rare adverse events, the number of subjects that are treated in randomized controlled trials is invariably inadequate to determine the safety of the new pharmaceutical. Identifying safety signals for new and/or existing drugs is a major priority in the protection of public health. Unfortunately, design, analysis, and available data are often quite limited for detecting in a timely fashion any potentially harmful effects of drugs. In this review, we examine a variety of approaches for determining the possibility of adverse drug reactions. Our review includes spontaneous reports, meta-analysis of randomized controlled clinical trials, ecological studies, and analysis of medical claims data. We consider both experimental design and analytic problems as well as potential solutions. Many of these methodologies are then illustrated through application to data on the possible relationship between taking antidepressants and increased risk of suicidality.

Keywords: Poisson regression, propensity scores, adverse events, meta-analysis, mixed-effects models, suicide

INTRODUCTION

Post-marketing studies are a major activity in the life cycle of a licensed drug/medicinal product and are regularly conducted by pharmaceutical companies and contract research organisations. Regulatory agencies rely on such industry funded studies for surveillance of drug safety. In particular, the detection of “rare” (1 in 1000) and “very rare” (1 in 10 000) adverse drug reactions is often possible only with post-marketing studies.[1]

According to the German Medicinal Products Act (Arzneimittelgesetz, AMG) all companies initiating a post-marketing study in the German drug market are required by law to register their study. The act specifies that the purpose of such studies is to investigate the use of medicinal products in daily routine, to assess rare adverse drug reactions, and to improve long term drug safety.[2] To our knowledge there is no such law in other countries

requiring all post-marketing studies to be registered, and there is considerable variation in the definition of such studies and the scope of registration in other EU countries.[3] In this context, it should be of note that drug licensing and pharmacovigilance activities have been harmonised in the EU since 2001.[4]

In the US, regulatory approval and registration of some post-marketing studies is required (such as interventional studies that must be registered under the US Food and Drug Administration Amendments Act of 2007[5]), but, unlike Germany, not all post-marketing studies have to be registered. In light of the documented lack of knowledge about rare adverse drug reactions from pre-marketing randomised controlled trials[6] and systematic under-reporting of spontaneous reporting schemes,[7] German regulators,[8] physician bodies,[9,10] and statutory health insurers [11] have re-emphasised the importance and necessity of post-marketing studies for evaluating newly authorised drugs.

Despite Germany requiring the registration of all post-marketing studies, little is known on their size, cost, and nature. We therefore initiated freedom of information requests to obtain registration documents to understand the current state of post-marketing studies and evaluate whether these studies meet the aims specified in the Medicinal Products Act, particularly their potential to assess rare adverse drug reactions and thus help improve long term drug safety.

Randomized controlled trials (RCTs) have been considered the gold standard to demonstrate efficacy since the 1960s.[12,13]While current routes to market for investigational drugs typically require at leasttwo pivotal RCTs, these are time-consuming, costly, and produce evi-dence that can have limited applicability in real-world clinical practice. There is, therefore, a move towards investigating innovative ways to improve the efficiency of clinical research.[14,15]

The controlled nature of an RCT offers advantages in evidence generation as there are standard methods to reduce bias (like random-inaction and blinding), and they have comprehensive measurement of outcomes to demonstrate efficacy against both active and placebocontrols.[16]

However, RCTs do not accurately reflect real-world circumstances under which patients are treated; thus, there is often need for observational studies to support additional evidence generation, particularly around questions of safety. Real-world data (RWD) forms the basis for real-world evidence(RWE) and can be extracted from a broad range of sources such as patient registries, health care databases, claims databases, patient net-works, social media, and patient-generated data from wearables.[17-20]The definitions of RWD and RWE are relatively consistent between key regulatory agencies (see Table 1).[21]

While RWE from observational studies is well accepted for post-approval safety monitoring and to answer pharmacy economic questions3,[22,23] its contribution to regulatory decisions around effectiveness has been more limited. Indeed, evidence quality can be compromised by confounding by indications or a general lack of rigorous collection standards. There is, therefore, a need for the development of novel trial methodologies that can take the best parts of traditional RCT and observational study designs to produce RWE that provides adequate scientific evidence for regulatory decision-making. It has already been recognised byhealth authorities that there is a wide spectrum of potential uses ford/RWE in clinical studies, some of which preserve key features such as randomization.

