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ADVANTAGES AND DISADVANTAGES OF VASCULITIS SCORING SYSTEMS

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Abstract:
Vasculitides are a heterogeneous group of chronic progressive remitting and relapsing inflammatory diseases of blood vessels with serious morbidity and mortality due to disease itself and its treatment with corticosteroids and other immunosuppressive drugs. At present, disease-specific biomarkers are not available to assess vasculitis activity and damage, so various clinical tools for the assessing disease activity, disease and treatment-induced organ damage, and prognosis are required for clinical practice and research purposes. These clinical and research tools have dramatically supported good structured clinical research and validated outcome measures as well as clinical record keeping and management of these disorders. In this article, we intend to analyze some of these clinical tools in relation to disease activity and prognosis in a clinical setting.

Introduction.

Vasculitides are a heterogeneous group of uncommon diseases characterized by inflammation of vessel walls (A Adebajo et al. 2018). The severity of vasculitis is related to the size and site of the vessel affected. They are classified according to the Chapel Hill nomenclature published in 1994 and were revised in 2012 as demonstrated in Table (1) below:

Table (1): The revised international Chapel Hill nomenclature of vasculitides
Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium vessel vasculitis Polyarteritis nodosa.
Kawasaki disease
Small vessel vasculitis
A. ANCA-associated vasculitis Microscopic polyangiitis. Granulomatosis with polyangiitis (GPA). Eosinophilic granulomatosis with polyangiitis (EGPA)
B. Immune complex
Anti-GBM disease (Goodpasture's). Cryoglobulinaemic vasculitis.
IgA vasculitis (Henoch-Schönlein).
Hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis).
Variable vessel vasculitis Behçet's disease.

Cogan's syndrome
Single organ vasculitis
Cutaneous leukocytoclastic angiitis.
Cutaneous arteritis.
Primary CNS vasculitis.
Isolated aortitis. Others.
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis.
Sarcoid vasculitis.
Others
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinaemic vasculitis.
Hepatitis B virus-associated vasculitis.
Syphilis-associated aortitis.
Drug-associated immune complex vasculitis Drug-associated AAV.
Cancer-associated vasculitis.
Others.

Until recently little was known about the incidence and prevalence of vasculitides. Data from Europe suggests that these conditions can occur at extremes of age. For example, Kawasaki disease seems to occur more frequently in the younger Asian population with an annual peak incidence of 90/10000 aged less than 5 years, R Watts et al (2005). Henoch-Schnolein purpura is also more common in the Asian population, and it has an incidence of 70/10000 in those aged 4 to 7 years old, R Watts et al (2005)

Vasculitis may be primary or secondary. The primary vasculitis consists of diseases like granulomatosis with polyangiitis or Wegner's granulomatosis, eosinophilic granulomatosis with polyangiitis or EGPA, also known as Chrug Strauss syndrome, microscopic polyangiitis, and polyarteritis nodosa, etc, S Monti et al (2020)

Primary systemic vasculitis is most common in those aged 65 to 74 years old and it has a peak incidence of 6/100000. Giant cell arteritis is most common in Caucasians, and it rarely occurs in the population, younger than 70 years. It has a peak incidence of 53/100000, R Watts et al (2005). Secondary vasculitis occurs due to another underlying condition like a connective tissue disorder (such as rheumatoid arthritis), infection, or malignancy.

Although laboratory, histopathology, and imaging investigations are vital in establishing the diagnosis, they are of limited importance in evaluating the severity of the disease, treatment response, and the course of the disease (Luqmani 2015). Further, as stated by Ponte, Sznajd, Neill and Luqmani (2014), rigorous and well-validated biomarkers for vasculitides are currently not available, therefore, once the diagnosis of vasculitis has been established, comprehensive clinical and research tools are required for the assessment of disease activity, course, and prognosis. These tools should be able to precisely quantify disease activity and its variations with time, should be able to distinguish disease activity from disease remission, provide information about prognosis, be simple to use, and must be feasible in clinical trials and clinical practice (S Monti et al 2020).

