BENRALIZUMAB AS A STEROID-SPARING TREATMENT OPTION IN EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA).

Journal Club Presentation

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BACKGROUND

- **Eosinophilic Granulomatosis with Polyangiitis (EGPA),** also known as formerly *Churg-Strauss Syndrome*, is associated with significant morbidity and mortality.

- Multi-system, hyper-eosinophilic disorder that lies at the nexus of asthma, eosinophilia and vasculitis (of both small and medium sized vessels).

- **EGPA** often affects the respiratory system (asthma, chronic rhinosinusitis), but can also involve the nervous system, the kidneys, the GI tract, the heart, the skin and cause various systemic symptoms.

BACKGROUND

- **EGPA** is overall rare (least common vasculitis) with an incidence of approximately 6 to 35/million/year. Very rare in children but follows more aggressive course.
- Mean age of diagnosis is 40
- No gender predominance

- Key Lab findings include:

  EOSINOPHILIA (MUST!!!), elevated ESR & CRP, + IgE, + ANA, + RF; ANCA Positivity (often associated with renal involvement, neuropathy, relapses; p-ANCA is more common). **ANCA Positivity is not always present**.

BACKGROUND

- **EGPA** is a disorder of proliferation and regulation that leads to organ infiltration and necrotizing granulomatous inflammation and tissue damage by **eosinophils.**

- The exact etiology and underlying mechanisms remain unclear, but there are a lot of theories that continue to evolve.

- **IL-5** plays an important role in **EGPA** because it causes eosinophils to migrate, proliferate, differentiate, mature, degranulate.

BACKGROUND

- Historically management of EGPA revolved around **Steroids, Steroids, and more Steroids…**
- **Immunosuppressants** (MTX, Cyclophosphamide, Azathioprine) have been used but have had variable efficacy and toxicity.
- In 2017, **Mepolizumab**, an anti-IL-5 monoclonal antibody, was approved by the FDA for use in adults with EGPA after a 52-week clinical trial showed that subjects who received mepolizumab were more likely to achieve remission, remain in remission and decrease their daily oral corticosteroid dose compared to placebo.
- But if **Mepolizumab** can safely help in EGPA, what about other IL-5 antagonists?
- A study recently published in the UK (*Kent et al*.) showed a reduction in daily corticosteroid use with **Reslizumab**.
- What about **Benralizumab**?

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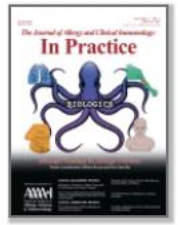

Original Article

Benralizumab as a Steroid-Sparing Treatment Option in Eosinophilic Granulomatosis with Polyangiitis

Vamsi P. Guntur MD, MSc [a, *], Laurie A. Manka MD [a, *], Joshua L. Denson MD, MS [b], Ryan M. Dunn MD [c], Yeshai T. Dollin BA [d], Mary Gill RN, BSN [a], Christena Kolakowski MS [a], Matthew J. Strand PhD [e], Michael E. Wechsler MD, MMSc [a]

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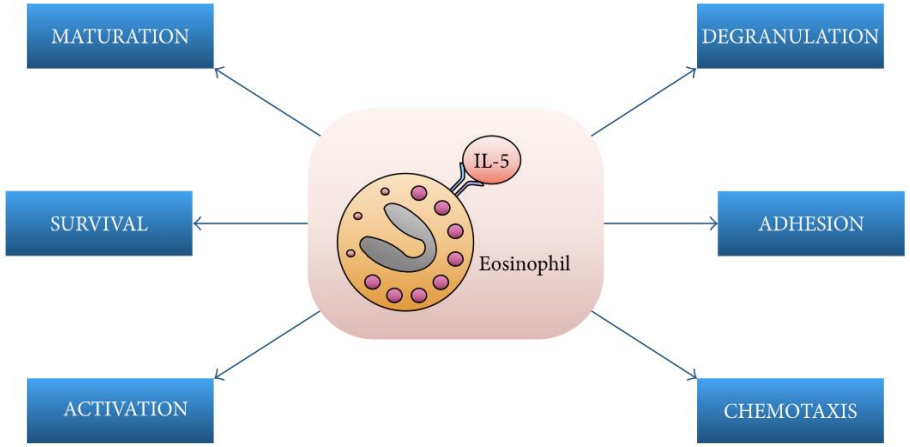

