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Gene variants and treatment outcomes in antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

The introduction of immunosuppressive therapy for ANCA-associated vasculitis (AAV) has greatly improved outcomes, though patients now accumulate damage from vasculitis activity and adverse effects of treatment. Prediction of treatment outcomes using gene variants might help reduce this damage by allowing for personalized treatment. Several studies have studied genetic polymorphisms in relation to treatment outcomes of AAV. This review gives an overview of these studies, discussing both gene polymorphisms associated with inflammatory pathways (potentially influencing disease outcomes such as activity, severity, and relapse risk) and pharmacogenetics (potentially influencing drug metabolism and/or drug response). Subsequently, potential benefits of testing genetic variants for AAV and the steps needed for its implementation in clinical practice are discussed. The conclusion of this review is that measurement of most polymorphisms is currently not indicated in clinical practice.

Introduction

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a group of autoimmune diseases affecting mainly small blood vessels. They are frequently associated with the presence of antibodies directed against proteinase 3 (PR3) or myeloperoxidase (MPO), both of which are present in the cytoplasm of neutrophils and expressed on the cell membrane during active inflammation. Three subtypes of AAV are distinguished based on clinical characteristics: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1].

The etiology of autoimmune diseases is thought to be multifactorial, involving an interaction between genetics and environmental factors [2]. To illustrate, family members of patients with rheumatoid arthritis (RA) and

systemic lupus erythematosus (SLE) not only have an increased risk of developing RA or SLE, but also of developing other autoimmune diseases [3, 4]. In a large genome-wide association study, several genes were associated specifically with either PR3-AAV (*HLA-DP* and the genes encoding alpha-1-antitrypsin (*SERPINA-1*) and PR3 (*PRTN3*)) or MPO-AAV (*HLA-DQ*) [5]. Furthermore, the incidence of different types of AAV differs between patients from different ethnicities. For example, although the overall prevalence of AAV is similar in Europe and Asia, GPA is more prevalent in Europeans, while MPA is more prevalent in Chinese and Japanese patients [6, 7].

Several environmental factors have previously been associated with the risk of developing AAV and ANCA specificity. *Staphylococcus aureus* infection is thought to play a role in pathogenesis of GPA, since it is a risk factor for disease relapse and treatment with the antibacterial agent Trimethoprim/sulfamethoxazole reduces relapse risk [8, 9]. The incidence of GPA and EGPA increases with higher geographical altitude and less ambient ultraviolet radiation exposure [10]. ANCA specificity also differs between geographic regions, with MPO-AAV being more prevalent in Japan and China; PR3-AAV being more prevalent in Northern Europe, the Middle East and India; and prevalence of MPO-AAV and PR3-AAV being similar in Caucasian America and Southern Europe. As a last example, silicon

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exposure has been associated with the risk of developing GPA and MPA [11].

Over the years, treatment of AAV has greatly improved. After the introduction of combined therapy using cyclophosphamide (CYC) and high doses of glucocorticoids, it has turned from a lethal disease to a chronic relapsing-remitting condition with much improved patient survival [12, 13]. Treatment toxicity was reduced by shortening CYC exposure and switching to azathioprine (AZA) maintenance therapy after stable induction of remission [14]. More recently, the monoclonal anti-CD20 antibody rituximab (RTX) was introduced, both as an alternative to CYC for induction therapy [15], as well as an alternative to AZA for maintenance therapy [16, 17].

Despite these advances, patients still accumulate damage. This damage not only results from vasculitis activity, but also from adverse effects of treatment [18, 19]. The balance between disease activity and treatment toxicity could potentially be improved using personalized therapy. Studying genetic variation in relation to disease and treatment outcomes might be an interesting approach to achieve this [20]. Some genetic factors predict individual handling and/or sensitivity to a drug (i.e., pharmacogenetics), possibly allowing for individual dosing to achieve maximum efficacy and minimum toxicity. Other genetic factors affect inflammatory pathways and may indirectly affect drug response. These factors might help in guiding drug choice [21].

Employing genetics to apply personalized medicine has been studied before for several drugs used in several autoimmune diseases (reviewed in [20]). Since the genes studied are frequently associated with metabolic pathways of drugs or common inflammatory pathways, genetic factors found to be associated with relevant clinical outcomes in one type of autoimmune disease may also be relevant for patients with other autoimmune diseases (e.g., AAV) using the same drug for treatment.

This review will discuss gene polymorphisms studied in relation to outcomes of currently used treatment in AAV. Some of these polymorphisms are associated with inflammatory pathways, implying they might be mainly involved with disease outcomes such as disease activity, severity, and risk of relapse. Other polymorphisms are associated with pharmacogenetics, potentially affecting drug metabolism, and/or response to drugs. Subsequently, the likelihood of and steps needed for practical usage of these polymorphisms to improve AAV treatment will be discussed.

