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Is ibrutinib-related atrial fibrillation dose dependent? Insights from an individual case level analysis of the World Health Organization pharmacovigilance database

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Whether ibrutinib-related atrial fibrillation (IRAF) is a dose-dependent adverse drug reaction (ADR) and whether ibrutinib should be discontinued or dose-reduced in case of IRAF occurrence remains unknown. Using the World Health Organization individual case safety report pharmacovigilance database, VigiBase®, we aimed to determine the association between ibrutinib dosing regimens and IRAF reporting. Ibrutinib daily dose was extracted from IRAF cases from VigiBase® and was divided into 5 ibrutinib dosing regimen (140–280–420–560 and >560 mg/day). Disproportionality analysis was used to evaluate the association between IRAF reporting and ibrutinib daily dose, through logistic regression. Single term deletions produced the ibrutinib daily dose global *p*-value. Then, a multivariable adjusted reporting odds-ratio with its 95% confidence interval was calculated for each ibrutinib dosing regimen, against the lowest dosing regimen (140 mg/day) as reference. A total of 1162 IRAF cases were identified in VigiBase® ($n = 62$ for ibrutinib 140 mg/day, 114 for ibrutinib 280 mg/day, 811 for ibrutinib 420 mg/day, 164 for ibrutinib 560 mg/day and 11 for ibrutinib >560 mg/day). After adjustment on several variables of interest, IRAF reporting was not significantly associated with ibrutinib dosing regimen ($p = 0.09$). Our results from Vigibase® do not support IRAF as a dose-dependent ADR (ClinicalTrial registration number: NCT06224452).

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BACKGROUND

Ibrutinib, an orally administered Bruton's tyrosine kinase inhibitor (BTKi), has substantially transformed the therapeutic landscape of various chronic B-cell malignancies, particularly chronic lymphocytic leukemia (CLL) [1]. Early on, atrial fibrillation (AF) was identified as a cardiovascular adverse drug reaction (ADR) attributable to ibrutinib. In phase 3 randomized clinical trials (RCTs), ibrutinib has been associated with an approximately fourfold increased risk of AF compared with control groups (pooled relative risk 3.9; 95% confidence interval (CI): 2.0–7.5) [2]. The estimated annualized incidence rate of ibrutinib-related AF (IRAF) in clinical trials is 4.9 (95% CI: 2.9–8.3) per 100 person-years [3]. The risk of IRAF appears persistent over the course of ibrutinib therapy and may be cumulative, correlating with the duration of follow-up and increased intensity of cardiac monitoring [4, 5].

The underlying mechanisms of IRAF are not yet fully elucidated. The binding of ibrutinib to off-target kinases (e.g., EGFR, TEC) at therapeutic concentrations [6] may potentially contribute to the development of IRAF, which is corroborated by observations in a mouse model treated with ibrutinib where BTK was not the relevant kinase target associated with IRAF development [7]. A cardiovascular magnetic resonance imaging study indicated that ibrutinib exposure resulted in fibrosis and inflammation of the left atrium (LA), potentially leading to increased AF inducibility [8]. This role of LA fibrosis and inflammation in the development of IRAF is further supported by observations of increasing incidence rates of persistent and permanent IRAF from 15% to 38% and from 0% to 15%, respectively, over a follow-up period of 2 years in a prospective cohort study of 53 patients administered ibrutinib [4].

While dose reduction or interruption of ibrutinib is advised in its labeling [9], the beneficial impact on IRAF management of such an intervention remains inconclusive. Once LA fibrosis is established, it is questionable whether ibrutinib discontinuation or dose-reduction may not conduct to restore and maintain sinus rhythm.

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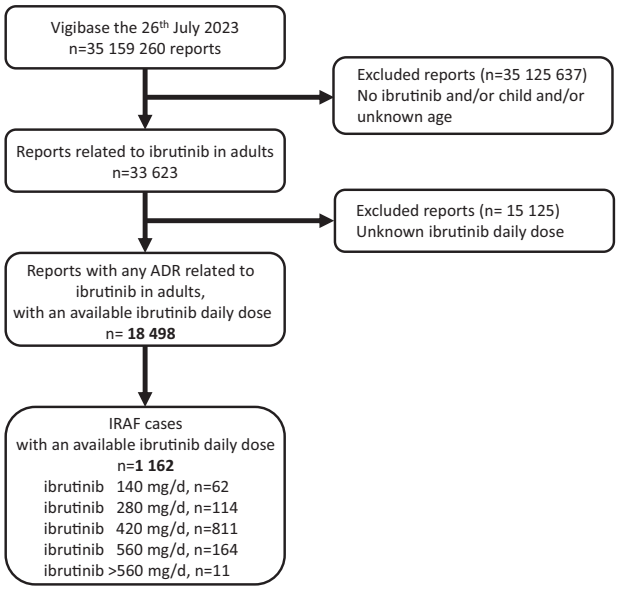

Fig. 1 Flow-chart for the primary analysis. AF atrial fibrillation, ADR adverse drug reaction.

Moreover, ibrutinib discontinuation or dose-reduction may influence the progression of the underlying chronic B-cell malignancy [10]. Consequently, there is ongoing uncertainty regarding both the mechanisms underlying IRAF and its clinical management, compounded by the observation that various AF phenotypic presentations [11–13]have been described, leading to heterogeneous therapeutic approaches [11–13].

The primary objective of this study was to ascertain whether IRAF is a dose-dependent ADR in patients with chronic B-cell malignancies by examining the association between ibrutinib dosing regimens and IRAF reporting in VigiBase®, the pharmacovigilance database of the World Health Organization (WHO).

