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Practice Patterns of ANCA-Associated Vasculitis: Exploring Differences Among Subspecialties at a Single Academic Medical Center

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Abstract

Objective—Clinical trial data helps guide physician treatment choices for ANCA-associated vasculitis (AAV), but when data is lacking, treatment choices are largely driven by physician preference. Our aim was to examine AAV treatment preferences to determine if patient gender and age, and physician subspecialty affect treatment choices.

Methods—Rheumatologists, nephrologists and pulmonologists from an academic medical center participated in a web-based survey. Three scenarios (remission induction in severe disease; remission maintenance in severe disease; remission induction in limited disease) were presented for 4 patient profiles (28 and 68 year-old female/male). Physician treatment choices and reasons for these choices were obtained. Differences between groups were analyzed using Chi-Square and Fisher's exact tests.

Results—Physicians were significantly more likely to choose rituximab for young females for remission induction in severe AAV, with toxicity being the main reason for this choice. There was a trend toward rheumatologists choosing rituximab over cyclophosphamide compared with other subspecialties for this scenario. Most physicians switched to a less toxic agent for remission maintenance, but there was little agreement as to choice of maintenance therapy among subspecialties. For remission induction in limited disease, most physicians chose rituximab, particularly for young females.

Conclusion—Currently, there is little data for remission maintenance therapy following rituximab in severe disease, as well as the use of rituximab in limited disease. Choices for treatment of AAV differ among subspecialties, are affected by patient gender and age, and tend to be largely driven by physician preference when data is limited or lacking.

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Keywords

Vasculitis; Physician practice patterns; Antineutrophil cytoplasmic antibodies; Immunosuppressive agents; Wegener's granulomatosis; Granulomatosis with polyangiitis; Microscopic polyangiitis; Clinical practice guidelines

Introduction

Randomized controlled trial evidence helps guide physician treatment choices for ANCA-associated vasculitis (AAV) [1]. Microscopic polyangiitis (MPA) and Granulomatosis with polyangiitis (GPA) are small vessel vasculitides associated in most instances with detectable ANCA. Limited AAV refers to upper and/or lower respiratory tract disease, possibly with other minor manifestations such as rash or arthralgias/arthritis, but without any other organ-threatening systemic involvement. Severe AAV refers to disease with renal involvement or other organ-threatening disease [2].

The therapeutic approach to AAV has evolved to include a remission induction phase, followed by a remission maintenance phase using less toxic immunosuppressive agents once remission is achieved [3–4]. Cyclophosphamide (CYC) plus glucocorticoids have been historically recommended for the induction of remission of severe disease followed by maintenance with methotrexate (MTX) or azathioprine (AZA) [5–7]. Mycophenolate mofetil (MMF) has been studied as a remission maintenance agent in AAV and was found to be inferior to AZA in this setting. MMF has not been studied extensively as induction therapy in severe or limited disease [7]. MTX, however, has been shown in a clinical trial setting to be a viable and less toxic alternative to CYC for limited disease [8].

Two randomized controlled trials demonstrated that a single course of treatment with rituximab (RTX) was as efficacious as CYC followed by AZA for induction of remission in severe AAV [9–10]. These results led to the FDA approval of RTX for the treatment of AAV in April 2011, thereby giving physicians another option besides CYC for the induction of remission of severe AAV. Data for remission maintenance therapy following RTX in severe disease, as well as the use of RTX in limited disease is currently lacking [11]. In the absence of such data, treatment choices are largely driven by physician preferences.

Our aim was to examine AAV treatment preferences to determine if patient gender and age, and physician subspecialty affect treatment choices. Potential reasons for differences in AAV treatment preferences among subspecialists include variation in literature accessibility, differences in initial disease presentations and severity level, diversity of comfort level with medications used, and disparate ability to administer infusions in clinical practice.

Materials and Methods

We invited rheumatologists, nephrologists and pulmonologists from an academic medical center to participate in a web-based survey (see supplementary data available at *Rheumatology* online). Only those that spent 20% of their time in clinical practice were

invited to complete the survey. Three hypothetical scenarios were presented for 4 patient profiles (28 and 68 year old female/male):

1. Remission induction in severe disease.
2. Remission maintenance in severe disease.
3. Remission induction in limited disease.

Physician treatment choices and reasons for these choices (medication efficacy, toxicity, cost/availability, comfort with use) were obtained. The scenarios were limited to patients with GPA and MPA, and did not include any with Churg-Strauss syndrome.

Multiple choice treatment options for remission induction in severe disease included CYC, RTX, MMF, MTX, AZA and no preference. Those for remission maintenance in severe disease included those above plus leflunomide, trimethoprim sulfamethoxazole (TMP/SMX), and expectant observation off medication. Options for remission induction in limited disease included those for remission induction in severe disease plus TMP/SMX.

