Letter

Treatment of life-threatening digoxin toxicity with digoxin-specific antibody fragments: results from a prospective, non-interventional observational UK patient registry study

Digoxin is expected to remain a widely prescribed medication for atrial fibrillation and cardiovascular disorders generally. Digoxin toxicity can occur, and severe toxicity represents a medical emergency, with intravenous administration of digoxin-specific antibody fragments (DIF; DigiFab, Protherics Medicines Development Ltd) indicated in the presence of life-threatening arrhythmias.[1 2]

In the prospective, non-interventional observational UK DigiFab Patient Registry study, carried out as a post-authorisation requirement from the Medicines and Healthcare Products Regulatory Agency, we evaluated real-world safety and efficacy of DIF for treating known or strongly suspected life-threatening digoxin toxicity. Physicians at UK hospitals were invited to submit registry forms for any patient receiving DIF according to indication (known or strongly suspected life-threatening digoxin toxicity associated with ventricular arrhythmias or bradyarrhythmias unresponsive to atropine, where measures beyond withdrawal of digoxin and correction of serum electrolytes are considered necessary).[2] Assessment of completed forms and administration of the registry was managed by Protherics Medicines Development Ltd. Reports of adverse events (AEs), adverse drug reactions or lack of efficacy were followed up to collect missing data.

Ninety-eight patients were included in the registry between April 2012 and March 2018. Eleven patients were excluded from analysis (off-label DIF use: n=2; unrecorded treatment outcome: n=9); thus, analysis was based on data from 87 patients. Patient demographics are shown in table 1. Among 51 forms where amount of digoxin ingested was recorded, digoxin toxicity was of the chronic type in 80% of patients, acute in 2% and unknown in 18%. Median (range) serum digoxin concentration before DIF treatment was 4.4 (1.1–21.3) µg/L. The most common symptoms of digoxin toxicity were bradycardia (n=64; 73.6%), abnormal mental status/visual disturbance (n=34; 39.1%), hyperkalaemia (n=29; 33.3%) and gastrointestinal effects (n=27; 31.0%) (table 1).

Table 1 Patient demographics and digoxin toxicity symptoms

Patient demographics (N=87)	Patients receiving DIF
Sex, n (%)	
Male	35 (40.2)
Female	50 (57.5)
Unknown	2 (2.3)
Age, years*	
Mean (SD)	80.2 (10.1)
Median (range)	83.0 (43–96)
<18, n (%)	0 (0.0)
≥18 to <65, n (%)	7 (8.0)
≥65 years, n (%)	80 (92.0)
Ethnicity, n (%)	
White	80 (92.0)
Indian	1 (1.1)
Western Asian	1 (1.1)
Unknown/other/left blank	5 (5.7)
Weight, kg (N=23)†	
Mean (SD)	67.6 (16.8)
Median (range)	66.6 (37–111)
Baseline (pre-DIF treatment) serum digoxin concentration, µg/L (N=76)	
Mean (SD)	4.6 (2.5)
Median (range)	4.4 (1.1–21.3)
Toxicity symptoms, N=87‡	
Bradycardia	64 (73.6)
Abnormal mental status/visual disturbances	34 (39.1)
Hyperkalaemia	29 (33.3)
Gastrointestinal effects	27 (31.0)
Second- or third-degree heart block	16 (18.4)
Atrial fibrillation	11 (12.6)
Other arrhythmia	12 (13.8)
Other non-arrhythmia symptoms§	6 (6.9)
Lethargy/weakness/generally unwell	9 (10.3)
Acute kidney injury/increased acute kidney injury/renal failure	5 (5.7)
Asystole	5 (5.7)
Ventricular tachycardia	4 (4.6)
Arrhythmia symptoms combined¶	74 (85.1)

*Mean (SD) age was 76.4 (10.9) years in men (n=35) and 82.4 (8.6) years in women (n=50).
†Mean (SD) body weight was 84.0 (21.9) kg in men (n=5) and 62.8 (12.6) kg in women (n=17).
‡Patients may have reported >1 toxicity symptom.
§Other symptoms included continuous seizure activity (n=1), loss of consciousness (n=1), hypothermia with hypertension (n=1), hypotension (n=1), raised inflammatory markers with unrecordable blood pressure (n=1) and dizziness (n=1). All were reported in conjunction with cardiac arrhythmia, except in the patient with hypothermia and hypertension.
¶Bradycardia, second- or third-degree heart block, asystole, ventricular tachycardia, atrial fibrillation or other arrhythmias.
DIF, digoxin-specific antibody fragments; SD, standard deviation.

