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Regular Article

Frequent off-label use of fondaparinux in patients with suspected acute heparin-induced thrombocytopenia (HIT) – findings from the GerHIT multi-centre registry study ☆

Marc Schindewolf [a,*], Julia Steindl [a], Jan Beyer-Westendorf [b], Sebastian Schellong [c], Pascal Maria Dohmen [d,1], Johannes Brachmann [e], Katharina Madlener [f], Bernd Pötzsch [g], Robert Klamroth [h], Johannes Hankowitz [i], Norbert Banik [j,2], Sonja Eberle [j,2], Stefan Kropff [k], Markus Michael Müller [k], Edelgard Lindhoff-Last [a]

[a] Department of Internal Medicine, Division of Vascular Medicine/Haemostaseology, Goethe University Hospital, Frankfurt/M., Germany
[b] Department of Medicine III, Division of Angiology, University Hospital Carl Gustav Carus Dresden, Dresden, Germany
[c] Medical Department II, Municipal Hospital Dresden Friedrichstadt, Dresden, Germany
[d] Department of Cardiovascular Surgery, Charité Hospital, Medical University Berlin, Berlin, Germany
[e] II. Medical Clinic, Department of Cardiology, Klinikum Coburg, Coburg, Germany
[f] Department of Haemostaseology and Transfusion Medicine, Kerckhoff-Klinik, Bad Nauheim, Germany
[g] Institute of Experimental Haematology and Transfusion Medicine, University Hospital Bonn, Bonn, Germany
[h] Department of Internal Medicine, Haemophilia Treatment Centre, Vivantes Klinikum im Friedrichshain Berlin, Berlin, Germany
[i] Institute of Pharmacology and Preventive Medicine, München, Germany
[j] GlaxoSmithKline, Biostatistics & Epidemiology, München, Germany
[k] GlaxoSmithKline, Cardiovascular and Antithrombotics, München, Germany

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ABSTRACT

Introduction: In life-threatening immune heparin-induced thrombocytopenia (HIT), treatment with an approved non-heparin anticoagulant is essential. However, off-label use with fondaparinux has been reported in the literature. The study aim was to collect data on "real-life" management of patients with suspected acute HIT regarding diagnostic and therapeutic strategies.
Patients and Methods: In a national multi-centre registry study, patients with a 4 T's HIT-probability score of ≥4 points and treatment with at least one dose of (A)rgatroban, (L)epirudin, (D)anaparoid, or (F)ondaparinux were retrospectively evaluated.
Results: Of 195 patients, the 4 T's scores were 4/5/6/7/8 points in 46 (23.6%)/50 (25.6%)/74 (38.0%)/13 (6.7%)/7 (3.6%) patients, respectively. During heparin therapy, 47 (24.1%) thromboembolic events, 5 (2.6%) skin lesions, 1 (0.5%) amputation, 24 (12.3%) Hb-relevant bleedings, and 2 (1.0%) fatalities occurred. A functional heparin-induced platelet activation assay was performed in 96.9%, a platelet factor 4/heparin-dependent enzyme immunoassay in 89.2%, a particle gel immunoassay in 12.3%, and a serotonin-release assay in none of the patients. Argatroban was used in 16.4%, lepirudin in 2.1%, danaparoid in 23.6%, fondaparinux in 40.0% of the patients; the sequential therapy strata were: AF (5.6%), DA (5.6%), DF (2.6%), DL (2.1%), ADF (1.5%), and DFL (0.5%).
Conclusions: The current diagnostic laboratory strategy for suspected HIT is mostly (>96%) based on the recommended 2-step strategy (immunoassay plus functional assay). However, there is a wide fondaparinux off-label use (up to 50.3%) for suspected HIT, even in those patients with a high clinical pretest probability. Efficacy and safety of fondaparinux for HIT-treatment require further evaluation.

