Nat. Volatiles & Essent. Oils, 2021; 8(6): 5453-5471

NVEO
Natural Volatiles & Essential Oils

Evaluation of Eltrombopag Efficacy in Patients with Hepatitis C-induced Thrombocytopenia: Systematic Reviews of Meta-Analysis

Abdullah Mohammed AL-Dhuraibi[*1-2] Mikhail Vladimirovich Pokrovskiy[1], Ahmad khalaf alkhawaldeh[3- 4], Wadah Mohammed AL-Dhuraibi[5]

[1]Department of Pharmacology and Clinical Pharmacology, Medical Institute, Belgorod National Research University, Russia

[2]Department of Pharmacology and Clinical Pharmacology, Aden University, Aden, Yemen

[3] Department of Pharmaceutical Science; Faculty of Pharmacy, Jerash University, Jordan

[4]Chemistry Department, The Hashemite University, P.O. Box 150459, Zarqa 13115, Jordan

[5]Chemistry Department, Abian University, Abian, Yemen

Corresponding author: Abdullah Mohammed AL-Dhuraibi

Abstract:

Thrombocytopenia is a popular hematological disorder seen in infected patients having the hepatitis C virus (HCV). Eltrombopag was approved to be used in thrombocytopenia associated with HCV. The aim of our meta-analysis is to produce evidence about the efficacy and safety drug of Eltrombopag in the prevention and treatment Thrombocytopenia caused by HCV-associated cirrhosis. We searched for computer literature from Cochrane Central, Elsevier, Springer and PubMed. For qualifying research, records were screened, and data was collected and synthesized by using Windows Review Manager 5.3. Result: Three randomized controlled trials (N = 1886 patients) in the final analysis were included. The overall effect estimate favored the Eltrombopag group (RR = 2.37; 95% CI [1.28, 4.37] P = 0.006), pooled studies showed significant heterogeneity (I^2 = 85%; P = 0.0002). The pooled RR for adverse effects was as follows: severe adverse effects (RR = 1.30; 95% CI [1.10-1.52]; P =0.001); headache (RR = 1.10; 95% CI [0.89, 1.35]; P = 0.37), diarrhea (RR

= 1.73; 95% CI [1.31-2.29]; P =0.0001); and Abdominal pain (RR = 1.33; 95% CI [0.79-2.26]; P =0.28) for all the effect estimate of adverse effect were not heterogeneous (X^2; P > .1). Of the 3 included studies, only 2 studies 1- Afdhal et al 2012 reported the occurrence of thromboembolic events in the Eltrombopag group 2% (6 patients) 1 received placebo and in the McHutchison et al 2007 study no thromboembolic events were reported and identified during the study. There was no significant difference between the Placebo and Eltrombopag groups in (World Health Organization [WHO] Grade 2 or higher bleeding episodes, which were recorded in 17% and 23% of patients, respectively. 2- In a 2014 study by Afdhal et al, 34 thromboembolic events were reported in 31 eltrombopag patients (3%) and 5 thromboembolic events in 5 placebo patients during the antiviral phase (1%). The most common thromboembolic event in both treatment groups (n 12, 1% eltrombopag; n 2, <1% placebo) was portal vein thrombosis (PVT). This study suggests Eltrombopag is efficient and safe in patients with HCV-associated thrombocytopenia.

Keywords: Eltrombopag - hepatitis C virus - thrombocytopenia - thrombopoietin agonists.

Background:

Thrombocytopenia is usually observed in patients have chronic liver disease, with research indicating that it occurs in up to 76% of patients with cirrhosis [1-4]. The low number of platelets is largely due to the symptoms of portal hypertension and hypersplenism [5-7]. Where the level of thrombocytopenia is related to liver disease severity [8-10]. After or during invasive procedures, thrombocytopenia raises the risk of bleeding and can result in the termination or postponement of elective procedures [11, 12]. Reduced synthesis of thrombopoietin,[8,13-15], and virus-induced suppression of the bone marrow,[16,17] platelet transfusions are widely used to minimize the risk of bleeding during the operation, but their short period of effectiveness and the risk of transfusion reactions minimize their use [18-20]. In addition, the production of antiplatelet antibodies (alloimmunization) may induce refractory thrombocytopenia in up to half of patients receiving multiple transfusions [21, 22]. Clinical trials of interferon and ribavirin have routinely excluded patients with chronic liver disease caused by hepatitis C virus (HCV) infection who have thrombocytopenia (< 75,000 platelets / cubic millimeter), and few published studies have identified the treatment of chronic HCV infection in patients with platelet number (> 50,000 / cubic millimeter). Although the decreased platelet count does not constitute an absolute contraindication to pegylated interferon (peginterferon) and ribavirin therapy, product labels recommend that caution should be used in the care of patients with clinically relevant thrombocytopenia. In addition, if thrombocytopenia occurs during antiviral therapy, peginterferon can need to be administered or discontinued at a reduced dose [23-25]. For HCV -associated thrombocytopenia, the use of thrombopoietin-mimetic agents, in particular Eltrombopag, was approved. Eltrombopag interacts with the thrombopoietin receptor on megakaryocyte precursors and megakaryocytes and stimulates their differentiation and proliferation to raise platelet production [26, 27]. Some data have been recorded for the safety and efficacy drug of Eltrombopag therapy in hepatitis C virus -associated thrombocytopenia patients.

No research on the predictor variables of response to Eltrombopag treatment have yet

been published [26-28]. We therefore conducted this study to evaluate the efficacy of Eltrombopag drug in patients with thrombocytopenia associated with HCV.

Main text:

Objectives:

To assess the effects of Eltrombopag to prevent and treat thrombocytopenia caused by hepatitis C virus -related cirrhosis.

Methods:

We followed the guidelines for the PRISMA statement through the planning this study and meta-analysis [29].

Inclusion and Exclusion Criteria:

Randomized controlled trials (RCTs) were included with these criteria: 1- studies investigating the efficacy of Eltrombopag in patients have thrombocytopenia caused by hepatitis C infection -related cirrhosis. 2- studies in which the sample was participants (children or adults) with a clinical diagnosis of thrombocytopenia caused by HCV -related cirrhosis and platelet >) 30 × 109 / L) 3- studies providing ample reliable data for meta-analysis pooling; and 4- studies are written in English. We analyzed the data from the most complete data in the case of different reports for the same sample population data set.

For the following purposes, studies were excluded: 1- review article 2-Encyclopedia 3-Book chapters 4- Case reports 5- Correspondence 6- Discussion 7- Editorials 8- Errata 9- Examinations 10- Mini reviews 11- Practice guidelines 12- Short communications, and 13- conference papers and thesis papers.

