UNIVERSITÄTS KLINIKUM jena

Klinik für Innere Medizin II

Abt. Hämatologie und Onkologie

Nichts geht mehr?
Die multipel-rezidivierte, multiresistente ITP

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Disclosures

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker	Scientific Advisory Board	Other
Novartis	X		X		X	X	
Amgen	X				X	X	
Alexion					X		
Janssen					X		
AOP					X		
Celgene/BMS							X
Sobi	X				X		
Argenx	X						
Grifols	X				X		
AstraZeneca					X		

Definition refraktäre ITP

- 2009[1]: keine Response auf Standardtherapien inklusive Splenektomie
- 2016[2]: keine Response auf Standardtherapien ohne Splenektomie
- 2020[3]: keine Response auf mind. 2 Standardtherapien (Rituximab + TPO-RA), sehr niedrige Thrombozytenwerte und Blutungszeichen
- 2022[4]: anhaltend niedrige Thrombozyten trotz Ausschöpfung aller für den Patienten zu Verfügung stehenden Therapien, unabhängig von Blutungszeichen

[1]Rodeghiero Blood. 2009, [2]Cuker Blood 2016, [3]Miltiadous Blood 2020, Vianelli Ann Hematol. 2022

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REVIEW

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Refractory immune thrombocytopenia in adults: Towards a new definition

Donald M. Arnold[1] | Bianca Clerici[1,2] | Ekaterina Ilicheva[3] | Waleed Ghanima[4,5,6]

- 20 ITP Experts of Cooperative ITP Study Group in September 2022 answered a web-based survey:
  “95% felt that there was a need for a new definition of refractory ITP for clinical and research purposes“

  - anhaltende Thrombozytopenie < 20 Gpt/l und Blutungszeichen
  - refraktär auf Rituximab, 2 TPO-RAs und 1 Immunsuppressivum
  - nur kurzes Ansprechen (< 7 Tage) auf IVIG oder Steroid

Arnold et al BJH 2023

Häufigkeit der refraktären ITP - In Abhängigkeit von der Definition

Patient group	McMaster ITP registry	Norwegian ITP registry
ITP patients in the Registry	*N* = 531 including primary (*n* = 408) and secondary ITP (*n* = 123)	*N* = 255 including primary (*n* = 236) and secondary ITP (*n* = 19)
First-line therapy[a] + any second-line[b] therapy	225 (42%)	116 (45.5%)
First-line therapy + rituximab + TPO-RA	40 (7.5%)	28 (11%)
First-line therapy + rituximab + TPO-RA + splenectomy	25 (4.7%)	8 (3.1%)
First-line therapy + rituximab + TPO-RA + any immune suppressant medication[c]	30 (5.6%)	4 (1.6%)
First-line therapy + rituximab + TPO-RA + any immune suppressant medication + splenectomy	20 (3.8%)	1 (0.4%)

Arnold et al. BJH 2020

Der (multi-)refraktäre ITP Patient

✓ Fehldiagnose - Re-Diagnostik erforderlich (!!!)

✓ Medikamententoxizität (Steroid!)

✓ hat ein hohes Risiko für Blutungen und Infektionen

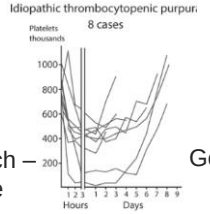
✓ Reduzierte Lebensqualität

Hohe Morbidität und Mortalität

„The mortality among refractory patients (n=37) defined as unresponsive to splenectomy, RTX, 2 TPO-RAs was 14%, all patients had been hospitalized more than once, 24% had been admitted to an intensive care unit, and 40% had developed at least one infection“

Miltiadous et al. Blood 2020; Mahevas Blood 2016

ITP – Timeline[1,2,3,4,5]



