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Variability in Experts' Opinions Regarding Risks and Treatment Choices in Patients with ANCA Associated Vasculitis

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Abstract

Objective—There are insufficient toxicity data available to guide treatment decisions in patients with ANCA-associated vasculitis (AAV). The objective of this study was to obtain expert input related to available treatment options.

Methods—We performed a web-based survey of experts (defined as physicians whose practices focus on vasculitis and physicians engaged in research in vasculitis) regarding adverse events (AEs) associated with cyclophosphamide and/or rituximab, the two treatment options for remission-induction of severe AAV. Using scaled measures, experts rated i) the probability of 30 AEs associated with the treatments; ii) the importance of disclosing each AE, and reported iii) their treatment preferences using standardized scenarios.

Results—Ratings of the probabilities of specific AEs associated with cyclophosphamide and rituximab varied significantly among the experts. The majority agreed that AEs related to fertility, infections, and serious infusion reactions were “extremely” or “very important” to disclose. Less than half of the experts surveyed endorsed disclosing the risks of progressive multifocal leukoencephalopathy, hepatitis reactivation, or zoster. For patients with newly-diagnosed AAV, the majority of experts preferred IV cyclophosphamide for older adults and rituximab for younger women with newly-diagnosed AAV. For patients with recurrent disease who had been previously treated with cyclophosphamide, the majority of experts preferred rituximab, regardless of age or gender.

Conclusion—The variability noted in this study suggests that the information and treatment patients receive may differ depending on where they receive their care. This type of unwarranted variability could be reduced if data from long-term extension and observational studies generate more precise outcome estimates for treatment-related AEs in AAV.

The RAVE (Rituximab versus Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitis) and RITUXVAS (Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis) trials found that rituximab was as effective as cyclophosphamide followed by azathioprine at inducing and maintaining remission for up to 18 months for patients with severe ANCA-associated vasculitis (AAV) (1–3). Given the

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CONFLICT OF INTEREST STATEMENT

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results of these studies, treatment for AAV now frequently involves a choice between two markedly different drug regimens. Additionally, there are data demonstrating that oral and intravenous (IV) cyclophosphamide have similar efficacy in treatment of severe AAV (4). Thus, the decision regarding which treatment to prescribe for severe AAV involves difficult trade-offs and requires that physicians effectively inform their patients of the risks and benefits associated with both treatment options.

To date, there are insufficient data describing the magnitude of risks associated with cyclophosphamide or rituximab regimens used for treatment of AAV. Randomized controlled trials are not able to provide estimates of uncommon adverse events (AEs) and observational studies of larger cohorts have not yet been published. Until more data are available, it would be helpful to outline how physicians with expertise in vasculitis perceive the risks related to these two treatment options. The objective of this study was to obtain expert ratings of 1) the risks associated with available treatment options for AAV, 2) the importance of disclosing specific adverse events (AEs), and 3) preferences for treatment of patients with newly-diagnosed and recurrent AAV.

METHODS

We created a web survey in which we asked vasculitis experts (defined as physicians whose practices focus on vasculitis and physicians engaged in research in vasculitis) to rate the magnitude of risk for 30 AEs for treatment with oral and IV cyclophosphamide, and for rituximab. The AEs were presented in alphabetical order. Respondents were asked to indicate the probability of each AE using a drop-down list of 16 prespecified response options ranging from 50% to 0% risk (See Appendix A) and to rate the importance of disclosing each AE on a 5-point scale (“Extremely important” to “Not important at all”).

The survey included the following instructions:

Please indicate the risk of each adverse event for each treatment option assuming a patient with NEWLY diagnosed ANCA associated vasculitis (AAV) and no comorbidities.

The list of adverse events is meant to be exhaustive and includes items you may not usually discuss with your patients. A drop down list is provided for each adverse event. Please choose the answer closest to your best estimate.

Assume that:

- The patient has had no previous exposure to cyclophosphamide, rituximab or any other immunosuppressive medications.
- Patients treated with oral cyclophosphamide are treated with 2 mg/kg/day orally for 3–4 months and then switched to azathioprine.
- Patients treated with intravenous cyclophosphamide are treated with 15 mg/kg every 2–3 weeks for 3–4 months (CYCLOPS regimen) and then switched to azathioprine.

Treatment choices were elicited for three scenarios: 1) newly-diagnosed severe AAV in a treatment-naïve patient without co-morbidities, 2) recurrent severe AAV in a patient without comorbidities who was previously treated with oral cyclophosphamide, 3) recurrent severe AAV in a patient without co-morbidities who was previously treated with IV cyclophosphamide. For each scenario, experts were asked to indicate their preferred treatment option for four patient profiles: a 22 year-old woman, a 62 year-old women, a 22 year-old man, and a 62 year-old man. Respondents rated a list of seven possible reasons underlying their preference for the first scenario (newly-diagnosed AAV) using a 5-point scale ranging from “Not important at all” to “Extremely important”. We compared

preferences for rituximab against both oral cyclophosphamide and IV cyclophosphamide, using a generalized estimating equation model.