Literature Search Strategy

We checked for all randomized controlled trials studies published in the following online databases: PubMed, Elsevier, Springer and Cochrane Central from 1993 to March 2021. The following keywords and web searches were used: ‘‘Thrombocytopenia’’ AND ‘‘Eltrombopag’’ OR ‘‘, thrombocytopenia caused by hepatitis C virus -related cirrhosis ", AND ‘‘Eltrombopag’’ OR "thrombocytopenia caused by liver disease, "AND ‘‘Eltrombopag’’. One author screened the title and abstract of the documents for eligibility. Full texts of possibly eligible studies have been checked for the collection of appropriate studies for meta-analysis [30, 31].

Data Extraction

Using an online data extraction method. Two authors extracted the data independently. The following were included in the extracted data:

(1) Design of the study; (2) Population of the study; (3) Risk of bias; and (4) Outcomes of the study: total platelet response, and adverse effect.

Quality Assessment

In accordance with the Cochrane Handbook of Systematic Reviews of Interventions 5.1.0 (updated March 2011), the accuracy of the retrieved randomized controlled trials was

evaluated. The likelihood of bias evaluation included the following domains: sequence generation (selection bias), sequence concealment allocation (selection bias), participant and staff blinding (performance bias), outcome evaluation blinding (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other possible reporting risk sources of bias. The decision of the authors is classified as “low risk”, “high risk”, or “uncertain risk” of bias. In the same book, we used the quality evaluation table given in [32].

Measures of Treatment Effect

The primary outcome of the studies assessing the efficacy of Eltrombopag in thrombocytopenia caused by HCV-related cirrhosis was the overall platelet response defined as platelet counts of at least (50 × 109 / L) in the absence of rescue therapy, the occurrence of significant bleeding (WHO grades II-IV) according to the WHO bleeding scale, the occurrence of any bleeding (WHO grades I-IV), number of cases required to recover from treatment, occurrence of adverse effects and the avoidance of platelet transfusion prior, during and up to seven days after the procedure.

Treating Missing Data

In the situation of a missing standard deviation of mean shift from baseline, it was determined from a standard error or 95 % confidence interval (CI) as per Altman [33, 34].

Data Synthesis

We used fixed-effect model using the Mantel-Haenszel (M-H) process, dichotomous data were collected as relative risk (RR) [35, 36], when heterogeneity was not significant (P > 0.1and I2 > 50%); And when heterogeneity was significant (P ≤ 0.1and I2 ≤ 50%); the Random-effect model was used. Fixed-effect model using the Mantel-Haenszel (M-H) on the hypothesis that the included studies were comparable in terms of research design, quality evaluation and treatment effect calculation. For Windows, we applied Review Manager 5.3.

Sensitivity Analysis

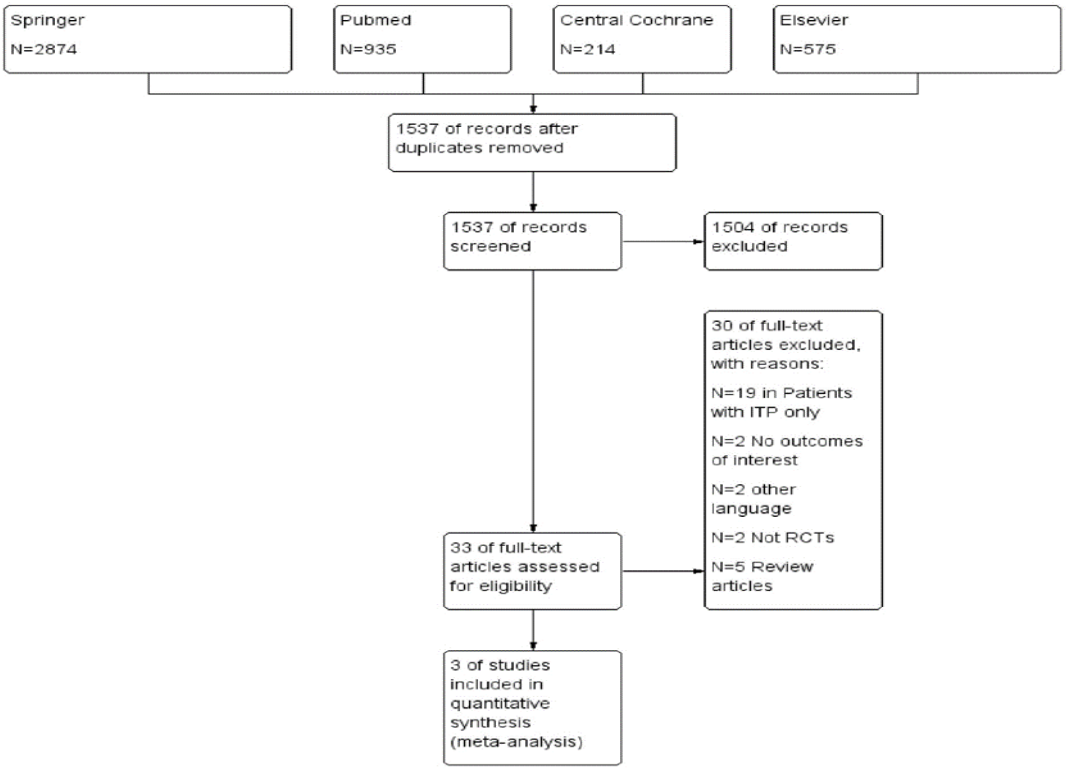
We conducted a sensitivity analysis except 1 study in each case in order to ensure that no particular study influences the findings, and to assess if the overall impact size is statistically robust.

Assessment of Heterogeneity

Visual examination of the forest plots and calculation by I2 and x2 experiments were used to determine heterogeneity. The x2 was used to assess the presence of substantial heterogeneity while the variability in impact estimates due to heterogeneity, if present, is quantified by I2. According to the recommendations of the Cochrane Handbook of Systematic Reviews and Meta-Analysis, the I2 test was interpreted (0-40%): may not be important; (30-60%): may reflect moderate heterogeneity; (50-90%): significant heterogeneity can be represented; and (75-100%): considerable heterogeneity). A random

effect model was used in the situation of significant heterogeneity (x2; P < .1). The model was otherwise used to have a fixed effect.