METHODS

Data source

VigiBase®, the WHO global database of individual case safety reports, served as the data source for this investigation [14]. Managed by the Uppsala Monitoring Centre in Uppsala, Sweden, VigiBase® encompasses over 35 million reports from no fewer than 130 member countries since its inception in 1967. The reports, submitted by healthcare professionals, patients, and pharmaceutical companies post-marketing, encompass administrative details (country, report type, reporter qualification), patient demographics (age, sex), ADR onset data, and ADR nature, using the most recent version of MedDRA (Medical Dictionary for Regulatory Activities) terminology. Pertinent drug information (names, initiation and cessation dates, duration until ADR onset, indications, dosages, dosage unit [e.g. mg, g…], frequency of administration [once or twice a day…] is documented, and the drugs are catalogued using the WHO drug dictionary, which spans over 150,000 medicinal products and vaccines. This study utilized the Vigibase® Extract Case Level relational database, whose report-level structure facilitates multi-variate adjustments for potential confounders, including concurrent diseases or conditions and concurrent medications [14]. The use of pharmacovigilance confidential, electronically processed de-identified patient data was approved by the Caen University Hospital Research Ethics Committee (No. #2646). No individual patient informed consent was required because this was a retrospective analysis of anonymized data from the WHO pharmacovigilance database.

Primary objective and analysis

To investigate the association between ibrutinib dosing and IRAF reporting in VigiBase®, we performed on an observational, retrospective,

Table 1. Characteristics of IRAF cases in Vigibase®.

Ibrutinib dosing regimen	No	Female	Age >65 years	MedianTime to onset, days, (IQR; n available)	Concurrent drugs [availability is equal to the number of IRAF cases]				Concurrent diseases or conditions [availability is equal to the number of IRAF cases]									Cases resulted in death at the time of reporting
					Cardiovascular or diabetes drugs	Anticoagulants	AADs	Systemic corticosteroids	Haemorrhage	Sepsis	Hyperthyroidism	Hypokalemia	Dehydratation	HTN	Heart failure	Ischemic cardiopathy	Noninfectious myocarditis and/or pericarditis	Stroke/TIA	
Ibrutinib 140 mg/day	62	25	56	104 (73–146; 4)	31	10	6	5	12	0	0	0	0	0	9	2	0	1	3
Ibrutinib 280 mg/day	114	37	99	131 (101–201; 8)	61	28	12	12	30	3	0	1	5	7	28	5	2	1	15
Ibrutinib 420 mg/day	811	269	694	122 (48–274; 95)	422	187	53	79	202	40	1	20	19	62	221	39	8	36	68
Ibrutinib 560 mg/day	164	45	140	91 (46–241; 27)	84	35	13	21	41	16	0	5	4	8	45	11	1	6	26
Ibrutinib >560 mg/day	11	4	9	84.5 (25–179; 4)	6	5	2	3	1	1	0	0	0	1	2	0	0	1	2
Total (all ibrutinib regimens)	1162	380 (32.9%) [1156]	998 (85.9%) [1162]	120 (46–271; 138)	604 (51.9%) [1162]	265 (22.8%) [1162]	86 (7.4%) [1162]	120 (10.3%) [1162]	286 (24.6%) [1162]	60 (5.1%) [1162]	1 (0.1%) [1162]	26 (2.2%) [1162]	28 (2.4%) [1162]	78 (6.7%) [1162]	305 (26.2%) [1162]	57 (4.9%) [1162]	11 (0.9%) [1162]	45 (3.9%) [1162]	114 (9.8%) [1162]

Data are *n* (%) [availability] or the median (interquartile range) [availability].
AADs class I or III antiarrhythmics drugs or digoxin, *HTN* hypertension, *TIA* transient ischemic attack.

