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## Treatment outcomes in ANCA-associated vasculitis

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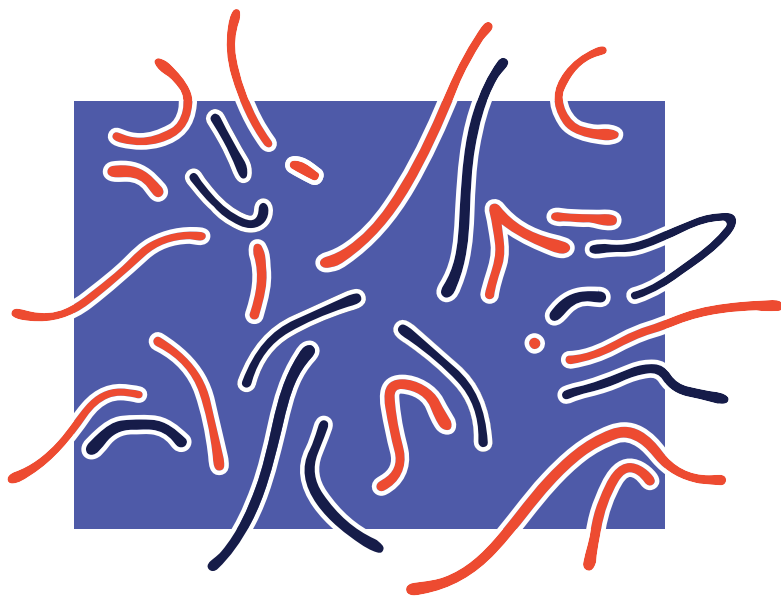
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# 08 Chapter

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## **Summary and future perspectives**





## SUMMARY

In **Chapter 1**, characteristics of the different diagnostic classes of ANCA-associated vasculitis (AAV) (i.e., granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], eosinophilic granulomatosis with polyangiitis [EGPA]) are summarized. We conclude that evidence for classification based on ANCA specificity (PR3-ANCA versus MPO-ANCA) rather than clinical diagnosis is increasing [1,2]. We also note that the relation between ANCA specificity and clinical characteristics differs between geographical regions [3].

Subsequently, we provide an overview of important developments in AAV treatment. An example is the introduction of azathioprine and low-dose glucocorticoids as maintenance therapy following remission induction with cyclophosphamide and high-dose glucocorticoids [4]. Another example is the introduction of rituximab as an alternative to cyclophosphamide and azathioprine for induction and maintenance of remission, respectively [5,6]. We also note the recent shift of research focus towards disease- and patient-tailored medicine [1].

We conclude the first chapter with the challenges we still face in AAV treatment, including a high risk of relapse [7], disease- and treatment-related mortality [8,9], accumulation of damage from disease and treatment [10,11], and a reduced quality of life (QoL) despite control of disease activity [12,13]. All of these are items that may benefit from individualized therapy based on disease and patient characteristics. Currently, few studies are available that study this topic in AAV.

### Part 1: Pharmacogenetics

In the chapters of part 1 we explore the current knowledge and results of our own studies with respect to genetic factors that are potentially associated with treatment outcome of AAV.

In **Chapter 2**, we summarize the current literature on gene variants in relation to efficacy and/or toxicity of current treatment in AAV. In addition to the results from chapters 3 and 4 from this thesis, we find that the Cytochrome P (CYP) 450 related CYP2C9 polymorphism has been associated with clinical response to cyclophosphamide [14]. Additionally, genetic polymorphisms related to B cell activator of the tumor necrosis factor family (BAFF) [15], the interleukin (IL)2-IL21 genetic region [15], Fcγ receptor IIa [16], and IL6 were associated with response to rituximab [17]. These studies add genetic markers for potential application of personalized therapy in AAV. Their value for clinical practice will need to be evaluated in future studies.

The gene encoding the enzyme Thiopurine methyltransferase (TPMT) is well-known and used for pharmacogenetics. Genotyping before starting thiopurine therapy and adjustment of initial dose in patients carrying genetic variants is recommended to prevent bone marrow toxicity [18,19]. In **Chapter 3**, we find that AAV patients carrying a TPMT variant do not have an increased risk of adverse effects during azathioprine maintenance therapy, at least if they receive strict surveillance of hematological parameters and clinical follow-up. On the other hand, lower leukocyte counts after cyclophosphamide therapy, possibly reflecting a small bone marrow reserve or 'fitness', are strongly associat-

ed with bone marrow toxicity during azathioprine treatment and relapse, indicating that response to cyclophosphamide might be a stronger predictor of these outcomes than TPMT variants, even after switch to azathioprine [20]. Of note, none of the patients in the study is homozygous for TPMT variants, while this is associated with the highest risk of severe thiopurine-induced bone marrow suppression [21]. Also, frequent laboratory evaluation is performed in the UMCG after switch to azathioprine, allowing for early dose reduction in TPMT variant carriers. The results of this chapter indicate that TPMT pretesting might be less useful for AAV patients compared to other populations.

