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Safety and effectiveness of biosimilar enoxaparin (Inhixa) for the prevention of thromboembolism in medical and surgical inpatients

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Abstract
In 2016, biosimilar enoxaparin (Inhixa®, Techdow) was introduced in European markets with the same indications as branded enoxaparin (Clexane®, Sanofi). Its use is constantly increasing in clinical practice, however, little information from post-marketing clinical trials is available on its safety and effectiveness. We conducted an observational, retrospective study to assess the safety and effectiveness of Inhixa in preventing venous thromboembolism (VTE) in medically ill patients and in patients undergoing major abdominal surgery. We then compared our results with the incidence of symptomatic VTE and bleeding events during treatment with Clexane by pooling the results of clinical studies carried out in the same settings. We enrolled 381 patients, 189 admitted to a Medical Department and 192 to a Surgical Department from two single institutions. The incidence of major bleeding events was 1.8% globally (95% IC 0.7–3.8), 1.6% in medical patients (95% IC 0.3–4.6) and 2.1% in surgical patients (95% IC 0.6–5.3). VTE rate was 0.5% in the whole population (95% IC 0.1–1.9) and 0.5% (95% IC 0.01–2.9) in each group, respectively. The pooled estimate of the incidence of major bleeding with Clexane was 0.5% (IC 95%: 0.2–1.1) in medical patients and 2.6% (IC 95% 1.3–5.1) in surgical patients. The incidence of thrombotic events was 0.6% (IC 95%: 0.2–1.8) and 0.7% (CI95% 0.3–1.6), respectively. The incidence of bleeding and thrombosis in medical and surgical patients receiving Inhixa was low suggesting biosimilar enoxaparin is a valid alternative to branded enoxaparin.

Keywords Inhixa · Enoxaparin · Biosimilar · LMWH · Prevention

Introduction

Patients undergoing general surgery and hospitalized acutely ill medical patients are at increased risk of venous thromboembolism (VTE) [1, 2]. Several randomized clinical trials have demonstrated the efficacy and safety of low-molecular-weight heparin (LMWH) in preventing VTE in this setting and, based on these findings [3, 4], international guidelines recommend their use as first choice in patients with high thrombotic risk and acceptable bleeding risk [5, 6].

Over the last years, several biosimilar LMWHs have become available worldwide, and their use in clinical practice is constantly increasing. According to a recent position paper of the European Medicines Agency (EMA), the therapeutic equivalence between originator and biosimilar products should be derived from physicochemical, functional and pharmacodynamics comparisons in preclinical and clinical studies, while dedicated head-to-head clinical trials comparing efficacy and safety are no longer considered necessary [7].

However, an intensive post-marketing follow-up and pharmacovigilance plan is of critical importance to monitor the safety and immunogenicity of these products.

In 2016, Inhixa® (Techdow), biosimilar of enoxaparin sodium, received a marketing authorization from EMA and became available in Europe with the same indications as enoxaparin originator (Clexane®, Sanofi) [8]. Nowadays, the

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safety of Inhixa in general surgical and in medical patients has not been investigated yet.

The aim of this study was to assess the safety and effectiveness of Inhixa in preventing VTE in medically ill patients and in patients undergoing major abdominal surgery admitted to two Italian hospitals.

Methods

We conducted an observational, retrospective study in two Italian hospitals (Ospedale di Circolo, Varese and Ospedale San Paolo, Milan), including patients admitted to an Internal Medicine department for acute illness from June 2018 to November 2018 in Varese and to a General Surgery department from July 2018 to January 2019 in Milan. All surgical patients underwent major abdominal surgery (elective or emergency).

Patients were excluded if they had another indication to anticoagulant treatment (e.g., for atrial fibrillation, acute VTE, or in the presence of a mechanical prosthetic heart valve) or if they were receiving therapeutic or intermediate doses of LMWH. The decision on VTE prophylaxis, dose, molecule and duration of treatment was left to clinicians' decision.

For each patient, we collected information on baseline characteristics (sex, age, body weight), type and dose of LMWH prescribed (Clexane, Inhixa, others), baseline laboratory findings (haemoglobin levels, platelet count, creatinine and creatinine clearence calculated using the Cockcroft–Gault formula), degree of mobility defined as no change in mobility, reduced mobility, confined to bed.