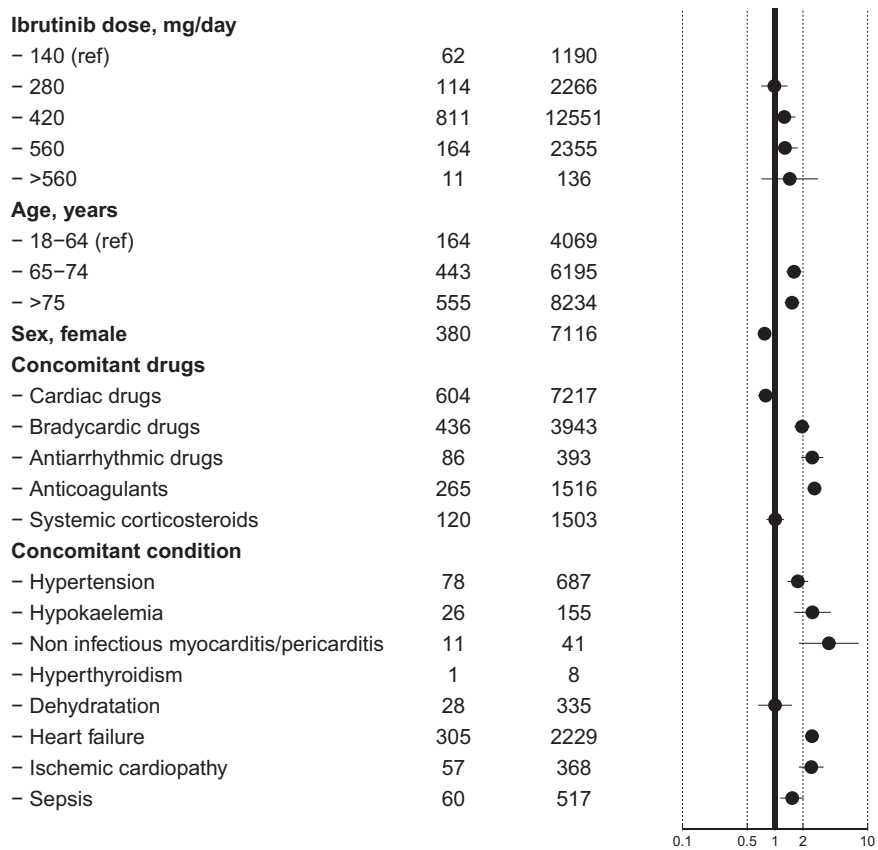

Fig. 2 Ibrutinib daily dose and ibrutinib-related atrial fibrillation (IRAF) reporting. Disproportionality analyses evaluating the association between ibrutinib daily dose and IRAF. Multivariable adjusted reporting odds-ratios (with 95% confidence interval) for each ibrutinib dosing regimen are presented against the lowest dosing regimen (140 mg/day). The ibrutinib daily dose global p-value indicates statistical significance if <0.05.

pharmacovigilance study employing disproportionality analysis [15]. The protocol of our study was registered on ClinicalTrials.gov, NCT06224452. The study population was confined to reports concerning adult patients treated with ibrutinib and for whom the daily dose was available (Fig. 1). IRAF cases were identified using MedDRA's 'Preferred Term' "Atrial fibrillation" until the 26th of July, 2023. Non-cases comprised all other ibrutinib reports that did not report IRAF. The daily dose extracted from IRAF case reports was stratified according to the dosing regimens specified on the ibrutinib product label (140–280–420–560, and >560 mg/day) [9]. Regarding IRAF cases with several ibrutinib doses, only the highest dose was retained. All IRAF cases were considered eligible regardless of the interval between drug initiation and the reporting of IRAF. The primary objective was to determine the association between ibrutinib dosing regimens and IRAF reporting.

Secondary objectives and analyses

IRAF cases were described according to each of the five ibrutinib dosing regimens. Variables such as age, sex, vital status at the time of reporting, concomitant diseases or conditions, ibrutinib indication, time to IRAF onset, and concurrent drugs were described.

The analyses encompassed: i. Evaluating the association between ibrutinib dosing regimens and IRAF reporting after excluding cases with concurrent administration of anticoagulants and/or antiarrhythmics, assuming this approach could eliminate cases with history of AF preceding IRAF reporting; ii. Stratified analyses according to the underlying chronic B-cell malignancy, with separate analyses for CLL and Waldenström macroglobulinemia (WM) indications and for mantle cell lymphoma (MCL), evaluating the association between ibrutinib dosing regimens and IRAF reporting; and iii. Examining whether the time to IRAF onset was dependent of ibrutinib dosing, with the time to onset calculated in days as per the internal procedures recommended by the Uppsala Monitoring Centre.

Positive controls were used in disproportionality analysis to validate the study setting. Two ibrutinib related ADRs well documented to be dose-dependent [9, 16] were tested against ibrutinib daily dose, in our dose-dependency research model: neutropenia and thrombocytopenia. Given that our primary analysis model was adjusted for multiple potential confounders pertinent to AF but not to neutropenia and thrombocytopenia, only univariate analyses were executed to explore the association between ibrutinib dosing regimens and reporting of these two ADRs.

Statistical analyses

VigiBase® allows disproportionality analyses—also referred to as case–noncase analyses—which compare the proportion of a specific ADR reported for a particular drug or group of drugs or drug dosing regimen to the proportion of the same ADR among a control drug group within a predefined population (e.g., the entire database cohort or particular subset). The denominator for these analyses constitutes the total number of ADRs reported for each drug grouping. Disproportionality is inferred when the odds of a specific ADR for a given drug exceeds the odds of the same ADR for the control drugs. This comparative metric can be quantified as a reporting odds ratio (ROR). In our study, a univariate analysis was first conducted, and RORs with their 95% CIs were then adjusted (aRORs) using a multivariate logistic regression model on age (categorized into "18–64 years", "65–74 years", and "≥75 years); sex; geographic region (African region, region of the Americas, South-East Asia region, European region, Eastern Mediterranean region, and Western Pacific region); concurrent drug reporting; and concurrent disease or condition reporting (see Supplementary Data 1). Ibrutinib daily dose was an explaining variable in our models. Hence, we first calculated its global p-value through single-term deletions, based on a Chi-square test. Second, we presented multivariable aRORs for each ibrutinib dosing regimen against the lowest dosing regimen (140 mg/day) as reference.