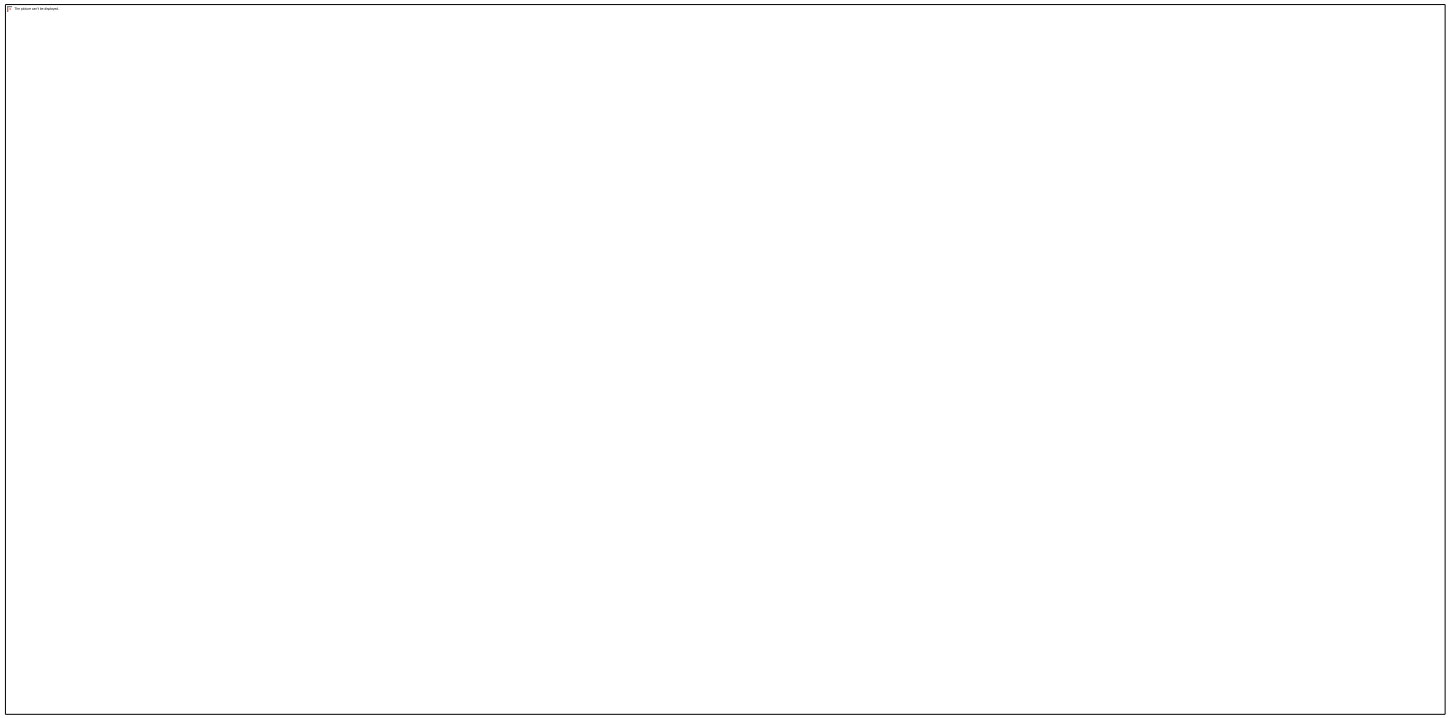

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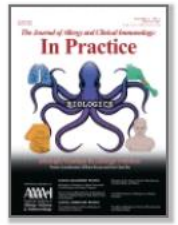

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OBJECTIVES

- Determine the safety and efficacy of Benralizumab in EGPA.

HYPOTHESIS

- Use of Benralizumab will provide a safe and steroid sparing treatment option for patients with EGPA.
- Use of Benralizumab will reduce the rate of EGPA exacerbations.
- Use of Benralizumab will improve clinical markers of disease activity.

