CHEST

Association of Pulmonary Hypertension With Trastuzumab Emtansine

An Analysis of French Pulmonary Hypertension Registry and WHO Pharmacovigilance Database

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BACKGROUND: Trastuzumab emtansine has been recently suspected to be associated with the development of pulmonary arterial hypertension (PAH).

RESEARCH QUESTION: Is there an association between trastuzumab, trastuzumab emtansine, or trastuzumab deruxtecan and the development of PAH?

STUDY DESIGN AND METHODS: Characteristics of incident PAH cases treated with trastuzumab, trastuzumab emtansine, or trastuzumab deruxtecan were analyzed from the French Pulmonary Hypertension Registry, the VIGIAPATH program, concurrently with a pharmacovigilance disproportionality analysis using the World Health Organization pharmacovigilance database using a broad definition of pulmonary hypertension (PH) and a narrow definition of PAH. A signal of disproportionate reporting was deemed significant if the lower boundary of the 95% credibility interval of the information component (IC) was superior to 0. The variables were expressed as median (interquartile range [IQR]).

RESULTS: In the French PH Registry, we identified 8 incident cases of PAH after trastuzumab emtansine exposure and none with trastuzumab alone or trastuzumab deruxtecan. All cases occurred in female patients (age, 56; IQR, 49-61 years) with breast cancer. The delay between first exposure and PAH diagnosis was 43 months (IQR, 4.5-55). At diagnosis, 5 were in New York Heart Association functional class III/IV with severe hemodynamic impairment (mean pulmonary artery pressure, 42 mm Hg; cardiac index, 2.51 L/min/m^2; pulmonary vascular resistance, 9.7 Wood units). Disproportionality analysis showed that only trastuzumab emtansine demonstrated a significant signal of disproportionate reporting using both a broad definition of PH (IC, 1.46; 0.86-1.95) and a narrow definition of PAH (IC, 1.76; 0.83-2.46). Trastuzumab displayed a significant signal using only the broad definition of PH, whereas trastuzumab deruxtecan was not associated with any significant signals of disproportionate reporting.

INTERPRETATION: Our results suggest that more patients exposed to trastuzumab emtansine developed PH compared with trastuzumab alone. Further assessment of this safety signal and exploration of pathophysiologic mechanisms is needed. CHEST 2025; 167(5):1468-1480

KEY WORDS: chemotherapy; disproportionality analysis; emtansine; pharmacovigilance; pulmonary hypertension; trastuzumab

Take-Home Points

Study Question: Trastuzumab emtansine, mainly used as a treatment for breast cancer, has been recently suspected to be associated with the development of pulmonary arterial hypertension (PAH). We aimed to evaluate the association between trastuzumab, trastuzumab emtansine, or trastuzumab deruxtecan and PAH using a comprehensive analysis from the French Pulmonary Hypertension Registry, the VIGIAPATH program, concurrently with a pharmacovigilance disproportionality analysis using the World Health Organization pharmacovigilance database.

Results: We identified 8 incident cases of PAH after trastuzumab emtansine exposure and none with trastuzumab alone or trastuzumab deruxtecan. Disproportionality analysis confirmed that only trastuzumab emtansine demonstrated a significant signal of disproportionate reporting using both the broad definition of pulmonary hypertension and narrow definition of PAH.

Interpretation: Our findings suggest a potential association between PAH and trastuzumab emtansine treatment; however, it appears to be a rare complication. Further research is needed to elucidate the underlying pathophysiologic mechanisms, identify individual risk factors, and assess the role of dosage and duration of exposure in the development of PAH. Regular symptoms monitoring and periodic echocardiographic assessments may facilitate the early detection and timely management of this life-threatening adverse event.

Pulmonary arterial hypertension (PAH) is a form of precapillary pulmonary hypertension (PH), defined by an elevated mean pulmonary arterial pressure (mPAP) of $>$ 20 mm Hg, a pulmonary arterial wedge pressure (PAWP) of $\leq$ 15 mm Hg, and a pulmonary vascular resistance (PVR) $>$ 2 Wood units (WU), all measured by right heart catheterization (RHC).[1,2] PAH may present as idiopathic, heritable, associated with various conditions, or associated with drugs and toxins exposure. The most recent guidelines categorize drugs at risk as either possibly or definitely associated with PAH.[1,2]

Trastuzumab, a recombinant humanized IgG1 monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2), has been approved in France since 2000. It was most commonly used to treat HER2-positive breast cancer, particularly in the first-line treatment of metastatic disease.[3] Trastuzumab emtansine received marketing authorization in 2014 for the treatment of unresectable metastatic or locally advanced HER2-positive cancers and in the treatment of other HER2-positive tumors (eg, gastric and gastroesophageal junction cancers, salivary gland tumors, non-small cell lung cancer).[4-10] Emtansine, derived from mertansine, is a microtubule inhibitor covalently bound to trastuzumab, providing additional cytotoxic activity alongside antitumor effects of trastuzumab.[11] More recently, an association of trastuzumab covalently linked to a derivative of exatecan, a topoisomerase I inhibitor, has been developed (trastuzumab deruxtecan).

ABBREVIATIONS: DLCO = diffusion capacity of carbon monoxide corrected for hemoglobin concentration; HER2 = human epidermal growth factor receptor 2; IC = information component; ICSR = individual cases safety report; IQR = interquartile range; mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAWP = pulmonary arterial wedge pressure; PDE5i = phosphodiesterase 5 inhibitor; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RHC = right heart catheterization; WHO = World Health Organization; WU = Wood units

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In a phase I study of trastuzumab emtansine including 24 patients with breast cancer, 1 patient developed severe precapillary PH, confirmed by RHC and considered possibly related to the treatment.[12] Additionally, Kwon et al[13] reported a case of a patient who developed hereditary hemorrhagic telangiectasia-like symptoms and precapillary PH confirmed by RHC, after initiation of trastuzumab emtansine. The patient showed significant improvement in exercise capacity and right ventricular function after drug withdrawal and treatment with PAH-approved drugs. Another case reported by Umoru et al[14] suggested the association between PH and trastuzumab emtansine, reinforced by a pharmacovigilance analysis.

