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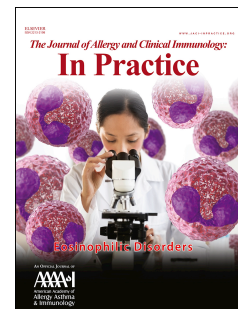
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ABSTRACT**(Word count = 245/250 Words)**

BACKGROUND: Eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis associated with significant morbidity and mortality that has historically been treated with systemic corticosteroids and immunosuppressants. The interleukin-5 (IL-5) antagonist mepolizumab was FDA approved in 2017 after demonstrating safety and efficacy in EGPA. We hypothesized that benralizumab, an IL-5 receptor (IL-5R) antagonist approved for eosinophilic asthma, would demonstrate safety and efficacy in EGPA.

OBJECTIVES: To determine the safety and efficacy of benralizumab in EGPA as measured by reduction in oral corticosteroid dose and EGPA exacerbations.

METHODS: We conducted a prospective 40-week open-label pilot study of benralizumab 30 mg administered subcutaneously in 10 EGPA patients. Adverse events, oral corticosteroid dosing, exacerbations and lung function were evaluated before, during and after benralizumab treatment. Paired tests and tests derived from longitudinal models were used to compare outcome variables between phases or visits.

RESULTS: Benralizumab was well tolerated and resulted in reduction of median corticosteroid dose from 15 mg at start to 2 mg at end of treatment. Geometric mean corticosteroid dose was reduced from 11.6 mg during pre-treatment to 6.3 mg during treatment phase. Five patients were able to achieve a dose of 0 mg. Mean annualized exacerbation rate was lowest during the treatment (1.5) compared to the pre- and post-treatment phases (4.6, $p=0.008$ for treatment versus pre and post-phases combined).

CONCLUSIONS: Benralizumab was well tolerated, facilitated oral corticosteroid reduction and reduced exacerbations in EGPA. Larger controlled trials are warranted to further evaluate the role of benralizumab in EGPA

Registered on Clinicaltrials.gov: NCT03010436

HIGHLIGHTS:

1. What is already known about this topic?

- Oral corticosteroids have been the mainstay of therapy for EGPA for years. More recently mepolizumab, an anti-IL-5 monoclonal antibody, was approved for use in EGPA.

2. What does this article add to our knowledge?

- In this phase II study, Benralizumab, a monoclonal antibody that targets the IL-5 receptor α subunit (IL-5R α), shows safety and efficacy in the treatment of EGPA.

3. How does this study impact current management guidelines?

- Benralizumab may represent a new treatment option for EGPA.

KEY WORDS

1. Eosinophilic granulomatosis with polyangiitis (EGPA)
2. Churg-Strauss syndrome
3. Biologic therapy

79 4. Monoclonal antibody

80 5. Benralizumab

ABBREVIATIONS

ACQ = Asthma Control Questionnaire

ANCA = Anti-neutrophilic Cytoplasmic Antibody

AQLQ = Asthma Quality of Life Questionnaire

BVAS = Birmingham Vasculitis Activity Score

CBC = Complete Blood Count

CPK – Creatinine Phosphokinase

CRP = C-reactive Protein

EGPA = Eosinophilic Granulomatosis with Polyangiitis

FeNO = Fractional Exhaled Nitric Oxide

FEV₁ = Forced Expiratory Volume in One Second

GGT = Gamma-glutamyl Transferase

IgE = Immunoglobulin E

IL = Interleukin

IL-5 = Interleukin 5

IL-5R α = Interleukin 5 Receptor Alpha

LDH = Lactate Dehydrogenase

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a hypereosinophilic disorder characterized by asthma, blood eosinophilia, chronic rhinosinusitis, pulmonary infiltrates and ANCA-associated vasculitis in one or more end organs. The skin and nervous system are commonly affected; presence of cardiac, renal or GI involvement predicts worse outcomes (1). Although the disease is rare, with an incidence of approximately 6-35 patients/million/year(2, 3), morbidity and mortality are high. Historically, EGPA management revolved around utilization of systemic corticosteroids to induce or maintain remission, but chronic daily use and frequent bursts of oral corticosteroids result in significant adverse effects, including osteoporosis, diabetes, and cataracts. Immunosuppressant therapies such as cyclophosphamide, azathioprine or methotrexate are often used to induce remission or facilitate corticosteroid withdrawal, but have variable efficacy and moderate toxicity (4).

