
Assessment of glucocorticoid tapering in large-vessel and anti-neutrophil cytoplasmic antibody-associated vasculitides

A. Mendel¹, D. Ennis², S. Carette³, C. Pagnoux³

¹Division of Rheumatology,
Montreal General Hospital,
McGill University, Montreal;

²Division of Rheumatology,
University of British Columbia,
Vancouver;

³Division of Rheumatology,
Mount Sinai Hospital,
University of Toronto, Canada.

Arielle Mendel, MD, MSc

Daniel Ennis, MD

Simon Carette, MD, MPhil

Christian Pagnoux, MD, MSc, MPH

Please address correspondence to:

Arielle Mendel,

McGill University Health Centre,

1650 Cedar Ave,

Montreal, QC, H3G 1A4, Canada.

E-mail: arielle.mendel@mcgill.ca

Received on August 3, 2020; accepted in
revised form on November 9, 2020.

Clin Exp Rheumatol 2021; 39 (Suppl. 129):
S119-S124.

© Copyright CLINICAL AND
EXPERIMENTAL RHEUMATOLOGY 2021.

Key words: large-vessel-vasculitis,
ANCA-associated vasculitis,
glucocorticoids

ABSTRACT

Objective. *Glucocorticoids (GC) remain integral to large-vessel vasculitis (LVV) and ANCA-associated vasculitis (AAV) treatment. We aimed to assess real-world GC tapering trajectories among patients referred for LVV or AAV and identify factors associated with ‘delayed’ tapering.*

Methods. *Patients first assessed at a vasculitis clinic July 2017-August 2019 for LVV or AAV and taking GC were included. Delayed tapering was defined as prednisone >10 mg above target based on tapering recommendations (2010 British Society of Rheumatology Guidelines for Giant Cell Arteritis, 2015 CanVasc AAV Recommendations). We compared characteristics of patients with delayed and appropriate tapering and assessed barriers to timely tapering through chart reviews and referring physician surveys.*

Results. *160 patients (65 LVV, 95 AAV) were taking GC at their first visit. Among the 42 (26%) patients with delayed tapering, mean daily prednisone dose was 39.2 mg (SD 14) compared to a target of 15.2 mg (SD 15). Pulse GC were administered to 19/42 (45%) patients with delayed tapering compared to 26/118 (22%) with appropriate tapering ($p < 0.05$). Mean Birmingham Vasculitis Activity Score at treatment onset and GC duration were not significantly different between the two groups. Vision loss and/or stroke was more frequent in LVV referrals who experienced delayed (9/21, 43%) vs. appropriate (6/44, 14%) tapering ($p < 0.05$). Managing risk of vasculitis flare was the most common challenge to tapering GC among surveyed referring physicians.*

Conclusion. *In one quarter of patients referred for LVV or AAV taking GC, tapering was slower than recommended. Promoting timely tapering may reduce GC toxicity.*

Introduction

Prompt glucocorticoid (GC) therapy remains a mainstay in the initial management of large-vessel vasculitis (LVV) and anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), but prolonged exposure to high-dose GC can lead to significant toxicity, including infection, diabetes, hypertension, and osteoporosis (1).

In clinical trials of systemic vasculitis, GC tapering protocols are often pre-specified, but the degree of adherence to these protocols is rarely reported (2). Tapering recommendations have been published by several groups. The Canadian Vasculitis Research Network (CanVasc) AAV recommendations suggest tapering high-dose prednisone to approximately 15 mg by the end of the third month of treatment (3), based on tapering protocols used in randomised controlled trials (4-7). In LVV, a target dose of 15–20 mg per day by 3 months is also recommended (8, 9). GC tapering in vasculitis and adherence to recommended tapering schedules is extremely relevant, as the risk GC-related harm increases with cumulative GC dose and duration (10-13). GC-associated adverse events are also costly (14) and a primary concern for patients (15-18). Although treatment with GC (and the associated potential toxicity) may be yet unavoidable for patients with LVV or AAV, some may be exposed to prolonged courses of high-dose GC and/or experience slower tapering, without an apparent need.

