Immune thrombocytopenia: exploring antibodies, scintigraphy and immune modulation. Moving towards a new era for patients with ITP

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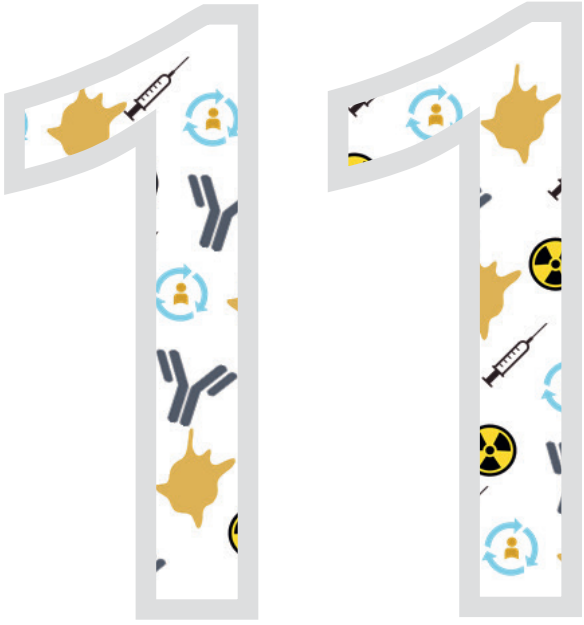


Chapter 11

General Discussion

Sufia N Amini

Introduction to discussion

This thesis examines the role of anti-glycoprotein antibodies in relation to sequestration and destruction of platelets using platelet scintigraphy, the role of TPO-receptor agonists in possible tolerance induction and treatment free remission in ITP patients. Furthermore, this thesis investigates the use of patient reported outcomes (PROMs) to eventually implement these into clinical practice. In this final chapter the main findings of this thesis will be summarized, discussed and interpreted per aim. The clinical implications and suggestions for future research are discussed. Lastly, we will look ahead to how a new era for ITP patients could look like.

This chapter will shortly state the research question and currently literature per theme and then discusses the results found per chapter.

Main findings, discussion and relevance per aim

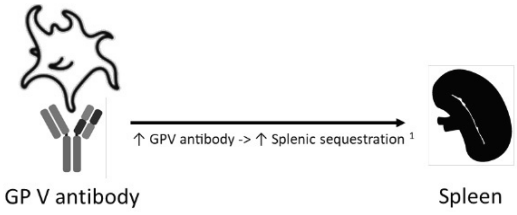
Theme 1a: Pathophysiology: the role of Glycoprotein antibodies (II-IV)

Question: What is the role of anti-glycoprotein antibodies in relation to platelet site sequestration and endogenous TPO level?

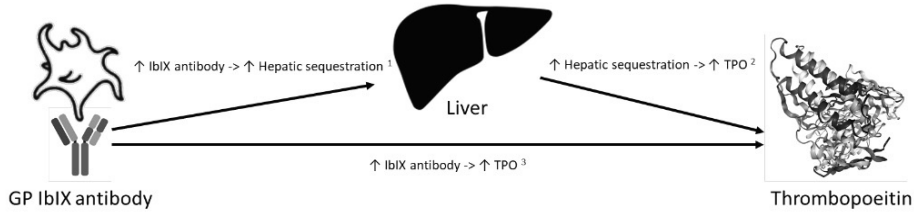
Literature: There is paucity of in vivo studies on the role of anti-glycoprotein. It is unknown if the presence and type of anti-glycoprotein antibodies is associated with platelet sequestration site. There is conflicting data on the association between anti-glycoprotein Ib and TPO levels.

Chapter II In chapter 2 we studied the possible associations between GP-antibodies and Indium-111 labelled sequestration pattern and clearance rate. We found a significant association between platelet sequestration site and anti-GPV antibodies (β 0.011 (95% CI 0.001 - 0.021), p=0.034). β-coefficients for anti-GPIIb/IIIa and anti-GPIb/IX antibodies was 0.003 (95% CI -0.009-0.015) p=0.635 and 0.001 (95% CI -0.012-0.014) p=0.853 respectively. Multivariate models, including age, sex, platelet count and treatments confirmed the results. Furthermore, we found an association between splenic sequestration and faster clearance in patients with GP-antibodies. Our data suggest that patients with a predominant / or mixed hepatic clearance have a higher prevalence of GPIb/IX antibodies. Until recently, it was thought that GPV and Ib/IX similarly enhanced non-Fc mediated clearance in the liver. Our study however, suggests that antibodies against GPV are more associated with platelet clearance in the spleen and probably having a distinct effect in ITP pathophysiology. (1)

Figure 1 – Simplified visual representation of the hypothesized pathways and associations between glycoprotein (GP) antibodies, platelet sequestration (in spleen or liver) and thrombopoietin levels.



