Review

Systemic vasculitis: a critical digest of the recent literature

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ABSTRACT

Herewith we provide a critical digest of the recent literature on systemic vasculitis. In this manuscript, we reviewed all the articles published during the last 12 months on large-, medium- and small-vessel vasculitis and selected the most relevant studies regarding the epidemiology, pathogenesis and management of systemic vasculitis. In particular we focused the attention on giant cell arteritis, ANCA-associated vasculitis and cryoglobulinaemia.

Introduction

Recently, systemic vasculitis have been the subject of considerable immunologic and clinical research which have led to significant advances in the management of these challenging disorders.

In the footsteps of our previous annual reviews (1, 2), herewith we provide a critical digest of the recent literature; a Medline search of English language articles published in the PubMed database from January 2012 to date, using the following key words: "vasculitis", "giant cell arteritis", Takayasu arteritis", "cytoplasmic antibodies (ANCA) associated vasculitis", "microscopic polyangitis, granulomatosis with polyangiitis (formerly Wegener's)", "eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss)" and "cryoglobulinaemia" formed the data sources.

We reviewed all the articles and selected the most relevant manuscripts regarding classification, epidemiology, pathogenesis and management of systemic vasculitis.

Novel insights into nomenclature of vasculitis

Vasculitis are a heterogeneous group of autoimmune mediated inflammatory diseases with a high medical and societal impact, involving blood vessels of different type and size (3, 4).

A key event that has taken place in the past few months has been the release of the novel nomenclature system for the various forms of systemic vasculitis (5). This new, 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitis (CHCC2012) represented an international effort aimed at replacing the previous CHCC1994 nomenclature system (6) with names and disease definitions currently in usage, based on the latest advances in the understanding of disease manifestations. More specifically, this new system separates vasculitis due to known causes such as infections from those without known causes. CHCC2012 categorises noninfectious vasculitis by integrating knowledge about predominant type of vessels involved, pathogenesis, demographics and clinical manifestations. The major changes of this novel CHCC2012 version include the addition of a new category of vasculitis, referred to as antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, or AAV. These diseases include microscopic polyangitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss). Polyarteritis nodosa (PAN) was recognised as not ANCA related. The use of eponyms was phased out in the naming of these AAV vasculitis. Some other innovations include the addition of two more categories: one including vasculitis of variable vessel types (*i.e.* Cogan's, Behçet's) which are forms of vasculitis which do not involve a single predominant size of blood vessel and another category for Single Organ Vasculitis which includes vasculitis occurring in a single organ such as central nervous system vasculitis, cutaneous leukocytoclastic vasculitis or isolated aortitis.

Novel insights into large-vessel vasculitis

Diagnosis and assessment of disease

Giant cell arteritis (GCA) is the most common form of systemic inflammatory vasculitis of the adults; it affects the aorta and its major branches. Diagnosis should be performed as early as possible to avoid ischaemic complications and the mainstay of the diagnosis remains histopathologic examination of the temporal arterial biopsy. Several imaging techniques have been used to explore temporal artery but their utility a alternatives to temporal biopsy is controversial. Recently, a blind prospective study on 30 consecutive patients has shown a sensitivity to change of colour Doppler ultrasound (CDUS) in GCA and emphasised the advantages of using CDUS to monitor disease activity; specifically, the results suggested that halo disappearance seems rare before two weeks and it frequently persists during the first two months after initiating glucocorticoids (GC) (7). Moreover, recent advances in imaging techniques have shown a utility in detecting the prevalence of LVV involvement in GCA, that should help to tailor treatment according vascular systemic complications (8).