1735
Purpura haemorrhagica

1916
Erste Splenektomie durchgeführt

1950
Harrington Selbstversuch – Autoimmune Genese

1951
Kortisonbehandlung Case Report

1960-2000
Azathioprin, CSA, MMF

1980
Immunglobuline Case Report

2003
Gehemmte Thrombopoese nachgewiesen

2006
Erste Rituximab Studie

2009
Zulassung Romiplostim

2010
Zulassung Etrombopag

2016
Studie DEX vs. PSL

2019
Zulassung Avatrombopag

2020
Zulassung Fostamatinib

2022
Ph3 - Efgartigimod / Ph2 - Rilzabrutinib

2024
Ph3 - Rilzabrutinib
PH2 - Ianalumab

2025
Ph3 - Ianalumab

1 Aktuelle Onkopedia-ITP-Leitlinie; https://www.onkopedia.com/de/onkopedia/guidelines/immunthrombozytopenie-itp/@@guideline/html/index.html
2 Fachinformation Nplate®; Aktueller Stand.
3 Fachinformation Revolade®; Aktueller Stand.
4 Fachinformation Doptelet®; Aktueller Stand.
5 Fachinformation Tavlesse®; Aktueller Stand.

Markers of refractoriness to ITP treatments

splenectomy

- Older age
- Multiple previous lines of treatment
- Absence of previous response to corticosteroids and IVIg (debated)
- Low peak of platelet count after splenectomy
- Hepatic/mixed platelet sequestration on Indium-labeled autologous platelet study

rituximab

- Older age and male sex ? (debated)
- Chronic ITP (one study)
- Absence of previous response to corticosteroids (one registry)
- Absence of antinuclear antibodies (one study)

TPORAs

- Chronic ITP (debated)
- Previous splenectomy (debated)
- High TPO level in serum (debated)
- Complement activation (one study)

fostamatinib

- Used as >2nd line of treatment ? (one study)

multirefractory

- Bleeding at ITP diagnosis
- Absence of response to corticosteroids (one study)
- Presence of gammopathy of unknown significance (one study)

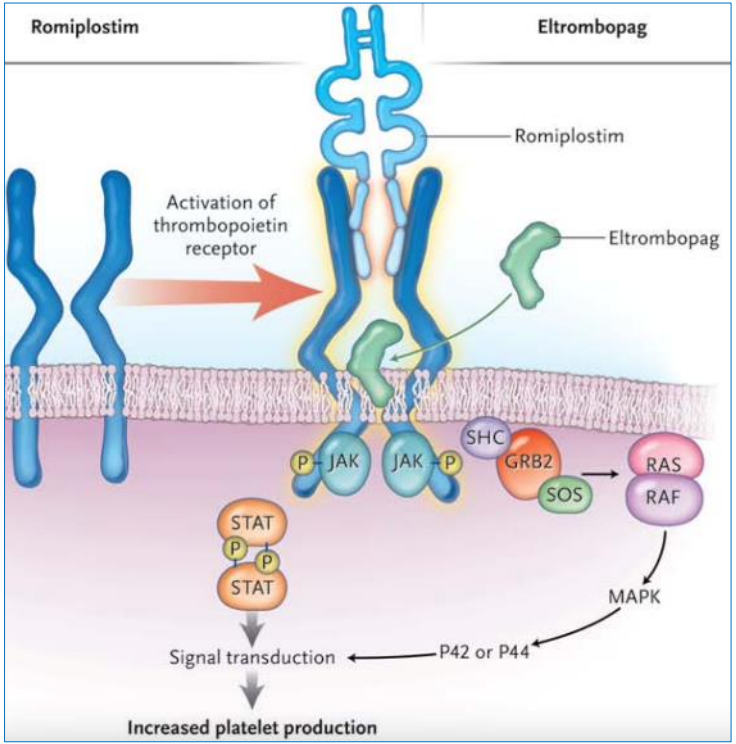
Moulis G et al BJH 2023

Thrombopoetin Receptor Agonists (TPO-RAs)

- Problem der Adhärenz
  - Orale Einnahme vs s.c. Gabe
  - Wirksamkeitsreduktion durch Nahrungsmittel

- Verschiedene Ansatzpunkte am Rezeptor

—> Keine Kreuzresistenz



Imbach P et Crowther M. *N Engl J Med* 2011;365:734-41.