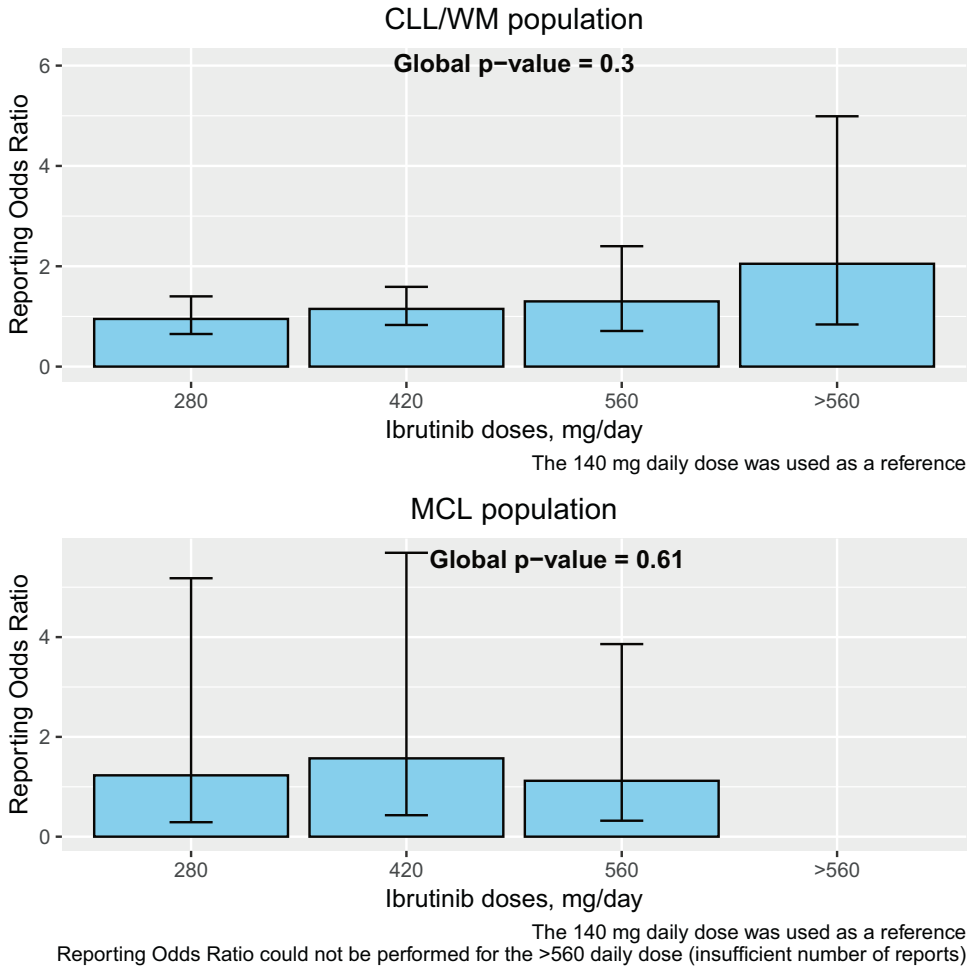

Fig. 3 Ibrutinib daily dose and ibrutinib-related atrial fibrillation (IRAF) reporting according to underlying chronic B-cell malignancy. Disproportionality analysis evaluating the association between ibrutinib daily dose and ibrutinib related atrial fibrillation, according to underlying chronic B-cell malignancy, with separate analyses for chronic lymphocytic leukemia (CLL)/ Waldenström macroglobulinemia (WM) and for mantle cell lymphoma (MCL) indication. Multivariable adjusted reporting odds-ratios (with 95% confidence interval) for each ibrutinib dosing regimen are presented against the lowest dosing regimen (140 mg/day). The ibrutinib daily dose global p-value indicates statistical significance if <0.05.

A p-value < 0.05 was considered indicative of statistical significance, that is, there was a significant association between ibrutinib dosing and IRAF reporting, thereby establishing IRAF as a dose-dependent ADR in VigiBase®. On the basis of the presumption that 10% of reports in each ibrutinib dosing regimen would be IRAF cases, a sample size 109 reports per ibrutinib dosing regimen was calculated to yield 90% power at $p < 0.05$ to detect a small-sized effect (ROR 2.5) [17]. Association between time to IRAF onset and ibrutinib daily dose was assessed with a linear regression model, followed by single-term deletion and Fisher test.

RESULTS

Primary objective and analysis

From the VigiBase® database, a total of 18,498 ibrutinib related-reports in adult patients, inclusive of ibrutinib daily dosage, were identified (constituting the primary analysis population), among which 1162 (6.3%) were IRAF cases (depicted in Fig. 1). Table 1 delineates the clinical characteristics of IRAF cases. Overall, IRAF cases concerned female patients (32.9%), aged over 65 years (85.9%), with CLL/WM being the main underlying chronic B-cell malignancy indication (85.8%), with concurrent cardiovascular or diabetes drugs in 51.9%, anticoagulants in 22.8%, antiarrhythmic drugs in 7.4%, concurrent hypertension in 6.7%, heart failure in 26.2%, stroke/transient ischemic attack in 3.9% and a fatality rate of 9.8% at the time of report.

In univariate analysis, ibrutinib dosing was significantly associated with IRAF reporting ($p = 0.02$). In the 2-by2 comparison against the lowest dosing regimen, as the dosing regimen increased, the ROR also increased but was not significantly superior to the lowest dosing regimen except for the 560 mg/day dosing regimen (see Supplementary Table 1). After adjustment for sex, age, geographic region, concurrent diseases or conditions and concurrent drugs of interest, ibrutinib dosing was not significantly associated with IRAF reporting ($p = 0.09$, illustrated in Fig. 2 and Supplementary Table 2). Factors such as age ≥65 years and multiple concurrent diseases or conditions (inclusive of hypertension, heart failure, and myocardial infarctions) and concurrent drugs (including antiarrhythmics and anticoagulants) exhibited a significant association with IRAF reporting (Fig. 2).

Secondary objectives and analyses

After exclusion of IRAF cases containing concurrent anticoagulant and/or antiarrhythmic drugs, in both univariate and multivariate analyses, there was no significant difference between ibrutinib dosing regimens and IRAF reporting (Supplementary Tables 3 and 4).

