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Thrombopoietin receptor agonists and risk of portal vein thrombosis in patients with liver disease and thrombocytopenia: A meta-analysis

Lorenzo Loffredo*, Francesco Violi

Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Italy

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ABSTRACT

Background: Treatment of thrombocytopenia with thrombopoietin receptor agonists (TPORAs) seems to be associated with portal vein thrombosis (PVT) in patients with chronic liver disease (CLD). We performed a meta-analysis of the trials carried out in this clinical setting to assess if such association is detectable.
Methods: We performed a meta-analysis with studies that compared the effect of TPORAS vs placebo in patients with CLD and thrombocytopenia.
Results: Four studies, including 1953 patients, reported the incidence of PVT in patients with CLD and thrombocytopenia treated with TPORAs or placebo. No significant difference was found for incidence of PVT in patients treated with TPORAs compared with placebo (O.R.: 2.8; 95% C.I., 0.97–8.16; p = 0.055). A significant association between PVT and TPORAs was observed only in patients treated with eltrombopag (O.R.: 3.8; 95% C.I., 1.14–13.2; p = 0.03). Three studies, including 514 patients who were undergoing an elective invasive procedure, analyzed the incidence of PVT in TPORAs—treated patients with CLD and thrombocytopenia; no significant difference was found for incidence of PVT in patients treated with TPORAs compared with placebo (O.R.: 2.6; 95% C.I., 0.6–11.6; p = 0.212). A significant difference was found for incidence of arterial and venous thrombo-embolic events in CLD patients treated with eltrombopag compared with placebo-treated patients (O.R.: 3.4; 95% C.I., 1.5–7.7; p = 0.003).
Conclusion: The results of this meta-analysis show that TPORAs are not associated with PVT in CLD patients even in the case of surgical procedure. PVT risk seems to be associated only with eltrombopag use.

1. Introduction

Chronic liver disease (CLD) is believed to be associated with a bleeding risk because of coexistence of a so-called "coagulopathy", which is characterized by prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and low platelet count [1]. Thrombocytopenia is relatively frequent in CLD but the occurrence of platelet count <50,000/mm, which is considered a warning sign of bleeding, is rare (<1%) and detectable essentially in patients with severe liver failure [2,3]. A recent study from our group demonstrated that low platelet count, per se, is not a predictor of bleeding but its association with bleeding risk in case of platelet count <50,000/mm could not be excluded [4]. Despite these uncertainties, the increase of platelet count in CLD patients with low platelet count and potentially at elevated risk of bleeding such as those undergoing surgical procedures is a relevant clinical issue, which has been recently approached with the use of thrombopoietin receptor agonists (TPORAs). The increase of venous thrombosis may limit TPORAs use in clinical practice [5]. In a study of CLD patients, TPORAs administration resulted in an increased platelet count with a risk of portal vein thrombosis (PVT) [6]. A meta-analysis including two TPORAs, namely eltrombopag and avatrombopag, confirmed the association with PVT, therefore highlighting the potentially negative impact of this kind of molecules in CLD patients in terms of bleeding risk and survival [5]. A recent publication with a novel thrombopoietin agonist prompted us to re-examine the interplay between TPORAs and thrombosis with particular reference to the occurrence of PVT [7]. Here we show that the negative impact between TPORAs and PVT seems to be attenuated, which opens new perspectives for the use of these molecules in CLD patients.

* Corresponding author at: Divisione I Clinica Medica, Viale del Policlinico 155, Rome 00161, Italy
E-mail address: lorenzo.loffredo@uniroma.it (L. Loffredo).

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2. Methods

2.1. Eligibility criteria

2.1.1. Types of studies

Clinical studies that assessed the effect of TPORAs vs placebo in patients with CLD and PVT were included. No language, publication date, or publication status restrictions were imposed.

2.2. Information sources

The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane database. The last search was run on April 18th, 2018. Reference lists of all studies included in the present meta-nalysis were screened for potential additional eligible studies.