Cyclophosphamide (CYC)

CYC has been the main drug used for induction therapy of AAV since its first introduction [12], and is still one of

the primary options advocated for active AAV [17]. Unfortunately, CYC use is associated with adverse events such as leukopenia, infections, haemorrhagic cystitis, and development of infertility and malignancies.

CYC is a prodrug that requires activation by cytochrome P (CYP)450 enzymes in the liver into the active metabolites 4-hydroxycyclophosphamide and aldophosphamide. Catalysts for this conversion include CYP2B6, CYP2C9, CYP2C19, and CYP3A4 [22]. Several studies performed in SLE patients found that the genetic variant *CYP2C19**2 (681G>A; rs4244285) was associated with a reduced risk of ovarian toxicity [23–25], possibly at the cost of a reduced clinical response [23]. Two studies have investigated the clinical implications of *CYP450* gene variants for AAV.

Schirmer et al. studied several gene variants of *CYP2C9* and *CYP2C19* in relation to treatment outcomes of 196 mostly Caucasian AAV patients (166 GPA, 30 EGPA) treated with CYC. The presence of genetic variant *CYP2C9**2 (430C>T; rs1799583; minor allele frequency in reference population (MAF-RP) 0.267) or *CYP2C9**3 (1075A>C; rs1057910; MAF-RP 0.073), as was the case in 65 (33%) patients, was associated with a higher risk of leukopenia, with 36/65 (55%) variant carriers experiencing leukopenia compared to 49/131 (37%) patients with a wildtype genotype of *CYP2C9* (OR 2.1 [95% CI 1.1–3.8]). This difference existed only in patients treated with oral (not intravenous) CYC, and carriers of a *CYP2C9* variant (*CYP2C9**2 or *CYP2C9**3) treated with oral CYC also showed a trend towards a lower risk of refractory disease, with 20/65 (31%) variant carriers having refractory disease compared to 55/131 (42%) patients with a wildtype genotype of *CYP2C9* (OR 0.6 [95% CI 0.3–1.1]). *CYP2C9**2 and *CYP2C9**3 have been shown to result in a slower conversion of CYC to active metabolites [26, 27]. This slower activation might result in prolonged exposure to active metabolites, with increased CYC efficacy and toxicity as a result. *CYP2C19**2 (681G>A; rs4244285; MAF-RP 0.112), present in 55 (28%) patients, was not related to clinical endpoints in this study [28].

A study by Cartin-Ceba et al. based on data from the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (a randomized controlled trial (RCT) comparing RTX to CYC as induction therapy for AAV) analyzed 93 patients treated with CYC (out of 98 CYC treated patients in RAVE trial; 24 MPA, 74 GPA), most frequently of Caucasian ethnicity. In this study, carrying one or two variant SNPs of *CYP2B6* (1459C>T, rs3211371; MF-RP 0.07), present in 16 (17%) patients (HR 1.1 [95% CI 0.5–2.9]), or *CYP2C19* (681G>A, rs4244285; MF-RP 0.11), present in 18 (19%) patients (HR 1.4 [95% CI 0.6–3.7]), was not associated with time to complete remission compared to a homozygous wildtype.

Unfortunately, due to a relatively small sample size, statistical power of these findings is limited and more common SNPs (e.g., *CYP2C9*) could not be addressed [29]. Confirmation in a larger cohort study is still required to determine clinical relevance.

In conclusion, genetic variants of *CYP2C9* may be associated with clinically relevant differences in efficacy and toxicity of CYC. Especially the associations of *CYP2C9**2 and *CYP2C9**3 with leukopenia and treatment response warrant further study in a larger cohort.

Azathioprine (AZA)

AZA is currently the main drug used for maintenance therapy of AAV, after disease remission has been attained [17]. The Randomised Trial of CYC versus AZA during Remission in ANCA Positive Systemic Vasculitis (CYCAZAREM), published in 2003, showed that switching to AZA after induction of remission with CYC was equally effective as continued CYC therapy for prevention of relapse, allowing for reduced exposure to the cumulative toxic effects of CYC [14].