1 Association found between GP V antibody levels and increased splenic sequestration of platelets.



Footnote:

1 Association found between GP IbIX antibody levels and increased hepatic sequestration of platelets.

2 Association found between hepatic sequestration and increased TPO levels.

3 Direct association between GP IbIX antibody levels and increased TPO levels.

Chapter III In Chapter 3 we more specifically studied the association between GPIb/IX-platelet antibodies, the site of platelet sequestration, and TPO levels in a cohort of ITP patients. Interestingly, a positive association was observed between GPIb/IX-antibody levels and TPO levels (β 0.092 [95% CI 0.012-0.172], p=0.03), and GPIb/IX-antibodies and hepatic sequestration (β 0.026 [95% CI 0.006 – 0.045], p=0.02), in patients with severe thrombocytopenia (< 25 x 10^9/L), but not in patients with mild or moderate thrombocytopenia. Moreover, hepatic sequestration and TPO levels were positively associated (β 0.228 [95% CI 0.126 – 0.331], p=0.002). This is the first human study that suggests that that under severe thrombocytopenic conditions, GPIb/IX-induced platelet-desialylation induces hepatic clearance via the Ashwell Morel Receptor, which in turn results in increased TPO-levels. However, one must keep in mind that these data involve a limited number of patients which prohibits strong conclusions. Notwithstanding this, our findings confirm animal studies on the pathophysiology of ITP and could ultimately help the development of new individualized treatment options for patients suffering from ITP. (2)

Chapter IV Chapter 4 describes a short report of a novel case of adalimumab (TNFα-inhibitor) induced ITP in which anti-glycoprotein antibodies were present, while other causes of thrombocytopenia were ruled out. After stopping adalimumab the platelet counts restored to normal. The potential mechanism leading to this type of thrombocytopenia in this case is not described in the current literature, and could be due to 1) interaction with the platelet membrane, 2) causing conformational change of the platelet membrane or 3) due to induction of Th1/Th2 imbalance, leading to antibody production by enhancing Th2.

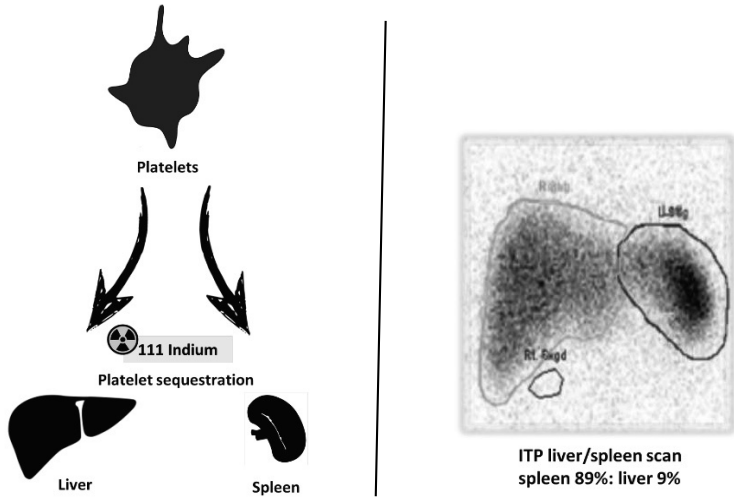
Theme 1b: Pathophysiology and prognosis: the role of platelet scintigraphy (V-VI)

Question: Which tools can aid in treatment choice and response? What is the role of platelet scintigraphy in the decision to perform a splenectomy?

Literature: There is only sparse clinical data on the association between platelet scintigraphy and clinical outcomes in ITP patients; and sequestration studies are not performed at a large scale in ITP patients before performing a splenectomy.

