Personalized medicine for the vasculitis patient: hope for the future?

Personalized medicine is a rapidly emerging and exciting field in medicine. It brings with it the hope of applying patient-specific information, including not only general family and personal history, environmental exposures and clinical findings, but also information regarding the genetic make-up of the patient, to effectively diagnosing the disease, predicting disease severity and treating the disease. In vasculitis, the most immediate application of emerging genetic and proteomic information is possibly in the targeted selection of medications, which may be useful for the particular patient while avoiding adverse drug effects based on understanding of the patient's genetic and proteomic profile. Clinical trials of new drugs for vasculitis should seek to discover and exploit these principles of personalized medicine.

KEYWORDS: clinical trials ■ genomics ■ individualized medicine ■ personalized medicine ■ vasculitis

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An emerging theme in vasculitis research, and in medicine broadly, is the application of the principles of personalized medicine to the field of autoimmune diseases. Knowledge of the genetic make-up of the patient suffering from vasculitis, as well as environmental factors that influence how genes may be activated or function, will increasingly contribute to a better understanding of the vasculitic diseases, both with respect to diagnosis and classification, and to factors that govern response to therapy.

In the field of vasculitis, a number of genes have been identified that are risk factors for, or are strongly associated with, vasculitis, such as *HLA-DRB1**04 in giant cell arteritis (GCA). However, very little is known beyond this with respect to the genetic and epigenetic factors that govern disease predisposition. Headway is being made in this field by understanding the profiles of gene products, such as cytokines, that are involved in disease expression; however, application of this knowledge to specific forms of vasculitis and individual patients is still in the future. Currently, there is limited understanding of how an individual's genetic make-up governs the response to therapy, particularly how the drugs used for the treatment of vasculitis are metabolized, and how the genes and gene products may be related to a positive response to the drug as well as adverse reactions.

Personalized medicine has been defined as "the management of the patient's disease, or predisposition towards a disease, by using molecular analysis to achieve the optimal medical outcome for that individual therapy, improving the quality of life and health, and potentially reducing overall healthcare costs" [101].

For an individual patient, personalized medicine means that when the patient is seen by the physician, factors concerning the patient's individual characteristics, including age, gender, weight, smoking history, family history and effects of medications, as well as their molecular genetic profile, will contribute to the diagnosis of the disease and selection of a therapy that will benefit the patient. Importantly, this information will provide clues as to whether the patient is at risk of a particular adverse event occuring as a result of the medication.

Progress towards making individualized medicine a reality took a strong step forward with the completion of the Human Genome Project in 2003, although much remains to be understood regarding the gene function and gene products and their importance in vasculitis.

Perhaps the two vasculitic diseases in which the most knowledge regarding genetic and cytokine profiles has been developed are GCA and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Giant cell arteritis

In GCA, genetic polymorphisms associated with disease susceptibility are most strongly associated with *HLA-DRB1**04, although a number of other gene products, such as TNF-α and endothelial nitric oxide synthase, have also been identified as possible susceptibility factors

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(**Box 1**) [1]. Genetic polymorphisms associated with disease risk and/or severity in GCA include intercellular adhesion molecule-1 (*ICAM-1*), *VEGF* and *IFN-γ* (**Box 1**) [2–5]. However, it should be noted that most studies have included relatively small groups of patients and, therefore, the reported genetic associations will require validation in different and/or larger patient cohorts. However, disease cohorts that are large enough to have sufficient power to address genetic associations are difficult to collect and typically require a collaborative effort among several tertiary referral centers.

IL-6 levels are increased in the serum of patients with GCA and IL-6 elevation may persist after several months of corticosteroid therapy, despite normalization of acute-phase markers [6]. Although corticosteroids reduce IL-6 production, they do not correct the underlying mechanism inducing the increased IL-6 levels [7]. IL-6 is a very sensitive marker of disease activity in GCA and out-performs the erythrocyte sedimentation rate (ESR). Indeed, 89% of GCA recurrences in one study were associated with increased plasma IL-6 levels, often despite a normal ESR [8]. Serial IL-6 measurement may therefore allow more accurate tailoring of steroid therapy [9].