According to Luqmani (2015), Robson et al (2018) and Seo et al (2007) various tools available to assess disease activity and prognosis are as follows:

Birmingham Vasculitis Activity Score (BVAS)

BVAS 1&2

BVAS/GPA

BVAS 3

Disease Extent Index (DEI)

Five-factor score (FFS)

Japanese Vasculitis Activity Score (JVAS)
Paediatric Vasculitis Score (PVAS)
Pediatric Vasculitis Damage Index (PVDI)
Vasculitis Damage Index (VDI)
Combined Damage Assessment (CDI)
ANCA-Associated Vasculitis Index of Damage
ANCA -Patient-related outcomes questionnaire (ANCA-PRO)
Vasculitis Integrated Assessment Database (VICAD)

According to S Monti et al (2020), French vasculitis study group (FVSG) established the five-factor score (FFS), which has a significant prognostic value in PAN, MPA, and EGPA. This scoring system has not been validated for GPA. The presence of any of the following five factors predict a poor prognosis and higher mortality:

1. Proteinuria >1g/day
2. Renal insufficiency with creatinine >140 micromol/L
3. Cardiac involvement
4. Gastrointestinal manifestations.
5. Central nervous system involvement.

A revised FFS has been published and includes age >65 years and absence of ENT manifestations as indicators of poor prognosis. This scoring system has not been validated on non-French patients and therefore, should not be used when deciding optimal treatment.
The Birmingham Vasculitis Assessment Score (BVAS) is a weighted scoring system both for assessing activity and prognosis, which has been validated for small and medium vessel vasculitis. It represents a relatively reversible disease. It can measure the level of disease activity and critical organ involvement with higher scores being associated with higher mortality.
Vasculitis Damage Index is a prognostic indicator representing irreversible disease (features that have persisted at least for a minimum period of 3 months), damage due to disease, its treatment or from an unknown cause,
Different clinical tools, like PVAS and PVDI, are required in children, as disease presentation, activity associated damage and prognosis are different in them.
VICAD is a computer-based combination of BVAS and VDI, which provides a means for storing a variety of clinical information. This removes the time-consuming, error-prone paper-based conventional system, which delays data analysis.
This essay will be looking at these scoring systems in more depth focusing on their advantages and disadvantages in relation to the assessment of disease activity and prognosis in a clinical rather than a research/ trial setting.

Discussion.

Advantages of vasculitis activity scoring systems.

Extrapolating vasculitis activity scoring systems from clinical trials to clinical practice is increasingly implemented for their effectiveness and practicality. Although clinical assessment is the gold standard for evaluating disease activity in vasculitis, this evaluation depends on the experience of the observer. On the other hand, well-structured validated tools provide reproducible results of the disease activity. Moreover, there are currently no biomarkers that can reliably assess disease activity or response to therapy. For example, serological markers do not necessarily reflect disease activity, high inflammatory markers could be seen secondary to an infection, and impaired renal function may be due to previous unreversible damage. On the contrary, validated vasculitis activity scoring systems provide a structured approach to justify treatment that is often expensive and frequently associated with a large burden of side effects (Suppiah, Robson and Luqmani, 2010) Vasculitis activity scoring

systems facilitate documentation of the disease activity, which can be challenging due to the complexity of the vasculitis spectrum. Even though these tools may not be comprehensive, they form the core of clinical assessment in vasculitis. Also, online training is available to explain the proper use of these tools (Luqmani, 2015).

According to Luqmani (2015), The BVAS is an effective and practical method for evaluating patients with vasculitis for several reasons. Firstly, It involves a comprehensive checklist of clinical manifestations that may occur in active vasculitis which can also be used to remind treating physicians about different aspects of organ involvement. Secondly, due to the quantitative nature of BVAS, it can be used to follow up disease activity in individual patients and to compare disease activity between patient groups receiving different therapies. Finally, changes in BVAS and BVA/GPA scores can be used to define response to treatment, remission, and relapse. NICE recommendations on rituximab therapy in ANCA-associated vasculitis require measuring BVAS score before and during treatment (NICE, 2014).
Disease Extent Index (DEI) is a reliable, easy to use, and reproducible tool that can be used in conjunction with BVAS as it evaluates different aspects of disease activity than BVAS. It was validated by De Groot et al. (2001) who found it to have high convergent validity with both BVAS and some surrogate markers of disease activity in granulomatous polyangiitis.