Figure 1. The flow diagram of studies (PRISMA):



Publication Bias:

For less than 10 pooled trials, publication bias evaluation is not accurate, as per Egger and colleagues [37, 38]. Therefore, the presence of publication bias via the Egger test for funnel plot asymmetry could not be tested in the present analysis.

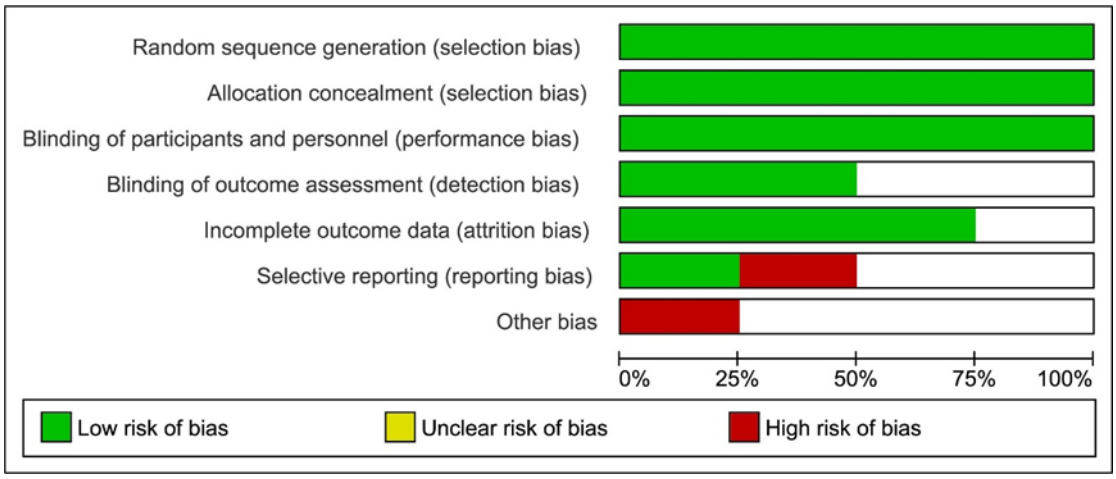
Results:

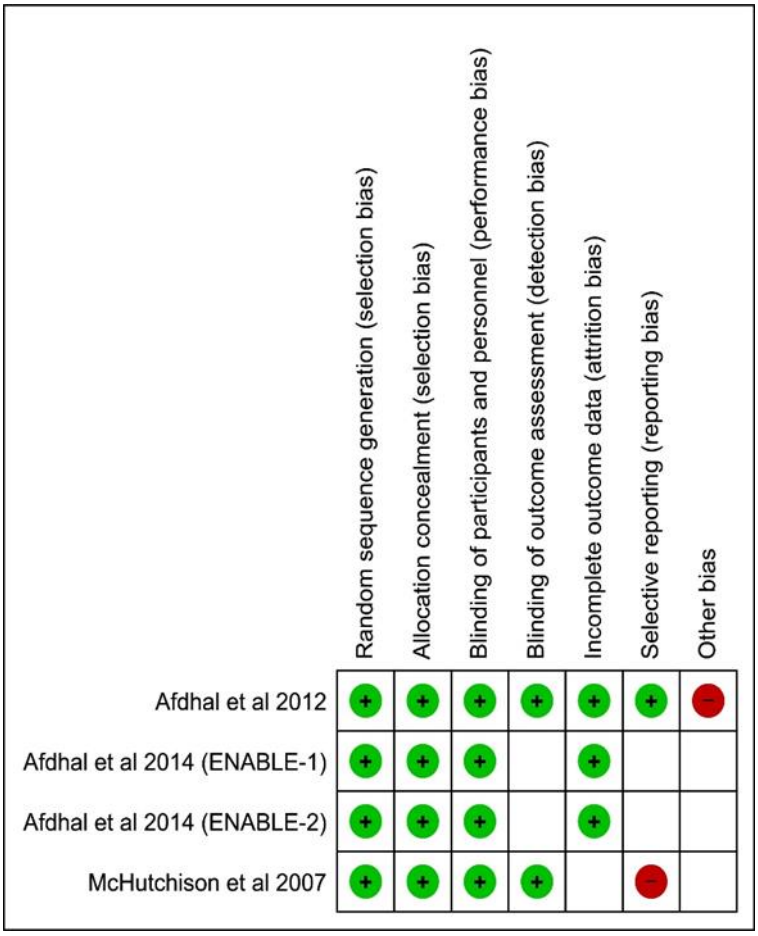
We retrieved 1537 unique articles during our search. A total of 33 full texts were extracted for eligibility and checked. In this analysis, 30 articles were removed and 3 RCTs were included (N = 1886 patients) (Figure 1). Reasons for exclusion from the sample are shown in (Figure 1). One study evaluated Eltrombopag for 2 weeks, a second study evaluated it for 4 weeks and third study evaluated it for 24 weeks. In the McHutchison et al 2007 study [39], Eltrombopag was administered at 30, 50, or 75 mg daily, in the Afdhal et al 2012 study, [40] at 75 mg and in the Afdhal et al 2014(5) study Eltrombopag was administered at 25, 50,75 or 100 mg daily (Table I) shows the overview of the included studies and their major results, and (Table II) shows the baseline characteristics of their samples.

Quality of Included Studies:

According to the Cochrane risk of bias evaluation method, the quality of the included

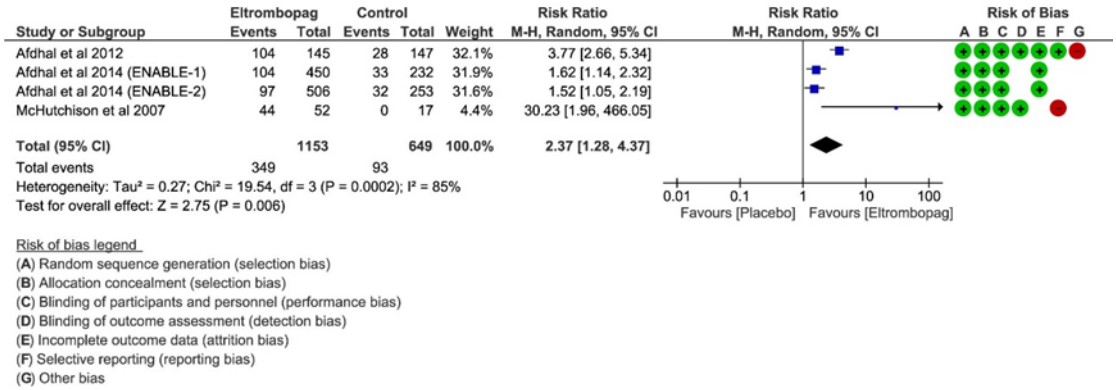
studies was from moderate to high quality. The overview of the fields of quality evaluation of the studies included is shown in (Figure 2 (A-B).) The judgments of the authors with justification are provided in Supplementary (File).