For each medical patient, we also collected information on the clinical indication for VTE prophylaxis (heart failure, respiratory failure, acute infection, rheumatic disease, acute ischemic stroke), and we estimated thrombotic and bleeding risk based on Padua Prediction Score and Improve Bleeding Score [9, 10], and laboratory tests (haemoglobin levels, platelet count, creatinine) at discharge.

For every surgical patient, we collected information about the indication to surgical procedure. Laboratory tests at discharge were not available.

We collected information on bleeding and thromboembolic events occurred during hospitalization. For each bleeding event, we documented the site, the need for transfusion, variations in haemoglobin levels, and the need for surgical or medical treatment.

For medical patients, we also collected information on the occurrence of cutaneous side effects (allergy or cutaneous ecchymosis).

The primary outcomes of the study were the incidence of major bleeding and symptomatic VTE. Major bleeding events were defined based on the International Society on Thrombosis and Haemostasis (ISTH) criteria for surgical and non-surgical patients [11, 12].

The diagnosis of symptomatic DVT was established with the use of compression ultrasonography, while symptomatic PE was confirmed by lung CT scan or perfusion lung scintigraphy.

The diagnosis of allergic or cutaneous side effects was based on reports from nurses and clinicians.

Safety was assessed during the time on prophylactic therapy, while effectiveness was assessed until discharge regardless of the duration of prophylaxis.

To collect information about the efficacy and safety of enoxaparin originator in medical and surgical patients, we performed a non-systematic review of 25 studies in literature, which we considered among the most relevant in the field and including patients as similar as possible to our population [13–37]. These studies included both randomized clinical trials and large observational studies.

Statistical methods

Descriptive analysis was carried out for patients on prophylactic therapy with Inhixa.

Absolute and relative frequencies in the case of discrete variables, with mean and standard deviation for continuous variables were reported.

For medical patients, the Padua score and the Improve bleeding score were categorized in "low" and "high" considering as high values of at least four and at least seven, respectively [9, 10].

The proportion of patients with bleeding and thrombotic events during hospitalization was calculated for the whole population and then for medical and surgical patients, separately, with 95% confidence interval.

The rates of events were compared with incidence rates reported in the literature. For medical patients, the results of eight studies [13–20] reporting incidence rates of major bleeding and thrombotic events during prophylaxis with enoxaparin, and for surgical patients, the results of 17 studies were pooled [21–37]. Using a generalized linear model, a meta-analysis was performed and the mean value of the proportions of major bleeding and thrombotic events were calculated with the relative 95% confidence interval.

The analyses were performed with the SAS v9.4 software.

Results

Patients characteristics

A total of 381 patients admitted to Medical and Surgical departments received thromboprophylaxis with Inhixa (Fig. 1); 33 of 189 medical patients had a creatinine

