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Rapid policy statement

Interim Clinical Commissioning Policy: Thrombopoietin receptor agonists as first line therapy for new or relapsed immune thrombocytopenia in adults and children over the age of 1 year during the COVID-19 pandemic

22 February 2021 v1.1 Amends highlighted in yellow

Introduction

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England has established a rapid policy development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19 across the UK. This document sets out the interim clinical commissioning position for thrombopoietin receptor agonists (TPO RAs) as first line therapy for new or relapsed acute immune thrombocytopenia (ITP) in adults and children over the age of 1 year.

Commissioning position

The policy is for TPO RAs as first line therapy for new or relapsed ITP in adults and children over the age of 1 year.

Implementation

Eligibility criteria

Adults and children aged over 1 year with newly diagnosed ITP or acute relapse of ITP, who require treatment for bleeding, profound thrombocytopenia or to cover surgery.

Dose

The recommended starting dose of eltrombopag is 50 mg once daily for adults and children aged 6 years to 17 years. For patients of Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), eltrombopag should be initiated at a reduced dose of 25 mg

once daily. The recommended starting dose of eltrombopag is 25 mg once daily for children aged 1 to 5 years.

Romiplostim, is given subcutaneously and can be administered and monitored in the outpatient setting. The recommended starting dose of romiplostim is 1 mcg/kg once weekly for children from 1 year to adults as per licence (though clinicians may prefer to start at 3mcg/kg). Refer to the Summary of Product Characteristics (SmPC) for more information on dose adjustments of romiplostim in ITP patients.

After initiating TPO RA, the dose must be adjusted to achieve and maintain a platelet count ≥50,000/µl as necessary to reduce the risk for bleeding. A daily dose of 75 mg eltrombopag must not be exceeded in any age group.

See the SmPC for more information on dose adjustments of TPO RAs in ITP patients after platelet count ≥50,000/µl has been achieved.

Contraindications and precautions

TPO RA treatment should be initiated by and remain under the supervision of a physician who is experienced in the treatment of haematological diseases. Dietary restrictions around the time of taking eltrombopag must be adhered to so that absorption is optimised. See SmPC.

Patients hospitalised with COVID-19 may require steroids to dampen the hyperinflammatory response and TPO RAs may not be appropriate in this setting (Pavord et al, 2019).

Plain language summary

Overview

The condition

ITP is an autoimmune disease that results in a low platelet count, despite normal bone marrow and an absence of other causes of low platelets. The incidence of ITP in the UK is estimated to be around 1,500 per year, with 5000 people affected at any one time in England and Wales (NICE Evidence Summary, ESUOM35, 2014). Severe COVID-19 infection may also cause thrombocytopenia from increased activation and coagulopathy, with studies showing that platelet counts were lower in patients with very severe COVID-19 and thrombocytopenia was associated with a three-fold increased risk of worsening disease (Lippi et al 2020). As viral infections may trigger acute ITP, the incidence is anticipated to be slightly higher (1:10,000) in the setting of the current pandemic.

Intervention

Current Treatment

The treatment for ITP is tailored towards the patient, with relevant factors contributing to management decisions including the extent of bleeding, comorbidities predisposing to bleeding, complications of therapies, activity and lifestyle, tolerance of side-effects, accessibility of care and patient expectations. Treatment for ITP is based on recommendations from an international consensus report (Provan et al 2019). First-line treatment for newly diagnosed or relapsed ITP, outside the context of the COVID-19 pandemic, is corticosteroids or intravenous immunoglobulin (IVIg).

Serious adverse effects of steroids include diabetes, osteoporosis, psychosis and immune suppression. There are various second-line treatment options including azathioprine, cyclosporin, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab,

splenectomy, thrombopoietin receptor agonists and vinca alkaloids. Immunosuppressants take time to have an effect, often several weeks. In the context of COVID-19, the World Health Organisation recommend avoidance of steroids and other immunosuppressants when alternate treatment options are available.