The emerging rules for rwe thatis fit for regulatory purposes

The 21st Century Cures Act and PDUFA VI requires the FDA to accelerate drug development and approval processes, and more specifically, to produce guidance on how to incorporate patient perspectives and innovative study designs, including RWE, into the drug development process. The recently published FDA framework for evaluation of how RWE can be incorporated into the regulatory approval process highlights the key topics for which full evaluation will be undertaken.

There is a need to define the rules for RWE that is fit for regulatory purposes. However, while the development of innovative trial designs is being actively encouraged by the major regulatory agencies, particularly with the FDA's Complex Innovative Trial Designs Pilot Program and Clinical Trials Transformation Initiative and the EMA's adaptive pathways initiative, the required standards to produce RWE that is acceptable for regulatory decision-making havenot yet been fully defined. Although regulators are open top roposals for studies with RWD and receiving RWE, the decision topursue an innovative study design as part of a clinical development program and regulatory approval strategy is not straightforward, asthe routes to obtaining pilot guidance are complex and the“rules”for acceptance of evidence in regulatory decision-making are not yet firmly defined. It is therefore essential to engage with regulatory authorities early to obtain alignment on objectives, inform the studydesign, and ensure the study design and data are acknowledged as“fit-for-purpose”before conducting a study that may not meet the regulatory goals.

To aid this process, several stakeholders have published frame-works and recommendations for the creation of RWE suitable for use in regulatory decisions. The Duke-Margolis Center for Health Pol-icy, with support from the FDA, released a white paper on the regulatory use of RWE in 2017 following open consultation with academics, patients, and industry.48Emphasizing considerations for developing RWE that is fit for regulatory purposes, they identified several areas for practical improvement, including the need to ensure that the appropriate

RWD sources are matched with appropriate study designsand data collection and handling methods to address the research question. They also encourage the formation of transparent collaborations and the sharing of datasets. Professional societies have also weighed in here too, with the International Society for Pharmaco economics and Outcomes Research and the International Society for Pharmacoepidemiology publishing recommendations forgood procedural practices for RWE, aiming to build trust and expandits current use in health care decision-making.Many of the recom-mendations made in these aforementioned publications have beenformalized in the FDA framework document.

An important part of planning innovative studies to produce RWE that provides adequate scientific evidence for regulatory decision-making is preparation of a thorough analytical plan at the outset ofthe study. This is already an integral part of most traditional pivotaland post-safety trials and should reasonably be extended to effective-ness studies that use RWD. Some also argue that pivotal and safety outcome RCTs and observational post authorization safety studies should be registered on appropriate repositories (eg, ClinicalTrials.gov or the EU PAS Register) prior to study initiation as a requirementof the regulatory process. Whether RWE studies will be required to beregistered in such a way is a topic of ongoing debate, with opinionsharply divided. Registration by itself is no guarantee of study quality,and any benefit from registration would be heavily dependent on whatinformation would be required to be posted (eg, study protocols,methodological details, etc.). Further discussions between stake-holders will be required before a consensus develops.

In a separate framework on the regulatory use of RWE, Dreyer(2018) has discussed the requirement and transferability of key RCTstudy design elements to real-world studies. This builds on the cur-rent thinking around clinical outcomes from RWD analysis, suggest-ing that outcomes should be patient-centric and should beobservable and relevant to daily clinical practice. Specific issues areaddressed, such as blinding, which is routinely used in RCTs, but isoften impractical to achieve under“real-world”circumstances, espe-cially when comparing pharmacologic and nonpharmacologic treat-ments and when using a selection of“standard of care”comparators, which differ by locale, and while informative, wouldbe impossible to blind. Furthermore, blinding might not be necessaryfor objective outcomes such as the results of a blood tests and imag-ing, for example, where in most cases, third-party raters, such aspathologists, are essentially blinded to treatment.The importanceof using data sources that are“fit for purpose”and the familiarityof researchers with potential sources of bias or error so that themost appropriate study methodology is employed is also emphasized.Analytical methods should be transparent, defined up front, and opti-mized to answer the research question.