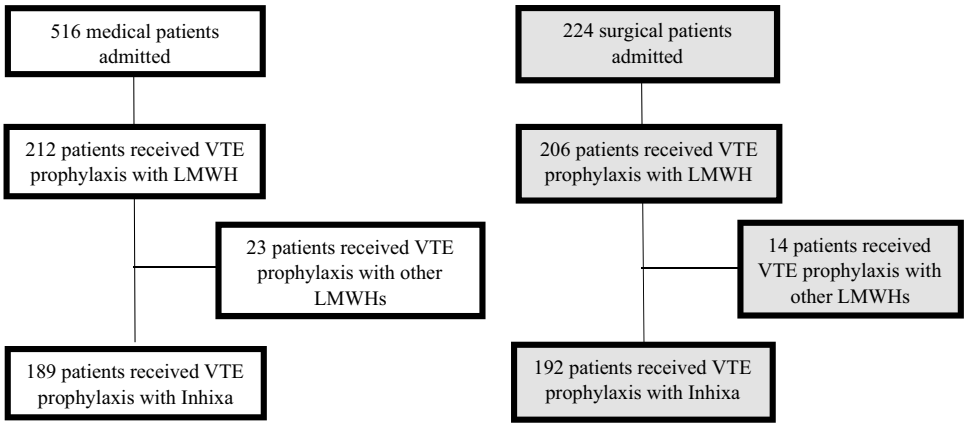

Fig. 1 Enrollment flow diagram

Table 1 characteristics of the whole study cohort, surgical and medical patients

		All		Medical patients		Surgical patients	
		n	%	*n*	%	*n*	%
N		381	100.0	189	100.0	192	100.0
Sex	Female	198	52.0	99	52.4	99	51.6
	Male	183	48.0	90	47.6	93	48.4
Age	Mean-SD	69.1–15.2		75.2–13.6		63.0–14.2	
	Median–Min/max	72–16/99		78–27/99		78–27/99	
Body weight (kg)	Mean-SD	72.0–18.7		71.5–21.0		72.3–16.7	
	Median–min/max	70–24.7/176		70–24.7/176		70–44/152	
Hb (g/dL)	Mean-SD	12.7–2.4		12.4–2.8		13.1–1.2	
	Median–min/max	12.8–3.9/35.1		12.2–3.9/35.1		13.3–7.7/17.3	
PLT (10^3/uL)	Mean-SD	241.6–93.1		245.3–97.5		238.0–88.7	
	Median–min/max	231–7/664		225–13.8/664		235–7/546	
Creatinine (mg/dL)	Mean-SD	1.0–0.5		1.2–0.6		0.9–0.2	
	Median–min/max	0.9–0.3/4.9		1.1–0.3/4.9		0.8–0.5/3.0	
Mobilization	No change	242	63.5	113	59.8	129	67.2
	Reduced	98	25.7	38	20.1	60	31.3
	Confined to bed	41	10.7	38	20.1	3	1.6

clearance between 20 and 29 mL/min and received Inhixa 2000 IU daily, all other patients received 4000 IU daily. All surgical patients received 4000 IU daily.

Baseline characteristics of the whole study population are shown in Table 1. The mean age was 69.1 years, 52% were females and the mean body weight was 72 kg. Most of the patients had no mobility restrictions (63.5%), while 25.7% had a reduced mobility and 10.7% were completely bedridden.

We included 189 acutely ill patients admitted to the Medical Department. The mean age was 75.2 years and most of the patients were females (52.4%); 20.1% of patients were totally confined to bed, 20.1% had reduced mobility, 59.8% had no change in mobilization. As shown in Table 2, the most frequent indication for thromboprophylaxis was acute infection (67, 7%), 14.8% of patients had heart failure, 6.4%

Table 2 Medical inpatients: indication to prophylactic anticoagulant treatment, PADUA Prediction Score and Improve Bleeding Score

	Total (189)	
	n	%
Heart failure	28	14.8
Respiratory failure	12	6.4
Acute infection	128	67.7
Rheumatic disease	2	1.1
Ischemic Stroke	10	5.3
PADUA prediction score ≥ 4	115	60.9
IMPROVE bleeding score ≥ 7	40	21.2

respiratory failure, 5.3% had ischemic stroke, and 1.1% had rheumatic disease. Based on prediction scores, 60.9% of patients were at high risk of thrombosis, 21.2% had a high risk of bleeding.

As regards the 192 surgical patients included, the mean age was 63 years and most of the patients were females (51.6%); 67.2% of the patients had no change in mobilization while 31.3% had reduced mobility. Only 1.6% of the population was completely confined to bed (Table 1).

As reported in Table 3, gallstones were the most frequent indication to surgery (40.4%), 18.2% of the patients had liver cancer (primary or metastatic) and 16.1% had bowel cancer, 3.6% had pancreatic or gastric cancer or suffered from hernias.

All the patients included in the study received thromboprophylaxis with Inhixa for the entire period of the admission, except for patients who presented with bleeding or thromboembolic events who were treated accordingly.

Outcomes

As shown in Table 4, 1.8% (95% IC 0.7–3.8) of the whole study population had a major bleeding event, 1.6% (IC 95% 0.3–4.6) in medical patients and 2.1% (95% IC 0.6–5.3) in surgical patients.