Abbreviations: A, argatroban; aPTT, activated partial thromboplastin time; BMI, body-mass index; CRF, case report forms; CRO, Contract Research Organisation; D, danaparoid; DIC, disseminated intravascular coagulation; DTI, direct thrombin inhibitors; DVT, deep vein thrombosis; F, fondaparinux; GerHIT, German HIT registry; GFR, glomerular filtration rate; Hb, haemoglobin; H-EIA, heparin-dependent enzyme immunoassay; HIPA, heparin-induced platelet activation assay; HIT, heparin-induced thrombocytopenia; ICD, International Statistical Classification of Diseases and Related Health Problems; INR, International Normalised Ratio; L, lepirudin; LMWH, low-molecular weight heparin; NYHA, New York Heart Association; PaGIA, particle gel immunoassay; PE, pulmonary embolism; PF4, platelet factor 4; SRA, serotonin-release assay; UFH, unfractionated heparin.

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* Corresponding author at: Department of Internal Medicine, Division of Vascular Medicine and Haemostaseology, Goethe University Hospital Frankfurt/M., Theodor-Stern-Kai 7, Bldg. 13A, 60590 Frankfurt am Main, Germany.
E-mail address: marc.schindewolf@kgu.de (M. Schindewolf).
[1] current affiliation: Department of Cardiac Surgery, Heart Centre Leipzig, University of Leipzig, Germany.
[2] current affiliation: Winicker Norimed Medical Research GmbH, München, Germany.

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Introduction

Immune heparin-induced thrombocytopenia (HIT) is a rare prothrombotic complication of heparin therapy that occurs when the platelet factor 4 (PF4)/heparin-complex exposes an epitope that triggers the formation of pathogenic anti-PF4/heparin antibodies, which can subsequently activate platelets via cross-linking of the antibody/PF4/heparin-complexes with FcγRIIa-receptors on platelets [1–3]. The predominant clinical features are thrombocytopenia and possibly life-threatening venous and arterial thromboembolic complications. Rare manifestations can involve the skin and adrenal glands [4–6].

Although the immediate alteration of therapy with heparins to a non-heparin anticoagulant is pivotal to prevent or treat the complications of HIT, there are currently no legal German guidelines for the management of HIT. The therapy in Germany generally follows the American guidelines as published by the American College of Chest Physicians [7]. The approved and licensed alternative anticoagulants for the therapy of acute or suspected acute HIT are argatroban, lepirudin, and danaparoid. Patients undergoing percutaneous coronary interventions or urgent cardiac surgery can alternatively be treated with bivalirudin [8]. Furthermore, on the basis of clinical experiences published as single case reports or cases series, the synthetic ultra-low molecular weight pentasaccharide fondaparinux has been applied successfully in patients with acute or suspected acute HIT [9–16], although it is not licensed for this indication. However, a few potential fondaparinux-induced HIT cases [17–22] have sparked a scientific debate about this "off-label" indication [23–27].

The aim of our retrospective multi-centre registry study of patients with suspected acute HIT was to collect data on the "real-life" management of these patients in German hospitals.

Patients and methods

Study design

The study was planned as a retrospective, national, multi-centre, non-interventional, observational registry study. The Ethics Committee of the State Chambers of Physicians (Landesaerztekammer) Bavaria confirmed that ethical approval for this registry study was not required because all of the collected patient data were completely anonymised. The data were extracted retrospectively from patient files, so the patient information and informed consent form were not required. The study was registered at ClinicalTrials.gov (NCT01304238).

