Arthritis Care & Research
DOI 10.1002/acr.23099

Disease Activity, Glucocorticoid Exposure, and Rituximab Determine Body Composition Changes during Induction Treatment of ANCA-Associated Vasculitis

Zachary S. Wallace, M.D., Eli M. Miloslavsky, M.D., Matthew Cascino, M.D., Sebastian H. Unizony, M.D., Na Lu, M.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., Carol A. Langford, M.D., M.H.S., Peter A. Merkel, M.D., M.P.H., Paul A. Monach, M.D., Ph.D., Philip Seo, M.D., M.H.S., Robert Spiera, M.D., E. William St. Clair, M.D., Ulrich Specks, M.D., Paul Brunetta, M.D., Hyon K. Choi, M.D., Ph.D., John H. Stone, M.D., M.P.H.

Corresponding author:

Dr. John H. Stone
Rheumatology Clinic / Yawkey 2
Massachusetts General Hospital
55 Fruit Street
Boston, MA. 02114

Financial Disclosures/Support:

The authors have no financial conflicts of interest to disclose. This research was performed as a project of the Immune Tolerance Network (NIH contract N01-AI-15416; protocol number ITN021AI). Supported by the National Institute of Allergy and Infectious Diseases, the Juvenile Diabetes Research Foundation, Genentech, and Biogen Idec. At the Mayo Clinic, the trial was supported by a Clinical and Translational Science Award (CTSA) grant (UL1 RR024150-01) from the National Center for Research Resources (NCRR). At Johns Hopkins, the trial was supported by a CTSA grant (UL1 RR025005) from the NCRR and by grants (K24 AR049185, to Dr. Stone; and K23 AR052820, to Dr. Seo) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). At Boston University, the trial was supported by CTSA grants (UL1 RR025771 and NIH M01 RR00533) from the NCRR and a grant (K24 AR02224) from the NIAMS (all to Dr. Merkel) and an Arthritis Foundation Investigator Award (to Dr. Monach).

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/acr.23099

Received: Mar 15, 2016; Revised: Aug 03, 2016; Accepted: Sep 20, 2016

Abstract

Introduction: We investigated the relationships between glucocorticoid (GC) use, disease activity, and changes in body mass index (BMI) in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: We analyzed AAV patients enrolled in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial. GC use, BMI, and disease activity were measured regularly during the trial period. We performed mixed effects regressions to examine the associations of time-dependent cumulative average GC use and disease activity with changes in body mass index (BMI) over time, while adjusting for potential confounders.

Results: The baseline BMI among the 197 patients enrolled was 28.8 (±6.3) kg/m^2. Patients with newly-diagnosed AAV tended to have a lower mean BMI compared to those with relapsing disease (28.0±5.7kg/m^2 vs 29.6 ±6.8kg/m^2) and a higher disease activity Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG, 8.7±3.3 vs 7.4±2.7). The most significant change in BMI occurred during the first six months of the trial (+1.1±2.2 kg/m^2, P<0.0001). Disease activity improvement, GC exposure, and randomization to rituximab were each independently associated with increase in BMI (P<0.001 for all analyses).

Discussion: Our findings suggest that changes in BMI are independently associated with improvements in disease activity as well as GC exposure in AAV. Rituximab may also have effects on BMI independent of its impact on disease activity.

Significance and Innovation

1. Increases in BMI in ANCA-associated vasculitis (AAV) are associated with improvements in disease activity as well as cumulative glucocorticoid exposure even after adjustment for important confounders.

2. Rituximab therapy in AAV was also independently associated with increased BMI, even after adjustments for disease activity and glucocorticoid exposure.

Introduction

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are types of ANCA-associated vasculitis (AAV) characterized by necrotizing inflammation that can lead to life-threatening complications[1]. Remission induction often requires high doses of glucocorticoids as well as immunosuppressive medications such as cyclophosphamide or rituximab[2]. Such treatments are associated with potential adverse events and can lead to damage beyond that caused by the underlying disease. Weight gain is one of the most common patient-reported adverse events related to glucocorticoid therapy[3].