Proposed Treatment

Eltrombopag (EPAG) is a thrombopoietin receptor agonist that binds to and activates the thrombopoietin (TPO) receptor, increasing platelet production. EPAG is licensed for use in patients aged 1 year and above with ITP lasting 6 months or longer from diagnosis and who are refractory to other treatments (for example corticosteroids or immunoglobulins). A NICE technology appraisal (NICE Technology Appraisal, TA293, 2013, updated in 2018) recommended EPAG for this indication only when the patient's condition is refractory to standard active treatments and rescue therapies or if they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.

Romiplostim is a protein that mimics the action of thrombopoietin by acting as an agonist at thrombopoietin receptors. Romiplostim is licensed for use in patients aged 1 year and above with ITP lasting 6 months or longer from diagnosis and who are refractory to other treatments (for example corticosteroids or immunoglobulins). A NICE technology appraisal (NICE Technology Appraisal, TA221, 27 April 2011). It stimulates the differentiation and proliferation of bone marrow cells responsible for producing platelets (megakaryocytes), thereby increasing platelet production and platelet counts (concentrations).

Whilst both TPO RAs are recommended by NICE for use for chronic ITP due to their efficacy, experience of earlier use is growing rapidly in acute ITP.

Evidence summary

A summary of the evidence is at Annex A.

Monitoring

The lowest dose of TPO RA to achieve and maintain a platelet count ≥50,000/μl should be used. Dose adjustments are based upon the platelet count response. Normalisation of the platelet count is not necessary and increasing TPO RAs to achieve a normal platelet count is not appropriate.

During therapy with TPO RAs full blood counts (FBCs), including platelet count, should be assessed weekly until a stable platelet count (≥50,000/μl for at least 4 weeks) has been achieved. FBCs including platelet counts should be obtained monthly thereafter.

Safety reporting

Any suspected adverse drug reactions (ADRs) for patients receiving TPO RA should be reported directly to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme at https://yellowcard.mhra.gov.uk/.

No evidence is available for the use of TPO RAs in patients with COVID-19, caution is advised. The SmPC should be checked for further information.

Governance

Data collection requirement

Provider organisations in England should register all patients using prior approval software (alternative arrangements in Scotland, Wales and Northern Ireland will be communicated) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Effective from

This policy will be in effect from the date of publication.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. This policy will be reviewed on 31 March 2021.

Definitions

Haematological diseases	These are a wide range of conditions affecting the parts of the blood
Platelets	Cell fragments that are part of the clotting process
Thrombocytopaenia	A shortfall of platelets in the blood

References

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Annex A

Evidence summary

Three papers were presented for review by NHS England. Paper 1 is a non-inferiority randomised trial of eltrombopag compared to intravenous immunoglobulin (IVIg) in 74 perioperative immune thrombocytopenia (ITP) patients from eight academic hospitals in Canada. Paper 2 is a pooled analysis of subgroup data by ITP duration (ITP ≤1 year and ITP >1 year) taken from nine studies primarily from Europe and North America assessing romiplostim efficacy in patients with newly diagnosed or persistent ITP for up to one year and patients with chronic ITP for more than one year. Paper 3 is a phase 2 uncontrolled trial of 75 romiplostim patients with primary ITP diagnosed in the past six months from 32 sites in Europe, North America and Australia.

Paper 1: Arnold DM et al 2020. Perioperative oral eltrombopag versus intravenous immunoglobulin in patients with immune thrombocytopenia: a non-inferiority, multicentre, randomised trial

This paper reports a non-inferiority, randomised, open-label trial of eltrombopag compared to IVIg in perioperative ITP patients. Patients were recruited between June 2013 and March 2019 from eight academic hospitals in Canada. Patients (≥18 years) with primary or secondary ITP were eligible with platelet counts less than 100×10^9/L before major surgery or less than 50×10^9/L before minor surgery. Key exclusion criteria included abnormal liver enzymes, thrombosis or myocardial infarction within 12 months, bone marrow reticulin or fibrosis, active malignancy, new or increase in dose of ITP treatments within two weeks, IVIg within two weeks or thrombopoietin receptor agonists within four weeks before randomisation.

