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Systematic Review

Eltrombopag for Adults and Children with Immune-Refractory Thrombocytopenic Purpura: A Systematic Review

Supplemental material

Search strategy

1. "immune thrombocytopenia".ab,ti,kw.
2. exp Purpura, Thrombocytopenic, Idiopathic/
3. exp Receptors, Thrombopoietin/ or Thrombopoiesis/ or Thrombopoietin/
4. thrombocytopeni*.ab,ti,kw.
5. "Thrombopoietin Receptors".ab,ti,kw.
6. "Thrombopoie*".ab,ti,kw.
7. Eltrombopag.ab,ti,kw. or Eltrombopag/
8. 1 or 2 or 3 or 4 or 5 or 6
9. (randomized or randomised).ab,ti.
10. placebo.ab,ti.
11. dt.fs.
12. randomly.ab,ti.
13. trial.ab,ti.
14. groups.ab,ti.
15. Animals/
16. Humans/
17. or/9-14
18. 15 not (15 and 16)
19. 17 not 18
20. 7 and 8 and 19

Table S1. Characteristics of the studies included in the analysis

Study	Country	Sample characteristic	Number of patients with <15,000/mm^3	Intervention/control group	Outcomes analyzed	Duration
Cheng et al., 2011 [22]	United States, Austria, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, India, Italy, Netherlands, New Zealand, Peru, Poland, Russian, Slovakia, Spain, Tunisia, Croatia, England and Vietnam	Total: 197 patients with ITP Eltrombopag: *n* = 135; M, 42; F, 93; median age, 52.5 years (IQR, 43–63 years) Placebo: *n* = 62; M, 19; F, 43; median age, 47.0 years (IQR, 34–56 years)	Placebo 30 Eltrombopag 67	Eltrombopag 50 mg/day; maximum dose, 75 mg/day (platelets <50 ×10^3/mm^3 after day 22) Platelets >200 × 10^3/mm^3: 25 mg/day Platelets >400 ×10^3/mm^3: suspend Week 6: platelets >100 ×10^3/mm^3 in two consecutive weeks, reduce or discontinue treatment. Previous concomitant treatment Placebo	Median platelet count Clinically significant bleeding Reduced or discontinued treatments Rescue treatment	**6 months**
Bussel et al., 2015 [8]	22 centers in the US, UK, Canada,	Total: 67 patients	Placebo 11 Eltrombopag 23	Double blinded phase:	Platelet response for more than 6 weeks Need for rescue therapy	**24 weeks**

Study	Country	Sample characteristic	Number of patients with <15,000/mm³	Intervention/control group	Outcomes analyzed	Duration
	Spain, France, and the Netherlands	Eltrombopag: *n* = 45; M, 18; F, 27; median age, 9 years (IQR, 8–10 years) Placebo: *n* = 22; M, 9; F, 13; median age, 10 years (IQR, 8–12 years)		12–17 years: 37.5 mg/day (initial dose) 6–11 years: ≥27 kg, 50 mg/day (25 mg Asians) ; <27 kg, 25 mg/day (12.5 mg Asians) 1–5 years: 1.5 mg/kg/day (0.8 mg/kg/day Asians) Placebo: GlaxoSmithKline	Clinically significant bleeding (WHO grades 2–4) Grade 3 or greater bleeding events Grade 3 or 4 adverse events	
Bussel et al., 2009 [23]	23 centers: Germany, Greece, China, Korea, New Zealand, Pakistan, Poland, Romania, Russia, Slovenia, Thailand, England and Taiwan	Total: 114 patients Eltrombopag: *n* = 76; M, 33; F, 43; median age, 47 years (IQR, 19–84 years) Placebo: *n* = 38; M, 27; F, 11; median age, 51 years (IQR, 21–79 years)	Placebo 17 Eltrombopag 38	Eltrombopag (GlaxoSmithKline, Ware, UK) 50 mg/day Platelets <50 × 10^3/mm^3 after 3 weeks: increase dose to 75 mg/day Platelets >200 ×10^3/mm^3: discontinue Placebo: GlaxoSmithKline for 6 weeks	Platelet counts: ≥50 × 10^3/mm^3 and at least twice the baseline value: Eltrombopag: 42 (58%) Placebo: 5 (14%) Bleeding symptoms: Eltrombopag: 20 (39%) Placebo: 18 (60%) Grade 3 or 4 adverse events:	6 weeks