Other cytokines may be involved in the pathogenesis of GCA. IL-1β was found to be elevated in a small series of patients with GCA compared with healthy controls [10]. Levels of monocyte chemotactic protein (MCP)-1 were also significantly raised in untreated GCA patients compared with controls [11].

Box 1. Genes associated with giant cell arteritis.

Genetic polymorphisms associated with susceptibility to giant cell arteritis

- *HLA-DR4* [1]
- Matrix metalloproteinase-9 (*MMP9*) [41]
- *CD24* [42]
- Endothelial nitric oxide synthase [43,44]
- *TNF-α* [45]
- Monocyte chemotactic protein-1 (*MCP-1*) [46]
- Myeloperoxidase promoter [47]
- IL-10 promoter [48,49]
- HLA Class I (*MICA* and *HLA-B*) [49]
- Inducible nitric oxide synthase promoter (*NOS2A*) [50]
- Fc-γ receptors [51]

Genetic polymorphisms associated with disease risk and severity in giant cell arteritis

- Intercellular adhesion molecule-1 (*ICAM-1*) [2]
- *VEGF* [3,4]

Genetic polymorphisms associated with disease severity in giant cell arteritis

- *IFN-γ* [5]
- Platelet glycoprotein receptor IIIA [52]

Cytokine levels appear to correlate with disease severity and may also be useful for predicting disease-related complications. GCA patients with a strong initial systemic inflammatory reaction have more elevated circulating levels of IL-6 and TNF-α, have higher and more prolonged corticosteroid requirements, and experience a greater number of disease flares during corticosteroid therapy than patients with a weak systemic acute-phase response [12]. GCA patients with ischemic complications have lower tissue expression and circulating levels of IL-6 than patients with no ischemic events [13]. Weyand *et al.* found increased expression of IFN-γ mRNA and IL-1β in the temporal arteries of patients with ischemic symptoms [14].

A greater knowledge of disease pathogenesis in GCA may lead to novel, more targeted therapeutic approaches. For example, the finding that TNF-α is highly expressed in the inflammatory lesions in GCA led to conduction of a randomized, controlled clinical trial of anti-TNF therapy for this condition [15]. While the results of this particular clinical trial were disappointing, similar approaches using anticytokine or immunomodulatory biologic agents hold significant promise for the future.

Necrotizing vasculitis associated with antineutrophil cytoplasmic antibody

Genetic polymorphisms associated with susceptibility to necrotizing granulomatous vasculitis associated with ANCA include the cytotoxic T-cell antigen-4 (*CTLA-4*), *TNF-α* and *PTPN22* (**Box 2**) [16–18]. Killer cell immunoglobulin-like receptors and *CD18* gene polymorphisms, among others, have been suggested as susceptibility risk factors for microscopic polyangiitis. Genetic polymorphisms of the *IL-10* and *HLADRB1* genes may predispose to Churg–Strauss syndrome (CSS) (**Box 2**) [19–21]. Genetic polymorphisms associated with clinical phenotypes of necrotizing vasculitis associated with ANCA include *IL-10* and *CTLA-4* (**Box 2**) [22,23]. Although a few genetic associations have been confirmed in different disease cohorts [20,21], most other findings need to be validated in future studies.

Adaptive and innate immune pathways are activated in these forms of vasculitis. Circulating T cells from patients with necrotizing granulomatous vasculitis associated with ANCA exhibit a Th1 phenotype and overproduce the cytokines IFN-γ and TNF-α [23]. Monocytes from these patients have an activated phenotype and secrete increased amounts of IL-12 [24,25]. In the serum,

levels of TNF-α and IL-6 are significantly elevated during active disease [25,26]. Other studies have demonstrated an elevation of serum IL-8 and IL-10 in patients with necrotizing granulomatous vasculitis compared with healthy controls [25,27]. Levels of TGF-β are reported to be similar in these patients and healthy controls, while data for MCP-1 are variable [25,27].

