A Canadian vasculitis patient-driven survey to highlight which prednisone-related side effects matter the most

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Abstract

Objective

Although management of vasculitis has evolved over the last decades, glucocorticoids (GC) have remained the cornerstone of treatment. The side effects (SE) of GC are well known by the clinicians; their importance for patients with vasculitis has not been investigated as extensively as in other rheumatological conditions.

Methods

An online questionnaire surveyed between April 29th. to July 31st, 2022 with Vasculitis Foundation Canada about the patient experience and SE of prednisone. The survey included 5 questions about prednisone dose and duration, 21 about specific SE (with a rating of 1-10, and one question each on worst prednisone, and worst vasculitis, SE), and four other questions about knowledge and perception of possible alternatives to prednisone (namely, avacopan).

Results

A total of 97 patients (53 GPA/MPA, 44 other vasculitides) completed the survey. Their mean duration of GC use was 62.7±83.7 months, and 49.5% of patients were still on GC (daily dose, 8.4±6.2mg). All the patients reported ≥1 GC-related SE, and 67.0% reported ≥11/19 pre-specified SE of interest. Among ranked SEs, acne was the lowest score, whereas moon face/torso hump had the highest score, just above weight gain, insomnia and decreased quality of life. Around half of the GPA/MPA patients and one-third of the others had heard about avacopan, and 68% of patients (similarly in both groups) stated they would prefer being the first to take a very new medication, such as avacopan, instead of prednisone.

Conclusion

Ranking given to some GC-related SEs may differ between patients and physicians. GC toxicity/SE indexes should reflect this difference.

Key words

glucocorticoid side effects, vasculitis, ANCA-associated vasculitis, prednisone, avacopan

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Received on February 15, 2023; accepted in revised form on March 14, 2023.

Funding: this project has received funding from the Vasculitis Foundation Canada.

Competing interests: C. Pagnoux reports grants and personal fees from Roche, GSK, Otsuka, Pfizer, personal fees from ChemoCentryx, Astra-Zeneca, and InflaRx GmbH, outside the submitted work. J. Stewart reports incidental support from Otsuka outside this work. G.K. Yardimci reports no competing interests.

Introduction

Systemic vasculitides, are autoimmune diseases that can cause severe organ failure and premature death. Glucocorticoids (GC), with other immunosuppressive agents, have been the mainstay of treatment for many decades (1). Over the past years, reduced-dose GC regimens became more widespread (2), but standard management of vasculitis still requires medium-high dose GC therapy (3). Moreover, vasculitis patients often need to be treated several times, due to frequent disease relapses, and may be exposed to GC for prolonged periods of time due to refractory disease (4).

High cumulative exposure to GC is associated with considerable toxicity, including osteoporosis, myopathy, cutaneous, endocrine, metabolic, cardiovascular, and neurologic disorders, and infections. An outcome-based instrument of GC-related toxicity index (GTI) was recently developed, but the insight from patients was sought only at a late stage (5).

Data on the perception and importance of side effects (SE) of GC from the patient's perspective in systemic vasculitis is scarce (6). We conducted a patient-centered survey to identify the relative importance of GC-associated SE among vasculitis patients. This survey was launched after avacopan was approved by Health Canada (April 2022), as a new option in the treatment of ANCA-associated vasculitis.

Materials and methods

The online questionnaire was developed by JS (President of Vasculitis Foundation Canada [VFC]) and CP to survey vasculitis patients linked with VFC, about their GC experience and side effects. The survey was conducted April 29th to July 31st, 2022. Multiple email invitations, FaceBook posts and a VFC website post were made to invite patients to complete the survey.

The first part of online questionnaires recorded demographics (age, sex and diagnosis), and 5 questions about the GC use (current dose and cumulative duration of GC exposure), and 21 questions about the presence of pre-specified GC-related SEs (see Online Appendix). For 11 of these pre-specified SEs (negative impact on quality of life, acne, bruising/thinning of the skin, gastrointestinal symptoms, weight gain, insomnia, mood change, anxiety/depression, lower self-esteem, night sweats and moon face/torso hump) respondents were also asked to rate their levels of impact or impairment (on a Likert scale, between 1 to 10, with higher scores indicating more severe impact). The study participants were also asked to identify which of these pre-specified SEs were the most important to them, and to briefly describe their worst GC and vasculitis experience or SE in a text box.

After these questions about GC SE, patients were asked to report their knowledge and perception about possible alternatives to prednisone (namely, avacopan).