METHODS

- Open Label pilot study (Clinicaltrials.gov NCT03010436)
- Approved by the *National Jewish Health Institutional Review Board*
- Funded by *AstraZeneca*, that also provided the study drug.
- Subjects were recruited through referrals and through approved advertisement
- 10 subjects were included in the study based on set criteria
- Length of trial was 40 weeks

METHODS

Inclusion Criteria

- Subjects must be 18 or older
- Have a diagnosis of EGPA as defined in Table 1
- Subjects on other immunosuppressive therapies were allowed to enroll but were required to maintain a stable dose for the entirety of the study, to minimize confounding.

METHODS

METHODS

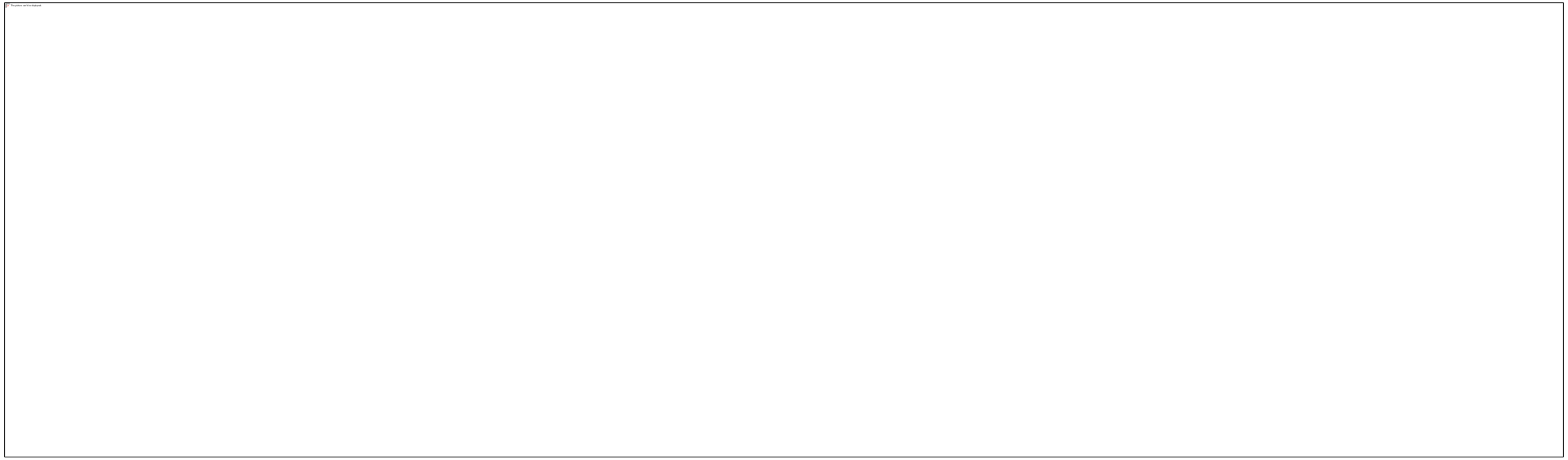
Exclusion Criteria

- Subjects with other hypereosinophilic syndromes , other vasculitides, history of malignancy, parasitic infections were excluded.
- Subjects who had received other monoclonal antibodies in the past 3 months were excluded.
- Pregnant or nursing females were excluded because of the unknown safety profile of benralizumab.

METHODS : STUDY DESIGN

- Study included 4 phases: screening phase, wash-in phase, treatment phase, post-treatment phase.
- Pre-treatment/screening phase: 4 weeks before visit 0. All patients remained on stable doses of steroids.
- Visit 0: Day of first injection of benralizumab 30 mg; **Start of 40 weeks long trial**.
- Wash-in period: 4 weeks after visit 0. No oral corticosteroids taper during this period.
- If Clinically stable, **steroid taper was started at week 4** based on a predetermined schedule.
- Treatment phase: Week 4 to week 28. Additional benralizumab injections were given**.**
- Patient received subcutaneous **benralizumab injections of 30 mg at Visit 0, week 4, week 8, week 16 and week 24.**
- Post treatment phase: Lasted 12 weeks and included washout period (first 4 weeks after treatment phase) followed by an 8-week long safety monitoring phase. **Ends at week 40.**

METHODS : STUDY DESIGN



METHODS : STUDY DESIGN

- **Pretreatment/Screening phase**: informed consent, medical history review, physical exam, pregnancy testing, confirmation of EGPA diagnosis, determination of stable corticosteroid dose, baseline spirometry, FeNO, blood/serum biomarkers (CBC, ESR, CRP, ANCA, IgE), UA, and completion of EGPA and asthma questionnaires (Juniper AQLQ/ACQ and BVAS) were obtained.