In contrast, no cases of PH have been reported with the use of trastuzumab alone, despite its widespread use over many years, nor with trastuzumab deruxtecan. This suggests that the addition of emtansine to trastuzumab could increase the likelihood of inducing PH. In this study, we aimed to investigate the epidemiology and characteristics of trastuzumab-associated PH by combining two complementary approaches. First, we identified patients within the French PH network who developed PH after exposure to trastuzumab alone or associated with emtansine or deruxtecan. Second, we analyzed the World Health Organization (WHO) pharmacovigilance database (VigiBase) to estimate and compare signals of disproportionate reporting associated with these drugs.

Study Design and Methods

Identification of Cases in the French PH Registry and VIGIAPATH Database

We reviewed all cases of precapillary PH associated with exposure to trastuzumab alone or in combination with emtansine or deruxtecan, recorded in the French PH Registry (including the PH reference center at Hôpital Bicêtre, University Par is-Saclay, and 28 other PH expert centers) and the French pharmacovigilance database (VIGIAPATH) between May 1, 2004, and April 1, 2024. The inclusion criteria were a confirmed diagnosis of new-onset precapillary PH by RHC after drug exposure or clinical and/or hemodynamic worsening of preexisting PH. The diagnosis of precapillary PH confirmed by RHC was based on the hemodynamic definition in use at the time of inclusion in the registry.[1,15] The date of PH diagnosis was defined as the date of the initial RHC. A comprehensive etiologic evaluation of PH was conducted in accordance with European Society of Cardiology/European Respiratory Society guidelines,[1] and other potential causes of PH were excluded.

The registry was established in accordance with French bioethics laws (Commission Nationale de l'Informatique et des Libertés No. 842063), and all patients gave their informed consent.

Clinical, Functional, Radiologic, and Hemodynamic Evaluation

We collected data on the chemotherapy regimen, duration of trastuzumab alone or in combination with emtansine or deruxtecan, indication for treatment, and the cancer status at the time of PH diagnosis. Additionally, New York Heart Association (NYHA) functional class, N-terminal pro-brain natriuretic peptide, pulmonary function tests, and arterial blood gases (Pa_{O_2} and Pa_{CO_2}) were collected. Pulmonary function tests included FEV_1, total lung capacity, and diffusion capacity of carbon monoxide corrected for hemoglobin concentration (D_{LCO}). Chest CT scans obtained at the time of diagnosis were reviewed for all patients.

Hemodynamic parameters recorded during RHC included mPAP, PAWP, and right atrial pressure. Cardiac output was measured using the thermodilution technique, and cardiac index was calculated by dividing cardiac output by the body surface area. PVR was calculated as (mPAP − PAWP)/cardiac output expressed in WU. Acute vasodilator testing was performed using inhaled nitric oxide, with patients classified as responders if they exhibited a reduction in mPAP of $\geq$ 10 mm Hg, achieving an absolute mPAP value of $\leq$ 40 mm Hg with an increased or unchanged cardiac output.

When available, these parameters were also collected during follow-up.

Analysis From the WHO Pharmacovigilance Database

We reported this disproportionality analysis following the READUS-PV recommendations[16] (https://readus-statement.org) (e-Table 1). The protocol of the study was preregistered in Open Science Framework (https://osf.io/yzf8p/).

On August 1, 2024, we extracted all individual cases safety reports (ICSRs) of PH and PAH associated with

trastuzumab, trastuzumab emtansine, or trastuzumab deruxtecan from the WHO pharmacovigilance database, VigiBase. Reports of suspected adverse drug reactions were collected among the 134 countries participating in the WHO Program for International Drug Monitoring since 1968. At the date of extraction, almost 30 million ICSRs were reported in VigiBase. Drugs and adverse events are coded through Anatomical Therapeutical Chemical and MedDRA System Organ Class classifications, respectively. Cases were identified using a prespecified collection of MedDRA Preferred Terms related to PH, including the following: cor pulmonale, cor pulmonale acute, cor pulmonale chronic, pulmonary arterial hypertension, pulmonary arterial pressure abnormal, pulmonary arterial pressure increased, pulmonary artery dilatation, pulmonary artery wall hypertrophy, pulmonary hypertension, pulmonary hypertensive crisis, pulmonary valve incompetence, pulmonary vascular resistance abnormality, pulmonary veno-occlusive disease, and vascular resistance pulmonary increased.

Statistical Methods

Quantitative variables from the French PH registry were expressed as median (interquartile range [IQR]), whereas those from the WHO pharmacovigilance database were expressed as mean ± SD. We used the Wilcoxon signed-rank test to compare variables at diagnosis and after treatment initiation. All analyses were performed using GraphPad Prism software, version 10.0 (GraphPad Software, Inc).