A total of 74 patients were randomised, 38 to oral eltrombopag (50mg daily from 21 days before surgery to 7 days after surgery with weekly dose adjustments based on platelet counts), and 36 to IVIg (1g/kg or 2g/kg 7 days (+/- 2 days) before surgery). Around half of patients were women, (53% in the eltrombopag group and 50% in the IVIg group) and the mean age was around 60 years (59.8 years eltrombopag and 62.1 years IVIg). The median duration of ITP was 8 years amongst the eltrombopag group and 5.6 years in the IVIg group and baseline platelet count was 42 x 10^9/L and 37 x 10^9/L, respectively. Eight patients (21%) in the eltrombopag group and 2 patients (8%) in the IVIg group were on concomitant prednisone at baseline. The median number of prior ITP treatments were 1 (interquartile range (IQR) 1.0 to 3.0) in the eltrombopag group and 2 (IQR 1.0 to 3.0) in the IVIg group. Patients were followed up weekly from 21 days before surgery to 28 days after surgical haemostasis. The median follow-up was 50 days (IQR 49 to 55). One (3%) patient in the eltrombopag group and 4 (11%) patients in the IVIg group did not complete study treatment. Of the eltrombopag patients, 19 (50%) patients remained on 50mg daily dose, 15 patients (40%) required a dose escalation to 75mg preoperatively and 4 patients (10%) required a dose reduction of eltrombopag to 25mg daily preoperatively.

Paper 2: Kuter DJ et al 2019. Romiplostim in adult patients with newly diagnosed or persistent immune thrombocytopenia (ITP) for up to 1 year and in those with chronic ITP for more than 1 year: a subgroup analysis of integrated data from completed romiplostim studies

This paper reports a pooled analysis of subgroup data by ITP duration (ITP ≤1 year and ITP >1 year) taken from studies assessing romiplostim efficacy in patients with newly diagnosed or persistent ITP for up to one year and patients with chronic ITP for more than one year. Data were pooled from nine studies conducted from 2002 to 2014 primarily in Europe and North America. No details were provided on study selection other than that all the included studies enrolled adult patients with ITP for one year or less who had failed first-line treatments and subsequently received romiplostim, placebo or standard of care in romiplostim ITP studies. The majority of included studies (eight studies) also included patients with ITP for more than one year. Four dose finding studies were excluded. Four of the nine included studies were controlled trials (three placebo controlled and one standard care controlled) and three were uncontrolled trials. The remaining two studies appear to be extension studies of these seven trials. Eligibility criteria, treatment regimens and length of follow-up were not provided for each study.

The pooled subgroup analysis included 1,037 patients, 277 patients with ITP ≤1 year and 634 with ITP >1 year in the romiplostim group and 34 patients with ITP ≤1 year and 92 with ITP >1 year in the combined placebo/standard of care group. The majority of patients came from the uncontrolled trials: 405 patients from a large compassionate use study, 169 patients from a 3-year bone marrow study, and 75 patients from a platelet response and remission study. The majority of patients were Caucasian with a median age range across the groups of 52 to 54 years. Of the patients with ITP ≤1 year, 155 (50%) had newly diagnosed ITP (<3 months) and 156 (50%) had persistent ITP (3 to 12 months). The median duration of ITP was 3 months for those with ITP ≤1 year and 72 months for those with ITP >1 year. Both ITP subgroups had a median baseline platelet count of 18 x 10^9/L (IQR 10 to 29). Amongst patients with ITP ≤1 year, 25 (8%) patients had prior splenectomy and 21 (7%) had prior rituximab treatment and for those with ITP >1 year, 320 patients (44%) had prior splenectomy and 134 (18%) prior rituximab. A quarter of patients discontinued the studies, mostly due to withdrawal of consent (n=59), requirement for alternative therapy (n=34), death (n=22) or adverse events (n=34). The median weekly romiplostim dose was reported to be around 3 to 4µg/kg per week across the ITP subgroups.