Regulators and industry have acknowledged the value of scientifi-cally rigorous and innovative study methodologies as the key route toachieving the standard of substantial evidence for RWE.As ameans to achieve this, the FDA framework proposes that the follow-ing should be considered: (a) whether the RWD are fit for use; (b)whether the trial or study design used to generate RWE can provideadequate scientific evidence to answer or help answer the regulatoryquestion; (c) whether the study conduct meets FDA regulatoryrequirements (eg, for study monitoring and data collection).8It shouldbe noted that strict applicability of these rules, particularly for moni-toring, is rarely feasible for studies that rely on existing data, sincethe identities of patient and care providers are masked to protect pri-vacy in most secondary data sources.

Similarly, the EMA in its recent report on the use of large datasetsfor RWE made several recommendations to improve the quality ofRWE, including the need to define standard formats for documentingdatasets, protocols, and tools used to ensure study reproducibility. Inaddition, it emphasizes the need to ensure that outcome measuresfrom novel data sources such as wearables should be reflective of adefined clinical benefit.If these considerations and recommenda-tions are fully addressed by novel study methodologies, the qualityof RWE will improve, and studies using RWD could increasingly beused in support of decisions about therapeutic effectiveness. Thedevelopment of sufficiently robust RWE will ultimately depend onthe ability of experts such as pharmacoepidemiologists, statisticians,data scientists, and academics to develop these new methodologiesto optimize hybrid study designs, RWD collection and analysis in away that is compliant with our current understanding of best practicefor RWE generation, and open to regulatory scrutiny.Sponsors anddata owners should proactively identify and develop standard operating procedures to be prepared for FDA audits and oversight bydefining requirements for record retention, auditing, and patientprivacy.

Modernizing the classical rct

Some specific hybrid study designs under consideration for regulatory decision-making by the FDA fall into three broad categories: (a) inves-tigational new drug submissions for RCTs that use RWD to capture clinical outcomes or safety data, including pragmatic and large simple trials; (b) protocols for single-arm trials that use external controls; (c)clinical trials using RWE to fulfil a post-marketing requirement for further evaluation of safety or effectiveness to support a regulatory decision.

Pragmatic and large simple trials

Pragmatic and large simple trials mirror many of the features of RCTs including randomization but are typically very large RCTs and enable broader patient group to participate. These trials are increasingly being used

to demonstrate effectiveness in a daily clinical practice setting and allow more clinically meaningful outcomes to be studied, creating readily transferable benefits for patients. This notion links in with the ever-developing narrative around patient-centric care and the increasing involvement of patients in the drug development process, aiming to increase the relevance of new therapeutic interventions to the patient experience.52,53One of the first examples of a large simple trial was the Salk polio vaccine field trial of 1954, which led to regulatory approval of the vaccine and a nationwide public health response to eradicate polio. More recently, the feasibility of pragmatic trials was also tested by the label expansion achieved for Janssen's INVEGASUSTENNA (Case study 3) that was based on the findings of the Paliperidone Palpitate Research in Demonstrating Effectiveness(PRIDE) trial which was designed to include treatment randomization and pragmatic out comes. The trial was uniquely designed to mirror the population of adults living with serious and poorly controlled schizophrenia that health care professionals commonly see in clinical practice.

Chronic obstructive pulmonary disease (COPD) is the major cause of mortality and morbidity in the USA and growing cause of chronic disease globally. The current pharmacological therapies for COPD, such as corticosteroids and β2 agonists, may provide symptom relief, reduce the rate of exacerbations, hospitalisations and possibly mortality, but despite this, many patients still experience symptoms, exacerbations and disease progression. Although the exact cellular mechanisms underlying COPD pathogenesis are not completely understood, the consensus is that oxidative stress and inflammation induced by exposure to cigarette smoke or other environmental or occupational hazards are responsible for development of COPD.[24] Therefore, a neutraceutical with potent antioxidant and anti-inflammatory properties and relatively few side effects could be an attractive treatment option for COPD.

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a dietary flavonoid and has potent antioxidant and anti-inflammatory properties. We have demonstrated that oral treatment with a low dose of quercetin decreases inflammation, oxidative stress and matrix metalloproteinase production in a mouse model of COPD.[25] Quercetin supplemented diet also alleviates rhinovirus-induced lung inflammation in mice with COPD phenotype.[26] Recent studies have also demonstrated amelioration of hyperglycaemia, reduction of blood pressure and improvement of cardiovascular health by inhibiting platelet aggregation in experimental models.