Disproportionality analysis was conducted using the Bayesian neural network method, developed by the Uppsala Monitoring Centre research team. This method displays the best sensitivity and specificity when the number of ICSRs is low, which is expected for rare diseases and/or exposure.[17,18] The information component (IC) quantifies the disproportionality between the number of cases observed and the number of cases expected, based on the number of cases reported with the drug, all cases in the event, and all cases in the database. Positive IC values indicate a higher-than-expected drug-event associations, and a signal of disproportionate reporting was considered significant if the lower boundary of the 95% credibility interval of the IC (IC025) was > 0.[17,19] In the primary analysis, we used the entire database as comparator. Disproportionality analyses were performed using 2 definitions of PH: a narrow definition (Preferred Term pulmonary arterial hypertension PAH only) and broad definition (a collection of MedDRA terms related to PH). Trastuzumab deruxtecan, like trastuzumab emtansine, is indicated as a second-line treatment for unresectable HER2-positive breast cancer; therefore, we used trastuzumab deruxtecan as a negative control.

Several sensitivity analyses were performed (using the broad definition of PH), including the following: (1) excluding competitors: we excluded drugs competitor drugs (benfluorex, fenfluramine, dexfenfluramine, and dasatinib[20]) to limit potential masking effects; (2) excluding cases with PAH drugs: we excluded reports involving PAH-approved drugs to exclude misclassified cases and patients with preexisting PAH; (3) modified comparator group: we restricted the comparator group to L01F monoclonal antibodies and antibody drug conjugates to reduce confounding by indication; (4) time-restricted analysis: we recalculated the IC using only ICSRs reported after the date of the first ICSR for each drug (approximating the market release date) to limit dilution bias; (5) health care professionals only: we restricted the analysis to cases reported exclusively by health care professionals; and (6) adjusted for sex and age: we adjusted the IC estimates on age and sex by stratification using the Mantel-Haenszel method. Data from the WHO pharmacovigilance database were extracted and analyzed using Python 3.10.12 (Python Software Foundation) with packages including NumPy and Pandas.

Results

Characteristics of Patients From the French PH Registry and VIGIAPATH Database

Eight cases of PAH after treatment by trastuzumab emtansine were identified (Table 1). No cases of PH were reported after exposure to trastuzumab alone or trastuzumab deruxtecan. All 8 cases were incident, with no evidence of preexisting PH. The median age at PAH diagnosis was 56 years (IQR, 49-61). None of the patients were diagnosed with associated hereditary hemorrhagic telangiectasia. Ventilation/perfusion lung scans and/or CT angiograms showed no signs of chronic thromboembolic PH. Notably, 1 patient developed PAH after exposure to trastuzumab emtansine during follow-up in the DELPHI-2 screening program (DELPHI-2 study; NCT01600898[21]), which is dedicated to healthy individuals carrying a *BMPR2* mutation.[22] Another patient had Bethlem muscular dystrophy complicated

TABLE 1] Characteristics of Patients: Clinical, Functional, and Hemodynamic Evaluation at the Time of PH Diagnosis

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age at PH diagnosis, y	62	58	64	51	54	41	60	47
Duration of treatment with T-DM1, mo	47	63	67	1	8	5	47	9
Delay between T-DM1 initiation and PH diagnosis, mo	47	63	63	1	7	2	46	40
NYHA functional class, I-IV	II	III	II	IV	III	IV	III	II
6MWD, m	NA	390	410	NA	397	NA	NA	375
Hemodynamics							[a]	
mPAP, mm Hg	42	32	35	25	43	53	22	57
PAWP, mm Hg	2	8	4	3	7	8	4	4
Cardiac index, L/min/m^2	2.51	3.56	2.57	3.22	2.31	2.30	4.71	1.90
PVR, WU	10.2	4.5	7.5	3.8	9.2	14.2	2.5	14.6
Acute vasodilator response, yes/no	NA	No	No	NA	No	No	No	NA
NT-pro-BNP, ng/L	1,430	NA	NA	599	484	1,390	144	1,241
DLCO, % predicted	94	20	56	52	42	NA	43	79

6MWD = 6-min walk distance; DLCO = diffusion capacity of carbon monoxide corrected for hemoglobin concentration; mPAP = mean pulmonary arterial pressure; NA = not applicable; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; NYHA = New York Heart Association; T-DM1 = trastuzumab emtansine; WU = Wood units.
[a]Right heart catheterization 4 mo after T-DM1 discontinuation for pulmonary arterial hypertension suspicion (symptoms and elevated systolic pulmonary artery pressure measured by echocardiography). Excluded from statistical analysis.

with restrictive ventilatory disorder, requiring noninvasive mechanical ventilation.

In all patients, the indication of trastuzumab emtansine was for breast cancer. PAH was diagnosed after a median time of 43 months (IQR, 4.5-55) from the initiation of the treatment. The median duration of drug exposure was 28 months (IQR, 6.5-55). At the time of PAH diagnosis, all patients had previously received 1 or 2 chemotherapy regimens, including trastuzumab alone, and all were receiving trastuzumab emtansine. Details of chemotherapy history are provided in e-Figure 1.

Since the approval of trastuzumab emtansine in 2014, 4,619 patients with newly diagnosed PAH, including 365 cases of drug-associated PAH, have been included in the French PH registry. Indeed, the 8 cases of trastuzumab emtansine-associated PAH represent 0.2% of all patients with PAH and 2.2% of drug-associated PAH cases.

Clinical, Functional, and Hemodynamic Characteristics at PAH Diagnosis

All patients reported exertional dyspnea, with five classified as NYHA functional class III or IV. RHC confirmed precapillary PH with a median mPAP of 42 mm Hg (IQR, 32-53), a median cardiac index of 2.51 L/min/m^2 (IQR, 2.3-3.3), and a median PVR of 9.7 WU (IQR, 7.5-14.2). Acute vasodilator testing was performed in 4 patients, with none showing an acute response (Table 1). The median N-terminal pro-brain natriuretic peptide level was 920 pg/mL (IQR, 484-1,390). Pulmonary function tests showed no abnormalities in lung volumes, except for the patient with known restrictive ventilatory disorder. DLCO was reduced, with a median of 52% (IQR, 42-79) of predicted values (Table 1). High-resolution chest CT scans showed no evidence of pulmonary venoocclusive disease (PVOD). Two patients had sequelae from thoracic radiotherapy: one had bilateral metastatic pleural effusion and another had known bullous dystrophy.