Received: 1 November 2021 | Accepted: 26 January 2022
DOI: 10.1111/bjh.18081

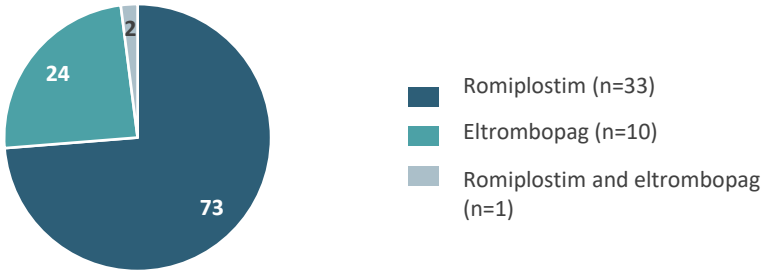
RESEARCH PAPER

Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: A multicentre US study

Hanny Al-Samkari[1,2] | Debbie Jiang[3,4] | Terry Gernsheimer[3,4] | Howard Liebman[5] | Susie Lee[5] | Matthew Wojdyla[6] | Michael Vredenburg[6] | Adam Cuker[7]

N=44 patients with cITP
median (range) age of 61
52% female
mean ITP duration of **8.3 years**

Type of treatment patients switched from prior to avatrombopag treatment (% of group; N=44)



Switched due to:

52% convenience
23/44 patients

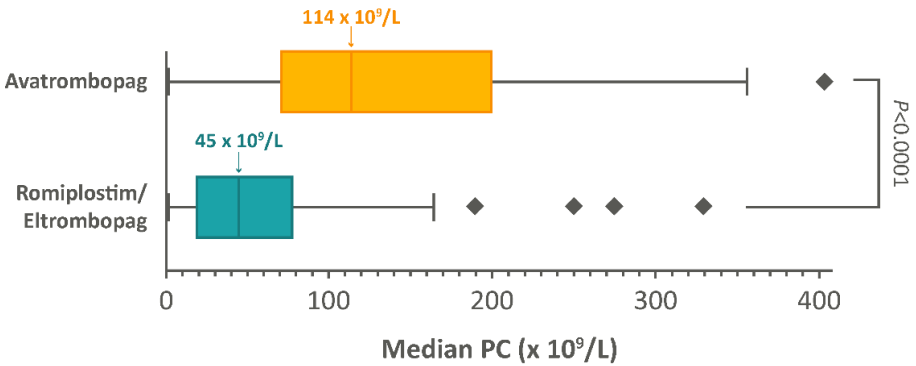
32% lack of effectiveness
14/44 patients

16% adverse events
7/44 patients

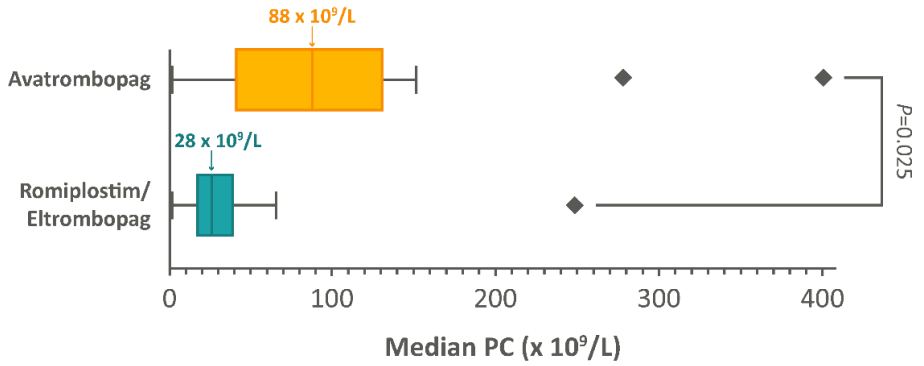
Al-Samkari et al. Br J Haematol 2022
1. Al-Samkari et al. Br J Haematol 2022

Platelet response after switching to avatrombopag from romiplostim or eltrombopag

Median Platelets, all patients (N=44)



Median Platelets, patients who switched due to ineffectiveness of romiplostim/eltrombopag (n=14)



Al-Samkari et al. Br J Haematol 2022
1. Al-Samkari et al. Br J Haematol 2022

POSTER 2596. AVATROMBOPAG PLUS FOSTAMATINIB# COMBINATION EFFICACY AND SAFETY IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

ME Mingot-Castellano[1], B Pedrote Amador[1], R Tomasello[2], W Ghanima[2]

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2.Departments of Research and Haemato-oncology, Østfold Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

INTRODUCTION

Avatrombopag (AVA) is a thrombopoietin receptor agonist (TPO-RA), approved for the treatment of immune thrombocytopenia (ITP), as second line in subjects with chronic ITP unresponsive to other treatments. At day 8, 65% patients present a reponse and global response rate of AVA is 69% with a mean duration of 12.4 weeks in its pivotal study[1].