Accumulating epidemiological evidence suggests that quercetin-rich diets are associated with lower incidence of asthma[27]and reduce disease severity in subjects with COPD.[28] Treatment with quercetin decreased markers of oxidative stress and inflammation in plasma of patients with pulmonary sarcoidos is, another chronic lung inflammatory disease driven by oxidative stress.[29,30] In another study, quercetin was shown to reduce blood pressure and plasma lipids in overweight or obese subjects with a high cardiovascular disease risk.[31] Daily intake of quercetin-rich onion peel extract (equivalent to 100 mg of quercetin/day) for 10 weeks decreased blood pressure, serum lipids and blood glucose levels in male smokers.[32] Additionally, treatment with quercetin for 12 weeks reduced the risk of acquiring upper respiratory infection in a large population of healthy adults.[33] The latter study also suggests that quercetin treatment in healthy volunteers has no adverse effects. Furthermore, a meta-analysis of randomised controlled trials indicated treatment with quercetin reduces plasma C reactive protein[34] and blood pressure in hypertensive subjects.[35] despite these epidemiological and experimental pieces of evidence, there have been no clinical trials examining the therapeutic effects of quercetin in COPD. An objective of this study was to determine the safety of quercetin supplementation in patients with COPD, because it is the first step towards using quercetin as a therapeutic agent in these patients.

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder with an increasing worldwide prevalence. Following seminal studies identifying the pulmonary veins (PVs) as the primary triggering sites of origin for AF, catheter-based electrical isolation of the PVs has emerged as an effective means to treat AF. Both procedural technique and catheter ablation technology—using either radiofrequency, cryothermal or laser energy—have improved over time such that AF is now the most commonly ablated arrhythmia. Indeed, clinical data support its use as first-line therapy to not only improve quality of life, but also mortality in heart failure patients, and, in concert with antiarrhythmic drugs, significantly decrease the rates of stroke and mortality in a broad spectrum of AF patients.Despite improvements in procedural outcomes, there remain safety considerations including stroke, PV stenosis, phrenic nerve palsy, pericardial tamponade and atrio-oesophageal fistula—the latter being the most dreaded complication because of an 50% rate of associated mortality. These complications highlight the weak link shared among all thermal energy-based ablation platforms: as the ablative heat (or cold) wave propagates through tissue, its destructive effect is tissue indiscriminate. Thus, collateral damage to surrounding tissue is the potential price paid for ablation transmurality. In contrast, pulsed field ablation (PFA) is a novel ablation modality that, in pre-clinical and clinical studies, has displayed preferential tissue ablation. Pulsed field ablation involves the application of ultra-rapid (microseconds to nanoseconds) electrical pulses to generate strong electrical fields causing, among other effects, irreversible nanoscale pore formation and, ultimately, cellular death. Pre-clinical and clinical studies have demonstrated that by optimizing voltage amplitude, phasic waveforms and pulse sequences, one can completely avoid damage to peri-cardiac structures such as the oesophagus and phrenic nerve. While there are several PFA catheter technologies in development, the technology with the greatest amount of pre-clinical and clinical evidence is the multi electrode pent spline PFA catheter— also the only PFA

catheter with regulatory approval (CE Mark). This pent spline PFA catheter has been studied in both paroxysmal AF patients in the IMPULSE, PEFCAT, and PEFCAT2 trials, and persistent AF patients in the Persephone trial. On the one hand, these trials demonstrated that AF ablation was not only feasible and effective, but the theoretical safety benefits observed preclinically were indeed realized in clinical practice. This included the absence of: (i) oesophageal damage as evaluated by oesophagi oduodenoscopy and thoracic MRI, (ii) phrenic nerve injury, or iii) PV stenosis/narrowing. On the other hand, these studies included only a modest number of patients (,150) and relatively few operators— raising the question of the pent spline PFA catheter safety profile in a large 'real world' environment. Since this technology commenced limited market utilization in March 2021, we conducted the MANIFEST-PF survey of its performance in an unselected patient population in routine clinical practice. We evaluated the catheter's acute effectiveness and safety, including rare oesophageal effects not discernable after the treatment of only 150 patients, and unforeseen rare PFA-related complications.

Psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) result from a complex interplay among environmental, genetic and immune triggers. Treatment is typically intended for a long duration; therefore, understanding the long-term safety profile of therapeutic agents is essential for clinical decision-making.