Paper 3: Newland A et al 2015. Remission and platelet responses with romiplostin in primary immune thrombocytopenia: final results from a phase 2 study

This paper reports a phase 2 uncontrolled trial of romiplostim in 32 sites in Europe, North America and Australia. The recruitment time period is not reported. Patients (≥18 years) diagnosed with primary ITP in the past 6 months and who had only received first-line ITP treatments were enrolled if observed to have a single platelet count ≤30 x 10^9/L during a four week screening period. Key exclusion criteria included a known history of bone marrow stem cell disorder, splenectomy, history of recurrent venous thromboembolism or thrombotic events within five years of enrolment, previous use of romiplostim, pegylated recombinant human megakaryocyte growth and development factor, eltrombopag or other platelet-producing agents, previous use of rituximab or use of haematopoietic growth factors, including interleukin-11, within four weeks of the screening visit. Patients were treated with romiplostim (starting dose of 1µg/kg) for 12 months with dose adjustments based on platelet counts. Treatments started before enrolment to increase platelet counts were permitted to continue at a fixed dose and schedule.

A total of 75 patients were enrolled in the trial, of which 59% were women and the median age was 39 years. The median ITP duration prior to enrolment was 2.2 months and the median platelet count at screening was 20 x 10^9/L. 57% of patients had received one previous first-line ITP treatment and 43% had received 2 or more previous first-line ITP

treatments. 96% had received corticosteroids, 44% IVIg, 8% platelet transfusion and 1% anti-D immunoglobulin antibody. Overall, 16 patients (21%) discontinued romiplostim due to withdrawal of consent (n=4), requirement for alternative treatment (n=4), adverse events (n=3), lost to follow-up (n=2), protocol deviation (n=1), death (n=1) and splenectomy (n=1). During the 12-month treatment trial period, the median weekly dose of romiplostim was 2.6µg/kg and the median duration was 51 weeks (IQR 18 to 52).

Effectiveness

Platelet response

Arnold et al 2020 reported that 30 (79%) of eltrombopag patients achieved perioperative platelet count targets[1] compared with 22 (61%) of IVIg patients, meeting the criteria for non-inferiority (absolute risk difference (ARD) 17.8%, one-sided lower limit of the 95% CI 0.4%; $p_{non\text{-}inferiority}$=0.005). In the subgroup of patients with major surgery[2], perioperative platelet count targets were achieved in 14 (82%) eltrombopag patients and 7 (50%) IVIg patients (ARD 32.4%, one-sided lower limit of the 95% CI 4.7%; $p_{non\text{-}inferiority}$=0.006), and for minor surgery[3] targets were achieved in 16 (76%) eltrombopag patients and 15 (68%) IVIg patients (ARD 8.0%, one-sided lower limit of the 95% CI –14.7%; $p_{non\text{-}inferiority}$=0.095). Overall, the median time to reach the platelet count targets were 12 days for eltrombopag and 6 days for IVIg.

Kuter et al 2019 reported a median time to first platelet response[4] of two weeks for romiplostim patients in each ITP duration subgroup. This was 4 weeks for placebo/standard of care patients with ITP ≤1 year and 12 weeks for those with ITP >1 year. For patients with ITP ≤1 year, platelet response rates were 86% for the romiplostim group and 62% for placebo/standard of care group and for patients with ITP >1 year, 87% for romiplostim and 33% for placebo/standard of care. Durable platelet response rates[5] were 53% for romiplostim and 24% for placebo/standard of care for patients with ITP ≤1 year and 49% for romiplostim and 10% for placebo/standard of care for patients with ITP >1 year. Confidence intervals and p-values were not reported.