2.3. Search

One investigator (L.L.) independently searched in the electronic databases combining the following text terms and MeSH terms: ("receptors, thrombopoietin"[MeSH Terms]) OR ("receptors[All Fields] AND 'thrombopoietin'[All Fields]) OR "thrombopoietin receptors"[All Fields] OR ("thrombopoietin"[All Fields] AND "receptor"[All Fields]) OR "thrombopoietin receptor"[All Fields]) AND agonist[All Fields]) AND ("liver"[MeSH Terms] OR "liver"[All Fields]) AND portal[All Fields].

2.4. Study selection

One author (L.L.) independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis.

Studies not including an untreated control group and animal studies were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines were also excluded from the analysis.

We defined the following exclusion criteria: (1) studies where PVT developed in patients with non-liver disease; (2) studies unrelated to our topic; (3) studies where PVT developed after liver transplantation.

2.4.1. Main analysis

We evaluated the effect of TPORAs vs placebo on PVT in patients with CLD and thrombocytopenia. Furthermore, this review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). A further analysis to assess arterial and venous thrombo-embolic events was performed; the following arterial and venous thrombo-embolic events were considered: PVT, deep venous thrombosis, acute myocardial infarction, unstable angina, ischemic stroke, retinal vascular disorder, pulmonary embolism, femoral artery occlusion.

Further statistical information in supplementary data.

3. Results

Four studies [6–9], including 1953 patients, assessed the effect of TPORAs treatment vs placebo on PVT in patients with CLD and thrombocytopenia (see figure in supplementary data); clinical characteristics of the studies are reported in table (see supplementary data). Three TPORAs were tested (eltrombopag, avatrombopag and lusutrombopag). Follow-up ranged from 1 month (3 studies) to 24 weeks. PVT was 1.6% and 0.6% in TPORAs and placebo group, respectively. There was a trend for an enhanced incidence of PVT in patients treated with TPORAs compared with placebo, but the difference did not reach significance (O.R.:2.8; 95% C.I.:0.97–8.16; $p = 0.055$) (Fig. 1, panel A). No heterogeneity ($I^2 = 0$, $p = 0.718$) between trials was observed; the publication bias was not statistically significant (Egger's test, $p = 0.4$). Interestingly, a significant association between PVT and TPORAs was observed only in patients treated with eltrombopag (O.R.:3.8; 95% C.I.:1.14–13.2; $p = 0.03$) (Fig. 1, panel B).

A further analysis was performed to assess the effect of TPORAs vs placebo on PVT in patients with liver disease and thrombocytopenia, who were undergoing an elective invasive procedure. Three studies, including 514 patients, were analyzed (Fig. 1, panel C); the follow-up was about 1 month. PVT was 2.8% and 0.9% in TPORAs- and placebo-treated patients, respectively. No significant difference was found for incidence of PVT in patients treated with TPORAs compared with placebo (O.R.:2.6; 95% C.I.:0.6–11.6; $p = 0.212$) (Fig. 1, panel C). No heterogeneity ($I^2 = 0$, $p = 0.515$) between trials was observed; the publication bias was not statistically significant (Egger's test, $p = 0.3$).

In addition we analyzed the incidence of arterial and venous thrombo-embolic events in two studies, including 1727 patients randomized to eltrombopag or placebo (Fig. 1, panel D). The rate of arterial and venous thrombo-embolic events was 3.6% and 1.1% in TPORAs and placebo, respectively. A significant difference was found for incidence of arterial and venous thrombo-embolic events in patients treated with eltrombopag compared with placebo (O.R.:3.4; 95% C.I.:1.5–7.7; $p = 0.003$) (Fig. 1 panel D). No heterogeneity ($I^2 = 0$, $p = 0.899$) between trials was observed.

