

Development of Canadian Recommendations for the Management of ANCA-Associated Vasculitides: Results of the National Needs Assessment Questionnaire

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Abstract: *Objectives:* To study variations in Canadian clinical practice patterns for the management of ANCA-associated vasculitis (AAV) and identify points to consider for the development of national recommendations.

Material and Methodology: A 30-item needs assessment questionnaire was sent to all members of the Canadian Vasculitis network (CanVasc), Canadian Rheumatology Association (CRA), Canadian Thoracic Society (CTS) and Canadian Society of Nephrology (CSN). Respondent characteristics, practice patterns, concerns and expectations were analyzed.

Results: Among 132 physicians who followed at least 1 vasculitis patient and responded to the survey, 39% stated that they felt confident in their management of AAV. Several variations in practice were observed regarding diagnostic procedure, induction and maintenance treatments and use of biologics; some were due to logistic constraints (difficulties in access to some specific tests, drugs or care; lack of health care coverage for the costs). The top 5 topics for which recommendations are expected involve treatment for remission induction, maintenance, refractory disease, and relapse as well as biologics.

Conclusion: Practice variations identified in this needs assessment survey will serve to formulate key questions for the development of CanVasc recommendations.

Keywords: ANCA-associated vasculitis, CanVasc, physician practice patterns.

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§A complete and updated list of CanVasc founders, bureau, core, associated and affiliated members can be downloaded from: <http://www.canvasc.ca/InfomationCanVasc.htm>.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) refers to granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) [1]. Combined estimates of prevalence and incidence of these 3

systemic diseases are 56–273 per million population and 3–39 per million population per year, respectively, according to studies conducted in North America, Europe and Asia [2, 3]. Frequencies of AAV in Canada are likely to be comparable [4]. This rarity limits both the personal and general clinical experiences with such patients and potentially makes their diagnosis and treatment challenging. All 3 diseases are potentially life-threatening, and tissue or organ damage from the disease or treatment is common in survivors. Hence, clinical practice guidelines can be useful for synthesizing and transmitting evidence-based management strategies to appropriate users.

The Canadian Vasculitis research network (CanVasc) was created in November 2010 and gathered several physicians across Canada with experience and interest in vasculitis. The ultimate objective of this group is to improve the diagnosis, management and outcomes of vasculitis in Canadian patients. The stated aims of CanVasc include the initiation and development of Canadian-specific recommendations for AAV clinical management, taking into account cultural and healthcare variations in Canada, and incorporating results of recent randomised controlled trials [5, 6]. As recommended and illustrated with other disorders [7], an initial needs assessment questionnaire was distributed to Canadian healthcare professionals from different medical specialties involved in vasculitis management. Input was sought regarding current knowledge, knowledge gaps, uncertainties and challenges in the diagnostic, therapeutic and follow-up management of AAV in Canada. The specific objectives were to formulate a series of relevant clinical questions to direct the literature search and guide the development of practice recommendations.

MATERIALS AND METHODOLOGY

A questionnaire asking about demographic/practice characteristics and including general questions on diagnostic investigations, treatments, follow-up practice for AAV patients and gaps in knowledge about the management of these patients was developed by CanVasc core members (primarily by L.F., M.T., C.Pa. and P.L. - available as an online Supplementary material). The questionnaire was submitted for review to the Canadian Rheumatology Association (CRA) Therapeutics Committee, Canadian Thoracic Society (CTS) and Canadian Nephrology Society (CSN). The questionnaire was developed by use of Survey Monkey (www.surveymonkey.com) and a pilot version was tested in Spring 2012. The questionnaire was distributed in Summer 2012 to all members of the CRA anonymously. A link inviting CTS and CNS members to complete the survey was also added to their respective newsletters for dissemination.

The survey remained open for 3 months, with one reminder email sent to CanVasc and CRA members as well as CSN and CTS administrative offices 1 month before survey closure on October 15, 2012. The collected data were then extracted to Microsoft Excel® for descriptive analysis.

