



Vasculitis Pathogenesis: Can We Talk About Precision Medicine?

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Precision medicine is designing the medical care by taking into account the individual variability for each person. We have tried to address whether the existing data may guide precision medicine in primary systemic vasculitides (PSV). We have reviewed genome-wide association studies (GWAS) data, lessons from monogenic mimics of these diseases, and biomarker studies in immunoglobulin A vasculitis/Henoch–Schönlein purpura, Kawasaki disease, anti-neutrophil cytoplasmic antibody-associated vasculitis, polyarteritis nodosa (PAN), Takayasu arteritis, and Behçet's disease (BD). GWAS provide insights about the pathogenesis of PSV while whole exome sequencing studies lead to discovery of monogenic vasculitides, phenotype of which could mimic other types of vasculitis such as PAN and BD. Monogenic vasculitides form a subgroup of vasculitis which are caused by single gene alterations and discovery of these diseases has enabled more specific therapies in these patients. With increasing number of studies on biomarkers, new targets for treatment appear and better and structured follow-up of PSV patients will become possible. Proteomics and metabolomics studies are required to better categorize our patients with PSV so that we can manage them appropriately and offer more targeted therapy.

Keywords: systemic vasculitis, genome-wide association studies, monogenic vasculitis, biomarker, precision medicine

INTRODUCTION

Precision medicine is defined as designing the medical care for each person with optimum efficiency in prevention and treatment by considering the individual variability in genes, environment, and life style (1). Precision medicine enables to translate benchside knowledge to bedside and provide “targeted” treatment for the patient. Genetic or molecular profiling of patients is very important for precision medicine; however, there are limited data in primary systemic vasculitides (PSV).

Primary systemic vasculitides are heterogeneous. Since these are mostly rare diseases, we lack the vast translational medicine data we have in common diseases such as rheumatoid arthritis. Furthermore, controlled studies in PSV might not reflect the real-life scenarios. Thus, it is important to tailor treatment according to each patient instead of applying general recommendations which are based on controlled studies.

Thanks to improved and *cheaper* genomic techniques, we have gathered important data that may be used on the bedside. Genetic studies including mainly genome-wide association studies (GWAS) and whole exome sequencing studies have led to important discoveries in disease pathogenesis of PSV. However, we lack pharmacogenomics studies. We are also in need of more biomarker studies to

provide novel candidate targets for therapy and help us to predict prognosis. Predicting poor prognosis or high relapse rate through biomarkers could guide physicians to tailor treatment according to the patient. More intensified immunosuppressive therapy could be required in patients with poor prognosis while longer maintenance therapy could prevent relapses in patients with high relapse risk.

In this article, we review the GWAS results, monogenic vasculitis, and existing biomarkers, which have implications on precision medicine in treatment of PSV. We have mainly focused on immunoglobulin A vasculitis/Henoch–Schönlein purpura (IgAV/HSP), Kawasaki disease (KD), polyarteritis nodosa (PAN), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), Takayasu arteritis (TA), and Behçet's disease (BD).

WHAT WE HAVE LEARNED FROM GWAS IN PSV

Genome-wide association studies provide an important step forward in our understanding of vasculitis pathogenesis. Focusing on subgroups of patients with PSV will provide further insight while profiling patients to tailor treatment individually. There are several GWAS in patients with different types of PSV such as IgAV/HSP, KD, AAV, TA, and BD (Table 1). There is no GWAS in PAN patients at present.

Immunoglobulin A Vasculitis/Henoch–Schönlein Purpura

In the GWAS of 285 Spanish patients with IgAV/HSP, Lopez-Mejias et al. observed *p* values of potential relevance (below genome-wide significance) for the positions 11 and 13 of *HLA-DRB1* (2). This study implicated HLA Class II in the pathogenesis

of the disease. Larger multinational studies may be needed to confirm this association and look for associations with certain cytokines and aberrant glycosylation of IgA1. Investigation of the association of the IgAV/HSP kidney disease with IgA nephropathy in a combined study will also be of major interest, since the IgA nephropathy has been claimed to be in the spectrum of the disease, lacking systemic features. So far, the GWAS in IgAV/HSP has not had a substantial offer to precision medicine.

