Med Clin (Barc). 2015;**145(12)**:511–519

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

Risk of thromboembolism with thrombopoietin receptor agonists in adult patients with thrombocytopenia: Systematic review and meta-analysis of randomized controlled trials

Ferrán Catalá-López[a,b,*], Inmaculada Corrales[a], César de la Fuente-Honrubia[a], Diana González-Bermejo[a], Gloria Martín-Serrano[a], Dolores Montero[a], Diego Macías Saint-Gerons[a]

[a] *Division of Pharmacoepidemiology and Pharmacovigilance, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain*
[b] *Fundación Instituto de Investigación en Servicios de Salud, Valencia, Spain*

ARTICLE INFO

Article history:
Received 7 January 2015
Accepted 12 March 2015
Available online 4 June 2015

Keywords:
Eltrombopag
Meta-analysis
Randomized controlled trials
Romiplostim
Thromboembolism
Thrombosis
Thrombocytopenia

ABSTRACT

Background and objective: Romiplostim and eltrombopag are thrombopoietin receptor (TPOr) agonists that promote megakaryocyte differentiation, proliferation and platelet production. In 2012, a systematic review and meta-analysis reported a non-statistically significant increased risk of thromboembolic events for these drugs, but analyses were limited by lack of statistical power. Our objective was to update the 2012 meta-analysis examining whether TPOr agonists affect thromboembolism occurrence in adult thrombocytopenic patients.
Materials and methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs). Updated searches were conduced on PubMed, Cochrane Central, and publicly available registries (up to December 2014). RCTs using romiplostim or eltrombopag in at least one group were included. Relative risks (RR), absolute risk ratios (ARR) and number needed to harm (NNH) were estimated. Heterogeneity was analyzed using Cochran's Q test and I^2 statistic.
Results: Fifteen studies with 3026 adult thrombocytopenic patients were included. Estimated frequency of thromboembolism was 3.69% (95% CI: 2.95–4.61%) for TPOr agonists and 1.46% (95% CI: 0.89–2.40%) for controls. TPOr agonists were associated with a RR of thromboembolism of 1.81 (95% CI: 1.04–3.14) and an ARR of 2.10% (95% CI: 0.03–3.90%) meaning a NNH of 48. Overall, we did not find evidence of statistical heterogeneity ($p = 0.43$; $I^2 = 1.60\%$).
Conclusions: Our updated meta-analysis suggested that TPOr agonists are associated with a higher risk of thromboemboembolic events compared with controls, and supports the current recommendations included in the European product information on this respect.

Riesgo de tromboembolismo con agonistas del receptor de la trombopoyetina en pacientes adultos con trombocitopenia: revisión sistemática y metaanálisis de ensayos clínicos aleatorizados y controlados

Palabras clave:
Eltrombopag
Ensayo clínico aleatorizado controlado
Romiplostim

RESUMEN

Fundamento y objetivo: Los agonistas del receptor de la trombopoyetina (TPOr) (romiplostim y eltrombopag) promueven la diferenciación megacariocítica, la proliferación y la producción de plaquetas. En 2012, una revisión sistemática y metaanálisis informó de un aumento no estadísticamente significativo del riesgo tromboembólico para estos medicamentos, pero los análisis presentaban limitaciones por la falta de potencia estadística. El objetivo es actualizar el metaanálisis de 2012 examinando si los agonistas del TPOr afectan a la incidencia de tromboembolismos en los pacientes adultos con trombocitopenia.

* Corresponding author.
E-mail address: ferran_catala@hotmail.com (F. Catalá-López).

http://dx.doi.org/10.1016/j.medcli.2015.03.014
0025-7753/

Trombocitopenia
Tromboembolismo
Trombosis
Trombopoyetina

Material y métodos: Se llevó a cabo una revisión sistemática y metaanálisis de ensayos clínicos aleatorizados y controlados (ECA). Se actualizaron búsquedas llevadas a cabo en PubMed, Cochrane Central, y registros públicos (hasta Diciembre de 2014). Se incluyeron ECA en los que se administrara romiplostim o eltrombopag en al menos uno de los grupos de pacientes tratados. Se calcularon los riesgos relativos (RR), la diferencia absoluta de riesgo (ARR, por sus siglas en inglés) y el número necesario de pacientes para dañar (NNH). Se examinó la heterogeneidad estadística mediante la *Q* de Cochran y el estadístico I^2.
Resultados: Se incluyeron 15 estudios con 3026 pacientes adultos diagnosticados de trombocitopenia. Las frecuencias de acontecimientos tromboembólicos fueron de 3.69% ([intervalo de confianza] IC del 95%: 2,95–4,61%) para los agonistas del TPOr y de 1,46% (IC95%: 0,89–2,40%) para los controles. Los agonistas del TPOr se asociaron con un riesgo relativo de tromboembolismo de 1,81 (IC95%: 1,04–3,14) y una ARR del 2,10% (IC95%: 0,03–3,90%), que significa un NNH de 48. En general, no se encontró evidencia de heterogeneidad estadística ($p = 0{,}43$; $I^2 = 1{,}60\%$).
Conclusiones: El metaanálisis actualizado sugiere que los agonistas del TPOr están asociados con un mayor riesgo de eventos tromboembólicos en comparación con los controles. Estos resultados apoyan las precauciones incluidas en la información del medicamento en la Unión Europea en relación con el riesgo tromboembólico.