Not all weight gain is hazardous, however. Untreated or poorly controlled inflammatory conditions, such as AAV, are associated with increased catabolic activity which can lead to cachexia, manifested as weight loss due to muscle and fat loss[4]. In other conditions, cachexia has been associated with a lower quality of life and increased morbidity and mortality[4]. To that end, weight gain and increasing BMI during treatment of inflammatory conditions may in fact be beneficial[4]. The ability to classify increased BMI (e.g., weight gain) accurately as either an adverse event related to glucocorticoid exposure or a positive outcome reflecting improved disease activity is therefore important in studies investigating glucocorticoid -sparing strategies.

To our knowledge, only one study has investigated the relationship between AAV treatment and changes in BMI. In the Wegener's Granulomatosis Etanercept Trial (WGET), weight gain over the course of the trial was not associated with glucocorticoid exposure[5]. This finding was somewhat counterintuitive given the well-known association between glucocorticoid use and weight gain. Thus, we sought to confirm the findings from the earlier study and extend the investigation to examine the relationship between increases in BMI and improved disease control using data from the Rituximab in ANCA-Associated Vasculitis (RAVE) trial[2].

Methods

RAVE Trial

Details of the RAVE trial design have been reported[2,6]. ANCA-positive patients with GPA or MPA and severe disease (Birmingham Vasculitis Activity Score for Wegener's Granulomatosis [BVAS/WG] of > 3, or one major item) were assigned to either: 1) CYC (2mg/kg, adjusted for renal insufficiency) for 3-6 months, followed by azathioprine (AZA) (2mg/kg) for a total of 18 months; or, 2) RTX (4 weekly infusions of 375mg/m^2) followed by placebo. Patients in both groups received the same glucocorticoid protocol, which included 1-3 days of IV methylprednisolone followed by 1mg per kilogram per day of prednisone. The prednisone dose was then tapered until discontinuation by 5.5 months if the patient had achieved and maintained remission. Data for analysis of the RAVE trial was accessed from the Immune Tolerance Network (https://www.itntrialshare.org/, on January 5, 2016).

BVAS/WG and Weight Assessment

The BVAS/WG was assessed at baseline and then at months 1, 2, 4, 6, 9, 12, 15 and 18. During the trial, the patient's weight (in kilograms) was measured weekly during the first month and then at months 2, 4, 6, 9, 12, 15, and 18. Height, measured at the baseline visit, was assumed to remain unchanged over the course of the trial. The body mass index (BMI) was calculated as kg/m^2. Patients were categorized by BMI according to World Health Organization definitions of underweight, normal weight, overweight, and obese[7]. Change in BMI was chosen as the primary outcome because of its standardization for height, as opposed to crude weight change which can have varying significance based on the patient's height and baseline weight. A cumulative average score for BVAS/WG was determined for each visit in the first six months of the trial.

Glucocorticoid Assessment

The patient's glucocorticoid exposure since the previous visit was assessed weekly during the first month and then at months 2, 4, 6, 9, 12, 15, and 18. In addition, glucocorticoid exposure in the two weeks prior to randomization was assessed at baseline. For the purposes of this study, methylprednisolone doses were converted to the equivalent prednisone dose (5mg of prednisone for every 4mg of methylprednisolone). Beginning with the first visit following enrollment, the total dose and cumulative average dose of glucocorticoid administered during the trial was calculated.