The Vasculitis Clinic at Mount Sinai Hospital, Toronto, Canada, is a tertiary clinic with an estimated 300 new patient referrals each year. Our objectives were to assess the frequency of ‘delayed’ GC tapering, compared to existing recommendations, among patients referred for evaluation of LVV and AAV, and identify causes of ‘delayed’ tapering to inform potential improvement strategies.

Competing interests: none declared.

Patients and methods

Study population

Consecutive new patients assessed at the Vasculitis Clinic (Mount Sinai Hospital) for either LVV (giant cell arteritis [GCA], idiopathic aortitis, or Takayasu's arteritis [TAK]) or AAV (granulomatosis with polyangiitis, microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis) from July 2017–August 2019 and who were receiving treatment with GC were included. Patients taking ≤ 10 mg prednisone for >1 year, who often represent patients dependent on long-term, low-dose GC, were excluded.

Data sources and collection

Referral date, appointment date, referral diagnosis, referring physician specialty, GC use (initial daily oral prednisone-equivalent dose in milligrams [mg], date of initiation, dose at the first Vasculitis Clinic visit) and concurrent immunosuppressive therapy was recorded. GC duration (days) was determined from the date of GC initiation (or re-initiation/escalation in the event of a vasculitis relapse) to the date of the first Vasculitis Clinic visit. The use of 'pulse' GC, defined as at least one dose of IV methylprednisolone (250–1000 mg) given at treatment onset, was also recorded. Birmingham Vasculitis Activity Score (BVAS, version 3) (19) at the time of diagnosis/relapse was retrospectively calculated. Among patients referred for LVV, the presence of vision loss (*i.e.* anterior ischaemic optic neuropathy or retinal artery occlusion) or stroke at the time of diagnosis/relapse was determined. Renal involvement in AAV was defined as proteinuria $>1+$ or haematuria with >10 red blood cells/high power field, attributed to active renal vasculitis, with or without concurrent serum creatinine rise. Severe renal involvement was defined as serum creatinine rise $>30\%$ from baseline or >500 $\mu\text{mol/L}$ attributed to active renal vasculitis. Vasculitis Clinic wait time was defined as the number of days between referral date and first Vasculitis Clinic visit. Detailed chart reviews were performed to identify possible contributing factors to delayed tapering. Of interest was whether GC taper-

ing decisions were being deferred to the Vasculitis Clinic, and/or whether the treating physician had concerns for persistent disease activity or relapse with GC tapering.

GC tapering trajectories

Based on GC start dose and duration of use, target prednisone-equivalent dose at the first clinic visit was determined according to the 2010 British Society of Rheumatology (BSR)/British Health Professionals in Rheumatology guidelines for the management of GCA (8) for LVV referrals, and the 2015 CanVasc recommendations for the Management of AAV (3), for AAV referrals. The BSR guidelines suggest maintaining a prednisone dose of 40–60 mg for up to 4 weeks followed by reductions of 10 mg every 2 weeks until 20 mg daily, then by 2.5 mg every 2 weeks until 10 mg, then by 1 mg every 1–2 months until cessation. The GC tapering schedule reflecting the 2015 CanVasc AAV recommendations was based on the RAVE trial protocol (4), whereby prednisone is reduced to 40 mg daily by the end of month 1, then reduced by 10 mg every 2 weeks until 20 mg daily, then by 5 mg every 2 weeks until 10 mg daily, then by 2.5 mg every 2 weeks until cessation (See Supplementary Tables S1 and S2 for precise LVV and AAV tapering schedules). A patient's GC tapering trajectory was classified as 'delayed' if the daily prednisone dose at the first clinic visit was >10 mg above the respective target dose.

Statistical analysis

GC tapering trajectories (GC start dose, duration, current dose, target dose) were compared between patients who had undergone 'appropriate' and 'delayed' tapering. In addition, patients with appropriate and delayed GC tapering were compared according to referral diagnosis, referring physician specialty, BVAS at treatment onset (or at the time of GC escalation for relapse), presence of specific severe disease features (vision loss or stroke among LVV patients, renal disease or pulmonary haemorrhage among AAV patients), induction immunosuppression and use of pulse GC at treatment onset, and

Vasculitis Clinic wait time. Differences in means (standard deviation, SD) for continuous variables were computed using the Student's *t*-test, and differences in proportions for categorical parameters were compared with Pearson's χ^2 Square test or Fisher's exact test where applicable. In a sensitivity analysis, tapering was considered 'delayed' if the target prednisone dose represented a $\geq 33\%$ reduction from a current dose of at least 20 mg per day (to assess the relative rather than absolute dose difference), and the above comparisons were repeated.

