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Childhood immune thrombocytopenia (ITP)

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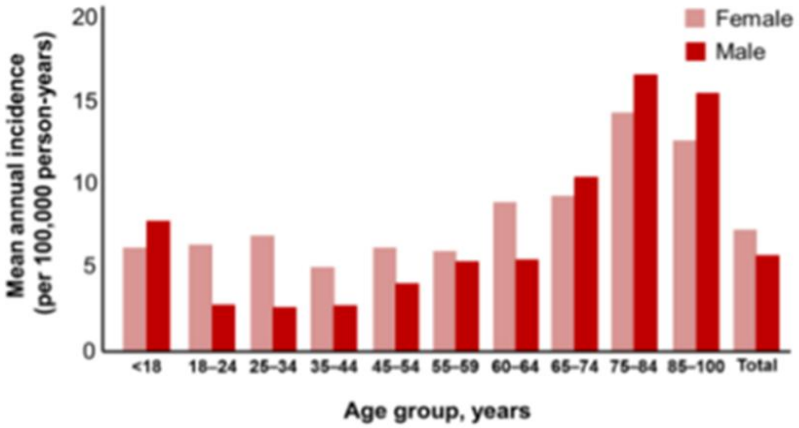
Immune Thrombocytopenia (ITP)

- Immune-mediated acquired disease of adults and children
- ITP is characterized by:
  - A low platelet count (<100 x 10^9/L, transient or persistent)[1]
  - An increased risk of bleeding due to impaired clotting mechanism[2-4]
- The overall incidence of ITP among adults is estimated at 3.3 per 100,000 person-years[5]
  - Higher incidence in women *versus* men[6]
    - Male:female ratio increases with age
  - Higher incidence at older ages[6]



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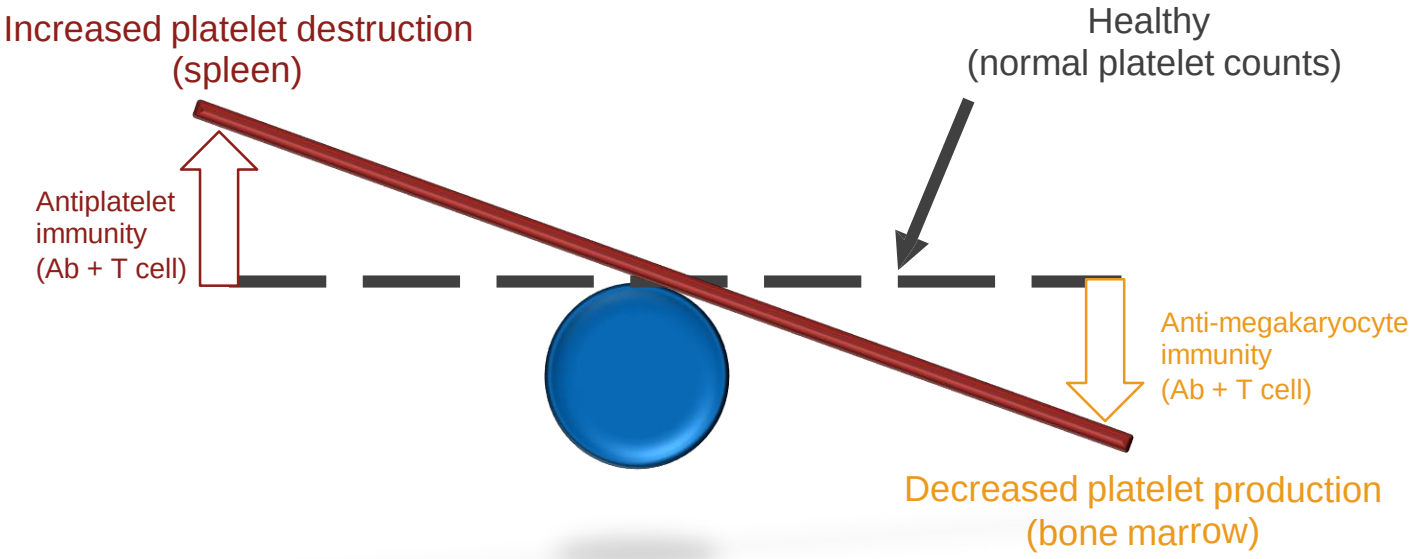
ITP: Acquired disorder of autoimmune-mediated platelet destruction and reduced platelet production



Platelet destruction and suppressed platelet production in ITP appear to be mediated by autoantibodies and cytotoxic T lymphocytes[1]
ITP presents clinically with varying degrees of petechiae, purpura, and mucosal bleeding.[2] Symptoms generally appear when platelet counts fall to <30 ·10^9/L[3,4]

1. Nugent D *et al. Br J Haematol* 2009;146:585–596;
2. Cines DB *et al*. *Annu Rev Med* 2005;56:425–442;
3. Cooper N. *Br J Haematol* 2017;177:39–54;
4. Provan D *et al. Blood* 2010;115:168–186

Ab, antibody

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Signs and Symptoms

ITP manifests:

Bleeding tendency
Easy bruising (purpura)
Extravasation of blood from capillaries into skin and mucous membranes (petechiae)

Most cases of acute ITP, particularly in children, are mild and self-limited bleeding

Intracranial hemorrhage may occur when the platelet count drops below 10 Ч 109/L (< 10 Ч 103/μL)

Incidence of ICH 0.5-1% of children, and half of these cases are fatal

Butros LJ, Bussel JB. Intracranial hemorrhage in immune thrombocytopenic purpura: a retrospective analysis. J Pediatr Hematol Oncol. 2003 Aug. 25(8):660-4.

Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. Curr Opin Hematol. 2007 Sep. 14(5):515-9.

History

The medical history in a patient with a clinical suspicion of immune thrombocytopenia (ITP) should focus on the following:

1. Factors that suggest another disease for which thrombocytopenia is a complication
2. Signs and symptoms that differentiate mild, moderate, and severe bleeding tendencies

Secondary Thrombocytopenia

Post viral illness
HIV
Drug induced
Hereditary bleeding tendency

Nugent D et al. Br J Haematol 2009;146:585–596

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Physical Examination

Like the medical history, the physical examination should focus on the following:

1. Findings that suggest another disease for which thrombocytopenia is a complication
2. Physical signs that suggest serious internal bleeding

General health
Vital signs
Skin and Mucous membranes
Spleen
Nervous system
Lymphadenopathy
Constitutional symptoms

Cooper N. Br J Haematol 2017;177:39–54;
Provan D et al. Blood 2010;115:168–186

Guidelines for diagnosis of ITP

- ITP remains a diagnosis of exclusion of other conditions or factors that cause thrombocytopenia[1]
- Assessment of the following is needed to diagnose ITP:[1]
  - Patient and family history
  - Physical examination
  - Complete blood count
  - Peripheral blood film
  - Other laboratory investigations

  } Results do not suggest other aetiologies for thrombocytopenia[1]

- There is no robust clinical or laboratory test that can establish a diagnosis with accuracy[1]
- A platelet count <100 x 10^9/L has been defined as the threshold for diagnosis[2]

1. Provan D, *et al. Blood* 2010; **115**: 168–86; 2. Rodeghiero F, *et al. Blood* 2009; **113**: 2386–93

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Diagnostic Approach in Suspected ITP

Basic evaluation

- Patient/family history
- Physical examination
- CBC and reticulocyte count
- Peripheral blood film
- **Quantitative immunoglobulin level measurement***
- **Bone marrow (in selected patients)**
- Blood group (Rh)
- Direct antiglobulin test
- ***H. pylori*****/*****; HIV/HCV****

Tests of potential utility

- Glycoprotein-specific antibody
- Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant)
- Antithyroid antibodies and thyroid function
- Pregnancy test in women of childbearing potential
- Antinuclear antibodies***
- PCR for parvovirus and CMV

Tests of unproven benefit

- TPO
- Reticulated platelets
- PaIgG
- Bleeding time
- Platelet survival study
- Serum complement

*Should be considered in children; recommended in children with persistent or chronic ITP
**Recommended for adult patients regardless of geographic location
***Not recommended in children according to the American Society of Hematology guidelines (2011)[1]

CBC, complete blood count; CMV, cytomegalovirus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PaIgG, platelet-associated immunoglobulin G; PCR, polymerase chain reaction; Rh, rhesus

1. Neunert C, *et al. Blood* 2011; **117:** 4190–207; Table reproduced with permission from Provan D, *et al. Blood* 2010; **115:** 168–86

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Table 4. Disease phases and treatment goals [4]

Phase	Definition	Treatment goal
Newly diagnosed	Up to 3 months after diagnosis Spontaneous remissions common	Prevention or termination of bleeding, cure. Because treatment might only take a short time period side effects are more acceptable.
Persistent	Between 3 and 12 months after diagnosis Spontaneous remissions less common	Prevention or termination of bleeding, cure. Since therapy now extends over a longer time period, the benefits and side effects must be weighed more strongly against each other.
Chronic	More than 12 months after diagnosis Spontaneous remissions uncommon.	Prevention or termination of bleeding, cure. Patient should accept that thrombocytopenia will most likely be chronic. Quality of life and avoidance of side effects become more important than platelet count. Therapy only mandatory for severe bleeding, in oligo- or asymptomatic patients also 'watch & wait' possible
Before 2009, there was only the distinction between 'acute' and 'chronic' ITP depending on whether the disease lasted less or more than 6–12 months.		

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Factors That Contribute to ITP Management Decisions

The goal of treatment in chronic ITP is not well defined and depends on balancing efficacy against the adverse effects of a given treatment[1]

- In patients with platelet counts >50 x 10^9/L treatment is not usually indicated unless the patient has other risk factors (e.g. bleeding or surgery)[1]
- A platelet count of <30 x 10^9/L is commonly used as the threshold for treatment in asymptomatic patients

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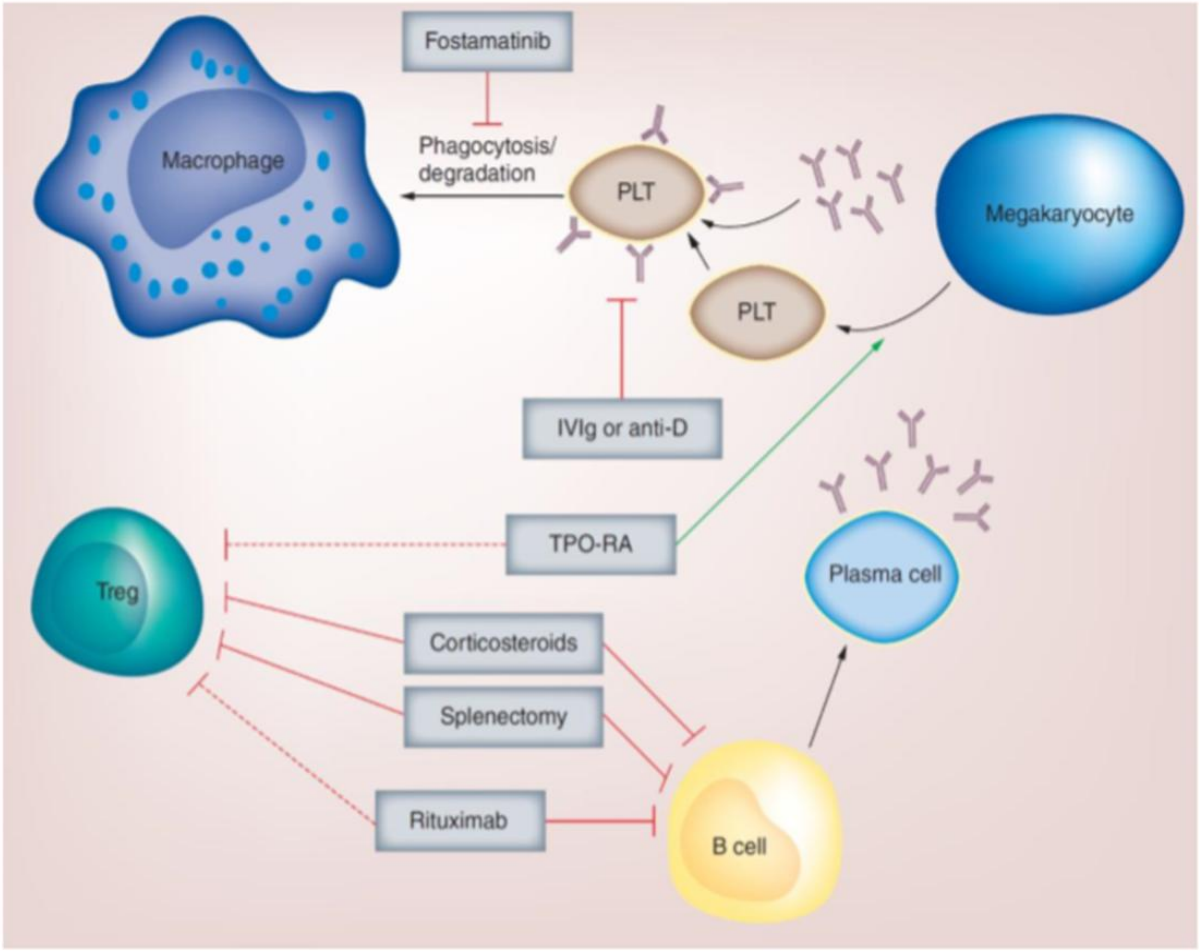
Treatment