Combination of TPO-RA plus immunosuppressive or immunomodulatory drugs could optimize treatment results in ITP, addressing different pathophysiological pathways[2]. The most widely used immunomodulatory drugs in these circumstances are steroids, azathioprine and mycophenolate. Fostamatinib (FOS) is a splenic tyrosine kinase (SYK) inhibitor. FOS blocks the cascade of signals mediated by SYK after the activation of FcγRs, reducing macrophage activity, proliferation of B lymphocytes and production of antibodies[3].

AIM

We present the experience in the **combined use of AVA with fostamatinib in non-responders to this TPO-RA**, an experience not reported to date.

METHOD

- **Retrospective, multicenter, international, observational, non-interventional** study in patients diagnosed of primary ITP who have received treatment with AVA and FOS in combination between August 2022 and June 2023.
- We included **patients who have not reached platelets >30x10e9/L after at least two weeks of treatment with daily 40mg of AVA, FOS was prescribed in combination** in these circumstances.
- Epidemiological characteristics, type of ITP, previous treatments received, starting dose, response, concomitant ITP treatment and toxicity are collected. ITP definition and response criteria are based on Provan et al[4]: Response (R) as platelets 30-100x10e9/L and complete response (CR) as platelets > 100x10e9/L.
- Data are described in percentages for the categorical variables and in medians and ranges for the quantitative ones.

RESULTS

In the period of time evaluated, **a total of 55 patients received treatment with AVA** in both Centers. The Norwegian data was acquired from the Norwegian ITP registry. In **16 of 55 patients (29%)**, there was no response after 2 or more weeks with AVA 280 mg weekly. **In 6 of these patients, FOS was combined with AVA** at a dose of 280mg weekly. Table 1. describes the characteristics of the 6 patients treated with the combination. Median time from initiation of AVA to combination with FOS was 14 days (Range: 14-21 days). **The overall response of the combination was 100% (1 R, 5 CR). Median time to R was 25 days** (Range: 3-42 days) and to CR 31 days (Range: 4-153 days). Table 2 describes the characteristics of each patient's response. With a median follow-up from the start to last follow up of treatment in combination was 212 days (Range: 45-313 days), no relapse has been identified. Tapering of AVA and/or FOS was attempted in 5 patients by reducing the dose of FOS in 1 patient and the dose of AVA in 4. In patients 1 and 4, AVA was stopped, but this resulted in drop in the platelets counts. CR was achieved after reintroduction AVA in combination.

With regard to toxicity, in the 6 patients treated with the combination AVA plus FOS, only two adverse events were described, both of them non-serious. One case of headache encountered with the use of AVA, before the initiation of FOS. The other event, was WHO grade 2 liver toxicity attributed to AVA. Hypertransaminasaemia was resolved after the interruption of avatrombopag for 6 days and reduction of AVA from 140mg to 60mg weekly.

Table 1. Patients Characteriscs

Patient	Sex	Age (years)	Phaseof ITP	Lines of treatment before AVA	Treated with TPO-RA before AVA	Treated with ELT	Treated with ROM
1	Women	22	Chronic	4	No	No	No
2	Man	28	Persistent	5	Yes	No	Yes, R***
3	Women	24	Chronic	4	Yes	Yes, R	Yes, CR*
4	Man	66	Chronic	4	Yes	No	Yes, CR**
5	Man	58	Chronic	5	Yes	No	Yes, R***
6	Man	60	Chronic	5	Yes	Yes, R***	Yes, R***