4. Discussion

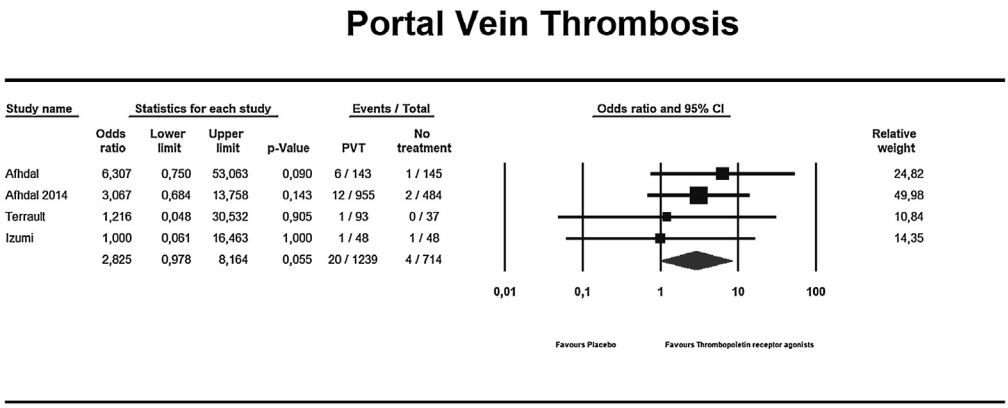
This meta-analysis provides evidence that, globally considered, TPORAs do not increase the risk of PVT in patients with CLD and thrombocytopenia. However, we observed differences between the TPORAs in terms of thrombotic risk.

To the best of our knowledge, there is only one meta-analysis on this topic, which showed an increased risk of PVT in patients with CLD and thrombocytopenia treated with TPORAs [5]. Compared to the previous one [5], we added a recent study which randomly assigned 96 CLD patients undergoing elective surgical intervention to a novel thrombopoietin agonist, i.e. lusutrombopag (3 mg od) or placebo [7]. This study showed only 2 episodes of PVT, one in lusutrombopag- and one in placebo-treated patients [7]. Inclusion of this study in the present meta-analysis provided different results compared with the previous one. We observed, in fact, a trend towards an enhanced PVT risk by TPORAs but the difference was not significant anymore. We further analyzed the relationship between TPORAs and PVT only in CLD patients undergoing surgical procedures and, in this case, the lack of negative impact between TPORAs and PVT was even more evident as no significant difference in terms of PVT risk was detected between TPORAs and placebo.

This finding prompted us to evaluate if the risk of PVT could vary among TPORAs. For this reason, we analyzed separately the impact of single TPORA versus PVT. The novelty of this analysis was in demonstrating a different PVT risk between TPORAs. Eltrombopag was the only one carrying a significant enhanced thrombotic risk. The negative impact of eltrombopag towards the thrombotic risk was further evidenced by analysis of its association with thrombosis, not only in portal but also in systemic venous and artery circulation. We found that eltrombopag-treated patients had an enhanced risk of venous and arterial thrombosis, but we must acknowledge that data regarding the impact of the other TPORAs versus artery and venous circulation districts were not reported.

The reason for this different relationship between TPORAs and thrombotic risk cannot be firmly clarified but the dosage may pro-

A



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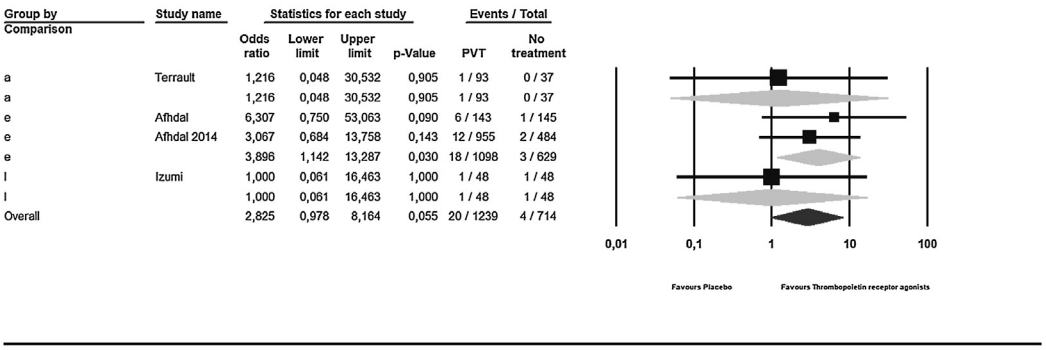