Treatments for ITP: mechanisms of action



Newland A, et al. Immunotherapy (2018) 10(1), 9–25

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Treatment of ITP with corticosteroids

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Clinical situation	Therapy option

First-line therapy (initial treatment for newly diagnosed ITP)	• Corticosteroids (standard initial treatment)
	  • Dexamethasone
	  • Methylprednisolone
	  • Prednis(ol)one
	• Intravenous anti-D (Rho) immunoglobulin
	• IVIg

Second-line therapy	
Treatment for patients failing first- and second-line therapies	

IVIg, intravenous immunoglobulin

Adapted with permission from Provan D, et al. Blood 2010; 115: 168–86

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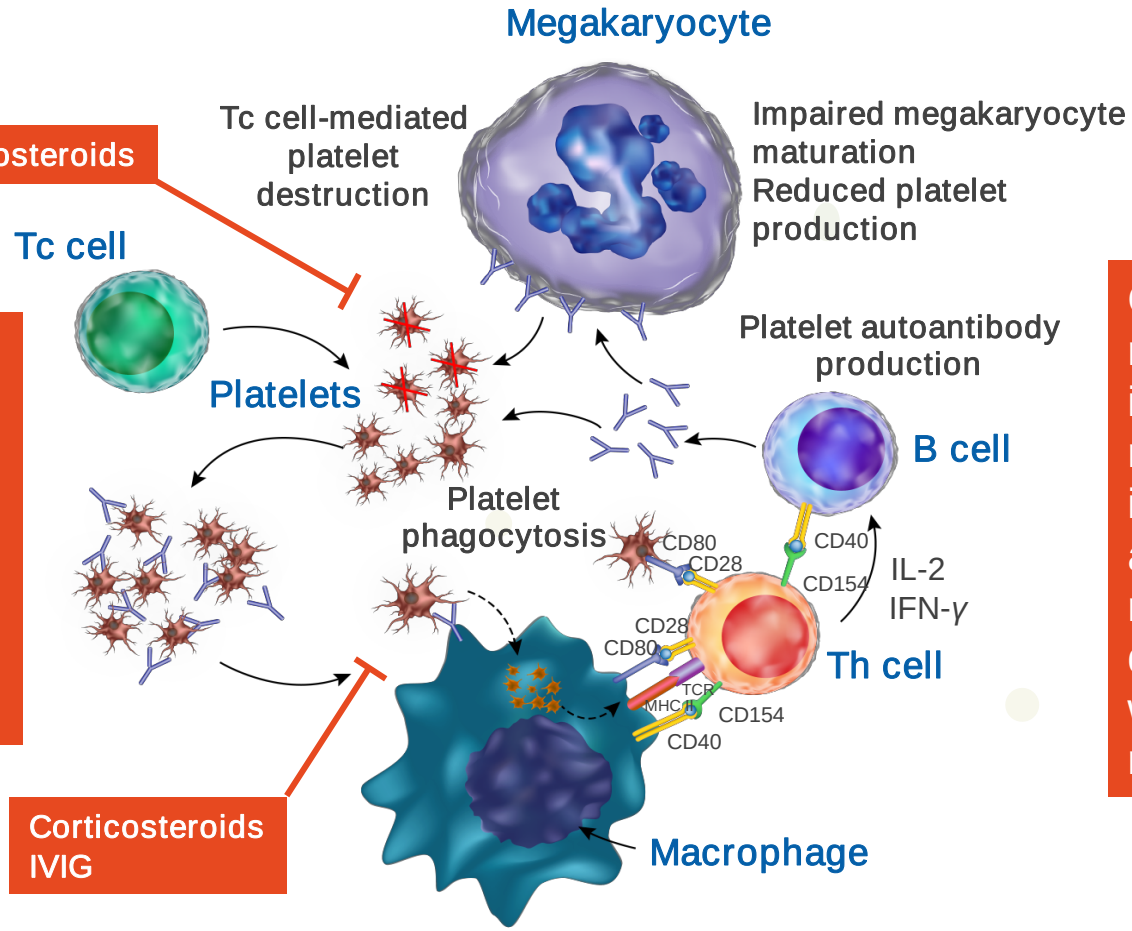
Corticosteroids and IVIG are the first-line treatment for ITP



Corticosteroids and IVIG can impair the clearance of autoantibody-coated platelets by macrophages

Corticosteroids may also increase platelet numbers by impairing the ability of macrophages to destroy platelets within the bone marrow

IVIG, intravenous immunoglobulin

Adapted from Stasi R *et al. Thromb Haemost* 2008;99:4–13

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Corticosteroids and IVIG elicit a platelet response in most patients

Treatment	Approximate response rate	Approximate time to response
Corticosteroids		
Dexamethasone	Up to 90% of patients respond initially	Several days to several weeks
Methylprednisolone	As high as 5~	%95days
Prednis(ol)one	70–80% of patients respond initially	Several days to several weeks
IVIG	Up to %80of patients respond initially, half achieve normal platelet count	Many respond in 24hours, typically 2–4 days

A good response rate is generally achieved within days in the majority of patients, although the various response rate criteria between studies make direct comparison between individual treatments difficult

Provan D *et al. Blood* 2010;115:168–186

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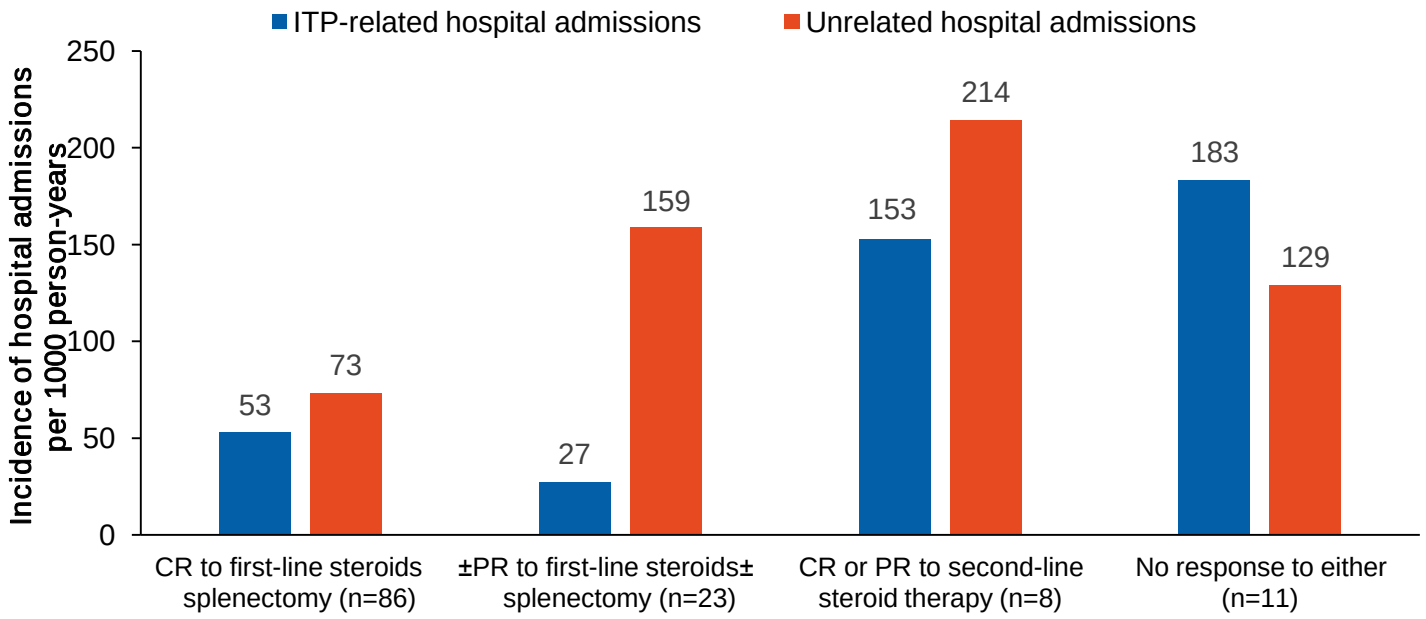
Use of corticosteroids/IVIG is limited by short response and adverse effects

Treatment	Common adverse events	Duration of sustained response
Corticosteroids		
Dexamethasone	Hypokalemia, gastric upset, sodium and fluid retention, hyperglycemia, hypertension, myopathy, osteoporosis, infection risk, psychosis[1–3]	50–80% had sustained response after 3–6 cycles over 2–5 years of follow-up[4]
Methylprednisolone		23% of patients had sustained platelet count at 39 months[4]
Prednis(ol)one		41.2% of patients had sustained platelet response at 6 months[5]
IVIG	Headaches, transient neutropenia, renal insufficiency, aseptic meningitis, thrombosis[4]	Usually transient, with platelet counts returning to pre-treatment levels 2–4 weeks after treatment[4]

- The use of IVIG is especially limited by a short duration of response
  Adverse effects of corticosteroids rapidly become apparent, which often outweigh their benefits with time

1. Berti D *et al. Clin Ther* 2008;30:1540–1552; 2. McDonough AK *et al. Curr Opin Rheumatol* 2008;20:131–137
3. Mathias SD *et al. Health Qual Life Outcomes* 2008;6:13; 4. Provan D *et al. Blood* 2010;115:168–186; 5. Wei Y *et al. Blood* 2016;127:296–302

ITP-related hospital admissions increased with repeat corticosteroid use after failed first-line use

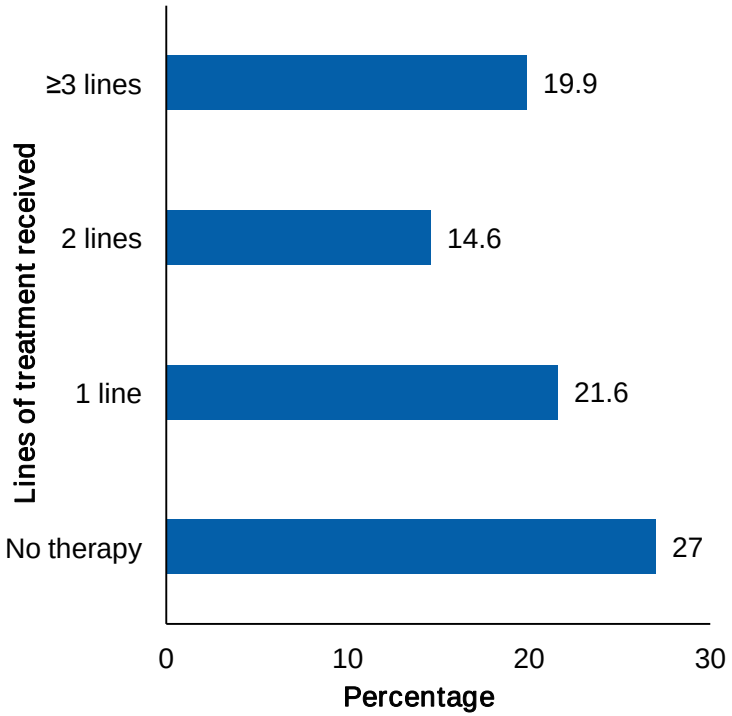


Patients who received an additional course of prednisone after the first course and subsequent splenectomy have failed, experienced a higher incidence of ITP-related hospital admissions irrespective of response

CR, complete response (platelets ≥100 ·10⁹*/L without therapy for* ≥2 months);
PR, partial response (platelets ≥30 ·10⁹*/L without therapy for* ≥2 months)

Portielje JEA *et al. Blood* 2001;97:2549–2554

20% of primary ITP patients in the UK required additional therapy after first-line treatment



UK Adult ITP Registry (2010–2018)

- 27% of patients with primary ITP required no therapy
- Steroids (78.4%) and IVIG (31.5%) were the most common first-line therapies*
- %20of patients required additional therapy after first-line treatment
- No safety information was reported in the abstract

*Steroids and IVIG were taken concurrently in some patients
PR, partial response (platelets ≥30 ·10⁹/L)

Zaidi A *et al.* Presented at EHA 2018 Abst 215104 (available at https://learningcenter.ehaweb.org/eha/2018/stockholm/215104/ (accessed 29 May 2018)

Corticosteroids: Summary

- Corticosteroids are recommended as the first-line treatment of ITP
- Despite a good initial response in the majority of patients, the sustained response rate is low
- When repeat cycles of corticosteroids are used to try and achieve or sustain platelet response, adverse effects can outweigh treatment benefits

ITP: Intravenous Immunoglobulin (IVIg) Therapy

Profile

- Have an initial response rate comparable to corticosteroids with a shorter time to response
- Many recipients attain a platelet increase within 24 hours at a dose of 1 g/kg
- In some patients, corticosteroids may enhance the IVIg response

Safety and efficacy

- Associated with higher toxicity than corticosteroids, especially headaches
- There is a need for a prolonged infusion over several hours
- Rare but serious toxicities include renal failure and thrombosis
- Transient response

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ITP: Intravenous Anti-D Immunoglobulin

Profile

- Appropriate for Rhesus D-positive, non-splenectomised ITP patients[1,2]
- May be an effective alternative to IVIg:[1]
  - It can be infused in a shorter time
  - It has a potentially longer response
  - May reduce the need for splenectomy