Study	Country	Sample characteristic	Number of patients with <15,000/mm^3	Intervention/control group	Outcomes analyzed	Duration
					Eltrombopag: 2 (3%) Placebo: 1 (3%)	
Bussel et al., 2007 [24]	44 centers: Germany, Greece, China, Korea, New Zealand, Pakistan, Poland, Romania, Russia, Slovenia, Thailand, England) between February and November 2005; at least 18 years of age	Total: 117 patients Eltrombopag 30 mg: *n* = 30; M, 14; F, 16; median age, 51 years (IQR, 23–79 years) Eltrombopag 50 mg: *n* = 30; M, 9; F, 21; median age, 45 years (IQR, 23–81 years) Eltrombopag 75 mg: *n* = 28; M, 8; F, 20; median age, 55 years (IQR, 18–85 years)	Placebo 14 Eltrombopag 30 mg 15 Eltrombopag 50 mg 12 Eltrombopag 70 mg 15	Received placebo or eltrombopag 30, 50, or 75 mg Withhold treatment if platelet count >200 × 10^9	Platelet count ≥50 × 10^3/mm^3: Eltrombopag 75 mg: 21(81%) Eltrombopag 50 mg: 19 (70%) Eltrombopag 30 mg: 8 (28%) Placebo: 3 (11%) Incidence of bleeding events: Eltrombopag 75 mg: 8 (4%) Eltrombopag 50 mg: 2 (7%) Eltrombopag 30 mg: 5 (17%) Placebo: 4 (14%) Adverse effects (grades 3 and 4) Eltrombopag 75 mg: 3 (11%) Eltrombopag 50 mg: 4(13%) Eltrombopag 30 mg: 2 (7%)	6 weeks

Study	Country	Sample characteristic	Number of patients with <15,000/mm³	Intervention/control group	Outcomes analyzed	Duration
		Placebo: *n* = 29; M, 13; F, 16; median age, 42 years (IQR, 18–85 years)			Placebo: 4 (14%)	
Grainger et al., 2015 [9]	38 centers in 12 countries (Argentina, Czech Republic, Germany, China, Israel, Italy, Russia, Spain, Taiwan, Thailand, UK, and USA)	Total: 92 patients Eltrombopag: *n* = 63; M, 33; F, 30; median age, 9.4 years (IQR, 8.2–10.5 years) Placebo: *n* = 29; M, 15; F, 14; median age, 9.8 years (IQR, 8.3–11.3 years)	Placebo 19 Eltrombopag 38	Eltrombopag: 1–5 years: 1.2 mg/kg/day (0.8 mg/kg/day for East Asian patients) 6–11 years: ≥27 kg, started treatment at 50 mg/day (25 mg/day for East Asian patients); <27 kg, started treatment at 37.5 mg/day (25 mg/day for East Asian patients) 12–17 years: ≥27 kg, 50 mg/day (25 mg/day for East Asian patients); <27 kg, 37.5 mg/day (25 mg/day for East Asian patients Placebo	Platelet count >50× 10^3/mm^3: Eltrombopag 25 (40%) Placebo 1 (3%) Bleeding grades 2–4: Eltrombopag 3 (5%) Placebo 2 (7%) Serious adverse events: Eltrombopag 5 (8%) Placebo 4 (14%)	24–28 weeks