- **At each visit injections**: spirometry, FeNO, blood markers and EGPA and asthma questionnaires were done.

- **Post treatment phase**: subjects were monitored for safety and adverse events. Spirometry, FeNO, blood markers of disease, asthma/EGPA questionnaire were obtained.

METHODS : STATISTICAL ANALYSIS

- **Arithmetic means (Averages)** were used for normally distributed variables. Arithmetic means take in consideration all values but tend to be very sensitive to outliers.
- **Geometric means (GM)** are not as sensitive to outliers and were used for right-skewed variables.
- **Medians** were used to describe corticosteroid use. Medians tend to ignore extreme values.
- Annualized exacerbation rates (short term rate expressed as an annual rate) and average corticosteroid use were compared using the **Wilcoxon signed-rank test** as it is less sensitive to outliers and focuses more on central tendency.
- Biochemical tests and markers of diseases (ESR, CRP, FeNO, Asthma/EGPA Questionnaires…) and prednisone use were analyzed using **linear multilevel models** to help deal with repeated measures during visits (i.e measuring the same people multiple times, duplicating/multiplying data sets) and to help deal with the correlated nature of the data and not violate the assumption of independence…

OUTCOMES

Primary outcome: safety and efficacy of Benralizumab therapy in subjects with EGPA.

- Efficacy included evaluation of:
    1. Corticosteroid-sparing effect
    2. Rate of EGPA exacerbations, requiring increase in corticosteroids
    3. Signs and symptoms of EGPA
    4. Physiologic and blood biomarkers of disease (FeNO, Spirometry)
    5. Patient-reported outcomes, EGPA/asthma questionnaires

RESULTS

- All subjects attended all visits.
- All had a diagnosis of asthma/eosinophilic asthma.
- 3 Subjects were ANCA + (2 p-ANCA and 1 c-ANCA at the beginning of the trial). At the end of the trial, only 1 (c-ANCA) remained +
- Mean absolute blood eosinophils was 350 cells/mcl at the beginning of the trial.
- Mean duration of disease since diagnosis was 3.05 years.

RESULTS

- Linear mixed models showed **higher use of prednisone** during the pre-treatment phase relative to the treatment phase and the post-treatment phase as will be seen in Table 3.

- Logistic regression models showed **higher use of prednisone** once patients were **off benralizumab therapy**. Use of **prednisone was lower** during the treatment phase compared to both pre-treatment and post-treatment.

    - Odds of at least 20 mg of prednisone use was higher in post-treatment vs treatment (OR=3.6, SE=0.64, P=0.05) and vs pre-treatment (OR=4.6, SE=0.79, P=0.06).

    - Odds of at least 5 mg of prednisone use was higher in pre-treatment compared with treatment (OR= 4.2, SE=0.81, P=0.08) and vs post-treatment (OR=5.9, SE=0.93, P=06).

- **8 out 10 subjects** reached a minimum oral steroid dose of **< 5 mg daily.** Of those 8 subjects, **5 reached 0 mg**. **3 subjects failed** to achieve a reduced corticosteroids dose at the end of the treatment phase. It was a challenge for subject D to reach a dose of < 5 mg; by the end of the treatment phase, subject D had failed to achieve reduction and required a higher corticosteroid dose.

RESULTS

Entries represent means **(95 % CI)** during the treatment phases.
The * represents geometric means (GM) for the right skewed variables. Arithmetic means for the others

RESULTS

- **All 10 Subjects experienced an EGPA exacerbation at various points of the study.**
- **Mean annualized exacerbation rate was lower** during the treatment phase (1.5) compared with the screening and post-treatment phase (4.6; P=0.008).
- **Eosinophils declined with Benralizumab therapy** from GM 265 (pre-treatment) to 1.1 cells/mcl, P<0.0001) post-treatment.
- **FeNO did not change** much from pre-treatment to treatment (GM=51.9 VS 47.3 ppb, P=0.47) but declined from treatment to posttreatment phase (GM=47.3 vs 33.5 ppb, P=0.02) due to high doses of steroids use in the post-treatment phase for exacerbations of symptoms.
- **Other markers that were used** (ESR, CRP, IgE, AQLQ and BVAS, FEV_1) **did not demonstrate significant differences between phases--** although pre-bronchodilator FEV_1 was highest during the treatment phase.
- **Mean ACQ was higher in the** post treatment phase vs treatment phase (P=0.01).