Limitations

- Not recommended for use in patients with autoimmune haemolytic anaemia to avoid exacerbation of haemolysis[1,2]
- Mild anaemia is expected and may be dose-limiting[1]
  - It has a small donor pool and therefore the potential for limited availability[1]

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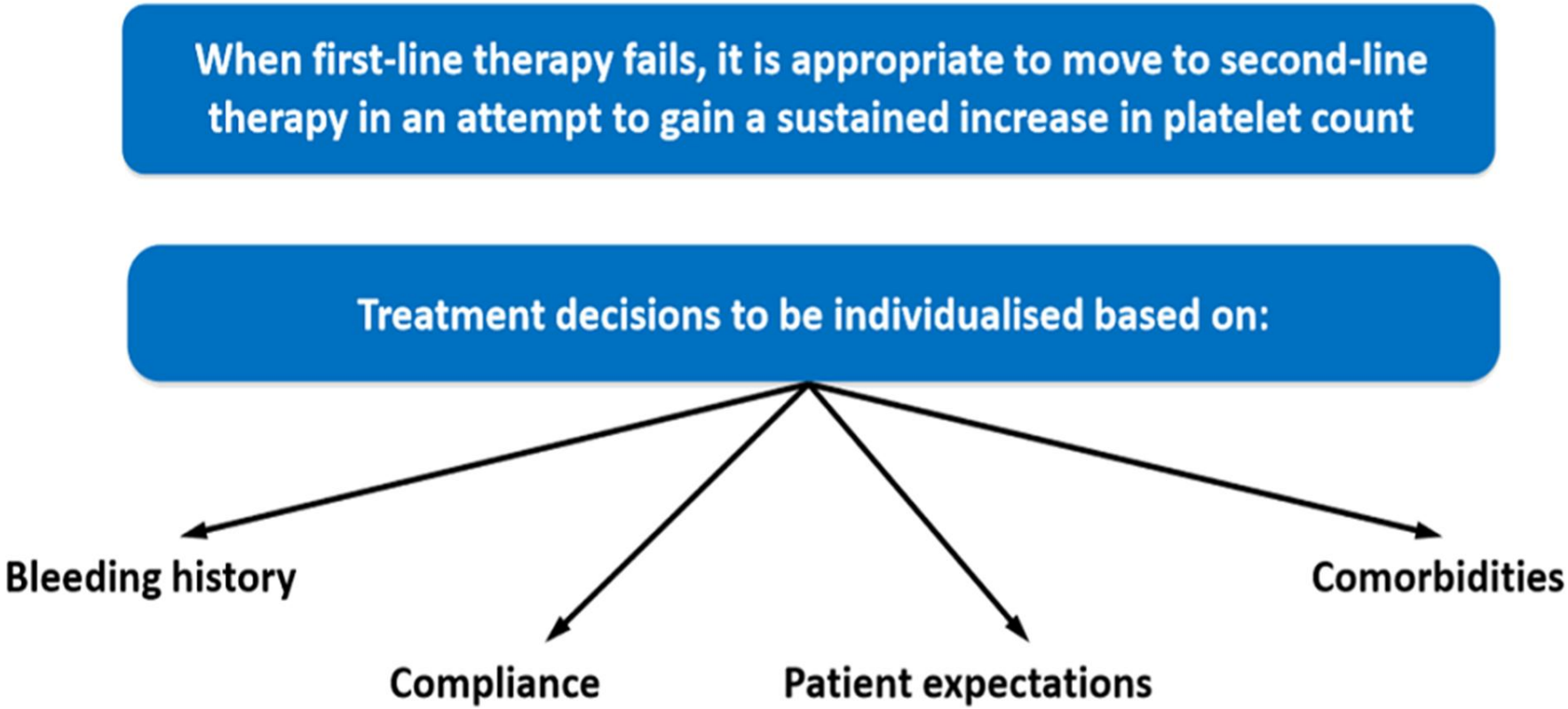
ITP: Second-line Therapy



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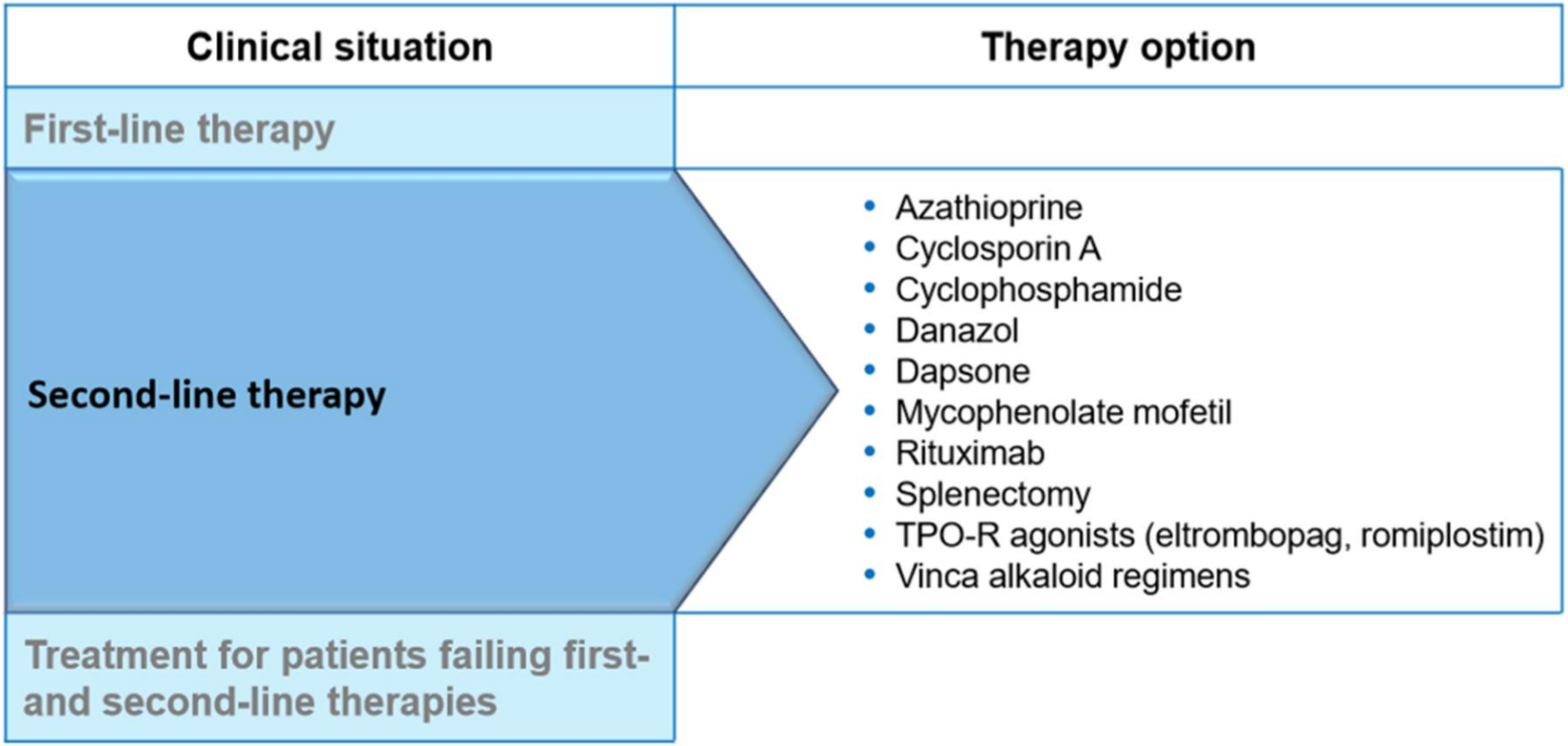

Adapted with permission from Provan D, et al. Blood 2010; 115: 168–86

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ITP treatment patterns in routine clinical practice

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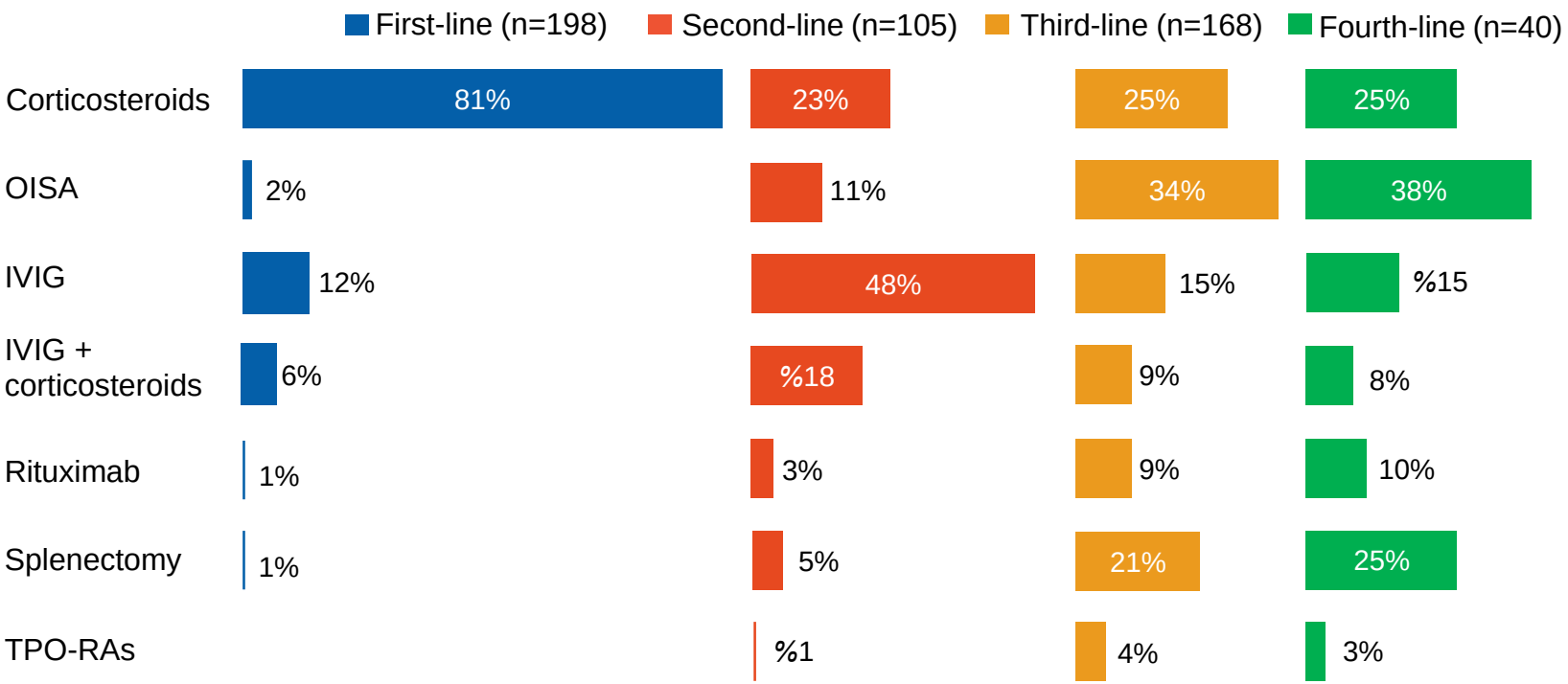
Percentage use of ITP treatments in a single clinical practice in Germany, 1995–2014



Retrospective analysis of all patients with ITP who were seen by five hematologists at the Praxisklinik für Hämatologie und Onkologie in Koblenz between 06/1995 and 12/2014
OISA, other immunosuppressive agent