Serum cytokines in necrotizing granulomatous vasculitis may correlate with disease activity. Ohlsson *et al.* demonstrated that elevated levels of IL-8 were associated with adverse events and poor prognosis, while lower levels of IL-10 and higher levels of IL-6 were predictive of disease relapse [28]. In a study of 23 patients with active necrotizing granulomatous vasculitis associated with ANCA, serum VEGF levels were found to be markedly elevated, and levels appeared to correlate with disease severity [29]. Other putative biomarkers include serum levels of soluble TNF receptor and soluble IL-2 receptor (sIL-2R), both of which correlate with disease activity in these patients [30].

Similar to findings in necrotizing granulomatous vasculitis associated with ANCA, sIL-2R is elevated in CSS [31]. Furthermore, an elevated level of IL-5 in serum and bronchoalveolar fluid of CSS patients has been reported [32]. T-cell lines from patients with CSS produce mainly IL-4 and IL-13, suggesting that T cells may drive eosinophilic inflammation [33]. In patients with microscopic polyangiitis, serum levels of IL-6 and IL-8 are reported to be increased in those with active disease [34].

Box 2. Genes associated with antineutrophil cytoplasmic antibody-associated vasculitis.

Genetic polymorphisms associated with susceptibility to ANCA vasculitis

- Cytotoxic T-cell antigen-4 (*CTLA-4*)* [16,17]
- *TNF-α** [23]
- *IFN-γ** [23]
- *PTPN22** [18]
- *CCR5** [53]
- *IL-10* [54–56]* [19]‡
- *HLA-DPB1** [57,58]
- Killer cell immunoglobulin-like receptors§ [22]
- Leukocyte immunoglobulin-like receptors§ [59]
- *CD18*§ [60]
- *HLA-DRB1*‡ [20,21]

Genetic polymorphisms associated with clinical phenotype of ANCA vasculitis

- *IL-10* [23]
- Cytotoxic T-cell antigen-4 (*CTLA-4*) [23]
- Fc-γ receptors [61]

**Necrotizing granulomatous vasculitis.*
‡Churg–Strauss syndrome.
§Microscopic polyangiitis.
ANCA: Antineutrophil cytoplasmic antibody.

Applying personalized medicine principles to drug development & drug toxicity in vasculitis

The most immediate hope for individualized medicine from a therapeutic standpoint is the development of more targeted drugs that focus on specific immune dysregulation in vasculitis, and avoidance of drug toxicity. In addition, better use of existing drugs, perhaps in customized combinations, could improve outcomes in vasculitis. Most immediately, this means understanding which drug, or drug combination, is right for which patient based on available disease-severity markers, as is being pioneered in rheumatoid arthritis [35,36]. Adverse drug reactions accounted for more than 2.2 million hospitalizations in the USA in 2003 and are one of the leading causes of death in the USA, accounting for over 100,000 deaths in that period [101]. Many of the drugs used for the treatment of vasculitis have a narrow therapeutic range. Work over the past several years has uncovered genes that affect drug sensitivity, including receptor markers to cortisone, and genes affecting drug toxicity, including the metabolism of azathioprine, methotrexate and mycophenolate mofetil [37].

Studies directed at the genetic variation in drug metabolism have elucidated enzyme products of genes such as thiopurine methyltransferase, the measurement of which is beginning to be used in routine clinical practice. Patients who are homozygote-deficient for this enzyme are at increased risk of azathioprine toxicity [37].

The value to an individual patient of a unidimensional test, such as thiopurine-methyltransferase testing to evaluate potential toxicity, does offer the prospect of safer and more effective treatment; however, its role in reliably predicting azathioprine toxicity, including neutropenia, has not yet been established [38–40].

