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References


L50. The future of international clinical trials in vasculitis

Introduction

Great progress has been made in the past 20 years in the treatment of various forms of vasculitis. This progress has been the direct result of the vasculitis clinical research community working collaboratively to successfully complete multi-centered randomized clinical trials (RCTs). These trials include seminal studies defining the evolving standard of care for various forms of vasculitis, especially ANCA-associated vasculitis [1–8] but also key studies in giant cell arteritis [9–12].

cryoglobulinemic vasculitis [13,14], and other vasculitides. Success of these RCTs is exemplified by the US Food and Drug Administration decision to approve the use of rituximab for the treatment of vasculitis; this was the first drug ever approved by FDA for vasculitis. Similar approvals were provided by the European Medicines Agency, Health Canada, and other regulatory agencies. Key factors in the growth and success of international trials in vasculitis have included:

- formation of international vasculitis research networks and the willingness of experts and centers to collaborate;
- development and adoption of standardized outcome measures for use in RCTs in vasculitis;
- expansion of research funding for RCTs from various sources to conduct increasingly high-quality studies.

Furthermore, the success of the first few international RCTs demonstrated to both the vasculitis research community and to funding sources that such trials are possible. This article will review these key factors leading to the current status of international clinical trials of new therapies in vasculitis and outline important themes emerging that will influence the next generation of international research trials in vasculitis.

Formation of multinational vasculitis research networks

The necessity for conducting research trials in vasculitis through networks and international collaborations stems from the fact that all of the idiopathic vasculitides are considered “rare” or “orphan” diseases. Even large regional or national centers of excellence do not have enough patients available to complete RCTs in a reasonable timeframe. Furthermore, as the treatment of vasculitis improves, the primary outcomes of RCTs will focus on narrower differences in efficacy and thus larger numbers of subjects from smaller disease subsets will be required, further necessitating access to an increased number of study sites worldwide. Additionally, larger international trials allow for more rapid completion of studies, international “buy-in” of the methods and study results, and broader generalization of the findings across different populations.

The history of clinical trials in vasculitis has followed a steady evolution from single center studies, to trials run by national groups, and now to RCTs conducted through larger international research networks. Some single center studies have been quite influential, including the initial studies at the US National Institutes of Health of cyclophosphamide and methotrexate for the treatment of granulomatosis with polyangiitis (Wege ner’s) [15–17]. The formation of single-country (national) research groups facilitated the conduct of RCTs and has included important studies [3,5,9]. The French Vasculitis Study Group (FVSG, www.vascularites.org) has for over 30 years advanced the treatment for various forms of vasculitis by conducting clinical trials through a large network of French academic medical centers.

International research networks have led to the conduct of large and sophisticated RCTs and inclusion of productive research sites from countries that otherwise not have been able to take part in trials on their own. The International Network for the Study of the Systemic Vasculitides (INSSYS) conducted several clinical studies [11,18] but is no longer active. The two largest active international vasculitis research networks are the Vasculitis Clinical Research Consortium (VCRC, www.RareDiseasesNetwork.org/VCRC) and the European Vasculitis Society (formerly the European Vasculitis Study Group, EUVAS, www.vasculitis.org). These two groups are each conducting a series of clinical research studies, including clinical trials. Importantly, the VCRC and EUVAS are now partnering on combined RCTs, further internationalizing and expanding the reach of clinical research in vasculitis [19,20] with plans underway for additional combined trials. The FVSG, VCRC, and EUVAS are all investigator-led research groups. However, the biopharmaceutical industry has also taken the lead on conducting international RCTs [12,21,22]. The growing internationalization of vasculitis clinical research will continue to increase the number, size, and quality of clinical trials testing new therapies for these serious illnesses.

Development and adoption of standardized outcome measures for use in randomized clinical trials in vasculitis

The development of standardized instruments to measure clinically meaningful outcomes in research protocols has been an essential element in the conduct of RCTs in vasculitis [23]. Validated outcome tools are critical to the conduct of studies, acceptance of trial findings by regulatory agencies, and strongly influences the willingness of industry executives to commit resources to trials. The Outcome Measures in Rheumatology group (OMERACT, www.omeract.org) has endorsed a Core Set of outcomes and validated measures for use in clinical trials in ANCA-associated vasculitis [24]. The Core Set includes measures of disease activity (based on versions of the Birmingham Vasculitis Activity Score, BVAS), disease damage (the Vasculitis Damage Index), patient-reported outcomes (SF-36 with newer measures under development), and mortality. Primary outcomes in RCTs for vasculitis have mostly been based on induction or maintenance of remission with disease activity usually considered as a dichotomous outcome (remission or active). Future trials will likely include more intermediate disease states and subtler clinical differences as outcomes of interest. Only for ANCA-associated vasculitis has there been widespread acceptance of validated outcome tools. There is a substantial need to develop validated outcomes for other forms of vasculitis and such initiatives are underway for large vessel vasculitis and Behçet’s disease [25–27].