Referring physician survey

All physicians who had referred ≥ 2 patients to the vasculitis clinic within the last year (27 rheumatologists, two respirologists, one nephrologist, one otolaryngologist), were invited to complete an online anonymous survey. The survey included questions to identify referring physicians' self-reported comfort level with GC tapering in different vasculitides ("not comfortable", "somewhat comfortable", "very comfortable"), factors contributing to GC tapering decisions, challenges in tapering GC in vasculitis, and beliefs on possible ways to encourage timely GC tapering.

Ethical approval

This study complies with the Declaration of Helsinki and was approved by the Mount Sinai Hospital Research Ethics Board (number 18-0264-E). All patients provided written informed consent. Surveyed physicians implied their consent to participate by submitting their survey responses for the study.

Results

Patient characteristics

160 newly referred patients (65 LVV, 95 AAV) assessed July 2017–August 2019 were taking GC at the time of their first visit. Eighty-one (50%) patients were referred by general rheumatology, 25 (16%) by nephrology, 15 (9%) by general practitioners, 14 (9%) by respirology, 17 (11%) by other medical specialties, and 8 (5%) by surgical specialties (ophthalmology, otolaryngology, and vascular surgery). Thirty-six (23%) were referred for relapsing disease.

Table I. GC tapering trajectories, overall and according to vasculitis subtype.

Referral diagnosis	Overall n=160		LVV n=65		AAV n=95	
	Appropriate n=118 (74%)	Delayed n=42 (26%)	Appropriate n= 44 (68%)	Delayed n= 21 (32%)	Appropriate n= 74 (78%)	Delayed n= 21 (22%)
GC tapering trajectory						
Oral prednisone start dose mean mg/day \pm SD	50.6 \pm 16.5*	56.3 \pm 14.1*	49.3 \pm 16.5	51.4 \pm 13.1	51.3 \pm 16.6*	61.1 \pm 13.6*
Prednisone dose at first visit, mean mg/day \pm SD	23.7 \pm 16.7*	39.2 \pm 14.1*	22 \pm 13.6*	36.9 \pm 11.6*	24.6 \pm 18.3*	41.4 \pm 16.1*
Target prednisone dose at first visit, mean mg/day \pm SD	20.6 \pm 16.4*	15.2 \pm 15.2*	18.5 \pm 13.8	16.5 \pm 8.4	21.9 \pm 17.7*	13.9 \pm 10.6*
GC duration, mean days \pm SD	121.7 \pm 132.6	108.5 \pm 52.4	134.8 \pm 126.4	117.9 \pm 60.6	114.1 \pm 136.3	99.0 \pm 42.2
GC duration >60 days n (%)	71/117 \pm (61)*	35 \pm (83)*	32/43 \pm (74)	18 \pm (86)	42 \pm (57)*	17 \pm (81)*

* $p < 0.05$ between paired comparisons (appropriate vs. delayed).

GC: glucocorticoid; SD: standard deviation; AAV: ANCA-associated vasculitis; LVV: large-vessel vasculitis.

Among patients referred for LVV, mean BVAS was 4 (SD 3.6) and 15 (23%) had vision loss or stroke at the time of GC initiation. Among patients referred for AAV, mean BVAS at GC initiation was 13.8 (SD 7.7), 10 (11%) had diffuse alveolar haemorrhage, 48 (51%) had renal involvement, and 31 (33%) had severe renal involvement. Pulse GC (in the majority of cases, 1g for 3 consecutive days) was administered in 45 (28%) patients at the start of therapy and mean oral GC start dose was 52.1 mg (SD 16).

