Thrombopoietin-receptor agonist-*i*mmunomodulation in young and midlife adult primary immune thrombocytopenia (ITP): A multi-center open label trial with *rom*iplostim *(iROM)*

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Introduction: Primary immune thrombocytopenia (ITP) is an autoimmune disease characterized by increased platelet destruction and impaired production leading to thrombocytopenia and bleeding symptoms. To date most of treatment strategies are symptomatic and focus on prevention from premature platelet destruction (immunosuppression, splenectomy) and on increasing platelet production (Thrombopoeitin-receptor agonist (TPO-RA)). A majority of adults (≈70%) will exhibit a chronic course of their disease so as a high disease burden. New treatment strategies should focus on treating the immune dysregulation, rather than treating the platelet count. Various drugs have been studied that have the potential to induce tolerogenic mechanisms. Long-term remission may be achieved after rituximab or dexamethason pulses, however with moderate results (20-30%). TPO-RAs obviously have the potential to affect the course of the disease with approximately 30% of patients terminating safely the drug after months or years of treatment. TPO-RAs stimulate platelet production and platelets may modulate the immune system to restore immune tolerance in ITP. However, the mechanisms of action are still unclear and some hypotheses may be considered. The *iROM* study aims to investigate immunomodulatory effects of romiplostim in young adult patients with primary ITP.

Methods: The *iROM* study is a multi-center, open label, single arm pilot study. Patients who failed first-line treatment were included. Five study centers in Switzerland participated: University Hospitals of Basel and Bern, and Cantonal Hospitals of Lucerne, Liestal and Aarau. We included 15 adults aged 18-60 years. Weekly Romiplostim was administered subcutaneously for 22 weeks. Patients were observed until week 52 and closely monitored for bleeding signs and blood counts. Peripheral blood was drawn for immunologic tests at 5 pre-determined time points (weeks 1, 6, 12, 22, 52) with the aim to investigate the Th1/Th2 ratio and T-regulatory cells. Blood tests included lymphocyte FACS, cytokines and mRNA. We here present preliminary clinical data.

Results: Between December 2016 and February 2020, 15 patients were recruited, including 2 patients prematurely withdrawn because of non-response to study drug. Of the 13 patients analyzed, 9 were patients with newly diagnosed ITP (<3 months), median age 31 years (IQR 8) and 4 patients had chronic ITP, age 31.5 years (IQR 8.75). Initial median platelet count was $26x10^9$/l (IQR 41) and $49.5x10^9$/l (IQR 88.5), respectively. At the end of treatment (week 22) median platelet count was $191x10^9$/l (IQR 9) and $88.5x10^9$/l (IQR 47.5) and at the end of the study (week 52) $168x10^9$/l (IQR 88) and $96x10^9$/l (IQR 23.5), respectively. Initial bleeding manifestations were petechiae and hematomas (n=12), epistaxis (n=8), oral cavity bleeds (n=5), hematuria (n=1), muscle bleed (=1) and menorrhagia (n=1). At week 22, only 2 patients exhibited mucocutaneous symptoms and 2 patients skin bleeding, and at week 52 one patient was still symptomatic. In 6 patients, discontinuation of romiplostim was successful after 22 weeks with sustained complete remission at week 52. All 6 patients had newly diagnosed ITP, leading to a remission rate of 66% in this subgroup. The remaining patients restarted on ITP drugs in the follow-up period between week 22 and 52.

Discussion: These results support the assumption that early treatment of ITP with Romiplostim could positively influence the natural course of the disease. In our study only 33% of patients with newly diagnosed ITP developed a chronic course compared to up to 80% in the literature. In one pooled data analysis (Kuter et al, 2019), and one prospective trial (Newland et al, 2016) sustained remission after Romiplostim treatment was reported in 16% and 32%, respectively. We assume that strict patient selection may have improved treatment success in our study. Indeed, immunomodulation and induction of tolerance may be more successful in the early stage of an autoimmune disorder and in younger patients because of potentially reduced immunosenescence.

Conclusion: Our study is the first study analyzing the possible tolerogenic mechanisms of Romiplostim. The preliminary clinical data are promising. The pending laboratory evaluations will probably help to further understand the underlying immunomodulation pathway.