Kawasaki Disease

There are more than 10 GWAS performed in KD (3–16). The results of these GWAS may affect our medical practice since these help us to define KD patients who are at risk of developing intravenous immunoglobulin (IVIG) resistance and/or coronary involvement. The susceptibility genes associated with the development and severity of coronary involvement were mainly identified as *KCNN2*, *TIAM1*, *NEBL*, *TUBA3C*, *PEL11*, and *PLCB4/PLCB1* (3, 6, 7, 13, 14). Shimizu et al. performed a pathway-based association analysis on a GWAS data set to identify risk alleles for coronary artery abnormalities in KD (17). They demonstrated susceptibility variants in the *SLC8A1* calcium signaling pathway which were associated with development of KD and coronary artery abnormalities (17). Their results suggested this pathway as a therapeutic target supporting the use of calcineurin inhibitors in acute KD.

Recently, Kwon et al. have performed an IVIG-response stratified GWAS to search for IVIG-response-specific genetic variants associated with KD (11). They have identified an intronic single-nucleotide polymorphism (SNP) in *BCL2L11* which was significantly associated with KD in IVIG responders but not in non-responders (11). In the first weighted genetic risk score study based on a GWAS in KD, Kuo et al. have presented the predictive

TABLE 1 | The GWAS in primary systemic vasculitides.

Disease	Number of GWAS performed	Reference	The country of origin	Number of patients ^a	Genes found	Implications in treatment
IgAV/HSP	1	(2)	Spain	285	<i>HLA-DRB1</i> (potential relevance; not genome-wide significance)	–
KD	14	(3–16)	Taiwan, Korea, and Japan	262–1,182	<i>BCL2L11</i> , <i>KCNN2</i> , <i>TIAM1</i> , <i>NEBL</i> , <i>TUBA3C</i> , <i>PEL11</i> , <i>PLCB4/PLCB1</i> , <i>CRP</i> , <i>HLA</i> , <i>CD40</i> , <i>BLK</i> , <i>FCGR2A</i> , <i>NMNAT2</i> , <i>HCP5</i> , <i>COPB2</i> , <i>ERAP1</i> , <i>NAALADL2</i> , <i>ZFX3</i> , <i>NFKBIL1</i> , <i>LTA</i> , <i>DAB1</i> , <i>IGHV</i>	<i>SLC8A1</i> (Ca signaling pathway): use of calcineurin inhibitors in KD
AAV	3	(21–23)	European countries and UK	492–1,986	<i>HLA-DQ</i> , <i>HLA-DP</i> , <i>SERPINA1</i> , <i>PTPN22</i> , <i>PRTN3</i> , <i>SEMA6A</i>	–
TA	3	(24–26)	Turkey, North America, and Japan	379–693	<i>HLA-B/MICA</i> , <i>HLA-DQB1/HLA-DRB1</i> , <i>FCGR2A/FCGR3A</i> , <i>IL12B</i> , <i>IL6</i> , <i>RPS9/LILRB3</i>	IL6: use of anti-IL-6 drugs IL12B: use of therapies targeting IL-12/IL-23
BD	9	(27–35)	Turkey, UK, China, Korea, Japan, Thailand, Iran, Afghanistan, Lebanon, Cape Verde, Curacao, Dominican Republic, Greece, Israel, Jordan, Morocco, and Surinam	152–3,645	<i>HLA class I</i> (especially <i>HLA-B51</i>), <i>IL10</i> , <i>IL23R-IL12RB2</i> , <i>ERAP1</i> , <i>STAT4</i> , <i>GIMAP</i> , <i>CCR1</i> , <i>KLRC4</i> , <i>FUT2</i> , <i>IL12A</i> , <i>NAALADL2</i> , <i>YIPF7</i> , <i>KIAA1529</i> , <i>CPVL</i> , <i>UBAC2</i> , <i>LOC100129342</i> , <i>UBASH3B</i>	IL12A, IL23R-IL12RB2: use of therapies targeting IL-12/IL-23