GC tapering trajectories

Mean GC dose at the first visit to the Vasculitis Clinic was 27.7 mg (SD 17.4), which did not differ between patients referred for LVV (27 mg) or AAV (28 mg). In 42/160 (26%) patients, GC tapering was determined to be 'delayed'. In the delayed group, mean prednisone dose at the first visit was 39.2 mg (SD 14) per day, despite a mean target dose of 15.2 mg (SD 15) per day. Tapering had not started in 12 (29%) such patients, who took a mean of 51.7 mg (SD 15) prednisone per day for a mean of 68.5 (SD 24) days. In contrast, patients with appropriate GC tapering were taking a mean of 23.7 mg (SD 17) prednisone per day, with a mean target dose of 20.6 (SD 16) mg per day. Mean GC duration was 118.2 days (SD 116) and was similar among patients with delayed vs appropriate tapering. However, a greater proportion of patients with delayed tapering had taken GC for >60 days (35/42, 83%) compared with patients with appropriate

tapering (71/117, 61%; $p < 0.05$). Table I reports GC tapering trajectories in the study population, overall and according to vasculitis subtype (LVV or AAV). Supplementary Figure S1 provides a graphical depiction of GC trajectories in LVV and AAV groups, according to whether tapering was 'appropriate' or 'delayed'.

Factors associated with delayed GC tapering

The proportion with delayed GC tapering was not significantly different among patients referred for LVV (n=21, 32%) compared with AAV (n=21, 22%). Pulse GC at treatment onset was administered in 19/42 (45%) patients with delayed tapering compared to 26/118 (22%) with appropriate tapering ($p < 0.01$). This difference was observed in both LVV (29% vs. 7%; $p < 0.05$) and AAV subgroups (62% vs. 31%; $p < 0.05$). Patients who had delayed tapering also started at higher daily oral prednisone doses compared to patients with appropriate tapering (mean 56.3 mg vs 50.6 mg, $p < 0.05$). Patients with relapsing disease comprised 5/42 (12%) of the delayed tapering group and 31/118 (26%) of the appropriate tapering group ($p = 0.06$).

Among patients referred for LVV (Table IIa), mean BVAS at diagnosis was 5.2 (SD 3) in patients with delayed tapering and 3.4 (SD 4) in patients with appropriate tapering ($p = 0.05$). However, 9/21 (43%) LVV patients in the delayed tapering group had experienced vision loss and/or stroke at the time of GC initiation, compared to 6/44 (14%)

with vision loss and/or stroke who had appropriate tapering ($p < 0.05$). Aside from use of pulse GC, no differences were observed in therapy, in particular use of steroid-sparing therapy, between groups.

Among patients referred for AAV (Table IIb), mean BVAS at GC initiation was 16.1 (SD 8) in patients with delayed tapering and 13.1 (SD 8) in patients with appropriate tapering ($p = 0.12$). Aside from use of pulse GC, the only difference identified between groups was that more patients in the delayed tapering group had received cyclophosphamide for induction compared to those with appropriate tapering (57% vs. 20%, $p < 0.01$).

Mean wait time to the vasculitis clinic from the time of referral was 63.2 days (SD 30) and did not differ among patients with delayed vs. appropriate tapering. In addition, no significant differences were observed in referral specialties between patients with appropriate and delayed GC tapering. Review of clinical charts identified one or more of the following other possible contributing factors to delayed tapering: in 10/42 (24%), patients had ongoing symptoms which were determined at the Vasculitis Clinic not to be secondary to active disease; in 2 (5%) patients had persistently elevated inflammatory markers and no other symptoms; in 6 (14%), patients had been discharged from hospital without tapering instructions; in 3 (7%), physicians explicitly deferred GC tapering to the vasculitis clinic in their clinical notes; in one case, referral to the Vasculitis Clinic was delayed due to

Table IIa. Characteristics of patients referred for LVV according to GC tapering trajectory (n=65).