Weide R *et al*. *Oncol Res Treat* 2016;39:41–44

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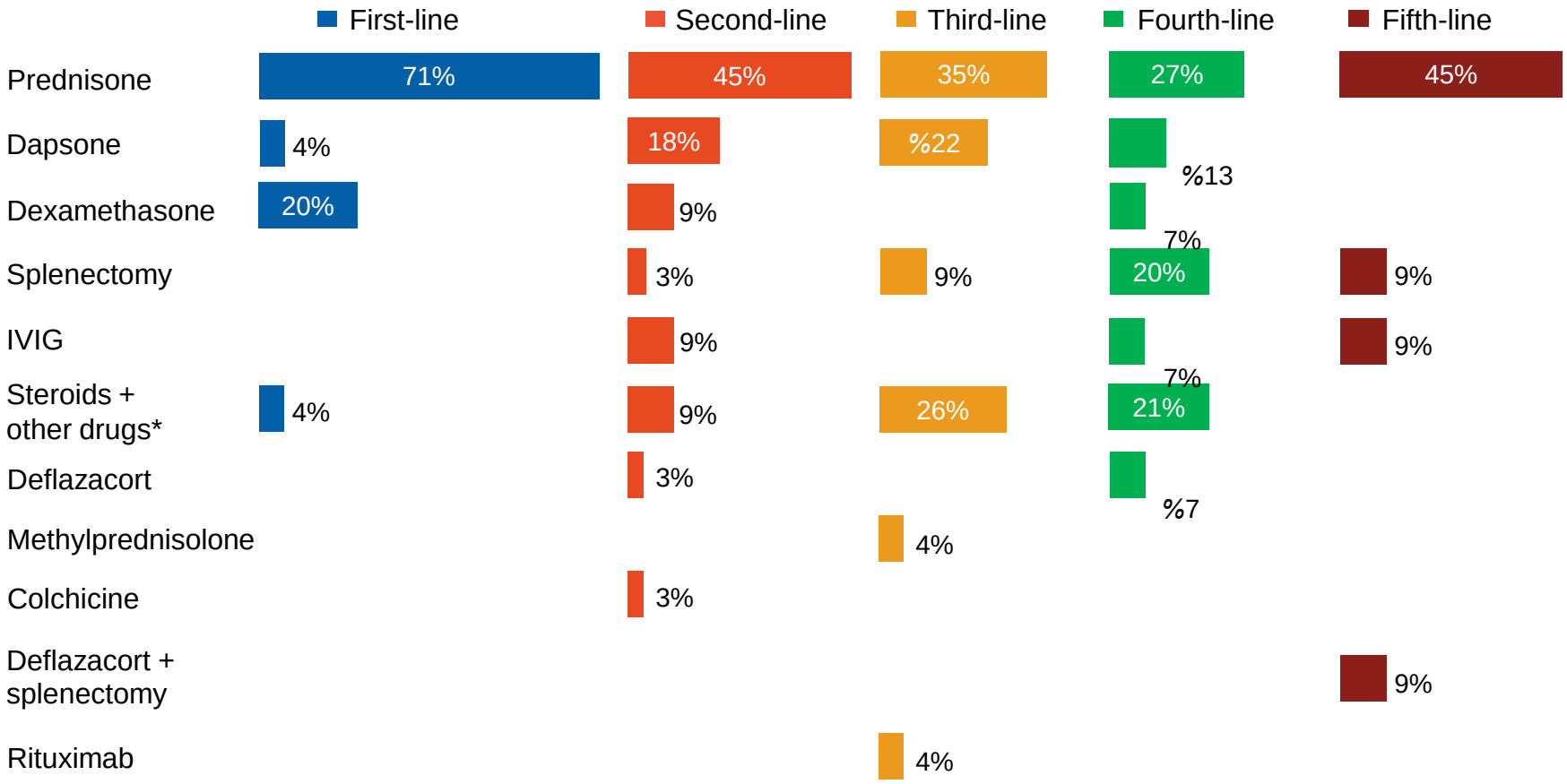
Percentage use of ITP treatments in five clinical practices: Brazil, 2014–2015

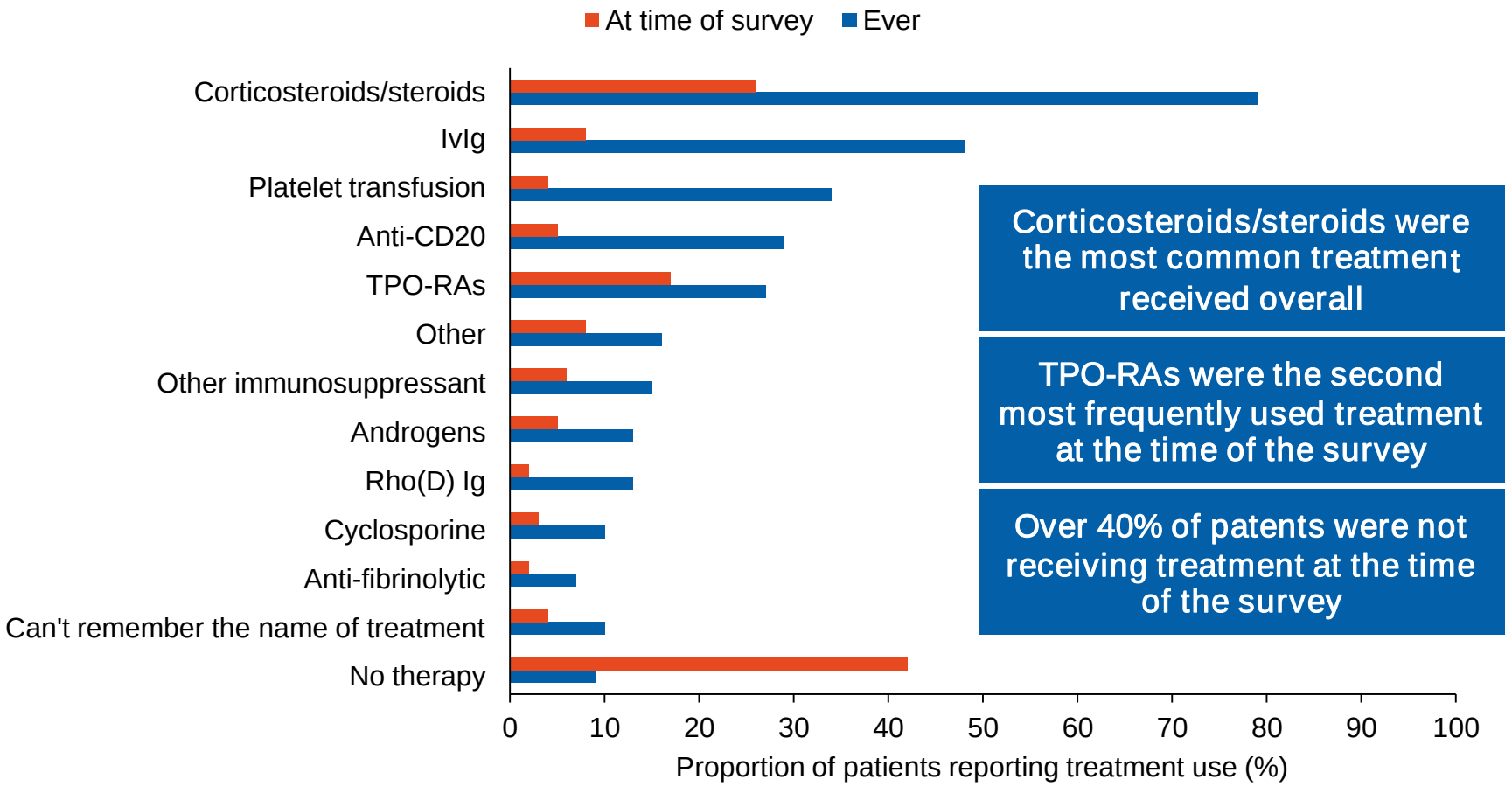


Retrospective chart review, observational cohort study conducted in five Brazilian institutions between 12/2014 to 08/2015; TPO-RAs were not incorporated into Brazilian guidelines for the treatment of ITP until 2016

*Other drugs included other steroids, azathioprine, colchicine, danazol, cyclophosphamide, and hydrocortisone

do Nascimento ACKV *et al*. *J Med Econ* 2017;20:884–892

Percentage use of ITP treatments reported by patients in the international I-WISh survey



I-WISh, ITP World Impact Survey

Cooper N *et al.* Manuscript in preparation

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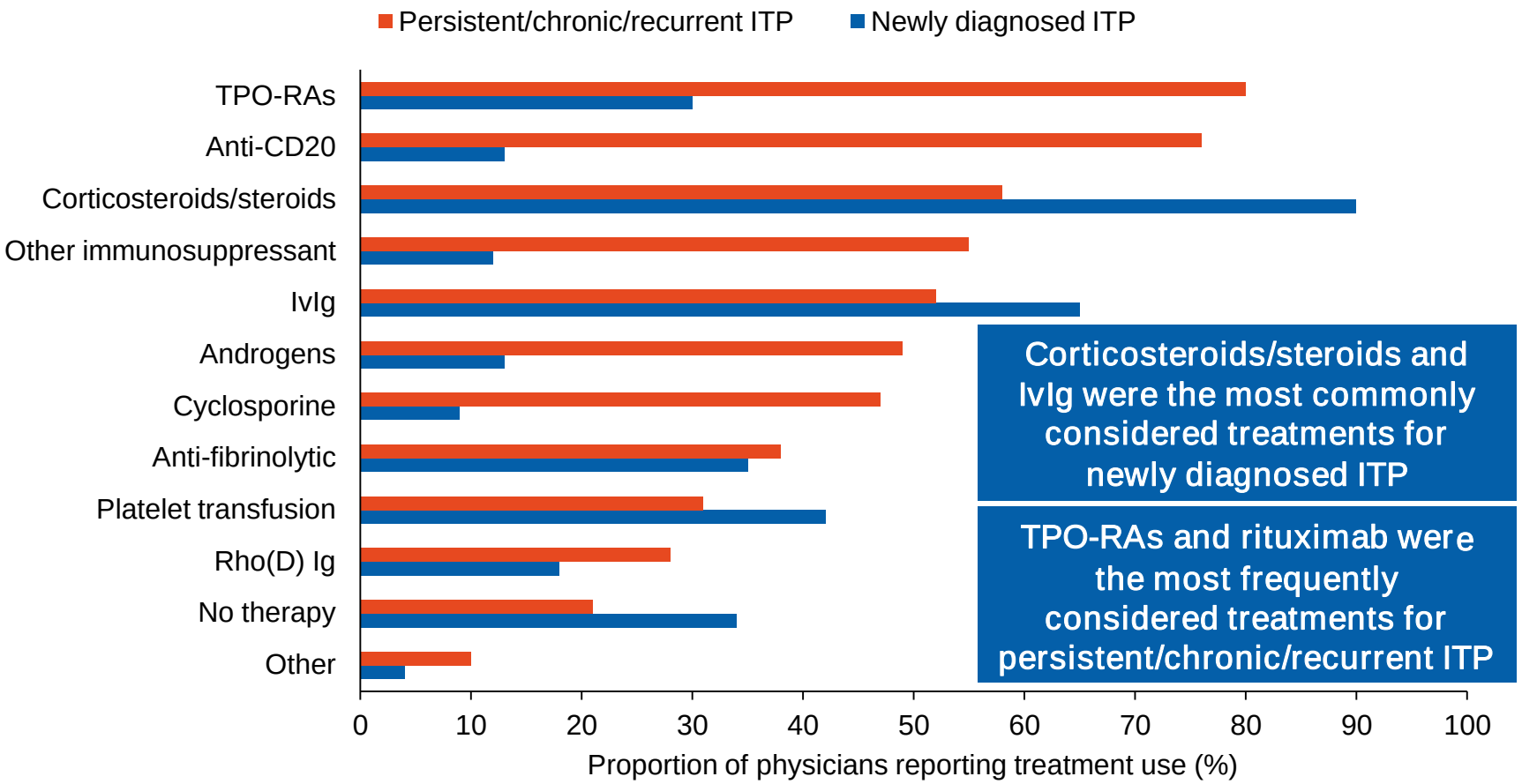
Percentage use of ITP treatments reported by physicians in the international I-WISh survey