RESULTS

In all, 136 members of the CRA, CTS and/or CanVasc responded to the survey, and 132 completed it. Four

respondents were not invited to go beyond the first question because they reported not seeing any vasculitis patients. The mean age of the respondents was 48 ± 11 years and 62% had been in practice for >10 years. About half (52%) were male and the greatest proportion of respondents resided in Ontario (n=54), followed by Québec (n=25), then the western provinces (British Columbia n=13; Alberta, n=18; Saskatchewan n=3; Manitoba, n=2) and eastern provinces (New Brunswick, n=5; Nova Scotia, n=4) (8 did not respond to the question about their work location). A total of 64% of respondents reported practicing in academic or teaching hospitals. Respondents in order of frequency were rheumatologists (adult, 63%; pediatric, 6%), respirologists (23%), internists (4%) and primary care physicians (1.5%). A small insert with a link to the survey was provided in the CSN newsletter, but no nephrologists completed the online questionnaire.

Overall, 77% of respondents reported seeing 3 cases of GPA/MPA or more per year, and 33% reported seeing 3 cases of EGPA or more per year in their center (24 respondents reported being members of a vasculitis network such as CanVasc or A Registry for Children with Vasculitis: e-entry [ARCHiVe]); 77 of 108 respondents (71%) not self-declared as members of a vasculitis network reported managing AAV in patients themselves without “referring them to a referral center for vasculitis at least once to be enrolled in a cohort study”. A total of 15 respondents (11%) reported that their center had some local written protocol for treatment of AAV.

As shown in Table 1, most diagnostic investigations were ordered homogeneously by most physicians, including complete blood cell count, renal parameters, C-reactive protein level and/or sedimentation rate (both ordered systematically by >85% of the respondents), as well as testing for ANCA (ordered systematically by 91% of the respondents, with 2 respondents reporting that the cost of the test for patients was prohibitive). Testing for complement fractions (C3 and C4), serum protein electrophoresis and screening for lupus anticoagulant were ordered systematically by 76%, 47% and 42% of respondents, respectively, during diagnostic work-up. Screening for anti-glomerular basement membrane (anti-GBM) antibodies, voluntarily not included in the list of possible diagnostic investigations, was added in the text box for “other tests/comments” by 3 respondents. Chest plain X-ray was ordered systematically by most physicians (96%), tuberculin skin test by 25% and some CT scan of organs involved by 57% of respondents.

For remission induction, almost all respondents reported that they regularly used corticosteroids, intravenous (IV) or oral cyclophosphamide. A total of 68% and 64% reported having used rituximab or methotrexate for induction; 33% reported that they had used mycophenolate mofetil and 7% an anti-tumor necrosis factor alpha agent for induction. Only 48% reported having used plasma exchange as part of induction therapy. Two respondents commented on the sequential use of IV then oral cyclophosphamide, and 3 on practical difficulties in setting up IV cyclophosphamide infusions. The mean duration of induction was ≤ 6 months for 88% of respondents. One question asked about the use of

Table 1. Main results from the needs assessment questionnaire on practice patterns for management of ANCA-associated vasculitis (number of respondents seeing at least 1 vasculitis patient = 132).