Chapter V In chapter 5 we systematically review the association between platelet sequestration patterns as measured by scintigraphy and post-splenectomy platelet response. In this chapter a meta-analysis was performed to gain insight in the strength of this association. We found that the response rate after splenectomy was highest in patients with a predominantly splenic pattern: 87.1 % in splenic versus 47.1 % in mixed and 25.5 % in hepatic patterns. Pooled data of 8 studies showed an odds ratio of 14.21 (95 % CI: 3.65-55.37) for response in splenic vs. hepatic clearance. This strong association should be interpreted with caution, since most studies were retrospective and heterogeneous in their methods. The critical question if a splenectomy should only be performed in patients with a splenic platelet sequestration remains to be studied in an adequately powered prospective trial. Moreover, in such a trial the scintigraphy result should be blinded for both patient and physician to ensure that the effect of a splenectomy can be studied in patients without a predominantly splenic clearance pattern . Although the latter study is critical for assessing the actual predictive power of scintigraphy, the mechanistic principle of this assay can already helpful in the decision making for patients and clinicians.

Figure 2 Visual summary of ^{111}Indium autologous platelet sequestration scintigraphy (left) and actual imaging from a patient (right).



Footnote: Platelet sequestration in Immune Thrombocytopenia has been visualized using 111 Indium labeled autologolous platelets.

Chapter VI

There is a need for tools that support the decision making process for the indication of splenectomy in patients with chronic immune thrombocytopenia. This study was designed to describe the methodology and additionally to test the robustness of the Indium-111 scan by measuring the interobserver variability and showed substantial to excellent agreement between two nuclear medicine physicians. Besides being of use in the decision making process before splenectomy, scintigraphy helps to understand the pathophysiology of ITP and eventually distinguishing different types of ITP.

Theme 2: Treatment: the role of TPO-receptor agonists (VII-VIII)

Question: Can we taper and eventually stop TPO receptor agonists after one year of treatment and is the treatment free remission due to TPO-RA induced immune modulation? Can we use TPO receptor agonists for peri-operative bridging?

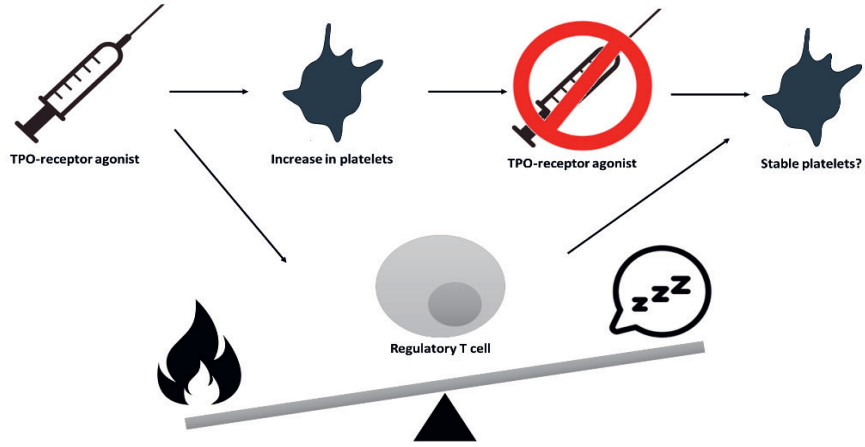
Literature: There is data indicating that TPO-RA can be stopped with prolonged platelet response after stopping. However, an adequately powered trial is lacking. The safety and efficacy of TPO-RA used for raising platelets before elective surgery had not yet been investigated in a clinical trial. There is no recent meta-analysis on thrombosis risk associated with TPO-receptor agonists.

Chapter VII Chapter 7 describes the STIP study protocol on the discontinuation of TPO-RA treatment. TPO-RAs have been designed to stimulate megakaryopoiesis and thus inducing higher platelet count. These drugs, however, are thought to be a lifelong treatment. In recent years, TPO-RA tapering and discontinuation showed a surprisingly high proportion of successful remission after stopping TPO-RA's, with 30-40% of patients having stable platelet counts after discontinuation of TPO-RA's. The mechanisms for this possible immune modulatory effect of TPO-RA's is unknown. This study aims to get insight in the pathophysiology of immune functions in ITP and the sequestration pattern of platelets in ITP pre- and post TPO-RA treatment. Understanding the pathophysiology of immune modulation and tolerance via TPO-RA can not only help patients with chronic ITP, but also ITP patients with acute or persistent ITP who may have an easily reversible immune status.