Interleukin(IL)-5 is a cytokine that regulates release, migration, and activation of eosinophils (5). The introduction of agents that target IL-5 or its receptor has resulted in reduction in exacerbations and improvement in lung function in patients with severe eosinophilic asthma (6-10). Patients with EGPA, similar to those with eosinophilic asthma, have higher levels of circulating IL-5 compared to healthy controls (11). In 2017, mepolizumab, an anti-IL-5 monoclonal antibody, was approved for use in EGPA after a phase III trial showed subjects receiving mepolizumab were more likely to achieve remission, remain in remission longer, and reduce their dose of oral corticosteroids compared to those receiving placebo (12).

Benralizumab is a monoclonal antibody that targets the IL-5 receptor α subunit (IL-5R α) on eosinophils and basophils, preventing IL-5 from binding and inducing apoptosis, thereby yielding both neutralizing and cytotoxic effects (13). In this pilot study, we hypothesized that

benralizumab would provide a safe and steroid-sparing treatment option for patients with EGPA, reducing the rate of EGPA exacerbations, and resulting in improvement in clinical markers of disease activity.

METHODS

This open label pilot study (Clinicaltrials.gov NCT03010436) was approved by the National Jewish Health Institutional Review Board. Subjects were recruited through referrals to the investigators' clinical practice and through IRB-approved study advertisements.

Inclusion and Exclusion Criteria

Ten subjects aged 18 or older with a diagnosis of EGPA, as defined in Table 1, were recruited and enrolled in this study. All subjects were maintained on a stable dose of corticosteroids from the time of enrollment to starting open-label study drug, which was 4 weeks. No tapering oral corticosteroid dosing was allowed during this time period. Subjects on other immunosuppressive therapies, such as methotrexate, azathioprine, or mycophenolate mofetil, were allowed to enroll but were required to maintain a stable dose for the entirety of the study, so as not to confound study treatment.

Subjects with other hypereosinophilic syndromes, other vasculitides (e.g. granulomatosis with polyangiitis), history of malignancy, or parasitic infections were excluded. Subjects who had received other monoclonal antibodies within 3 months were excluded. Pregnant or nursing females were excluded due to unknown safety profile of the study medication.

Study Design

The study included 4 phases (Figure 1). During the Screening phase (4 weeks leading up to and including Visit 0, the date of first injection of 30mg of benralizumab), subjects provided informed consent and underwent medical history review, physical exam and urine pregnancy testing. After diagnosis of EGPA was confirmed and stable dose of oral corticosteroids was determined, baseline measurements were evaluated for spirometry, asthma and EGPA symptom questionnaires (Juniper ACQ (14)/AQLQ (15), Birmingham Vasculitis Activity Score (BVAS) (16), EGPA Clinical Activity Score), blood/serum biomarkers (CBC with differential, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), anti-neutrophil cytoplasmic antibody (ANCA), IgE), urinalysis, and fractional concentration of exhaled nitric oxide (FeNO).

The Wash-in phase included the 28 days following Visit 0. Oral corticosteroids were not tapered during this phase.

During the Treatment phase (followed Wash-in up through Visit 5, lasting approximately 24 weeks), subjects received 2 more monthly subcutaneous injections of 30 mg benralizumab at approximately 4 and 8 weeks after Visit 0 (the first benralizumab injection) then followed by bimonthly injections at approximately 16 and 24 weeks after Visit 0. At each injection visit, spirometry, blood markers of disease, FeNO, and asthma/ EGPA questionnaires were collected. If clinically stable, corticosteroid tapering was initiated at week 4, and continued based on a predetermined taper schedule (Online Repository Text).

The post-treatment phase included a Washout period (4 weeks following treatment period) and a Safety Monitoring period (the subsequent 8 weeks). Oral corticosteroid doses were recorded, subjects were monitored for safety and adverse events, and spirometry, blood markers of disease, FeNO, and asthma/EGPA questionnaire administration were performed.

Outcomes

The primary outcomes of this pilot study were to document the safety and efficacy of benralizumab therapy in subjects with EGPA. Efficacy outcomes included evaluation of a) corticosteroid-sparing effect b) rate of EGPA exacerbations (i.e. any worsening of a subject's EGPA symptoms requiring an increase in corticosteroids); c) signs and symptoms of EGPA; d) physiologic and blood biomarkers of disease including spirometry, FeNO, and; e) patient reported outcomes including asthma/ EPGA activity questionnaires.

