Treatment innovation in ANCA-associated vasculitis: unleashing real-world data

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Introduction

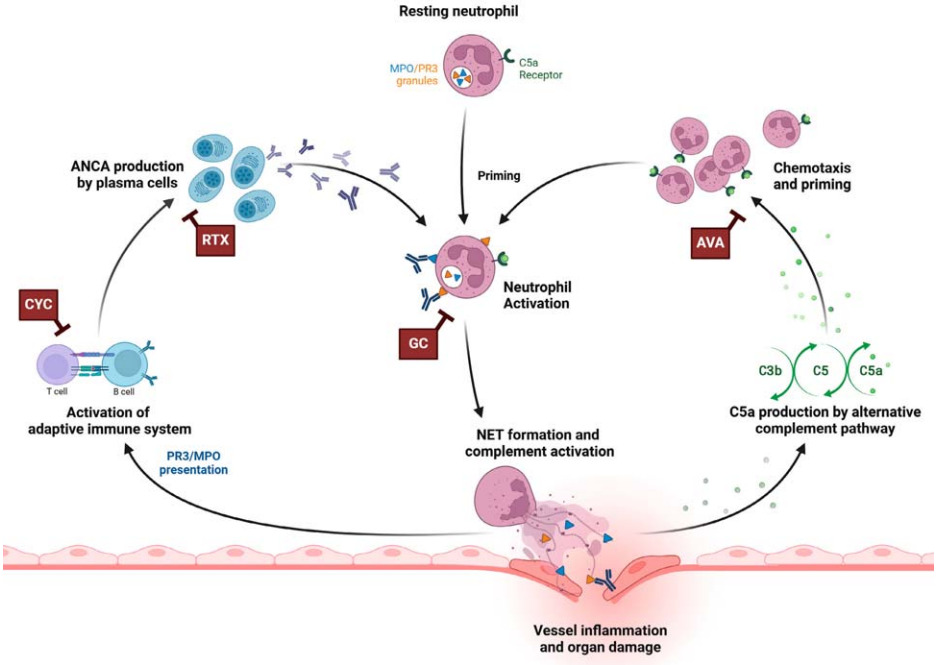
ANCA-associated vasculitis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare, systemic autoimmune disease which causes relapsing inflammation of the small vessels resulting in organ damage that can be organ and life-threatening.[1-3] The pathophysiology of AAV is based on the loss of tolerance of B-cells and T-cells against one of the proteins commonly present in neutrophils: proteinase 3 (PR3) or myeloperoxidase (MPO) which results in the production of auto-antibodies (ANCAs) by plasma cells.[2] Recognition of the protein by the antibody results in activation of the innate and adaptive immune system (**figure 1**).

In resting neutrophils PR3 and MPO are found in intracellular granules, but when neutrophils are primed for activation by activation of the innate immune system, PR3 and MPO migrate to the outer cell membrane.[2,4] Expression on the outer cell membrane creates the possibility of binding of ANCA's to PR3 or MPO which leads to activation of the neutrophil.[2,4] Activation initiates a cascade of inflammation, leading to neutrophil extracellular trap formation, release of lytic enzymes and activation of the alternative complement system.[2,4] Activation of the alternative complement pathway is pivotal in the pathophysiology as it creates a vicious amplifying loop of inflammation driven by C5a, one of end products of this pathway. C5a induces chemotaxis of additional neutrophils to the site of inflammation and mediates activation of neutrophils by priming them.[2,4,5] The enhanced cascade of inflammation leads to vessel injury and ultimately organ damage in AAV patients.[2,4,5]

Since AAV can affect almost all organs the clinical presentation varies depending on the organs involved. In nearly 80% of patients the kidneys are involved where it can induce crescentic glomerulonephritis resulting in acute and chronic kidney injury, which progresses towards end-stage renal disease in approximately 20% of these patients.[1,6] Other severe manifestations of AAV are pulmonary hemorrhage due to pulmonary involvement or mononeuritis multiplex due to nerve involvement.[1-3] Based on the clinical and pathological features, three phenotypes can be specified within AAV: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA). The AAV subtypes can be further specified by their type of ANCAs: proteinase 3 (PR3) or myeloperoxidase (MPO). GPA-patients often have PR3-ANCAs, MPA patients mostly have MPO-ANCAs and EGPA patients are often ANCA-negative.[1-3] As such, EGPA is often studied as a separate entity with a different treatment strategy, while GPA and MPA have similar treatment strategies and are often studied together. Similarly, in this thesis we will primarily focus on innovation of treatments for GPA and MPA patients.