Several haplotypes of the glucocorticoid receptor (GR) have been identified that affect glucocorticoid (GC) sensitivity in the general population [22]. In **Chapter 4**, we investigate whether these haplotypes affect disease- and treatment related outcomes in a cohort of AAV patients treated with GCs combined with other immunosuppressive drugs. We find that GR haplotype 1 (minor variant of Bcll), associated with increased GC sensitivity, results in an increased risk of developing dyslipidemia. GR haplotype 4 (minor ER22/23EK+9 $\beta$ +Tthll1), associated with glucocorticoid resistance, results in increased risks of end-stage renal disease and death, suggesting a more severe inflammatory disease phenotype and/or reduced treatment response. A genetic variant of 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1), associated with reduced local GC activation [23], results in an increased risk of relapse, but only in non-carriers of GR haplotype 1. We conclude that inter-individual differences in glucocorticoid sensitivity affect clinically relevant outcomes in AAV. As no such data are currently available, future studies will need to assess whether adjustment of treatment based on 11 $\beta$ -HSD1 genotype or GR haplotype will result in improvement of inflammatory and/or metabolic outcomes.

## **Part 2: characterizing treatment outcomes**

In the second part, several treatment outcomes are characterized in more detail, in order to formulate points of consideration for clinical practice.

Clinical characteristics of AAV differ between geographical regions and ethnic groups [3,24,25]. Also, MPO-ANCA is associated with a different disease phenotype, different clinical outcomes and different genetic associations than PR3-ANCA [1,2,26]. In **Chapter 5**, we compare Dutch, Brazilian and Chinese cohorts of AAV patients and test whether geographical differences in organ manifestations and clinical outcomes are independent of ANCA-specificity. We find that differences in eye/mucosa and ear-nose-throat involvement between China and other countries can be explained by the lower frequency of PR3-ANCA positive patients in this country. Other differences in organ manifestations between countries cannot be explained by differences in ANCA-specificity. This is in agreement with earlier studies comparing organ manifestations of GPA and MPA patients between Japan and the United Kingdom [24,25]. Despite an expected lower risk of relapse based on a lower frequency of PR3-ANCA positive patients and ear-nose-throat involvement, as well as a higher frequency of end-stage renal disease, relapse risk of Chinese patients is similar to Brazilian and Dutch patients. Also, Chinese patients have a lower overall survival compared to both other countries, even after adjustment for other factors associated with mortality such as age, end-stage renal disease, pulmonary involvement and induction treatment. These findings indicate additional, yet unidentified, risk factors for relapse and mortality in this Chinese AAV population.

Toxicity and severe adverse effects are well-known and important aspects related to induction and maintenance therapy in AAV. A somewhat neglected and probably underestimated adverse effect of azathioprine is the azathioprine hypersensitivity syndrome (AHSS), characterized by fever and several other possible skin and systemic symptoms [27]. In **Chapter 6**, we describe the AHSS within our observational cohort of AAV patients. We find an estimated incidence of 9% (95% CI 6 to 13%) in AAV, which is more frequent than the 2% previously reported for IBD patients using 6-mercaptopurine (6-MP) [28]. AHSS is associated with lower TPMT activity in our cohort, although most patients (80%) still have a TPMT activity in the normal range. We find similar (frequencies of) symptoms to those described previously [27]. Eosinophilia that is characteristic of other drug hypersensitivity reactions is absent. Instead, the laboratory abnormalities of elevated CRP, leukocytosis and neutrophilia resemble infection and a relapse of vasculitis. In multivariable Cox regression, after adjustment for PR3-ANCA (lower frequency in hypersensitive patients of our cohort) and TPMT activity (lower in hypersensitive patients of our cohort), AHSS is a risk factor for relapse. A likely explanation for this is that immunosuppressive therapy in patients with AHSS is often temporarily discontinued because it is confused with an infection. We conclude that AHSS is more common than previously reported, that lower TPMT activity might facilitate its initial development, and that AHSS negatively impacts the efficacy of remission maintenance therapy.