Statistical Analysis

Arithmetic means were used to summarize approximately normally distributed variables, while geometric means (GM) or medians were used for right-skewed variables. For right-skewed variables with zeros, geometric means were computed by adding 1 to all values, averaging the natural-logged values, exponentiating, then subtracting 1, resulting in '0-corrected' geometric means. Statistical analyses used the 4 previously defined phases (combining Washout and Safety Monitoring periods).

Annualized exacerbation rates and average corticosteroid use were compared between pairs of phases using the Wilcoxon Signed-Rank (WSR) test, a nonparametric test less sensitive to outliers, such that comparisons are based more on the central tendency of subjects.

Biochemical, physiologic and quality of life markers of disease (eosinophils, ESR, CRP, IgE, FeNO, FEV₁, AQLQ, BVAS and ACQ) as well as prednisone use were analyzed using linear mixed models to account for repeated measures over visits. A random intercept was included for subjects, and the spatial power structure used for the error covariance matrix to account for different lengths of time between visits; the 4-level phase was the main predictor in these

models, treated as a class variable. Comparisons between pairs of phases (except Wash-in) were conducted based on t-tests derived from these models. Eosinophils, ESR, CRP, IgE FeNO, ACQ and prednisone use were natural-log transformed before analysis (1 added to eosinophils, ACQ and prednisone use before logging due to presence of 0 values). For prednisone use, additional longitudinal logistic regression models were fit to compare little or no use versus some or high use, and separately, high use (i.e., spiked use) versus some or no use. This was achieved by using cut-points at 5 and 20mg to create binary variables (at least 5mg='High', <5mg='Low'; similar for 20mg). Pseudo-likelihood methods were employed (17) to fit these models, and the same methods were used to account for repeated measures (a random intercept for subject plus a spatial power structure for the unequally spaced visits).

RESULTS

Baseline characteristics and clinical biomarkers

All ten enrolled subjects met criteria for EGPA (Table 1), completed the clinical trial, and attended all visits. Demographics and baseline characteristics of all subjects are listed in Table 2. The mean age of subjects was 47, with equal sex distribution. All had a diagnosis of asthma and met criteria for type 2 eosinophilic asthma. Six of the ten subjects had histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation. The four that did not have histopathology (subjects B, D, E, F) met EGPA criteria with a history of asthma, eosinophilia, neuropathy, pulmonary infiltrates and sino-nasal abnormality. Three subjects were ANCA positive at the beginning of the trial (subject A: cANCA positive; subjects D and E: pANCA positive); one (subject A) remained positive at end of trial. Mean absolute blood eosinophils was 350 cells/mcl at beginning of trial (median=250 cells/mcl), and all subjects, except one, had an absolute blood eosinophil count of

>150 cells/mcl. All 10 subjects had BVAS >0, indicating active disease, with a mean score of 10. Mean duration since EGPA diagnosis prior to study enrollment was 3.05 years (SD 4.11 years, range 0.44-14.1 years). Four of 10 subjects were also treated with another immunosuppressive agent prior to initiation of the study. A summary of outcome variables (prednisone dose, biochemical and physiologic variables) of the 10 subjects throughout the study are reported in Table 3.

Corticosteroid use

Median prednisone dose for the group was reduced from 15 mg at start of treatment (1st quartile=10, 3rd quartile=15) to 2 mg at the end of treatment (1st quartile=0, 3rd quartile=13). The linear mixed model fit of prednisone use by visit demonstrated higher use during the Pre-treatment phase (geom. mean=11.6) relative to Treatment (geom. mean=6.3; $p=0.02$) and relative to Post-treatment (geom. mean=5.3; $p=0.01$) (Figure 2). Similarly, logistic regression models showed odds of at least 5mg prednisone use was higher in Pre- compared to Treatment (OR=4.2, SE=0.81, $p=0.08$) and compared to Post- (OR=5.9, SE=0.93, $p=0.06$). Odds of at least 20mg use was higher in the Post period compared to Pre (OR=4.6, SE=0.79, $p=0.06$) and compared to Treatment (OR=3.6, SE=0.64, $p=0.05$). These results demonstrate that minimal use was reduced during Treatment and Post- phases compared to Pre-, but that higher use was in fact elevated once the Treatment phase was over, once patients were off benralizumab therapy. Eight of 10 subjects (A, B, D, F, G, H, I, J) reached a minimum oral steroid dose of <5 mg daily, with five (A, F, H, I, J) reaching 0 mg (Figure 3). Three subjects (C, D, E) failed to achieve a reduced corticosteroid dose at the end of treatment compared with baseline.