Inflammatory Marker and Renal Function Assessment

During the first six months of the trial, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatinine were assessed at each visit. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation[8]. A cumulative average for each measure (ESR, CRP, eGFR) was determined for each visit in the first six months of the trial. For missing datapoints, the last average was carried forward.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation or 95% confidence interval (95% CI). Categorical variables are reported as number (%). Unpaired and paired student T-tests were used to evaluate differences in weight over time. Fisher's exact tests were used to compare categorical variables between groups. To replicate the methods of the previous study of BMI changes in AAV[5], linear regression was used to assess the relationship between BMI change and glucocorticoid dosing with and without adjustment for potential confounders, including glucocorticoids administered prior to baseline, age at the time of consent, gender, disease status at baseline (new diagnosis versus flaring), ANCA status (PR3-ANCA or MPO-ANCA), baseline creatinine, baseline BMI, flares during the trial, and randomization to RTX or CYC. With adjustment for the same confounders, a multivariate analysis of response profile using a mixed regression model was performed to compare the change in BMI over time

between those with new disease at baseline and those with relapsing disease at baseline. We used mixed-effects multiple regression models to estimate the impact of a number of factors on fluctuations in BMI first six months of trial. Cumulative averages of disease activity measures (BVAS/WG, ESR, and CRP), glucocorticoid expsoure, and GFR were analyzed individually as time-dependent covariates. We assessed eGFR in this model without adjustment for age or gender since these are included in the formula to calculate eGFR and were highly correlated with eGFR. Interaction between new disease status at baseline and time was investigated. We used SAS, version 9.3 (SAS Institute, Cary, North Carolina, USA) for all statistical analyses.

Results

Baseline Cohort Demographics

RAVE enrolled 197 patients. **Table 1** describes the characteristics of the patients included in the RAVE trial. The mean age was 52.8 (± 15.5) years and 50% of the patients were male. The majority of patients (131, 67%) were PR3-ANCA positive. At baseline, the mean BVAS/WG was 8±3.1, reflective of the severity of the disease in these patients. At baseline, the mean BMI was 28.8±6.3kg/m^2; the mean weight was 85.2±20.9kg. Of the 197 patients in the study, 1 (0.51%) was underweight (BMI category 1), 56 (28.4%) were of normal weight (BMI category 2), 69 (35%) were overweight (BMI category 3), and 71 (36.6%) were obese (BMI categories 4-6). Thus, more than 70% of patients were overweight or obese prior to enrollment.

Glucocorticoid Administration During the Study

Before enrollment, 179 (91%) patients had received glucocorticoids, and their mean cumulative dose prior to entry was 1,218±1,462mg. Over the course of the trial, patients were treated with a mean cumulative glucocorticoid dose of 5,038±2,638mg. The greatest glucocorticoid exposure occurred during the first six months of the trial, when patients received a mean of 4,295±1,663mg. Between months 6 and

12, 61 patients received a mean cumulative dose of 1,156±1,317mg of glucocorticoids. Between months 12 and 18, 43 patients received a mean cumulative dose of 1,767±2,251mg of glucocorticoids.

BMI Change During the Study

The most significant change in BMI occurred during the first six months of the trial (**Figure 1**) when the mean BMI increased by 1.1±2.2 kg/m^2 (P<0.001 compared to baseline). At months 12 and 18, the mean BMI remained significantly higher than at baseline (29.7± 6.3kg/m^2 and 29.8± 6.4kg/m^2, respectively, P<0.001 for both comparisons to baseline BMI of 28.8±6.3kg/m^2). There was no significant change in mean BMI at months 12 and 18 when compared to BMI at month 6 (-0.2kg/m^2 (95% CI: -0.5 to 0.04) P=0.1) and 12 (-0.06 kg/m^2 (95% CI: -0.4 to 0.2) P=0.7), respectively. Of the 136 patients followed for 18 months, 30 (22%) ended the trial in a higher BMI category compared to baseline. Thirteen (9.5%) were in a lower BMI category.

When we applied the same methodologies used in a previous study and conducted a multivariate linear regression analysis adjusted for potential confounders of the relationship between BMI change and glucocorticoid exposure at months 6, 12, and 18 of the trial[5]. We confirmed the findings of the previous study that, using this methodology, there was no significant association between the quantity of glucocorticoids administered and change in BMI during the trial (**Supplementary Table**).

