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The Netherlands

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

Amini, S.N.

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Appendices

English Summary

English Summary

Chapter I: Introduction

This chapter introduces the complex disease Immune Thrombocytopenia (ITP). ITP is an auto-immune disease characterized by low platelets ($<100 \times 10^9/L$) in the absence of other irregularities. The pathophysiology of ITP is not fully understood and studies are ongoing on different pathways, diagnostics and treatment in ITP. Further, research on the reduced quality of life in ITP patients is performed and to manage these complaints and symptoms in this patient population.

With the data from our different cohorts and studies, we tried to gain insight in the following research questions:

1. Pathophysiology: What is the role of glycoprotein antibodies in relation to platelet site sequestration and TPO level?
2. Treatment: Can we stop TPO receptor agonists due to immune modulation or is it a life-long treatment? Can we use TPO receptor agonists for peri-operative bridging? What is the risk of thrombosis when using TPO receptor agonists?
3. Implementation: Can we develop a ITP tailored patient reported outcome measure and decision making tool for Dutch ITP patients? Should the Dutch ITP guideline be updated using new scientific insights?

Section on the pathophysiology of platelet destruction: anti-glycoprotein antibodies and scintigraphy

There are no human studies in on the role of glycoprotein antibodies and sequestration pattern or TPO-levels. In **Chapter II** we examine the association between GPV antibodies and sequestration pattern in ITP. In this study, GPV was associated with splenic platelet sequestration. This suggests that a GPV antibodies may be involved in a distinct pathway in ITP. In **Chapter III** we examined the association between GPIb/IX antibodies and sequestration pattern and TPO-levels. This study finds an association between GPIb/IX antibodies and TPO-levels and hepatic sequestration. Also an association is found between hepatic sequestration and TPO-levels. **Chapter IV** describes a first case report of a TNF α -inhibitor (adalimumab) induced ITP with anti-glycoprotein antibodies. **Chapter V** is a systematic review and meta-analysis on platelet scintigraphy scans and the association between results of the scan and outcome of splenectomy. **Chapter VI** is an interobserver study comparing the finding of two radiologists on platelet scintigraphy scans showing good to excellent interobserver agreement.

Section on TPO-receptor agonists and immune modulation

TPO-RAs are effective medication for most ITP patients, however side effects like thrombosis and immunomodulatory effects of TPO-RAs are not fully established. Further, the use of TPO-RA before bridging to surgery in ITP patients was investigated. **Chapter VII** is a systematic review and meta-analysis on the association of thrombosis in ITP patients using TPO-RA treatment. This study shows a positive association, however this is not a significant association. We suggest hematologists monitor carefully when prescribing TPO-RA to patients with a history of thrombosis. **Chapter VIII** describes the protocol of the STIP study, a study examining immune assays and tapering/discontinuation of romiplostim in ITP patients. **Chapter IX** described the BRIDGING trial where eltrombopag is compared to IVIG in the bridging phase of an ITP patient before undergoing a surgery.

Section on implementation of research into clinical practice

The implementation of research in the clinical practice is highlighted in **chapter X**. Here we report the new Dutch ITP guideline, the PROMs that were developed by our group for the use in the clinical practice and a report and illustrative screenshots of the decision-making aid that was developed in cooperation with the Dutch Patient Organization for ITP.

Chapter XI Discussion: moving to a new era for ITP patients?

The final chapter in this thesis aims to interpret all results and explore what can be done to improve quality of life for ITP patients. In this chapter the suggestions and recommendations are discussed how the care for ITP patients can be improved, which include:

- The relevance of pathophysiology, diagnostics and new treatment options for ITP patients
- Implementation of PROMS in Value Based HealthCare initiatives
- Aiding hematologists in improving symptoms such as Fatigue and Health Related Quality of Life
- Discussing the position of ITP as a 'not so benign' disease