Chapter VIII Chapter 8 describes the STIP study protocol on the discontinuation of TPO-RA treatment. TPO-RAs have been designed to stimulate megakaryopoiesis and thus inducing higher platelet count. In this regard, these drugs, are thought of as lifelong treatment. However, in recent years, TPO-RA tapering and discontinuation surprisingly showed a high proportion of successful remission after stopping TPO-RA's, with 30-40% of patients having stable platelet counts after discontinuation of TPO-RA's. The mechanisms for this possible immune modulatory effect of TPO-RA's is unknown. This STIP study aims to get insight in the

pathophysiology of immune functions in ITP and the sequestration pattern of platelets in ITP pre- and post TPO-RA treatment (Figure 3) . Understanding the pathophysiology of immune modulation and tolerance via TPO-RA can not only help patients with chronic ITP, but also ITP patients with acute or persistent ITP who may have a more easily reversible immune status.

Figure 3 Visual summary of the Stopping TPO-receptor agonists in ITP Patients (STIP) study, including a possible pathophysiological pathway via immune modulation of regulatory T cells.



Footnote: TPO-receptor agonists are given to patients which may increase their platelet count. After 1 year, the TPO-receptor agonist is tapered off. Literature shows that a substantial number of patients have a persistent stable platelet count after discontinuation of the TPO-receptor agonist. The hypothesis include immune modulation of regulatory T cells by TPO-receptor agonists leading to an increase of regulatory T cells leading to more balance in the immune status of the patient.

Chapter IX

Chapter 9 describes the results from the BRIDGING-trial, a randomized, open-label trial to establish whether perioperative eltrombopag was non-inferior to intravenous immunoglobulin in ITP patients to raise platelet counts. In the intention-to-treat analysis, platelet count targets were achieved for 30 (79%) of 38 patients assigned to eltrombopag and 22 (61%) of 36 patients assigned to intravenous immunoglobulin (p non-inferiority=0·005). The non-inferior result suggests that either eltrombopag or intravenous immunoglobulin are reasonable treatment options to increase platelet counts for bridging to surgery. The decision to choose one over the other should hence depend on other factors including patient preference, cost, and individual risk profiles.

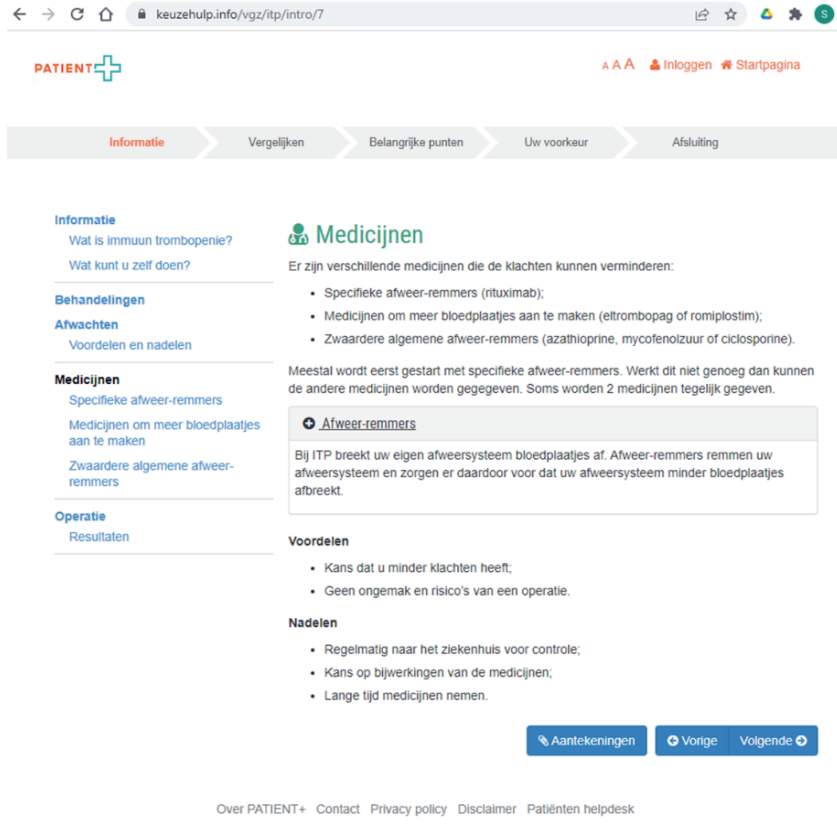
Theme 3: Implementation: PROM, guidelines and decision-making (X)

Question: Can we develop an ITP tailored patient reported outcome measure and decision making tool for Dutch ITP patients?

