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Long-term treatment of venous thromboembolism with tinzaparin compared to vitamin K antagonists: A meta-analysis of 5 randomized trials in non-cancer and cancer patients ☆

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ABSTRACT

Purpose: Due to its specific pharmacokinetic profile, tinzaparin, a low-molecular-weight heparin (LMWH), appears not to be associated with anti-factor Xa accumulation. Our meta-analysis aimed at determining whether long-term curative doses of tinzaparin is a valuable alternative to vitamin K antagonists (VKA) for the treatment of symptomatic venous thromboembolism (VTE), especially in patients with cancer who are at higher risk of recurrence and bleeding.

Materials and Methods: A systematic literature search identified randomized studies on long-term tinzaparin compared to VKA in patients with VTE. Outcome measures were VTE recurrence, major bleeding, deaths and net clinical benefit combining the three endpoints during the treatment period and at one year. Pooled relative risk was estimated using the logarithm of the relative risk (RR) method based on a fixed-effect model in the overall population and cancer population.

Results: Five randomized controlled studies were eligible. No difference between groups in VTE recurrence was found in the overall population (RR = 0.85 [0.55; 1.31]). In cancer patients, a non-significant 38% VTE risk reduction in favor of tinzaparin was observed on treatment (RR = 0.62 [0.30; 1.31]). The difference was significant at the end of follow-up at one year (RR = 0.40 [0.19; 0.82], $p<0.01$). The incidence of major bleeding in the tinzaparin group was not significantly different from the VKA group in the overall population and cancer patients.

Conclusions: Tinzaparin appears as a valuable option for long-term treatment of patients in whom VKA are contraindicated or difficult to monitor. Tinzaparin may have a more favorable benefit-risk ratio than VKA in patients with cancer and VTE.

Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep-vein thrombosis (DVT) is a major cause of morbidity and mortality, affecting over 2 million people in the United States [1–3]. Patients with cancer face a significant increase in the incidence of VTE compared to non-cancer patients, of at least 7-fold in certain malignancies [4].

Patients with proximal DVT or PE require anticoagulant treatment for at least 3 months to prevent symptomatic extension and/or recurrent VTE [5,6]. Standard therapy includes initial unfractionated heparin (UHF), low-molecular-weight heparin (LMWH) or pentasaccharides followed by vitamin K antagonists (VKA) which have been considered for decades as the reference long-term anticoagulant therapy in patients with symptomatic VTE as oral administration is effective and more convenient for long-term treatment [7,8]. VKA reduce the risk of VTE recurrence as long as they are used [9]. However, the high variability in the response to VKA requires regular INR monitoring and dose adaptation. Although VKA achieves a low rate of recurrent VTE in the general population of patients with VTE (10), its use is associated with a high recurrence rate in patients with cancer (11).

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LMWH has been considered as an effective and safe alternative for the long-term anticoagulant treatment in patients with side effects or other complications on VKA [10] or in patients in whom the use of VKA would be contraindicated or problematic [11]. The issue of the benefit-risk ratio of long-term curative doses of LMWH and their potential advantage compared to VKA is not fully addressed [12]. Based on a meta-analysis of randomized trials, early comparisons of LMWH to VKA for the long-term treatment of symptomatic VTE showed a statistically non-significant reduction in the risk of VTE at 3 months (OR 0.66 [95%CI 0.41; 1.07]) and in the risk of bleeding (OR 0.45 [95%CI 0.18; 1.11]) in favor of LMWH treatment [11]. Previous reviews or meta-analyses in adult patients with cancer have shown that the long-term use of LMWH after the acute first week of treatment is superior to VKA for secondary prevention of venous thromboembolism [13–15]. Overall, meta-analyses on LMWH show a reduction of VTE recurrence and bleeding risk compared to VKA but statistical significance is not reached. This may be due to: i) old studies with sub-optimal methodology, ii) the mix in clinical studies of cancer and non-cancer patients who are at different levels of risk, iii) the inclusion of different LMWHs in the same analyses.

Only one of the available LMWH, dalteparin, has received formal approval for the long term treatment of patients with cancer at curative doses, based on the CLOT study [16]. However, enoxaparin and tinzaparin (Innohep®, LEO Pharma) curative doses are also recommended by academic and regulatory guidelines for the long-term treatment of symptomatic VTE in patients with cancer [7,8,17–19]. Tinzaparin has the highest molecular weight compared to other LMWH. It is not exclusively eliminated by the kidney as the reticulo-endothelial system and the liver contribute to tinzaparin metabolism (21). Therefor unlike other LMWHs such as enoxaparin, tinzaparin does not seem to cause an accumulation of anti-factor Xa activity in patients with renal insufficiency [20,21] which is of particular interest in patients with cancer with a high prevalence of renal impairment (24) in whom tinzaparin could be associated with a lower risk of bleeding.