One of the strongest predictors of BMI change at 6, 12, and 18 months that emerged from this analysis was whether the patient had a new diagnosis of AAV or was relapsing at baseline. For instance, in the first six months of the trial, those with a new diagnosis of AAV had an increased BMI of 0.8±0.3 kg/m^2 (P=0.008) compared to those with relapsing disease at enrollment. Randomization to rituximab also emerged as a predictor of BMI change at months 6 and 12 such that those randomized to rituximab had an increase in their BMI at month 6 of 0.9±0.3 kg/m^2 compared to those randomized to cyclophosphamide/azathioprine (P=0.002). When analyzed according to randomization with no further

adjustment, we found that those randomized to rituximab experienced a significant increase in BMI at 6 and 12 months (1.0 kg/m^2±0.3, P=0.003 at 6 months; 0.8 kg/m^2±0.4, P=0.04 at 12 months).

BMI Change and New Diagnosis at Baseline

Given the results of the linear regression analysis which indicated that patients with a new diagnosis of AAV at baseline had a greater increase in BMI, we further evaluated the change in BMI within each group during the trial. Patients with a new AAV diagnosis tended to be older (55 years ± 16.4 vs. 51 ± 14.3, P=0.045), were less likely to be PR3-ANCA+ (52% vs. 80%, P<0.001), and had a higher baseline BVAS/WG (8.7 ± 3.3 vs. 7.4 ± 2.7, P=0.002) (**Table 2**). There was no significant difference in the glucocorticoids received prior to baseline (1,341 (±1,408) mg vs 1,101 (±1,509) mg, P=0.3) or over the course of the study (4,914 (±3,114) mg vs 5,157 (±2,096) mg) between those with and without a new diagnosis at enrollment. There was no significant difference in BMI at baseline between those with new diagnoses and those with relapsing disease at baseline, but there was a trend towards a higher BMI among patients with relapsing disease (29.6 ±6.8 kg/m^2 vs. 28.0 ±5.7 kg/m^2; P=0.09). In a multivariable analysis of response using a mixed regression model adjusted for potential confounders, those with a new diagnosis at enrollment had a significantly greater increase in their BMI at 6 (+1.1kg/m^2±0.3), 12 (+1.2kg/m^2±0.4), and 18 (+1.6kg/m^2±0.4) months (P=<0.002 for all comparisons, **Figure 2**).

BMI Change and Disease Activity

To further investigate possible explanations for changes in BMI during the first six months of the trial (when the greatest change in BMI occurred), we used mixed effects modeling to account for frequent changes in disease activity, glucocorticoid exposure, and BMI while adjusting for potential confounders (**Table 3**). We determined that the change in BMI over the first six months of the trial was associated with changes in disease activity (as reflected by BVAS/WG, ESR, and CRP), glucocorticoid exposure, and randomization to rituximab. For instance, in the fully adjusted BVAS/WG model (**Table 3**) the BMI

increased by 0.2±0.04 kg/m^2 per 1,000mg of prednisone, decreased by 0.09±0.02 kg/m^2 per BVAS/WG point increase, and increased by 0.7±0.2 kg/m^2 for patients randomized to rituximab. Estimates were similar when ESR and CRP were substituted for BVAS/WG (**Table 3**). There was no association between changes in renal function (eGFR) and BMI (data not shown), thus excluding any contribution to these findings of advancing renal dysfunction, fluid retention, and weight gain. In a BVAS/WG mixed effects model (data not shown) that also included an interaction term for new diagnosis at enrollment and visit, those with a new diagnosis at enrollment had a significant increase in their BMI over the first six months of the trial (+1.1±0.2 kg/m^2, P<0.0001) compared to those with relapsing disease at enrollment when adjusted for disease activity, cumulative glucocorticoid exposure, and other confounders.

Discussion

Using prospectively collected data from a large randomized controlled trial in AAV, we found that increases in BMI are multifactorial and associated with improvements in disease activity, cumulative glucocorticoid exposure, and randomization to rituximab. These findings essentially replicate those from an earlier study using data from the WGET trial[5] but demonstrate that when a more granular analysis is conducted, changes in BMI during induction treatment do in fact have complex associations with glucocorticoid exposure, disease activity, and randomization to rituximab.