EGPA exacerbations

All 10 subjects experienced an EGPA exacerbation at various timepoints of the study. Mean annualized exacerbation rate for the group was lower during the treatment phase (1.5) compared with the screening and post-treatment phases combined (4.6; $p=0.008$). Types of exacerbations among the group varied, with chest symptoms being the most commonly observed (Table 4).

Biomarkers of inflammation and Disease Activity

As expected, eosinophils declined with benralizumab treatment between pre-treatment and treatment phases (geometric mean from 265 to 1.1 cells/ μ cl, $p<0.0001$). FeNO did not change from baseline to end of treatment (geometric mean 51.9 vs. 47.3 ppb $p=0.47$) but declined from treatment to post-treatment phases (geometric mean=47.3 to 35.5 ppb, $p=0.02$) while some patients received increased corticosteroid dose. Other outcomes (ESR, CRP, IgE) did not demonstrate significant differences between phases ($p>0.1$ for all pairwise comparisons between phases).

Lung function

Average pre-BD FEV₁ was highest during the treatment phases (75.5 percent of predicted), compared with the pre-, wash-in and post- phase means (74.5, 72.8 and 70.9, respectively), but phase means were not significantly different ($p=0.25$).

Quality of life markers, Disease control, and Disease Activity scores.

AQLQ and BVAS were measured and did not demonstrate significant differences with treatment from beginning of the study through the end of the study. Mean ACQ was higher in the post-treatment phase than the treatment phase ($p=0.01$).

253 *Tolerability of benralizumab*

254 Benralizumab was well tolerated throughout the study. The majority of adverse events
255 were mild or moderate and were not felt to be related to study drug (Table 5); URI that did not
256 require steroid dose increase was the most frequently occurring adverse event. Only one of the
257 23 events, a vertebral bone fracture, was classified as severe, but did not require withdrawal from
258 the study. A single subject (subject H) experienced abdominal and GI symptoms in the setting of
259 poorly controlled underlying ulcerative colitis for which he took prednisone during the treatment
260 phase; this subject's data after week 16 were excluded from analyses.

DISCUSSION

Treatment strategies for EGPA have historically been limited to systemic glucocorticoids and a variety of immunosuppressants such as cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab. However, these therapies are often associated with significant toxicity and none of these therapies have been studied in double blind placebo controlled studies in EGPA. As eosinophils have been implicated in EGPA pathogenesis, and since IL-5 is involved in eosinophilopoiesis, targeting IL-5 has more recently become a cornerstone of EGPA therapy. The anti-IL-5 agent mepolizumab was approved for use in EGPA based on its ability to safely reduce corticosteroid dose and EGPA relapses (12). More recently, Kent, *et al*, published a small study of 9 subjects from the United Kingdom who received reslizumab for EGPA. This small study also showed a significant reduction in daily oral corticosteroid dosing (18).

Our open label pilot study demonstrated that benralizumab, a monoclonal antibody that binds to the IL-5R α , was well tolerated in subjects with EGPA, and allowed for a clinically significant reduction in oral corticosteroid dosing while lowering EGPA exacerbations. The >50% corticosteroid reduction from a median prednisone dose of 15 mg daily pretreatment to a median dose of 3.5 mg daily at the end of the treatment phase was substantial and comparable to that seen with mepolizumab.