Literature: There is no PROM or easily accessible treatment decision aid for Dutch ITP patients, in contrast to other countries. (3) Furthermore, the Dutch guideline for ITP was over 7 years old, not including the vast recent literature on TPO-RA, scintigraphy, platelet antibodies and more.

Chapter X Chapter 10 shows local and national initiatives of our research group for implementing new scientific work in the clinical use. Patient reported outcome measures were developed in close cooperation with the Dutch ITP Patient Organization. Stakeholders included hematologists, nurses, researchers, ITP patient representatives and VBHC/PROMs consultants from the Decision Group. Further we developed a web based decision aid to help patients with their treatment choices. Lastly, the Dutch National ITP Guideline has been updated with the newest insights for diagnostics and treatment of ITP patients, and has been adopted and implemented by the Dutch Association of Hematology (NVvH).

Figure 4 Decision-aid for Dutch ITP patients, printscreen



Footnote: This page shows a sample of the decision aid (in Dutch) for ITP patients.

Clinical implications and future research

"ITP is a disorder that usually follows a benign route but every hematologist in practice has witnessed ITP with a shattering, tragic, and bloody course." – Sholzberg M. (4)

This thesis highlights the route from pathophysiology to treatment and implementation of new ways to look at patients with ITP.

What is important to move toward a new era in diagnostics and treatment in ITP?

Pathophysiology

Immune thrombocytopenia (ITP) is no longer known as "idiopathic thrombocytopenic purpura" as this is no longer an idiopathic disease and patients usually don't present with purpura. (5) New possible pathways are presented in this thesis, but ITP remains a disease with a complex and heterogenous pathophysiology. Antibody-mediated pathways has been the most researched and referenced since the Harrington–Hollingsworth experiment. (6, 7)
In this thesis we found two new associations between different anti-glycoprotein antibodies, sequestration pattern and TPO-levels. These results seem to support distinct pathophysiological pathways between anti-GPV antibodies and splenic clearance, and between anti-GPIb/IX antibodies and liver clearance & additional TPO production. These findings point to new pathophysiological pathways, however they need to be reproduced in larger prospective cohorts to draw definitive conclusions. Future studies must make the translation from the laboratory to clinical relevance for ITP patients. This theses found several pathogenic mechanisms regarding platelet glycoprotein, platelet sequestration sites and TPO levels. These immunological studies could aid in the change of moving from the understanding of primary ITP as a heterogeneous disease per exclusion into (multiple) new diseases with a specific diagnosis and pathophysiology.
New tools, such as bio-assays and scans could aid in discriminating different types of heterogenous disease. (7, 8) Furthermore, by combining these tools with real life clinical (prognostic) data, a more personalized treatment plan can be developed.
In this thesis we showed the association between the indium labeled platelet scan and the results from splenectomy, as well as antibodies and TPO-levels. Future studies are needed to better understand the pathophysiological role of the site of platelet sequestration, both in ITP patients as well as in healthy volunteers. Furthermore, the (long-term) effects of immune therapy on bio-assays should be studied to better understand immune modulatory effects.

Treatment

The future of treating ITP will probably be a shift from standardized treatment lines to a more personalized approach in which treatment success can be predicted and where patient preference should play a larger role. The change from only having broad immunosuppressive agents to having possible immune modulating drugs such as TPO-receptor agonists with good tolerability, safety and effectivity. (9) However, these agents are still expensive and not globally accessible. In the Netherlands these agents are now being used for more than a decade and their use is just now becoming more common in the use for second or third line therapy. (10) Studies examining the use of TPO-receptor agonist in the first line are on-going (11, 12), whilst splenectomies are performed less. (13) As TPO-RAs lose their patents in the next decade, these drugs eventually will become more affordable and accessible for more patients. The studies for the effective use of these agents in the first line might help patients to spare on corticosteroid use and research is needed per specific patient group for success rate in treatment options to aid in clinical decision making. (7, 14, 15)