AAV, ANCA-associated vasculitis; BD, Behçet's disease; GWAS, genome-wide association studies; IgAV/HSP, immunoglobulin A vasculitis/Henoch–Schönlein purpura; KD, Kawasaki disease; TA, Takayasu arteritis; IL, interleukin; CRP, C-reactive protein.

^aThe minimum and maximum number of patients were shown when there are more than one GWAS.

model integrating the additive effects of 11 SNPs to provide a prediction for IVIG responsiveness (18). Thus these studies may be regarded to have an effect on precision medicine since they may define how we treat these patients in the coming days.

On the other hand, other GWAS have identified susceptibility genes associated with KD (mainly *HLA*, *CD40*, *BLK*, *FCGR2A*, *NMNAT2*, *HCP5*, *COPB2*, *ERAP1*, *NAALADL2*, *ZFHX3*, *NFKBIL1*, *LTA*, *DAB1*, *IGHV*) (4, 5, 9, 10, 12, 15, 16).

In a study of replication and meta-analysis of GWAS in KD, Chang et al. identified risk alleles confirming the importance of B lymphoid tyrosine kinase (*BLK*) which suggested a role for B-cell-mediated therapies in KD (19). Lv et al. reviewed the genes which had statistically significant associations with KD, from candidate gene studies and GWAS (20). They showed that cellular calcium ion hemostasis, immune and inflammatory responses were the main functional categories representing associated genes (20).

ANCA-Associated Vasculitis

The GWAS of AAV has indeed provided quite important data on the genetic disparities of these diseases. In the first GWAS in AAV, Lyons et al. demonstrated that granulomatous polyangiitis (GPA, Wegener's) and microscopic polyangiitis were genetically distinct diseases and anti-myeloperoxidase ANCA was associated with *HLA-DQ* while anti-proteinase 3 (anti-PR3) ANCA was associated with *HLA-DP*, *SERPINA1*, and *PRTN3* (21). This study has revealed the antigenic specificity of ANCA forms the strongest associations in AAV. Xie et al. identified risk variants for GPA in *SEMA6A* and *HLADP* (22). Thus, these GWAS have not only had an impact on our vasculitis classification but also provided us data on how to predict the course in these patients.

On the other hand, Merkel et al. identified genome-wide significant associations for AAV at the *HLA-DPB1*, *SERPINA1*, *PTPN22*, and *PRTN3* loci with the largest effect coming from *HLA-DPB1* polymorphisms (23).

Takayasu Arteritis

In a GWAS of TA patients from Turkey and North America, Saruhan-Direskeneli et al. identified susceptibility loci as *HLA-B/MICA*, *HLA-DQB1/HLA-DRB1*, and *FCGR2A/FCGR3A* (24). They also identified additional association effects of *PSMG1*, *IL12*, and *IL23* that could not reach genome-wide significance. The association with *IL12B* variants were confirmed in Japanese TA patients in a genome scanning study (25). In the most recent GWAS of TA, Renauer et al. identified susceptibility variations for TA at *IL6*, *RPS9/LILRB3*, and an intergenic locus on chromosome 21q22 (26). Two of these loci, *IL6* and *RPS9/LILRB3* have roles in immunoregulatory pathways which could enlighten the immunopathogenesis of TA. This may be reflecting our bedside experience for the use of anti-interleukin-6 (IL-6) in TA patients and thus serve as an example for precision medicine if we could have genotyped all these patients. On the other hand, blocking IL-12/IL-23 pathway may also be an option for selected patients.