Follow-Up and Outcomes

PH occurred during trastuzumab emtansine treatment in all patients, leading to the discontinuation of the drug at the time of PAH diagnosis. PAH-approved drugs were initiated in 7 patients, with 5 receiving dual oral combination therapy (phosphodiesterase 5 inhibitor [PDE5i] and endothelin receptor antagonist) and 2 receiving PDE5i monotherapy (Table 2).

Reassessment conducted 4 months after starting PAH-approved drugs in 5 patients showed significant clinical improvement, with dyspnea improving to NYHA class I

or II. Hemodynamic improvements were also observed with a decrease in PVR from a median 9.2 (IQR, 6-12.4) to 4.4 (IQR, 2.3-4.8) WU, and an increase in cardiac index from a median 2.51 (IQR, 2.11-3.07) to 3.56 (IQR, 3.29-4.09) L/min/m^2 (Fig 1, Table 2).

In 1 patient (patient 7), PAH was initially suspected based on echocardiographic findings (systolic PAP of 85 mm Hg) and NYHA class II, prompting the discontinuation of trastuzumab emtansine. After discontinuation, there was an initial improvement in dyspnea, and a first RHC performed 4 months later confirmed mild precapillary PH (mPAP: 22 mm Hg, PVR: 2.5 WU). However, a follow-up reassessment 4 months later revealed significant hemodynamic worsening (mPAP: 89 mm Hg, PVR: 5.7 WU), leading to the initiation of dual oral therapy (PDE5i and endothelin receptor antagonist).

One patient (patient 4) died 3 months after the PAH diagnosis. The patient experienced worsening of dyspnea, requiring intensive care hospitalization due to acute respiratory distress and right-sided heart failure. The evaluation revealed progression of breast cancer with peritoneal and pulmonary metastases. The patient's condition rapidly deteriorated, resulting in death from hemodynamic and respiratory failure. Additionally, 1 patient was diagnosed with portal hypertension during follow-up.

Results of Pharmacovigilance Disproportionality Analysis in the WHO Database

As of August 1, 2024, the WHO pharmacovigilance database contained reports for 53,135 cases with trastuzumab, 8,383 cases with trastuzumab emtansine, and 9,565 cases with trastuzumab deruxtecan. Using the broad definition of PH, 82 cases were identified with trastuzumab, 27 were identified with trastuzumab emtansine, and 8 were identified with trastuzumab deruxtecan. Among these, 27 cases fulfilled the narrow definition of PAH, including 11 with trastuzumab, 5 with trastuzumab emtansine, and 3 with trastuzumab deruxtecan. Additionally, 7 cases involved both trastuzumab and trastuzumab emtansine, and 1 case involved both trastuzumab and trastuzumab deruxtecan.

Most ICSRs were reported by health care professionals (n = 92, 87.6%), with the United States accounting for the most reports (n = 36, 34.3%). Most cases involved female patients (n = 95, 90.5%), and there were 7 fatal cases (6.7%) (see Table 3 for detailed characteristics by drug). Pertuzumab was the most frequently coreported

TABLE 2] Initiation of PAH-Approved Drugs and Evaluation After Treatment

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
PAH-approved drugs	PDE5i	PDE5i + ERA	PDE5i + ERA	PDE5i	PDE5i + ERA	PDEI5 + ERA	No	PDE5i + ERA
Delay between diagnosis and reassessment, mo	4	4	4	NA	5	NA	4	2
Reassessment								
NYHA functional class, I-IV	I	II	I	NA	II	NA	II	III
6MWD, m	562	450	NA	NA	454	NA	520	340
NT-pro-BNP, ng/L	127	38	NA	NA	66	NA	170	107
mPAP, mm Hg	28	21	31	NA	28	NA	39[a]	49
Cardiac index, L/min/m^2	3.07	4.36	3.56	NA	3.82	NA	3.31[a]	3.50
PVR, WU	5.1	1.6	4.5	NA	3.0	NA	5.7[a]	4.4
Outcomes	Alive (after 39 mo)	Alive (after 25 mo)	Alive (after 70 mo)	Death (after 3 mo)	Alive (after 66 mo)	Alive (after 18 mo)	Alive (after 12 mo)	Alive (after 12 mo)

6MWD = 6-min walk distance; ERA = endothelin receptor antagonist; mPAP = mean pulmonary arterial pressure; NA = not applicable; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase-5 inhibitor; PVR = pulmonary vascular resistance; NYHA = New York Heart Association; WU = Wood units.
[a]Delay between first right heart catheterization without PAH-approved drug initiation and second right heart catheterization. Excluded from statistical analysis.