EGPA exacerbations (i.e. worsening EGPA symptoms accompanied by corticosteroid increase) were reduced with benralizumab treatment despite concurrent corticosteroid reduction. Upon withdrawal of study drug, we observed a substantial rise in frequency of EGPA exacerbations, suggesting a lack of sustained effect after discontinuing benralizumab therapy. It is encouraging that annualized exacerbation rate was lowest during the lengthier 24-week

treatment phase, even though patients were on higher corticosteroid dose during the pre-treatment and post-treatment phases that were of limited duration (8 and 12 weeks, respectively) and were subject to participation in a clinical trial environment. The fact that there wasn't complete abrogation of exacerbations during the treatment phase suggests that mechanisms other than eosinophilic inflammation, such as neutrophilia or adrenal suppression, could be at play in some patients as they tapered corticosteroid dosing. Similar to other oral corticosteroid studies with benralizumab in asthma (19) and mepolizumab in EGPA (12), we did not observe a statistically significant improvement in FEV₁ with benralizumab during the treatment phases; other patient reported outcomes also remained largely unchanged.

A dramatic and significant decline in absolute blood eosinophils at one month after last benralizumab treatment compared with baseline was observed. The likely mechanism of this expected phenomenon relates to both blocked IL-5 mediated eosinophilopoiesis as well as antibody dependent cell-mediated cytotoxicity resulting in eosinophil apoptosis. All except two subjects (subject A & subject C) demonstrated completely suppression of blood eosinophils with treatment. It was not surprising, however, that there was no significant reduction in FeNO when comparing the baseline to treatment phases, since eNO production is predominantly IL-13 mediated and would not be expected to be affected by IL-5 receptor blockade (20). The statistically significant reduction in FeNO observed in the post-treatment phase compared to the treatment phase was likely related to reinstitution of higher dose of oral corticosteroids for exacerbations of symptoms after withdrawal of the study drug. In terms of other biomarkers, the effect of benralizumab on ANCA positivity remains unclear. While 3 patients were ANCA + at baseline but negative by the end of the study, subject A was consistently c-ANCA positive throughout the entire study.

While most subjects did well with benralizumab, response to treatment was heterogeneous. Thus, with a small study population, several subjects deserve closer review. Subjects A, B, and J all appeared to be true-responders to benralizumab (Figure 3A, 3B, 3J), as they had no exacerbations while on study drug and were able to decrease their daily corticosteroid dose by the end of the treatment phase. Subject I had a substantial decrease in steroids use from 15mg to 0mg but experienced an exacerbation towards end of trial that required an increase to baseline dose of 15mg. Subjects C and E (Figures 3C and 3E) appeared to be true non-responders throughout the study as both experienced exacerbations throughout the study, showing no capacity for corticosteroid dose tapering. Subject D had variability in her oral corticosteroid dosing (Figure 3D). She took increased doses at the end of the wash in, as well as towards the end of the treatment phase and maintained high dose at end of trial. This variability of dosing came at her own discretion without appropriate communication with study staff. Subject H responded to treatment early in the study (Figure 3H) but then required 2 more oral corticosteroid bursts during the treatment and post-treatment phase due to ulcerative colitis (UC) exacerbations. These exacerbations were determined to not be due to EGPA given his, lack of asthma and sinus symptoms, lack of eosinophilia or vasculitis on colonoscopy, and ongoing gastrointestinal symptoms.

This pilot study was limited by its small sample size, its relatively short duration, and the lack of a double-blind placebo control or other comparator. We were also unable to adequately differentiate ANCA positive from ANCA negative EGPA subjects and their variable response to study drug. While these limitations and the lack of blinding of eosinophil count could certainly result in some bias, the relative improvement of a majority of subjects during treatment and the

rapid worsening in the post treatment phase in the context of drug withdrawal is reassuring that the drug could be effective for many EGPA patients.

Overall, this pilot study suggests that the anti-IL-5R α agent benralizumab safely reduces systemic corticosteroid dose and EGPA exacerbations in subjects with refractory, corticosteroid-dependent EGPA. These benefits and the mechanisms thereof need to be evaluated in a larger randomized prospective double blind clinical trial.

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340 **HUMAN SUBJECTS**

341 Approval from institutional review board was obtained prior to initiation of the study.

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Figure Legends

Figure 1. Study Design Schema. Screening phase was defined as the 4 weeks preceding start of trial leading up to Visit 0. First administration of benralizumab, at Visit 0, defines start of trial. The first 4 weeks after initial benralizumab administration was defined as Wash-in phase, during prednisone dose remained stable and study drug was allowed to reach steady state. The Treatment phase included the following 24 weeks up through Visit 5, which ended approximately four weeks after last drug administration. Subjects did not receive any study drug during Washout and Safety Monitoring Periods (remaining 12 weeks).