Behçet's Disease

There are nine GWAS performed in BD patients that have indeed served us to understand the pathogenesis of the disease

(27–35). These studies have shown genome-wide significant associations with *HLA class I* (especially *HLA-B51*), *IL10*, *IL23R-IL12RB2*, *ERAP1*, *STAT4*, *GIMAP*, *CCR1*, *KLRC4*, *FUT2*, *IL12A*, *NAALADL2*, *YIPF7*, *KIAA1529*, *CPVL*, *LOC100129342*, *UBASH3B*, and *UBAC2* regions in BD (27–35). It is important to note that endoplasmic reticulum aminopeptidase 1 (ERAP1) is an endoplasmic reticulum protein functioning as an aminopeptidase trimming peptides for loading onto MHC Class I (36). It has been demonstrated that ERAP1 contributed to the risk for BD in *HLA-B51* positive individuals (31). The variants identified in BD GWAS suggest defects in pathways of adaptive and innate immune responses, sensing/processing of microbial and danger signals, and inflammatory pathways shared with spondyloarthropathies (37). These studies have suggested that the improper folding of *HLA-B51* is to trigger endoplasmic reticulum stress leading to the IL-12/IL-23 pathway activation. Bakir-Gungor et al. performed a pathway analysis using BD GWAS data from two populations and demonstrated that shared pathways were mitogen-activated protein kinase signaling, transforming growth factor β signaling, focal adhesion, extracellular matrix–receptor interaction, complement and coagulation cascades, and proteasome pathways (38). Thus, GWAS in BD have mainly provided us answers for the pathogenesis of the disease. However, blocking IL-12/IL-23 pathway is being considered in light of these findings. Whether the benchside will hold true *in vivo* remains to be seen.

All these GWAS performed in PSV patients points to certain mechanisms in the pathogenesis. We clearly lack data on pharmacogenomics. And we need larger cohort of patients who are profiled genetically and phenotypically, to identify the pathogenesis and possibly the disease course and highlight treatment options.

CAN MONOGENIC VASCULITIDES TEACH US ANYTHING?

Most of our common rheumatic diseases are multifactorial diseases with the contribution of certain SNPs (as described above) for disease risk. These SNPs have a rather small impact or introduce a small risk factor for the occurrence of that vasculitis. However, in recent years we have become aware of single gene defects that have a major impact in the inflammatory pathway, causing a phenotype often mimicking a well-known vasculitis (39). Description of monogenic vasculitides has provided novel insights into disease pathogenesis and pathways of inflammation in general. On the other hand, they have enabled targeted therapies in these single-gene disorders. Deficiency of adenosine deaminase 2 (*DADA2*), stimulator of interferon genes (*STING*)-associated vasculopathy with onset in infancy (*SAVI*), and haploinsufficiency of *A20* (*HA20*) are the recently defined monogenic vasculitides. Indeed, the association of monogenic complement deficiencies with systemic lupus erythematosus had taught us the role of complement in lupus pathogenesis. Similarly, the affected pathways in these diseases may enable us to design more targeted therapies in vasculitides. For example, one may need to concentrate more on the nuclear factor- κ B (*NF- κ B*) pathway or the role of macrophages.

Deficiency of Adenosine Deaminase 2

Deficiency of adenosine deaminase 2 is associated with *CECR1* mutations and causes a PAN-like vasculopathy and autoinflammatory features (40). ADA2 is thought to trigger the macrophages to have an inflammatory phenotype and endothelial integrity is compromised in DADA2 (41). As a result of these, vasculopathy and inflammation occur.

The phenotype mimics PAN with the presence of aneurysms in visceral arteries. Clinical presentation is a spectrum from only cutaneous lesions to full blown systemic disease (40–42). DADA2 patients may also present with only hematological features such as pure red cell anemia (43). Anti-tumor necrosis factor (anti-TNF) drugs are effective in the treatment of patients with vasculitis whereas response to conventional treatment is poor. Hematopoietic stem cell transplantation is needed in severe cases (40, 44, 45). Hematopoietic stem cell transplantation should be especially considered in DADA2 patients with bone marrow failure who display predominant hematological features (46).