Table 3 Surgical inpatients: indications to surgical procedures

	Total (192)	
	n	%
Gallstones	44	40.4
Liver cancer (primary or secondary)	35	18.2
Bowel cancer	31	16.1
Pancreatic cancer	7	3.6
Gastric cancer	7	3.6
Hernias	7	3.6
Biliary cancer	6	3.1
Acute appendicitis	5	2.6
Obesity	5	2.6
Acute cholecystitis	4	2.0
Acute diverticulitis	2	1.0
Inflammatory bowel disease	2	1.0
Colitis (ischaemic, others)	2	1.0
Others	35	18.2

The incidence of thromboembolic events was 0.5% (IC 95% 0.1–1.9) in total, 0.5% (IC 95% 0.01–2.9) in medical patients and 0.5% (IC 95% 0.01–2.9) in surgical patients.

As regards the occurrence of other adverse events in acutely ill medical inpatients during treatment with Inhixa, 2.7% (IC 95% 0.9–6.1) of patients had an allergic cutaneous reaction, while 8 patients presented ecchymosis in the site of injection; half of which had a diameter > 5 cm (2.1%, IC 95% 0.6–5.3).

No heparin-induced thrombocytopenia events occurred in both groups.

Results of the pooled analysis

Of the 25 selected studies, 16 were RCTs, six in medical and ten in surgical patients, and nine were observational studies, two in medical and seven in surgical patients. The pooled incidence of major bleeding events calculated in medical inpatients was 0.5% (IC 95%: 0.2–1.1), while in patients undergoing major abdominal surgical procedures was 2.6% (IC 95% 1.3–5.1). The definition of major bleeding events in these studies was based on authors' opinion.

The incidence of symptomatic VTE events was 0.6% (IC 95%: 0.2–1.8) in medical patients and 0.7% (CI95% 0.3–1.6) in surgical patients.

Discussion

To the best of our knowledge, this is the first observational report on the safety and effectiveness of biosimilar enoxaparin in medical inpatients and the first to report on the Italian population. Overall, the incidence of bleeding and VTE events was low. Similarly, the incidence of other adverse events collected in medical inpatients was low without any severe adverse reaction. These data support the use of biosimilar enoxaparin in clinical practice, despite the absence of prospective head-to-head comparisons.

In our study, symptomatic, objectively documented VTE events occurred in 0.5% of medical and surgical patients, respectively, a rate that well compares with the estimated rates of 0.6% and 0.7%, respectively, from our pooled analysis of the literature. These reassuring results need to be interpreted with some caution since the 95% upper limit of the confidence intervals reported from the

Table 4 Clinical outcomes

	ALL			Medical patients			Surgical patients		
	n	%	95% IC	*n*	%	95% IC	*n*	%	95% IC
	381	100.0		189	100.0		192	100.0	
Major bleeding	7	1.8	0.7–3.8	3	1.6	0.3–4.6	4	2.1	0.6–5.3
VTE	2	0.5	0.1–1.9	1	0.5	0.01–2.9	1	0.5	0.01–2.9

study population exceed those estimated from the literature, suggesting the need for continuous pharmacovigilance and new, larger observational studies to confirm our findings.

Also major bleeding rates in the surgical population were comparable with the rates obtained from pooling the results of the literature (2.1% and 2.6%, respectively), with similar 95% upper limits of the confidence intervals. Conversely, the rate of major bleeding in medical inpatients was higher than that estimated from the analysis of the literature (1.6% vs. 0.5%) and this rate also exceeded the upper limit of the 95% confidence intervals in the pooled analysis (1.1%). However, this pooled rate is mainly driven by the results of randomized clinical trials and it is well known that patients enrolled in these studies are more selected and, possibly, at lower risk than "real world" patients. Indeed, only looking at incidence rates reported in selected observational studies [14, 20], the incidence rate of major bleeding events was closer to that found in our study or even higher (2.5% and 1.1%, respectively).

Two relevant post-marketing studies have previously investigated the safety and effectiveness of biosimilar enoxaparin (Cistàlia and Neoparin).