Questionnaire Items	Answers*		Comments
	Always	Never	
Diagnostic investigations			
Which laboratory investigations for patients with suspected AAV?			
Complete blood count	100%	0	
Liver function test	94%	0	
Renal function test	100%	0	
C-reactive protein	88%	1%	
ESR	87%	0	
Urinalysis (routine and microscopic analysis)	98%	1%	
Von Willebrand factor antigen	7%	58%	
Complement C3/C4	76%	2%	
ANCA	91%	6%	“Some refuse ANCA testing because of the cost”
Antinuclear autoantibody	85%	0	
Serum protein electrophoresis	47%	11%	
Lupus anticoagulant and/or anticardiolipin	42%	6%	
Which other investigations for patients with suspected AAV?			
Chest X-ray	96%	0	“Depends on clinical presentation”
Tuberculin skin test	25%	11%	
Tuberculosis interferon assay (if available)	3%	47%	
Pulmonary function tests	45%	2%	
Bronchoscopy + bronchoalveolar lavage	16%	7%	
Biopsy of involved organ system	48%	1%	
CT scan /MRI of involved organ	57%	0	
Echocardiogram	30%	2%	
Cardiac MRI (EGPA)	7%	31%	
IgE level (EGPA)	52%	4%	
Electromyogram	4%	11%	
Induction treatments			
Which of the following treatments do you use to induce remission?			
Corticosteroids (intravenous pulse)	94%	6%	
Oral corticosteroids	94%	0%	
Oral cyclophosphamide	87%	13%	
Intravenous cyclophosphamide	91%	9%	“IV cyclophosphamide not infused at my centre”, “initial IV cyclophosphamide pulse then switch to daily oral”
Methotrexate	64%	36%	“methotrexate and azathioprine for mild/limited disease”
Azathioprine	47%	53%	
Mycophenolate mofetil	33%	67%	
Rituximab	68%	32%	“would use rituximab if approved”†
Leflunomide	10%	90%	
Anti-tumor necrosis factor alpha agent(s)	7%	93%	
Plasma Exchange	48%	52%	
Maintenance treatment			
What medications do you use?			
Methotrexate	86%	14%	
Azathioprine	96%	4%	
Cyclophosphamide (oral)	23%	77%	
Rituximab	32%	68%	“would use rituximab if could get it before relapse”
Infliximab	3%	97%	
Leflunomide	17%	83%	
Mycophenolate mofetil	53%	47%	
Trimethoprim / sulfamethoxazole (160/800 mg) twice daily	60%	40%	
Follow-up			
Which of the following tests to monitor your patients?			
Complete blood count	100%	0	
Liver function tests	86%	2%	
Creatinine	98%	0	
ANCA	57%	7%	
ESR	79%	1%	
C- reactive protein	84%	3%	
Urinalysis	91%	1%	
CT scan of chest and/or sinus	17%	6%	
Pulmonary function tests	30%	7%	
Electromyogram	0	41%	
Bone mineral density	49%	6%	
CD19+ B cell count (in patients who received rituximab)	14%	67%	
Urine cytology (patients who received cyclophosphamide)	43%	22%	
Cystoscopy (patients who received cyclophosphamide)	9%	33%	“cystoscopy only if persistent microscopic hematuria”

Data are percentage of respondents.

* Respondents could skip questions, or chose between Always / Sometimes / Never.

† At the time the survey was conducted, rituximab was not yet approved in all Canadian provinces for induction in adult patients with severe AAV (and certain other specific criteria that may vary according to each province).

AAV: ANCA-associated vasculitis; ANCA: anti-neutrophil cytoplasmic antibodies; EGPA: eosinophilic granulomatosis with polyangiitis; ESR: erythrocyte sedimentation rate.

rituximab for first-line induction treatment, assuming that it was approved and covered without restriction: 72% of respondents stated that they would not use it systematically for all their newly diagnosed patients and would thus still use cyclophosphamide. In contrast, 80% would use rituximab systematically for all newly diagnosed women of child-bearing age, and 89% would use it systematically to induce remission in relapsing patients, regardless of the previous dosing of cyclophosphamide they may have received. Prophylaxis against *Pneumocystis jiroveci* pneumoniae when using cyclophosphamide was prescribed systematically by 83% of respondents, and sometimes by 16%. Gonadotropin-releasing hormone for women of child-bearing age, oocyte collection or sperm preservation when using cyclophosphamide had never been used or considered a possibility for 39%, 33% and 25% of respondents, respectively, mainly because of the difficulty in obtaining coverage for the drugs, non-availability of the technique locally, and/or acuteness of AAV precluding any delay in cytotoxic initiation.

For remission maintenance, azathioprine and methotrexate were the most commonly used agents. In all, 23% of the respondents also selected continuous oral cyclophosphamide as a possible maintenance drug, 53% mycophenolate mofetil, and 32% rituximab re-infusions. Before prescribing azathioprine, 24% of the prescribers systematically genotyped or measured thiopurine methyltransferase activity, and a further 17% reported they would do so if the test were available at their institution and/or if the patient did not have to pay for it. Planned and/or optimal duration of maintenance therapy was up to 18 months for 18% of the respondents and longer than 4 years for 22% (“as long as required”, “as long as tolerated”, “maybe forever”). Average duration of corticosteroid therapy was \leq 6 months for 10% of respondents and exceeded 2 years for 12%.

For patient follow-up, in parallel with standard tests such as complete blood cell count or C-reactive protein level, 57% and 49% always ordered serial ANCA testing and bone mineral density testing, respectively. For past recipients of cyclophosphamide, repeat urine cytology was ordered systematically by 43% of the respondents and regular cystoscopy by 9%.