Newland et al 2015 reported that 70 (93%) out of 75 patients had a peak platelet count of ≥50 x 10^9/L during the 12-month treatment period and the median time to platelet response[6] was 11 months (IQR 8 to12). Most patients (61%) had either 11 or 12 months of platelet response. The median time to platelet response was 2.1 weeks (95% CI 1.1 to 3.0).

Remission

[1] 45 × 10^9/L or higher for minor surgery or 90 × 10^9/L or higher for major surgery from day –1 before surgery to day 7 after surgical haemostasis without rescue treatment
[2] aortic valve replacement, arthrodesis, back surgery (placement of titanium wedge L4-5-6), breast reduction, colonoscopy, coronary artery bypass graft, epidural injection, gum graft, hip arthroplasty, invasive spinal denervation, knee arthroplasty, laparoscopic splenectomy, pelvic organ prolapse repair, peritoneal dialysis catheter insertion, platelet-rich plasma injection, thyroidectomy, or thyroid goiter resection
[3] breast augmentation, cardiac defibrillator implant, carpal tunnel repair, cataract surgery, cholecystectomy, colonoscopy (with or without polypectomy), dental extraction, inguinal hernia repair, laparoscopic splenectomy, lung biopsy, myomectomy, nipple reconstruction, or skin biopsy
[4] a platelet count ≥50 x 10^9/L, excluding platelet counts obtained in the eight weeks after rescue medication use
[5] a platelet response (as defined above) for ≥6 weeks of weeks 17–24 (to allow time for dose titration and effects on thrombopoiesis to be captured)
[6] a median platelet count ≥50 x 10^9/L, excluding platelet counts in the four weeks following rescue medication use/splenectomy

Kuter et al 2019 reported that of the patients with ≥9 months on study (n not stated), 16% (95% CI 11 to 21) with ITP ≤1 year and 6% (95% CI 4 to 8) with ITP >1 year discontinued romiplostim and maintained platelet counts ≥50 x 10^9/L for ≥6 months without ITP treatment (treatment-free remission).

Newland et al 2015 reported that 24 out of 75 patients (32%; 95% CI 22 to 44) entered ITP remission[7] during the 12-month treatment period or tapering period. The median time to onset of ITP remission was 27 weeks (range 6 to 57) with the majority of patients in remission (20/24 patients; 83%) starting before the forced taper after 12 months of romiplostim. The only factor found to be significantly associated with remission was mean platelet count for the first two months. Of the 24 patients who achieved remission, 19 (79%) were able to maintain platelet counts ≥100 x10^9/L and 13 (54%) patients had platelet counts ≥150 x 10^9/L for 24 weeks without ITP medications.

Rescue treatment

Arnold et al 2020 reported that rescue treatment[8] was required for 7 (18%) eltrombopag patients and 7 (19%) IVIg patients (p=1.00). Rescue treatments consisted of prednisone, methylprednisolone, IVIg, platelet transfusions and dexamethasone. Postoperative blood transfusion (red blood cell, platelet, plasma, or cryoprecipitate) was administered to 2 (5%) eltrombopag patients and 4 (11%) IVIg patients (p=0.42).

Kuter et al 2019 reported that 44% of romiplostim patients with ITP ≤1 year and 50% of those with ITP >1 year required rescue medications[9] (~60% corticosteroids and ~20% IVIg). The paper reports that the use of rescue medication decreased over time and appeared to be higher in the first few weeks when the romiplostim dose was being titrated and other ITP therapies were being reduced or discontinued.

Newland et al 2015 reported that rescue medication use was lower in the 24 patients in ITP remission compared to the 51 patients who did not enter remission (25% vs 31%).