In both univariate (Supplementary Table 5) and multivariate (Supplementary Table 6 and Fig. 3) analyses, there was no significant difference in IRAF reporting between the ibrutinib

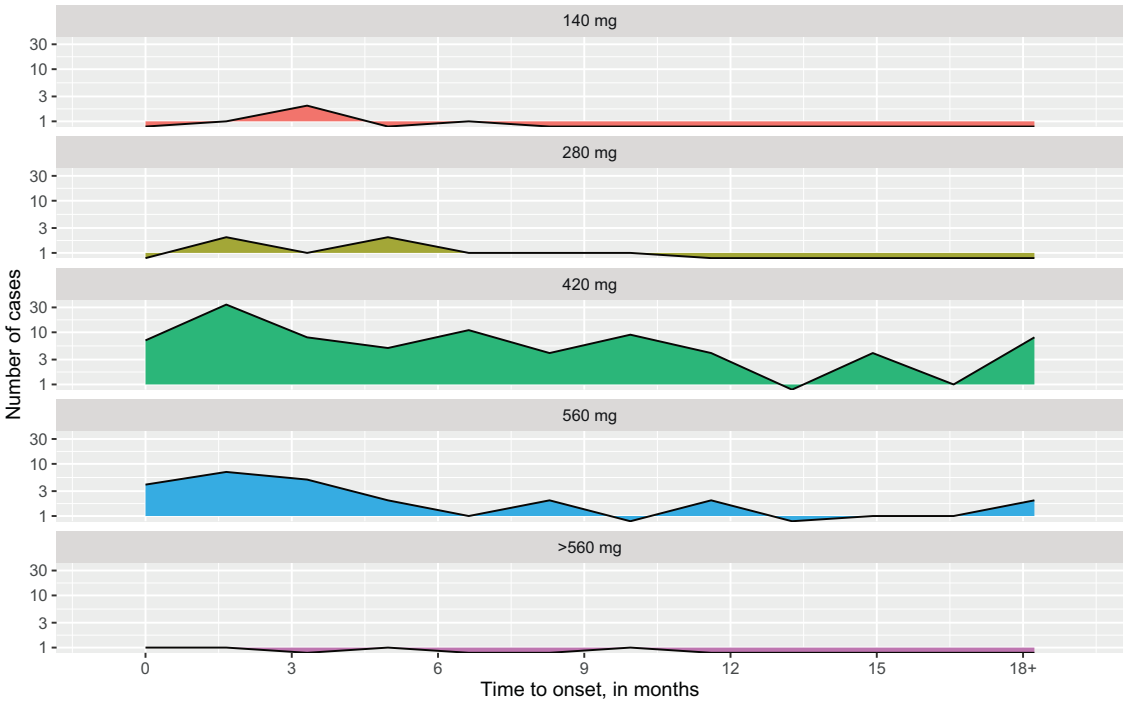

Fig. 4 Ibrutinib daily dose and time to ibrutinib-related atrial fibrillation (IRAF) onset. Multivariate analyses regarding the association between time to IRAF onset and ibrutinib dosing regimen. Time to onset was calculated in days, based on the method recommended by the Uppsala monitoring Center internal procedures.

dosing regimens, regardless of the specific underlying chronic B-cell malignancy, including CLL/WM and MCL. Furthermore, in both univariate and multivariate models, the time to IRAF onset did not display a significant association with ibrutinib dosing (Supplementary Table 7 and Fig. 4).

Positive control analysis of neutropenia and thrombocytopenia indicated a positive and significant association between ibrutinib daily dose and each of those ADRs reporting (Supplementary Table 8 and Fig. 5).

DISCUSSION

In VigiBase®, there was no evidence that IRAF reporting was influenced by ibrutinib daily dose. Stratified analyses on specific conditions, or analyzing time to onset did not lead to different conclusions. Underlying IRAF mechanisms remain largely unknown. Notwithstanding the diversity in the postulated mechanisms, atrial structural modifications, notably LA remodeling and fibrosis [18, 19], consistently emerge as the principal determinant in the development of IRAF *through* modulating off-target kinases, such as the C-terminal Src kinase (CSK) [8, 10]. An ibrutinib-treated mouse model exhibiting increased AF inducibility, it was demonstrated that BTK was not the relevant target and that IRAF was induced by the modulation of an off-target kinase [7]. Moreover, 4 weeks of ibrutinib treatment led to inducible AF, LA enlargement, myocardial fibrosis and inflammation, while comparable treatment with acalabrutinib did not [7]. Chemoproteomic profiling and knockout experiments in mice suggested that CSK may be responsible for IRAF but not for acalabrutinib-related AF [7]. Acalabrutinib does not appear to inhibit any of the Src kinases at physiologically relevant concentrations and peripheral blood samples from patients with CLL showed that ibrutinib inhibited CSK pathway whereas acalabrutinib did not [20, 21] even if acalabrutinib was also associated with AF development [22]. Our results showing no significant association between ibrutinib dose and IRAF reporting are consistent with an underlying mechanism involving LA structural remodeling which is supposed to include delayed changes in atrial tissue properties (most notably fibrosis), size, and cellular ultrastructure, that will remain established over time and that are considered poorly reversible [23]. Atrial size is a long-recognized determinant of AF likelihood, both at the experimental and clinical levels [23] and pre-ibrutinib atrial size has been consistently associated with higher IRAF rates in several cohorts [4, 10]. More acute and direct atrial arrhythmogenesis induced by ibrutinib were also described and may contribute to LA structural remodeling. Acute delivery of ibrutinib (10 mg/kg) increased pacing-induced AF in mice and this effect was reversible within 24 h of drug washout even after 14 consecutive days of drug delivery [24]. In patch-clamp studies, acute delivery of ibrutinib (0.1 and 10 µmol/L) reduced action potential upstroke velocity and Na^+ current whereas acalabrutinib did not and both ibrutinib and acalabrutinib (10 and 50 µmol/L) increased action potential duration [25], a well-known effect associated with LA structural remodeling [23]. As LA structural remodeling contributes to the "AF begets AF" phenomenon, once an AF episode has occurred, other AF episodes will probably occur again over time even if the initial etiology causing LA remodeling was ousted [23]. In a retrospective cohort study including 56 CLL patients who developed IRAF and without any continuous AF monitoring, Ibrutinib was stopped or dose-reduced in 35 patients (62%). Among these 35 patients, AF recurred or was persistent in 19 patients (54%) in comparison with 13/21 (61.9%) patients who continued full dose of ibrutinib, indicating no real benefit of ibrutinib discontinuation of dose-reduction [11]. Taken together, all these results indicate that it may be possible that ibrutinib discontinuation or dose-reduction in case of IRAF may not conduct to restore and maintain sinus rhythm and are in line with the 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology that recommend ibrutinib continuation at the same dose in case of IRAF occurrence [26]. Importantly, both 2020 ESC guidelines on AF and 2022 ESC guidelines on Cardio-Oncology remind via the "integrated ABC pathway" that the classification of AF (first diagnosed, paroxysmal or persistent…)