GC tapering trajectory	Appropriate n=44 (68%)	Delayed n=21 (32%)
Referral specialty n (%)		
Rheumatology	32 (73)	14 (67)
Primary care	5 (11)	1 (5)
Other medical subspecialty	5 (11)	2 (10)
Surgical subspecialty	2 (5)	4 (19)
Referral diagnosis n (%)		
Giant cell arteritis	32 (73)	17 (81)
Takayasu's arteritis	7 (16)	2 (10)
Undifferentiated	5 (11)	2 (10)
Disease relapse n (%)	11 (25)	3 (14)
BVAS at diagnosis or relapse, mean ± SD	3.4 ± 3.5	5.2 ± 3.4
Vision loss or stroke n (%)	6 (14)*	9 (43)*
Received pulse GC n (%)	3 (7)*	6 (29)*
Induction therapy (prior to referral)		
GC alone	38 (86)	19 (90)
Cyclophosphamide + GC	0 (0)	1 (5)
Methotrexate + GC	4 (9)	1 (5)
Azathioprine + GC	2 (5)	0 (0)
Wait time to vasculitis clinic, mean days ± SD	67.4 ± 32.0	70.9 ± 19.9

*p<0.05 between paired comparisons (appropriate vs. delayed).

GC: glucocorticoid; SD: standard deviation; BVAS: Birmingham Vasculitis Activity Score (version 3).

Table IIb. Characteristics of patients referred for AAV according to GC tapering trajectory (n=95).

GC tapering trajectory	Appropriate n=74 (78%)	Delayed n=21 (22%)
Referral specialty n (%)		
Rheumatology	29 (39)	6 (29)
Primary care	6 (8)	3 (14)
Nephrology	16 (22)	9 (43)
Respirology	14 (19)	0 (0)
Other medical subspecialty	7 (9)	3 (14)
Surgical subspecialty	2 (3)	0 (0)
Referral diagnosis n (%)		
GPA	32 (43)	8 (38)
MPA	31 (42)	9 (43)
EGPA	11 (15)	4 (19)
Disease relapse, n (%)	20 (27)	2 (10)
BVAS at diagnosis or relapse, mean ± SD	13.1 ± 7.6	16.1 ± 7.9
Pulmonary haemorrhage n (%)	7 (9)	3 (14)
Renal involvement, n (%)	35 (47)	13 (62)
Serum creatinine >500 micromol/L, creatinine rise >30%, or fall in creatinine clearance by 25%	21 (28)	10 (48)
Received pulse GC, n (%)	23 (31)*	13 (62)*
Induction therapy (prior to referral)		
GC alone	24 (32)	5 (24)
Cyclophosphamide + GC	15 (20)*	12 (57)*
Rituximab + GC	12 (16)	2 (10)
Cyclophosphamide and rituximab + GC	4 (5)	0 (0)
Mycophenolate mofetil + GC	5 (7)	0 (0)
Methotrexate + GC	8 (11)	1 (5)
Azathioprine + GC	6 (8)	1 (5)
Wait time to vasculitis clinic, mean days ± SD	59.7 ± 32.7	58.8 ± 25.5

*p<0.05 between paired comparisons (appropriate vs. delayed).

GC: glucocorticoid; SD: standard deviation; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; BVAS: Birmingham Vasculitis Activity Score (version 3).

a clerical error, and in another, treating specialists had disagreed on whether to taper GC or not.

Sensitivity analysis

In the sensitivity analyses, using the alternate definition of delayed tapering (current prednisone dose ≥20 mg per day with target dose that was ≥33% lower), 57 (36%) patients (AAV 43%, LVV 31%) were classified as having delayed tapering. Comparisons of referral, treatment, and main disease characteristics between delayed and appropriate GC tapering groups yielded similar estimates to the primary analysis (Suppl. Tables S3 and S4).

Referring physician survey

In total, 15/31 (48%) referring physicians returned the completed survey, with responses shown in Table III. Clinicians reported making GC tapering decisions primarily based on clinical assessment (100%) and literature/guidelines (93%), while 67% and 47% considered patient co-morbidities and patient side effects in the decision, respectively. The most often cited challenges in GC tapering were managing the risk of disease flare (80%) and differentiating active disease from damage (67%), while patient comprehension and preferences were less often reported as challenges. In response to the question of how the vasculitis clinic could encourage timely GC tapering, the most commonly chosen answer was providing GC tapering suggestions at the time of referral (93%), followed by email availability to discuss GC tapering (73%) and reducing wait times for patients on high-dose GC (60%). The majority (73%) felt “very comfortable” with GC tapering in GCA, while only 40% and 20% felt “very comfortable” tapering GC in systemic AAV and TAK, respectively (Suppl. Table S5).