Treatment failure

Arnold et al 2020 reported 8 (21%) treatment failures (not defined) in the eltrombopag group (5 failures by day 0 and 3 failures from day 0 to 7) and 14 (39%) in the IVIg group (10 by day 0 and 4 from day 0 to 7).

Newland et al 2015 reported 7 (9%) patients with treatment failure[10], of which 4 (5%) required alternative treatment, 1 (1%) did not respond, 1 (1%) died and 1 (1%) had a splenectomy.

Bleeding

Arnold et al 2020 reported grade ≥2 (severe) bleeding events in 9 (24%) eltrombopag patients and 8 (22%) IVIg patients and grade 1 bleeding events in 27 (71%) patients and 25 (69%) patients, respectively.

Kuter et al 2019 reported an incidence of bleeding in 52% (95% CI 46 to 58) of romiplostim patients and 62% (95% CI 44 to 78) of placebo/standard of care patients with ITP ≤1 year

[7] platelet count ≥50 x 10^9/L for 24 consecutive weeks with no ITP treatments

[8] defined as any additional treatment administered during the perioperative period to increase the platelet count or prevent bleeding. Stress doses of corticosteroids and intraoperative platelet transfusions without thrombocytopenia were not considered rescue treatment

[9] added per investigator to treat or prevent bleeding and could include newly introduced ITP medications and dose or frequency increase of baseline ITP medications other than romiplostim

[10] as platelet counts ≤20 x 10^9/L for four consecutive weeks at 10µg/kg a week, alternative treatment, or death

and 60% (95% CI 56 to 63) and 59% (95% CI 48 to 69), respectively for patients with ITP >1 year. After adjustment for time on study, exposure-adjusted rates of bleeding in both ITP duration subgroups were statistically significantly lower for romiplostim (ITP ≤1 year: 130 per 100 patient-years (95% CI 118 to 142); ITP >1 year: 182 per 100 patient-years (95% CI 174 to 190)) than placebo/standard of care (ITP ≤1 year: 192 per 100 patient-years (95% CI 150 to 242); ITP >1 year: 266 per 100 patient-years (95% CI 229 to 306)). Overall, exposure-adjusted bleeding rates were higher in patients with ITP >1 year than in those with ITP ≤1 year. In the romiplostim group, exposure-adjusted rates of any bleeding event and grade ≥2 bleeding events decreased over time to similar extents in both ITP duration subgroups. Newland et al 2015 reported that bleeding episodes occurred in 23 (31%) patients with the most common being haematoma (11%), petechiae (9%) and epistaxis (8%). The paper reports that no bleeding events were considered serious and only 1 was considered treatment-related (a case of haematoma in a patient without remission).

Treatment satisfaction

Arnold et al 2020 reported patient-reported treatment satisfaction measured by the Treatment Satisfaction Questionnaire for Medication (TSQM)[11]. TSQM scores were statistically significantly higher for eltrombopag patients than for IVIg patients on day –1 (median 91.7 (IQR 75.0 to 100.0) vs 83.3 (IQR 66.7 to 83.3); p=0.012) and on day 7 after surgery (median 91.7 (IQR 83.3 to 100.0) vs 75 (IQR 66.7 to 83.3); p=0.0002). The paper states that most of these differences were attributable to ease of administration, planning and dosing.

Safety

Arnold et al 2020 reported that no patients died during the study. Two serious adverse events occurred in the eltrombopag group. These were pulmonary embolism and vertigo and the paper reported that only pulmonary embolism was possibly related to study treatment. Five serious adverse events were reported in the IVIg group, with 3 occurring after major surgery (atrial fibrillation, pancreatitis and vulvar pain) and 2 after minor surgery (chest tube malfunction and conversion to open splenectomy). None were thought to be related to IVIg treatment. In the eltrombopag group, 2 patients (5%) developed increased liver enzymes and 2 (5%) developed rebound thrombocytopenia after stopping eltrombopag. Of the 19 patients undergoing splenectomy (10 in the eltrombopag group and 9 in the IVIg group), 2 eltrombopag patients developed postoperative thrombocytosis (platelets >1000 x 10^9/L) without clinical sequelae.