AZA is a prodrug that is converted enzymatically into 6-mercaptopurine (6-MP). Subsequently, it is converted into 6-thioguanine nucleotides (6-TGN), the active metabolite responsible for the immunosuppressive effects, by the enzyme hypoxanthine phosphoribosyltransferase. Two competitive pathways exist that instead convert 6-MP to inactive metabolites. The most well-known is the enzyme thiopurine methyltransferase (TPMT), that converts 6-MP into 6-methylmercaptopurine. The other pathway, xanthine oxidase, converts it into thiouric acid instead [30]. Several SNPs of *TPMT* resulting in reduced activity of the enzyme have been described. Reduced *TPMT* activity indirectly results in higher levels of 6-TGN [30, 31]. Because of a strongly increased risk of myelosuppression resulting from these increased 6-TGN levels, it has been advised that patients homozygous for genetic variants of *TPMT* either start with a tenfold reduced dose of AZA or use a different immunosuppressive drug [31]. Patients heterozygous for gene variants of *TPMT* are advised to start with a 30–70% reduced dose of AZA [31]. In an RCT performed in 2015, dose reduction in patients heterozygous for *TPMT* variants resulted in a strong reduction of adverse effects in this subgroup of inflammatory bowel disease patients, while maintaining efficacy. Because of the low frequency of *TPMT* variant carriers, with only 10% of patients in the intervention group requiring dose adjustment, no effect was shown in intention-to-treat analysis [32].

Two studies on *TPMT* genotype have been performed in AAV patients. The first study included 108 mostly

Caucasian patients, of whom 84 were diagnosed with GPA and 24 with MPA [33]. The second study included 207 Caucasian patients, including 152 GPA and 55 MPA patients [34]. Both studies combined heterozygous carriers of *TPMT**2 (238G>C, rs1800462, MAF-RP 0.006), *TPMT**3A (both of 460G>A, rs1800460, MAF-RP 0.028 and 719A>G, rs1142345 MAF-RP 0.029), *TPMT**3B (rs1800460) and *TPMT**3C (rs1142345) into one group ($n = 7/108$ (6%) [33], $n = 19/207$ (9%) [34], respectively) and contained no homozygous or compound heterozygous carriers of *TPMT* variants. Neither study found a significant association of *TPMT* genotype with adverse effects or efficacy of AZA therapy [33, 34]. This indicates that *TPMT* pretesting might not be as useful for AAV patients as it is in other types of inflammatory disease. However, the most recent study showed a trend towards a higher sensitivity to leukocytopenia in patients with lower *TPMT* activity, as well as a trend towards better relapse-free survival in patients with lower *TPMT* activity [34]. This suggests that there might be a small effect of *TPMT* genotype on AZA efficacy and toxicity, and that the sample size of these studies might simply be too small to detect these effects, in particular because of the low frequency (6–10%) of *TPMT* variant carriers. Of note, neither of these studies included patients that were homozygous for *TPMT* variants (prevalence ~0.3%) [33, 34].

In conclusion, adjustment of initial AZA dose may be less relevant for AAV patients carrying one gene variant of *TPMT*, as long as dose is adjusted based on frequent blood count measurements. This is not to say that *TPMT* pretesting is irrelevant in AAV, since homozygous variant carriers (1 in 178 to 1 in 3736 patients) have a strongly increased risk of severe myelosuppression from AZA [31].

Prednisolone (PRED)

Glucocorticoids, usually PRED, form a standard part of induction and maintenance therapy for AAV [17]. Although effective, PRED treatment in AAV is associated with a wide range of adverse effects affecting, among others, inflammation, the cardiovascular system and glucose, lipid, and bone metabolism. Some of these adverse effects contribute to treatment-related mortality [35–37]. A simplified scheme of glucocorticoid action is shown in Fig. 1. Several gene polymorphisms of the *glucocorticoid receptor* (*GR*) and *11 β -Hydroxysteroid dehydrogenase type 1* (*HSD11B1*) have been studied in relation to clinical outcomes [38, 39]. To our knowledge, only one observational cohort study has been performed that related gene polymorphisms affecting glucocorticoid sensitivity to relevant clinical outcomes in AAV [40].

Fig. 1 Simplified scheme of glucocorticoid action. Cortisol/prednisolone (blue) enters a cell through the cell membrane. Subsequently, it can be converted to inactive cortisone/prednisone (red) by hydroxysteroid dehydrogenase 11 β type 2 (HSD11B2), or reactivated by hydroxysteroid dehydrogenase 11 β type 1 (HSD11B1). Cortisol/prednisolone binds the glucocorticoid receptor (GR) in the cytoplasm. After binding, the complex moves to the nucleus where it affects expression of genes related to inflammation, volume homeostasis and carbohydrate, lipid, and protein metabolism. Gene polymorphisms of proteins marked with “*” are discussed in this review.