Discussion

Among patients taking GC who were referred to a tertiary vasculitis clinic for assessment of LVV or AAV, 26% experienced delayed tapering compared to recommendations (3, 8). Within this group, the greater than two-fold difference between the current mean pred-

Table III. Responses to referring physician needs assessment questionnaire (n=15).

Survey question	Responses n (%)
<i>1. How frequently, on average, do you see a patient with vasculitis in your clinical practice?</i>	
Daily to weekly	5 (33)
At least once monthly	3 (20)
Once every few months	6 (40)
Rarely	1 (7)
<i>2. After initiating glucocorticoids in a patient with suspected vasculitis, how do you decide when/how to initiate tapering?</i>	
Clinical assessment of disease activity	15 (100)
Available literature and guidelines	14 (93)
According to patient co-morbidities	10 (67)
Patient reported side effects	7 (47)
Would not initiate substantial tapering until direction given from Vasculitis Clinic	0 (0)
Would generally not initiate GC	0 (0)
<i>3. What aspects of glucocorticoid tapering in vasculitis do you find challenging?</i>	
Uncertainty over which provider should be initiating tapering	3 (20)
Managing risk for disease flare with GC tapering	12 (80)
Lack of clinical expertise or experience with GC tapering in vasculitis	3 (20)
No time to initiate and monitor GC tapering	0 (0)
Differentiating active disease from damage and non-vasculitic symptoms	10 (67)
Patients not understanding tapering instructions	2 (13)
Navigating patient preferences	2 (13)
I do not have difficulty tapering GC in vasculitis	2 (13)
<i>4. How do you think the Vasculitis Clinic can encourage timely glucocorticoid tapering in vasculitis?</i>	
Providing suggested tapering regimens at the time of referral	14 (93)
Decreasing wait times to the Vasculitis Clinic for patients on high dose GC	9 (60)
Being available by email to discuss tapering strategies	11 (73)
Patient educational interventions	3 (20)
Other	2 (13)

GC: glucocorticoids.

nisone dose (39.2 mg) and the target dose (15.2 mg), given mean GC duration of >100 days, is suggestive of a substantial excess in cumulative GC exposure. To our knowledge, this is the first assessment of real-world GC tapering practices in vasculitis and identifies a potentially inadvertent source of GC toxicity in this population.

The reasons for delayed tapering in this group are likely multiple. We observed an association between pulse GC and subsequent delayed tapering. Pulse GC are generally administered in severe, organ-threatening disease, and clinicians may be hesitant to taper GC in such patients due to the belief that more severe disease requires slower tapering. Ischaemic complications of LVV (vision loss, stroke) occurred more often in patients with delayed tapering, lending support to this hypothesis. Cyclophosphamide was also administered more often among AAV patients with delayed tapering, although

BVAS, severe renal involvement, and diffuse alveolar haemorrhage did not significantly differ between groups. Of note, in both LVV and AAV, there no evidence that slower GC tapering in patients with greater disease severity leads to improved clinical outcomes, and clinical practice guidelines do not suggest that patients with more severe disease require slower GC tapering (3, 8). In the PEXIVAS trial, patients with severe AAV who received a reduced-dose GC taper had no difference in end-stage renal disease or death but had fewer serious infections (20). In both LVV and AAV groups, the proportion of patients who had not yet started any steroid-sparing therapy prior to referral was similar regardless of GC tapering trajectory, suggesting that this was not a contributor to delayed tapering. While the administration of pulse GC may reflect more severe disease, it also indicates that the patient was likely hospitalised, and a lack of prompt clin-

ical follow-up after discharge could have been a reason for tapering delays. While data on hospitalisations or the post-discharge follow-up prior to referral were not systematically available for this study, chart reviews did identify instances where prednisone tapering was not initiated at the time of hospital discharge. Physicians' personal tendencies towards prescribing pulse GC may also correlate with more liberal oral GC use and slower tapering.