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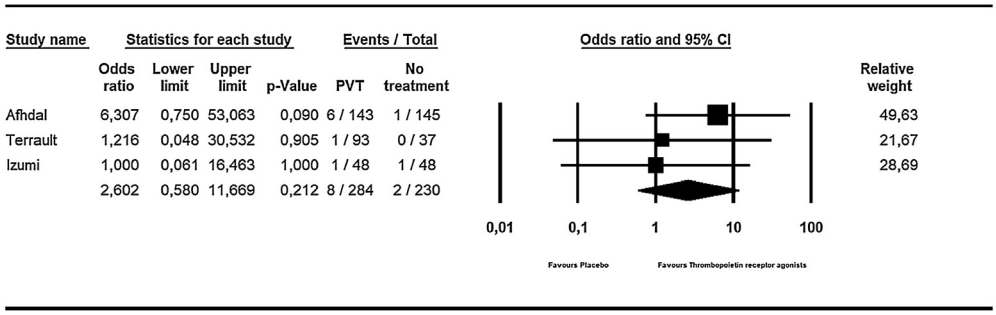

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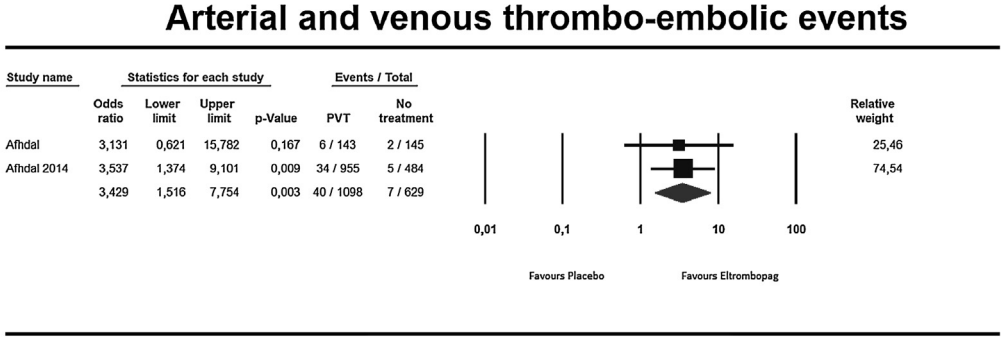

Fig. 1. Panel A: incidence of PVT in patients treated with TPORAs compared with placebo. Panel B: incidence of PVT in patients treated with eltrombopag (e), avatrombopag (a) and lusutrombopag (l) compared with placebo. Panel C: incidence of PVT in patients with liver disease and thrombocytopenia, who were undergoing an elective invasive procedure, treated with TPORAs compared with placebo. Panel D: incidence of arterial and venous thrombo-embolic events in patients treated with TPORAs compared with placebo.

vide a potential explanation. Thus, eltrombopag has been used at higher dosage compared to the other two TPORAs and this could result in achieving an elevated platelet number in the systemic circulation, which could predispose to thrombosis. Thus, most of eltrombopag-treated patients experiencing PVT showed a platelet count close to 200,000/mm^3, which may be particularly deleterious in CLD patients, in whom platelets display an enhanced response to common agonists in vitro and may be more prone to aggregate and facilitate thrombosis in case of abrupt increase in the circulatory system [10]. However, the reason for the eltrombopag-associated rise in platelet count and enhanced thrombotic risk, particularly in the portal circulation where theoretically the role of platelets should be less relevant compared to the clotting system activation, remains to be clarified.

The study has implications and limitations. This meta-analysis is limited by small sample size, low rate of events and lack of information regarding a direct comparison among the type of TPORAs from randomized controlled trials. It is possible that the reduced risk of PVT with the new TPORAs may be dependent upon a lower dosage and an achievement of a safer platelet count, i.e. <200,000/mm^3, but more data are necessary to investigate this issue.

In conclusion, the results of this meta-analysis show that therapy with TPORAs is not associated with enhanced PVT risk. Caution should be used in case of eltrombopag treatment, which is the one more frequently associated with thrombotic risk.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.06.005.

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