Patient	Initial weekly dose of FOS * (mg)	Type of Response	Time from combination to platelets>30x10⁹/L (days)	Time from combination to platelets>100x10⁹ /L (days)	Follow up since combination start (days)	Last weekly dose of FOS (mg)	Last weekly dose of AVA (mg)	Platelet count in last visit (x10⁹/L)
1	1400	CR	3	5	45	1400	60	383
2	2100	CR	42	112	313	2100	280	145
3	1400	CR	4	4	232	1400	60	160
4	2100	CR	24	31	159	700	60	102
5	2100	R	26	NCR	277	2100	280	44
6	2100	CR	32	153	192	2100	140	129

CONCLUSIONS

- In subjects with a lack of response to thrombopoietin analogues, the combination with immunosuppressants is an alternative to consider.
- The combination of avatrombopag and fostamatinib has been shown to be effective and safe, although longer series are needed to support these data.

REFERENCES

1. Jurczak W, Chojnowski K, Mayer J, et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. Br J Haematol. 2018;183(3):479-490.
2. Arai Y, Jo T, Matsui H, et al. Comparison of up-front treatments for newly diagnosed immune thrombocytopenia -a systematic review and network meta-analysis. Haematologica. 2018;103(1):163-171.
3. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018;93(7):921-930.
4. Provan D, Arnold DM, Bussel JB, et al Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-3817

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- Any person or institution you want to

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- Your email Waleed or from your colleagues.

Avatrombopag Plus Fostamatinib Combination Efficacy and Safety in Patients with ITP – Results

Efficacy

- Median time from initiation of avatrombopag to combination with FOS was 14 days (Range: 14-21 days).
- The **overall response of the combination was 100% (**1 R, 5 CR) with the **median time to R of 25 days** (Range: 3-42 days) and to CR of 31 days (Range: 4-153 days).
- With a median follow-up from the start to the last follow-up of treatment in combination of 212 days (Range: 45-313 days), **no relapse was identified**.

Safety

- In the 6 patients treated with the combination avatrombopag plus fostamatinib[#], **only two adverse events were described, both were non-serious.**
- One case of **headache** encountered with the use of avatrombopag, before the initiation of FOS.
- One **WHO grade 2 liver toxicity** attributed to avatrombopag. Hypertransaminasaemia

Patient	Initial weekly dose of FOS[#,*] (mg)	Type of response	Time from combination to platelets>30x10⁹/L (days)	Time from combination to platelets>100x10⁹/L (days)	Follow-up since combination start (days)	Last weekly dose of FOS[#] (mg)	Last weekly dose of AVA (mg)	Platelet count at last visit (x10⁹/L)
1	1400	CR	3	5	45	1400	60	383
2	2100	CR	42	112	313	2100	280	145
3	1400	CR	4	4	232	1400	60	160
4	2100	CR	24	31	159	700	60	102
5	2100	R	26	NCR	277	2100	280	44
6	2100	CR	32	153	192	2100	140	129

Mingot Castellano ME, Presented at ASH 2023, Poster #2596.

Avatrombopag Plus Fostamatinib Combination Efficacy and Safety in Patients with ITP – Conclusions

Authors Conclusion

- In subjects with a lack of response to thrombopoietin analogues, the combination with immunosuppressants is an alternative to consider.
- The combination of avatrombopag and fostamatinib # was shown to be effective and safe, although longer series are needed to support the presented data.

My Conclusion

- Interesting therapy concept for multirefractory patients:
    - 2 weeks Avatrombopag -> combination with Fostamatinib

Mingot Castellano ME, Presented at ASH 2023, Poster #2596.

CASE III - 65-YEAR-OLD WOMAN

Immune thrombocytopenia, first diagnosis 12/2013

- WHO bleeding grade 0, thromb. 5 Gpt/l
- Prednisone McMillan 1mg/kg – complete remission