RESULTS

Entries represent means **(95 % CI)** during the treatment phases.

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RESULTS

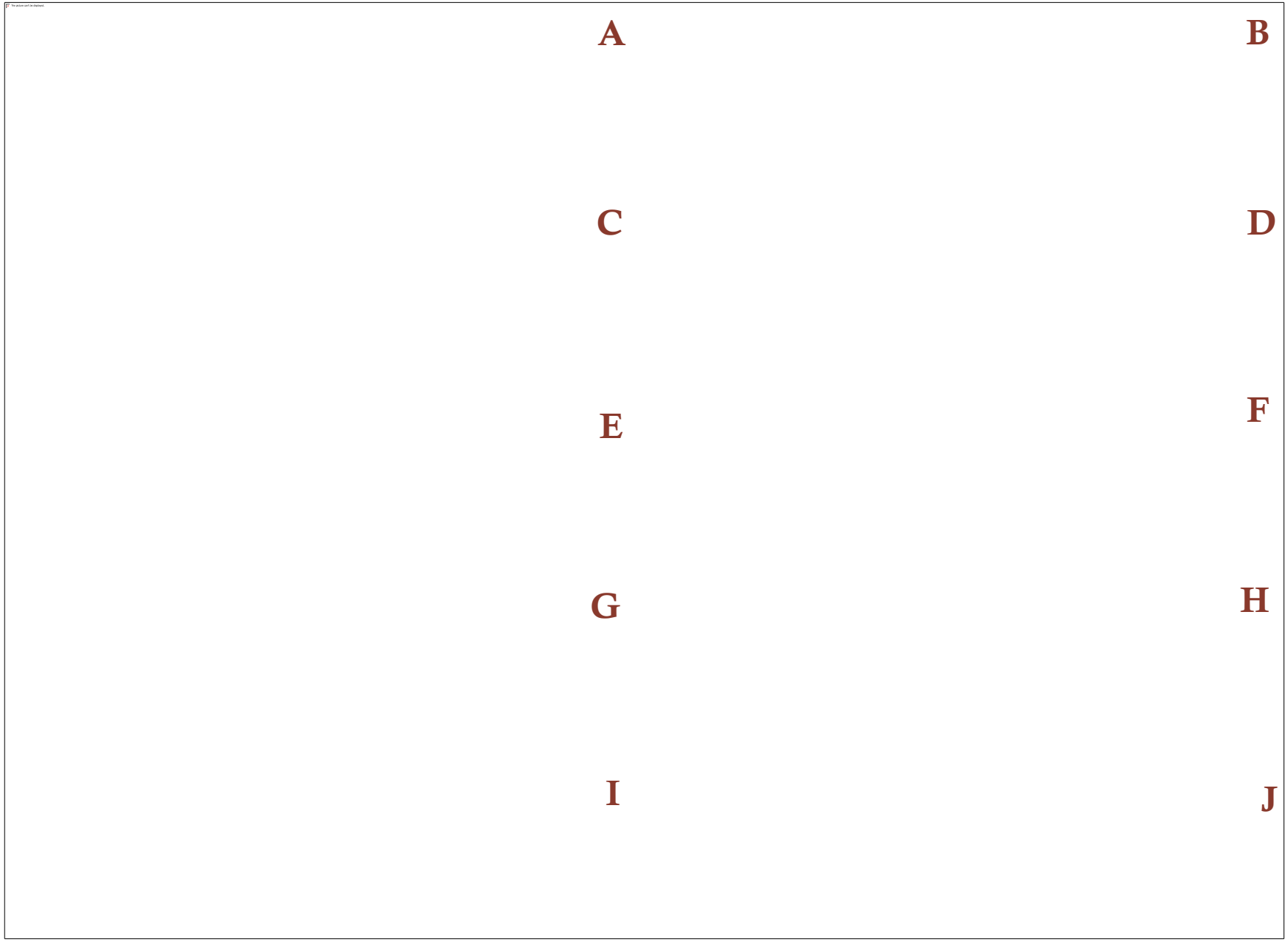
A,B,F,G,H,I,J reached < 5mg of daily steroid use during the treatment phase.