Physical quality of life (QoL) is reduced in AAV patients compared to the general population, even in remission [13]. In **Chapter 7**, we sought to investigate whether reduced physical QoL in AAV might in part be explained by steroid myopathy and reduced physical performance. The main predictors of lower age-adjusted physical QoL in our study are lower knee extension force, younger age and vasculitis relapses. We find that the majority of AAV patients have lower muscle strength than expected based on age, sex, height and weight. While cross-sectional measurements do not show an association between muscle strength and prednisolone use, muscle strength improves within patients after prednisolone tapering. Lastly, knee extension force of relapsing patients decreases over time. We conclude that reduced muscle strength results from prednisolone use as well as damage from vasculitis activity, and contributes to reduced physical QoL in AAV. Alternatively, reduced physical QoL results in decreased exercise capacity and less physical activity, in turn resulting in muscle wasting and reduced muscle strength.

## DISCUSSION AND FUTURE PERSPECTIVES

### Pharmacogenetics: possible role in AAV

Several genetic factors have been identified by others (**Chapter 2**) and our group (**Chapters 3 and 4**) that have been associated with response to drugs used for AAV treatment [14-17,20,29]. In theory, adjusting therapy based on these genetic factors could improve treatment outcomes for individual patients by reducing treatment toxicity while maximizing efficacy.

The cytochrome P (CYP)2C9 variant was associated with a higher risk of leukopenia and showed a trend towards increased treatment response in cyclophosphamide-treated

AAV patients. Also, gene variants of B cell activator of the tumor necrosis factor family (BAFF), Fcγ receptor (FcγR) IIA, the interleukin (IL)2-IL21 region and IL-6 have been associated with response to rituximab therapy, although these effects are most likely independent of induction therapy used. Treatment outcomes might improve by adjusting cyclophosphamide dose based on CYP2C9 genotype. Also, it may be interesting to investigate additional targeted therapy, such as belimumab (targeting BAFF signaling), and tocilizumab (targeting the IL-6 receptor), in patients carrying genetic variants related to BAFF and IL-6.

An example of clinical application of pharmacogenetics is adjustment of thiopurine dose based on TPMT genotype, which reduces thiopurine toxicity in IBD patients carrying a TPMT variant while maintaining efficacy [30]. TPMT gene variants have less predictive value for outcome of azathioprine maintenance therapy in AAV [20,31], although we do see a trend of higher relapse-free survival in patients with low TPMT activity, as well as an increased bone marrow susceptibility to azathioprine in carriers of a genetic TPMT variant. TPMT genotyping may still be relevant to detect the occasional patient that is homozygous for TPMT variants, since these patients have an increased risk of severe bone marrow toxicity [32], and require a 10-fold dose reduction or alternative therapy [30].

Carriers of genetic variants that reduce GC sensitivity are associated with adverse disease outcomes such as relapse and end-stage renal disease. This suggests that AAV patients with these genetic variants might benefit from more intensive treatment. On the other hand, a genetic variant that increases glucocorticoid sensitivity is associated with lower relapse risk and an increased risk of adverse metabolic outcomes. AAV patients carrying this variant might benefit from reduced GC exposure. Interestingly, none of the genetic factors was associated with speed of GC tapering. While this may be the result of the protocol-based tapering schedule, another possibility is that genetic variation in 11β-HSD1 and the GR mainly affect the effects of cortisol, in patients not receiving prednisolone treatment. Indeed, prednisolone is given in supra-physiological dosages, suppressing the endogenous production of cortisol, thereby removing (inter-individual variation in) hypothalamic-pituitary-adrenal axis regulation of GC production. The most appropriate way to adjust treatment in order to improve the measured outcomes will need to be investigated in randomized controlled trials.

Before gene variants can be applied for clinical practice, several hurdles need to be overcome. Firstly, most of the findings were only shown in a single cohort; they require confirmation in independent replication cohorts. Because of the low prevalence of AAV [33], replication of findings in a large enough cohort will require a multicenter approach. Secondly, after confirmation of results, a multicenter randomized controlled trial (RCT) would need to be performed to find the appropriate dose reduction and to evaluate the effect of this adjustment on treatment efficacy and toxicity. Because most gene variants are only present in a minority of patients, the number of patients included will need to be much larger than the number of patients receiving dose adjustment.