Treatment of LVV

The therapy of GCA and Takayasu arteritis (TA) is mainly based on GC; however, since LVV are characterised by a chronic-relapsing course, growing attention has been focused on the use of steroid-sparing agents and there is some evidence that azathioprine and methotrexate may be used with efficacy. Recently, Loock *et al*. (9) have evaluated the efficacy and safety of cyclophosphamide (CYC) for remission induction in 35 GCA patients with persistent disease activity despite standard immunosuppressive treatment. Patients with persistently active GCA unresponsive to treatment with GC plus at least either methotrexate or azathioprine for a minimum of 3 months and unable to reduce daily glucocorticoid dose to <10 mg prednisolone equivalent were evaluated; about 90% of the patients responded with improved disease activity and sustained reduction of daily prednisolone intake to <10 mg. Moreover, at one year follow-up, with an acceptable safety profile, doses <7.5 or <5 mg were achieved in about 89% and 67% of the patients on maintenance immunosuppressive treatment, respectively. More recently, a French group reported the effectiveness of CYC to treat GC-dependent GCA and/or severe GC-related side effects (10). The study included 15 patients responded to monthly pulses of CYC, all experiencing a GC-sparing effect, including one third patients who discontinued GC long term. In the light of these results and on the literature review performed from the same group, CYC should be considered a therapeutic option for remission induction in GCA refractory to standard immunosuppressive treatment.

Nevertheless, optimal therapeutic approach of LVV should take into account of pharmacological progresses and growing interest has been pointed on biological agents. Recently, Pipitone *et al*., in order to provide recommendations on behalf of the Italian Society for Rheumatology for the off-label use of biologic agents in the treatment of LVV, have performed an exhaustive review of the published evidence on the treatment of GCA and TA with biological agents (11). While literature data regarding the use of TNF-α inibitors in GCA have provided conflicting results, the efficacy in refractory TA seems to be more suitable, although a dose escalation was required to maintain clinical efficacy. Nowadays, lacking data are published on the use of B-cell depleting monoclonal antibody rituximab. Since interleukin-6 pathway is up-regulated in LVV, growing data suggest the potential crucial role of anti-IL-6 monoclonal antibody tocilizumab in the treatment of GCA and TA. After the first reports in 2008 (12), many studies have reported the efficacy of tocilizumab, both in patients with GCA and Takayasu arteritis. Although we need evidence from randomised controlled trials to support the effectiveness of tocilizumab in the treatment of GCA patients and even though we do not know how tocilizumab should prevent ischaemic complications, data nowadays available are surely encouraging (13-18). Similarly, many reports have shown the successful response to tocilizumab in patients with TA (18-21).

Novel insights into ANCA vasculitis (AAV)

Genetic differences and clinical phenotypes in AAV

The three types of AAV (*i.e*. GPA, MPA, EGPA) have been classified together in the vast majority of the classification systems. However, despite their similarities, a number of studies have provided during the last few months important evidence on the epidemiologic, clinical and genetic differences between EGPA, GPA and MPA.

From this perspective, the first study which deserves to be quoted is the prospective epidemiological study by Watts R *et al*. (22). In their study the authors by using the Norfolk Vasculitis Register (NORVASC) identified between 1998-2010, 111 GPA and 58 MPA incident cases in patients attending the Norfolk and Norwich University Hospital, indicating that the annual incidence of GPA was higher in northern Europe with respect to MPA and supporting the hypothesis that GPA and MPA should be viewed as separate conditions with a different genetic background. These findings have been consistently confirmed by the genomewide association study which has been recently completed (23). This genomewide association study was performed in a discovery cohort of 1233 U.K. patients with ANCA-associated vasculitis and 5884 controls and was replicated in 1454 Northern European case patients and 1666 controls. The genetic associations were studied for ANCA specificity (PR3 and MPO) and clinical phenotype. The strongest genetic associations were with the antigenic specificity of ANCA, not with the clinical syndrome. Anti-proteinase 3 ANCA (PR3-ANCA) was associated with HLA-DP, SERPINA1 (encoding alpha-1 anti-trypsin) and PRTN3(encoding PR3). Anti-myeloperossidase ANCA was associated with HLA-DQ.