Cooper N *et al.* Manuscript in preparation

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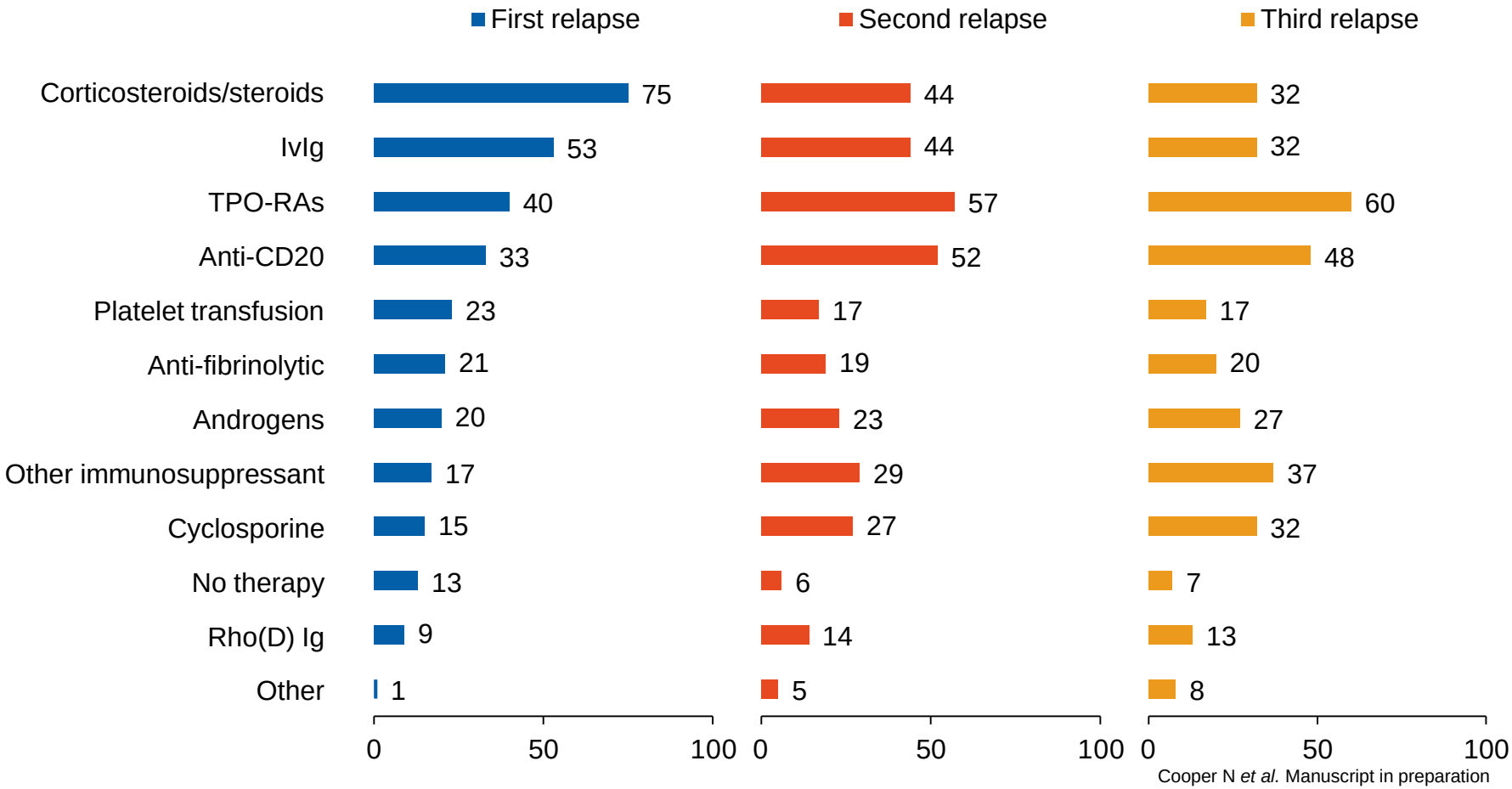
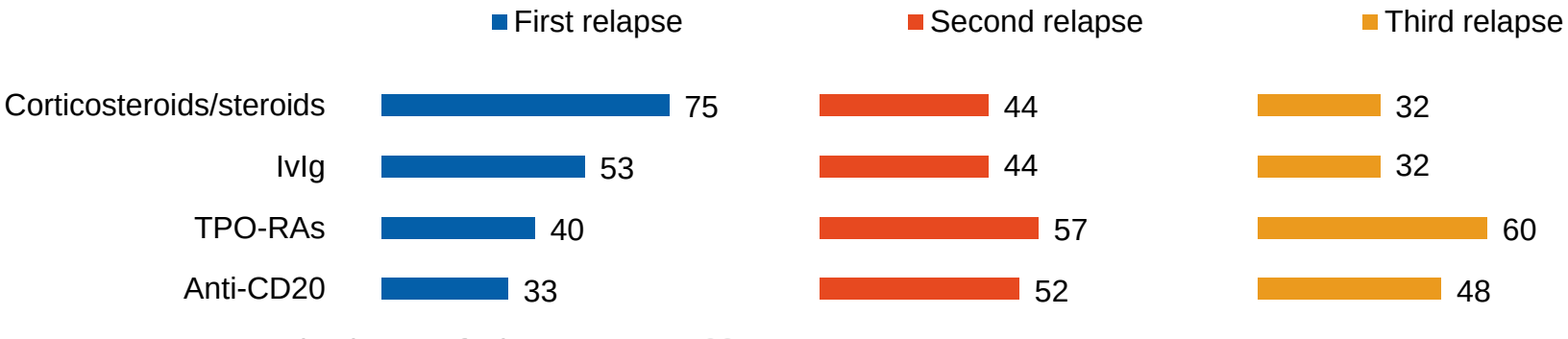
Percentage use of ITP treatments reported by physicians for relapsing patients: The I-WISh survey



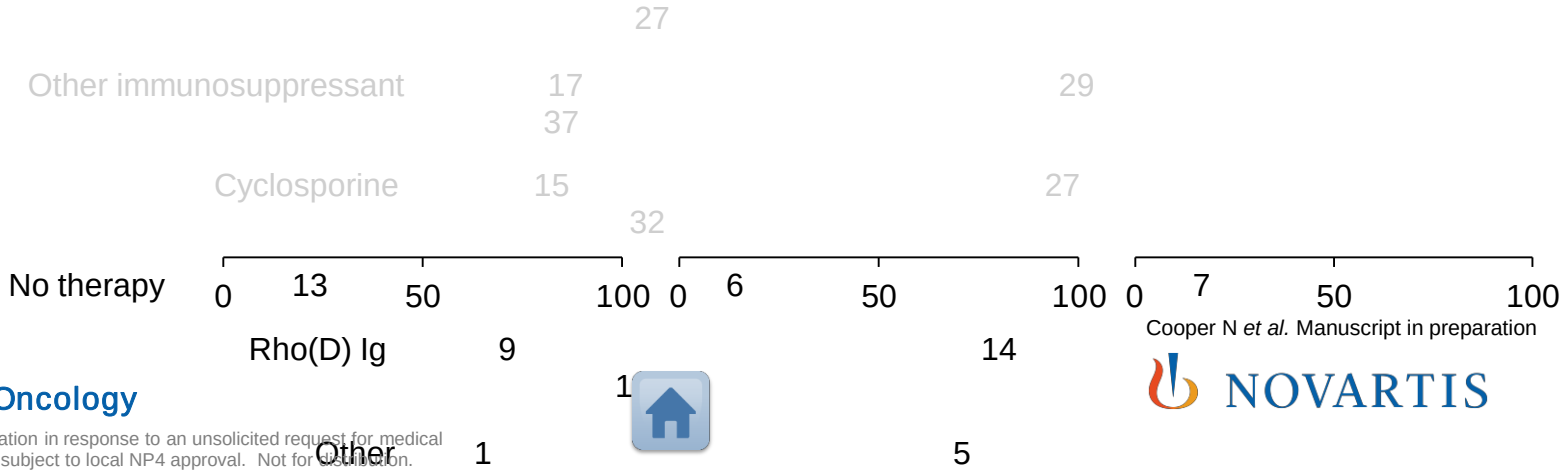
Cooper N *et al.* Manuscript in preparation

Percentage use of ITP treatments reported by physicians for relapsing patients: The I-WISh survey



Corticosteroids/steroids, IvIg, TPO-RAs and anti-CD20 dominate physician preferences overall

Following the first relapse, physicians more frequently prescribe TPO-RAs and anti-CD20, while use of corticosteroids/steroids and IvIg declines



Cooper N *et al.* Manuscript in preparation

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 For presentation in response to an unsolicited request for medical information subject to local NP4 approval. Not for distribution.

Alternative therapies should be used to mitigate the burden of repeat cycles of corticosteroids

- Selected treatments for managing chronic ITP in clinical practice were similar between the studies in Germany and Brazil, and also similar to the reports from the I-WISh survey
  - Corticosteroids were predominantly used to treat both first-line and non-responsive ITP

Considering the morbidity associated with repeated cycles of corticosteroids (see slide 12), alternative treatments are needed in clinical practice to manage ITP following initial non-responsiveness to these drugs[1]

1. Neunert C *et al*. *Blood* 2011;117:4190–4207

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The evolving therapeutic landscape for resistant/ non-responsive ITP

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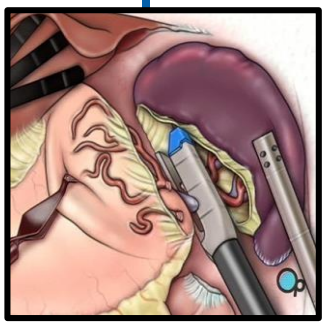
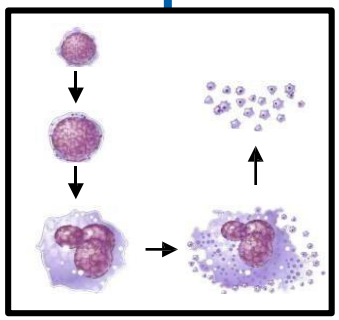
Second-line treatment options for resistant/non-responsive ITP

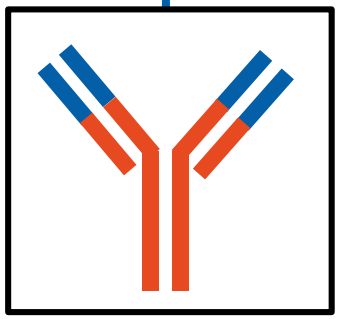
Alternative therapeutic strategies to corticosteroids for resistant/non-responsive ITP



Splenectomy



Thrombopoiesis-stimulating agents



Rituximab

Other medical therapies*

*Other therapies include mycophenolate mofetil, cyclosporin A, dexamethasone, cyclophosphamide, and danazol

Thrombopoiesis figure adapted from Kaushansky K. *N Engl J Med* 1998;339:746–754

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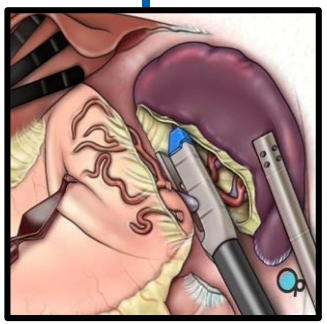
Second-line treatment options for resistant/non-responsive ITP

Alternative therapeutic strategies to corticosteroids for resistant/non-responsive ITP



Splenectomy

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Thrombopoiesis figure adapted from Kaushansky K. *N Engl J Med* 1998;339:746–754

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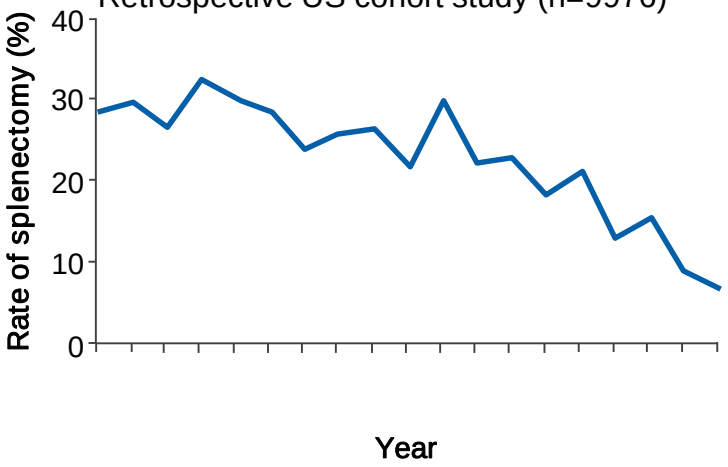
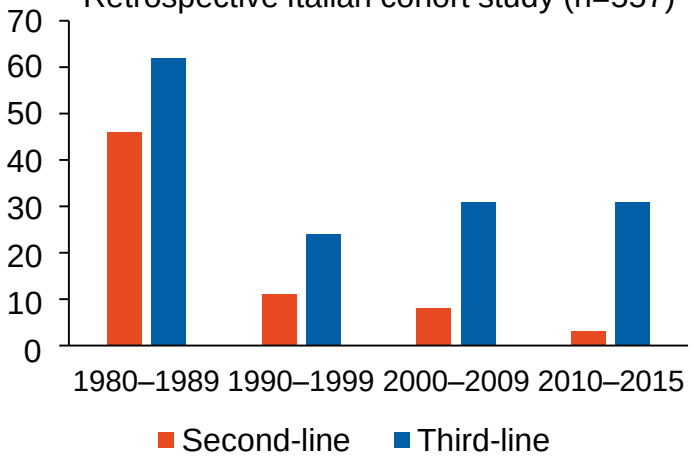
Although splenectomy can be effective, its use in patients with ITP is decreasing

- A systematic review of 1223 patients with ITP undergoing laparoscopic splenectomy showed a 5-year success rate of 72%[1]
- However, its use has been decreasing in Europe and the USA in adults because of the availability of alternative treatment options[2–4]

Retrospective US cohort study (n=9976)[2]



Retrospective Italian cohort study (n=557)[4]



- An analysis of the US National Inpatient Sample (n=37,844) showed that pediatric splenectomy rates have declined from 3.4% (2005–2006) to 1.6% (2013–2014) ($p<0.001$)[5]

1. Mikhael J *et al. Am J Hematol* 2009;84:743−748; 2. Boyle S *et al. Blood* 2013;121:4782–4790; 3. Chaturvedi et al. Blood 2018 131:1172−1182; 4. Palandri F *et al. Am J* Hematol 2016;91:E267–E272; 5. Bhatt NS *et al. Pediatr Blood Cancer* 2018;65:e27072