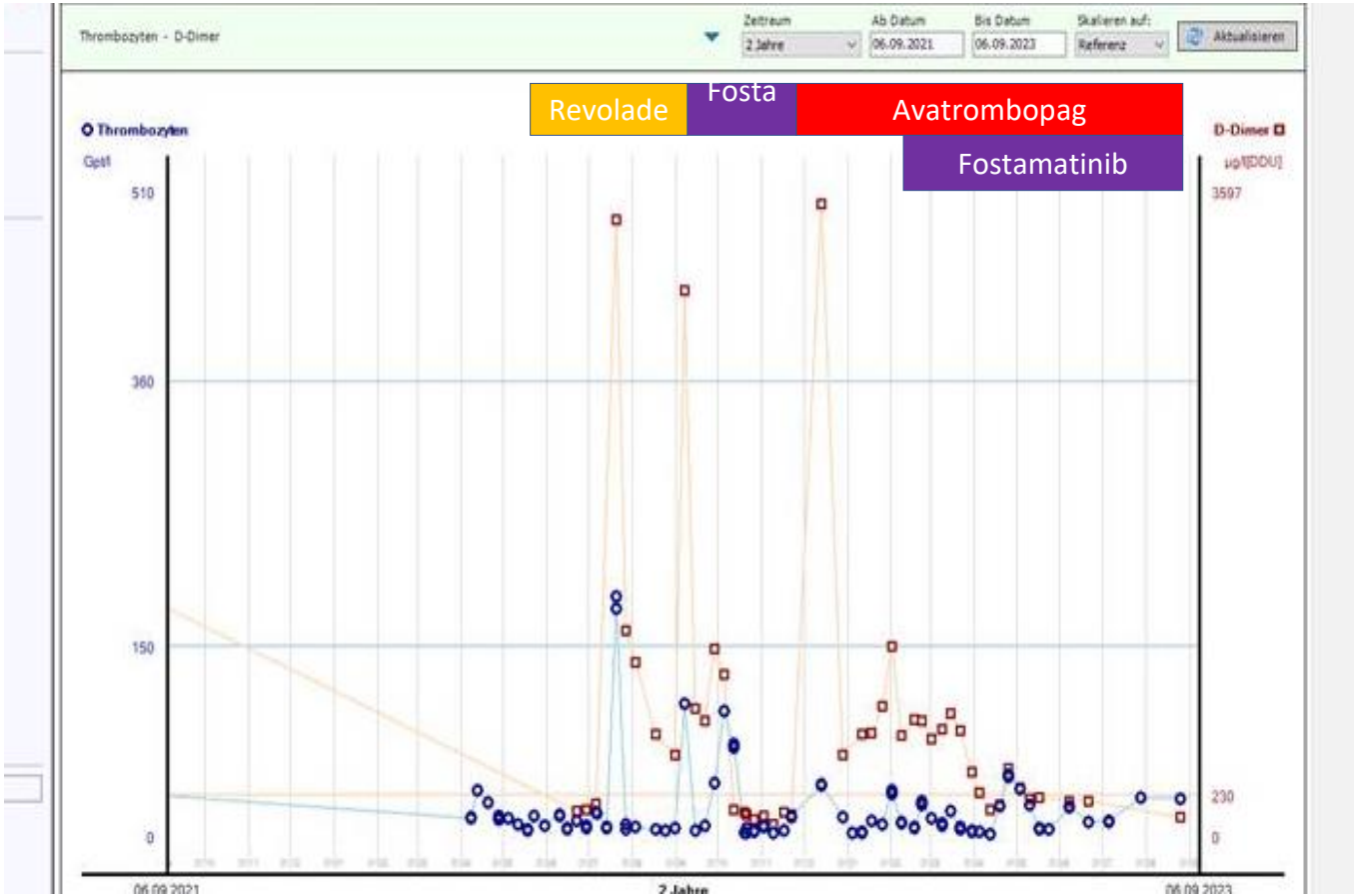
- **Thromboembolic events:**
  - Sinus vein thrombosis ´2012
  - DVT and pulmonary embolism ´2015
  - 2015: low molecular weight heparin -> subsequently rivaroxaban

CASE III - 65-YEAR-OLD WOMAN

- **Relapse: 12/17 Thromb. 7 Gpt/l**
  - **start PSL 100 mg TD, Maintenance therapy alternating 5 - 40 mg**
- **04/19 Influenca Infection : Thromb. 39 Gpt/l -> Prednisolone 50mg**
- **02/20 Thromb. drop to 12 -> 70g Ivlg**
  - **no Prednisolone due to gastritis and mood disorder**
- **03/20 - 04/20 4x Rituximab (weekly)**
- **10/20 Splenectomy**
- **04/22 Platelet drop since July 2021, Thromb.10g Gpt/l, Rivaroxaban stopped**

What now?