Interleukin (IL)-17-mediated inflammation plays a pivotal role in the pathogenesis of chronic immune-mediated inflammatory diseases (IMIDs). Therapeutic blockade of the IL-17 pathway results in the inhibition of both pathological and physiological mechanisms. The IL-17 family members IL-17A and IL-17F have pleiotropic effects on multiple immune cell types and play an important role in host defence against infections (specifically fungal infections). Therefore, it is important to address the effect of IL-17 blockade on opportunistic infections.

The pathogenesis of PsO, PsA and AS share common systemic inflammatory pathways and cytokines. Because of the inflammatory disease burden and genetic overlap, patients with IMIDs are more susceptible to cardiovascular disease (CVD), metabolic comorbidities and inflammatory bowel diseases (IBDs) vs the general population. These comorbidities, along with the concomitant medications used to treat these conditions, may affect the safety profile of treatments for PsO, PsA and AS.

Assessing the safety profile of a drug using data from multiple clinical trials and post-marketing experience across indications is best suited to identify risks that may become evident in a larger dataset. Secukinumab, a direct IL-17A inhibitor, has shown long-lasting efficacy and safety in treating the complete spectrum of psoriatic and spondyloarthritis (SpA) disease manifestations, including the nails, scalp, palms and soles, as well as PsA and axial SpA (axSpA) .

Secukinumab is currently approved in more than 100 countries for use in PsO, PsA and axSpA. Over 20,000 patients have been treated with secukinumab in a clinical trial setting, and approximately 500,000 patients have been treated worldwide since launch. A longer-term report of pooled safety and tolerability data for secukinumab across the 3 indications (up to 5 years of treatment in PsO and PsA; up to 4 years in AS) was consistent with the safety profile observed in individual clinical trials.

This integrated safety assessment (ISA) in PsO, PsA and AS patients who received secukinumab treatment for up to 5 years included pooled clinical trial data and post-marketing safety surveillance data. The current report enhances the previously published pooled safety report with a larger dataset and longer exposure to secukinumab.

Biopharmaceutical companies and their development partners increasingly use data from real-world settings to generate evidence that can support regulatory decision making and approvals of their manufactured medical products. The use of such real-world evidence (RWE) can complement[1] or, in some cases, serve as an alternative to evidence traditionally yielded by randomized controlled trials (RCTs). For example, the use of external control arms[3] can have considerable benefits, including accelerating the development process or reducing burden on trial participants. RWE can also provide investigators the opportunity to ask more questions and to understand broader, more diverse populations, as compared to RCTs.

The US Food and Drug Administration (FDA; also referred to here as the Agency) has taken significant steps to advance the use of RWE in regulatory decision making. This momentum has grown after the 21st Century Cures Act passed in December 2016; the act required FDA to develop a program for evaluating the use of RWE to support new indications for already-approved drugs and fulfil post approval study requirements. In 2018, FDA published a framework for its RWE program and is currently drafting guidance on its regulatory expectations regarding the use of RWE in medical product approvals As part of its broad impact, FDA's framework has helped to promote common definitions for real-world data (RWD; defined as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources") and RWE (defined as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD"[4]). This is part of a worldwide interest in the use of RWE, including by regulatory agencies, such as the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the National Medical Products Administration (NMPA) in China.

Much of FDA's regulatory use of RWE to date has been in the context of post market surveillance through programs like FDA's Sentinel initiative, a system initially designed to aid the Agency in evaluating medical product safety, and which has more recently expanded in scope. Current goals include enhancing

Sentinel's ability to evaluate effectiveness[8] and extending the evaluation of safety. In parallel, FDA also created a pilot project in 2008 to provide for the evaluation of vaccine effectiveness and, in 2017, launched the Biologics Effectiveness and Safety (BEST) system to enhance FDA's use and analysis of data to assure the safety and effectiveness of biological products.