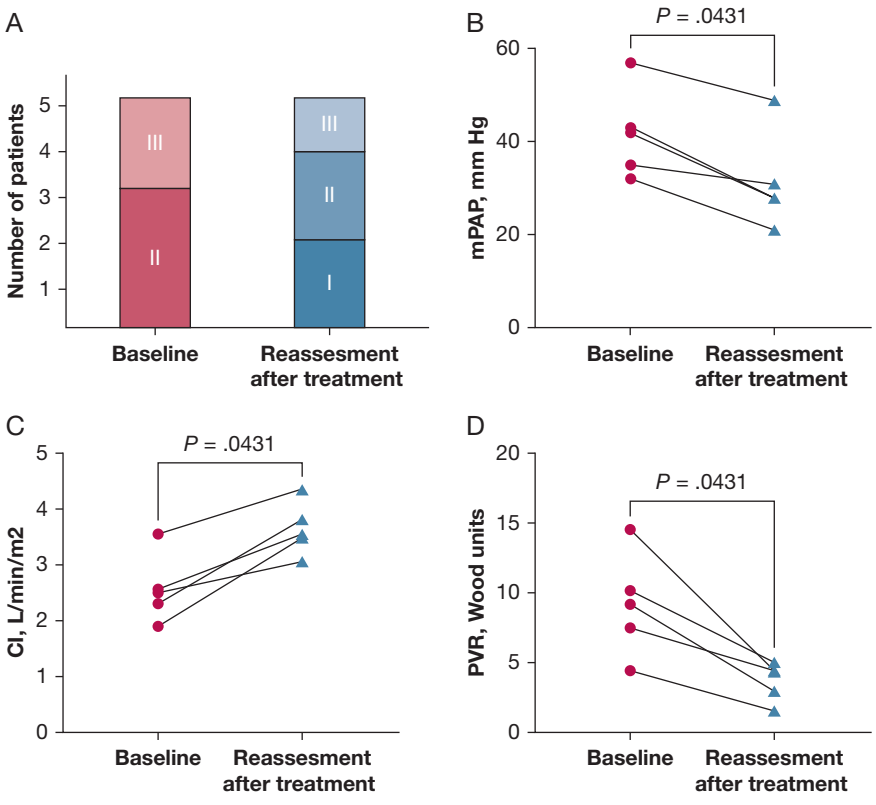

Figure 1 – *A-D, Evolution of clinical and hemodynamic parameters after pulmonary arterial hypertension-approved drugs initiation: (A) dyspnea assessed by New York Heart Association functional class, (B) mPAP, (C) CI, and (D) PVR, with statistical significance except for mPAP. CI = cardiac index; mPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance.*

drug with trastuzumab, whereas trastuzumab was most often coreported with trastuzumab emtansine. The median time ± SD to onset of PH was 742 ± 1,254 days for trastuzumab and 1,021 ± 801 days for trastuzumab emtansine. Symptoms improvement after drug withdrawal was reported in 1 case with trastuzumab emtansine and in 5 cases with trastuzumab.

Only trastuzumab emtansine demonstrated a significant signal of disproportionate reporting using both the broad definition of PH (IC, 1.46; 0.86-1.95) and the narrow definition of PAH (IC, 1.76; 0.83-2.46). Trastuzumab displayed a significant signal using only the broad definition of PH but no significant signal for the narrow definition of PAH. Trastuzumab deruxtecan was not associated with any significant signals of disproportionate reporting (Fig 2).

In sensitivity analyses, only trastuzumab emtansine consistently showed significant signals of disproportionate reporting both in the main analysis and all sensitivity analyses. In contrast, trastuzumab deruxtecan was not associated with any significant signals (e-Fig 2).

Discussion

Our results indicate that more patients exposed to trastuzumab emtansine develop PAH than those treated with trastuzumab alone or trastuzumab deruxtecan. Indeed, 8 cases of PH related to trastuzumab emtansine treatment were reported in the French PH registry, and despite its long-standing use, has not been linked to any cases of PH. Furthermore, the disproportionality analysis demonstrated higher and stronger signals of disproportionate reporting with trastuzumab emtansine compared with trastuzumab and trastuzumab deruxtecan. Collectively, these findings suggest a greater risk of PAH in patients treated with the combination of trastuzumab and emtansine than with trastuzumab alone.

Several lines of evidence support a plausible causal relationship between PAH onset and trastuzumab emtansine exposure. Data from the French PH registry showed a delayed onset of PAH after exposure, with a median latency of 43 months. Similarly, the VIGIBASE study reports a median latency period of approximately 34 months. This temporal pattern of PAH development during treatment is consistent with that seen in patients treated with other drugs known to cause PAH (eg, dasatinib, mitomycin-C, proteasome inhibitors).[20] Some patients developed PAH within the first 2 months of drug initiation, resembling cases in patients treated with proteasome inhibitors.[23] Further evidence supporting a causal link includes the clinical and hemodynamic

TABLE 3] Characteristics of Cases of Pulmonary Arterial Hypertension (Broad Definition) Reported in the World Health Organization Pharmacovigilance Database for Trastuzumab, Trastuzumab Emtansine, and Trastuzumab Deruxtecan