Figure 1.1: Overview of the pathophysiology of ANCA-associated vasculitis and the primary target of each treatment option.



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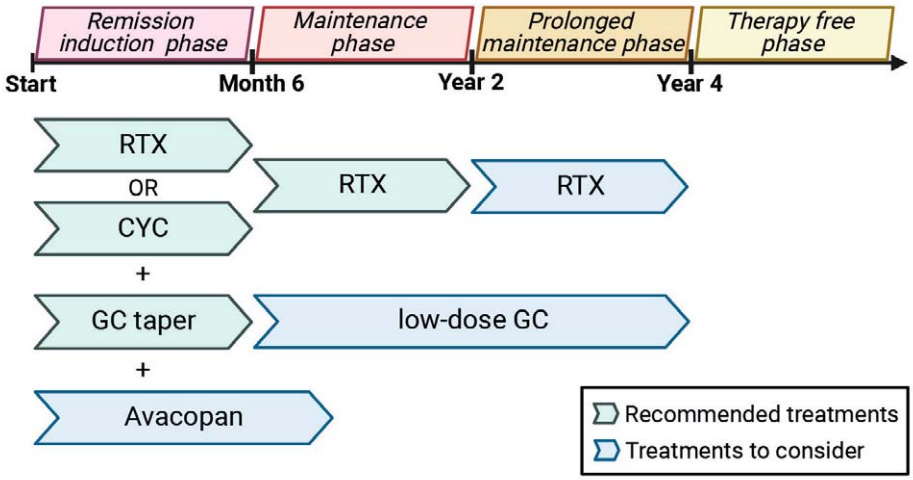
Treatment in AAV

The treatment strategy for GPA and MPA patients involves of a combination of anti-inflammatory and immunosuppressive treatments. Treatment starts with a remission induction treatment and is followed by a maintenance treatment once remission is achieved, typically within approximately 6 months.[1,3] Maintenance treatment is essential to reduce the risk for relapse, but still approximately 50% of patients experience a relapse within 5 years.[2,7] It is recommended to continue maintenance treatment for at least two years, though research indicates that prolonged maintenance treatment reduces the risks for relapse.[1,8] However, prolonged immunosuppression also increases the risk of toxicity, including infections, side effects or the development of malignancies.[1,3,9] Theore, current guidelines recommend to consider prolonged treatment up to 4 years with the duration tailored for each individual patient based on risk characteristics for relapse, risk for toxicity and preference of the patient.[1,3] Due to the risk for relapse and for toxicity, patients need life-long monitoring by AAV experts.

In recent decades, the treatment for AAV patients has significantly improved, with multiple treatment options now available. Currently, the most commonly used immunosuppressive agents in treatment of severe AAV include glucocorticoids (GC), cyclophosphamide, rituximab, and, more recently, avacopan (**figure 2**):

Figure 1.2: Recommended treatment strategy for management of severe ANCA-associated vasculitis.



CYC; Cyclophosphamide; GC, glucocorticoids; RTX, Rituximab.
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Glucocorticoids

Remission induction treatment starts with high dose GC, which provide rapid anti-inflammatory and immunosuppressive effects on nearly all cells. [1-3] High-dose GC are recommended to be tapered to low-dose GC in 4-6 months. [1, 3] The impact of low-dose GC as maintenance therapy is unsure and guidelines recommend to determine duration of low-dose GC for individual patients based on disease course, comorbidities and preferences. [1] Fast tapering and discontinuation of GC is necessary because high cumulative GC doses are associated to multiple complications, such as (severe) infections, weight gain, diabetes, hypertension, cardiovascular disease, osteoporosis and -necrosis and neuropsychological problems. [1-3, 9] The currently recommended tapering schedule, based on one of the largest recent AAV trials, reduced cumulative doses by approximately 50% compared to previous recommendations. [1, 3, 10] However, the optimal tapering strategy that maintains efficacy but minimizes toxicity is still unknown and remains a key area of interest for physicians and researchers.

