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Editorial

Predicting Disease Activity in Systemic Vasculitides: On the Hunt for Potential Candidates



Balancing the risk of disease recurrence and damage attributable to the prescribed immunosuppressive measures is one of the most important issues in the management of vasculitides in the 21st century. Several aspects may be taken into account to measure disease activity (i.e., imaging methods, disease activity scores, and biomarkers) potentially distinguishing between active and quiescent disease. There is ongoing debate over how such a biomarker is defined, but in the context of vasculitides, this definition may be most appropriate: "A biological observation that substitutes for and ideally predicts a clinically relevant endpoint or intermediate outcome that is more difficult to observe"[1]. While this is a general assumption, biomarker biology in systemic vasculitides is a complex issue. Several biomarker classes have been proposed, highlighting unmet needs in the management of these diseases: (1) at the time of diagnosis to predict remission (early assessment of treatment response) or prediction of relapse; (2) to stage the respective disease (either to replace invasive or improve existing techniques); (3) to assess current vasculitis activity (especially in those with mild disease activity and to rule out potential differential diagnoses, i.e., infections); and (4) to predict longterm prognosis (prediction of treatment response, relapse probability, damage attributable to the disease or therapy, and other outcomes)[2].

In this issue of *The Journal*, Rodriguez-Pla and colleagues[3] analyzed a panel of biomarkers in 4 vasculitides: giant cell arteritis (GCA, 60 patients), Takayasu arteritis (TA, 29 patients), polyarteritis nodosa (PAN, 26 patients), and eosinophilic granulomatosis with polyangiitis (EGPA, 37 patients).

The hypothesis-generating approach used by the authors included 22 biomarkers potentially involved in the pathogenesis of at least 1 of the studied diseases, subdivided into the following categories: cytokines, chemokines, soluble receptors, markers of microvascular damage, markers of tissue damage and repair. Further, C-reactive protein and erythrocyte sedimentation rate (ESR) were studied as part of the routine clinical followup[3]. Comparisons were performed of biomarkers between active disease and remission within each studied vasculitis and between different vasculitides. Assessing this predefined panel of biomarkers raises this question: does one size fit all? The answer is a solid "no": the authors found more pronounced differences in biomarker levels across different diseases during clinical remission than differences related to disease activity. However, most of the patients received corticosteroid and/or immunosuppressive agents during sample collection and specifically during active disease (Table 1), possibly affecting the analyses; nevertheless, information regarding immunosuppressant dose was not provided[3]. Further, the ages of the patients and time to inclusion were different among the diseases, likely reflecting the epidemiological features of the different vasculitides studied.

On the other hand, these findings reflect a real-life setting of treated patients, and therefore information provided may be relevant for patients routinely followed by clinicians.

Despite the relatively limited number of patients included, this study provides interesting insights on biomarkers of vasculitis disease activity.

Table 1. Prescribed immunosuppression (steroids and any immunosuppressant) at the time of remission and during phases of active disease.

	GCA	TA	PAN	EGPA
Remission (any immunosuppression)	98.1	94	93.2	92.4
Active (any immunosuppression)	75.4	86.7	100	89.2
Remission (steroids)	90.4	70	79.5	84.8
Active (steroids)	83.6	70	88.5	81.1

Data are percentages. EGPA: eosinophilic granulomatosis with polyangiitis; GCA: giant cell arteritis; PAN: polyarteritis nodosa; TA: Takayasu arteritis.

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In patients with GCA, analysis retained B cell–attracting chemokine 1 (BCA)-1/CXC motif ligand 13 (CXCL13), ESR, soluble interleukin 2 receptor α (sIL-2Rα), and tissue inhibitor of metalloproteinase-1 (TIMP-1) as elevated and reduced expression of interferon-γ–induced protein 10/CXC motif chemokine 10 during active disease.

The expressions of granulocyte colony-stimulating factor, granulocyte-macrophage–CSF, IL-6, IL-15, sIL-2Rα, and BCA-1/CXCL13 (the latter after adjustment for treatment) were higher in active EGPA compared to inactive disease states.

In PAN, ESR was higher and levels of matrix metalloproteinase-3 (MMP-3) were lower during active disease, while no single marker was significantly regulated in TA[3].

About 2 decades ago, it was shown that IL-6 levels were significantly higher in patients with GCA compared to healthy individuals and significantly higher during active disease compared to remission. Because the plasma half-life of IL-6 is short, an abrupt decrease was observed following corticosteroid initiation[4]. These and other findings paved the way for the GiACTA trial, showing that patients treated with the IL-6Rα inhibitor tocilizumab had a higher probability of a sustained remission compared to prednisone regimen at the end of the trial, further underlining the importance of IL-6 in GCA[5]. Surprisingly, the current study did not find statistically different levels of IL-6 during active phases compared to remission of disease[3], perhaps suggesting that corticosteroid treatment prior to the blood sample interfered.

ESR values show sex- and age-related differences, being increased in females and older patients[6]. Further, active cases with GCA and negative inflammatory variables were infrequently reported. In an analysis of the population of Olmsted County, Salvarani and Hunder reported 9 out of 167 patients (5.4%) with an ESR below 40 mm/h. The authors found a lower frequency of systemic symptoms, and no patient with low ESR developed blindness[7]. In the present study, patients with GCA were more frequently elderly females (80%; mean age 71 yrs)[3].

Nevertheless, the median (interquartile range) value of ESR was 26 (12–44) mm/h in active patients and 20 (10–27) mm/h during remission[3], in both cases within the normal levels for healthy individuals. This argues for either localized active disease or that samples might have been obtained after the treatment was already intensified.