As suggested by survey responses, referring physicians (the majority of whom were rheumatologists) may lack confidence with GC tapering in vasculitis due to concern for persistent disease activity or relapse with tapering. Prioritising referrals of patients taking high-dose GC may allow tapering to be initiated sooner by the Vasculitis Clinic. In general rheumatology clinics, triaging has successfully reduced wait times for urgent referrals by 50% (21-23). However, reducing wait times may not have a sufficient impact on the initial GC tapering trajectory if treating physicians initiate GC long before the referral date (in our cohort, by a mean of 53.9 days ± SD 109). This may explain in part why we did not observe a difference in wait times among patients with delayed and appropriate GC tapering.

Although novel vasculitis therapies (24, 25) and treatment regimens (26) have been evaluated in therapeutic studies with the aim of reducing GC exposure(27, 28), adherence to a GC tapering schedule remains an important strategy for minimising toxicity. Clinical practice guidelines can influence prescribing practices (29-31), and emphasising timely GC tapering in LVV and AAV within therapeutic recommendations may encourage cultural change. Providing GC tapering suggestions to referring physicians is another potential intervention which was supported by 93% survey respondents.

Our study has some limitations. The study population was referred to a tertiary academic centre and may be biased towards higher clinical complexity and a propensity towards delayed GC tapering, thus representing the "worst case scenario". Community-based practice audits may serve to further

validate our findings. Although there is no universally accepted GC tapering protocol in vasculitis and no validated definition of ‘delayed’ tapering, we used tapering protocols published within clinical practice recommendations (3, 8) as reference standards, and used two different definitions for ‘delayed’ tapering, which strengthens the validity of our findings. This study characterised real-world GC tapering in vasculitis to lay the groundwork for a quality improvement initiative. It thus purposely did not assess detailed clinical and serological manifestations and their association with GC tapering trajectories, analyses which would have been underpowered. Finally, we did not collect data on GC toxicity (1) including infections, or patients’ experiences with tapering GC, but infer both the risk of GC adverse effects (10, 11, 14, 32) and patient perceptions of GC therapy (16, 17, 33) from prior studies.

In conclusion, delayed GC tapering occurred in over one quarter of GC users referred for assessment of LVV and AAV. Initial disease severity, fear of disease relapse, or persistent (damage-related) symptoms might potentiate this outcome. Our findings have important safety implications for a group already vulnerable to significant medication toxicity and secondary co-morbidities. Decision support for referring physicians and emphasis on tapering within clinical practice recommendations may promote timely GC tapering in vasculitis.

Acknowledgements

The authors acknowledge the assistance of Dr Shirley Lake in the design of referring physician survey questions.

References

1. MILOSLAVSKY EM, NADEN RP, BIJLSMA JW *et al.*: Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Ann Rheum Dis* 2017; 76: 543-6.
2. PAGNOUX C, DECHARTRES A, GIRAudeau B, SEROR R, GUILLEVIN L, RAVAUD P: Reporting of corticosteroid use in systemic disease trials: evidence from a systematic review of the potential impact on treatment effect. *Arthritis Care Res* (Hoboken) 2010; 62: 1002-8.
3. MCGEOCH L, TWILT M, FAMORCA L *et al.*: CanVasc recommendations for the management of antineutrophil cytoplasm antibody-