Efficacy analysis:

In terms of overall platelet response, the overall effect estimate favored the Eltrombopag group (RR = 2.37; 95% CI [1.28, 4.37] P = 0.006); Figure 3), pooled studies were significant heterogeneity (I2 = 85%; P = 0.0002). With best reasonable excluding McHutchison et al 2007 study [39].



Thromboembolic events.

Of the 3 included studies, only 2 studies 1- the (Afdhal et al 2012 study) [40], reported the occurrence of thromboembolic events in the Eltrombopag group 2% (6 patients), 1 received placebo, Afdhal et al (2014) reported 34 thromboembolic events in 31 eltrombopag patients (3%) and 5 thromboembolic events in 5 placebo patients (5%) during the antiviral phase of treatment (1%). The most common thromboembolic event in both groups was PVT (12 cases in the eltrombopag group 1% and 2 in the placebo group <1%). In addition, the remaining study (McHutchison et al 2007 study) [39], reported that no thromboembolic events were identified during the study.

Other adverse events.

There was no major difference in the overall number of adverse effects recorded in both groups; the incidence of adverse effects was not higher in the Eltrombopag group compared with placebo. The pooled RR for adverse events was as follows: severe adverse events (RR = 1.30; 95% CI [1.10-1.52]; P =0.001); headache (RR = 1.10; 95% CI [0.89, 1.35]; P = 0.37), diarrhea (RR = 1.73; 95% CI [1.31-2.29]; P =0.0001); and Abdominal pain (RR = 1.33; 95% CI [0.79-2.26]; P =0.28) for all the effect estimate of adverse effect were not heterogeneous (X2; P > .1).

Table I. Summary of involved studies.

Study ID	Design	Population	Dose	Sample Size	Follow Up	Results
1- Afdhal et al 2012	Multicenter, Double-blind, RCT	Adults with 18 years of age or older, had chronic liver disease and a platelet number > 50,000 /cubic millimeter	75 mg daily	292	2weeks	Eltrombopag lowered the required for platelet transfusions but was related with a higher risk of portal-vein thrombosis compared to placebo. In patients have cirrhosis disease who underwent elective invasive procedures.
2- McHutchison et al 2007	Multicenter, Double-blind, RCT	Adults with Eligible patients were 18 years of age or older and had chronic HCV Infection	30, 50, or 75 mg daily	74	4 weeks	Eltrombopag therapy increases the platelet count in patients have thrombocytopenia caused by cirrhosis associated with HCV, allowing the starting of antiviral therapy.
3- Afdhal et al 2014 Enable-1 and Enable-2)	Multicenter, Open-label (OL) Pre-Antiviral Treatment, Double-blind, RCT with combination with antiviral therapy (peginterferon alfa-2a and ribavirin	With Eligible patients, range was 19–83 years with a sample mean of 52.	25, 50, 75 or 100 mg daily	ENABLE-1 (n 715) or ENABLE-2 (n 805)	24 or 48 weeks	Eltrombopag increases platelet numbers in thrombocytopenic patients with HCV and advanced fibrosis and cirrhosis, allowing otherwise ineligible or marginal patients to begin and maintain antiviral therapy, leading to significantly increased rates of sustained virologic response

Abbreviations: HCV, Hepatitis C Virus; RCT, randomized controlled trial.

Table II. Baseline Characters of involved studies.

Study ID	Group	Female, N %)	Male, N%)	Age, Median (Range)	Weight, Median)Range	Prior Therapy 2, N(%)	Splenectomy, N (%)	Baseline Platelet Count (10^9 per L), Median (IQR)	Platelets- >50,000/mm3 —N(%)
1- McHutchison et al 2007	Placebo	7 (39)	11 (61)	)41–71 (52	NA	NA	NA	55,000 (27,000–75,000)	11 (61)
	Eltrombopag 30 mg	4 (29)	10 (71)	56) 43–74)	NA	NA	NA	59,000 (34,000–94,000)	7 (50)
	Eltrombopag 50 mg	7 (37)	12 (63)	)30–72 (50	NA	NA	NA	52,000 (26,000–66,000)	12 (63)
	Eltrombopag 75mg	4 (17)	19 (83)	51(38–60)	NA	NA	NA	54,000 (28,000–75,000)	13 (57)
2 -Afdhal et al 2012	Placebo	17/55 (31)	92 (63)	54(19–83)	NA	NA	NA	NA	20 (94)
	Eltrombopag	41/49 (84)	96 (66)	52(19–79)	NA	NA	NA	NA	14 (92)
3- Afdhal et al 2014 Enable-1 and Enable -2)	Placebo	33/232	NA	Antiviral phase: Enable-1: 51 (23–72) and Antiviral phase: Enable -2: 53 (26–74)	NA	NA	NA	NA	Antiviral phase : Enable-1: 170 (73) and Antiviral phase : Enable -2: 176 (70)

	Eltrombopag 25 mg	389 (43)	NA	52.8 (8.7)	NA	NA	NA	NA	61.7 (10)
	Eltrombopag 50 mg	112 (29)	NA	51.5 (8.0)	NA	NA	NA	NA	51.9 (13)
	Eltrombopag 75mg	34 (29)	NA	50.9 (8.3)	NA	NA	NA	NA	44.6 (14)
	Eltrombopag 100mg	12 (26)	NA	47.9 (9.3)	NA	NA	NA	NA	35.9 (14)

Discussion

Summary of Main Results

In HCV-infected patients, thrombocytopenia is a common clinical problem. Multiple studies have consistently shown an increase in platelet count after successful HCV treatment, demonstrating a cause-and-effect relationship. Even though many therapeutic strategies have been tried in the past (e.g. oral steroids, interferon dose reductions, splenectomy, intravenous immunoglobulins, etc.), success rates have been variable and not always reproducible. Eltrombopag, a non-immunogenic second-generation thrombopoietin-mimetic, has opened up a new treatment option for HCV-related thrombocytopenia after clinical trials were discontinued due to immunogenicity issues. The randomized, double blind, placebo-controlled phase II and III trials of eltrombopag therapy have shown that the primary endpoint platelet counts of ≥50,000/μL can be achieved [41].