The interpretation of the findings is particularly difficult when taking a closer look at the expression levels of selected biomarkers such as MMP-3, strongly associated with disease activity in GPA and microscopic polyangiitis (MPA) in a previous study (6.2-fold higher in active disease vs remission)[8], but not with EGPA in the current study. In EGPA, MMP-3 levels were 1.3-fold higher during active disease, thus resulting in a limited capability to act as a biomarker to predict active disease on treatment[3]. Overall, MMP-3 expression is likely influenced by immunosuppressive treatment, and therefore one could speculate that the lower levels of MMP-3 observed in subjects with PAN were a consequence of more frequently prescribed immunosuppression during active episodes[3] (Table 1).

Overall, this study included patient groups with rare diseases, and new biomarkers in these diseases are desirable, primarily but not only to differentiate patients according to various levels of disease activity.

Specifically, this "pilot" approach used by Rodriguez-Pla and colleagues[3] could be a way to screen promising biomarkers in rare diseases such as these vasculitides, before better-designed, prospective, and more expensive hypothesis-driven studies are performed. Such studies are definitely needed to validate the role of promising biomarkers.

The finding that serum marker concentrations differed more between diseases, which was independent of disease activity or concurrent treatment, is of particular interest and may also be useful to gain insight into the complexity of these diseases. For example, sIL-2Rα was particularly high in cases of EGPA[3], and this merits further investigation.

In a way, the authors aimed to investigate changes in serum biomarkers attributable to active disease (a sort of early flare biomarker panel) for routinely followed patients with vasculitis taking immunosuppressive treatment. However, the limitations of this approach should be kept in mind when interpreting the results of this study. In a systematic literature review[9] aiming to validate previous biomarker findings in cases with GPA/MPA, we observed several shortcomings related to reported potential markers of disease activity:

- The direct influence of immunosuppressive measures and differences among the used agents (before sampling patients and when obtaining "remission samples")
- Assessment of disease activity may vary among investigators
- Differences among ethnic groups
- Differences in the laboratory kits used to analyze the respective markers
- Replication cohort confirming the results.

The latter is of great importance, because small sample sizes and the artifice of discovery strategies may lead to the identification of false-positive candidates. This evidence on GPA/MPA might be extended to other vasculitides as well. It was proposed that unbiased, semiquantitative strategies are needed to discover candidate biomarkers, which are further validated by targeted and quantitative strategies[10]. Overall, research involving rare diseases bears the potential of small-study effects (limited by the number of patients affected by a particular disease), with small studies generally having a stronger effect than larger studies[11].

While this study undoubtedly adds to the current knowledge of regulated markers in the 4 studied diseases, questions remain regarding which approach is the most useful

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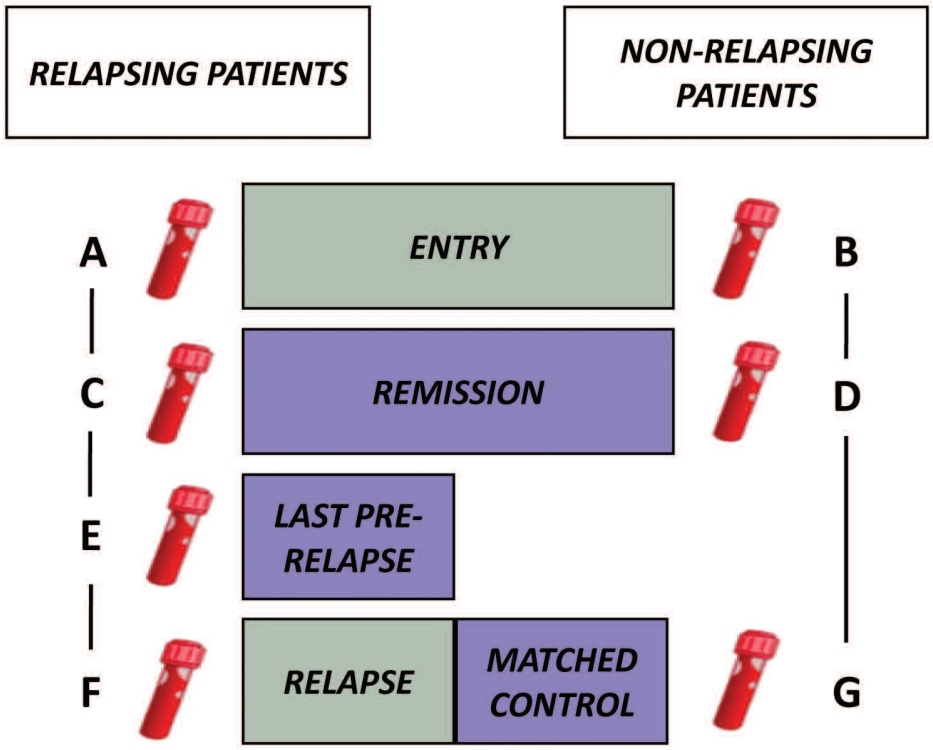

Figure 1. A schematic overview of the ideal biomarker detection pipeline in vasculitis. Such biomarker detection should include relapsing and nonrelapsing patients and might lead to the identification of candidates involved in disease pathophysiology or predict response to therapy (parts A and B). It also might display remission after induction therapy/during maintenance (parts C and D). The detection may decrease/increase ahead of relapse (i.e., act as a relapse predictor; part E). It is altered during a relapse, which might help in the diagnostic pathway (part F).

to identify candidate markers of interest, and how biomarker studies in vasculitis should be designed. The ideal approach may be as displayed in Figure 1, differentiating between patients at risk of relapse versus those in stable remission already at the time of diagnosis, and leading to the prescription of tailored immunosuppression. More efforts are needed to drive this field of research forward, and larger cohorts are essential to hunt for the ideal biomarker candidates in rare vasculitides.

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