The future of clinical trials for vasculitis will be dependent on development and adoption of highly feasible, validated, and...
cost-effective outcome measures that provide a pathway to definitively establish the efficacy of new therapies. Such outcomes will need to take into consideration the variable resources available at international research sites and the need for translations of any patient-completed instruments.

**Research funding for international trials in vasculitis**

Clinical trials in vasculitis have been funded through a wide variety of mechanisms ranging from fully unfunded trials to completely industry-supported studies. The availability of funding from government agencies and industry partners has been a major factor in the development and implementation of successful RCTs in vasculitis. The field has seen the transition from underfunded, often single-institution-sponsored studies to RCTs supported by government research grants [1–3,11] to studies in which drug was supplied by the manufacturer [3,6], to trials in which the source of financial support was a combination of government grants, private foundations, and industry contracts [7,8,19,20], and to trials fully funded and directed by industry [12,21,22,28]. The continued conduct of RCTs in vasculitis, especially large, multinational studies designed to gather data for submission for regulatory approvals, will require ongoing substantial investment by government granting agencies and the biopharmaceutical industry.

**New directions and challenges in conducting international trials in vasculitis**

Expansion in the range of countries involved in trials in vasculitis

Most multinational studies in vasculitis have enrolled the majority of subjects from North America and Western Europe. However, it is well known that substantial differences in disease prevalence, severity/outcome, clinical presentation, and treatment approaches exist for some vasculitides based on geographic, racial, and ethnic differences. Multinational studies increase the generalizability and feasibility of RCTs in vasculitis but also introduce variability that may need to be considered. Randomization might need to be stratified by geographic region. However, geographic setting may be a proxy for other factors. For example, the vast majority of patients with ANCA-associated vasculitis in Japan are MPO-ANCA positive [29]; this finding raises the question of whether a trial that includes Japanese sites should stratify randomization by both ANCA type and/or geographic site. For other forms of vasculitis, the geographic variation may be more complex. For example, cohort studies in Takayasu’s arteritis suggest that substantial differences exist in clinical outcomes and severity of disease in different countries, possibly due to racial differences in disease expression but also potentially due to treatment variations [30].

As the standard of care increasingly includes use of often expensive medications (such as biologics and newer small molecules) and costly monitoring (such as repeated MR angiograms for large vessel vasculitis or serial testing of CD19 levels in ANCA-associated vasculitis), there may develop a growing divide in the treatment of patients with vasculitis between richer and poorer countries or based on national policies regarding approvals of expensive therapies and diagnostic tests. Such economically based geographic variations in healthcare could substantially impact where new trials in vasculitis are conducted. Lack of access to more advanced and often more expensive therapies in some countries may make it more acceptable in such countries to conduct RCTs comparing new therapies to standard therapies. However, discrepancies in access to care could encourage patient recruitment into experimental studies and raises important ethically issues of fairness and concern over inadvertent coercive recruitment practices. The international vasculitis research community needs to work closely with the pharmaceutical industry to help ensure the highest standards of ethical research practices are upheld and advocate for open-label extension of both standard and experimental therapies for patients enrolled in clinical trials.

**Maintenance of international vasculitis research networks**

It is important that investigator-led collaborative international vasculitis research networks continue to thrive in the face of expansion and increased oversight by industry funders. The intellectual independence of academic investigators is important to maintain even as academic–industry partnerships grow stronger. Similarly, the contributions of all participating centers and investigators in large clinical trials must continue to be recognized in publications and presentations of research results. It is also quite important for research groups to successfully meet recruitment goals for studies in vasculitis; this will be an increasing challenge with parallel studies potentially competing for the same subjects.

**Trials of different forms of vasculitis**

Although the emphasis of international clinical trials has been on ANCA-associated vasculitis, giant cell arteritis, and Behçet’s disease, there are many unmet needs for effective treatments for many other forms of vasculitis, including Takayasu’s arteritis, IgA vasculitis (Henoch-Schönlein), cryoglobulinemic vasculitis, and others. The expansion of the international vasculitis research community participating in trials could provide access to a collective study population adequate to study the less common vasculitides.