Patients

In November 2008, a Contract Research Organisation (CRO) was assigned to independently contact German hospitals for participation in this retrospective registry study on patients treated for suspected acute HIT. Potential study centres with an expertise in the management of HIT were identified on the basis of a recent literature search [9]. A total of nine hospitals across Germany participated in the study. All patients hospitalised between January 19, 2005 and October 25, 2009 were screened via electronically registered discharge diagnosis codes (ICD-10 codes, International Statistical Classification of Diseases and Related Health Problems) by each centre. The pre-selection of possibly eligible patients was conducted on the basis of ICD D68.53, the respective code for immune HIT, and the erroneously coded ICD D68.52 (non-immune HIT type I). In total, 261 patients with these codes were identified, and the anonymised Screening-Logs were returned to the CRO. Afterwards, the CRO supplied the participating centres with the respective numbers of standardised paper case report forms (CRF) for further data documentation. The questionnaire was developed by the Division of Vascular Medicine and Haemostaseology at the Goethe University Hospital Frankfurt/M., Germany prior to study initialisation. The 261 pre-selected patients were assessed by the assigned investigators of each centre according to the well-established pretest probability score for HIT (4 T's score) [28] on the basis of the patients' individual clinical records. Only the patients with a 4 T's score ≥ 4 and treatment with at least one dose of one or several of the commercially available anticoagulants fondaparinux (F), argatroban (A), danaparoid (D), and/or lepirudin (L) were finally included in the study (Fig. 1).

In addition to the basic medical data, the 4 T's scores, ICD-10 codes for HIT, specifications of heparin therapy (including indication for prophylaxis or therapy; clinical setting, i.e., surgical or medical; and type of heparins (LMWH or UFH) used, including dosage, duration and alterations of therapy), HIT-specific complications (i.e., limb amputations, venous and/or arterial thromboembolic events, any bleedings with or without a documented drop in haemoglobin levels, cutaneous reactions or necroses, death (reported as in-hospital all cause fatalities)), specific HIT diagnostics (i.e., PF4/heparin-dependent enzyme immunoassay (PF4/H-EIA), specific for either anti-PF4/heparin IgG class or IgG/IgM/IgA class antibodies; particle gel immunoassay (ID-PaGIA heparin/PF4 antibody test (PaGIA); DiaMed AG, Cologne, Germany); functional heparin-induced platelet activation assay (HIPA) (performed using washed platelets); functional serotonin-release assay (SRA); platelet counts), and alternative anticoagulation regimens including the administered preparations and dosages were registered.

Study outcome measures

The primary outcome measures were the laboratory diagnostic strategies and prescription practices of anticoagulant therapy in patients with suspected acute HIT. Further outcome measures of interest were the characteristics of heparin treatment and its associated clinical complications.

Statistical Analysis

All statistics were descriptive. Categorical data were presented as absolute and relative frequencies. Numerical data were presented as the means, standard deviations, medians, minimums and maximums, and quartiles. The results were categorised as "total" and in "subgroups" based on the anticoagulant therapy (monotherapy or sequential therapy) after suspicion of HIT. The statistical analyses were performed using SAS® software package (SAS® Version 9.1; SAS Institute Inc., Cary, NC, USA).

Results

Study inclusion

Of the 261 patients with a D69.53 or D69.52 ICD-10 code discharge diagnosis, 195 (74.7%) were eligible for study inclusion after applying the 4 T's score. A total of 54 (20.7%) patients were not included due to a 4 T's score of <4 points (0 points: 11 patients, 1 point: 3 patients, 2 points: 11 patients, 3 points: 29 patients). Twelve (4.6%) patients were not eligible because the returned CRFs were incomplete (Table 1).

Study patients

Of the 195 included patients (110 male, 84 female, 1 nd, mean ± SD age: 68.5 ± 12.5 years [range: 24–92 years]; mean ± SD weight: 77.9 ± 15.5 kg [range: 43–125 kg]; mean ± SD body-mass index (BMI) 27.2 ± 5.5 kg/m^2 [range 14.7-48.8 kg/m^2]), 157 (80.5%) patients were diagnosed with the ICD-10 code D69.53 (immune HIT) and 12 (6.2%) patients with the ICD-10 code D69.52 (non-immune HIT). In 26 (13.3%) additional patients, the HIT code was not further sub-classified (Table 1).

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