Beyond post market surveillance, FDA considers RWE studies as part of the evidence package for submissions seeking authorization to market new medical products, including new drug applications (NDAs) and biologics license applications (BLAs). These submissions are reviewed and decisions are rendered primarily by two centers within the Agency: the Center for Drug Evaluation and Research (CDER), which focuses on drug products and therapeutic biological products, and the Center for Biologics Evaluation and Research (CBER), which focuses on biological products including vaccines. Studies submitted as part of a sponsor's overall evidence package will be considered in decision making. Approvals will then be based on, among other things, studies that provide "substantial evidence" (in CDER decisions) or "primary evidence" (in CBER decisions), which make the primary case for product safety and effectiveness, and "supportive evidence," which can serve to bolster the case. Submitted studies providing therapeutic context can help reviewers understand the landscape of the disease (such as disease prevalence and incidence) and any current standard of care, but may not directly affect decision making. Many submitted studies will be presented in the FDA-approved product label of an approved or licensed drug or biological product. As such, RWE studies have the potential to be directly influential in prescribers' decision making if FDA approves a product label that includes submitted RWE studies.

FDA and others have directly and indirectly provided insights into FDA's current approaches by speaking to and publishing select examples of successful and unsuccessful uses of RWE studies in medical product approvals, and FDA has provided publicly available guidance for industry and staff. However, RWE methodology is evolving, and on many important topics, RWE stakeholders lack a shared understanding of FDA's expectations around the use of RWE, particularly in the context of NDAs and BLAs.

To date, there are no published systematic assessments of the use of RWE studies in FDA-approved NDAs and BLAs, nor on FDA's feedback on and acceptance of such studies. In this paper, we address this gap by presenting a systematic review of FDA's written approval documents involving RWE studies in NDAs and BLAs to determine whether and how FDA incorporated that evidence in its final decision for approval. We summarize trends in recent use of RWE in FDA-approved NDAs and BLAs, as well as whether and how RWE supported FDA's approval decision. By distilling these reviews, we also seek to identify best practices for avoiding common design and analysis pitfalls identified by the Agency.

SARS-Cov-2, a member of the coronavirus family, has been ravaging the world for the past 18 months. Although an effective treatment has eluded the medical community, there have been several registered trials on finding new or repurposed drugs. Several studies have discussed the mechanism of the virus-host interaction and possible treatments[35], but safe and effective treatment for the disease is yet to emerge. Drug repurposing seems to be an immediate solution, and various drugs have been suggested for the COVID-19 treatment[36,37].

The drugs required to combat the pathogen may fall into one or more of the following categories: antivirals, anti-inflammatory agents, and supportive therapies[38,39]. According to V'Kovski the antiviral action can be based on the stages of viral-host interactions. These include attachment and virus neutralisation, host protease inhibitors that stop the entry of the virus, viral protease inhibitors, viral RdRp inhibitors, and viral maturation inhibitors. Frediansyah et al.[40] enumerated the possible antiviral solutions at various stages of interactions. The role of cathepsin L in cleavage of the S protein complex and subsequent release of virus genome is well documented. Inhibiting cathepsin L inhibits the entry of SARS-Cov-2 by 76%[41].

Pro-inflammatory cytokine production is natural during the immune response. The elimination of virus-infected cells is an essential step in disease control. If this step, which naturally follows virus entry and replication, is defective or prolonged, it can result in a cytokine storm[42], an uncontrolled release of pro-inflammatory cytokines. Several interleukins are involved in a cytokine storm, the foremost being interleukin 6 (IL-6), IL-1[43], and IL-17[44]. IL-17 also seems to have a role as the interaction partner of SARS-Cov-2. Therefore, anti-inflammatory drugs targeting the production of these interleukins are necessary for COVID-19 treatment.

Indomethacin as a drug for sars-cov-2

Amici et al.[45] were the first to identify the antiviral activity of indomethacin. They recorded the antiviral activities of indomethacin against SARS-Cov-1 in vitro. Xu et al.[46] presented evidence of its antiviral activity against SARS-Cov-2. Their investigations covered the antiviral effect of indomethacin in vitro, cellular, corona-infected canine models. They also stated that indomethacin does not reduce infectivity, binding, or entry into target cells. This conclusion is based on the results of for SARS-Cov-1, although computer models have indicated otherwise[47]. Downregulation of ACE2 and TMPRSS2 is important to reduce infectivity. Using an open-source code, Gene2Drug, Napolitano et al. showed in a computer model that indomethacin downregulates ACE2 by suppressing the genes in the ACE2 pathway. Raghav et al.[48] depicted the role of indomethacin in inhibiting cathepsin L activity required for fusion. Interestingly, no other non-steroidal anti-inflammatory drugs projected this quality.