In addition to these epidemiologic and genetic studies, two more studies need to be quoted. The first was promoted by the European Vasculitis Group (EUVAS) and the French Vasculitis Study

Group (FVSG). The study by Mahr *et al*. (24) is a cluster analysis on the data collected from 673 subjects enrolled in five prospective randomised clinical trials performed in order to explore the phenotypic spectrum of AAV. The analysis suggested that AAV encompassed five classes associated with different outcomes ranging from high relapse and death rates, to low death-high relapse risk and to high death-low relapse risk. These clusters were named "renal AAV with PR3-ANCA", "renal AAV without PR3-ANCA", "non-renal AAV", "cardiovascular AAV" and "gastrointestinal AAV". The results of this study reinforced the concept that it was appropriate to split AAV into more than the usual subgroups leading to more accurate stratification of patients into homogeneous disease groups for therapeutic, epidemiological and basic research. The second study focused on EGPA and investigated patients' long-term outcomes in a large cohort of 393 subjects followed up for more than 5 years, outlining the peculiarities of this AAV, especially in EGPA ANCA-negative patients (25). When compared to the EGPA ANCA-negative patients, the ANCA-positive patients had significantly more frequent ENT manifestations, peripheral neuropathy and renal involvement, but less frequent cardiac manifestations. Vasculitis relapses and mortality rates differed according to subjects ANCA status being more frequent in ANCA-positive patients.

Treatment of AAV: options for the future

The introduction of cyclophosphamide (CYC) has represented a cornerstone for AAV treatment. From this point of view, the data on long term outcome of the NORAM trial (Non renal Wegener's Granulomatosis treated alternatively with Methotrexate, MTX), published last October, have reinforced the evidence that when compared to first-line treatment with MTX, CYC-based induction therapy was associated with a more effective disease control over the follow-up in terms of shorter duration of corticosteroid therapy and longer cumulative relapse-free survival (26). Nonetheless, CYC-based regimens have been associated with a pronounced risk of toxicities including premature ovarian failure. It is not a case that, as the FertiPROTEKT registry has recently pointed out, fertility preservation techniques including gonadotropin releasing hormone analogues and cryoconservation have been increasingly and successfully offered to patients undergoing CYC (27). Recently, however, alternative approaches to CYC with new drugs targeting cytokines and cellular pathogenetic players have been explored, particularly in selected subsets of patients, with the ultimate aim of reducing exposure to CYC and CYC-related comorbidities. Among the studies published on this topic during the past twelve months the followings appeared to be of particular interest. Recommendations for the use of rituximab (RTX) in AAV have been developed by a multidisciplinary panel of experienced physicians (28). In newly diagnosed generalised AAV patients, RTX was considered equally efficient for standard remission induction as CYC. The avoidance of CYC was considered desirable in the presence of ongoing chronic infection, known CYC intolerance or hypersensitivity, or when there was a high risk of infertility. In refractory and or relapsing forms of AAV, RTX was also recommended when conventional therapy had failed. However, a great number of patients often experience a disease relapse after RTX. In these cases RTX retreatment has shown to be effective and well tolerated as maintenance therapy (Smith *et al*. (29); Roubaud-Baudron *et al*. (30)). A ten-year single-center observational study on 53 patients with refractory GPA, by Cartin-Ceba *et al*. (31) supported this hypothesis also underlining how repeated depletion of B lymphocytes might be associated with a low risk of infections. As far as refractory AAV vasculitis is related, conflicting data have been reported on whether RTX might represent a therapeutic option for GPA granulomatous manifestations (*i.e*. orbital granuloma, pachymeningitis, endobronchial lesions). Holle *et al*. (32) in a study on 59 GPA patients documented an excellent response rate in patients with vasculitic manifestations and only in a minority of patients with orbital masses. Similarly, Pullerits *et al* (33) reported a limited clinical response in patients with endobronchial lesions and tracheasubglottic granulomatous disease. By contrast, Baslund *et al*. (34) analysed the efficacy of RTX in ten patients with orbital inflammation and reported positive effects on symptoms, visual acuity and/or granuloma size in many of the patients enrolled. It has been generally hoped for a controlled trial to further evaluate the principle of B-cell-depleting treatment with RTX for refractory granulomatous AAV.

RTX was also reported to be beneficial in a number of EGPA patients who were mainly ANCA-positive. Conversely, RTX was reported to be ineffective and even incriminated as having provoked severe bronchospasm in ANCA-negative patients. Indeed, EGPA is a complex AAV involving different pathogenetic mechanisms and players. Recent developments in science and technology have opened new and unorthodox avenues for studying the complex mechanisms underlying EGPA and other rheumatic diseases (35). Exploring novel biomarkers might open enormous opportunities for targeted therapeutic strategy in EGPA (36, 37). In this scenario reports on the effectiveness of different biologic agents such as omalizumab and mepolizumab in definite disease subsets are increasingly reported and may enrich the therapeutic options for EGPA in the next future (38-43).