A,F,H,I,J reached 0 mg during the treatment phase.

Subject's H data were excluded from the analyses after week 16 because of UC flares that required steroid bursts.

C,D,E failed to reduce steroid doses by the end of the treatment phase.

Subject D had variability in her steroids dosing and took increased doses of steroids at her own discretion during the wash-in, treatment phase and post-treatment phase.



RESULTS

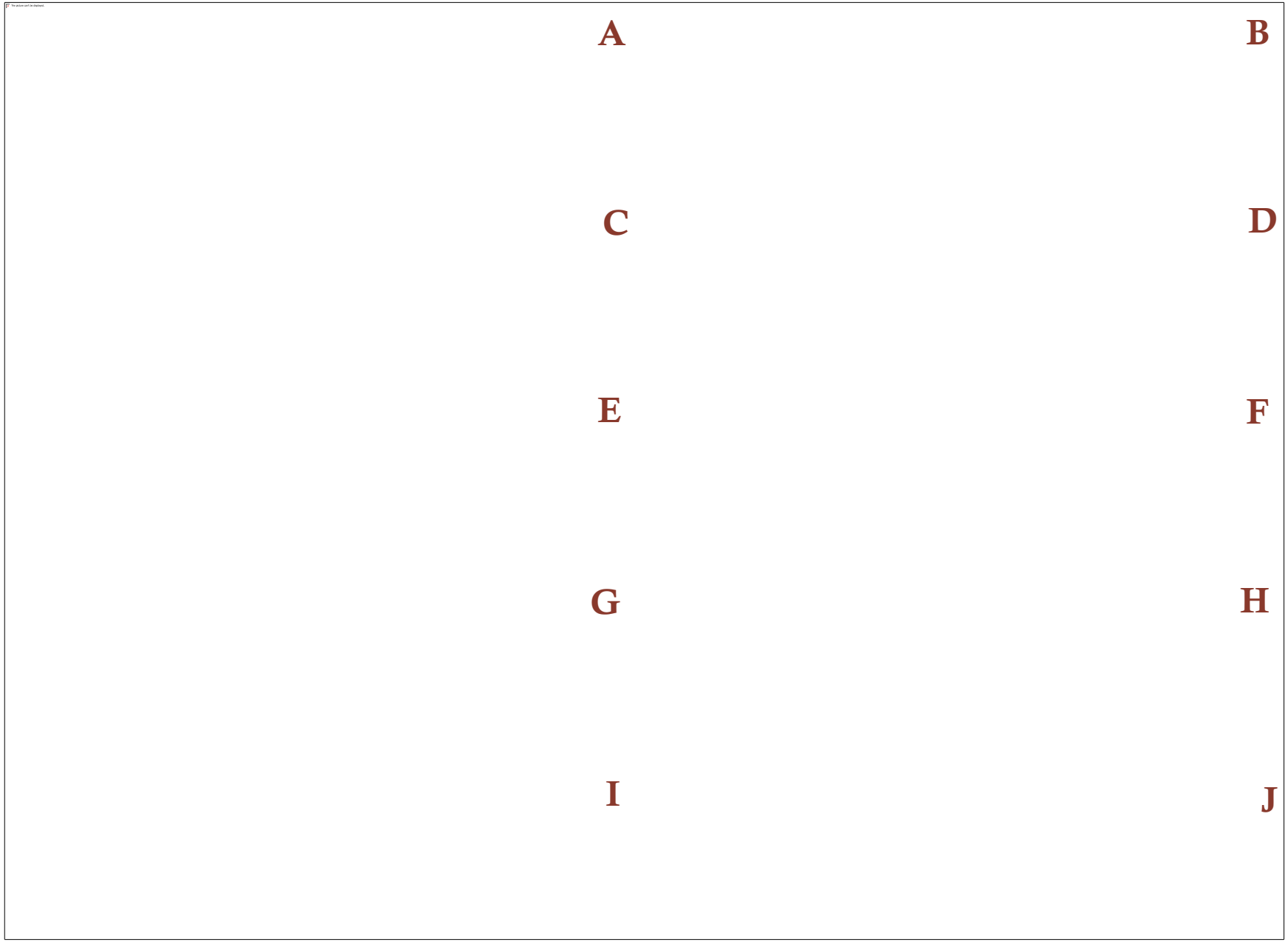
C,E (true non-responders) had exacerbations throughout the study and prednisone could not be tapered.