Overall, 39% of the respondents stated that they felt confident in their management of AAV in patients. Among the possible topics to be covered in recommendations for AAV management, those rated with highest priority were remission induction treatment (rated with highest priority for 47% of respondents), then treatment of refractory disease (for 29%) and relapse (for 25%), indication and use of biologics (for 24%) and maintenance therapy (for 19%). Diagnostic procedures, prevention and monitoring of drug-related toxicity, disease monitoring, and treatments for specific age groups (children, older adults) were the highest priority for only 13%, 10%, 9%, and 7% of respondents, respectively.

DISCUSSION

Through this needs assessment questionnaire completed by 132 Canadian healthcare professionals managing AAV,

practice variations were observed regarding diagnostic work-up, induction and maintenance treatments, use of biologics and patient follow-up. The identification of these variations across Canadian centers and the prioritization by the survey respondents of the topics to be covered are now being taken into account in the development of the CanVasc recommendations for the management of AAV.

This study is one of the first major collaborative and multidisciplinary efforts for vasculitis in Canada and included an extensive evaluation of all aspects of the management of AAV. However, the aim of this needs assessment questionnaire was not to extensively analyze and compare the practice patterns in Canada, as several limitations in our study precluded such analyses. The specific aim of the survey was to help identify all relevant topics that could warrant recommendations. There are no published guidelines to our knowledge for the development or reporting of the results of such a needs assessment questionnaire and no consensual definition of the threshold at which the variability in patient care would warrant actions to harmonize care, such as the development of recommendations. The interpretation of our findings and the observed practice variations must thus remain cautious and considered only as results of preliminary but required work, prior to the development of the recommendations.

Several specificities must be taken into account when considering access to care and therapeutic management of patients with these rare conditions in Canada. Although several referral centers for AAV have been identified to participate in CanVasc (<http://www.canvasc.ca>), mainly based on their recruitment and experience with AAV, the population density of Canada is highly variable and widely distributed. The cost coverage and access to some examinations, drugs and/or studies can be problematic for patients in non-referral centers; geographic isolation from major referral centers in the vast Canadian land mass might be a significant barrier.

Other possible reasons for the practice variations observed might include the variable personal experience of the respondents with these rare diseases and their knowledge of vasculitis in general and new developments in the field. For example, we found it surprising (and, if true, concerning) that 23% of the respondents reported the use of continuous oral cyclophosphamide for maintenance therapy after induction (the question was “For remission maintenance therapy of ANCA-associated vasculitis, what medications do you use [usually in combination with prednisone]?”).

However, we may have failed to identify all practice variations for AAV considered by Canadian physicians. Of note, no nephrologists answered the survey, likely because the survey was not advertised enough among them and they did simply not notice it. Our survey was concurrent with development of the Kidney disease/improving global outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis, [8] developed around the same time as the survey, and may also have diverted some nephrologists' attention from this survey. However, several nephrologists are members of CanVasc and are involved in the ongoing development of the recommendations, and, although important, renal disease remains only one of the numerous facets of the multi-system AAV. General internists were also

underrepresented among the respondents. However, in Canada, the primary care physicians who manage patients with vasculitis are more often rheumatologists, nephrologists and/or respirologists, as compared with several European countries in which general internists have a more central role. In addition, the survey questions were pilot-tested with a panel of CanVasc-affiliated rheumatologists, nephrologists and other specialists as well as internist experts and trainees who frequently co-manage AAV in patients.

Finally, the needs assessment questionnaire was conducted before rituximab was approved as induction therapy for adult patients with severe AAV in all Canadian provinces (official approval by Health Canada in December 2011, then first in Ontario in February 2012). However, we asked whether its approval would affect physicians' choice for induction treatment. Surprisingly, despite rituximab being approved only for induction treatment, almost one-third of the respondents reported its use for maintenance, as suggested by the results of a few recent series and studies [9-12], and likely covered by patients' own drug insurance plans.

Ultimately, reduced variation in practice could be achieved with the development, dissemination and acceptance of consensus recommendations. However, the impact on patient outcomes, before and after the dissemination of the recommendations, will need to be assessed.

CONCLUSION

Our needs assessment survey identified practice variations in Canada and the most important points to consider in the development of CanVasc recommendations for the management of AAV. Our article also provides a good example of the difficulties and limitations of such needs assessment questionnaires, for which there is at present, to our knowledge, no particular accepted method for development, interpretation or reporting.

CONFLICT OF INTEREST

We declare that there is no specific funding, financial contribution or conflict of interest to report in relation with the work being reported.

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