All self-identified vasculitis participants were eligible to respond if they were older than 18 years old. Since all responses were anonymous, the participation was voluntary, and this was a non-therapeutic, non-interventional survey, not requiring ethical approval. This study still followed the Principles of the Declaration of Helsinki.

Descriptive analyses are presented using numbers/percentages for categorical variables, means± standard deviation for continuous variables. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov test) to determine whether or not they were normally distributed. We compared answers between patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), with other vasculitis using Chi-square test for categorical variables. Continuous variables were compared using the Mann-Whitney test (non-parametric) and paired *t*-test (parametric). A *p*-value of less than 0.05 was considered statistically significant. SPSS v. 22 was used for these analyses.

Results

The survey was completed by 97 Canadian Vasculitis patients (53 with GPA/MPA, and 44 with other vasculitides); 77.3% were female. The mean age was 56.9 years, with a mean disease dura-

Table I. Demographics, prednisone dose and duration, and prednisone-related side effects of the patients.

	GPA/MPA patients n: 53	Other Vasculitis patients n: 44	*p*-value
Age (years), Mean (SD)	56.7 (14.5)	57.2 (15.9)	0.932
Female (%)	39 (73.6)	36 (81.8)	0.335
Disease duration (years), Mean (SD)	9.9 (7.3)	11.3 (11.2)	0.735
Total prednisone time (months), Mean (SD)	52.5 (59.4)	74.6 (104.5)	0.635
Still receiving prednisone (%)	22 (41.5)	26 (59.1)	0.085
Current dose of prednisone (mg), Mean (SD)	7.4 (5.5)	9.2 (6.7)	0.100
Prednisone related side effects, n (%)			
Impaired quality of life	51 (96.2)	43 (97.7)	0.570
Acne	21 (39.6)	21 (47.7)	0.423
Skin bruising or thinning	42 (79.2)	41 (93.2)	0.050
Gastrointestinal symptoms	40 (75.5)	37 (84.1)	0.296
Weight gain	51 (96.2)	40 (90.9)	0.255
Insomnia	49 (92.5)	42 (95.5)	0.431
Mood change	52 (98.1)	41 (93.2)	0.242
Anxiety or depression	46 (86.8)	40 (90.9)	0.380
Lower self-esteem	41 (77.4)	40 (90.9)	0.073
Night sweats	43 (81.1)	39 (86.6)	0.309
Body disfiguration (moon face or torso hump etc.)	51 (96.2)	38 (86.4)	0.083
Hip bone AVN requiring hip replacement	0 (0)	1 (2.3)	0.454
Diabetes requiring medication	8 (15.1)	10 (22.7)	0.241
High blood pressure requiring medication	21 (39.6)	14 (31.8)	0.280
Infections requiring antibiotics	28 (52.8)	22 (50.0)	0.471
Severe infection requiring hospitalisation	8 (15.1)	6 (13.6)	0.537
Bone fracture	6 (11.3)	6 (13.6)	0.483
Osteoporosis requiring treatment	12 (22.6)	12 (27.3)	0.385
Osteoporosis	15 (28.3)	14 (31.8)	0.438
Cataracts	15 (28.3)	18 (40.9)	0.138
Loss of tooth mass or teeth	12 (22.6)	14 (31.8)	0.216

GPA: granulomatosis polyangiitis; MPA: microscopic polyangiitis SD: standard deviation; AVN: avascular necrosis.

tion of 10.6 years. There was no significant difference between GPA/MPA and other vasculitis patients with regard to age, sex, or disease duration.

All vasculitis patients had received GC in the past, and 41.2% of them also reported having received intravenous (IV) GC. Mean treatment duration with GC was 62.7±83.7 months, and 48 (49.5%) were still taking GC, with a mean daily prednisone-equivalent dose of 8.4±6.2 mg. Patients with GPA/MPA had received significantly more, often IV GC (62.5% *vs*. 23.8% $p<0.001$), otherwise there was no difference in terms of GC usage (Table I).

All respondents reported having had ≥1 GC-related SE; 65 (67.0%) of them reported having had ≥11/19 pre-specified SE of interest. The SE reported most frequently included mood change in 93 (95.8%) patients, insomnia and weight gain in 91 (93.8%), and body disfiguration in 89 (91.7%). Fifty patients (51.5%) reported having had infections (14.4% severe requiring hospitalisation); 36.1% reported new-onset hypertension, and 18.5% diabetes (Table I).