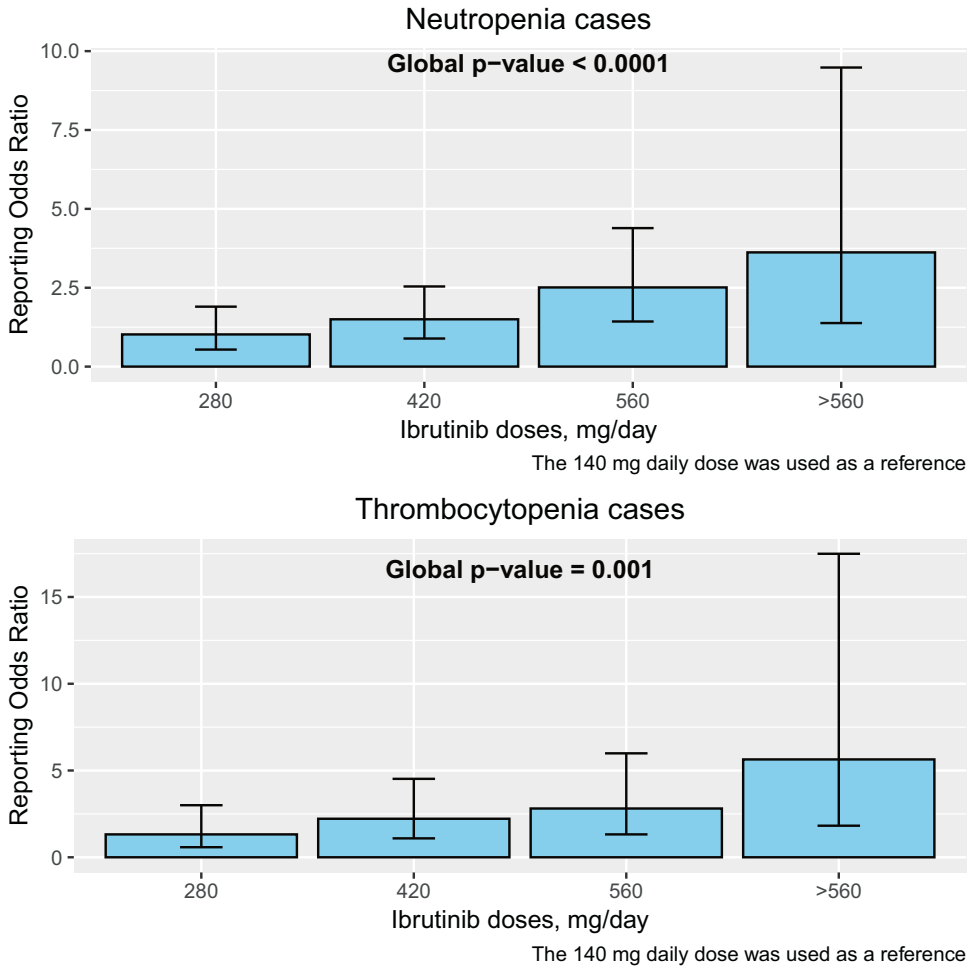

Fig. 5 Ibrutinib daily dose and neutropenia and thrombocytopenia reporting. Disproportionality analyses (univariate analyses) evaluating of the association between ibrutinib daily dose and neutropenia and thrombocytopenia reporting. Reporting odds-ratios (with 95% confidence interval) for each ibrutinib dosing regimen are presented against the lowest dosing regimen (140 mg/day). The ibrutinib daily dose global p-value indicates statistical significance if <0.05.