Cyclophosphamide

Cyclophosphamide is an alkylating agent which inhibits proliferation of immune cells, with the most pronounced effect on T-cells.[11] Cyclophosphamide has been used for the treatment of AAV since the 1970 and improved the 5-year survival rate from less than 20% to almost 80%.[12-14] However, high cumulative doses or cyclophosphamide increase the risks of toxicity including malignancies and infertility. The cumulative dosage and related toxicity can be reduced by administering IV pulses instead of daily oral treatment, which is recommended since 2016.[1, 12-14] Additionally, cyclophosphamide should be switched to less toxic medications when remission is reached. This used to be azathioprine, but since the last years rituximab is the recommended maintenance treatment.[1, 14]

Rituximab

Rituximab is a murine CD20-antibody with a B-cell depleting effect resulting in significant reduction of ANCA titers.[15, 16] Rituximab was demonstrated to be non-inferior to cyclophosphamide in achieving remission in two large trials.[15, 16] Since 2016 guidelines recommend to use either CYC or RTX for remission induction treatment.[1, 3, 14] However, since retrospective studies suggest the long-term toxicity for rituximab is lower than for cyclophosphamide, there seems to be a shift towards more RTX-based induction treatments.[1, 17, 18] Combining RTX with low-dose cyclophosphamide has shown promising clinical and immunological results in retrospective cohorts, and is currently studied in the ENDURRANCE trial.[19-22] For now, the combination treatment is often only used in patients with refractory of life-threatening disease.[1, 3]

Rituximab is also the recommended maintenance treatment since superiority was demonstrated for 6-monthly rituximab treatments over azathioprine.[1, 3, 23] An alternative dosing strategy is dosing tailored based on B-cell repopulation and ANCA-rise, which demonstrated non-inferiority in a randomized trial, but tailored dosing is not recommended because the trial was underpowered.[1, 3, 24]

Avacopan

Avacopan is a C5aR inhibitor which blocks the amplification loop of inflammation created by the alternative complement pathway.[1, 2, 4] Avacopan was developed after it was discovered that blockage of the alternative complement pathway at the level of C5/C5a could prevent and even treat crescentic glomerulonephritis in mice.[5, 25, 26] After proving safety in a phase 1 and two phase 2 trials, avacopan was studied in a phase 3 trial where it showed avacopan allows safe reduction of cumulative GC dose and had beneficial effects on GC-related toxicity and on kidney function recovery.[27-29] Based on these trials, avacopan has been approved for the treatment of AAV by the EMA and FDA.[30, 31] Current guidelines recommend to consider avacopan treatment for one year to reduce GC in AAV patients at high risk for GC toxicity.[1, 3] However, it remains unclear how, when and which patients can benefit the most from avacopan.[1, 3]

Treatment of each individual AAV patient requires a combination of the above mentioned drugs. Given that each drug has a different primary target (**figure 1**), it can be postulated they also have different, synergistic effects, which suggests that combining all of them could have an enhanced effect on disease control. Combining multiple drugs might be beneficial for treatment-refractory patients who do not achieve remission with standard combinations, but might also increase the risk for toxicity, including severe infections.[1-3] Better and more personalized treatment strategies for remission induction are needed to balance risks for relapse and risks for toxicity, which might differ between patients due to the significant heterogeneity among AAV patients. Additionally, some patients relapse while on rituximab maintenance treatment or become rituximab intolerant, highlighting the need to find better alternative for maintenance treatment.

This thesis explores various new, innovative treatment strategies, including an in-class alternative to rituximab, avacopan-based treatment strategies and the combination treatment of rituximab and low-dose cyclophosphamide. It also highlights important items regarding classification criteria, toxicity and hospital costs to consider when selecting novel treatment strategies.