Among ranked GC-related side effects, acne was weighted with the lowest score of 1.9±2.7/10 (Fig. 1). In contrast, body disfiguration (moon face/torso hump) had the highest ranking with a severity score of 7.7±3.3/10, followed by weight gain (7.5±2.9/10), insomnia (7.2±2.7/10) and decreased quality of life (7.2±2.6/10). Patients with other vasculitides ranked their experience of lower self-esteem (7.0±3.3 *vs*. 5.3±3.8, $p=0.020$), and increase in bruising or thinning of their skin (7.4±2.9 *vs*. 5.3±3.4, $p<0.001$) at a higher rate than MPA and GPA patients.

Responses to the question "In your experience, what was the worst experience, or side-effect from taking prednisone?" 37 (38.1%) respondents listed weight gain, followed by moon face/torso hump (23.7%) and mood change (22.6%).

When asked about their worst experience from their vasculitis in general, 32 (32.9%) patients reported fatigue, 15 (15.4%) reported kidney injury/kidney failure related problems, and 13 (13.4%) respiratory problems.

Of the respondents, 43 (44.3%) stated awareness of possible alternatives to prednisone (Table II). Patients with GPA/MPA had heard about avacopan more than other vasculitis patients (56.5% *vs*. 29.5%, $p=0.008$), but only one of them (with MPA) used it before. A total of 66 (68.0%) stated that they would prefer to be "one of the first patients, outside of any study, to take a very new medication such as avacopan, instead of going back on prednisone if they had a vasculitis flare".

Discussion

This survey confirms the high burden of GC-related SE in patients with GPA/MPA, or other vasculitis. The most frequent reported SE were mood change, insomnia, weight gain and body disfiguration.

The patients' perspectives of the adverse effects of GC use have been investigated to a great extent in rheumatological conditions other than vasculitis. A cross-sectional survey in rheumatic diseases, mainly patients with rheumatoid arthritis (RA), showed the most frequent and the worst GC side effects were thin skin or easy bruising, weight gain and sleep disturbance (7). Another study in systemic lupus erythematosus (SLE) patients reported weight gain 67%, swelling/moon face 36% and mood swings as the most common SE; weight gain 64% and sleeplessness 14% were the most bothersome (8).

A large study from the US included 2167 long-term GC users including RA, obstructive lung diseases, SLE and inflammatory bowel disease, and asked about 8 potential SE. The greatest self-reported side effects were weight gain, followed by skin bruising/thinning and sleep disturbances. A strong dose-related relationship was also observed between increased doses of GC and the SE examined (9).Globally, respondents suffered from similar GC SE as vascu-

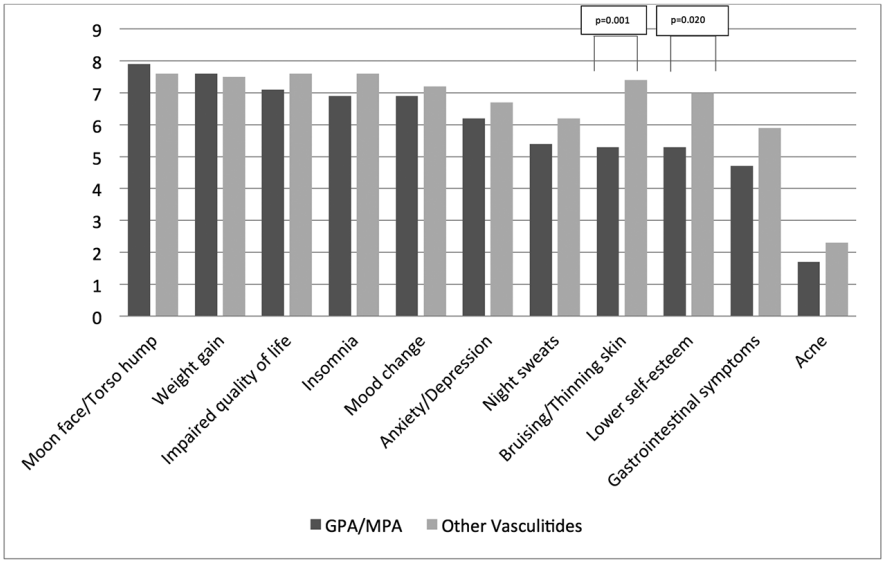

Fig. 1. The mean severity score of glucocorticoid side effects ranked by MPA/GPA patients (dark grey) and patients with other vasculitides (light grey).
GPA: granulomatosis polyangiitis; MPA: microscopic polyangiitis.