STING-Associated Vasculopathy With Onset in Infancy

Stimulator of interferon genes-associated vasculopathy with onset in infancy is a type I interferonopathy caused by gain-of-function mutations in *TMEM173* encoding for STING (47). STING hyperfunction results in constitutive transcription of type I interferons (IFNs) which bind to type I IFN receptors and signal through Janus activating kinase/signal transducer and activator of transcription (JAK/STAT) pathway (47, 48).

Phenotype of SAVI patients could resemble GPA with severe cutaneous vasculopathy, pulmonary involvement, and ANCA positivity in some patients (49). Recently, Sanchez et al. have shown improvement in SAVI patients with baricitinib which is a selective JAK1 and JAK2 inhibitor (50).

Haploinsufficiency of A20

Haploinsufficiency of A20 is a recently defined autosomal dominant autoinflammatory syndrome resembling BD, caused by loss-of-function mutations in *TNFAIP3* encoding for A20 protein (51). Restriction of A20 function augments NF- κ B signaling which makes NF- κ B-dependent proinflammatory cytokines such as TNF- α , IFN- γ , IL-17, IL-1 β potential targets for treatment in these patients. Around 50 HA20 patients have been reported so far with early-onset recurrent mucosal ulcers resembling BD being the hallmark feature in most (51–61). HA20 is classified as a monogenic vasculitis here since it resembles BD; however, it is important to note that the phenotype is very heterogeneous and it may mimic autoimmune diseases such as systemic lupus erythematosus and autoimmune lymphoproliferative syndrome. Furthermore, the evidence for vasculitis in tissue samples is deficient in most patients (52).

Familial Mediterranean Fever (FMF)-Associated Vasculitides

Familial Mediterranean fever is the most common autoinflammatory disease characterized by fever and polyserositis attacks

and caused by *MEFV* mutations (62). The mutations in this gene are associated with increased IL-1 production. Colchicine is the mainstay of FMF treatment (62). Certain vasculitides are more frequent in FMF patients than normal population (63). The most common vasculitis associated with FMF is IgAV/HSP, present in around 3% of FMF patients (63, 64). Another form of vasculitis is PAN which is also more common among FMF patients when compared to the expected frequency: almost 1% of FMF patients had PAN with distinctive features such as perinephric hematoma, severe myalgia, markedly high acute phase reactants, younger age, and better survival than classic PAN (39, 63, 65). In the eastern Mediterranean where the disease is frequent, physicians should ask for symptoms of FMF in patients with IgAV/HSP and possibly PAN. Concomitant occurrence of BD and FMF was also much higher than expected in several studies and a high frequency of *MEFV* mutations was reported in BD patients (66–68). In addition, a meta-analysis has confirmed the association between *MEFV* mutations M694V and M680I with BD (69). Other PSV such as AAV and TA may accompany FMF, as well; however, their association is not as apparent as the aforementioned diseases.

The association of PSV with this monogenic disease affects the way we treat these patients: colchicine needs to be initiated for FMF in addition to the conventional treatment of vasculitis in these patients. Anti-IL-1 therapies could be considered in resistant cases (62).

BIOMARKERS IN PSV

A biomarker is defined as an objectively measured characteristic marker which is evaluated as an indicator of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention (70). Biomarkers may be important for predicting the tendency to have the disease, disease activity, therapeutic options, disease flare, and disease course. For precision medicine, important biomarkers are the ones which guide us through choosing therapeutic options or determining patients with poor prognosis who need more aggressive treatment. Although there are recent studies addressing novel biomarkers, biomarker-driven treatment algorithms are not available in PSV. Furthermore, it is important to note that most of the existing biomarker studies in PSV involve mainly adult patients. Thus, the rheumatology community needs sophisticated work of proteomics and metabolomics to define the important pathways and biomarkers for our management of the patients. The main biomarkers that serve therapeutic targets in PSV are summarized in **Table 2**.