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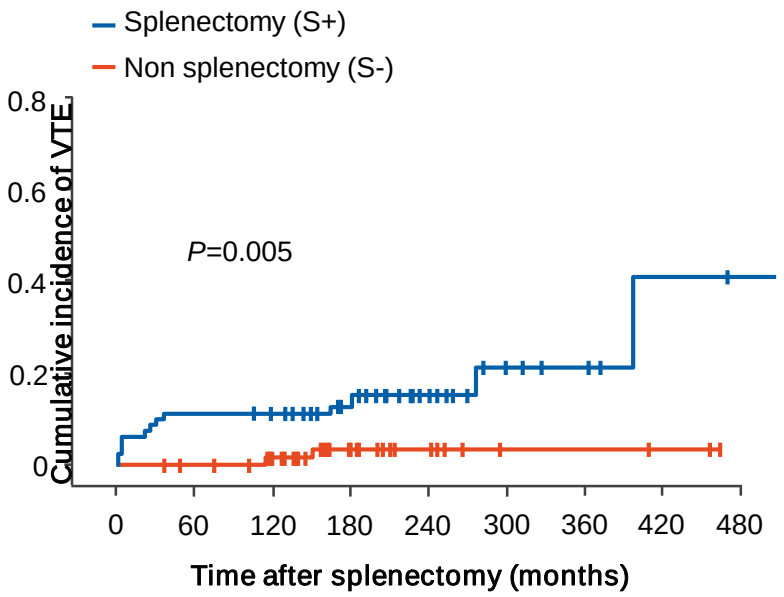
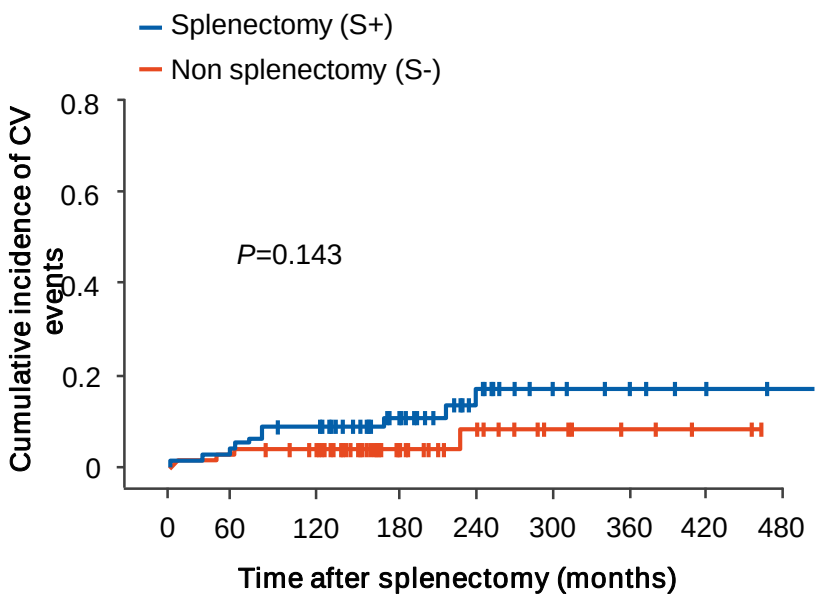
The decrease in splenectomy may be due to safety concerns and the emergence of novel medical therapies

Long-term complications of splenectomy

Venous thromboembolism



All cardiovascular events



Thai L-H *et al. Medicine (Baltimore)* 2016;95:e5098

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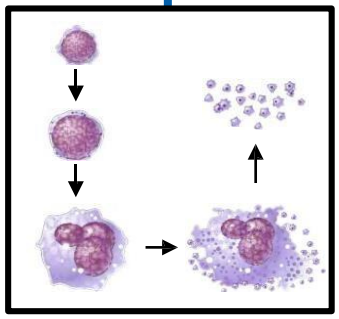
Second-line treatment options for resistant/non-responsive ITP

Alternative therapeutic strategies to corticosteroids for resistant/non-responsive ITP

Splenectomy



Thrombopoiesis-stimulating agents

Rituximab

Other medical therapies*

*Other therapies include mycophenolate mofetil, cyclosporin A, dexamethasone, cyclophosphamide, and danazol

Thrombopoiesis figure adapted from Kaushansky K. *N Engl J Med* 1998;339:746–754

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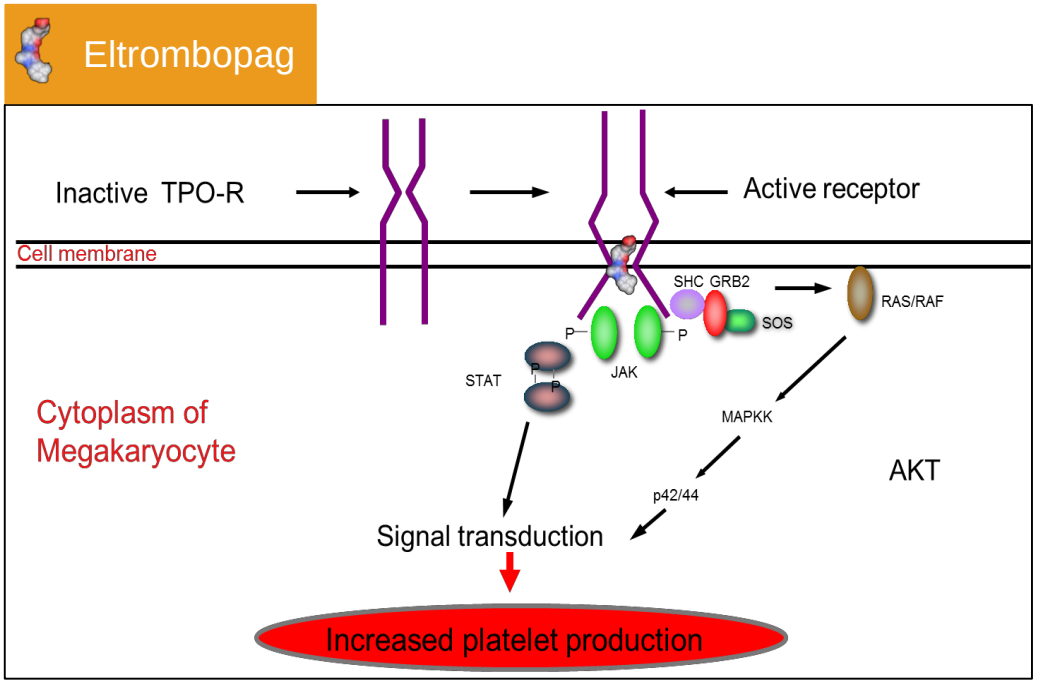
TPO-RAs for the treatment of ITP: Eltrombopag

Eltrombopag, a small-molecule, non-peptide TPO-RA, is an approved treatment option for adult and pediatric patients with resistant/non-responsive ITP*[1]



Interacts with the transmembrane domain of human TPO-R to initiate signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells

*Label update anticipated in 2019 in the European Union to state ITP duration of 6 months or more

Eltrombopag is marketed as Promacta in the US and Revolade in the EU

1. Eltrombopag US prescribing information, revised 11/2018: https://www.pharma.us.novartis.com/product/pi/pdf/promacta.pdf.
2. Eltrombopag SmPC, revised 07/2018: https://www.medicines.org.uk/emc/product/508/smpc

Figure from Kuter DJ *et al. Int J Hematol* 2013;98:10–23

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Eltrombopag for the treatment of ITP in the clinical trial setting

Adults (≥18 years)[1–3]

In three randomized, placebo-*controlled trials in adults with ITP of* ≥6 months duration, platelet response* rates of 59–79% were seen with eltombopag vs 11–28% with placebo

- Bleeding events occurred in 4–19% of eltrombopag recipients vs 13–31% of placebo recipients

Headache was the most common AE (8–30% vs 11–33%), and Grade 3/4 AEs were reported in 3–15% of eltrombopag vs 3–14% of placebo patients

Children (1–17 years)[4, 5]

In two randomized, placebo-*controlled trials in children with ITP of* ≥6 or >12 *months' duration,* platelet response* rates of 40–62% were seen with eltrombopag vs 3–32% with placebo

- Bleeding events occurred in 27–37% of eltrombopag recipients vs 55–59% of placebo recipients

Headache (30% vs 43%) and nasopharyngitis (17% vs 7%) were the most common AEs, and Grade 3/4 AEs were reported in 5–11% of eltrombopag vs 19–28% of placebo patients

*Defined as achieving a platelet count of ≥50x10^9/L; AE, adverse event

1. Bussel JB *et al*. *Lancet* 2009;373:641–648; 2. Cheng G *et al. Lancet* 2011;377:393–402; 3. Bussel JB *et al. N Engl J Med* 2007;357:2237–2247; 4. Grainger JD *et al*. *Lancet* 2015;386:1649–1658; 5. Bussel JB *et al*. *Lancet Haematol* 2015;2;e315–e325

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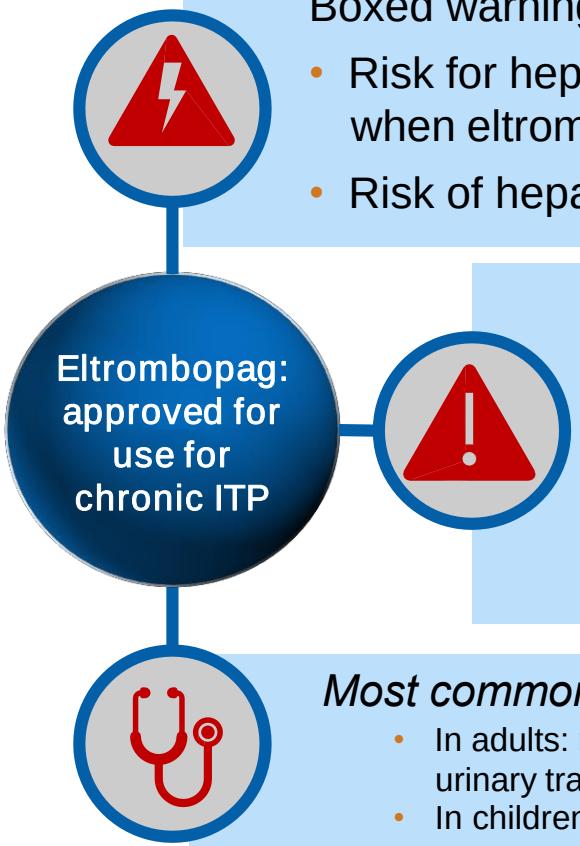
Eltrombopag: Warnings, contraindications precautions and common AEs



Boxed warning

- Risk for hepatic decompensation in patients with chronic hepatitis C when eltrombopag used in combination with interferon and ribivarin
- Risk of hepatotoxicity

- No contraindications
- Warnings and precautions
  - Hepatotoxicity
  - Increased risk of death and progression of myelodysplastic syndromes to acute myeloid leukemia
  - Thrombotic/thromboembolic complications

Most common AEs (≥5%) in patients with ITP:

- In adults: nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, urinary tract infection
- In children ≥1 year of age: upper respiratory tract infection, nasopharyngitis

ALT, alanine aminotransferase

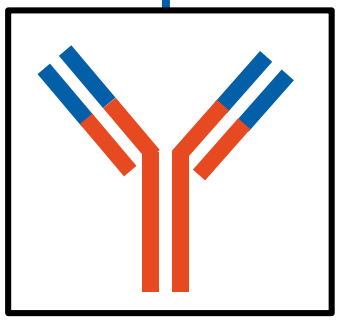
Prescribing information of SmPC available from
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207027s000lbl.pdf (accessed February 2019)
https://www.medicines.org.uk/emc/product/508/smpc (accessed February 2019)

Second-line treatment options for resistant/non-responsive ITP

Alternative therapeutic strategies to corticosteroids for resistant/non-responsive ITP

Splenectomy

Thrombopoiesis-stimulating agents



Rituximab

Other medical therapies*

*Other therapies include mycophenolate mofetil, cyclosporin A, dexamethasone, cyclophosphamide, and danazol

Thrombopoiesis figure adapted from Kaushansky K. *N Engl J Med* 1998;339:746–754

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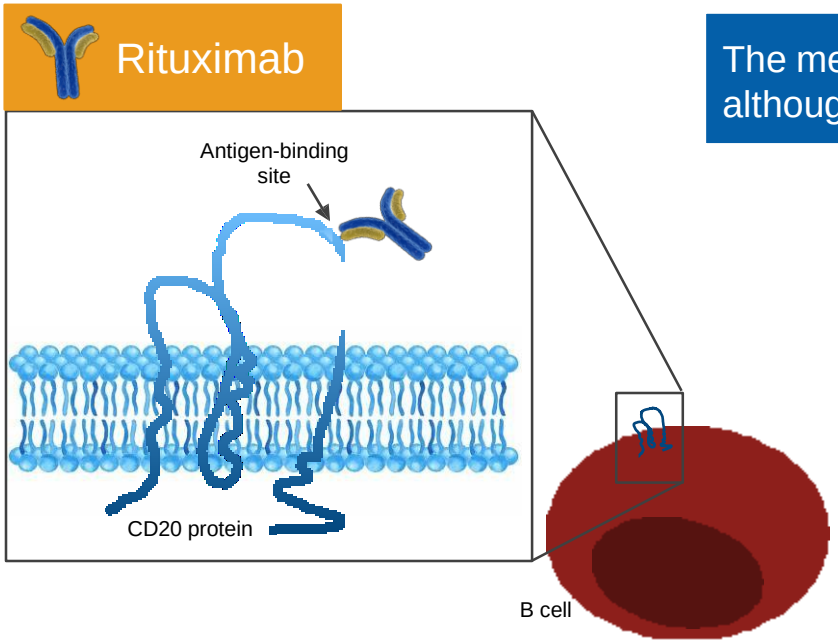
Rituximab for the treatment of ITP

Rituximab is a chimeric mouse-human anti-CD20 monoclonal antibody



The mechanism of action in ITP is not fully understood, although a number of hypotheses exist:

- Depletes CD20+ B cells and, subsequently, antiplatelet antibody production
- Changes T-helper subset ratio and improves regulatory T cell function
- Eliminates circulating and splenic B cells

Rituximab is not licensed for treating ITP (persistent or chronic) and so use for this indication is off-label

Godeau B. *Semin Hematol* 2013;50:S75–S82

Rituximab for the treatment of ITP in the clinical trial setting

Adults (≥18 years)[1–5]