The existing meta-analysis research provides level one indications that therapy with Eltrombopag raises platelet counts caused by hepatitis C virus -related cirrhosis in patients have thrombocytopenia. In patients have cirrhosis disease, who had elective invasive surgeries performed. Eltrombopag was approved for the treatment of adults with thrombocytopenia through European Medicines Agency and the US Food and Drug Administration [42]. Eltrombopag lowered the required for platelet transfusions but was related with a greater risk of portal-vein thrombosis compared to placebo. With this treatment's success, it was possible to test its effectiveness in raising platelet counts in HCV-related infection and myelodysplastic syndrome patients. However, preliminary results are very encouraging. Thrombocytopenia caused by HCV is the focus of this review [42].

Eltrombopag significantly improves the overall platelet response, reduces the incidence, and decreases the number of patients who require rescue treatment by significant bleeding or other bleeding events, despite the positive results; patients should be closely monitored for signs of rapidly progressing thrombocythemia and thromboembolic events. Eltrombopag was tested in ENABLE-1 and ENABLE-2, which looked at its ability boost platelet count in patients, allowing them to receive PEG and RBV therapy [30]. There was no significant difference between Eltrombopag and Placebo groups in WHO Grade 2 or higher bleeding episodes,

which were recorded in 17% and 23% of patients, respectively. In 6 patients receiving Eltrombopag, thrombosis events of the portal vein system were reported compared with 1 patient receiving placebo, resulting in early termination of the report. Platelet counts of less than 20 x109 L have been linked to an increased risk of thrombosis [43]. Our results show that eltrombopag significantly increases the rate of significant thrombosis, resulting in discrepancies with all RCTs and non-randomized trials that have shown that thrombosis risk in the eltrombopag group has been significantly reduced [44].

During antiviral treatment, more patients who received eltrombopag than those who received placebo maintained platelet counts of 50,000/L or higher (ENABLE-1, 69% vs 15%; ENABLE-2, 81% vs 23%). With the exception of hepatic decompensation (both studies: eltrombopag, 10%; placebo, 5%), and thromboembolic events, which were more common in the eltrombopag group of ENABLE-2, adverse events were similar between groups [45].

The severity and frequency of other adverse reactions in the Placebo and Eltrombopag groups were comparable there was no statistically significant difference in the risk of any adverse reactions, serious adverse reactions, headache, diarrhea, or abdominal pain. However, the fact that the analysis of their thrombosis included only 1 RCT that compared romiplostim to placebo can explain this discrepancy. In comparison to Eltrombopag, the medicine of interest and placebo our pooled analysis included 3 RCTs, which provide better analytical performance [46]. Figure 2 (A-B). The summary and graph risk of bias according to Cochrane Risk of Bias assessment tool.

Eltrombopag and Risk of Bleeding

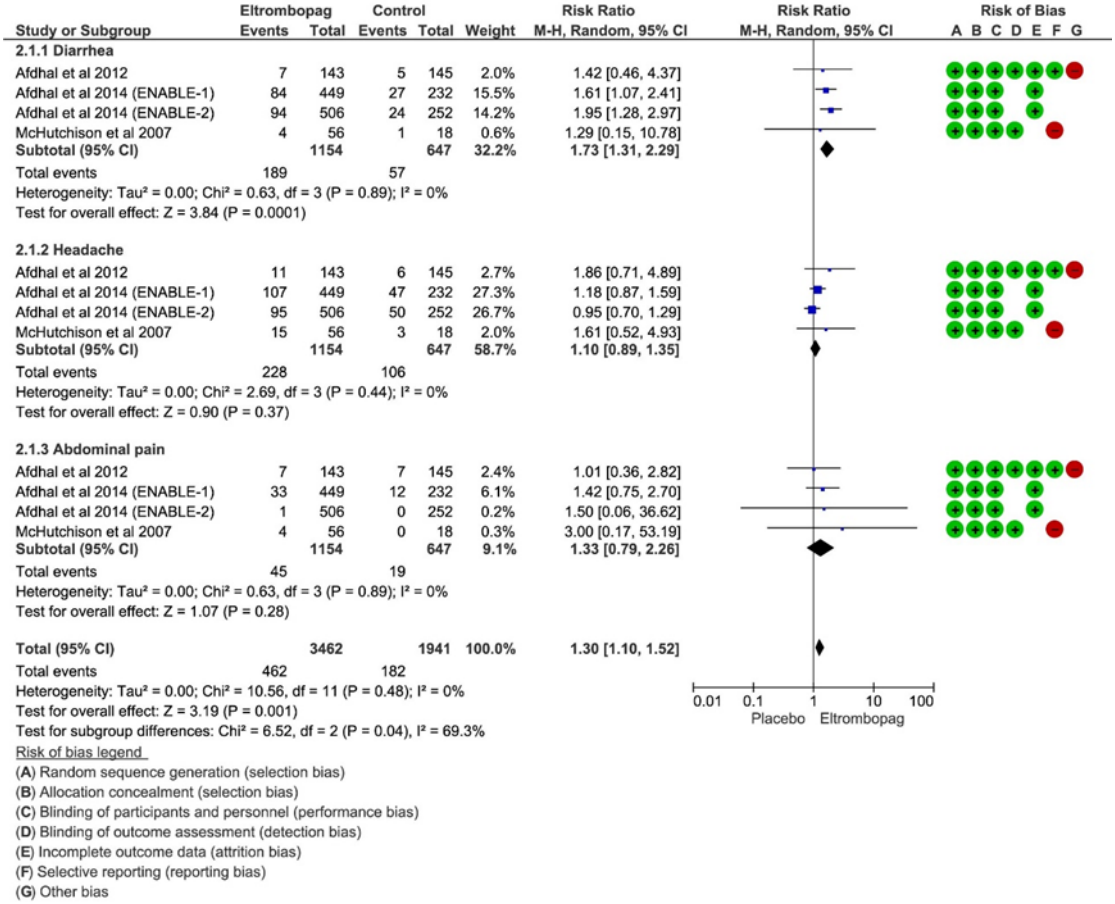
Thrombocytopenia is characterized by platelet loss, and raised risk of significant bleeding has been associated with lower platelet counts >) 50,000 / cubic millimeter). However, major difference was observed between the Placebo and Eltrombopag groups in WHO grade 2 or higher bleeding episodes, recorded in 17% and 23% of patients, respectively.