Figure 2. Linear mixed model fit of prednisone use by visit demonstrated higher prednisone use during pre-treatment phase (geometric mean=11.6) compared with treatment (geom. mean=6.3; $p=0.02$) and with post-treatment (geom. mean=5.3; $p=0.01$).

Figure 3. Corticosteroid use during screening, treatment and post-treatment phases of the study. All ten subjects are depicted in this figure. X-axis represents time from Visit 0, in weeks. Y-axis represents prednisone in milligrams. Week 0 (first benralizumab dose), week 4 (end of washin phase), and week 28 (approximate end of treatment phase) are delineated by vertical lines. Subjects 1, 2, 8 and 10 had consistent decrease in prednisone use and no EGPA exacerbations during and 4 weeks subsequent to treatment. Subjects 3 and 6 experienced only one exacerbation during treatment phase. Subjects 4, 5, and 7 experienced 2 exacerbations during treatment.

Table 1. EGPA Diagnosis of at least 6 months

Asthma with eosinophilia $>1.0 \times 10^9/L$ and/or $>10\%$ of leukocytosis

Plus at least two of the following

1. Histopathologic evidence of eosinophilic vasculitis, perivascular infiltration or eosinophilic granulomas
2. Neuropathy
3. Non-fixed pulmonary infiltrates
4. Sino-nasal abnormality
5. Cardiomyopathy
6. Glomerulonephritis
7. Alveolar hemorrhage by bronchoalveolar lavage
8. Palpable purpura
9. ANCA positive

Table 2. Demographics and Baseline EGPA Characteristics of Subjects Treated with Benralizumab

Characteristic	Baseline characteristics (N=10) Expressed as means
Age, years, Mean±SD	47 ± 17
Male, n (%)	5 (50%)
ANCA-positive, n (%)	3 (30%)
Biopsy proven, n (%)	6 (60%)
Absolute eosinophil count cells/mcl, Mean±SD	350 ± 311
BVAS >0, no (%)	10 (100)
Prednisone dose, mg/day, Mean/Median (Min-Max)	13.4 / 15 (5-20)
Immunosuppressive therapy at baseline, no. (%)	4 (40%)
Duration since EGPA diagnosis, years, Mean±SD (Min-Max)	3.05 ± 4.11* (0.44-14.1)
Immunosuppressive therapy since diagnosis, no. (%)	6 (60%)
*standard deviation expressed in years is higher than mean duration since EGPA diagnosis due to one outlier having been diagnosed 14 years prior to study enrollment. BVAS=Birmingham Vasculitis Activity Score.	

Table 3. Summary table of outcome variables in all 10 subjects (1 subject removed after Week 16 visit (i.e., Visit 3). Entries are means (95% CI) during these treatment phases. **Reported means are geometric means for these right-skewed variables (otherwise arithmetic). Statistics were derived from linear mixed models that accounted for correlation on repeated measures within subjects. See ‘Statistical Analysis’ for more detail.

Phase	Prednisone dose (mg)**	Absolute Eosinophils**	FEV ₁ (% Predicted)	FeNO (ppb)**	AQLQ Score	ESR (mm/h)**	CRP (mg/L)**	IGE (kU/L)**	ACQ score**
Pre	11.6 (6.4, 20.5)	265 (81, 863)	74.5 (61.6, 87.4)	51.9 (33.8, 79.8)	4.9 (3.8, 5.9)	7.2 (3.8, 13.7)	1.7 (0.8, 3.4)	126 (69, 231)	2.5 (1.7, 3.5)
Wash-in	13.4 (3.9, 40.8)	0.04 (-0.8, 4.8)	72.8 (56.8, 88.7)	57.8 (31.6, 105.6)	5.1 (4.0, 6.3)	5.4 (2.4, 12.3)	0.9 (0.3, 3.0)	116 (61, 223)	2.7 (1.8, 4.1)
Treatment	6.3 (3.6, 10.6)	1.1 (-0.2, 4.7)	75.5 (62.9, 88.1)	47.3 (31.8, 70.4)	5.1 (4.1, 6.2)	5.7 (3.2, 10.5)	1.6 (0.8, 2.9)	127 (70, 229)	2.3 (1.6, 3.3)
Post	5.3 (2.6, 9.85)	7.0 (1.5, 24.2)	70.9 (57.9, 83.9)	35.5 (23.1, 54.4)	5.0 (3.9, 6.1)	5.5 (2.9, 10.3)	2.1 (1.0, 4.3)	127 (70, 232)	2.7 (1.9, 3.8)

Table 4. Total exacerbations by system and annualized exacerbation rate for group.