Non-Structural Protein7 (Nsp7), along with Nsp12, is essential for RNA synthesis, as highlighted by recognised that prostaglandin E synthase 2 (PGES-2) is an "interactor" with Nsp7, and indomethacin inhibits PGES-2. Hence, indomethacin is an essential candidate for blocking RNA synthesis. reported this block of RNA synthesis. Amici et al.[49] also demonstrated that protein kinase R (PKR) activation by indomethacin inhibits virus protein translation. This follows the work of Brunelli et al.[50], where the role of indomethacin in activating PKR directly has been demonstrated.

Several publications[51,52] have highlighted the importance of preventing inflammation in Covid-19 patients. For example, indomethacin downregulates IL-6 by inhibiting the synthesis of PGES-2[53]. In addition, indomethacin has successfully contained cytokine reactions in kidney transplant patients receiving OKT3 therapy[54,55].

conducted one of the first indomethacin trials. The objective was to compare the data from open-label single-arm data for indomethacin; they showed the effect of indomethacin as a treatment option by matching propensity score with retrospectively collected data on paracetamol. Gordon et al. indicated by retrospective data analysis that indomethacin markedly reduces the need for hospitalisation. Two studies[56] have shown the effectiveness of indomethacin in treating a small number of SARS-Cov-2 patients with severe comorbidities. However, these were small case series, and a larger controlled trial is required to validate these findings.

The primary objective of this study is to determine the percentage of desaturating patients as a quantitative criteria $SpO_2 \leq 93$ has been used as a measure. The secondary outcome was symptomatic relief. Time to become afebrile, relief from cough, and myalgia are the significant symptoms for the secondary outcome. The safety profile of indomethacin was also monitored as a secondary outcome.

RET fusions are identified in 1%-2% of patients with non–small-cell lung cancer (NSCLC).[1] These fusions result in ligand-independent constitutive activation of the RET pathway and increased oncogenic signaling. Both selpercatinib and pralsetinib are selective RET inhibitors, which have demonstrated promising clinical activity in patients with *RET* fusion–positive NSCLCs. This underscores the benefit of including *RET* fusions as part of comprehensive oncogene driver testing in patients with NSCLCs.

On the basis of compelling and durable responses observed in the largest clinical study in RET-altered cancers, selpercatinib emerged as a new standard of care for patients with *RET*-altered lung and thyroid cancers. The drug was first approved in May 2020 by the US Food and Drug Administration for adult patients with *RET* fusion–positive NSCLCs and subsequently has gained regulatory approval in multiple geographies. Additional data regarding the drug's activity and safety, with increased patient numbers and longer follow-up, are valuable as more providers treat patients with this first-in-class, highly selective, and potent RET inhibitor.

In LIBRETTO-001, a registrational, phase I/II, single-arm, open-label study, selpercatinib demonstrated durable antitumor activity, including intracranial efficacy. In the initial registrational analysis set (n = 144), high response rates and favorable tolerability were observed in both treatment-naive (n = 39) and platinum-based chemotherapy pretreated (n = 105) patients with *RET* fusion–positive advanced NSCLC.However, since the majority of patients were alive and progression-free at the time of initial approval, the median duration of response (DoR) and progression-free survival (PFS) could not be accurately estimated.

In this article, we provide an updated analysis of the activity of selpercatinib in *RET* fusion–positive NSCLC. This includes efficacy in a total of 316 patients (172 additional patients). Furthermore, we provide 18 more months of follow-up than that previously published.

Aim and objectives

To enable timely access to innovative drugs, the European Medicines Agency (EMA) can conditionally approve drugs based on a less comprehensive evidence package when immediate availability of the drug outweighs the risks due to the less comprehensive evidence package. Importantly, the benefit-risk balance still needs to be judged positive, but more uncertainty may be considered acceptable in light of the drug's potential to address unmet medical needs.