should not drive AF management, which must focus on the thromboembolic risk (taking into account the hemorrhagic risk), an optimal control of AF symptoms and an optimal control of cardiovascular risk factors an concomitant diseases [26, 27]. In contradiction with the 2022 ESC guidelines on cardio-oncology and without any robust evidences, the ibrutinib summary of product characteristics proposed to modify ibrutinib dose or to discontinue ibrutinib based on i. if the IRAF is the first episode or not and ii. the Common Terminology Criteria for Adverse Events (CTCAE) classification. A dose-reduction to 280 mg/day is recommended in case of first grade 3 IRAF episode for CLL/WM patients and to 420 mg/day in MCL patients. For both CLL/WM and MCL indication, in case of grade 3 IRAF recurrence or first grade 4 IRAF episode, it is recommended to discontinue ibrutinib [9]. A strategy based on the detection of AF episodes (first episode and recurrences) without any systematic and standardized AF detection strategy to screen subclinical AF is clearly biased and non-optimal [28]. In the REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) controlled study using a smartphone/tablet-based single-lead ECG system twice weekly over 12 months vs. routine care resulted in a 3.9-fold increase in AF detection in patients aged ≥65 years [29]. The CTCAE classification is a comprehensive, standardized and multimodality grading system recommended for the reporting of ADRs associated with anticancer drugs [30]. The primary organization of the CTCAE classification is based on pathophysiological (e.g., allergy/immunology) and anatomical (e.g., dermatology/skin) categories to facilitate location of related ADRs. CTCAE grades, in a standardized way, all ADRs from "1" (asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated) to "5" (death related to ADR) and generally all grade ≥3 ADRs are associated with drug dose-reduction and/or drug discontinuation [30]. Regarding IRAF and AF as an adverse event in general, the CTCAE classification appear to be not clinically relevant, particularly regarding the stroke risk assessment associated with AF. For example, in daily clinical practice, according to ABC strategy recommended by the 2020 ESC guidelines on AF [27], the decision to introduce or not an oral anticoagulation is independent of whether the patient is hospitalized or not and therefore a grade 2 CTCAE AF may not present a lower stroke risk compared to an AF grade ≥3 CTCAE. Avoiding ibrutinib discontinuation or dose-reduction appear to be even more crucial as these strategies may also impact the progression of the underlying chronic B-cell malignancy. In a prospective cohort of 285 MCL/CLL patients treated with ibrutinib, those with early dose reductions (within the first eight weeks) had significant worse progression free survival (PFS, $p = 0.004$) and overall survival (OS, $p = 0.014$) and those with ibrutinib interruptions lasting >1 week had worse PFS ($p = 0.047$) but not OS ($p = 0.577$) [31]. Moreover, CLL patients at high risk for AF/AF-related stroke demonstrate similar benefit with ibrutinib exposure compared to CLL patients not at risk regarding the time to next

treatment across all lines of therapy [32]. In addition, time to next treatment was significantly longer for all patients treated with ibrutinib-based regimens than other regimens, arguing in favor of persistent ibrutinib effectiveness on the underlying chronic B-cell malignancy, independently regardless of IRAF occurrence or not. Finally and in line with the 2022 ESC guidelines on cardio-oncology [26], ibrutinib discontinuation or dose-reduction should be restricted to exceptional cases and this choice should not be based on the number of IRAF episodes, the CTCAE classification or time to IRAF onset as our results did not highlight any IRAF reporting difference according to the ibrutinib dose and time to IRAF onset.

Study limitations

Pharmacovigilance databases are subject to various biases such as underreporting, notoriety, halo, or lack of information concerning the exposed population and drug sales volumes. These databases are also constrained by missing crucial information, like specific dosing regimens, which could limit the generalizability of our results. A large number of cases were excluded from our analyses due to missing data regarding ibrutinib dosage. As missing ibrutinib dosage is likely independent of the drug ibrutinib, the underlying indication and the ADR studied (i.e. AF) and is more likely related to the reporting practices of the individual reporters or the pharmacovigilance systems in place, complete cases (i.e. with an available ibrutinib dosage) are assumed to be a random sample of the full dataset (i.e. missing completely at random). Therefore, dropping cases with missing ibrutinib dosage may give unbiased estimates [33]. Moreover, it is important to note that the >560 mg dosage group includes only 11 cases, which may affect the robustness of the findings. Furthermore, the 140 mg dosage group, which serves as the reference in our analysis, has 62 events. Given the adjustment for multiple cofactors in the multivariate analysis, the relatively small sample size in the reference group could potentially impact the stability and reliability of the estimates. The tendency of pharmacovigilance reporting to overrepresent ADRs manifesting shortly after drug introduction may bias our analyses concerning the correlation between the initiation of IRAF and ibrutinib daily dose. Furthermore, the case/non-case design of disproportionality analysis cannot conclusively establish causality between ibrutinib dose and IRAF.

CONCLUSIONS

Our study corroborates the understanding of AF as a dose-independent ADR related to ibrutinib. Consistent with the 2022 ESC guidelines on cardio-oncology that advocate the continuation of ibrutinib therapy following an IRAF event [26], we found from Vigibase® no substantiating evidence that ibrutinib discontinuation or dose reduction after IRAF would change the clinical management or natural history of IRAF. On the other hand, the possible progression of the underlying chronic B-cell malignancy would argue for the maintenance of standard doses of ibrutinib.

DATA AVAILABILITY

Actually, data from VigiBase® (the WHO pharmacovigilance database) are only freely available for national pharmacovigilance centers and the Uppsala Monitoring Centre. Public access to overview statistics from VigiBase® can be gained through the VigiAccess website, http://www.vigiaccess.org/.

