Thrombopoietin receptor agonists: ten years later

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Supplemental table 1 Incidence of thromboembolism with romiplostim and eltrombopag in phase 1-2 studies and in randomized phase 3 placebo-controlled studies in adults

N.	Ref.	Study characteristics and exclusion criteria for thrombosis^	N. exposed Dose Exposure time	N. controls*	Thrombosis in exposed (N pts/100 pt-yrs when reported)° [N events/100 pt-yrs]	Thrombosis in controls (N pts/100 pt-yrs when reported) [N events/100 pt-yrs]
Romiplostim						
1	Wang (1)	Pharmacodynamics/pharmacokinetics Double blind placebo-controlled in healthy non obese males Subjects with cardiovascular risk factors excluded	32 Single dose 0.1-10 mcg/kg (Observation 42 days)	16 placebo	0	0
2	Bussel (2)	Phase 2 double blind in ITP pts Pts with any risk factors for T or history of cardiovascular disease excluded	17 3 groups: 8 pts 1 mcg /kg; 8 pts 3 mcg /kg; 1 pt 6 mcg /kg for 6 weeks (Observation 78 days)	4 placebo	0	1 popliteal DVT post splx (for intracranial bleeding)
3	Kuter (3)	Two parallel placebo-controlled trials in ITP pts Pts with ≤ 1 yr history of arterial or any history of venous T or risk factors for T excluded	42 splx - 41 non-splx 1-15 mcg /kg weekly for 24 weeks (Observation 24-36 weeks)	21 splx -21 non-splx placebo	1 † cerebral thrombosis 1 arterial T	1 † PE
4	Kuter (4)	Randomized open-label in non-splx ITP pts No exclusion for thrombotic risk NCT00415532	157 adjusted dose max 10 mcg /kg weekly for 52 weeks	77 SOC	11 events in 6 pts (4.3) [7.8]	2 events in 2 pts (3.4) [3.4]
5	Shirasugi(5)	Randomized double-blind placebo-controlled phase 3 in Japanese ITP pts. Pts with history of arterial/venous T excluded NCT00603642	22 adjusted dose max 10 mcg /kg weekly for 12 weeks (Observation 30 days)	12 placebo	0	0
6	Yang (6)	Double bind placebo controlled phase 3 in	104 adjusted dose 25-75	51 placebo	1 cerebral infarction	0

		Chinese ITP pts Pts with history of arterial/venous T or risk factors for T including thrombophilia excluded	mg daily for 8 weeks		1 DVT	
Eltrombopag						
7	Jenkins (7)	Phase 1 placebo-controlled dose finding in 72 healthy subjects Pts with history of T excluded	54 9 pts for each of 6 dosage groups: 5, 10, 20 ,30, 50, 75 mg daily for 10 days	18 placebo	0	0
8	Bussel (1)	Phase 2, double blind, placebo controlled Pts with T < 1 yr, MI < 3 months or hormonal tx excluded	88 3 groups: 30 pts on 30 mg, 30 on 50, and 28 on 75 mg daily for 6 weeks	29 placebo	1 † for multiorgan failure (small vessels of the liver and kidneys on autopsy)	0
9	Bussel (8)	Phase 3, double blind, placebo controlled Pts with T < 1 yr, MI < 3 months or hormonal tx excluded	76 adjusted dose: 50 mg daily for 3 wks, increasable up to 75 mg daily for other 3 weeks	38 placebo	0	0
10	Cheng (9)	Phase 3, double-blind, placebo-controlled study Pts with history of arterial/venous T or risk factors for T including hereditary thrombophilia or family history of T excluded	135 adjusted dose: 50 mg daily up to day 22, then adjusted 25-75 for 6 months	62 placebo	2 PE 1 DVT	None
11	Tomiyama (10)	7-wk double-blind phase (15 eltrombopag 8 placebo) followed by 19 or 26-wk open-label phase (with eltrombopag) Pts with $\leq$ 1 yr suspected or confirmed history of arterial/venous T not on antiplatelet tx for thrombotic risk excluded	Double blind phase: 15 12.5 to 25 mg daily for 6 weeks Open-label phase: 23 (15 for additional 19 weeks and 8 for 26 weeks) adjusted dose 12.5 to 50 mg daily	Double blind phase: 8 placebo	Double blind phase: 1 TIA Open-label phase: none	Double blind phase: none

T, thrombosis; DVT, deep vein thrombosis; splx, splenectomy; †, death; PE, pulmonary embolism; SOC, standard of care; MI, myocardial infarction; TIA, transient ischemic attack

^Exclusion criteria for thrombosis as reported in http://clinicaltrials.gov under each study number or as described in the articles, whichever was more restrictive
*Same exposure time of treated with TPO-RA
°Incidence rate calculated censoring after 1st event during exposure (corresponding to the number of patients).

Supplemental table 2 Incidence of thromboembolism with romiplostim and eltrombopag in single-arm studies in adults

N.	Ref	Study characteristics and exclusion criteria for thrombosis^	N. exposed Dose Exposure time	Thrombosis (N/100 pt-yrs)
Romiplostim				
12	Bussel (2)	Phase 1 Pts with any known risk factors for T or history of cardiovascular disease excluded	24 6 groups of 4 pts: 0.2, 0.5, 1, 3, 6,10 mcg /kg 2 doses 1 week apart (Observation 78 days)	None
13	Newland (11)	Open-label phase 1-2 in ITP patients Pts with history of arterial/venous T or risk factors for T excluded	16 4 groups of pts: 30, 100, 300, 500 mcg total dose repeated after 2 or 3 weeks (Observation 13 weeks)	None
14	Shirasugiv (5)	Phase 2, open-label in Japanese ITP pts. Pts with history of arterial/venous T or risk factors for T excluded	12 3 groups of 4 pts: 1, 3, 6 mcg /kg, 2 weekly doses, then observation for 3 weeks 5 entered tx-continuation phase (up to 14-22 weeks)	None
15	Janssens (12)	Phase 4, prospective, open-label single-arm 3 sequentially staggered cohorts No exclusion criteria for T	169 adjusted dose for up to 3 yrs: cohort 1: 147 wks cohort 2: 155 wks cohort 3: 155 wks; 103 completed all 3 yrs Annualized incidence rate provided	21 events in 15 pts (8.9%) Event rate 3.9/100 pt-yrs + 1 death (concurrent causes)
16	Newland (13)	Open-label, phase 2 interventional single arm describing platelet responses and remission rates in adults with ITP ≤ 6 months Pts with history of T excluded	75 Estimated weekly dose of 2.9 mcg /kg, for up to 12 months; forced tapering once stable response reached	1 reversible ischemic neurologic deficit
Eltrombopag				
17	Bussel (14)	Open-label, single-arm intermittent dosing in pts with ITP > 6 months Pts with history of arterial/venous T or risk factors for T including hereditary thrombophilia or family history of T excluded	66 cycle 1 55 cycle 2 51 cycle 3 50 mg daily, increasable to 75 mg Each cycle up to 6 wks, with a 4-wk interval between cycles	None

Splx, splenectomy; DVT, deep vein thrombosis, T, thrombosis

^Exclusion criteria for thrombosis as reported in http://clinicaltrials.gov under each study number or as described in the articles, whichever was more restrictive

* In general, all studies had a minimum of 4-wks observation after treatment discontinuation. Beyond this time, no thrombotic events were reported.

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