Furthermore, the choice of which TPO-RA to use is difficult, since there are currently no studies that have performed a head-to-head comparisons between different kinds of TPO-RA. These studies could also aid in the better understanding of the possible immune modulatory effect of TPO-RA's. Lastly, tapering of TPO-RA need to be investigated in long-term immune-monitoring studies and translated into clinical guidelines. (16)

Implementation

Impact of ITP symptoms on Quality of Life

Patients with ITP not only suffer from low platelets, but also a substantially diminished quality of life. (3, 17) A cross-sectional survey on emotional, personal, social and work related health consisting of 1507 patients and 472 physicians, showed reduced energy levels in 85% of ITP-patients. Furthermore their capacity to exercise was reduced by 77%, and their ability to perform daily tasks was decreased in 75% of the patients. (2) 85% of the physicians treating ITP patients reported ITP-related fatigue in their patient population. These findings are not new, however literature shows that properly recognizing and treating these symptoms is difficult. (18, 19) In 2019 the international updated guideline for the treatment of ITP included a dedicated topic on quality of life in adult ITP patients. (20) However, an actual shift and propositions on how to deal with these real-life problems in patients has failed to be implemented in routine patientcare. Future studies are needed to analyze facilitators and barriers in the failure of properly implementing this in routine patientcare.

In addition, physicians need to be trained to handle symptoms such as fatigue, while awareness for these symptoms needs to be boosted. Finally clinicians should get help and tools for this. These tools include both PROMS, new guidelines and proper referral to other caregivers, such as psychologists, coaches and alternative forms of medicine, such as meditation, mindfulness, yoga, and so on depending on the patients preference. Although these options are not investigated in ITP patients, they have shown good response in other conditions. (8) It is not to be expected that hematologists need to treat and coach their patients themselves for these disease related symptoms, but it will help if they recognize their needs and refer them adequately. This will probably cost time, training and a different view on the 'benign' patient with ITP. Although ITP remains a 'benign' disorder, the fact that ITP patients often have to live life-long with their chronic illness, the total impact on the health related quality of life is large.

The main hypothesis is that patients do not start this conversation on fatigue, energy, social impact and quality of life by themselves. (3) They may become accustomed to their condition after some years of suffering from ITP. (3) Therefore, it is important to really assess their daily activities via a questionnaire, such as a PROM. Only in this way, we can get a proper insight and starting point for a conversation on the impact of ITP and the given therapies.

Building on current initiatives, such as Value Based Healthcare (VBHC) and Patient reported outcome measures (PROMs) may help to shift the focus from platelets-count to a more holistic approach of symptoms and inhibitions experienced by patients. (21) Therefore, the use of PROMs for patients with ITP should get a central role in the outpatient clinic and research which needs to include the use of PROMs and cost per patient / cost-effectivity-analyses. Furthermore, PROMs should be used as one of the primary outcomes in efficacy studies on treatments so it can be implemented in all outpatient clinics treating ITP.

Although this may sound straightforward, in clinical practice it seems to be challenging to accomplish. More (qualitative) research could aid in exploring the reasons for this hesitance, which might prevent patients from receiving optimal treatment. What are the barriers and facilitators on the implementation of PROMs in the outpatient clinic? Are there more lessons to learn from other diseases or specialties, in which PROMs are already part of daily clinical practice? Is it justifiable, that the most common bleeding disorder with a considerable impact on the personal life of patients still is considered "benign" and stands relatively low in the hierarchy within a hematology department compared to the malignant disorders seen. (4, 22)

Indeed, where ITP patients generally have a good prognosis considering mortality, the impact of their disease on quality of life is as substantial as observed in many malignancies. (23, 24) Future research should include this impact and symptoms in their outcome measures. Furthermore, these symptoms and Health Related Quality of Life should be a structural part of daily clinical practice for patients with ITP. What are we waiting for?

Moving towards a new era?

- New pathophysiological insights aid clinicians and patients in understanding the heterogeneous disease of immune thrombocytopenia.
- The understanding of the patient- specific pathophysiologic mechanism e.g. by new diagnostic assays will enable better informed and shared treatment decisions.
- New treatment options can offer patients a personalized and more targeted treatment plan, instead of broad immune suppressive therapy.
- Finally, insight and information is growing on the true, individual and for each patient specific perception of his/ her quality of life and how this is influenced by ITP and how it is modulated by the treatments we decide upon. PROMs in this light are indispensable.

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