In a randomised multicenter study conducted in Poland, 299 patients undergoing major orthopedic surgery were randomly assigned to receive biosimilar enoxaparin (Neoparin) or Clexane for 14 days after surgery [39]. In this analysis, Neoparin resulted non-inferior to Clexane as regards the incidence of any bleeding events (15.7% in the Neoparin group and 19.9% in the Clexane group, RR 0.79, $p < 0.001$, 95% CI 0.48–1.29). No statistically significant difference was registered for major bleeding events (8.5% vs. 10.3%, RR 0.83, 95% IC 0.41–1.68), VTE (3.27% vs. 4.11%, RR 0.80, 95% IC 0.25–2.55) and related adverse events (49% vs. 49.3%, RR 0.99, 95% IC 0.79–1.25).

In 2018, Ramacciotti and colleagues conducted a randomized clinical trial in Brazilian centers to compare the efficacy and safety of biosimilar enoxaparin Cristàlia to branded enoxaparin in patients undergoing major abdominal surgery [23]. In this study, the incidence of VTE was non-significantly higher in patients receiving biosimilar enoxaparin than in patients receiving branded enoxaparin (4.9% and 1.1%, $p = 0.19$), as well as the incidence of clinically relevant non-major bleeding (9.9% in the first group and 5.5% in the second group, $p = 0.21$). No major bleeding events according to the ISTH definition were recorded [12].

This trial was based on a previous exploratory clinical trial comparing the efficacy and safety of Clexane to a generic version of enoxaparin in a small group of patients undergoing major surgery [37]. In this study, no statistically significant differences between the 2 groups were detected in the incidence of VTE and minor and non-major bleeding events. No major bleeding events occurred in either group.

One additional concern with the use of biosimilar drugs is related to the possible occurrence of other adverse effects. In our study, 2.7% of acutely ill medical patients had an allergic cutaneous reaction during treatment with Inhixa while 2.1% presented with ecchymosis with a diameter > 5 cm in the site of injection. This rate well compares with those reported in previous studies with branded enoxaparin. For example, in the MEDENOX study, the authors registered an incidence of 1.4% of ecchymosis > 5 cm in the site of injection [13].

While the idea of the biosimilars revolution is attractive to replace the more expensive originator therapy, expert opinions and scientific societies still encourage well designed and powered studies to establish the efficacy and safety of biosimilar LMWH, together with a careful pharmacovigilance process [38]. However, it is unlikely that adequate randomized clinical studies will ever be conducted. In view of our findings, the use of biosimilar Inhixa for the prevention of VTE in hospitalized medical and surgical patients appears as a valid alternative to branded enoxaparin. The observed variations in outcome events across studies can be attributable to the heterogeneity of the study populations, of the study designs and on the definitions of outcomes. However, such heterogeneity and the lack of adequate head-to-head comparisons, at least in some settings, suggest that an accurate pharmacovigilance is of critical importance, especially in the first period of treatment, to rapidly detect adverse event and that larger observational studies should be developed.

A number of limitations of the present study need to be acknowledged. First, the retrospective design did not allow to collect all requested data; for this reason, some information on laboratory findings and their variations during treatment were missing. However, we paid meticulous attention to the detection of the study outcomes and collected all necessary information to confirm the reported objective diagnoses. Second, the limited sample of enrolled patients resulted in large confidence intervals, suggesting the need for larger observational studies. Third, the lack of a direct comparison with branded enoxaparin limits the validity of our conclusions. However, we believe that pooling the results of previous clinical studies conducted in similar populations offers a valid comparison, and the absence of substantial differences offers a strong support to our conclusions.

Conclusion

This study shows that the treatment with the biosimilar enoxaparin Inhixa is a safe and effective option for the prevention of VTE in medical and surgical patients and is an attractive alternative to branded enoxaparin.

Larger observational studies are necessary to consolidate our results and to further support the cost-effectiveness of this treatment.–

Compliance with ethical standards

Conflict of interest Walter Ageno received honoraria from Boehringer Ingelheim, Bayer Pharmaceuticals, BMS-Pfizer, Daiichi-Sankyo, Portola, Aspen, Sanofi and research support from Bayer Pharmaceuticals, outside the submitted work. The authors report no other conflicts of interest in this work.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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