Glucocorticoid receptor (GR)

PRED, as well as the endogenous glucocorticoid cortisol, exert most of their effects through interaction with the GR, a member of the nuclear receptor family. This receptor binds its ligand in the cytoplasm and subsequently moves to the nucleus, where it affects gene expression. This results in a multitude of cardiovascular, metabolic, and inflammatory effects [41]. Several functional variants of the gene encoding the GR have been identified. Some of them, including *N363S* (rs6195) and *BclI* (rs41423247), are associated with increased glucocorticoid sensitivity. Others, such as *ER22/23EK* (rs6189 and rs6190) and *9 β* (rs6198), are associated with glucocorticoid resistance [41]. Last, *TthIII1* (rs10052957) is associated with glucocorticoid resistance mainly through linkage disequilibrium with *ER22/23EK* [42]. Haplotypes of the GR have been defined based on frequent combinations of SNPs [43]. Genetic variation in the *GR* has been linked to various cardiometabolic and inflammatory outcomes in the general population [38, 39], as well as to disease severity and PRED response in inflammatory conditions such as multiple sclerosis and RA [44–48].

In an observational cohort study involving 241 Caucasian patients, including 181 GPA and 60 MPA patients, two haplotypes of the GR were related to relevant clinical outcomes in AAV. Haplotype 4 (*ER22/23EK* + *9 β* + *TthIII1*, haplotype frequency(HF)-RP 0.024), present in

6% of patients, was associated with an increased risk of end-stage renal disease (HR 7.4 [95% CI 1.9, 28.7]) as well as an increased risk of mortality (HR 4.5 [95% CI 1.6–12.8]), suggesting that patients with this haplotype have a more severe disease phenotype. Homozygous carriers of haplotype 1 (*BclI*, HF-RP 0.366), entailing 6% of patients, had an increased risk of developing dyslipidemia (HR 4.1 [95% CI 1.8–9.6]), suggesting a less favourable metabolic phenotype in these patients. These differences existed despite similar glucocorticoid exposure in all haplotypes [40].

11 β -Hydroxysteroid dehydrogenase type 1 (HSD11B1)

HSD11B1 is an enzyme present in most cells of the body that regulates local glucocorticoid levels. In vivo, it mainly converts cortisone to its active metabolite cortisol [49]. Based on findings from an earlier study, the A allele of rs11119328 SNP was hypothesized to be associated with reduced expression of *HSD11B1* compared to the C allele [50].

In a cohort study of 241 Caucasian AAV patients (181 GPA, 60 MPA), the A allele of rs11119328 (MAF-RP 0.173) was associated with an increased risk of relapse in AAV despite similar glucocorticoid exposure to noncarriers of this allele, but only in noncarriers of Haplotype 1 of the *GR* (HR 2.5 [95% CI 1.5–4.1]). This combination exists in 19% of patients. These findings suggest that reduced local activation of glucocorticoids as a result of rs11119328 A results in a pro-inflammatory phenotype, but can be compensated for by increased sensitivity of the GR. Interestingly, glucocorticoid exposure did not differ between carriers and noncarriers of rs11119328 [40].

Overall conclusions on SNPs in PRED treatment

Two haplotypes of the *GR* (Haplotypes 1 and 4) and one SNP of *HSD11B1* (rs11119328) were associated with relevant clinical outcomes of AAV in one study. After confirmation of the effects in an independent cohort, it might be interesting to investigate adjustment of treatment. For homozygous Haplotype 1 carriers this would entail reduction of glucocorticoid exposure, since these patients are apparently at increased risk of developing metabolic adverse events from PRED. For Haplotype 4 carriers, research on early aggressive treatment to prevent end-stage renal disease and subsequent mortality might be interesting. Carriers of rs11119328 without Haplotype 1 might benefit from prolonged maintenance therapy of glucocorticoids with or without another immunosuppressive drug, to compensate for the increased relapse risk when receiving standard treatment.

Rituximab (RTX)

RTX is a chimeric immunoglobulin 1 (IgG1) monoclonal antibody targeting CD20, present on B-cells. It is a relatively new drug for remission induction in AAV. The RAVE trial, published in 2010, showed it to be non-inferior to CYC [15, 51]. More recently, the results of the Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial indicated that RTX might be superior to AZA for maintenance of remission after CYC induction [16, 52].

As RTX is a monoclonal antibody targeting a specific inflammatory pathway, response to RTX is mainly influenced by genetic variation in its effector pathways rather than its metabolic pathway. Three studies have been performed investigating inflammation-related gene variants and their association with outcome of RTX treatment [29, 53, 54].

Fcγ receptor (FcγR)

RTX is capable of depleting B-cells through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) by binding of its Fc fragment to FcγR. The affinity of FcγR is affected by genetic variation and potentially influences RTX response. An *FcγRIIIa* SNP has previously been associated with clinical response to RTX in RA patients [55, 56], as well as other autoimmune diseases [57, 58].