Novel insights into cryoglobulinaemic vasculitis (CV)

Classification and pathogenesis

Preliminary classification for CV have been developed in a multicentre European study in 2011. During the last few months a comparison of the performance of these classification criteria was made between HCV-positive and HCV-negative patients with serum cryoglobulins, with high sensitivity and specificity (44-45) thus demonstrating that classification criteria for CV can be equally and reliably applied both in HCV-positive and -negative CV. Indeed, HCV still plays a central role in the pathogenesis of CV (46). Cryoglob-

ulins are generated by B-cells clonal expansion which finds its first step in HCV lymphotropism. A number of empirical observations, have recently reinforced the hypothesis that a process that escapes from HCV trigger, could be at play in some subjects with CV. In this regard, marginal zone-like lymphocytes (MZL) may persist for years after the eradication of HCV infection. These cells have been implicated in contributing to the accumulation of autoreactive B-cells in mixed cryoglobulinemia (47). However, it is not clear why cryoglobulinaemic syndrome affects only a minority of HCV infected patients. Recent studies have suggested that the host's genetic background may play an important role in determining the susceptibility to CV of some HCV-infected patients (48). T cell-mediated immune response seem to play greater importance in the production of antiviral cytokines but seems to have a role also in cytotoxic damage. In this regard, a substantial divergence in cytokine production have been claimed between subjects with HCV infection not associated with CV and patients with HCV-related CV (49-50). Since a number of studies have suggested an immunomodulatory role for vitamin D in various conditions such as autoimmune, neoplastic and infectious diseases, a possible role of Vitamin D deficiency have recently been claimed also in the expression of extrahepatic manifestations of HCV infection (51).

Treatment

Similarly to what has been described for the disease clinical expression and pathogenesis, potential differences in the response to immunosuppressive treatment and adverse events between HCV-positive and -negative CV have been noted increasingly. The potential goals of CV treatment are essentially to eradicate HCV (etiologic therapy); to limit or suppress B lymphocytes proliferation (pathogenetic therapy) and to ameliorate symptoms reducing the damage caused by circulating immune-complexes (symptomatic therapy) (46, 48, 52). Treatment should be tailored to the single patient focusing on the clinical history, disease manifestations, possible co-morbidities and previous therapies (46, 48). In cryoglobulinaemic patients with life-threatening manifestations (abdominal vasculitis, haemorragic alveolitis, hyperviscosity syndrome and sometimes acute motor neuropathy and rapidly progressive glomerulonephritis) a growing interest has focused on Rituximab treatment. Rituximab (RTX) was used successfully in patients with CV and severe vasculitis refractory to conventional therapies (53-55). Antiviral therapy should always be taken into consideration in HCV positive patients with CV, since immunosuppressant were previously found to be ineffective and associated with a poor out come with increased mortality (48, 56). Antiviral therapy represents a cornerstone for the management of CV in HCV-related cases and it should be used routinely for more stabilised patients. The decision to treat patients with chronic hepatitis C depends on multiple parameters including a precise assessment of the severity of liver disease, the presence of absolute or relative contraindications to therapy, its previous failure or intolerance. The HCV genotype is systematically determined before treatment since it determines the duration of treatment (46, 48) and the dose of RBV (57). When antiviral therapy is not effective, contraindicated or not tolerated, treating patients with RTX should be considered (52). The treatment of non-HCV-related CV is usually similar, although less well standardised, to that of other vasculitides, with steroids and immunosuppressant in most severe cases. In these cases treatment with RTX also seems effective (46, 48). In the future, the treatment of HCV-associated CV may be improved by the administration of an antiviral triple therapy in which the standard Peg-INF and RBV may be associated with one of the new protease inhibitors (telaprivis or boceprevir) especially in patients infected by genotype 1 b (46).

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