Treatment outcomes reported in the registry forms included resolution of toxicity in 60 (69.0%) patients, symptom persistence (persistence was recorded as ranging from 6 hours to 10 days) in 24 (27.6%) patients and death in 3 (3.4%) patients.

At least one AE (excluding delayed effect or lack of effect of DIF) was reported by 11 (12.6%) patients. Six (6.9%) experienced AEs reported in conjunction with either lack of efficacy (n=4) or incomplete drug effect (n=2). Serious AEs occurred in 8 (9.2%) patients. None experienced symptoms of hypersensitivity reactions following DIF administration. Three deaths were reported based on the outcome indicated in the registry form. Further follow-up identified a total of 10 deaths. Based on the investigator's assessment, seven deaths were considered unrelated to DIF treatment. For the other three, no cause was reported/established despite multiple follow-up requests. Therefore, these were conservatively assessed as possibly related to DIF but were most likely complications of underlying conditions.

The data captured in this registry study support a positive benefit:risk balance of DIF for the treatment of known or strongly suspected life-threatening digoxin toxicity, with DIF being highly effective in resolving life-threatening digoxin toxicity in a real-world setting. Our findings are consistent with those from previous clinical studies of the efficacy and safety of DIF, and with post-marketing safety and pharmacovigilance data.[3–5]

Emma Thomas ,[1] **Sam Tomlinson,**[2] **Siwan Thomas,**[2] **Suzanne Ward,**[3] **Claire Daugherty,**[3] **Eva Gallardo,**[1] **Christon Hill**[3]

[1]Protherics Medicines Development Ltd, Blaenwaun, UK
[2]Protherics UK Ltd, London, UK
[3]BTG International Inc, Conshohocken, Pennsylvania, USA

Correspondence to Dr Emma Thomas, Protherics Medicines Development Ltd, Blaenwaun, SW3 1HY, UK; emma.thomas@btgsp.com

Acknowledgements Data management and statistical analysis support was provided by Chris Sun of BTG International Inc. Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking and referencing) was provided by Ian Faulkner, PhD (Aspire Scientific Ltd, Bollington, UK), and funded by Protherics Medicines Development Ltd.

Contributors Conception and design of the study: STo and STh. Data acquisition: STo and STh. Data analysis and interpretation: ET, STo, STh, SW, CD, EG and CH. Drafting/revising the manuscript for critically important intellectual content: ET, STo, STh, SW, CD, EG and CH. All authors read and approved the final manuscript.

Funding This study was supported by Protherics Medicines Development Ltd.

Competing interests ET and EG are employees of Protherics Medicines Development Ltd. STo was an employee of Protherics UK Ltd at the time these analyses were performed. STh is an employee of Protherics UK Ltd. SW, CD and CH are employees of BTG International Inc.

Patient consent for publication Not applicable.

Ethics approval This was a post-marketing surveillance study conducted post-authorisation in agreement with the Medicines and Healthcare Products Regulatory Agency (MHRA). The observational study used anonymised routinely collected clinical data and the method of data collection was mutually agreed with the MHRA. The post-marketing surveillance study was not considered 'research' for the purposes of Research Ethics Committee review and therefore, the study was not deemed to require ethical approval or informed consent from patients, in accordance with the Medical Research Council Health Research Authority guidance.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used and analysed during the current study are available from the corresponding author.

OPEN ACCESS

To cite Thomas E, Tomlinson S, Thomas S, *et al*. *Eur J Hosp Pharm* 2023;**30**:e34.

Published Online First 21 October 2022

Eur J Hosp Pharm 2023;**30**:e34.
doi:10.1136/ejhpharm-2022-003416

ORCID iD
Emma Thomas http://orcid.org/0000-0002-4225-096X

REFERENCES

1 Pincus M. Management of digoxin toxicity. *Aust Prescr* 2016;39:18–20.
2 Protherics UK Ltd. DigiFab® summary of product characteristics, 2017. Available: https://digifab.health/getmedia/6f38d7ed-1832-4b7d-863a-9c71905e4d02/SmPC_DigiFab_Dec17.pdf [Accessed 10 May 2022].
3 Chan BSH, Buckley NA. Digoxin-specific antibody fragments in the treatment of digoxin toxicity. *Clin Toxicol* 2014;52:824–36.
4 Hickey AR, Wenger TL, Carpenter VP, *et al*. Digoxin immune fab therapy in the management of digitalis intoxication: safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol* 1991;17:590–8.
5 Antman EM, Wenger TL, Butler VP, *et al*. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific fab antibody fragments. final report of a multicenter study. *Circulation* 1990;81:1744–52.