Risk of Thrombosis events with thrombopoietin receptor agonist

Recent studies have reported increasing evidence of an association between autoimmune disorders, including Immune thrombocytopenia (ITP), and the occurrence of venous thrombosis and pulmonary embolism [47-51]. The possibility of thromboembolism is also one of the adverse effects of concern in patients treated with thrombopoietin receptor agonist [52, 53]. A recent meta-analysis found an elevated risk of thrombosis events in thrombopoietin receptor agonist-treated patients; however, in the subgroup analysis among ITP patients there was no statistically significant increase [54-56]. A higher incidence of portal-vein, however, between patients treated Eltrombopag, thrombosis was reported. Further study of Eltrombopag treatment, including better recognition of risk agents for developing therapy with Eltrombopag, control of doses and careful patient treatment choice. In

patients have cirrhosis disease who had elective invasive surgeries performed, Eltrombopag, as substitute to platelet transfusion, is not recommended until such trials have been conducted. Further Long-term studies are required to determine Eltrombopag's long-term safety.

Figure 4. Forest plot analysis of some adverse effects with 95% confidence intervals. CI indicates confidence interval, M-H, Mantel-Haenszel and RR relative risk.



Limitation of study

Discuss study and outcome limitations (e.g., risk of bias) as well as review limitations (e.g., incomplete retrieval of identified research, reporting bias). There are some limitations to our research that should be considered. To begin with, the number of relevant studies was limited, and the majority of their sample sizes were small. Second, differences in drug dosage and protocol can lead to heterogeneity, which can have an impact on clinical outcomes. The clinical outcomes assessed in the included studies were only short-term; these treatments may have different long-term outcomes. Third, a limitation of the current study is the retrospective analysis of data obtained in a prospective, randomized controlled trial. Finally, given the limitations and risks of these therapies, there is a clear need for effective and safe alternative therapeutic options for patients with chronic HCV infection.

Quality of the Evidence

Both steps were conducted in full compliance with the Cochrane Handbook of Systematic Intervention Evaluations and the PRISMA checklist was followed. This evidence is focused on RCTs; there were well-established search methods and eligibility requirements.

Conclusion

In conclusion, this study provides class 1 evidence that Eltrombopag raises platelet counts with patients with thrombocytopenia caused by HCV -related cirrhosis. In patients with cirrhosis disease who had elective invasive surgeries performed, Eltrombopag reduced a need for more platelet transfusions but was associated with a higher risk of portal-vein thrombosis when compared to placebo.

Reference:

1. Qamar, A. A., Grace, N. D., Groszmann, R. J., Garcia–Tsao, G., Bosch, J., Burroughs, A. K., Ripoll, C., Maurer, R., Planas, R., Escorsell, A., Garcia–Pagan, J. C., Patch, D., Matloff, D. S., Makuch, R., & Rendon, G. (2009). Incidence, prevalence, and clinical significance of Abnormal Hematologic indices in Compensated cirrhosis. Clinical Gastroenterology and Hepatology, 7(6), 689–695. https://doi.org/10.1016/j.cgh.2009.02.021.

2. GIANNINI, E. G. (2006). Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. Alimentary Pharmacology and Therapeutics, 23(8), 1055–1065. https://doi.org/10.1111/j.1365-2036.2006.02889.x.

3. Sigal, S., Mitchell, O., Feldman, D., & Diakow, M. (2016). The pathophysiology of thrombocytopenia in chronic liver disease. Hepatic Medicine: Evidence and Research, 39. https://doi.org/10.2147/hmer.s74612.

4. Nilles, K. M., & Flamm, S. L. (2020). Thrombocytopenia in Chronic Liver Disease. Clinics in Liver Disease, 24(3), 437–451. https://doi.org/10.1016/j.cld.2020.04.009 .

5. McCormick, P. A., & Murphy, K. M. (2000). Splenomegaly, hypersplenism and coagulation abnormalities in liver disease. Best Practice & Research Clinical Gastroenterology, 14(6), 1009–1031. https://doi.org/10.1053/bega.2000.0144.

6. Rajalingam, R., Javed, A., Sharma, D., Sakhuja, P., Singh, S., Nag, H. H., & Agarwal, A. K. (2012). Management of hypersplenism in non-cirrhotic portal hypertension: a surgical series. Hepatobiliary & Pancreatic Diseases International, 11(2), 165–171. https://doi.org/10.1016/s1499-3872(12)60143-x.

7. Tekola, B., & Caldwell, S. (2017). Endoscopy in the Setting of Coagulation Abnormalities in the Patient with Liver Disease. Endoscopy in Liver Disease, 29–41. https://doi.org/10.1002/9781118660799.ch3.

8. Peck-Radosavljevic, M. (2000). Thrombocytopenia in Liver Disease. Canadian Journal of Gastroenterology, 14(suppl d). https://doi.org/10.1155/2000/617428.

9. Sallah, S., & Bobzien, W. (1999). Bleeding problems in patients with liver disease. Postgraduate Medicine, 106(4), 187–195. https://doi.org/10.3810/pgm.1999.10.1.720.

10. Scharf, R. E. (2021). Thrombocytopenia and Hemostatic Changes in Acute and Chronic Liver Disease: Pathophysiology, Clinical and Laboratory Features, and Management. Journal of Clinical Medicine, 10(7), 1530. https://doi.org/10.3390/jcm10071530.

11. Peck-Radosavljevic, M. (2016). Thrombocytopenia in chronic liver disease. Liver International, 37(6), 778–793. https://doi.org/10.1111/liv.13317.

12. Dieterich, D. T., Bernstein, D., Flamm, S., Pockros, P. J., & Reau, N. (2020). Review article: a treatment algorithm for patients with chronic liver disease and severe thrombocytopenia undergoing elective medical procedures in the United

States. Alimentary Pharmacology & Therapeutics. https://doi.org/10.1111/apt.16044.

13. Adinolfi, L. E., Giordano, M. G., Andreana, A., Tripodi, M.-F., Utili, R., Cesaro, G., Ragone, E., Mangoni, E. D., & Ruggiero, G. (2001). Hepatic fibrosis plays a central role in the pathogenesis of thrombocytopenia in patients with chronic viral hepatitis. British Journal of Haematology, 113(3), 590–595. https://doi.org/10.1046/j.1365-2141.2001.02824.x .

14. Rios, R., Sangro, B., Herrero, I., Quiroga, J., & Prieto, J. (2005). The Role of Thrombopoietin in the Thrombocytopenia of Patients with Liver Cirrhosis. The American Journal of Gastroenterology, 100(6), 1311–1316. https://doi.org/10.1111/j.1572-0241.2005.41543.x .