	Screening Phase (-4 to Visit 0)	Wash-in Phase (+ 4 weeks after visit 0)	Treatment Phase (end of week 4- 4 weeks after 5 th benralizumab injection, approx. 24 weeks)	Post-treatment Phase (+4 weeks after 5 th benralizumab injection-study end, approx. 8 weeks)
Total exacerbation episodes	3	1	8	9
Chest	3	1	8	5
Sinus	1		1	2
Skin			2	0
Neuropathy	1		1	1
Abdominal			1	1
Hearing (tinnitus)			0	1
Constitutional (fatigue)	2		0	2
Annualized exacerbation rate (mean)	5.2*	1.3	1.5	4.3**

Number of subjects with exacerbation	3	1	6	8
*WSR test $p=0.19$; ** $p=0.03$, compared with treatment phase				

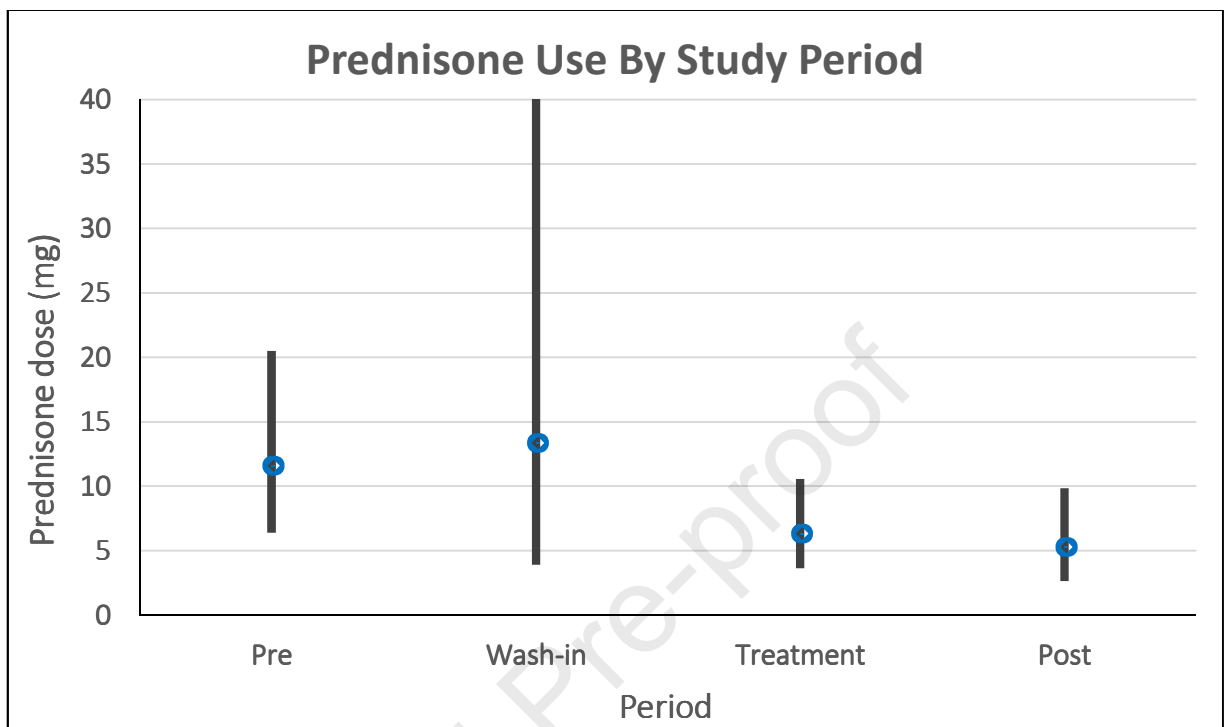
431 Note that one subject was removed during the Treatment Phase; annualized rates were adjusted
432 accordingly.