Immunoglobulin A Vasculitis/Henoch-Schönlein Purpura

Biomarker studies in IgAV/HSP have generally focused on finding non-invasive markers for diagnosis/prediction of nephritis and renal prognosis. A few studies are present on biomarkers of prognosis for gastrointestinal involvement, as well. Sun et al. have recently identified biomarkers by a combined clinical and metabolomics analysis in children with IgAV/HSP (71). They

TABLE 2 | The main biomarkers that serve targets for treatment in primary systemic vasculitides.

Disease	Biomarker	Treatment	Reference
IgAV/HSP	Factor XIII	Factor XIII concentrate to improve gastrointestinal complaints	(79, 80)
AAV	Neutrophil microparticles Endothelial microparticles	Plasma exchange treatment	(103)
AAV	Complement pathway proteins	Selective C5a receptor inhibitor in replacing high-dose corticosteroids	(107, 108)
TA	IL-6	Anti-IL-6 treatment	(117, 120, 121, 123)
TA	TNF- α	Anti-TNF treatment	(121, 124)
BD	JAK/STAT	JAK inhibitors	(129)
BD	A variety of cytokines (TNF, IL-1, IL-6, IL-12/IL-23)	Cytokine targeting therapies (anti-TNF, anti-IL-1, anti-IL-6, anti-IL-17/IL-23)	(131–138)

AAV, ANCA-associated vasculitis; BD, Behçet's disease; IgAV/HSP, immunoglobulin A vasculitis/Henoch-Schönlein purpura; IL, interleukin; JAK, janus kinase; KD, Kawasaki disease; STAT, signal transducer and activator of transcription; TA, Takayasu arteritis; TNF, tumor necrosis factor.

have shown that (s)-3-hydroxyisobutyric acid, p-Cresol sulfate, and 3-carboxy-4-methyl-5-pentyl-2-furanpropanoic acid were associated with kidney involvement in IgAV/HSP. These biomarkers allowed prediction of IgAV/HSP nephritis with high sensitivity (94.7%) and specificity (80.8%) when combined with D-dimer (71). Berthelot et al. have studied the value of biomarkers for predicting the outcome of IgAV/HSP nephritis in an adult prospective cohort (72). They have demonstrated that serum Gd-IgG1, urinary IgA, IgG, IgM, neutrophil gelatinase-associated lipocalin, IL-1 β , IL-6, IL-8, IL-10, IgA-IgG, and IgA-sCD89 complexes were associated with nephritis while urine IgA at disease onset could predict poor renal outcome in IgAV/HSP patients (72). Other biomarkers such as matrix metalloproteinase 9 (MMP-9), red blood cell distribution width, pentraxin 3, alpha-smooth muscle actin, and c-Met were also reported to be associated with the risk of nephritis in IgAV/HSP (73–76). As to the genetic factors, two recent studies have shown the association of inducible nitric oxide synthase (*iNOS*) gene and *IL1 β* gene polymorphisms with kidney involvement in IgAV/HSP (77, 78). Thus, these biomarkers may guide us in how we manage these patients in the coming days.

Decreased factor XIII activity was suggested as a prognostic biomarker for severe gastrointestinal system involvement in IgAV/HSP patients (79, 80). Administration of factor XIII concentrate lead to improvement of gastrointestinal complaints in anecdotal case reports (80).

Kawasaki Disease

Biomarker studies in KD are mainly focused on predicting patients who will not respond to IVIG treatment. A more intensified treatment with corticosteroids along with IVIG could be administered to the patients with high risk of IVIG unresponsiveness. Early use of biologics may also be indicated in selected cases. Elevated levels of IL-17A, IL-10 (81), ferritin (82), tenascin C (83), IL-6,

C-reactive protein (CRP), percentage of circulating neutrophils (84), increased QT interval dispersion (85), and increased ratio of CD8+ HLA-DR+ T cells/CD8+ CD69+ T cells (86) are main biomarkers reported to be used for predicting IVIG resistance in KD. Validation studies are required to use these biomarkers in daily clinical practice.