In a study using data from the RAVE trial, which included 96 mostly Caucasian patients receiving RTX treatment (out of 99 in RAVE trial; 74 GPA, 24 MPA, and 1 missing diagnosis), the 27 (28%) homozygous carriers of the *FcγRIIIa* 519 AA genotype (rs1801274 and MAF-RP 0.55), associated with increased receptor affinity for IgG3 and capability of binding IgG2, had a shorter time to complete remission compared to the GG and GA variants (HR 2.3 [95% CI 1.4–3.9]). Interestingly, this association was independent of the induction treatment used, as it was also present in the CYC-treated group. The combination of *FcγRIIIa* 519 (rs1801274) AA and *FcγRIIIa* 559 (rs396991; MAF-RP 0.28) GG genotypes ($n = 12$, five taking CYC, and seven taking RTX) was associated with a higher frequency of disease remission, again irrespective of induction treatment used (OR 8.2 [95% CI 1.5–152]) [29]. These results were in line with an earlier study showing that the combination *FcγRIIIa* 519 GG + *FcγRIIIa* 559 TT was associated with an increased risk of relapse in GPA [59]. Based on the results of these studies, the FcγRs seem to play a role in AAV pathogenesis. One hypothesis is that genetic variation in *FcγRIIIa* and *FcγRIIIa* affects the binding of ANCA to these receptors, resulting in increased ANCA clearance in those carrying *FcγRIIIa* 519 GG + *FcγRIIIa* 559

TT [29, 59]. Another hypothesis is that *FcγRIIIa* 519 GG + *FcγRIIIa* 559 TT reduces clearance of *S. aureus*, resulting in chronic nasal carriage as a risk factor for relapse [59, 60]. Alberici et al. did not find a relation of rs1801274 or rs396991 with treatment response, although they did not analyse homozygous variant carriers separately [53].

B-cell activator of the tumor necrosis factor family (BAFF)

BAFF is a cytokine relevant for B-cell development and survival. In autoimmune diseases, it is thought to promote inflammation by stimulating survival and proliferation of autoreactive B cells [61]. BAFF levels in AAV patients are increased compared to healthy controls. In contrast to other autoimmune diseases, BAFF levels showed no positive correlation with auto-antibody levels in AAV [62–64]. The rs9514828 SNP of BAFF has previously been associated with RTX response rate in RA [65].

In a European cohort of 213 AAV patients (185 GPA, 29 MPA) investigating a panel of 18 candidate SNPs potentially associated with response to RTX, the *BAFF* SNP rs3759467 (MAF-RP 0.173) was associated with shorter time to relapse within 12 months ($P = 2.9 \times 10^{-4}$) [53]. This finding was confirmed in a replication cohort of 109 patients from the United Kingdom ($P = 0.01$), but existed only in homozygous carriers of the C variant allele ($n = 7$, or 2% of combined cohort; HR 12.4, $P = 7 \times 10^{-4}$ for primary cohort, HR 5.4, $P = 0.002$ for replication cohort). Besides a shorter time to relapse within 12 months after first RTX infusion, patients with the CC genotype of rs3759467 had a higher rate of detectable peripheral B-cells ($3/6 = 50\%$ vs. $22/161 = 14\%$; $P = 0.01$) and less reduction of IgM levels ($1.0 [1.0–1.3]$ vs. $1.5 [1.0–10.9]$, $P = 0.02$) compared to TC and TT genotypes. The association was not present in MPO-ANCA positive patients, although this might be due to the limited sample size of the study and the low frequency of homozygous variant carriers. The study did not show any association of other BAFF-related SNPs such as rs9514828 with clinical response in AAV. The exact role of the rs3759467 SNP in RTX response is not yet clear. Most likely, the SNP affects B-cell survival, possibly through an increase in BAFF levels [53]. Hypothetically, patients with the rs3759467 SNP might benefit from addition of the monoclonal antibody belimumab, which blocks binding of BAFF to B-cell receptors [66].

Interleukin-6 (IL-6)

IL-6 is a cytokine with a wide range of functions. In the immune system, it is important for inducing the acute phase response and has a role in B-cell maturation and plasma cell proliferation. In autoimmune disease, it contributes to

on-going inflammation through stimulation of immune cell proliferation and activation of lymphocytes. It also skews development of naïve T-cells towards T helper (T_H)17 cells rather than forkhead box protein 3 positive regulatory T (FOXP3⁺ T_{reg}) cells [67]. In RA, being homozygous for the −174 (rs1800795) C variant of the *IL-6 promoter region* has been associated with poor response to RTX [68].

In 2012, Robledo et al. conducted an observational study investigating the −174 (rs1800795, MAF-RP 0.416) SNP in a Spanish Caucasian cohort of 144 patients with varying systemic autoimmune diseases, including 16 AAV patients (subtypes not specified). They found that homozygous carriers of the C variant of this SNP (9% of patients) had a significantly higher risk of nonresponse to RTX compared to carriers of CG and GG variants (4/13 [31%] vs. 13/118 [11%]; Fisher exact $P = 0.049$) [54]. Alberici et al. did not find such an association in their study of 213 European AAV patients (185 GPA, 29 MPA), although they did not analyse homozygous carriers of the C variant of rs1800795 separately [53].

