[Original Research]

CHEST

Comparative Safety of Drugs Targeting the Nitric Oxide Pathway in Pulmonary Hypertension

A Mixed Approach Combining a Meta-analysis of Clinical Trials and a Disproportionality Analysis From the World Health Organization Pharmacovigilance Database

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BACKGROUND: Recent guidelines recommend riociguat, a soluble guanylate cyclase (sGC) stimulator, and the type 5 phosphodiesterase inhibitor (PDE5i) tadalafil or sildenafil as treatments for pulmonary arterial hypertension. We compared the safety profiles of sildenafil, tadalafil, and riociguat in pulmonary hypertension.

METHODS: We combined two approaches. First, we performed a meta-analysis of safety data extracted from randomized controlled trials. Second, we conducted a disproportionality analysis of data from VigiBase, the World Health Organization's global database of individual case safety reports, to compare the safety profiles with real-life data.

RESULTS: In the meta-analysis, a significant difference between the three drugs was only detected for gastrointestinal disorders, in disfavor of riociguat ($P < .01$ for interaction). In the disproportionality analysis, the use of riociguat was associated with fewer reports of visual disorders but increased reporting of gastrointestinal, hemorrhagic, and musculoskeletal disorders compared with sildenafil and tadalafil. Pharmacovigilance signals of hearing/vestibular disorders were heterogeneous: vestibular disorders (dizziness) were reported more frequently for riociguat, whereas hearing disorders (deafness) were reported less frequently compared with PDE5is.

CONCLUSIONS: The safety profiles of PDE5is and sGC stimulators significantly differ in pulmonary hypertension. Accordingly, there is a safety rationale in switching between PDE5is and sGC stimulators because of their different side effects.

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KEY WORDS: adverse event; meta-analysis; phosphodiesterase 5 inhibitors; soluble guanylate cyclase stimulators

ABBREVIATIONS: ADE = adverse drug event; ADR = adverse drug reaction; GRADE = Grading of Recommendation Assessment, Development and Evaluation; ICSR = individual case safety report; NNH = needed to harm; NO = nitric oxide; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase-5 inhibitor; PH = pulmonary hypertension; PRR = proportional reporting ratio; RCT = randomized controlled trial; sGC = soluble guanylate cyclase; WHO = World Health Organization

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Pulmonary hypertension (PH) refers to diseases characterized by a mean pulmonary artery pressure > 25 mm Hg.[1] Currently, three main pathophysiologic pathways are targeted in the management of type 1 PH (pulmonary arterial hypertension [PAH]): the prostacyclin, endothelin, and nitric oxide (NO) pathways.[1,2] In the latter, phosphodiesterase-5 inhibitors (PDE5is) decrease the degradation of cGMP, which is responsible for vasodilation. PDE5is (sildenafil and tadalafil) have been approved for over a decade for PAH.[3-6] More recently, riociguat, a soluble guanylate cyclase (sGC) stimulator which increases the production of cGMP, has been approved to treat PAH and type 4 PH (chronic thromboembolic PH). Currently, the European Society of Cardiology/European Respiratory Society guidelines[7] recommend riociguat, tadalafil, or sildenafil for New York Heart Association functional class II and III PAH. Given that these drugs target the same pathway and cannot be combined,[1,8] thorough comparison of their respective safety profiles may guide clinicians in choosing the most appropriate one.[9]

Assessment of drug safety is complex and may require mixing methods and approaches beyond clinical trials to get a precise overview of the safety profile of a drug or a therapeutic class. Meta-analyses of safety data from randomized controlled trials (RCTs) provide precise quantification of adverse drug events (ADEs) collected in a standardized way but on limited and selected populations. Contrariwise, pharmacovigilance databases are based on spontaneous reporting of adverse drug reactions (ADRs) in the general population, allowing detection of associations between the reporting of an ADR and a drug (a pharmacovigilance signal). The strength of this association may be used as a proxy of the risk of an ADR.[10-12]

Therefore, we compared the safety profile of sildenafil, tadalafil, and riociguat in PH by combining these two approaches. First, we performed a meta-analysis of safety data extracted from RCTs. Second, we conducted a disproportionality analysis using the World Health Organization's (WHO's) global individual case safety report (ICSR) database, VigiBase, to compare ADRs in real life.

Methods

Study Design

Following a literature review to define the various categories of ADEs, we performed a meta-analysis and a disproportionality analysis using VigiBase (Fig 1).

Classification of ADEs

From the literature review we defined nine ADE categories from safety profiles of drugs targeting the NO pathway[9,13-17]: cardiac arrhythmias; ischemic heart disease; visual, musculoskeletal, hearing/vestibular, and gastrointestinal disorders; edema; hemorrhages; and vasodilatation-related disorders. These categories were coded according to the Medical Dictionary for Regulatory Activities classification as were ADEs extracted from studies included in the meta-analysis and ADRs from VigiBase (e-Appendix 1).

Meta-Analysis

The meta-analysis was conducted following a predefined protocol (registered on PROSPERO as CRD42016051986) and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.

Search Strategy: We searched MEDLINE, ClinicalTrials.gov, the Cochrane Library, and the reference lists of all included studies, from 1966 to January 2016. See e-Appendix 2 for details of the search strategy.

Eligibility Criteria: We included only RCTs assessing the efficacy of sildenafil, tadalafil, or riociguat on PH. Details of inclusion and exclusion criteria, the screening process, and data collection form are available in e-Appendix 3.

Data Extraction: For each published study included, we searched clinical trial registers for safety results. If not reported, we asked the authors for complete safety data.

The following data were collected for each study: study characteristics (author name, year of publication, total number of patients randomized, length of follow-up, and number of study sites), patient characteristics (age, sex, and PH etiology), intervention (treatment, dosage, add-on or not, and duration of treatment), and outcomes (the number of patients with at least one ADE was extracted, classified, and pooled according to the adverse event category).

Risk of Bias Assessment: Independent assessment of risk of bias was made according to the *Cochrane Handbook for Systematic Reviews of Interventions*[18] and using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) (e-Appendix 4).[19]

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