REFERENCES

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131:2745–60.
2. Leong DP, Caron F, Hillis C, Duan A, Healey JS, Fraser G, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016;128:138–40.
3. Alexandre J, Boismoreau L, Morice PM, Sassier M, Da-Silva A, Plane AF, et al. Atrial Fibrillation Incidence Associated With Exposure to Anticancer Drugs Used as Monotherapy in Clinical Trials. JACC CardioOncol. 2023;5:216–26.
4. Baptiste F, Cautela J, Ancedy Y, Resseguier N, Aurran T, Farnault L, et al. High incidence of atrial fibrillation in patients treated with ibrutinib. Open Heart. 2019;6:e001049.
5. Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. Blood. 2019;134:1919–28.
6. Wu H, Wang W, Liu F, Weisberg EL, Tian B, Chen Y, et al. Discovery of a potent, covalent BTK inhibitor for B-cell lymphoma. ACS Chem Biol. 2014;9:1086–91.
7. Xiao L, Salem JE, Clauss S, Hanley A, Bapat A, Hulsmans M, et al. Ibrutinib-Mediated Atrial Fibrillation Due to Inhibition of CSK. Circulation. 2020;142:2443–55.
8. Buck B, Chum AP, Patel M, Carter R, Nawaz H, Yildiz V, et al. Cardiovascular Magnetic Resonance Imaging in Patients With Ibrutinib-Associated Cardiotoxicity. JAMA Oncol. 2023;9:552–5.
9. EMA. European Medicines Agency. 2018. Imbruvica. Disponible sur: https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica
10. Quartermaine C, Ghazi SM, Yasin A, Awan FT, Fradley M, Wiczer T, et al. Cardiovascular Toxicities of BTK Inhibitors in Chronic Lymphocytic Leukemia: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol. 2023;5:570–90.
11. Thompson PA, Lévy V, Tam CS, Al Nawakil C, Goudot FX, Quinquenel A, et al. Atrial fibrillation in CLL patients treated with ibrutinib. An international retrospective study. Br J Haematol. 2016;175:462–6.
12. Singh A, El Hangouche N, McGee K, Gong FF, Lentz R, Feinglass J, et al. Utilizing left atrial strain to identify patients at risk for atrial fibrillation on ibrutinib. Echocardiography. 2021;38:81–8.
13. Brown JR, Moslehi J, O' Brien S, Ghia P, Hillmen P, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102:1796–805.
14. Alexandre J, Salem JE, Moslehi J, Sassier M, Ropert C, Cautela J, et al. Identification of anticancer drugs associated with atrial fibrillation: analysis of the WHO pharmacovigilance database. Eur Heart J Cardiovasc Pharmacother. 2021;7:312–20.
15. Faillie JL. Case-non case studies: Principles, methods, bias and interpretation. Therapie. 2018;73:247–55.
16. Sarosiek S, Gustine JN, Flynn CA, Leventoff C, Little M, White T, et al. Dose reductions in patients with Waldenström macroglobulinaemia treated with ibrutinib. Br J Haematol. 2023;201:897–904.
17. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. Commun Stat Simul Comput. 2010;39:860–4.
18. Jiang L, Li L, Ruan Y, Zuo S, Wu X, Zhao Q, et al. Ibrutinib promotes atrial fibrillation by inducing structural remodeling and calcium dysregulation in the atrium. Heart Rhythm. 2019;16:1374–82.
19. Isaza N, Bolen MA, Griffin BP, Popović ZB. Functional Changes in Acute Eosinophilic Myocarditis Due to Chemotherapy With Ibrutinib. CASE. 2019;3:71–6.
20. Kaptein A, De Bruin G, Emmelot-van Hoek M, Van De Kar B, De Jong A, Gulrajani M, et al. Potency and Selectivity of BTK Inhibitors in Clinical Development for B-Cell Malignancies. Blood. 2018;132:1871.
21. Patel V, Balakrishnan K, Bibikova E, Ayres M, Keating MJ, Wierda WG, et al. Comparison of Acalabrutinib, A Selective Bruton Tyrosine Kinase Inhibitor, with Ibrutinib in Chronic Lymphocytic Leukemia Cells. Clin Cancer Res. 2017;23:3734–43.
22. Brown JR, Byrd JC, Ghia P, Sharman JP, Hillmen P, Stephens DM, et al. Cardiovascular adverse events in patients with chronic lymphocytic leukemia receiving acalabrutinib monotherapy: pooled analysis of 762 patients. Haematologica. 2022;107:1335–46.
23. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res. 2014;114:1453–68.
24. Tuomi JM, Xenocostas A, Jones DL. Increased Susceptibility for Atrial and Ventricular Cardiac Arrhythmias in Mice Treated With a Single High Dose of Ibrutinib. Can J Cardiol. 2018;34:337–41.
25. Tuomi JM, Bohne LJ, Dorey TW, Jansen HJ, Liu Y, Jones DL, et al. Distinct Effects of Ibrutinib and Acalabrutinib on Mouse Atrial and Sinoatrial Node Electrophysiology and Arrhythmogenesis. J Am Heart Assoc. 2021;10:e022369.
26. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J. 2022;43:4229–361.
27. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373–498.

28. Font J, Milliez P, Ouazar AB, Klok FA, Alexandre J. Atrial fibrillation, cancer and anticancer drugs. Arch Cardiovasc Dis. 2023;116:219–26.
29. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. Circulation. 2017;136:1784–94.
30. Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP. 2024. Disponible sur: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.
31. Williams AM, Baran AM, Casulo C, Reagan P, Friedberg JW, Helber M, et al. Ibrutinib Dose Adherence and Therapeutic Efficacy in Non-Hodgkin Lymphoma: A Single-Center Experience. Clin Lymphoma Myeloma Leuk. 2019;19:41–7.
32. Narezkina A, Lu X, Emond B, Côté-Sergent A, Hilts A, Liu S, et al. Real-World Persistence and Time to Next Treatment with Ibrutinib Treatment in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Including Patients at High Risk for Atrial Fibrillation or Stroke. Blood. 2021;138:4112.
33. Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. BMC Med Res Methodol. 2019;19:53.

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AUTHOR CONTRIBUTIONS

JA, JF, CD and BC designed research; JA and BC performed research; JF, ADS, BD, GD, AFP, L, PM and CD contributed vital new reagents or analytical tools; JA, JF, ADS, DL, CD and BC analyzed data, and JA, JF, ADS, BD, GD, AFP, DL, PM, CD and BC wrote the paper.

COMPETING INTERESTS

JA reports honoraria for presentations and consulting fees from Biotronik, Bioserenity, Amgen, BMS, Pfizer, Boerhinger, Bayer, Astra Zeneca, Janssen, Servier, and Novartis, outside of the submitted work. DL reports honoraria for presentations and consulting fees from Astrazeneca, Boehringer Ingelheim, Lilly, Pfizer and Takeda, outside of the submitted work. CD reports honoraria for presentations and consulting fees from Bioserenity and Pfizer, outside of the submitted work. The remaining authors have nothing to disclose.

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