We collected the following physician characteristics: age, sex, specialty, work setting, country, and number of patients with AAV seen per year. The survey was emailed (October 2010) to 167 vasculitis experts. Of these, 145 were successfully delivered. After the first mailing, nonresponders were sent a single reminder email. Overall, the survey was opened by 94 subjects and completed by 50.

Experts' ratings are reported using descriptive characteristics (see Appendix B). We also summarize experts' ratings for the AEs most commonly reported in the literature (see Figures 1–3). To enable graphical representation of the range of risks studied, probabilities were collapsed from 16 discrete options into six groups: 30%–50%, 15%–25%, 1%–10%, 1 in 500 – 1 in 1000, 1 in 10,000 – 1 in 100,000, and no risk.

RESULTS

Seventy-nine percent of responders were male. The mean (SD) age was 48 (9), 30% of the experts surveyed were from North America and 60% were from Europe. 48% were rheumatologists and 38% were nephrologists. 70% worked in a university hospital setting, 66% reported spending the majority of their time in clinical practice, 30% in clinical research, and 1% in basic science research. 80% reported seeing more than 10 patients with AAV per year, 12% between 6 and 10 patients per year, and 8% between 1 and 5 patients with AAV per year.

The most frequent responses for each AE associated with oral cyclophosphamide, IV cyclophosphamide, and rituximab are provided in Table 1. However, as illustrated in the Appendix B, ratings of the probabilities of the 30 specific AEs potentially varied significantly. For example, experts' ratings ranged from 10% to 50% for the probability of leukopenia, 1% to 50% for the probability of infertility, and 1 in 10,000 to 50% for the probability of teratogenicity associated with oral cyclophosphamide. Except for specific risks not known to be associated with rituximab (infertility, bladder cancer, hemorrhagic cystitis), the most frequent responses were all below 50% indicating that there was little agreement on the probabilities of risk for almost all the AE listed. Figures 1, 2 and 3 summarize experts' ratings for the AEs most commonly reported in the literature.

The importance of disclosing specific AEs according to the surveyed experts is illustrated in Figure 4. Of the 23 AEs listed, 75% or more of the experts surveyed felt that 14 were “extremely” or “very important” to disclose. These AEs included those related to fertility, unspecified mild or serious infections, and serious infusion reactions. Fewer than 50% of the experts surveyed felt that it was very or extremely important to disclose the risks of progressive multifocal leukoencephalopathy, hepatitis reactivation, or zoster. Just over 12% of respondents felt that it was very or extremely important to disclose the possibility of a severe skin reaction.

Preferences for each scenario are described in Table 2. For patients with newly-diagnosed AAV, the majority of experts preferred IV cyclophosphamide for older adults and rituximab for younger women with newly-diagnosed AAV. For patients with recurrent disease who had been previously treated with oral or IV cyclophosphamide, the majority of experts preferred rituximab, regardless of age or sex.

Figure 5 described the importance of a prespecified list of 7 possible reasons underlying treatment preferences for patients with newly-diagnosed AAV. Efficacy, toxicity, and cost were all rated as “Very” or “Extremely important” reasons underlying choice of treatment

by the majority of respondents. Uncertainty regarding the efficacy of azathioprine and rituximab to maintain remission had much less influence (see Figure 5).

DISCUSSION

In this survey, physicians with expertise in AAV varied significantly in the risks of AEs they assigned to treatment options for AAV. Variability in estimates was most marked for oral cyclophosphamide. There was less variability in ratings assigned to rituximab, because of the number of AEs not associated with this option (e.g. infertility). We also found considerable variability in experts' opinions related to the importance of disclosing specific AEs. Most notably, disclosure of the rare but serious AEs for which there are black box warnings (progressive multifocal leukoencephalopathy, serious mucocutaneous reactions) were not endorsed by most of the experts surveyed. This may be because these AEs are extremely rare and the causal association between rituximab and these AEs is uncertain. While there are no uniform agreements on standards related to the extent of disclosure required, commonly cited professional standards in the US i.e. *what would a reasonably prudent physician with the same background, training, experience, and practicing in the same community, have disclosed to a patient in the same or similar situation?* favor disclosure of all serious AEs, even when they are rare. The impact of disclosure of extremely rare AEs, however, deserves further research given the known difficulties associated with understanding low probability events and the bias towards overweighting dreaded AEs, even when extremely rare.