15. Valva, P. (2016). Evaluation of immune system role in the pathogenesis of chronic hepatitis C viral infection. https://doi.org/10.26226/morressier.56d6be6fd462b80296c96de3.

16. Manzin, A., Candela, M., Paolucci, S., Caniglia, M. L., Gabrielli, A., & Clementi, M. (1994). Presence of hepatitis C virus (HCV) genomic RNA and viral replicative intermediates in bone marrow and peripheral blood mononuclear cells from HCV-infected patients. Clinical Diagnostic Laboratory Immunology, 1(2), 160–163. https://doi.org/10.1128/cdli.1.2.160-163.1994.

17. Lee, L. M., Johansen, M. E., Jy, W., Horstman, L. L., & Ahn, Y.-S. (2014). Second Generation Direct-Acting Antiviral Agents Eradicate Hepatitis C Virus (HCV) but Exacerbate Thrombocytopenia in a Patient with HCV-Associated Immune Thrombocytopenic Purpura (ITP): Case Report. Blood, 124(21), 5022–5022. https://doi.org/10.1182/blood.v124.21.5022.5022.

18. Trotter, J. F. (2006). Coagulation Abnormalities in Patients Who Have Liver Disease. Clinics in Liver Disease, 10(3), 665–678. https://doi.org/10.1016/j.cld.2006.08.006

19. Lozano, M. L. (2020). Avatrombopag for the management of thrombocytopenia in patients with chronic liver disease. Revista Española De Enfermedades Digestivas. https://doi.org/10.17235/reed.2020.7309/2020 .

20. Allen, L. F., Aggarwal, K., Vredenburg, M., Barnett, C., Mladsi, D., & Kim, R. (2019). Cost-Effectiveness of Avatrombopag for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease. Blood, 134(Supplement_1), 3454–3454. https://doi.org/10.1182/blood-2019-131822.

21. Wong, T. (2021). Transfusion Medicine. Blood and Marrow Transplant Handbook, 187–199. https://doi.org/10.1007/978-3-030-53626-8_12.

22. Zalpuri, S., Middelburg, R. A., Schonewille, H., de Vooght, K. M. K., le Cessie, S., van der Bom, J. G., & Zwaginga, J. J. (2013). Intensive red blood cell transfusions and risk of alloimmunization. Transfusion. https://doi.org/10.1111/trf.12312.

23. McHutchison, J. G., Manns, M., Patel, K., Poynard, T., Lindsay, K. L., Trepo, C., Dienstag, J., Lee, W. M., Mak, C., Garaud, J. J., & Albrecht, J. K. (2002). Adherence to combination therapy enhances sustained response in genotype-1–infected patients with chronic hepatitis C. Gastroenterology, 123(4),

1061–1069. https://doi.org/10.1053/gast.2002.35950 .

24. Shiffman, M. L., Ghany, M. G., Morgan, T. R., Wright, E. C., Everson, G. T., Lindsay, K. L., Lok, A. S. F., Bonkovsky, H. L., Di Bisceglie, A. M., Lee, W. M., Dienstag, J. L., & Gretch, D. R. (2007). Impact of Reducing Peginterferon Alfa-2a and Ribavirin Dose During Retreatment in Patients With Chronic Hepatitis C. Gastroenterology, 132(1), 103–112. https://doi.org/10.1053/j.gastro.2006.11.011.

25. Álvarez, G. C., Gómez-Galicia, D., Rodríguez-Fragoso, L., Marina, V. M., Dorantes, L. C., Sánchez-Alemán, M., Méndez-Sánchez, N., & Esparza, J. R. (2011). Danazol improves thrombocytopenia in HCV patients treated with peginterferon and ribavirin. Annals of Hepatology, 10(4), 458–468. https://doi.org/10.1016/s1665-2681(19)31513-3.

26. Burness, C. B. (2014). Eltrombopag: A Review of Its Use in the Treatment of Thrombocytopenia in Patients with Chronic Hepatitis C. Drugs, 74(16), 1961–1971. https://doi.org/10.1007/s40265-014-0312-7.

27. Elbedewy, T. A., Elsebaey, M. A., Elshweikh, S. A., Elashry, H., & Abd-Elsalam, S. (2019). Predictors for eltrombopag response in patients with hepatitis C virus-associated thrombocytopenia. Therapeutics and Clinical Risk Management, Volume 15, 269–274. https://doi.org/10.2147/tcrm.s186106.

28. Mihăilă, R.-G. (2014). Eltrombopag in chronic hepatitis C. World Journal of Gastroenterology, 20(35), 12517. https://doi.org/10.3748/wjg.v20.i35.12517.

29. Moher, D. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Annals of Internal Medicine, 151(4), 264. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.

30. Elgebaly, A. S., Ashal, G. E., Elfil, M., & Menshawy, A. (2016). Tolerability and Efficacy of Eltrombopag in Chronic Immune Thrombocytopenia: Meta-Analysis of Randomized Controlled Trials. Clinical and Applied Thrombosis/Hemostasis, 23(8), 928–937. https://doi.org/10.1177/1076029616663849.

31. Khelif, A., Saleh, M. N., Salama, A., Portella, M. do, Duh, M. S., Ivanova, J., Grotzinger, K., Roy, A. N., & Bussel, J. B. (2018). Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: Findings from the EXTEND study. American Journal of Hematology, 94(2), 200–208. https://doi.org/10.1002/ajh.25348.

32. Higgins, J. P. T., & Altman, D. G. (2008). Assessing Risk of Bias in Included Studies. Cochrane Handbook for Systematic Reviews of Interventions, 187–241. https://doi.org/10.1002/9780470712184.ch8.

33. Caldwell, D. M., Ades, A. E., & Higgins, J. P. (2005). Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ, 331(7521), 897–900. https://doi.org/10.1136/bmj.331.7521.897.

34. Mutz, D. C. (2011). Direct and Indirect Treatments. Population-Based Survey Experiments. https://doi.org/10.23943/princeton/9780691144511.003.0003.

35. Greenland, S., Pearl, J., & Robins, J. M. (1999). Causal Diagrams for Epidemiologic Research. Epidemiology, 10(1), 37–48. https://doi.org/10.1097/00001648-199901000-00008

36. Savitz, D. A., & Wellenius, G. A. (2016). Causal Diagrams for Epidemiologic Inference. Interpreting Epidemiologic Evidence, 21–34. https://doi.org/10.1093/acprof:oso/9780190243777.003.0003.

37. Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629.

38. Terrin, N., Schmid, C. H., Lau, J., & Olkin, I. (2003). Adjusting for publication bias in the presence of heterogeneity. Statistics in Medicine, 22(13), 2113–2126. https://doi.org/10.1002/sim.1461.

