Inflammation and Hypercoagulability in Anti-neutrophil Cytoplasmic Antibody associated Vasculitis

IMPACT PARAGRAPH

The World Health Organization declared COVID-19 as a pandemic on 11th of March 2020. The consequence was a global crisis with a tremendous impact on public health, social life, and economies. Evidence based treatment strategies were scarce at the beginning of the pandemic but substantial scientific and financial efforts led to a stepwise improvement in the understanding of the pathogenesis and therapeutic options for COVID-19.

Our research group entered the scientific COVID-19 rollercoaster early when SARS-CoV-2 made its debut in the Netherlands. As a team of immunologists, we were puzzled by the excessive systemic inflammation and damaged pulmonary vasculature observed in patients with severe COVID-19. We noticed striking homology with the pathogenesis of autoimmune diseases like AAV in which autoantibody and complement driven adverse neutrophilic responses (i.e., excessive NET formation) lead to vasculature inflammation, thrombosis and end-organ damage. The hypothesis was that SARS-CoV-2 elicited a dysregulated innate immune response with excessive complement activation and NETs formation that was linked to hypercoagulability in patients with severe COVID-19. The research presented in this thesis showed that, indeed, hypercoagulability in COVID-19 was associated with complement activation and NETs formation via the intrinsic pathway of coagulation. These findings were later confirmed and extended by other groups. The insights gained were socially and economically meaningful because they improved the understanding of the pathophysiology of COVID-19 and implicated a role for the inhibition of the complement system or the intrinsic coagulation pathway (i.e., plasma kallikrein and FXIa blocker) for the treatment of severe COVID-19. Indeed, as reported in this thesis C5a inhibition with vilobelimab was safe and had potential benefits on clinical outcomes in a phase two randomized controlled trial. The follow-up phase three randomized controlled trial confirmed these findings, leading to an emergency use authorization of vilobelimab for the treatment of patients with severe COVID-19 in 2023. Next, the conceptual insights gained on AnxA1 in patients with COVID-19 may present a novel anti-inflammatory treatment approach in infectious or auto-immune diseases, potentially avoiding the adverse side effects associated with currently used immunosuppressive drugs. Taken together, the findings described in this thesis indicated a successful application of translational basic science research resulting into a clinical intervention within a time frame of about three years and also directly impacted patients with COVID-19 and the health care system.

The thesis also aimed to better understand the link between adverse immune responses and hypercoagulability cross-sectionally in AAV. As previously outlined, one hypothesis was that comparable adverse (innate) immune responses and coagulation abnormalities might drive the course of disease in COVID-19 and AAV. Particularly during active disease, the number of thrombotic events is increased in patients with AAV. However,

the underlying mechanisms that contribute to hypercoagulability in AAV and how to prevent them are incompletely understood. Thrombotic events in AAV pose significant risks to patients' well-being and the health care system, as they can be potentially life-threatening and lead to long-term comorbidities. Consequently, gaining a better understanding of hypercoagulability in AAV is important for improved clinical management and patient outcomes. This thesis describes that hypercoagulability is, similarly to COVID-19, linked to activity of coagulation factors of the intrinsic coagulation pathway in patients with AAV. The driving mechanisms were not investigated but might also be linked to excessive complement and neutrophil activation leading to vascular inflammation and endothelial damage. The findings point towards inhibitors of coagulation factors of the intrinsic coagulation pathway or potentially complement inhibition as potential therapeutic targets to reduce the risk of thrombotic events in AAV.

Future directions

More than three years later, following the implementation of effective vaccination programs combined with a rather benign evolution of SARS-CoV-2 variants, the pandemic has come to an end. This does not mean that the impact of the findings described in this thesis are no longer relevant. SARS-CoV-2 is still present and there remains a potential risk that a new variant could lead to a severe course of disease. The insights obtained from this thesis regarding the pathophysiological mechanisms and the efficacy of C5a inhibition in COVID-19 can provide valuable guidance in mitigating the adverse effects in the event of a resurgence of a SARS-CoV-2 variant. This is particularly important for high-risk patients for whom COVID-19 can still be fatal and those who may progress to severe COVID-19 despite receiving widely recommended immunosuppressants like glucocorticosteroids or IL-6 inhibitors. Future studies should investigate the potential harms and benefits of combining vilobelimab with the previously mentioned immunosuppressants in COVID-19. Additionally, it would be valuable to explore whether vilobelimab could be considered as the first choice in selected patients with severe COVID-19. The lessons learned that the innate immune system is linked to the coagulation system and defines disease severity in COVID-19 (and AAV) should be applied and studied in other (infectious) diseases like influenza or bacterial sepsis. This includes further research on vilobelimab's efficacy in reversing systemic inflammation (and hypercoagulability) in conditions associated with sepsis, considering the unfavorable outcomes of glucocorticosteroid use in most of the sepsis studies in the past.

The exact driving mechanisms of hypercoagulability in AAV remain to be discovered. This thesis indicated a dominant contribution of the intrinsic coagulation cascade in the process of hypercoagulability in AAV. Future studies should address the underlying

driving factors that result into the activation of the coagulation system. Since the risk of thrombotic events is the highest during active disease, again, overactivation of the complement system, neutrophils and NETs formation are potential targets to focus on besides endothelial and vascular damage. Clinically, it is difficult to identify the patients at risk for a thrombotic event, future studies should explore predictors of hypercoagulability and whether the prophylactic use of anticoagulants can be preventive in these patients. The results of this thesis point towards a potential role for inhibitors of coagulation factors of the intrinsic pathway to prevent VTEs. Furthermore, C5aR1 inhibition with avacopan is now accessible for the treatment of patients with AAV. It would be interesting to explore whether C5aR1 or C5a inhibition with vilobelimab (the results of a phase 2 randomized controlled trials in AAV are in preparation) is associated with an improvement of the observed coagulation abnormalities and a reduced risk of thrombotic events.