- associated vasculitides. *J Rheumatol* 2016; 43: 97-120.
4. STONE JH, MERKEL PA, SPIERA R *et al.*: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
5. JONES RB, TERVAERT JW, HAUSER T *et al.*: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
6. DE GROOT K, HARPER L, JAYNE DR *et al.*: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-80.
7. WEGENER’S GRANULOMATOSIS ETANERCEPT TRIAL RESEARCH GROUP: Etanercept plus standard therapy for Wegener’s granulomatosis. *N Engl J Med* 2005; 352: 351-61.
8. DASGUPTA B, BORG FA, HASSAN N *et al.*: BSR and BHRP guidelines for the management of giant cell arteritis. *Rheumatology* (Oxford) 2010; 49: 1594-7.
9. HELLMICH B, AGUEDA A, MONTI S *et al.*: 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020; 79: 19-30.
10. GALE S, WILSON JC, CHIA J *et al.*: Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther* 2018; 5: 327-40.
11. ROBSON J, DOLL H, SUPPIAH R *et al.*: Glucocorticoid treatment and damage in the antineutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. *Rheumatology* (Oxford) 2015; 54: 471-81.
12. FAURSCHOU M, AHLSTROM MG, LINDHARDSEN J, OBEL N, BASLUND B: Risk of diabetes mellitus among patients diagnosed with giant cell arteritis or granulomatosis with polyangiitis: comparison with the general population. *J Rheumatol* 2017; 44: 78-83.
13. BEST JH, KONG AM, UNIZONY S, TRAN O, MICHALSKA M: Risk of potential glucocorticoid-related adverse events in patients with giant cell arteritis: results from a USA-based electronic health records database. *Rheumatol Ther* 2019; 6: 599-610.
14. SARNES E, CROFFORD L, WATSON M, DENNIS G, KAN H, BASS D: Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. *Clin Ther* 2011; 33: 1413-32.
15. ROBSON JC, DAWSON J, CRONHOLM PF *et al.*: Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Rheumatol Int* 2018; 38: 675-82.
16. NASSAR K, JANANI S, ROUX C, RACHIDI W, ETAOUIL N, MKINSI O: Long-term systemic glucocorticoid therapy: patients’ representations, prescribers’ perceptions, and treatment adherence. *Joint Bone Spine* 2014; 81: 64-8.
17. VAN DER GOES MC, JACOBS JW, BOERS M *et al.*: Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glu-

- cocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2010; 69: 1015-21.
18. MULLER S, O’BRIEN A, HELLIWELL T *et al.*: Support available for and perceived priorities of people with polymyalgia rheumatica and giant cell arteritis: results of the PMRG-CAuk members’ survey 2017. *Clin Rheumatol* 2018; 37: 3411-8.
19. MUKHTYAR C, LEE R, BROWN D *et al.*: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32.
20. WALSH M, MERKEL PA, PEH CA *et al.*: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; 382: 622-31.
21. FARRER C, ABRAHAM L, JEROME D, HOCHMAN J, GAKHAL N: Triage of rheumatology referrals facilitates wait time benchmarks. *J Rheumatol* 2016; 43: 2064-7.
22. HAZLEWOOD GS, BARR SG, LOPATINA E *et al.*: Improving appropriate access to care with central referral and triage in rheumatology. *Arthritis Care Res* (Hoboken) 2016; 68: 1547-53.
23. VILLENEUVE E, NAM JL, BELL MJ *et al.*: A systematic literature review of strategies promoting early referral and reducing delays in the diagnosis and management of inflammatory arthritis. *Postgrad Med J* 2013; 89: 231-40.
24. STONE JH, TUCKWELL K, DIMONACO S *et al.*: Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; 377: 317-28.
25. JAYNE DRW, BRUCHFELD AN, HARPER L *et al.*: Randomized trial of C5a receptor inhibitor Avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 2017; 28: 2756-67.
26. PEPPER RJ, MCADOO SP, MORAN SM *et al.*: A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology* (Oxford) 2019; 58: 373.
27. MONTI S, BOND M, FELICETTI M *et al.*: One year in review 2019: vasculitis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S3-19.
28. FELICETTI M, TREPPO E, POSARELLI C *et al.*: One year in review 2020: vasculitis. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S3-14.
29. CARLI C, BRIDGES JFP, ASK J *et al.*: Charting the possible impact of national guidelines on the management of rheumatoid arthritis. *Scand J Rheumatol* 2008; 37: 188-93.
30. LOPEZ AA, ASLANOVA R, BRIDGER N, CHAFE R: Antibiotic use for inpatient bronchiolitis: did national guidelines impact practice at a pediatric hospital? *Hosp Pediatr* 2020; 10: 147-52.
31. GIGUERE A, LEGARE F, GRIMSHAW J *et al.*: Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; 10: CD004398.
32. CURTIS JR, WESTFALL AO, ALLISON J *et al.*: Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; 55: 420-6.
33. COSTELLO R, PATEL R, HUMPHREYS J, MCBETH J, DIXON WG: Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. *BMJ Open* 2017; 7: e014603.