Polyarteritis Nodosa

There have been few studies on biomarkers related to disease activity in PAN. Several biomarkers such as D-dimer, anti-moesin antibody, and anti-endothelial antibodies have been associated with disease activity (87–89). However, none of these are currently being used in routine medical practice in the management of patients with PAN.

ANCA-Associated Vasculitis

In AAV, ANCAs are the most commonly studied biomarkers. These are mainly diagnostic biomarkers and their use for monitoring disease activity is controversial. However, recent studies have suggested that especially PR3-ANCA could be used to predict relapse in AAV (90–94). Besides ANCA, Kemna et al. have demonstrated that galactosylation and sialylation levels of IgG could predict relapse in PR3-AAV patients (95). In the recent targeted proteomics study, Ishizaki et al. have demonstrated the effectiveness of tissue inhibitor of metalloproteinase (TIMP1) as a disease activity marker for AAV and they have identified transketolase and CD92 as novel markers for evaluation of renal involvement and renal outcome in AAV (96). These may serve as valuable markers in our clinical practice. Two different proteomics studies demonstrated that serum proteomic profile differed between active systemic versus remitting patients with GPA (97, 98).

McKinney et al. studied gene-expression-based biomarkers in AAV and demonstrated that the poor diagnostic group were defined mainly by the IL7R pathway and T cell receptor signaling genes which were expressed by T cells (99). Their results also suggested that measuring the expression of only three genes; *ITGA2*, *NOTCH1*, and *PTPN22* could be used to define prognostic subgroups in AAV. These results raise the prospect of precision medicine in AAV, as the authors have concluded. In another study of the same group on gene-expression biomarkers, they demonstrated an association between T cell exhaustion and poor prognosis in AAV and suggested that this process could be targeted in AAV treatment (100).

As to biomarkers for response to treatment in AAV, Unizony et al. demonstrated that patients with PR3-AAV responded better to rituximab than to traditional induction/maintenance treatment with cyclophosphamide and azathioprine and suggested that an ANCA-based classification might guide immunosuppressive treatment in AAV (101). Haubitze et al. showed that immunosuppressive treatment in AAV changes the urine proteome toward remission (102).

Neutrophil microparticles (NMPs) and neutrophil extracellular traps (NETs) are biomarkers that could be targets for treatment in AAV and maybe other vasculitides as well. NMPs are membrane vesicles that induce endothelial damage in AAV,

released from neutrophils upon activation by ANCA (103). Hong et al. have demonstrated more NMPs in the plasma of children with AAV than patients with inactive vasculitis and healthy controls (103). AAV patients with increased NMPs might benefit from plasma exchange therapy (103). In the same lines, endothelial MPs, important biomarkers of endothelial injury, may be important targets to be removed by plasma exchange in AAV (103).

Neutrophil extracellular traps, composed of DNA, histones, and neutrophil proteins, are released by neutrophils under the influence of inflammatory stimuli (104). Kessenbrock et al. reported NET deposition in inflamed kidneys of AAV patients (105) while Wang et al. showed that circulating NETs did not differ between patients with active vasculitis and patients in remission (106). NETs could represent a novel target for therapy in AAV; however, further studies are required to determine the exact role of NETs in AAV pathogenesis.

Recent studies have highlighted the role of complement alternative pathway activation in AAV pathogenesis (107). In a recent randomized trial, Jayne et al. have demonstrated that avacopan, an orally administered selective C5a receptor inhibitor was effective in replacing high-dose corticosteroid treatment in AAV (108).

There are other biomarkers such as macrophage migration inhibitory factor, delta neutrophil index, mean platelet volume, rheumatoid factor, and serum ferritin most of which have been recently reported to be associated with disease activity in AAV (109–113). However, further validation studies are required for these biomarkers to be commonly used while profiling AAV patients with regards to disease course and prognosis.