The functional relation between this IL-6 SNP and RTX response is not entirely clear. A feasible hypothesis is that the reduced efficacy of RTX in −174 C homozygotes results from improved B-cell survival mediated by IL-6. An association of −174 genotype with serum IL-6 levels was not found, although a great interindividual variation was noted [68]. Theoretically, −174 C homozygotes might benefit from addition tocilizumab to treatment, as this drug blocks the IL-6 receptor [69].

IL-2–IL-21 region

The rs6822844 SNP in the *IL-2–IL-21* region on chromosome 4 has previously been associated with risk of autoimmunity and response to RTX therapy [70]. IL-2 induces T-cell proliferation and promotes differentiation of regulatory T-cells while inhibiting Th17 differentiation and inducing activation-induced cell death [71]. IL-21 has a broad range of effects on the immune system, including both stimulatory and regulatory effects. Several autoimmune diseases have been associated with increased levels of IL-21 [72].

When specifically analysing MPO-ANCA positive patients ($n = 29$), Alberici et al. found an association of SNP rs6822844 (MAF-RP 0.153) in the *IL-2–IL-21* area (MAF 0.127) with risk of relapse within 6 months (Bonferroni corrected log rank $P = 0.03$) and time to relapse within 12 months (Bonferroni corrected log rank $P = 0.007$) [53]. The mechanism behind this might be that the G variant of rs6822844 promotes ADCC through IL2-mediated stimulation of natural killer cell proliferation and cytotoxicity [70, 71]. The finding was not confirmed in a smaller replication cohort ($n = 19$; $P = 0.17$), although this could be

due to a lack of statistical power, as there was a trend towards a better treatment response in homozygous carriers of the G variant of rs6822844 (response in 15/16 [94%] with GG, 2/3 [66%] with GT genotype) [53].

Overall conclusion on SNPs in RTX treatment

In conclusion, the SNPs rs1801274 (*FcγRIIIa*), rs396991 (*FcγRIIIa*), rs3759467 (*BAFF*), rs1800795 (*IL-6*), and rs6822844 (*IL-2–IL-21*) all appear to affect response to RTX treatment. All studied polymorphisms are related to effector pathways rather than drug metabolism, contrary to the gene variants studied in relation to CYC and AZA treatment. Therefore, these effects are not specific to RTX treatment and affect treatment efficacy more than toxicity. In some cases, such as SNPs related to *BAFF* and *IL-6*, it might be interesting to study whether patients with specific gene variants might benefit from addition of therapy specifically targeting the respective factor, such as belimumab (targeting BAFF signalling) and tocilizumab (targeting the IL-6 receptor). This would first require confirmation of increased BAFF or IL-6 signalling in patients with the respective genotypes.

Other genetic associations with outcomes of ANCA-associated vasculitis

To our knowledge, no studies have been performed in AAV patients of gene variants in relation to efficacy and toxicity of methotrexate or mycophenolate mofetil (MMF).

Several other genetic variants, not related to a specific treatment, have been associated with clinical outcomes of AAV. Examples include gene polymorphisms of *monocyte chemoattractant protein-1* [73], *alpha-1 antitrypsin* [74], and *human leukocyte antigen (HLA)–DPB1* [75].

None of these gene variants currently has practical relevance in AAV treatment.

Discussion

Several observational studies have been performed regarding genetic factors associated with response to CYC, RTX, PRED, and AZA therapy in AAV. An overview of proteins encoded by potentially relevant SNPs per drug used in AAV treatment is shown in Fig. 2. The main results per study are summarized in Tables 1 and 2.

While pharmacogenetics in the case of synthetic immunosuppressive drugs such as CYC, AZA, and PRED involves mainly genetic variation in metabolic or functional pathways of these drugs, potentially allowing individual dosing of these drugs, genetic variants studied in relation to

RTX response are mainly involved in inflammatory pathways. The latter may not necessarily be specific to RTX-treatment, as was seen for gene variants of the *FcγR* [29, 59]. On the other hand, the inflammatory pathways identified might be interesting for targeted therapy, espe-

cially considering the large variety of targeted drugs currently available.

Theoretically, pretesting SNPs will help improve prediction of efficacy and toxicity of drugs used for AAV treatment. Treatment dose or modality could be adjusted in carriers of a genetic variant in order to optimize treatment outcomes for these patients. As a result, toxicity and healthcare costs would be reduced for these patients, especially considering the reduction of genotyping costs over recent years. Ideally, treatment modality and dose for the individual patient would become partly based on a panel of relevant SNPs.

Despite the theoretical benefits of applying genetic testing, several factors hinder (immediate) application of the reviewed findings to clinical practice.