Kuter et al 2019 reported the following adverse event rates (per 100 patient-years) for romiplostim and placebo/standard of care for the ITP ≤1 year and ITP >1 year patient subgroups.

Adverse event (AE) rate (per 100 patient-years) for romiplostim and placebo/standard of care by ITP patient subgroup

	ITP ≤1 year		ITP >1 year	
	Placebo/Standard of care (n = 34) 37 pt-yr	Romiplostim (n = 277) 382 pt-yr	Placebo/Standard of care (n = 92) 71 pt-yr	Romiplostim (n = 634) 1101 pt-yr
Grade ≥3 AEs	101 (71–140)	76 (67–85)	**134 (109–164)**	**84 (79–90)**
Grade ≥4 AEs[12]	16 (6–36)	11 (8–15)	24 (14–38)	15 (13–17)

[11] a validated tool that includes 11 items on medication effectiveness, side-effects, convenience and overall satisfaction. Each item is scored from 0 to 100 with higher values indicating higher satisfaction

[12] life-threatening conditions, such as cancer (e.g. liver, rectal) or organ failure (e.g. cardio-respiratory arrest, respiratory failure)

Serious AEs[13]	**90 (62–127)**	**51 (44–59)**	**99 (77–125)**	**56 (52–61)**
Treatment-related serious AEs	33 (17–57)	4 (2–7)	8 (3–18)	7 (6–9)
AEs leading to discontinuation of study drug	14 (4–32)	7 (5–11)	3 (0.3–10)	6 (5–8)
Fatal AEs	5 (1–20)	3 (2–6)	**8 (3–18)**	**2 (1–3)**
Treatment-related fatal AEs	0	0	0	5 (0.1–1)
Thrombotic/thromboembolic events	8 (2–24)	4 (3–7)	3 (0.3–10)	6 (5–8)
Bleeding	**192 (150–242)**	**130 (118–142)**	**266 (229–306)**	**182 (174–190)**

All data expressed as adverse events per 100 patient-years (95% CI). **Bolded** = non-overlapping 95% CI for placebo/standard of care group and romiplostim indicating statistical significance

Kuter et al 2019 reported that the rate of bleeding and rate of serious adverse events were statistically significantly higher in the placebo/standard of care group than the romiplostim group. As were grade ≥3 adverse events and fatal adverse events, but only for patients with ITP >1 year. All treatment related fatal adverse events occurred in romiplostim patients with ITP >1 year. These were aplastic anaemia, intestinal ischaemia, unstable angina, myocardial infarction and haemolysis secondary to a refractory urinary tract infection. The paper reports that the rate of thrombotic events for romiplostim patients increased with age and was similar between the two ITP duration subgroups. No differences were seen by prior splenectomy status or in arterial versus venous thromboses.

Newland et al 2015 (n=75) reported that the most common adverse events were headache (16%), arthralgia (15%), nasopharyngitis (12%) and haematoma (11%). Serious adverse events occurred in 14 patients (19%) and these were considered treatment related in 3 patients (gastritis, increased transaminases and reversible ischaemic neurological deficit). One death occurred during the study which was due to intracranial haemorrhage that was present before the patient received romiplostim. Neutralising antibodies to romiplostim were found in 1 patient during routine testing at the end of the study. No neutralising antibodies to thrombopoietin were detected. Of the 43 patients (57%) who self-administered romiplostim, 11 reported an adverse event in the four weeks before the start of self-administration, and 32 reported an adverse event after the start of self-administration.

[13] adverse events of any grade that required or prolonged hospitalization, including nonspecific conditions, such as bleeding (e.g. contusion, purpura) as well as general symptoms (e.g. dehydration, pyrexia)