Variable	Trastuzumab	Trastuzumab Emtansine	Trastuzumab Deruxtecan
No. of ICSRs	53,135	8,383	9,565
No. of cases, PAH/PH	19/82	12/27	4/8
Sex, female/male/unknown	74/1/7	26/0/1	6 /1/1
Age, y	60.71 [12.08]	56.32 [12.67]	64.8 [15.97]
No. suspect/interacting drugs	5.14 [6.31]	3.71 [3.17]	3.0 [1.83]
No. of fatal PH	6/82 (7.32)	1/27 (3.7)	1/8 (12.5)
Drug withdrawn	31/82 (37.8)	10/27 (37.04)	4/8 (50.0)
Outcome after drug withdrawal	Recovered: 2/31 (6.45)	Recovered: 1/10 (10.0)	Recovered: 1/4 (25.0)
	Recovering: 3/31 (9.68)	Not recovered: 5/10 (50.0)	Died: 1/4 (25.0)
	Recovered with sequelae: 1/31 (3.23)	Died: 1/10 (10.0)	Evolution unknown: 2/4 (50.0)
	Not recovered: 8/31 (25.81)	Evolution unknown: 3/10 (30.0)	
	Died: 1/31 (3.23)		
	Evolution unknown: 13/31 (41.94)		
Top country of primary source	United States: 29/82 (35.4)	France: 10/27 (37.0)	France: 3/8 (37.5)
	France: 11/82 (13.4)	United States: 7/27 (25.9)	United States: 2/8 (25.0)
	Germany: 9/82 (11.0)	Germany: 2/27 (7.4)	Italy: 1/8 (12.5)
	Japan: 4/82 (4.9)	Japan: 2/27 (7.4)	Belgium: 1/8 (12.5)
	Italy: 4/82 (4.9)	Australia: 2/27 (7.4)	Brazil: 1/8 (12.5)
Top coreported drugs	Pertuzumab: 22/82 (26.8)	Trastuzumab: 12/27 (44.4)	Pantoprazole: 2/8 (25.0)
	Docetaxel: 21/82 (25.6)	Pertuzumab: 6/27 (22.2)	Pantoprazole sodium sesquihydrate: 2/8 (25.0)
	Cyclophosphamide monohydrate: 16/82 (19.5%)	Cyclophosphamide monohydrate: 3/27 (11.1)	Bisoprolol: 2/8 (25.0)
	Cyclophosphamide: 16/82 (19.5)	Cyclophosphamide: 3/27 (11.1)	Levosulpiride: 1/8 (12.5)
	Paclitaxel: 14/82 (17.1)	Docetaxel: 3/27 (11.1)	Furosemide: 1/8 (12.5)
Reporter qualification	Health care professional: 70/82 (85.37)	Health care professional: 25/27 (92.59)	Health care professional: 8/8 (100.0)
	Non-health care professional: 12/82 (14.63)	Non-health care professional: 2/27 (7.41)	Non-health care professional: 0/8 (0.0)

(Continued)

TABLE 3 *(Continued)*

Variable	Trastuzumab	Trastuzumab Emtansine	Trastuzumab Deruxtecan
Top indications	Breast cancer: 31/82 (37.8)	Breast cancer: 6/27 (22.2)	HER2 positive breast cancer: 2/8 (25.0)
	Unknown: 14/82 (17.1)	HER2 positive breast cancer: 5/27 (18.5)	Breast cancer: 2/8 (25.0)
	HER2 positive breast cancer: 8/82 (9.8)	Breast cancer metastatic: 3/27 (11.1)	Metastatic breast cancer: 1/8 (12.5)
	Product used for unknown indication: 7/82 (8.5)	Metastatic breast cancer: 2/27 (7.4)	Breast cancer metastatic: 1/8 (12.5)
	Drug use for unknown indication: 7/82 (8.5)	Unknown: 2/27 (7.4)	Brain metastases: 1/8 (12.5)
Time to onset, d	742 [1,254]	1,021 [801]	91 [103]

Values are presented as mean [SD], No./total No. (%), or as otherwise indicated. HER2 = human epidermal growth factor receptor 2; ICSR = individual cases safety report; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

improvements observed in the patients after trastuzumab emtansine withdrawal (either alone or in combination with PAH-approved drugs), along with similar responses noted in some cases of the disproportionality analysis. The absence of other identifiable causes of PH in these patients, along with the observed clinical course, strongly suggests that trastuzumab emtansine should be considered as a drug at risk of PAH (drug-associated PAH, group 1 PH).

Our data confirm previous isolated reports of PH in patients exposed to trastuzumab emtansine. PH has previously been reported in a phase 1 study,[12] in a patient with hereditary hemorrhagic telangiectasia-like symptoms,[13] and in a case reported by Umoru et al[14] in 2020. Notably, none of the patients in our series presented with hereditary hemorrhagic telangiectasia symptoms. In the latter study, the authors also conducted a pharmacovigilance disproportionality analysis using data from the FDA Adverse Event Reporting System, which similarly identified a significant signal of disproportionate reporting with trastuzumab emtansine, but not with trastuzumab or pertuzumab.[14] The role of trastuzumab emtansine in the development of PAH requires further investigation through preclinical studies to explore potential mechanistic pathways. Additionally, pharmacoepidemiologic studies are needed to assess the risk of PAH in patients exposed to this drug. Importantly, registries and pharmacovigilance analyses are limited in their ability to estimate drug-related risk or the incidence of adverse reactions due to the lack of exposure data and the uncertain proportion of cases that are actually reported.[24] Moreover, confounding factors pose a significant challenge given the lack of comparator groups; however, the absence of a signal with trastuzumab deruxtecan suggests a limited role for underlying disease and associated comorbidities.

Chemotherapy agents known to cause PH (eg, alkylating agents) are often associated with venular involvement, leading to PVOD,[25] particularly drugs like mitomycin-C[26,27] and busulfan.[28] Interestingly, in the patients with PH associated with trastuzumab emtansine, no signs of PVOD were detected on CT scans, despite a significant reduction in D_{LCO}. Furthermore, none of the patients developed pulmonary edema after initiation of PAH-approved drugs, which can be a life-threatening complication in PVOD cases.[29] Of particular interest is 1 patient in our series with a known *BMPR2* mutation, identified