A,B,J, (true responders) to Benralizumab as they had no exacerbations and tolerated reduction in their steroid dose to the end of the treatment phase.

I reached 0 mg, but had an exacerbation & went back 15 mg.

However, All 10 Subjects experienced an EGPA exacerbation at various points of the study.

C, D, E, F, G had exacerbations during the treatment phase.



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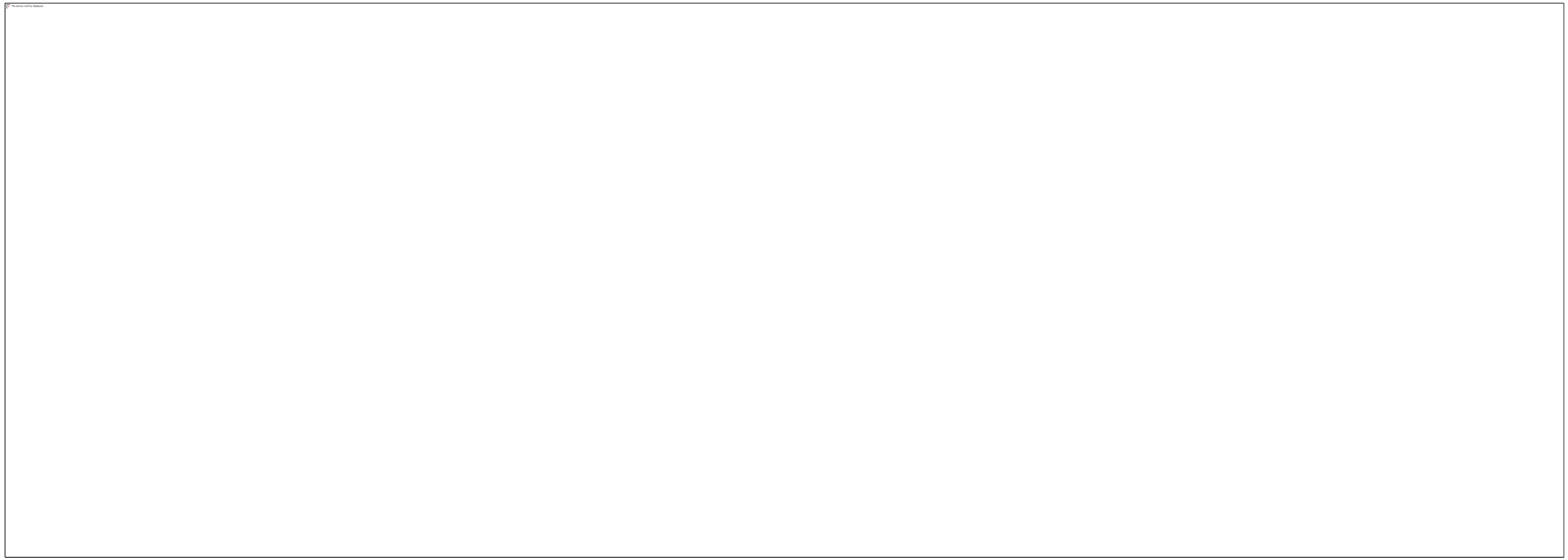
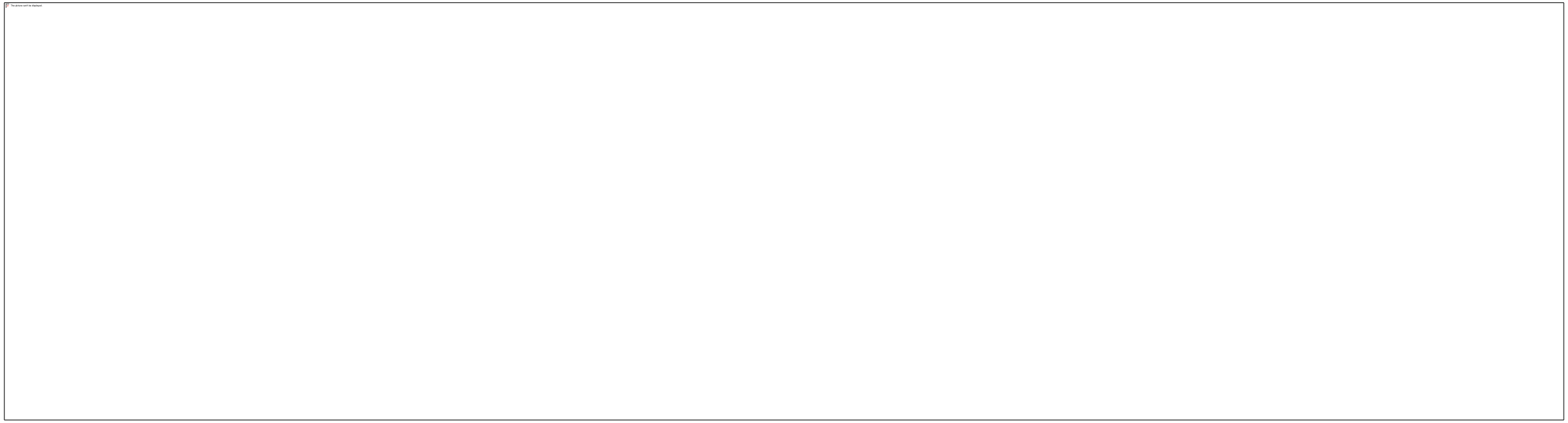