Takayasu Arteritis

Biomarker studies in TA are mainly focused on differentiating active disease from inactive disease. Different biomarkers such as erythrocyte sedimentation rate (ESR), CRP, IL-2, IL-3, IL-4, IL-6, IL-8, TNF- α , IFN- γ , MMPs, TIMP1, vascular cell adhesion molecules, RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted), and pentraxin 3 were associated with TA disease activity (114–122); however, none of them is validated for predicting outcome and only ESR and CRP are available in routine clinical practice. Some of the aforementioned biomarkers such as IL-6 and TNF- α serve targets for effective therapies in TA (123, 124). Goel et al. have recently demonstrated that myeloid-related protein 8/14 (MRP8/14) (S100A8/S100A9) levels were higher in patients with active disease than those with stable disease and change in MRP8/14 levels was significantly associated with the disease activity assessed by Indian TA Activity Score (125). Furthermore, MRP8/14 levels decreased significantly in responders during follow-up. They also showed that MRP8/14 was a better disease activity biomarker than ESR and nearly similar to CRP in this aspect in TA (125).

As genetic factors, a recently studied biomarker in TA, is human leukocyte antigen E (126). Goel et al. demonstrated that soluble HLA-E levels increased more frequently in TA patients with a persistently active, relapsing course than those with a

persistent stable course (126). HLA-Bw52 was previously shown to be associated with higher incidence of cardiovascular events and poorer prognosis in TA patients (127). Terao et al. showed that combination of SNPs on *IL12B* and *HLA-B52:01* was significantly associated with severity of aortic regurgitation, a severe complication of TA (25).

Imaging modalities such as computed tomography, magnetic resonance imaging, and positron emission tomography are important to detect vasculitic lesions in large vessel vasculitis and in practice are used as outcome tools.

Behçet's Disease

Lots of disease activity biomarkers have been reported in BD. None of these (except ESR and CRP as acute phase reactants) are currently being used in routine clinical practice to profile BD patients. However, several of these biomarkers may be targeted in BD treatment. Sadeghi et al. have recently studied the serum profiles of cytokines in BD patients and demonstrated significant elevation of IL-2 in patients with uveitis (compared to recovered patients or those without uveitis) (128). The authors have thus concluded that IL-2 may be a new target for treatment of refractory BD uveitis. Tulunay et al. demonstrated that JAK1/STAT3 signaling pathway was activated in BD, possibly through activation of Th1/Th17-type cytokines such as IL-2, IL-6, IL-17, IL-23, and IFN- γ (129). They suggested that ustekinumab (anti-IL-12/IL-23) and tofacitinib (inhibiting JAK1/3) could be novel therapeutic options for BD. On the other hand, several genetic associations have also been identified in BD, including mainly the genes encoding for HLA-B51, IL-6, IL-10, IL-1 β , IL-12R/IL-23R, intracellular adhesion molecule, nitric oxide, chemokine receptor type 5, toll-like receptors, and fucosyltransferase 2 (130). In the same lines, elevated levels of several pro-inflammatory cytokines including IL-1, IL-6, IL-17, and IL-23 have been demonstrated in patients with BD (131–137). Some of the pathways including these cytokines have been targeted successfully with biologic drugs such as etanercept (anti-TNF), infliximab (anti-TNF), tocilizumab (anti-IL-6), secukinumab (targeting IL-23/IL-17 pathway), and canakinumab (anti-IL-1) (130, 138).

CONCLUSION

Precision medicine is our new aim in clinics and translational medicine will surely guide this practice. With the recent genetic studies and promising biomarker discoveries, precision medicine will be possible in PSV. The existing data needs to be confirmed in large, multicenter studies. Further proteomics and metabolomics data enlightening the involved pathways are needed. These further studies are required to profile vasculitis patients better to tailor treatment individually.

AUTHOR CONTRIBUTIONS

EB prepared the first draft of the article. SO made the critical revision of the article. Both authors have seen and approved the final version of the manuscript.

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