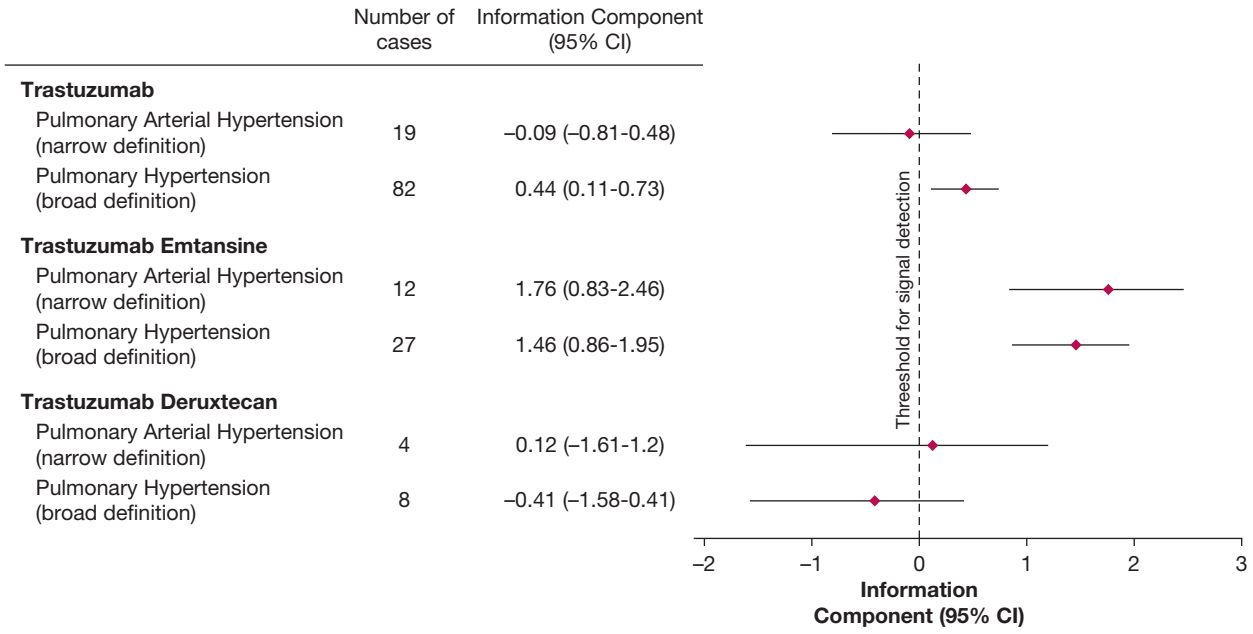

Figure 2 – *Result of disproportionality analysis information component (95% CI) in the World Health Organization pharmacovigilance database for pulmonary arterial hypertension reported with trastuzumab, trastuzumab emtansine, and trastuzumab deruxtecan.*

through genetic counseling as a first-degree relative of a patient with PAH, and monitored as part of a PAH screening program for individuals genetically predisposed to PAH (the DELPHI-2 study). This case aligns with the second-hit hypothesis of PAH, in which a predisposition may increase susceptibility to drug-induced PAH.[20,30,31] This reinforces the need to continue screening patients carrying genetic mutations, as is already proposed for *BMPR2*,[22] particularly in situations identified as being at risk (eg, exposure to chemotherapies).

The mechanisms by which trastuzumab emtansine may induce PAH remains unclear. Kwon et al[13] proposed that emtansine could induce apoptosis of HER2-expressing endothelial cells in distal small pulmonary vessels, leading to mucocutaneous telangiectasia and pulmonary vasculopathy. More recently, Taylor and Lindorfer[32] hypothesized that adverse events associated with antibody-drug conjugates like trastuzumab emtansine could be due to interaction of antibody-drug conjugates and Fcɣ receptors expressed on off-targeted cells and tissues, leading to inappropriate processing via pathways normally involved in immune complex clearance. The literature highlights differences in the adverse events profile between trastuzumab and its drug conjugates, such as emtansine, potentially due to differences in mechanism of action (Fig 3, e-Table 2). Compared with trastuzumab, trastuzumab emtansine exposure has been associated with additional toxicities such as thrombocytopenia, cardiotoxicity, and liver damage, including elevated liver enzymes, nodular regenerative hyperplasia, and noncirrhotic portal hypertension.[33,34] A study of 111 patients treated with trastuzumab emtansine reported significantly more cases of noncirrhotic portal hypertension, with manifestations such as splenomegaly, gastroesophageal varices, and portosystemic shunts compared with those treated with other breast cancer therapies. This suggest a vascular tropism of trastuzumab emtansine toxicity.[35] Interestingly, one of the patients in our study also developed gastroesophageal varices and portal hypertension. Although, cardiotoxicity of trastuzumab is well documented, echocardiography and RHC confirm the absence of significant left-sided heart dysfunction in the patients.[36]

This study has several limitations, including its retrospective design and the small sample size. Pharmacovigilance disproportionality analyses are useful for generating safety signals (ie, hypotheses about adverse drug reactions) but are limited by several factors. First, as previously mentioned in the discussion, the number of cases reported in pharmacovigilance databases and patients included in registries are influenced by selective reporting and selection bias.[37] Additionally, due to the lack of longitudinal data and detailed drug exposure