CASE III - 65-YEAR-OLD WOMAN



„Klassische“ Immunsuppressiva[1]

Azathioprin	Dosierung 1mg/kg/Tag -> 2mg/kg/Tag Die Therapie spricht langsam an und sollte mindestens 3–4 Monate gegeben werden. Ansprechraten 30-40%[2] Neutropenien sind häufig (ca. 30%)
Cyclosporin A	Ein CSA-Zielspiegel von 150–400 ng/mL wird angestrebt - 3-5 mg/kg/Tag Die Therapie spricht langsam an und sollte mindestens 2–3 Monate gegeben werden Nur Fallserien publiziert. Häufige Nebenwirkungen sind Erschöpfung, Schwäche, Niereninsuffizienz, Hypertonie, Neuropathie
Mycophenolat-Mofetil (MMF)	Zur besseren Verträglichkeit beginnt man in der Regel mit einer niedrigen Dosis und steigert dann langsam - 500mg/Tag -> 1g/Tag Ansprechraten 30-50%[3] Häufig sind gastrointestinale Nebenwirkungen wie Übelkeit, Appetitlosigkeit, Durchfall, Erbrechen

[1]Matzdorff et al. Oncol Res Treat 2022
[2]Mishra K et al. Am J Blood Res. 2021
[3]Abdelwahab OA et al. Clin Rheumatol. 2024

PERSPEKTIVEN IN DER BEHANDLUNG DER REFRAKTÄREN ITP

Fcn-Rezptor-Inhibitoren

- Efgartigimod i.v.
  - Zulassung möglich, s.c. Studien negativ

Koneczny I, Herbst R. Cells. 2019;8(7):671

BTK-Inhibitoren

- Rilzabrutinib
  - Phase 2 positiv, Phase 3 - Plenary ASH 2024

BAFF-Rezeptor Antikörper

- Ianalumab
  - 1st/2nd line - Phase III ongoing; >2nd line - ASH 2024

Komplementinhibitoren

- Sutimlimab
  - PH2 positiv - aber keine Weiterentwicklung geplant
  - Fatigue und ggf. bei C3, C4, and CH50 Mangel ??

CAR-T-Zelltherapie

- Erste pos. Heilversuche, pos. Studie China - ASH 2023

Since 2022 - German ITP-Registry

Leadership
Dr. med. T. Stauch
Dr. med. K. Trautmann-Grill

Steering Group
Prof. A. Matzdorff
PD Dr. med. Oliver Meyer
Dr. med. J. Middeke
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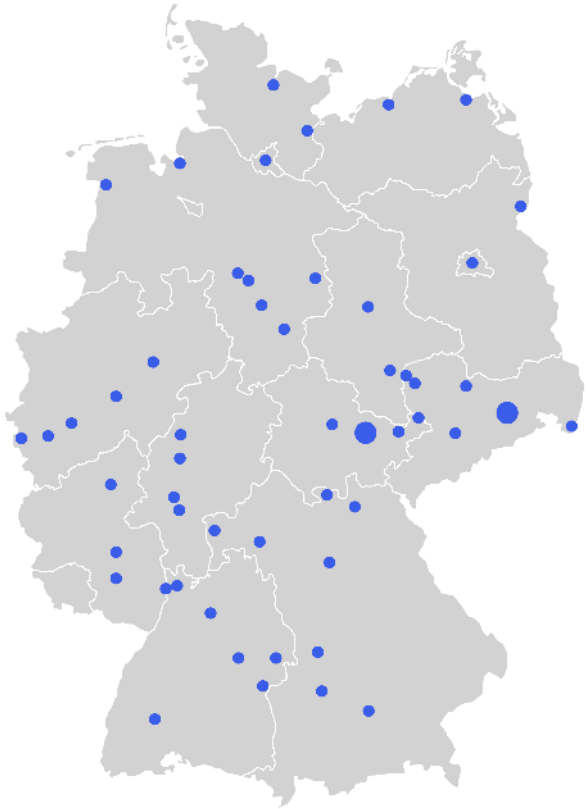

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