First, except for one study [53], none of the studies have used replication cohorts. Also, most of the studies do not mention correction for multiple comparisons. Therefore, in order to exclude type I errors (i.e., false-positive findings), the study results should be confirmed in replication cohorts.

Second, most of these studies have been performed in Caucasian patients. The frequency of genetic polymorphisms is known to vary greatly between ethnicities. Therefore, an important and frequent SNP in one population might be much less relevant in another, limiting the external validity of pharmacogenetics studies to the ethnic group in

Fig. 2 Treatment of ANCA-associated vasculitis and potential targets for personalized treatment. AZA azathioprine, BAFF B-cell activator of the tumor necrosis factor family, CYC cyclophosphamide, CYP cytochrome P, *FcγR* *Fcγ* receptor, GR glucocorticoid receptor, HSD11B1 11β-hydroxysteroid dehydrogenase type 1, IL interleukin, MMF mycophenolate mofetil, MTX methotrexate, PRED prednisolone, RTX rituximab.

Table 1 overview of drug metabolism-related gene polymorphisms in relation to clinical outcomes in ANCA-associated vasculitis.

Drug/gene	Participants (ethnicity)	MAF	Efficacy	Power	Toxicity	Power	Ref.
CYC							
CYP2C9	196 (96% Caucasian)	0.171	Trend: less refractory disease in carriers OR 0.44 (95% CI 0.19–1.05)	0.64	Higher risk of leukopenia in carriers OR 2.08 (95% CI 1.14–3.80)	0.83	[28]
CYP2C19	196 (96% Caucasian)	0.153	NS, refractory disease: OR 1.37 (95% CI 0.60–3.10)	0.16	NS, leukopenia OR 0.92 (95% CI 0.49–1.72)	0.07	[28]
	93 (97% Caucasian)	0.108	NS, complete remission (AA vs. GG/GA): HR 2.09 (0.31–7.82)	0.11	NS, data not shown	*	[29]
CYP2B6	93 (97% Caucasian)	0.091	NS, complete remission (TT vs. CC/CT): HR 0.31 (95% CI 0.01–1.62)	0.13	NS, data not shown	*	[29]
AZA							
TPMT	108 (Caucasian)	0.032	NS, relapse-free survival log rank $P = 0.50$	0.18	NS, leukopenia: Chi square $P = 0.69$	0.08	[33]
	207 (Caucasian)	0.046	NS, RFS, Cox regression $P = 0.66$	0.23	NS, Leukopenia: logistic regression $P = 0.85$	0.08	[34]
PRED							
GR HT 1	241 (Caucasian)	0.247	Counteracts relapse risk from HSD11B1 HR HT1*HSD11B1 0.3 (95% CI 0.1–0.6)	>0.99	Homozygous: more dyslipidaemia	0.80	[40]
GR HT 4	241 (Caucasian)	0.031	Higher risk of ESRD and mortality ESRD: HR 7.4 (95% CI 1.9, 28.7)	0.32	NS, data not shown	*	[40]
			Mortality: HR 4.5 (95% CI 1.6, 12.8)	0.78			
HSD11B1	241 (Caucasian)	0.190	Higher risk of relapse in carriers HR 2.5 (95% CI 1.5–4.1)	0.98	NS, data not shown	*	[40]

AZA azathioprine, CYC cyclophosphamide, CYP Cytochrome P, ESRD end-stage renal disease, GP general population, GR glucocorticoid receptor, MAF minor allele frequency, NA not analysed, NS no significant differences, PRED Prednisolone, TPMT thiopurine methyltransferase. An asterisk indicates insufficient information available to calculate statistical power.

Table 2 overview of inflammation-related gene polymorphisms in relation to clinical outcomes in ANCA-associated vasculitis.