The US FDA's Office of Clinical Pharmacology and other agencies have stressed the importance of critical pathways for biomarkers and drug development, with identification of stratification markers at the preclinical drug-development phase, studies of clinical utilities of the stratification markers during clinical development in Phase I, clinical validation for stratification markers in Phase II and drug labeling based on results from Phase III trials, prior to FDA filing approval.

Increasingly, such information is requested and sought after in the drug-development process, which has resulted in an ever increasing number of drugs with labeling containing pharmacogenomic information. More than 10% of approved drugs now have pharmacogenomic information on their labels, and this number is over 40% for drugs approved since 2006 [102]. This labeling is still mostly pharmacokinetic, as is mentioned for thiopurine methyltransferase for azathioprine metabolism; however, the trend is for the development of pharmacodynamic information as well, including TNF receptors and others, such as cellular receptors. These receptors play a major role in cancer treatment and treatment of some autoimmune rheumatic diseases.

In vasculitis, there is a significant need for diagnostic biomarkers and biomarkers to assess disease activity, as well as prognostic biomarkers. The challenge for the development of biomarkers is that vasculitic diseases are complex and, being multisystem diseases, have a complex dimension of disease involvement and clinical response. For example, the assessment of a biomarker for disease affecting the kidney will be different, in many cases, to the biomarker that predicts response of skin disease or peripheral-nerve disease. Current biomarkers are linked to single effects such as a metabolizing enzyme or drug, or for a single outcome such as improvement in blood pressure with an individual agent. In addition, since vasculitic diseases are rare, it is challenging to assemble patient cohorts that are homogenous and large enough to conduct biomarker-validation studies. Moreover, even when potential biomarkers are identified, there are several logistic and financial barriers that have to be overcome before the markers can be used in routine, clinical care.

Outcomes incorporating biomarkers in vasculitis do not currently utilize combinations of biomarkers that may be able to provide better predictive information. The NIH-funded Vasculitis Clinical Research Consortium (MA, USA) is a leading group seeking to develop such biomarkers. None of the efforts in biomarker development yet include tests for specific disease and drug metabolism pathways, nor are there any current clinical trials in vasculitis that incorporate biomarkers in the drug development programs of agents designed to treat these diseases.

Challenges in clinical trial designs that use biomarkers include limiting the number of patients that can be enrolled in trials, since random variability in potential biomarkers and disease expression will be difficult to assess, and the narrowly focused design of clinical trials that, in vasculitis, typically focus on one outcome such as improvement of renal disease, although the instruments developed for assessing patient outcome, including such measures as the Birmingham Vasculitis Activity Scale, provide a broader range of information that can also be used in retrospective studies.

In vasculitis research, a switch from voluntary to mandatory genomic data submission should improve the treatment and outcomes of patients with vasculitis, and advance the field from the current trial and error approach to one that is based upon a better understanding of individual patient risk factors for disease, treatment response and risk of adverse treatment events.

Financial & competing interests disclosure

Dr Warrington and Dr Matteson are investigators for the Vasculitis Clinical Research Consortium funded by the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Personalized medicine implies that patient-specific factors are considered when evaluating and treating a particular individual for vasculitis.

Perspectives

- The application of personalized medicine in vasculitis will ultimately contribute to better diagnosis of disease, assessment of disease severity and treatment needs, and the development of useful drugs.
- Achievement of these goals will improve treatment outcomes and quality of life for patients suffering from vasculitis, reduce overall health costs by avoiding misdiagnosis and use of ineffective therapies, and avoid adverse effects from therapy.
- Clinical trials of drugs for vasculitis should seek to discover and use genomic data from affected patients.

Conclusion

- Individualized care for patients with vasculitis requires an improved understanding of disease pathogenesis as well as the patient's genetic and proteomic profile.

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