Table II. Patients' knowledge and perception about possible alternatives to prednisone.

	GPA/MPA patients n: 53	Other vasculitis patients n: 44	*p*-value
Ever heard about avacopan, n (%)	**30 (56.5)**	**13 (29.5)**	**0.008**
Ever taken avacopan, n (%)	1 (1.8)	0 (0)	-
Would you prefer to go back on prednisone or be one of the first patients, outside of any study, to take a very new medication such as avacopan, instead of, or with less, prednisone? n (%)			0.290
New medication (avacopan)	33 (62.3)	33 (75.0)	
Back on prednisone	6 (11.3)	5 (11.4)	
Not sure	14 (26.4)	6 (13.6)	

GPA: granulomatosis polyangiitis; MPA: microscopic polyangiitis.

litis patients, but with lower frequency compared to our study, maybe due to lower doses, or the lower cumulative dose of GC in these other rheumatological conditions (10).

Existing literature in vasculitis GC toxicity is scare and has been mostly studied by physicians. A recent review of patients with vasculitis demonstrated significant disease impact on physical (fatigue), physiological (anxiety), social (decreased social involvement) and financial domains (decreased employment) (11). In ADVOCATE, a recent study on avacopan in AAV, GTI was used as an outcome to better document the GC-related SE (12). In another recent retrospective study using GTI, SE was reported by physicians, with 72% of the patients with ANCA-associated vasculitis having GC-related SE, the most common being infections (43.9%), reduced bone density (24.4%) and raised BMI (24.4%) (13). GTI is a tool to quantify the toxic effects of GC therapy, but is not specific to the vasculitis population, and needs further validation and input from patient support groups. Incorporating the patient's perspective with a standard approach, patient reported outcomes (PRO) in systemic vasculitis (PROMIS), and specifically ANCA-associated vasculitis (AAV-PRO), were both validated to assess the burden of disease (14, 15). A steroid-specific PRO is also currently under development to assess patients' perceptions particular to GC therapy (16). These scores or questionnaires should incorporate the respective importance of the various GC SE, which were ranked in only a few studies. Weight gain, insomnia and moon face were rated as the most important GC side effects in an online cross-sectional survey by GC users with a wide spectrum of diagnosis including lung diseases, hematologic conditions and rheumatological diseases (17). Lipodystrophy has been reported as both the most common and particularly distressing SE of long-term high dose GC therapy (18, 19). These are in keeping with our results, in which vasculitis patients rated body disfiguration (moon face/torso hump) as the worst SE of GC. Though physicians underrated this SE in several studies, patients who reported morphological changes strongly showed poorer adherence to treatments (20).

These many differences in the perspectives of patients versus rheumatologists on SE of GC therapy are important to consider. Less serious SE (as per physician's opinion) may be extremely worrisome and more significant to patients. A French study including various rheumatologic and non-rheumatologic long-term GC users, showed weight gain, diabetes, cutaneous complications, blood pressure imbalance and lipodystrophy were more worrisome for physicians, whereas neuropsychiatric symptoms were most distressing to patients and underestimated by physicians (19). A cross-sectional study of asthma patients in the UK also indicated that clinicians tend to underestimate the prevalence of all patients reported SE of GC (21). The EULAR task force on patient and rheumatologist perspectives on GC emphasised that clinicians overrated common and vital SE such as diabetes mellitus, osteoporosis, hypertension and infections, whereas patients ranked less vital SE (weight gain, fatigue and moon face) as the most bothersome SE (22).

This study has several limitations. This was a patient-driven survey, thereby including some unverified clinical data. However, this approach allowed patient engagement and better tracked self-reported SE that are frequently overlooked in observational studies that only use, possibly biased, medical data recorded by physicians, or interviews directed by physicians.

The findings of this survey help to further understand vasculitis patients' insights and concerns about the impact of GC, which should be considered when assessing outcomes in studies with GC. The development of the GTI has been an important step towards better quantifying GC-related SE in studies, but patient perspectives and ranking on several specific SE may differ with physicians and should be added to such assessment tools. This survey also emphasised the need for alternative therapies to GC, and how patients are eager to use any alternative to GC, even at the early steps of development or immediately after their approval.

Acknowledgments

We wish to express our special thanks to the patients linked with Vasculitis Foundation Canada who participated in this survey, and Velma Mockett, PhD and Lucy DeMatos, RHN for their valuable input.

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