In both the WGET and RAVE trials, which employed similar glucocorticoid treatment regimens, the greatest increase in BMI occurred in the first six months of treatment, followed by the achievement of a plateau. Understanding the etiology of increased BMI in patients treated with glucocorticoids is important because of patients' concerns over weight gain while on glucocorticoid therapy[3]. In addition, the associations of both glucocorticoids and weight gain with cardiovascular disease are well-established[9,10], and there is a growing recognition of the role of metabolism in immune-mediated disease risk[11,12] and response to treatment[13,14].

Our observation raises important questions pertaining to how one determines whether weight gain signifies an adverse event related to glucocorticoid therapy[15,16] or, conversely, that weight gain actually reflects an improving metabolic balance away from a highly catabolic state that drives cachexia[4]. One might postulate that increased BMI early in treatment (e.g., during induction therapy) may not be characterized as an adverse events related to glucocorticoid therapy. It is important to consider, however, that more than 70% of the subjects enrolled in RAVE were overweight or obese at baseline, raising questions of how this augments their risk for cardiovascular disease given its known independent associations with elevated BMI[17], glucocorticoids[9,10], and AAV[18].

In some circumstances, it seems likely that the occurrence of weight gain implies effective disease control. In contrast, the failure of a patient on glucocorticoid treatment to gain weight augurs poorly for long-term disease control. In the absence of effective disease control, the weight loss associated with active disease trumps even glucocorticoid treatment in the metabolic balance governing the gain or loss of weight, favoring weight loss. It is only when the inflammation associated with AAV has been controlled that the full impact of glucocorticoid treatment on weight gain is realized.

Although WGET and RAVE were similar with regard to the subjects' baseline age, gender distribution, and BMI, important differences between the two trials exist. Whereas WGET enrolled only patients with either severe or non-severe GPA, RAVE enrolled only patients with severe AAV (GPA or MPA). In the study by Wung et al., weight gain was independent of cumulative glucocorticoid exposure[5]. Although we confirmed this observation when replicating their methods, the mixed effects models that we employed demonstrated that increases in BMI are independently associated with improvements in disease activity, cumulative glucocorticoid exposure, and randomization to rituximab. Moreover, we also observed a significant difference in BMI changes between those with newly diagnosed as opposed to relapsing disease at enrollment. This was also confirmed in a mixed effects analysis.

In a post-hoc analysis of a methotrexate-based treatment strategy in rheumatoid arthritis patients (Computer Assisted Management in Early Rheumatoid Arthritis Trial-II, CAMERA-II), Jurgens et al. demonstrated that weight gain during treatment was attributable to a reduction in disease activity rather than to glucocorticoid exposure[19]. Patients in the CAMERA-II trial were treated with only 10mg of prednisone daily – a dose substantially lower than that received by patients in the RAVE trial.

A surprising observation in our study was that randomization to rituximab was associated with increased BMI, even after adjustments for disease activity and glucocorticoid exposure. A variety of explanations for this finding are possible. First, the association between rituximab treatment and increased BMI over the course of the trial may be a reflection of superior disease control not captured by our conventional measures of disease activity (e.g., BVAS/WG, ESR, CRP). Second, independent of the effect of B cell depletion on inflammation and disease control, rituximab may have effects on circulating hormones (e.g., leptin, adiponectin, grhelin) that regulate metabolism and body composition. No studies to date have evaluated this hypothesis. Third, one must consider the possibility that cyclophosphamide and/or azathioprine contribute to declines in BMI through similar but opposing mechanisms. Finally, it is also possible that anorexia associated with cyclophosphamide or azathioprine might account for the effects observed. Future studies might investigate the variation in BMI and circulating hormones in patients undergoing rituximab treatment for other immune-mediated conditions.