**Trials involving children with vasculitis**

There has been a paucity of international trials focusing on vasculitis in children and few trials have even included a substantive subset of enrollees who are children. There is an unmet research need to understand the effects of new...
therapies in children with vasculitis as well as to develop new treatments for forms of vasculitis that mostly affect children, such as Kawasaki disease or IgA vasculitis (Henoch-Schoenlein). Given the even greater rarity of most forms of vasculitis in children, the ability to include international centers in trials will be important to address this area of research deficiency.

Conclusion

The progress made in the treatment of vasculitis over the last several decades has been extraordinary and due in part to the development of international research collaborations and conduct of multi-centered clinical trials. The quality of trials in vasculitis continues to rise and the international vasculitis research community has demonstrated how successful clinical research can be conducted in rare diseases when a commitment to collaboration is combined with improved study methodologies and strong support by funding agencies and industry partners. The future of international trials in vasculitis should bring even more effective new treatments to more patients with these rare, fascinating, and serious diseases.

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References


L51. From immunosuppression to selective treatments: The benefit–risk ratio

Treatment of systemic necrotizing vasculitides is changing. New drugs are available that could revise our therapeutic strategies. Concomitantly, conventional regimen doses, administration routes and durations have also evolved, and attenuated their negative impact, while retaining therapeutic benefit. The choice of new or conventional drugs is not that easy and the balance between benefits and risks of therapies should be taken into consideration. We must keep in mind that the final objective is to cure the disease and, at present, no drug has demonstrated superiority to reach that objective. Here, we review some key points, which have to be taken into consideration to improve patient care.

**Corticosteroids**

They are extensively used, compulsory for most patients, and are still the first drug prescribed. Their main advantage is their ability to obtain clinical efficacy rapidly. High-dose pulse steroids are often administered to patients with the most severe disease. Although the benefits of steroids have been largely documented and their side effects are well known, we have not yet established the optimal dose to treat patients and alternative treatments should be considered for the most severely ill patients. In patients with poor renal function [1], plasma exchanges have been shown to be a reasonable alternative to pulse steroids and, indeed, more effectively improve renal function than steroids. In other clinical situations, such an approach has not been evaluated and it seems likely that some patients who initially received pulse methylprednisolone were overtreated. The infectious risk induced by pulse steroids is not negligible [2–4], even though it has not been assessed as an independent factor of infection.

A consensus on the minimization of daily dose has been reached, even though some differences persist among countries. In France, where corticosteroids have been prescribed at high doses for decades, our past and ongoing trials use lower doses, close to what is now recommended in Europe. However, treatment duration varies among countries, and its impact on relapse and side effect rates has not been explored. In the US, 6 months of steroid treatment was one endpoint of the rituximab study [5]. On the contrary, in most European countries and especially in France, patients receive an average dose of 5 mg/d for at least 1 year to 18 months after having entered remission. Walsh et al. [6] found a lower relapse rate when steroid administration was prolonged and that could also be said for the RAVE study [7], in which most patients stopped steroids at 6 months. Notably, the RAVE study relapse rate at 18 months was higher (32% in the rituximab arm vs 29% in the azathioprine arm) than in other prospective studies, i.e., the CYCAZAREM study at 18 months [8] (15.5% in the azathioprine arm vs 13.7% in the cyclophosphamide arm) and the WEGENT trial [9] at 28 months (36% in the azathioprine arm vs 33% in the methotrexate arm). Thus, the hypothesis of the effectiveness of prolonged steroid treatment to prevent relapses remains speculative and not supported by prospective trials. On the other hand, prolonged corticosteroid use can be responsible for specific adverse events, like cataract, diabetes, high blood pressure or obesity…

**Cytotoxic treatments**

These drugs are indicated for granulomatosis with polyangiitis (Wegener’s) (GPA) and severe forms of microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) according to the Five-Factor Score [10]. Their toxicities are well known, especially for cyclophosphamide. Fertility is a major concern, particularly for women. Based on what has been observed in systemic lupus erythematosus [11], physicians now prescribe cyclophosphamide more carefully and alternative treatments are used more frequently [12]. However, when low-dose cyclophosphamide is prescribed, the risk of sterility is limited, mainly to women less than 30 years old. However, over 30, the risk of sterility is very high and, in a previous study, we observed that the majority of patients became sterile [4]. Pertinently, the total dose cyclophosphamide can also be minimized to limit the severity and number of side effects. The results of the prospective CORTAGE trial, to be presented during this congress [13], demonstrated that it is possible to effectively treat vasculitides with a low steroid dose and only 3 g of cyclophosphamide.