- **The most common type of exacerbations involved the chest.**

RESULTS



- **23 adverse events** were recorded. Benralizumab was in general well tolerated. **URI was the most frequent event associated with benralizumab use.** **Some events were attributed to prolonged steroid use and 1 subject (subject H) developed ulcerative colitis flares** during the trial that required prednisone use. His data were excluded after week 16.

- Many of the recorded events throughout the study were not felt to be directly related to benralizumab therapy and were not severe, except the vertebral fracture, but the patient did not withdraw from the study.

DISCUSSION

- Dramatic **decline in absolute blood eosinophils** 4 weeks after last benralizumab injection.
- All subjects (except 2 A & J) showed **compete suppression of blood Eosinophils** during treatment.
- **Other mechanisms** other than just eosinophilic inflammation such as neutrophilic inflammation, adrenal suppression could be involved because some subjects were **still having exacerbations** during the treatment phase**.**
- **> 50% corticosteroid reduction** from a **median** dose of 15 mg daily (pre-treatment) to a **median** dose of (3.5 mg) daily (end of treatment phase).
- **Higher doses of prednisone** during the pre-treatment phase and post-treatment phase.
- Withdrawal of benralizumab at the end of the treatment phase → substantial rise in frequency of exacerbations.
- **Annualized exacerbation rates was lowest during the 24-week treatment phase.** All 10 Subjects experienced an EGPA exacerbation at various points of the study.

DISCUSSION

- Use of benralizumab did not demonstrate significant differences between phases for some clinical markers of disease (ESR, CRP, IgE, AQLQ and BVAS, FEV_1).
- Mean ACQ was higher in the post treatment phase vs treatment phase (P=0.01).
- FeNO showed no statistically significant reduction during the treatment phase vs baseline, but showed statistically significant reduction during post-treatment phase vs treatment due to use of high doses of steroids for exacerbations.
- The effect of benralizumab on ANCA positivity remains unclear.

LIMITATIONS

- Open-Label study
- No double blinded placebo, control group.
- Lack of blinding of eosinophil count
- Small sample sizes. Small samples can make it challenging to interpret confidence intervals and P value, can affect measures of central tendency (mean, median, mode…) and undermine reliability.
- In small lack of statistical confidence does not always means that there is no clinical effect.
- Some subjects were also on immunosuppressants in addition to prednisone. Confounders?
- ANCA+ vs ANCA- subjects showed variable responses to Benralizumab that could not be explained.

CONCLUSIONS

- Overall, benralizumab appears to be well tolerated, but response to the study drug was heterogenous.
- Results are encouraging but more clinical trials are needed with larger sample sizes and with placebo/control groups.

REFERENCES

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