Our study has certain limitations. First, we used randomized post hoc clinical trial data, which may limit the generalizability of our findings to patients treated outside the regimented conditions of a clinical trial. Second, we did not have knowledge of the trial participants' BMI prior to the onset of AAV. This limits our ability to comment on whether patients return to their "baseline" BMI or significantly surpass this measurement. Third, our analysis evaluated changes in BMI only up to month 18 – the period during which patients were treated according to protocol – so we are unable to comment on the potential impact of glucocorticoids on BMI beyond this follow up. Finally, BMI is influenced by multiple factors such as

adiposity as well as skeletal muscle mass. Data collected over the course of the trial did not permit us to investigate how differential variation in these components may have contributed to our observations.

Although it is widely acknowledged that glucocorticoid treatment leads to weight gain, especially when administered for prolonged periods of time[20], previous studies have been small in size, included patients with varying treatment regimens, and have rarely accounted for variations in disease activity and other confounders when investigating the relationship between glucocorticoids and BMI. Longitudinal studies in different inflammatory conditions are required to understand the trajectory of BMI and its determinants prior to, during, and following glucocorticoid therapy. It is important that such studies consider disease activity as a covariate. The potential relationships between the presence of certain genetic polymorphisms, glucocorticoid exposure, and weight gain may also confound such studies, and must be considered[21].

In conclusion, increased BMI during AAV treatment is independently associated with reductions in disease activity, increased glucocorticoid exposure, and randomization to rituximab. Improving our understanding of the complex factors mediating the relationship between glucocorticoid exposure and BMI variation is crucial to identifying and defining the significance and potential hazards of weight gain in the treatment of inflammatory conditions.

References

1. Hilhorst M, van Paassen P, Tervaert JW, Limburg Renal Registry. Proteinase 3-ANCA vasculitis versus myeloperoxidase-ANCA vasculitis. *J Am Soc Nephrol*. 2015;26(10):2314-2327.

2. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221-232.

3. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum*. 2006;55(3):420-426.

4. Laviano A, Koverech A, Mari A. Cachexia: Clinical features when inflammation drives malnutrition. *Proc Nutr Soc*. 2015;74(4):348-354.

5. Wung PK, Anderson T, Fontaine KR, et al. Effects of glucocorticoids on weight change during the treatment of wegener's granulomatosis. *Arthritis Rheum*. 2008;59(5):746-753.

6. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. 2013;369(5):417-427.

7. Obesity: Preventing and managing the global epidemic. report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253.

8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. *Ann Intern Med*. 1999;130(6):461-470.

9. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med*. 2004;141(10):764-770.

10. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: The framingham experience. *Arch Intern Med*. 2002;162(16):1867-1872.

11. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' health study II. *Arch Intern Med*. 2007;167(15):1670-1675.

12. Qin B, Yang M, Fu H, et al. Body mass index and the risk of rheumatoid arthritis: A systematic review and dose-response meta-analysis. *Arthritis Res Ther*. 2015;17:86-015-0601-x.

13. Sandberg ME, Bengtsson C, Kallberg H, et al. Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. *Ann Rheum Dis*. 2014;73(11):2029-2033.

14. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. *Ann Rheum Dis*. 2015;74(5):813-817.

15. Suppiah R, Flossman O, Mukhtyar C, et al. Measurement of damage in systemic vasculitis: A comparison of the vasculitis damage index with the combined damage assessment index. *Ann Rheum Dis*. 2011;70(1):80-85.

16. Seo P, Min YI, Holbrook JT, et al. Damage caused by wegener's granulomatosis and its treatment: Prospective data from the wegener's granulomatosis etanercept trial (WGET). *Arthritis Rheum*. 2005;52(7):2168-2178.

17. Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: Collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083-1096.

18. Morgan MD, Turnbull J, Selamet U, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: A matched-pair cohort study. *Arthritis Rheum*. 2009;60(11):3493-3500.

19. Jurgens MS, Jacobs JW, Geenen R, et al. Increase of body mass index in a tight controlled methotrexate-based strategy with prednisone in early rheumatoid arthritis: Side effect of the prednisone or better control of disease activity? *Arthritis Care Res (Hoboken)*. 2013;65(1):88-93.

20. Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: Published evidence and prospective trial data. *Ann Rheum Dis*. 2006;65(3):285-293.

21. Nakamura A. Genotypes of the renin-angiotensin system and glucocorticoid complications. *Pediatr Int*. 2015;57(1):72-78.

Table 1: Baseline Features of the RAVE Cohort

Variable (N=197)	
Age	52.8 (±15.5)
Male (N,%)	99 (50%)
Baseline BVAS-WG	8.0 (±3.1)
Disease Category (N,%)	
Granulomatosis with polyangiitis	147 (75%)
Microscopic polyangiitis	48 (25%)
Indeterminant	1 (0.5%)
PR3-ANCA+ (N,%)	131 (67%)
BMI and Glucocorticoid Dosing	
Baseline BMI	28.8 (±6.3)
Category 1 (Underweight)	1 (0.5%)
Category 2 (Normal Weight)	56 (28.4%)
Category 3 (Overweight)	69 (35%)
Categories 4-6 (Obese)	71 (36.6%)
GC prior to baseline (mg)	1,218 (±1,462)

*Mean ± SD unless otherwise labeled; GC=glucocorticoid

Table 2: Comparisons of AAV Patients with New Diagnosis versus Relapsing Disease at Enrollment

Variable	New Diagnosis (N=96)	Relapse at Baseline (N=101)	P -value
Age	55 (±16.4)	51 (±14.3)	0.045
Male	50 (52%)	49 (49%)	0.7
PR3-ANCA+	50 (52.1%)	81 (80.2%)	<0.001
Baseline BVAS-WG	8.7 (±3.3)	7.4 (±2.7)	0.002
Baseline BMI	28.0 (±5.7)	29.6 (±6.8)	0.09
Change in BMI 0-6 Mo	+1.7 (1.2-2.2)	+0.6 (0.1-1.0)	0.001
Change in BMI 6-12 Mo	-0.1 (-0.6-0.3)	-0.3 (-0.6-0.01)	0.5
Change in BMI 12-18 Mo	-0.18 (-0.2-0.6)	-0.31 (-0.7-0.1)	0.1
Total GC (mg) Prior to Baseline	1,341 (±1,408)	1,101 (±1,509)	0.3
Total GC (mg) Over 18 Months	4,914 (±3,114)	5,157 (±2,096)	0.5

BMI=Body Mass Index; GC=glucocorticoid

Table 3: Associations between Glucocorticoid Exposure and Change in BMI According to Various Disease Activity-Adjusted, Multi-Variable Mixed Models*

Model	Variable	Estimate	P-Value
BVAS/WG-Adjusted Model	Cumulative average of glucocorticoid during trial (/1000mg of prednisone)	0.2	<.0001
	Glucocorticoid administered prior to baseline (/1000mg of prednisone)	-0.04	0.5
	Cumulative average BVAS/WG	-0.09	0.0001
	Baseline BVAS/WG	0.04	0.1
	Baseline age	-0.02	0.004
	Rituximab exposure	0.7	<.0001
ESR-Adjusted Model	Cumulative average of glucocorticoid during trial (/1000mg of prednisone)	0.2	<.0001
	Glucocorticoid administered prior to baseline (/1000mg of prednisone)	-0.09	0.2
	Cumulative average ESR	-0.03	0.0004
	Baseline ESR	0.001	0.6
	Baseline age	-0.01	0.02
	Rituximab exposure	0.7	0.0002
CRP-Adjusted Model	Cumulative average of glucocorticoid during trial (/1000mg of prednisone)	0.2	<.0001
	Glucocorticoid administered prior to baseline (/1000mg of prednisone)	-0.04	0.6
	Cumulative average CRP	-0.1	<.0001
	Baseline CRP	0.03	<.0001
	Baseline age	-0.01	0.01
	Rituximab exposure	0.6	0.001

BVAS/WG = Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein.
*All mixed models were adjusted for baseline BMI, new diagnosis at enrollment, PR3-ANCA+, and sex, whereas disease activity variables were added to the final mixed model to avoid collinearity.