The Pediatric Vasculitis Activity Score was developed and validated by Dolezalova et al in 2012 based on the third version of BVAS. Children may behave differently from adults towards these rare diseases and are faced with distinct sequelae on their growing bodies. It incorporated age-specific reference ranges for blood pressure, renal function, and a pediatric definition of weight loss. PVAS is a validated feasible tool that is quick to fill, reproducible, and sensitive to changes in disease activity.

Disadvantages of Vasculitis activity scoring systems.
There are 2 scoring systems for disease activity in patients with vasculitis: The Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Damage Index (VDI). BVAS is used to specifically access disease activity, whereas VDI provides information on disease damage. Used together both scores are used to access the impact of the disease on the patient.
One of the main disadvantages of having this scoring system is that it is not specific for the type of vasculitis. Yet, there is evidence that patients with different forms of vasculitis share very similar clinical features. Another important disadvantage of having a very specific rather than generic classification system for vasculitis is that in some patients we might not be able to fit into a specific diagnostic label as they do not fulfill the diagnostic criteria of a specific form of vasculitis The BVAS scoring system assesses current disease activity, it is important that the abnormality recorded is attributed to the vasculitis, this can be sometimes tricky because a lot of symptoms and features of vasculitis can present due to other problems or as a side effect of treatment of vasculitis such as hematuria secondary to cyclophosphamide bladder toxicity.

An additional disadvantage is that the BVAS is not a very user-friendly system and studies have shown that even doctors with experience in managing vasculitis struggled to use the scoring system without training and there was a lot of intraobserver variation. The 2 areas that doctors struggled with is overscoring patients who present with items specifically listed on the BVAS, but underscoring items that represent continuing disease problem or worsening disease problem Another problem with BVAS score is the recording of “grumbling” disease activity. This is because the original score included only clinical features that were either new or worse 4 weeks ago, Then BVAS2 was added which was not very user-friendly and lead to more confusion among clinicians and academics, this was eventually removed.

Advantages of scoring systems in the prognosis of vasculitides Advantages
in clinical practice:
In clinical practice setting, different vasculitis scoring systems can be used to determine the prognosis of the individual patient. This can be helpful for the patients as well as the clinicians. These tools are also important clinically as at present there are no universally applicable biomarkers to assess disease activity or determine chronic sequelae in all patients with most forms of vasculitis (Ponte et al 2014). The regular use of scoring systems as part of routine care offers a structured approach, which can also guide treatment decisions. For example, British Society of Rheumatology (BSR) guidelines for the management of ANCA-associated vasculitis (Ntatsaki et al 2014) used BVAS to define patients' disease states (remission, major/minor relapse, active or refractory disease). Therefore the authors concluded that this would help in making treatment decisions, especially important when starting biologics.
Tools like BVAS also provide clinicians with a useful checklist to help them remember the most common manifestations of vasculitis. According to Flossmann et al (2011), this helps in a structured and complete assessment of suspected or diagnosed vasculitis patients.
In a retrospective study of vasculitis patients in intensive care setting, Biscetti and colleagues (2016) evaluated Birmingham Vasculitis Activity Score (BVAS) and found this to be an excellent tool for assessing prognosis and mortality risk in these patients. They concluded that BVAS >8 upon admission in ward and BVAS >10 in ICU predicted high mortality risk.
However, this has been contradicted in a recent study by Ozdemir et al (2021), who did not find significant difference in BVAS scores of vasculitis survivors and non-survivors in ICU. Instead, they found the APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system to be a better predictor of prognosis in this group of patients.
Advantages in clinical trials:
According to European Vasculitis Society (EUVAS 2020,) BVAS and VDI scores are used by most international vasculitis research groups in their clinical trials. BVAS and VDI are both internationally recognized assessment tools and this allows a standardized comparison of studies from different countries of the world. Using these scoring systems can easily help establish effective collaboration in multi-center studies.
Clinical trials using these standard validated scoring systems have, for the first time, provided a firm evidence base for treatment decisions in vasculitis and related conditions.
For example, an international, multicenter, prospectively randomized controlled trial was conducted by the European Vasculitis Study group to help establish the prognostic factors for long-term survival in ANCA vasculitis. Among other factors, Flossmann and colleagues (2011) also reported that a high BVAS score is an important negative prognostic factor.