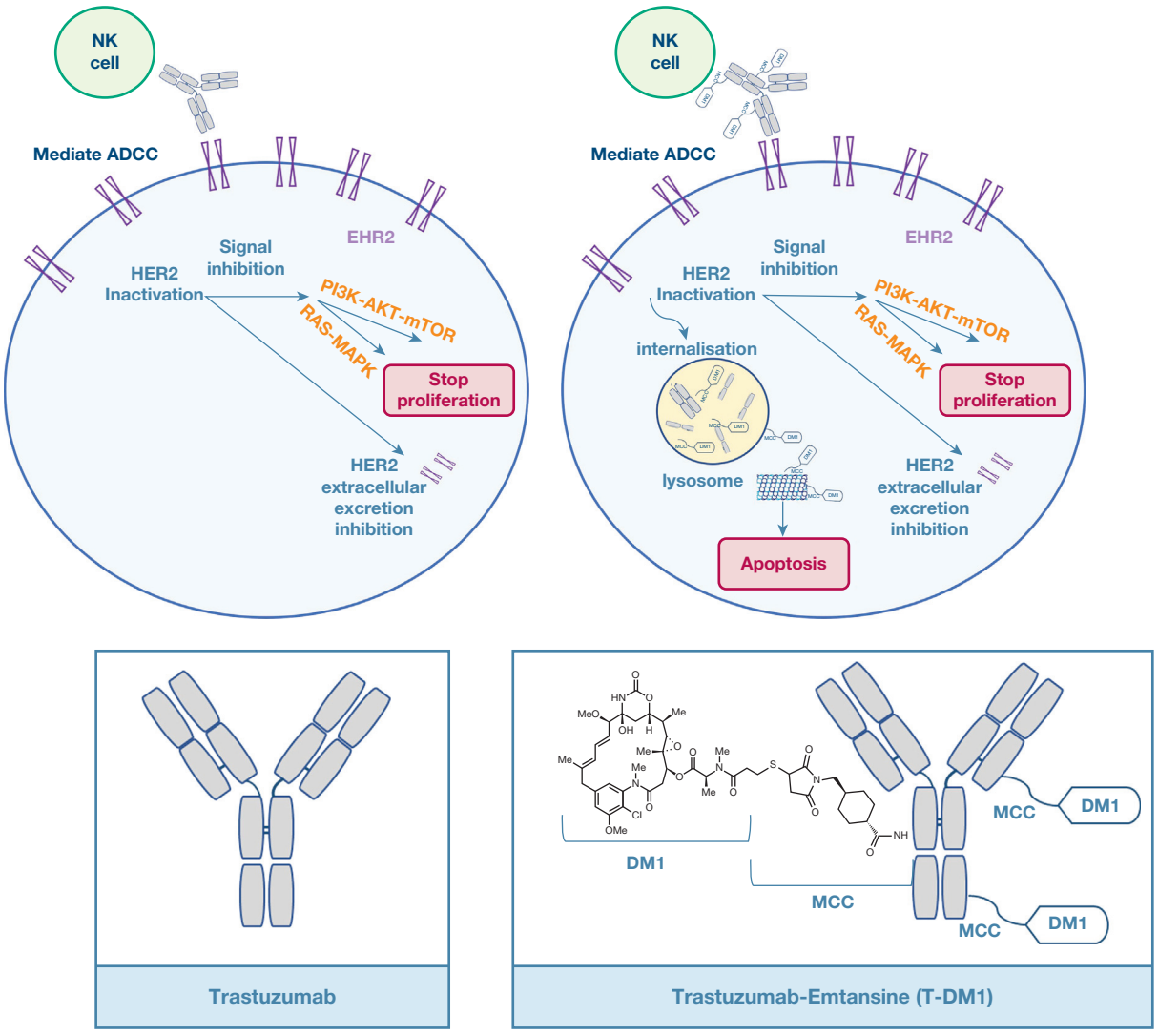

Figure 3 – *Diagram of trastuzumab and trastuzumab emtansine mechanisms of action. Trastuzumab is a recombinant humanized monoclonal antibody class IgG1, directed against HER2. Its fixation leads HER2 inactive through inducing transduction signal inhibition via PI3K-AKT-mTOR and RAS-MAPK pathways and therefore apoptosis. It also inhibits HER2 extracellular domains excretion. Trastuzumab plays also in immune adaptative response via activation of NK cells through the ADCC. Trastuzumab emtansine corresponds to the trastuzumab covalently linked with the carboxyl function of emtansine via the stable thioether linker MCC (around 3 to 5 DM1 per trastuzumab). In addition to effects of trastuzumab, release of DM1 after lysosome degradation blocks tubulin assembly into microtubules, leading to cell cycle arrest in G2/M phase and apoptosis induction. ADCC = antibody-dependent cell-mediated cytotoxicity; DM1 = maytansine-derived; HER2 = human epidermal growth factor receptor 2; MCC = MCC (4-[N-maleimidomethyl] cyclohexane-1-carboxylate); NK = natural killer.*

information, and the risk of confounding and competition bias, these analyses do not allow for the estimation of incidence rates or precise quantification of risk between trastuzumab and trastuzumab emtansine.[38] Through sensitivity analyses, we assessed the impact of several potential biases and consistently found higher signals of disproportionate reporting with trastuzumab emtansine compared with trastuzumab alone. Despite these biases, the positive predictive value of signals of disproportionate reporting range between 20% and 60%.[39,40] However, studies have shown that the performances of these analyses significantly improves when sensitivity and secondary analyses are consistent,[41] as was the case in this study for trastuzumab emtansine. Second, although we used a collection of codes related to PAH, we did not have access to definite diagnoses confirmed by RHC, which introduces the risk of PAH misclassification. Nonetheless, previous studies in France have shown that between 50% and 75% of reported PAH cases were confirmed by RHC.[23] Importantly, combining pharmacovigilance data with registry data, where the diagnosis of PAH is standardized and confirmed, strengthens the robustness of the results.

Interpretation

Our findings suggest a potential association between PAH and trastuzumab emtansine treatment; however, it appears to be a rare complication. Further research is needed to elucidate the underlying pathophysiologic mechanisms, identify individual risk factors, and assess the role of dosage and duration of exposure in the development of PAH. The potential for an underlying genetic mutation to act as a second hit in conjunction with trastuzumab emtansine treatment also warrants further investigation. Health care professionals should remain vigilant about the potential risk of PAH both before initiating trastuzumab emtansine therapy and during follow-up. Regular symptoms monitoring and periodic echocardiographic assessments, particularly in high-risk patient populations, may facilitate the early detection and timely management of this life-threatening adverse event.

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