### **Characterizing treatment outcomes**

Recent studies indicate that ANCA specificity is associated with distinct clinical manifestations and outcomes [26]. In **Chapter 5**, we show that a lower frequency of mucosa/eye

and ENT involvement in China can be explained by the lower frequency of PR3-ANCA positive patients in this country. ANCA-specificity does not fully predict clinical manifestations and outcomes, however. Several differences in organ manifestations between Brazil, China and the Netherlands could not be explained by ANCA-specificity. Also, Chinese patients had a higher risk of relapse and mortality than expected based on known risk factors for these outcomes. Therefore, we expect additional environmental and/or genetic factors to affect disease characteristics. Most of the RCTs performed so far have mostly included Caucasian patients [4,5,34]. Therefore, inter-ethnic differences in clinical response to drugs cannot be excluded, which may be mediated by genetic factors. Research into personalized treatment based on genetic factors in addition to ANCA specificity may be worthwhile.

In **Chapter 6**, the first cohort study on the azathioprine hypersensitivity syndrome in AAV, we found that it is more common in AAV than previously reported for IBD [28]. One explanation for this finding could be that patients in the previous cohort study received 6-MP, which lacks the imidazole group of azathioprine as an additional epitope [28]. Indeed, successful switch of azathioprine to 6-MP and vice versa have been reported for patients with hypersensitivity to either drug [27,28,35,36]. This indicates that the imidazole group of azathioprine as well as epitopes from other metabolites can trigger a hypersensitivity response. Also, other studies in patients using azathioprine rather than 6-MP, including a clinical trial conducted in AAV patients, found frequencies of azathioprine hypersensitivity closer to the one described in **Chapter 6** [4,37,38]. Another explanation could be the existence of a common susceptibility factor to both AAV and azathioprine hypersensitivity, for example a human leukocyte antigen (HLA) genetic association. This hypothesis requires further study for verification.

The mechanism of azathioprine hypersensitivity has not been fully elucidated. Most likely, based on the timing and clinical symptoms, the mechanism is either a type IV hypersensitivity reaction [39], or a pharmacological interaction of azathioprine with an immune receptor such as HLA or a T-cell receptor (TCR) [40].

Azathioprine hypersensitivity has previously been considered a dose independent reaction, supported by the low dose required upon rechallenge to elicit the same symptoms [27]. On the other hand, the association we found with a lower TPMT activity indicates that a higher exposure to some metabolites of azathioprine facilitates development of azathioprine hypersensitivity. Also, several cases of successful desensitization with very low doses of azathioprine have been reported [28].

Based on the results of **Chapter 7**, relapses of vasculitis have a cumulative negative effect on muscle strength. Whether this is the result of vasculitis activity and/or treatment toxicity could not be determined in this study. Nevertheless, muscle strength, exercise capacity and QoL are all reduced in vasculitis patients even after remission has been achieved [13,41,42], warranting intervention studies aimed at improving these outcomes. The difficulty in designing an effective physical activity intervention for AAV patients is that the cause of reduced exercise capacity likely differs between individual patients. While one patient may suffer from dyspnea due to subglottic stenosis, nasal obstruction or pulmonary damage, another patient may have difficulty walking due to pe



ripheral nerve damage. These differences make it difficult, if not impossible, to develop one intervention that is effective for all AAV patients. Preferably, a personalized training program should be designed based on the type of disease and treatment damage present. Alternatively, muscle strength, exercise capacity and QoL can improve by reducing exposure to glucocorticoids. The currently investigated drug CCX168 (avacopan) might help achieve a reduction of glucocorticoid exposure, possibly resulting in less muscle wasting [43].

The questionnaire most frequently used to measure QoL in AAV patients, the SF-36 [13,41,42], is a generic questionnaire, lacking items specific for the functioning of AAV patients. Recently, the AAV-PRO questionnaire has been developed, which includes categories such as disease symptoms, treatment side effects and physical functioning [44]. It may be interesting to investigate whether this measure will prove useful to monitor interventions aimed at improving physical functioning of AAV patients.

## **CONCLUSION**

Treatment of AAV has greatly improved over the years. Some interesting targeted therapies are on their way, but the balance between disease inflammation and treatment toxicity still needs improvement. The use of gene variants to optimize outcomes of currently used drugs is an interesting approach, but several hurdles need to be overcome before it can be implemented. Further improvement could be achieved by designing separate treatments based on ANCA type, gene variants related to drug efficacy or toxicity, and possibly other genetic factors.

Early recognition and further understanding of azathioprine hypersensitivity will hopefully prevent unnecessary hospitalizations and treatments, as well as improve efficacy of remission maintenance therapy. Lastly, specific interventions based on the underlying type of damage need to be developed to improve physical functioning of AAV patients during and after successful treatment of disease activity.

In summary, with this thesis we have made some small steps towards personalized medicine in AAV, which will hopefully be expanded upon in the coming years.

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