In three single-arm studies and one randomized, placebo-controlled trial in adults with ITP, platelet response rates of 28–73% were seen with rituximab vs 67% with placebo

→ Bleeding events occurred in 38% of rituximab recipients vs 50% of placebo recipients

Headache (6% rituximab vs 4% placebo) and influenza (15% vs 7%) were commonly reported AEs. Grade 3/4 AEs (bleeding events) were reported in 7% vs 4% of patients. One study reported 31 deaths after a median of 30 months from the first rituximab infusion

Children (1–17 years)[6]

In one single-arm study in children with severe, chronic ITP, a platelet response rate of 31% was seen with rituximab

→ *Bleeding events were considered 'mild'*

AEs were not reported prior to 12 weeks of treatment and no AEs were reported after 12 weeks. Grade 3 AEs (bleeding) were reported in three patients

*Defined as achieving a platelet count of ≥50x10^9/L,[1,2] ≥30x10^9/L[3–5] *and* ≥2x baseline value[1,3–5] *or a platelet count of* ≥50x10^9/L during four consecutive weeks starting during weeks 9–12[6]

1. Godeau B *et al*. *Blood* 2008;112:999–1004; 2. Tran H *et al. Br J Haematol* 2014;167:243251; 3. Khellaf M *et al. Blood* 2014;124:3228–3236;4. Deshayes *et al.* EHA 2018 abst S141; 5. Ghanima W *et al. Lancet* 2015;385:1653–1661; 6. Mueller BU *et al. Pediatr Blood Cancer* 2009;52:259–262

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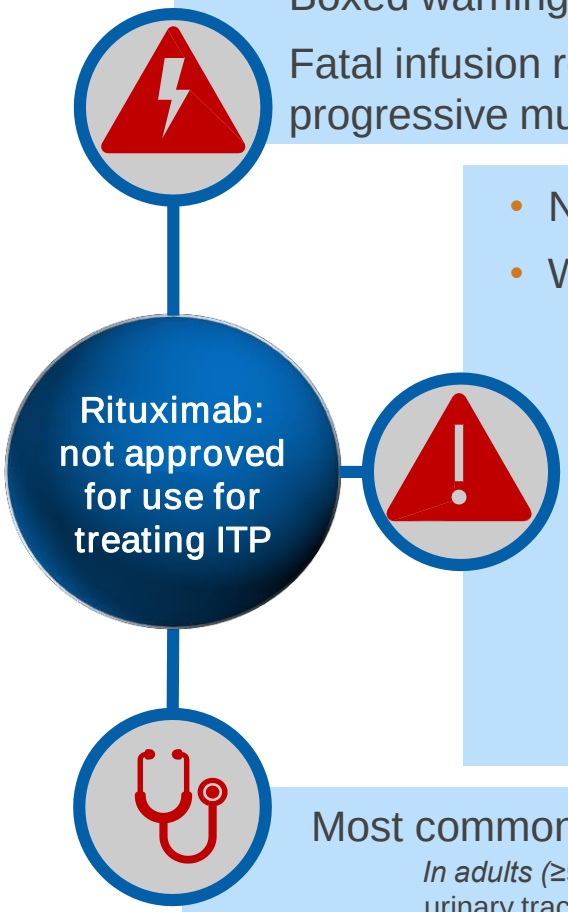
Rituximab: Warnings, contraindications, precautions and common AEs



Boxed warning

Fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML)

- No contraindications
- Warnings and precautions
  - Tumor lysis syndrome: administer aggressive IV hydration, anti-hyperuricemic agents, monitor renal function
  - PML: monitor neurological function, discontinue rituximab
  - Hepatitis B reactivation with fulminant hepatitis; monitor high-risk patients and HBV carriers
  - Infections: withhold rituximab and commence appropriate therapy
  - Monitor patients with cardiac arrhythmias and angina
  - Bowel obstruction and perforation; assess complaints of abdominal pain
  - Do not administer live virus vaccines during rituximab treatment
  - Monitor blood count at regular intervals for severe cytopenia

Most common AEs in patients with ITP:

In adults (≥5%): nausea, diarrhea, upper respiratory tract infection, vomiting, increased ALT, myalgia, urinary tract infection

- In children ≥1 year of age *(*≥10%): upper respiratory tract infection, nasopharyngitis

HBV, hepatitis B virus

Prescribing information available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207027s000lbl.pdf (accessed July 2018)

TPO-RAs and rituximab clinical trials: Summary

Based on published results of individual studies:

- Eltrombopag and romiplostim demonstrated good response rates in clinical trials
- Bleeding events appeared to be more common with romiplostim in pediatric patients
- Rituximab (not approved for treatment of ITP) showed a lower response rate than eltrombopag or romiplostim in clinical trials

There are no head-to-head trials comparing eltrombopag to rituximab or romiplostim so direct comparisons cannot be made

Real-world treatment of ITP with rituximab

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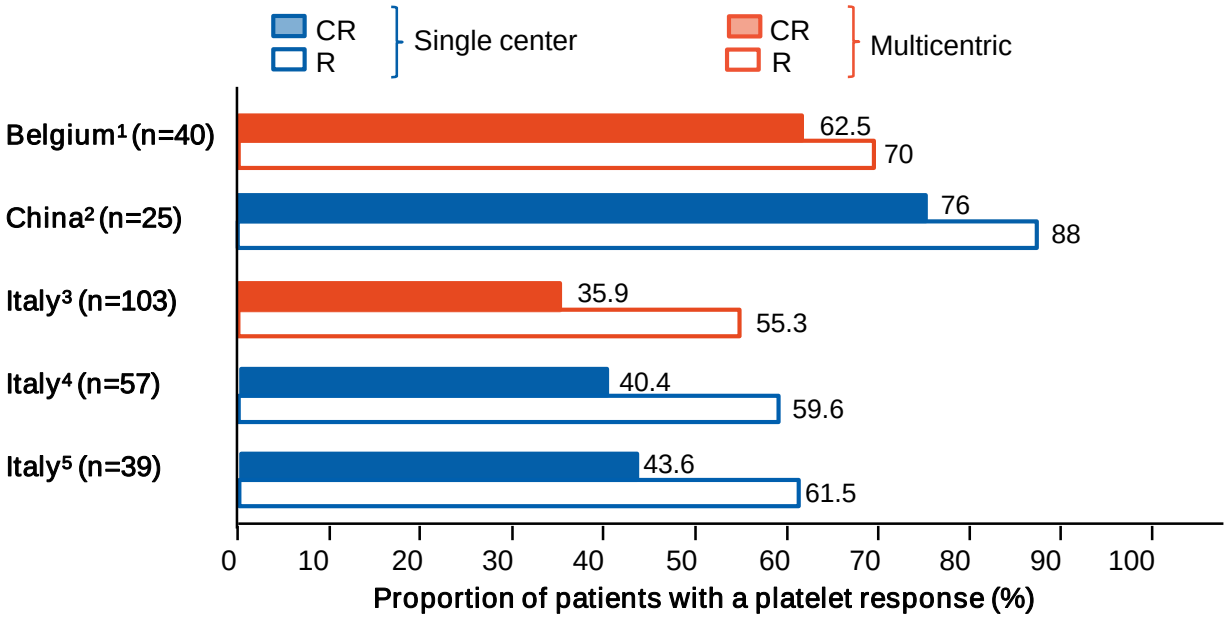
Design and characteristics of studies reporting the real-world efficacy of rituximab in ITP

Country (N)	Design	Patient population	Definition of response
Belgium (N=40)[1]	Retrospective, multicenter	• cITP • Median age 43 years (range, 9–86)	• **Response:** Platelet count 50–100 ·10^9/L • **Complete response:** Platelets 50–100 ·10^9/L without immunosuppressive drugs
China (N=25)[2]	Retrospective, multicenter	• cITP • Median age 25years)range, 12–(77	• **Response:** Platelet count 50–100 ·10^9/L • **Complete response:** *Platelets* ≥100 ·10^9/L
Italy (N=103)[3]	Retrospective, multicenter	• *c*ITP • Median age 46 years (range, 15–82)	• **Response:** Platelet count ≥30 ·10^9/L, ≥2 baseline values and without bleeding symptoms • **Complete response:** Platelets ≥100 ·10^9/L
Italy (N=57)[4]	Retrospective, single center	• cITP • Median age 47 years (range, 14–80)	• **Response:** *Platelet count* ≥30 ·10^9*/L,* ≥2 baseline values and without bleeding symptoms • **Complete response:** *Platelets* ≥100 ·10^9/L
Italy (N=39)[5]	Retrospective, single center	• *c*ITP • Median age 60 years (range, 29–91)	• *Res*ponse and complete response not defined

1. Dierickx D *et al*. *J Intern Med* 2009;266:484–491;
2. Zhang C *et al. Clin Ther* 2014;36:385–388;
3. Marangon M *et al. Eur J Haematol* 2017;98:371–377;
4. Zaja F *et al. Am J Hematol* 2012;87:886–889;
5. . Biagiotti C *et al. Haematologica* 2016;101:831

Response to rituximab in clinical practice was lower than with TPO-RAs

Real-world response to rituximab in ITP patients



Studies in clinical practice show that most patients achieve a response to rituximab, but overall, patients appeared less likely to attain a complete response

There are no head-to-head trials comparing eltrombopag to rituximab so direct comparisons cannot be made

1. Dierickx D *et al. J Intern Med* 2009;266:484–491; 2. Zhang C *et al. Clin Ther* 2014;36:385–388;
3. Marangon M *et al. Eur J Haematol* 2017;98:371–377; 4. Zaja F *et al. Am J Hematol* 2012;87:886–889;
5. Biagiotti C *et al. Haematologica* 2016;101:831

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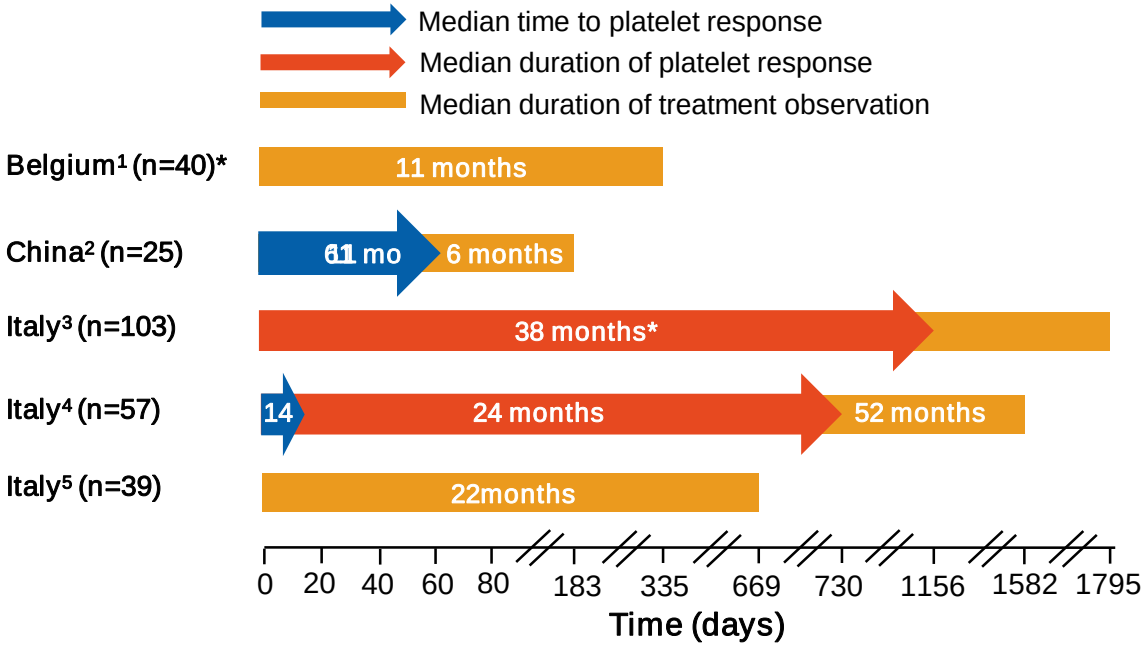
Patients achieving a platelet response maintained this response for ≥24 months



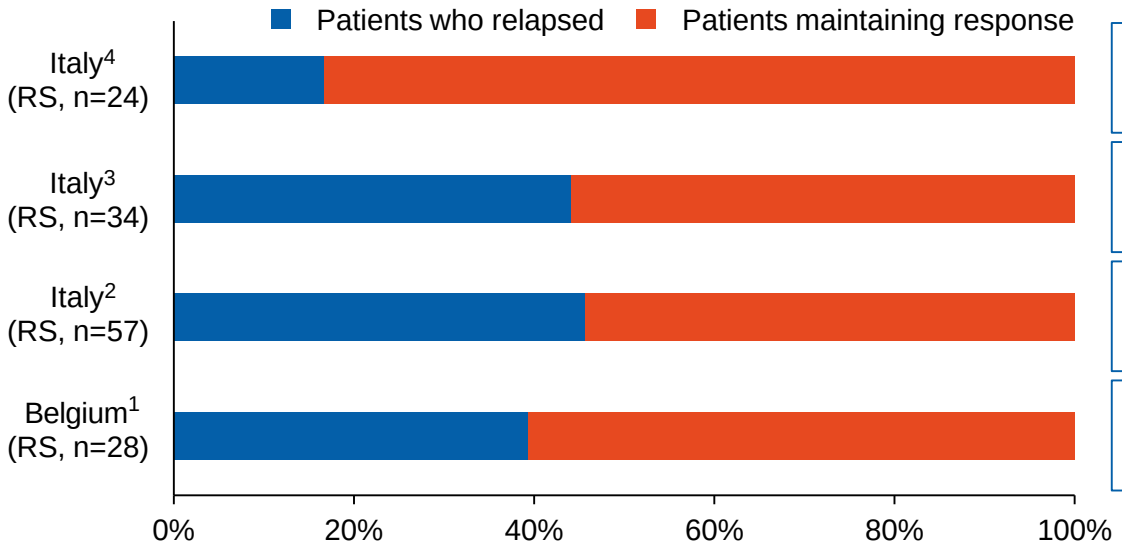
Time to response remains unclear from the contrasting results reported