The purpose of this meta-analysis is to assess the benefit-risk ratio of the LMWH, tinzaparin, when used at curative doses for the long-term treatment of patients with symptomatic VTE, in comparison to VKA.

Material and methods

Literature search and study identification

Our aim was to identify all the relevant published and unpublished randomized controlled trials (RCTs) comparing long-term tinzaparin (3–6 months), at the curative dosage of 175 IU/kg once daily for the treatment of VTE to a vitamin K antagonist adjusted to maintain an INR of 2 to 3. An exhaustive literature search, both manual and computer assisted, was performed without any restriction on language or dates. The computer-assisted search was carried out on electronic databases (MEDLINE, the Cochrane Library databases, Google Scholar and the National Institutes of Health RCT register [clinicaltrials.org] using the combination of 3 blocks of terms: i) venous thrombosis or venous thromboembolism or thrombosis; ii) randomized, controlled, or meta-analysis; iii) tinzaparin or innohep. In addition, conference proceedings from the International Society of Thrombosis and Haemostasis (ISTH), the International Congress on Thrombosis (ICT), the International Conference on Thrombosis and Haemostasis Issues in Cancer (ICTHIC), the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched for abstracts of relevant trials. We manually searched the bibliographies of journal articles to find additional studies. Particular attention was given to duplicate reports, and, when studies were published both in abstract form and as an original article, only the article was referenced. If more than one article was published for a single study, all citations were included.

Study selection

We selected open and double-blind randomized long-term tinzaparin trials which evaluated the effect of tinzaparin compared to vitamin K antagonists in the treatment of objectively confirmed venous thromboembolism. Randomized trials including both cancer and non-cancer patients were considered.

Endpoints

VTE recurrence was recorded at the end of the treatment period (i.e. 3 or 6 months), and during follow-up at 1 year. It was usually documented either by venous ultrasound or contrast venography for DVT or by high probability lung scan or spiral computed tomography of the chest or pulmonary angiography for PE.

Major bleeding under treatment was defined as follows: i) if it was overt and associated with a decrease in hemoglobin of 2 g/100 ml or more, ii) if it led to the transfusion of 2 or more units of blood, iii) if it was retroperitoneal, iv) if it occurred in a major joint or v) if it was intracranial.

Deaths were recorded whether or not they were VTE-related. Even though studies included in this meta-analysis were not powered to detect significant differences in mortality between treatment groups, mortality data were also extracted. Deaths were considered during the treatment period (i.e. 3 or 6 months) and at one year of follow-up.

The lack of a n*et clinical benefit* at the end of the treatment period was assessed as the combination of VTE recurrence, major bleeding and death.

Data extraction

When a trial was deemed eligible, all investigators and LEO Pharma (the manufacturer of tinzaparin) were contacted and asked to provide the protocol and statistical study report. Pre-defined data from individual trials were extracted independently by two of the authors (SL, LB). A concordance meeting was held, and, in the event of a discrepancy in either study selection or data extraction, agreement was reached. The following data were extracted: name of the first author and study acronym, year(s) of publication, study population (VTE, DVT, PE, cancer or not), number of randomized patients, treatment regimens and duration, follow-up and pre-defined endpoints. Endpoints were documented in the strata or subgroups of cancer patients when available. The methodological quality of each trial was documented according to the Cochrane "Risk of bias" tool [22]. This tool incorporates assessments of selection bias (random sequence generation), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data); reporting bias (selective reporting); and other bias (premature trial discontinuation).

Statistical analysis

Data were directly extracted from the full publications globally and then in cancer patients when available. All analyses were performed on an intent-to-treat basis. Analysis of outcomes was based on the pooling of logarithms of the relative risk (RR) of each study. Summary data were pooled by the inverse-variance weighting method. A RR of 1 indicated that there was no difference between the treatments. A RR$<$1 indicated that tinzaparin was superior to vitamin K antagonists, and a RR$>$1 indicated that vitamin K antagonists was superior. A fixed-effect model was used to estimate the pooled relative risk. To investigate the statistical heterogeneity between trials, the standard Q test was applied. When there was evidence of significant statistical heterogeneity at the level of 0.15, and in the absence of a clear explanation for heterogeneity, a random-effect model was employed, generating a more conservative estimate [23]. A funnel plot of treatment effect versus study precision was created