39. McHutchison, J. G., Dusheiko, G., Shiffman, M. L., Rodriguez-Torres, M., Sigal, S., Bourliere, M., Berg, T., Gordon, S. C., Campbell, F. M., Theodore, D., Blackman, N., Jenkins, J., & Afdhal, N. H. (2007). Eltrombopag for Thrombocytopenia in Patients with Cirrhosis Associated with Hepatitis C. New England Journal of Medicine, 357(22), 2227–2236. https://doi.org/10.1056/nejmoa073255.

40. Afdhal, N. H., Giannini, E. G., Tayyab, G., Mohsin, A., Lee, J.-W., Andriulli, A., Jeffers, L., McHutchison, J., Chen, P.-J., Han, K.-H., Campbell, F., Hyde, D., Brainsky, A., & Theodore, D. (2012). Eltrombopag before Procedures in Patients with Cirrhosis and Thrombocytopenia. New England Journal of Medicine, 367(8), 716–724. https://doi.org/10.1056/nejmoa1110709.

41. Danish, F. A., Koul, S. S., Subhani, F. R., Rabbani, A. E., & Yasmin, S. (2010). Considerations in the management of hepatitis c virus-related thrombocytopenia with eltrombopag. Saudi Journal of Gastroenterology, 16(1), 51. https://doi.org/10.4103/1319-3767.58772

42. Gilreath, J., Lo, M., & Bubalo, J. (2021). Thrombopoietin Receptor Agonists (TPO-RAs): Drug Class Considerations for Pharmacists. Drugs. https://doi.org/10.1007/s40265-021-01553-7.

43. Jane Bryer, E. (2019). Hemorrhage in the Setting of Acute Severe Refractory Immune Thrombocytopenic Purpura: A Case Report. Haematology International Journal, 3(2). https://doi.org/10.23880/hij-16000143.

44. Park, R. (2015). Eltrombopag: a new treatment option for chronic refractory adult immune thrombocytopenia. Blood Research, 50(1), 1. https://doi.org/10.5045/br.2015.50.1.1.

45. Afdhal, N. H., Dusheiko, G. M., Giannini, E. G., Chen, P. J., Han, K. H., Mohsin, A., Rodriguez–Torres, M., Rugina, S., Bakulin, I., Lawitz, E., Shiffman, M. L., Tayyab, G. U. N., Poordad, F., Kamel, Y. M., Brainsky, A., Geib, J., Vasey, S. Y., Patwardhan, R., Campbell, F. M., & Theodore, D. (2014). Eltrombopag increases platelet numbers in thrombocytopenic patients with hcv infection and cirrhosis, allowing for effective antiviral therapy. Gastroenterology, 146(2). https://doi.org/10.1053/j.gastro.2013.10.012

46. Puavilai, T., Thadanipon, K., Rattanasiri, S., Ingsathit, A., McEvoy, M., Attia, J.,

& Thakkinstian, A. (2019). Treatment efficacy for adult persistent immune thrombocytopenia: a systematic review and network meta-analysis. British Journal of Haematology, 188(3), 450–459. https://doi.org/10.1111/bjh.16161

47. Lamarre, Y., Romana, M., Waltz, X., Lalanne-Mistrih, M.-L., Tressieres, B., Divialle-Doumdo, L., Hardy-Dessources, M.-D., Vent-Schmidt, J., Petras, M., Broquere, C., Maillard, F., Tarer, V., Etienne-Julan, M., & Connes, P. (2012). Hemorheological risk factors of acute chest syndrome and painful vaso-occlusive crisis in children with sickle cell disease. Haematologica, 97(11), 1641–1647. https://doi.org/10.3324/haematol.2012.066670.

48. Zöller, B., Li, X., Sundquist, J., & Sundquist, K. (2012). Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. The Lancet, 379(9812), 244–249. https://doi.org/10.1016/s0140-6736(11)61306-8.

49. Wu, C., Zhou, X.-M., & Liu, X.-D. (2021). Eltrombopag-related renal vein thromboembolism in a patient with immune thrombocytopenia: A case report. World Journal of Clinical Cases, 9(11), 2611–2618. https://doi.org/10.12998/wjcc.v9.i11.2611.

50. Mohamed, S. E., & Yassin, M. A. (2020). Eltrombopag Use for Treatment of Thrombocytopenia in a Patient with Chronic Liver Disease and Portal Vein Thrombosis: Case Report. Case Reports in Oncology, 13(2), 863–866. https://doi.org/10.1159/000507987.

51. Swan, D., Newland, A., Rodegheiro, F., & Thachil, J. (2021). Thrombosis in immune thrombocytopenia — current status and future perspectives. British Journal of Haematology. https://doi.org/10.1111/bjh.17390.

52. Cuker, A., Chiang, E., & Cines, D. (2010). Safety of the Thrombopoiesis-Stimulating Agents for the Treatment of Immune Thrombocytopenia. Current Drug Safety, 5(2), 171–181. https://doi.org/10.2174/157488610790936196.

53. Depré , F., Aboud , N., Mayer , B., & Salama , A. (2018). Bidirectional inefficacy or intolerability of thrombopoietin receptor agonists: new data and a concise review. Blood Transfus, 16(3), 307–312. https://doi.org/10.2450/2017.0258-16.

54. Catalá-López, F., Corrales, I., Martín-Serrano, G., Tobías, A., & Calvo, G. (2012). Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: systematic review and meta-analysis of randomized controlled trials. Medicina Clínica, 139(10), 421–429. https://doi.org/10.1016/j.medcli.2011.11.023.

55. Loffredo, L., & Violi, F. (2019). Thrombopoietin receptor agonists and risk of portal vein thrombosis in patients with liver disease and thrombocytopenia: A meta-analysis. Digestive and Liver Disease, 51(1), 24–27. https://doi.org/10.1016/j.dld.2018.06.005.

56. Armstrong, N., Büyükkaramikli, N., Penton, H., Riemsma, R., Wetzelaer, P., Huertas Carrera, V., Swift, S., Drachen, T., Raatz, H., Ryder, S., Shah, D., Buksnys, T., Worthy, G., Duffy, S., Al, M., & Kleijnen, J. (2020). Avatrombopag and lusutrombopag for thrombocytopenia in people with chronic

liver disease needing an elective procedure: a systematic review and cost-effectiveness analysis. Health Technology Assessment, 24(51), 1–220. https://doi.org/10.3310/hta24510.