*Response duration based on 31/57 responders

1. Dierickx D *et al*. *J Intern Med* 2009;266:484–491;
2. Zhang C *et al. Clin Ther* 2014;36:385–388;
3. Marangon M *et al. Eur J Haematol* 2017;98:371–377;
4. Zaja F *et al. Am J Hematol* 2012;87:886–889;
5. Biagiotti C *et al. Haematologica* 2016;101:831

Up to 46% of patients treated with rituximab relapse from response

Relapse rates* in ITP patients achieving a response to rituximab in clinical practice



Median (range) time to relapse
30 months (8–45)

Median (range) response duration
24 months (3–120)

Median (range) response duration
38 months (1–152)

Median (range) time to relapse
11 months (1–49)

Relapse rates varied between 17% and 46%; the one study to date reporting relapse rates with TPO-RAs in clinical practice documented a relapse in 29% of chronic ITP patients attaining a response to eltrombopag[5]

There are no head-to-head trials comparing eltrombopag to rituximab so direct comparisons cannot be made

*Definition of relapse not provided
RS, responders

.1Dierickx D *et al. J Intern Med* 2009;266:484–491; 2. Marangon M *et al. Eur J Haematol* 2017;98:371–;377
.3Zaja F *et al. Am J Hematol* 2012;87:886–889; 4. Biagiotti C *et al. Haematologica* 2016;;101:831
.5González-López TJ *et al. Int J Hematol* 2017;106:508–516

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Safety of rituximab in clinical practice

Most common AEs during treatment with rituximab in clinical practice in ITP patients *

Adverse event, n (%)	China (N=25)[1]	Italy (N=103)[2]	Italy (N=57)[3]
Any	8 (32)†	17 (17)	9 (16)
Serious AEs	0 (0)	5 (5)	4 (7)
Respiratory tract infection	–	–	(4) 4
Serum sickness	–	2 (2)	2 (4)
Mild dyspnea	–	–	(2) 2
Cutaneous infection	–	2 (2)	–
Hypertension	–	1 (1)	–
Gastroenteritis	–	1 (1)	–
Urinary tract infection	–	–	–
Interstitial pneumonia	–	–	1 (2)
Abdominal herpes zoster	–	–	2 (4)

During treatment with rituximab, some malignancies were reported:

- Atypical ductal hyperplasia (n=1 [1%]), diffuse large B cell lymphoma (n=1 [1%]), lymphomatoid papulosis (n=1 [1%]), and follicular thyroid carcinoma (n=1 [1%]) were reported in one Italian study[2]
- Atypical ductal hyperplasia (n=1 [2%]), tubular adenoma (n=1 [2%]), lung cancer (n=1 [2%]), and carcinoid of the appendix (n=1 [2%]) were reported in a second study in Italy[3]

The safety profile of rituximab was consistent with reports from previous long-term clinical trials[4] *although carcinomas were more commonly reported in 'real world' studies*

*AEs not reported in the study from Belgium or Italy;
†Study reported AEs of chills, fever, and respiratory symptoms in eight patients

1. Zhang C *et al. Clin Ther* 2014;36:385–388;
2. Marangon M *et al. Eur J Haematol* 2017;98:371–377;
3. Zaja F *et al. Am J Hematol* 2012;87:886–889;
4. Zhou H *et al. Blood* 2015;125:1541–1547

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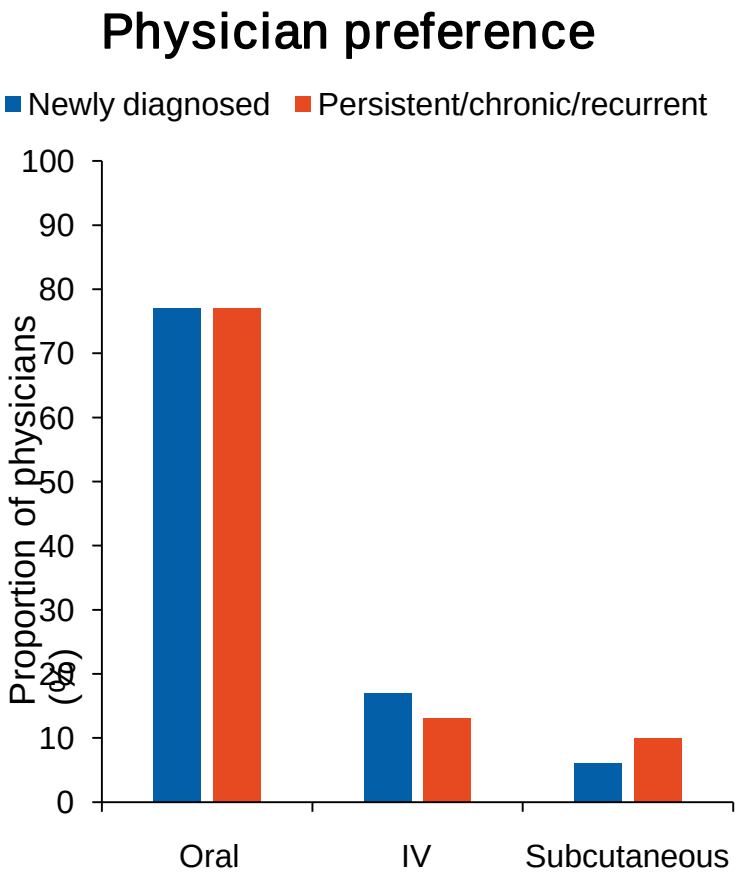
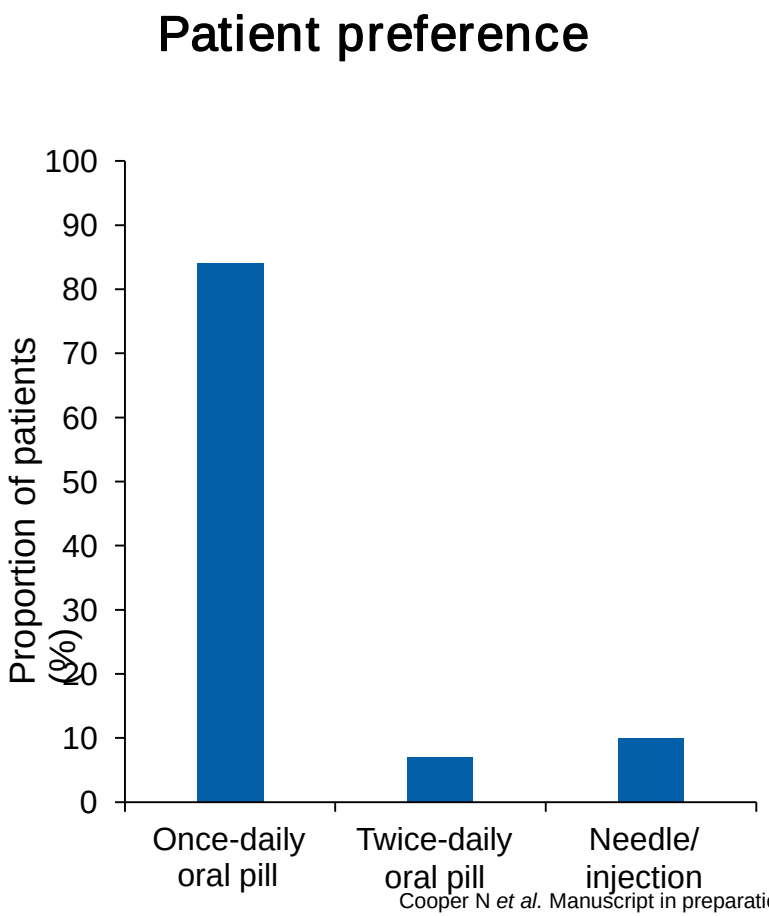
Patient and physician preference for ITP treatments

Physicians and patients indicate a preference for oral over IV or subcutaneous treatment: I-WISh survey





Cooper N *et al.* Manuscript in preparation

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Future considerations for the management of ITP in routine clinical practice

- Expand the pool of data on the effectiveness of TPO-RAs and rituximab in clinical practice to larger patient populations, describing relapse rates with TPO-RAs and confirming time to response for rituximab and romiplostim
- Assess the efficacy and safety of TPO-RAs over a longer observational period
- Examine predictive factors for achieving a durable response with TPO-RAs
- Further studies are required to ascertain the effectiveness of other therapies, such as mycophenolate mofetil and danazol, in this setting
- Given the effectiveness of TPO-RAs in treating ITP in the real-world setting, further studies are required on the effects of this class of drug earlier in the treatment cycle

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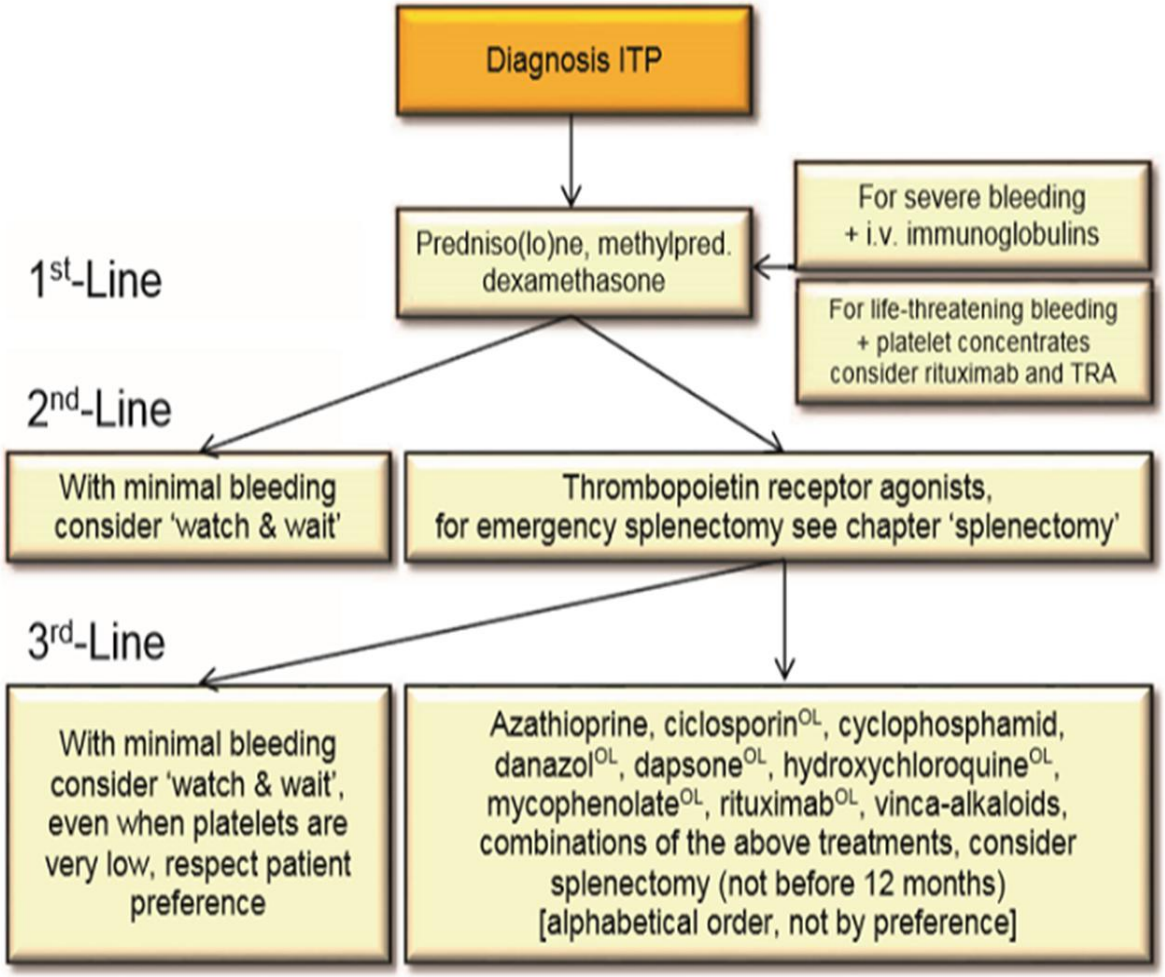

Fig. 1. Treatment algorithm (for details and special situations, see text). OL = Off-label.

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