Drug/gene	Participants (ethnicity)	MAF	Efficacy	Power	Toxicity	Ref.
BAFF	213 (Europe), 109 (UK)	0.172	Homozygous: higher risk of and shorter time to relapse Risk of relapse: OR 8.8, $P < 0.01$ Time to relapse: HR 7.3, $P 8.5 \times 10^{-6}$	*	NA	[53]
Complement C1QA	213 (Europe), 109 (UK)	0.380	NS, time to relapse $P > 0.99$	*	NA	[53]
FCγR IIA	96 (93% Caucasian)	0.500	Shorter time to complete remission in homozygous HR: 2.33 (95% CI 1.36–3.9)	0.86	NA	[29]
FCγR IIB	213 (Europe), 109 (UK)	0.495	NS, time to relapse $P > 0.99$	*	NA	[53]
	213 (Europe), 109 (UK)	0.110	NS, time to relapse $P > 0.99$	*	NA	[53]
	96 (93% Caucasian)	0.104	NS, complete remission HR 3.34 (95% CI 0.18–16.3)	0.16	NA	[29]
FCγR IIIA	213 (Europe), 109 (UK)	0.439	NS, time to relapse $P > 0.99$	*	NA	[53]
	96 (93% Caucasian)	0.280	NS, complete remission HR 1.44 (95% CI 0.67–2.78)	0.16	NA	[29]
IL-2-IL-21	213 (Europe), 109 (UK)	0.127	MPO-AAV: less relapse, longer time to relapse (not in UK cohort) Risk of relapse: $P = 0.03$ Time to relapse: $P < 0.01$	*	NA	[53]
IL-6	213 (Europe), 109 (UK)	0.359	NS, time to relapse $P > 0.99$	*	NA	[53]
	144 (Caucasian), 16 AAV	0.306	More non-response in homozygous carriers OR 4.03 (95% CI 0.78–16.97)	0.39	NA	[54]
NFKB1	213 (Europe), 109 (UK)	0.383	NS, time to relapse $P > 0.99$	*	NA	[53]
TGFB1	213 (Europe), 109 (UK)	0.090	NS, time to relapse $P > 0.99$	*	NA	[53]

BAFF B-cell activator of the tumor necrosis factor family, *FcγR* Fcγ receptor, *IL-6* interleukin-6, NA not analysed, NS no significant differences. An asterisk indicates insufficient information available to calculate statistical power.

which the studies were performed. To illustrate, Black and Hispanic lupus nephritis patients respond better to MMF than CYC, while MMF and CYC are equally effective in Asian and Caucasian patients [76].

Third, the studies deal with genetic variants that occur only in a minority of patients. This means that large sample sizes will be required to detect relevant differences in clinical endpoints associated with these variants. Furthermore, all patients need to be genotyped to find the few patients that might benefit from adjustment of therapy. As AAV is a rare disease group, the required sample size will often be difficult to achieve, especially in a single-center setting.

Last, all of these studies were small observational cohort studies. In order to find the right dose adjustment or alternative drug and to confirm that this will achieve the desired improvement in treatment outcomes, RCTs should be performed. These studies should use relevant clinical outcomes to evaluate adjustment of therapy based on gene variants. Again, these studies require large sample sizes because of the large number of patients needed to genotype to find a patient requiring adjustment of therapy and the even larger number needed in to prevent occurrence of an adverse effect. To illustrate, a large multicenter RCT investigating thiopurine dose reduction in inflammatory bowel disease patients carrying *TPMT* gene variants (Thiopurine response

Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics trial) did not find a reduction of thiopurine toxicity for the intervention group in intention-to-treat analysis, even though a large reduction of toxicity was found within *TPMT* variant carriers. This is most likely because the majority of patients (90%) had a normal *TPMT* genotype and received a normal thiopurine dose even in the intervention group [32]. Because of the tenfold increased risk of severe myelosuppression in the occasional homozygous variant carrier [31], *TPMT* pretesting may be relevant regardless. Because of small effects per genetic variant, combined with the low prevalence of both these gene variants and AAV, it might be most feasible to design one RCT in which multiple gene variants are measured simultaneously to inform treatment adjustment in the intervention group.

The studies reviewed in this paper have identified some interesting genetic variants that might be used to improve treatment outcomes after the previously mentioned hurdles have been overcome. On the other hand, based on the strength of current data, further confirmation of findings is needed before an RCT should be performed. Additional useful SNPs might be discovered by using data from genome-wide association studies, such as the one performed by Lyons et al. [5]. To illustrate, a GWAS study performed in RA patients identified several genetic variants

associated with response to anti-TNF therapy [77]. Furthermore, a systematic review of GWAS and meta-analyses of genetic variants associated with AAV identified several genetic variants associated with either PR3-AAV or MPO-AAV. One of the main implications from this study was the possible involvement of the interferon-gamma pathway in the pathogenesis of AAV, making it a possible target for future study on targeted therapy [78]. The association of these gene variants with relevant clinical outcomes may be tested by genotyping samples from previously performed multicenter clinical trials. The on-going plasma exchange and glucocorticoid dosing in the treatment of antineutrophil cytoplasm antibody associated vasculitis trial, for example, may provide interesting samples and data to this end [79].

In summary, several studies have been performed regarding genetic polymorphisms in relation to efficacy and toxicity of CYC, RTX, PRED, and AZA for treatment of AAV. Several challenges will need to be overcome for clinical application of these results, including independent replication of findings, identification of relevant SNPs per ethnic group, performing large enough multicenter studies to detect relevant clinical effects of SNPs that are present in a minority of patients, and performing large multicenter RCTs to evaluate personalized therapy based simultaneously on multiple SNPs to improve outcomes in this small group. Additional polymorphisms may be identified using GWAS data or samples from previously performed multicenter clinical trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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