Disadvantages of scoring systems in the prognosis of vasculitides.
A variety of vasculitis scoring systems is in use, although alike in many aspects, they still have enough differences to make patient data comparison during trials problematic.
How accurately can a single prognostic tool measure clinically separate and diverse disease groups like vasculitides? There is also confusion about defining disease states, classes and the methods to be followed to measure disease activity and damage.
Vasculitides have a wide variety of symptoms, of which, some are common overlapping manifestations and some are distinct features specific to a particular disease. Therefore, only disease-specific measurement tools can be precise, leading to the development of BVAS/WG from BVAS. This led to a large array of tools difficult to handle. According to Merkel et al 2005, the development of a modular tool can serve as a solution. This constitutes a base module for common manifestations of several vasculitides and a disease-specific module that measures information specific to that particular variant.

There is confusion regarding diagnosis, classification of vasculitides, like the use of terms such as ANCA Associated Vasculitis (AAV), Wegener's granulomatosis (WG), and ANCA Positive Vasculitis (APV), all represent granulomatosis with polyangiitis (GPA); also due to high similarities between GPA, MPA, and EGPA, they are often studied in combination with the same set of tools, which is controversial.

Since a large battery of parameters is needed in the generic tools to assess myriad disease-related information, it's a struggle to keep the tool comprehensive yet simple. Definitions of active disease, remission, and flare are often investigator dependent, causing problems in meaningful comparisons and also protocols for weighting and scaling of items in a tool are set through expert opinion instead of meaningful longitudinal data about prognosis. There is also a mismatch between disease state and score. The cumulative score for many clinically less significant items can be higher than a few highly significant items like alveolar hemorrhage.

How to differentiate disease activity from irreversible disease damage is a major clinical issue. Frequently damage and disease activity is present in the same organ system, this can lead to misinterpretation of true disease score. How to differentiate Grumbling disease from true disease activity is another problem.

All tools have an open subcategory ''other'' for accommodating unusual features (e.g., granulomatous breast mass) causing investigator-dependent non-standardization and variability in comparison studies.

VDI is constituted of 64 items grouped into 11 organ-specific systems. Damage is an irreversible pathology lasting for at least 3 months, which is somewhat arbitrary. Further, some pathologies, like peripheral neuropathy can reverse with time.

It is a damage index, which does not provide any information about etiology and it is not scaled also. As all the items are equally weighted, therefore, it may not reflect the relative severity of each. It does not have a scale for measuring different gradations such as mild, medium, and severe organ involvement

FFS is a good prognostic tool, which is dependable and highly simple. However, this scoring tool is not validated in non-French patients.

Conclusion

Vasculitides are a group of rare inflammatory disorders with a high burden of morbidity and mortality, thus require precise and timely assessment of disease activity, damage, and prognosis. Presently, due to the non- availability of reliable biomarkers and high variability in disease presentation, clinical assessment, management, and research is impossible without the availability of clinical and research-based assessment tools. Many generic and specific tools are available for vasculitis assessment. It is observed that due to the complex and varied natures of these disorders, only complex generic assessment tools can accurately quantify disease activity and prognosis. Generic tools like BVAS, BVAS 3, VDI, and FFS, and specific tools like BVAS/WG, PVAS, and PVDI are routinely used in clinical practice and research. British Society of Rheumatology (BSR) recommends BVAS to define disease states and their treatment, especially when starting biologics. FFS and VDI tools are fairly dependable, simple, and accurate prognostic tools. Differentiating disease activity, grumbling disease, and damage due to disease or its treatment are major issues. Tools, which can differentiate and accordingly score less severe from more serious manifestations/ items are still lacking. The complexity of the generic tools and poorly trained observers lead to low intra-observer reliability. Training for BVAS and VDI is now available on the Internet, also the availability of VICAD has removed the need for paper-based systems and made the tools easier to use and interpret. It has been suggested to develop modular tools, which can serve as a solution to the generic tool base. A modular tool constitutes a base module for common manifestations of several vasculitides and a disease-specific module that measures information specific to that particular variant, thus offering higher

reliability. Till the availability of novel disease activity, damage, and prognosis measurement systems, contemporary tools if used correctly are indispensable in both clinical practice and research.

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