Our survey suggests that rituximab is preferred over a repeat course of cyclophosphamide for patients with recurrent disease, irrespective of their age or sex. For patients with newly-diagnosed AAV, IV cyclophosphamide and rituximab were preferred over oral cyclophosphamide. IV cyclophosphamide was the preferred choice for older subjects, whereas rituximab was the most frequently chosen option for younger women, presumably because of the risk of infertility associated with cyclophosphamide. Preferences were less definitive for younger men.

There are several limitations of this study. While the participation rate is consistent with other surveys of physicians, the sample size and participation rate both limit the generalizability of our findings. However, to the best of our knowledge there are no other data currently available describing experts' preferences for this important decision. While we differentiated between initial and recurrent disease, our survey did not specify the interval at which flares occurred. It is likely, that physicians' would be less reluctant to prescribe a second course of cyclophosphamide after a prolonged remission.

Given the current availability of two competing options for the treatment of AAV, treatment planning should ideally be based on a shared decision making model in which physicians effectively inform their patients of the expected risks and benefits associated with each option and subsequently reach a decision together based on each individual patient's preferences. The variability noted in this study suggests that the information patients receive may differ substantially depending on where they receive their care. This extensive variability in data reliability and decision-making is expected to decrease once long-term extension and observational studies generate more precise outcome estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Experts' ratings of the probability of adverse events associated with IV cyclophosphamide

Figure 2.
Experts' ratings of the probability of adverse events associated with oral cyclophosphamide

Figure 3.
Experts' ratings of the probability of adverse events associated with rituximab

Figure 4.
Importance of disclosing specific adverse events

Figure 5.
Importance of reasons underlying treatment preference

Table 1Most frequent ^{*} responses provided by experts for each adverse event

	Oral Cyclophosphamide	IV Cyclophosphamide	Rituximab
Alopecia	50%	1%	0
Bone Marrow Suppression	50%	5%	1%
Bladder Cancer	1%	1 in 500	0
Hemorrhagic Cystitis	5%	1 in 500	0
Hepatitis Reactivation	5%	1 in 500	5%
Infections - Mild	50%	25%, 20%, 5%	20%, 10%
Infections - Serious	10%	5%, 1%	5%
Decreased Female Fertility	50%	5%	0
Decreased Male Fertility	50%	5%	0
Permanent Female Infertility	5%	1%	0
Permanent Male Infertility	5%	1 in 500	0
Infusion Reaction - Mild	0	1%	10%
Infusion Reaction - Serious	0	1 in 500	1%
Interstitial Lung Disease	1%	1 in 500	0
Leukopenia	50%	20%	5%
Lymphoma/Leukemia	1%	1 in 500	0
Malignancy	1%	1 in 500	1%
Myocardial Damage	1 in 500	1 in 10 ⁴	0
Myelodysplasia	5%, 1%, 1 in 500	1 in 500	0
Nausea and/or Vomiting	15%	50%	1%
Opportunistic Infection	5%	1 in 500	1%
Oral Mucosal Ulceration	5%, 1%	1 in 500	0
Premature Ovarian Failure	5%	1%	0
PML	1 in 10 ⁴	1 in 10 ⁵	1 in 10 ⁴
Sepsis	1%	1 in 500	1%
Skin Reaction: Mild	1%	1 in 500	1%
Skin Reaction: Severe	1 in 500	1 in 10 ³	1 in 500
Teratogenicity	50%	50%, 30%	0
Testicular Failure	5%, 1%	1 in 500	0
Zoster	5%	1%	1%

^{*} Multiple probabilities indicate that the most frequent responses were assigned to more than one probability estimate.

Table 2

Treatment preferences for age and sex-specific clinical scenarios

	Newly Diagnosed AAV: Treatment Naïve			Recurrent AAV: Received Oral Cyclophosphamide (on Azathioprine)			Recurrent AAV: Received IV Cyclophosphamide (on Azathioprine)		
	Cyclophosphamide		No Preference	Cyclo-phosphamide	Rituximab	No Preference	Cyclo-phosphamide	Rituximab	No Preference
	Oral	IV							
22 year old woman	2%	28.6%	57.1%	12.2%	2.1%	91.8%	6%	88%	6%
62 year old woman	10.2%	63.3%	10.2%	16.3%	18%	70%	18%	62%	20%
22 year old man	2%	46.9%	36.7%	14.3%	4.1%	83.7%	8.2%	79.6%	12.2%
62 year old man	12.2%	63.3%	10.2%	14.3%	16.3%	71.4%	16.7%	62.5%	20.8%