Introduction

Platelets are formed by fragmentation of mature megakaryocytes. They circulate in the blood for 7–10 days and play a critical role in haemostasis.[1] Thrombocytopenia is defined as a platelet count below the normal range for the population (e.g. a platelet count of less than $100 \times 10^9\ L^{-1}$) and results from disturbances in platelet production, distribution, or destruction. Thrombocytopenia is frequently found in a variety of disease conditions such as immune thrombocytopenic purpura (ITP), chronic liver cirrhosis, chemotherapy-induced myelosuppression and myelodysplastic syndromes.[1–3]

Romiplostim and eltrombopag are thrombopoietin receptor (TPOr) agonists that promote megakaryocyte differentiation, proliferation and platelet production. In the European Union, romiplostim and eltrombopag are approved for the treatment of chronic adult ITP splenectomised patients who are refractory to other treatments.[4,5] More recently, eltrombopag has been authorized for the treatment of thrombocytopenia in adult patients with chronic hepatitis C virus infection, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.[5] In healthy volunteers, romiplostim and eltrombopag increased platelet counts in a dose-dependent manner with platelet counts rising within the first 2 weeks after therapy has started.[4–6] In patients with thrombocytopenia, high levels of platelet counts above the normal ranges have been associated with thromboembolisms, although this relationship may be affected by a number of other factors.[7,8]

In 2011, we conducted a systematic review of the risk of thromboembolism with TPOr agonists in adult patients with thrombocytopenia.[9] The main findings were published in 2012 suggesting a non-statistically significant increased risk of thromboembolic events for these agents, but analyses were limited by lack of statistical power and incomplete outcome reporting. Since then, new therapeutic indications have been approved for some of these therapies,[5] and large randomized controlled trials (RCTs) have been recently published.[10–12] Therefore, we considered timely to update our original systematic review and meta-analysis examining whether TPOr agonists affect thromboembolism occurrence in adult thrombocytopenic patients.

Methods

For this updated systematic review, we largely followed the methods as our 2012 review.[9]

Search strategy and selection criteria

We searched PubMed/MEDLINE, and the Cochrane Central Register of Controlled Trials with the specific terms: "romiplostim" and "eltrombopag", for articles published from January 2011 to December 2014 and without language restriction. The Cochrane highly sensitive search strategy for identifying RCTs[13] was used (see Appendix AAppendix for specific search strategy). We also searched websites of the European Medicines Agency (www.ema.europa.eu) and of the U.S. Food and Drug Administration (www.fda.gov). On-line clinical trials registries, including government (www.clinicaltrials.gov) and manufacturers (www.amgentrials.com and, www.gsk-clinicalstudyregister.com) were also searched, to identify eligible unpublished reports.

The selection criteria followed those of the original review.[9] Briefly, selected studies had to be RCTs in adult thrombocytopenic patients exposed to romiplostim or eltrombopag in at least one treatment arm, and containing the outcome of interest (thrombotic and thromboembolic events). Only direct comparisons with control interventions (e.g., placebo and/or standard of care) were considered.

Data collection and quality analysis

Data extraction from source documents was done independently by two reviewers. Disagreements were resolved by consensus. Should more than one report of the same clinical trial exist, the report with the most updated or complete data was included. The quality of studies included was independently assessed by two reviewers without blinding to authorship or journal using the Jadad's scale.[14] As in the original report,[9] the number of patients with a thromboembolic event and total number of patients in each trial group were extracted and tabulated, along with other information including disease conditions studied, trial design and duration, age, sex, race, and platelet counts at baseline, among others (Tables 1 and 2).

Statistical analyses

We reported this systematic review and meta-analysis in line with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15,16] In the primary analyses, relative risks (RR) were provided to compare the likelihood of thromboembolisms between two groups. Absolute risk ratios (ARR) and number needed to harm (NNH) were also