Research and innovation in AAV treatment

Over the past decades, advancements and innovations in treatment have transformed AAV from a frequently fatal disease into a predominantly chronic condition.[1-3] With this transformation, the focus has shifted from short-term to long-term outcomes. Since remission is achieved in up to 90% of AAV patients, current research often focuses on preventing relapses and reducing toxicity and damage.[1-3, 13, 16, 19, 21, 32] Additionally, there is an increasing demand for personalized treatment, where the combination and duration of therapies can be tailored to the characteristics of the patient and the disease, such as organ involvement.[1, 33]

To compare long-term outcomes of different treatment strategies it is necessary to perform large clinical trials with significant follow-up time. However, due to the rarity of AAV with only 200-300 cases per million persons, assembling relevant cohort sizes is challenging.[2] This can be illustrated by in the time required for conducting some recent large AAV clinical trials: PEXIVAS (2010-2017), ADVOCATE (2017-2019), RAVE (2005-2010) and MAINRITSAN1 (2008-2013).[10, 15, 23, 28] But even in these large trials, cohorts were often not big enough to allow sensitive analysis of subgroups.[33] Subgroup analysis are particularly important to be able to further personalize treatment of AAV patients on organ involvement and/or ANCA-type. Additionally, since clinical trials have specific inclusion criteria and are performed in a strictly monitored research environment, their outcomes do not always reflect the real-world clinical practice, where patients often experience multimorbidity and polypharmacy.[34-36] This can limit the possibilities to apply evidence of clinical trials in real-world practice.

An alternative research approach that can overcome some of these limitations is using real-world data to create real-world evidence (RWE). There is growing recognition of the added-value and advantages of RWE as frequently described in case reports, case series, retrospective cohort studies and/or database studies.[34-38] One of the clear benefits of RWE is that collecting real-world data is much faster and less expensive than collecting data in clinical trials. Moreover, RWE facilitates the collection of data form large patient cohorts with long, unrestricted follow-up time. These cohorts will also include patients often excluded for clinical trials based on age, pregnancy, comorbidities and/or polypharmacy. As such, RWE can improve insight into epidemiology, assess long-term outcomes efficacy, determine safety outcomes outside clinical trial settings and enable subgroup analysis.[34-37] Additionally, real-world data from small, targeted patients groups can provide valuable insights in immunological or clinical outcomes for specific conditions, such as off-label drug use, that can be hypothesis generating and inspire new research. Nonetheless, creating RWE also presents challenges, such as accurate patient identification and unleashing large datasets from electronic health records.[34-37]

In this thesis we demonstrate how to unleash real-world data from EHRs to create RWE that can help innovate treatment and guide research in AAV.

Goal and outline of the thesis

The goal of this thesis was to innovate the treatment of AAV to assure AAV patients have more and better treatment options that minimize the burden of both disease activity and treatment related toxicity. While conducting the still ongoing ENDURRANCE trial (described in *chapter 9*), we focused on real-world data to help innovate AAV treatments and guide future research. Consequently, all chapters of this thesis, except for *chapter 9*, are unleashing real-world data to create impactful real world evidence:

In ***chapter 2***, we developed a method to accurately identify AAV patients within electronic health, which is the first step in collecting RWE. The cohort identified in this chapter was used for the collection of real-world data in *chapters 3-6*.

In ***chapter 3***, we described how the introduction of new classification guidelines can shift parameters associated with relapse risk in our previously identified AAV cohort.

In ***chapter 4***, we used real-world data of the AAV cohort to describe drivers of hospital costs and to determine which subsets of patients are responsible for disproportional high costs.

In ***chapter 5***, we compared immunological outcomes of obinutuzumab to rituximab in AAV patients who developed rituximab intolerance and received off-label obinutuzumab.

In ***chapter 6***, we described the real-world outcomes of 8 patients treated with avacopan before its approval, as part of the compassionate use program.

In ***chapter 7***, we reported real-world safety outcomes of all AAV patients treated with avacopan during the compassionate use program as reported to the pharmaceutical company.

In ***chapter 8***, we reviewed all data currently known about avacopan based on pre-clinical studies, clinical trials and real-world evidence, suggested how avacopan may be used in routine clinical practice and identified areas of for future research.

In ***chapter 9***, we outlined and discussed the protocol for the ongoing ENDURRANCE study which compares an induction treatment with rituximab to rituximab combined with low-dose cyclophosphamide.

In ***chapter 10*** we summarized the results of all chapters and discuss the implications of the work presented in this thesis.

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