Differences between groups were analyzed using Chi-Square and Fisher's exact tests. P value was set at a significance of 0.05.

Results

Of 117 surveys sent, 46 were opened by 29 rheumatologists (63%), 8 pulmonologists (17%) and 9 nephrologists (20%). Of these, 23 rheumatologists, 4 pulmonologists and 8 nephrologists spent 20% of their time in clinical practice and completed the survey.

For remission induction in severe disease, 52% of physicians selected RTX, 42% CYC, 3% MMF, and 3% had no preference. None chose MTX or AZA for remission induction in severe disease. Physicians were significantly more likely to choose RTX for young females compared with young males ($p=0.039$), older males ($p<0.001$), and older females ($p<0.001$). Medication toxicity was the most common reason for this choice. There was a trend toward rheumatologists choosing RTX over CYC compared with the other subspecialties, but this did not reach statistical significance.

Most physicians switched to a less toxic agent for remission maintenance (Table 1), but there was little agreement as to choice of maintenance therapy among subspecialties. It did appear, however, that pulmonologists were significantly less likely to choose AZA ($p=0.002$) and nephrologists MTX ($p=0.007$) than the other subspecialties.

For remission induction in limited disease, most chose RTX (36%), particularly for young females, followed by CYC (26%), MTX (24%), AZA (6%), trimethoprim sulfamethoxazole (4%) and 4% had no preference. Medication efficacy was cited as the most common reason for selecting RTX. Rheumatologists chose RTX (34%) and MTX (31%) about equally, whereas pulmonologists chose RTX (67%) and nephrologists chose CYC (40%) most often.

Discussion

Differences in AAV treatment preferences exist among subspecialties. Most physicians favor RTX for remission induction in young females with severe disease because of toxicity issues with CYC, with a trend toward rheumatologists prescribing RTX more frequently than other subspecialties in this setting. Surprisingly, most physicians preferred RTX for remission induction even for limited disease, and a small percentage of physicians chose MMF for remission induction in severe disease for young females, despite lack of clinical trial data supporting their use in these contexts. There was less agreement as to choice of remission maintenance therapy among subspecialties.

Our study has limited generalizability, as results are from physicians in a single academic medical center and the sample size is relatively small. However, if there is little agreement among subspecialists from a single academic medical center, it is unlikely that subspecialists from different areas around the country will show greater uniformity in treatment preferences. Another limitation is that the survey addressed hypothetical clinical scenarios, and treatment choices in clinical practice may differ and be influenced by patient preference. Our survey also had a relatively low response rate, but was consistent with what is generally seen among physicians participating in surveys.

The study highlights some interesting points regarding medical therapy for AAV. RTX has been recently introduced as a relevant agent in the treatment of AAV, and how it will ultimately be situated in our treatment paradigm remains to be defined [12]. Clinical trials have shown that a single course of RTX is as effective as CYC followed by AZA at 18 months of follow-up, but many questions remain about its optimal use [13]. For instance, what is the ideal dosing for RTX? When should RTX be re-dosed or should it be followed by another remission maintenance agent? Is there a role for RTX in limited disease? When should RTX be used instead of CYC for induction of remission in severe AAV? What are the long-term clinical and adverse event outcomes following use of RTX in AAV? This last point may be particularly relevant recognizing that it took some decades to appreciate the substantial toxicity of long term daily CYC as initially used by Fauci *et al.* [14].

These questions are currently being addressed in a number of follow-up studies and new clinical trials. Future collaboration and communication among rheumatologists, pulmonologists and nephrologists will be important to establish regimens that have maximum efficacy and the least toxicity for the treatment of AAV. Treatment of AAV is data-driven, but until further data is available regarding maintenance therapy following RTX and the use of RTX in limited disease, therapeutic agent choices in these instances will depend on physician and patient preference.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Physician Treatment Preferences for All Subspecialties for Remission Maintenance Therapy in Severe Disease

	AZA N (%)	Follow Expectantly N (%)	MTX N (%)	MMF N (%)	RTX N (%)	CYC N (%)	TMP/SMX N (%)	LFN N (%)	No Preference N (%)
After All Induction (N=128)	45 (35)	27 (21)	20 (16)	12 (9)	9 (7)	5 (4)	4 (3)	0 (0)	6 (5)
After CYC Induction (N=56)	13 (23)	9 (16)	16 (29)	8 (14)	3 (5)	5 (9)	0 (0)	0 (0)	2 (4)
After RTX Induction (N=64)	29 (46)	20 (31)	4 (6)	1 (2)	4 (6)	0 (0)	4 (6)	0 (0)	2 (3)

Key: AZA=azathioprine, MTX=methotrexate, MMF=mycophenolate mofetil, RTX=rituximab, CYC=cyclophosphamide, LFN=leflunomide, TMP/SMX= trimethoprim sulfamethoxazole