Study	Country	Sample characteristic	Number of patients with <15,000/mm^3	Intervention/control group	Outcomes analyzed	Duration
Liu et al., 2020 [25]	China	Total: 150 patients Eltrombopag: *n* = 100; M, 27, F, 73; median age, 45 years (SD 15.9 years) Placebo: *n* = 50; M, 11; F, 38; median age, 40.9 years (SD, 12.65 years) Placebo: *n* = 50; M, 11; F, 38; median age, 40.9 years (SD, 12.65 years)	Not specified	Eltrombopag: 25 mg/day (modified or suspended dose according to platelet value) If platelets <50 × 10^9, increase the dose by 25 mg, reaching a maximum dose of 75 mg day Placebo	Platelet count >50 × 10^3/mm^3: Eltrombopag 38 (38%) Placebo 10 (20%) Grade 2 to 4 bleeding: Eltrombopag 13 (13%) Placebo 3 (6%) Serious adverse events: Eltrombopag 11 (11%) Placebo 6 (12%)	**24 weeks**
Yang et al., 2016 [26]	China	Total: 155 patients Eltrombopag: *n* = 104; M, 27 F, 77; median age, 48 years (IQR, 18–84 years)	Placebo 28 Eltrombopag 54	Eltrombopag: 25 mg for 8 weeks (maximum 75 mg day) Placebo Stage II: Patients who received eltrombopag in Stage I continued on the dose	Platelet count >50 × 10^3/mm^3: Eltrombopag 60 (57.7%) Placebo 3 (6%) WHO grade 2-4 bleeding: Eltrombopag 14 (13.5%) Placebo 6 (11.5%)	**8 weeks**

Study	Country	Sample characteristic	Number of patients with <15,000/mm^3	Intervention/control group	Outcomes analyzed	Duration
		Placebo: *n* = 51; M, 11; F, 40; median age, 42 years (IQR, 22–66 years)		administered at the end of stage I, patients who received placebo in stage I started active treatment with an initial dose of 25 mg of eltrombopag day	Serious adverse events: Eltrombopag 5 (4.8%) Placebo 5 (9.8%)	
Tomiyama et al., 2012 [27]	Japan	Total: 23 patients Eltrombopag: *n* = 15; M, 7 F, 8; median age, 58 years (IQR, 26–72 years) Placebo n = 8; M,1 F,7; Median age 60.5 years (IQR:38-72)	Placebo 6 Eltrombopag 3	Phase 1: double-blind, randomized, placebo-controlled phase of 6 weeks Phase 2: open label for 6 weeks Eltrombopag 12.5 mg/day (maximum dose 50 mg/day) Placebo 25 mg/day	Platelet count >50× 10^3/mm^3: Eltrombopag 9 (60%) Placebo 0 (0%) Any adverse events: Eltrombopag 11 (6%) Placebo 2 (1%)	**26 weeks**
Huang et al., 2018 [28]	**China**	**Total: 35 patients ≥18 years**	**Placebo 6 Eltrombopag 3**	**If platelets <50 × 10^9/L: increase dose 25 mg (with a maximum of 75 mg) platelets (150–250) × 10^9/L: reduce to the nearest**	**Platelet count >50× 10^3/mm^3: Eltrombopag 11 (64%) Placebo 2 (11.1%) Use of rescue medication:**	**6 weeks**

Study	Country	Sample characteristic	Number of patients with <15,000/mm^3	Intervention/control group	Outcomes analyzed	Duration
		Eltrombopag: ***n* = 17; M, 2**; **F, 15; median age**, **50 years (IQR**, **24 62** years**)** **Placebo**: ***n* = 18; M, 4**; **F, 14; median age**, **39.5 years (IQR**, **22–66** years**)**; **25 mg/day**		**lower dose (example: 50 mg/day to 25 mg/day), or reduce the frequency of** the **dose (example: 25 mg/day to 25 mg once every 2 days**). If p**latelets >250 × 10^9/L**, **stop the drug and** resume **taking the drug after platelets <100 × 10^9/L**	**Eltrombopag 0 (0%)** **Placebo 8 (44.4%)** **Adverse events**: b**leeding:** **Eltrombopag 0 (0%)** **Placebo 4 (22.2%)**	

ITP, immune thrombocytopenic purpura; M, male; F, female; IQR, interquartile range.