Table 5: Group Adverse Events

Mild (no. of occurrences)	Moderate (no. of occurrences)	Severe (no. of occurrences)
shoulder pain (1)	URI (3)	vertebral bone fracture (1)
vaginal bleeding (1)	ulcerative colitis flare (3)	
blood-tinged sputum (1)	sinus infection (3)	
URI (1)	pneumonia (1)	
	syncopal event (2)	
	abdominal pain (2)	
	bone (toe) fracture (1)	
	vaginal candida (1)	
	elevated triglycerides (1)	
	chest pain (1)	

433

434

Figure 2

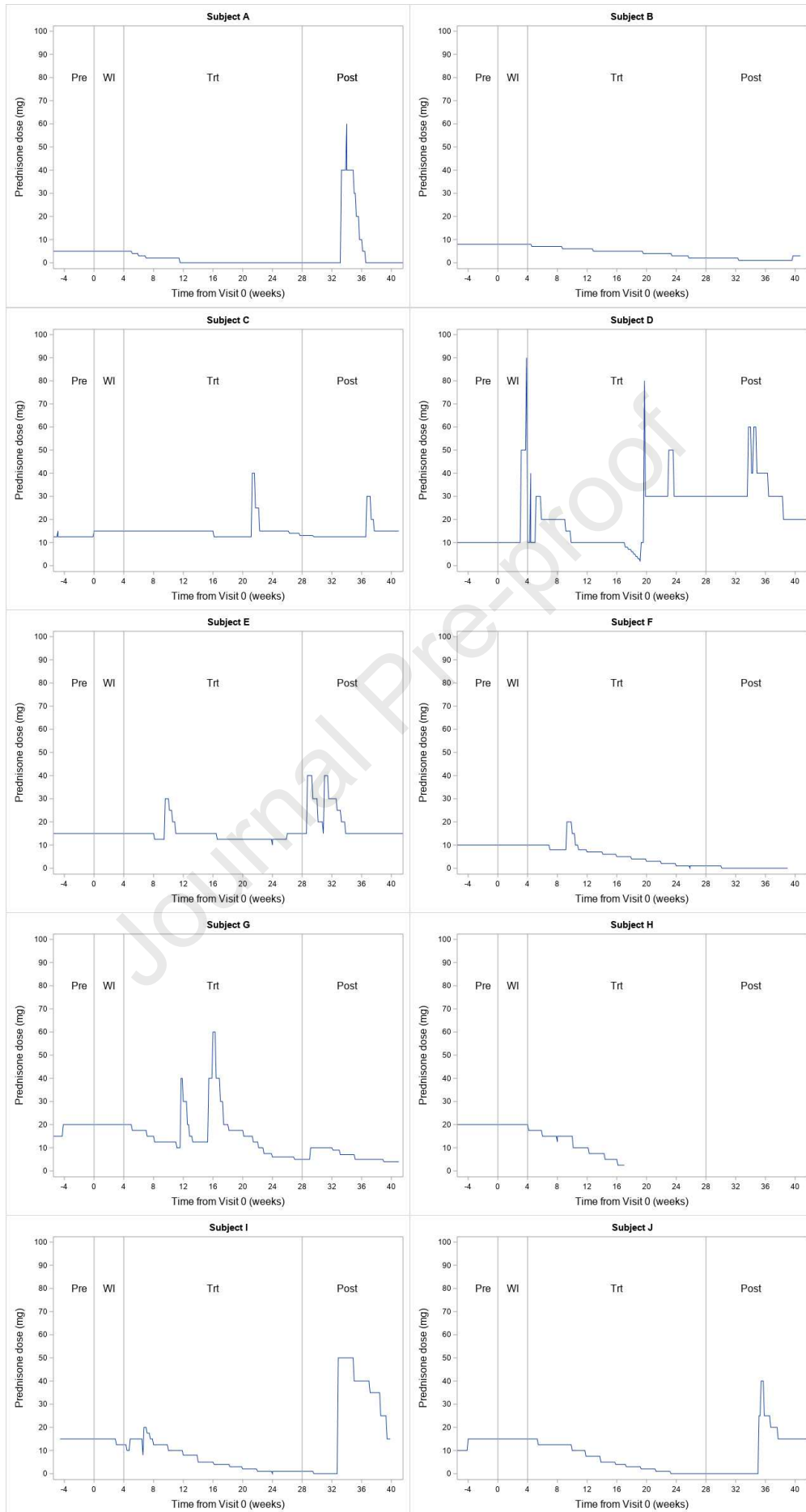


Figure 1.