CONCLUSION

Trials are usually powered to detect benefit and seldom designed with adverse events as primary outcome. It is not possible to design trials to evaluate unexpected or unknown adverse effects that have yet to be linked to the intervention. Clinical trials should include explicit pre specified monitoring of pharmacologically predictable adverse events and ensure adequate follow-up of withdrawn participants. Recent regulatory guidance from the FDA has limited the reporting of adverse events in clinical trials from sponsors to those that are unexpected and considered related to the drug. It is unclear how isolated investigators will determine the causal relationship between a drug and its adverse events. The expanding role of electronic trials registers with detailed study results has potential that can only be fully realized when sponsors provide reliable, accurate and complete dat. Empirical work is needed to evaluate whether novel approaches such as mechanism-based drug toxicity

prediction can complement safety data from clinical trials and improve an assessment of drug safety. Methodological research is needed to determine whether network meta-analysis techniques can provide reliable and valid comparative evaluation of drug safety. The European Medicines Agency has recently undertaken methodological work to enhance the consistency and transparency of their risk-benefit decision-making process. Current proposals emphasize the need to not just consider the magnitude and consequences of treatment effects, but also to evaluate less tangible factors such as the level of uncertainty and extent of risk tolerance. These developments are particularly relevant when considering rare but serious adverse events where the clinical trials may yield imprecise or even conflicting estimates. Multi-criteria decision analytical techniques that accurately capture quantitative inputs and qualitative values from various stakeholders for risk-benefit trade-offs and allow for quantitative analysis and modelling uncertainty on a range of outcomes can improve complex regulatory decisions about drug safety.

ACKNOWLEDGEMENT

The Authors are thankful to Sura Labs, Dilshukhnagar, Hyderabad for providing the necessary facilities for the research work.

REFERENCES

1. Council for International Organizations of Medical Sciences (CIOMS). Reporting Adverse Drug Reactions. Definitions of Terms and Criteria for their Use, CIOMS 1999. http://www.cioms.ch/publications/reporting_adverse_drug.pdf.
2. German Medicinal Products Act (AMG), section 4, subsection 23, version 2004. Bundesgesetzesblatt2004;356:2031.
3. McCully S. Conducting non-interventional studies in Europe. Attempts at Clarity lead to increased complexity. http://www.inventivhealthclinical.com/Collateral/Documents/English-US/landing/Non-Interventional%20Research_Jan_Feb%202015.pdf.
4. European Regulation (EC) No 726/2004. Official Journal of the European Union L 2004;136:30.4.
5. Food and Drug Administration Amendments Act. 2007. Section 801. https://clinicaltrials.gov/CT2/manage-recs/fdaaa.
6. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. BMJ. 1998; 356:1295-8. doi:10.1136/bmj.316.7140.1295 pmid:9554902.
7. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;356:19-31. doi:10.2165/00002018-200932010-00002 pmid:19132802.
8. von Jeinsen BKJG, Sudhop T. A 1-year cross-sectional analysis of non-interventional post-marketing study protocols submitted to the German Federal Institute for Drugs and Medicinal Devices (BfArM). Eur J Clin Pharmacol2013;356:1453-66. doi:10.1007/s00228-013-1482-z pmid:23512215.
9. Müller CH. Anwendungsbeobachtungen. Notwendig: Mehr Transparenz und Wissenschaftlichkeit. (Post-marketing non-interventional studies. More transparency and scientific value required.) [in German] Dtsch Arztebl2009;356:A2042-44.
10. Wink K. Anwendungsbeobachtungen in der ärztlichen Praxis. Im Auftrag der Arzneimittelkommission der Deutschen Ärzteschaft. 2. Auflage Berlin 2010. (Post-marketing non-interventional studies in clinical practice. On behalf of the Drug Committee of the German Medical Association, in German) http://www.akdae.de/Stellungnahmen/Weitere/20101218.pdf.
11. Dietrich ES, Zierold F. Evaluation der wissenschaftlichen Qualität von Anwendungsbeobachtungen (Evaluation of the scientific quality of post-marketing non-interventional studies, in German). https://www.tk.de/centaurus/servlet/contentblob/148560/Datei/1045/Anwendungsbeobachtungen-Zusammenfassung.pdf.
12. United States Food and Drug Administration, Center for Drug Evalu-ation and Research, and Center for Biologics Evaluation and Research.Guidance for Industry. Providing Clinical Evidence of Effectiveness forHuman Drugs and Biological Products. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf. Accessed July 9, 2019.
13. United States Food and Drug Administration. Kefauver-HarrisAmendments Revolutionized Drug Development. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm. AccessedJuly 9, 2019.
14. Ho PM, Peterson PN, Masoudi FA. Evaluating the evidence Circula-tion.2008;118(16):1675-1684.
15. Mahajan R. Real world data: additional source for making clinical deci-sions.Int J Appl Basic Med Res. 2015;5:82-82.