Brand Name: Cinqair

Generic Name: reslizumab

Manufacturer: Teva Respiratory [1]

Drug Class: Humanized monoclonal antibody [2, 3]

Uses:

Labeled Uses: Add-on for maintenance of asthma with eosinophilic phenotype [4]
Unlabeled Uses: None at this time [4]

Mechanism of Action: Reslizumab is an interleukin-5 antagonist. Interleukin-5 is a cytokine that is involved in many aspects of the eosinophil life cycle. Thus, reslizumab results in decreased production of eosinophils. [2]

Pharmacokinetics:

Absorption: [1]

T_{max}	End of infusion
V_d	5L
$t_{½}$	24 days
Clearance	7 ml/hr
Protein binding	N/A

Metabolism: Reslizumab is metabolized by enzymatic proteins into small peptides and amino acids. The targets that the drug binds to in the body are soluble; therefore the target binding has no bearing on the metabolism of the drug. No CYP450 interactions appear to exist. [4]

Elimination: Target-mediated clearance is not expected, since the target in question is soluble. [4]

Efficacy [5, 6, 7]

Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG Bardin P, et. al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel, double-blind, randomized, placebo controlled, phase 3 trials. Lancet Respiratory Medicine. 2015; 3(5): 355-66

Study Design: Multicenter, double-blind, placebo-controlled, parallel-group design study

Description of Study: *Methods*: A total of 953 patients were randomized between the two trials. Patients had a blood eosinophil count at or above 400 cells per microliter and were inadequately controlled on their current asthma regimen. They had to be receiving at least 440 micrograms per day of fluticasone propionate or equivalent. After randomization, a total of 476 patients received placebo and 477 received reslizumab. The participants received their study drug as an add-on to their current asthma treatment regimen. The primary outcome was annual frequency of clinical asthma exacerbations. *Outcome Results:* Results from this study were the following: Study 1, rate ratio [RR] 0.50 [95% CI 0.37–0.67]; Study 2, RR 0.41 [0.28–0.59]; both $p<0.0001$ when reslizumab was compared to placebo. Therefore the risk is 50% less in the treatment group compared to placebo in trial 1, and 41% less in trial 2. The commonly observed adverse effects were worsening asthma symptoms (more common in the placebo group), most other adverse effects were relatively similar between the treatment and placebo group. Therefore it cannot be stated that the adverse effects were directly associated with the treatment drug. Two reports of anaphylaxis were noted. These patients were removed from the trial.

Limitations: This study was funded by the Research and Development department at Teva Pharmaceuticals, the manufacturer of Cinqair. Also, the patients' other asthma therapies were not standardized reducing generalizability

Conclusion: These two trials demonstrated that reslizumab reduced the frequency of asthma exacerbations in patients who were uncontrolled on their current treatment plan and had an elevated eosinophil count. It also showed an improvement in Forced Expiratory Volume in the first second (FEV1) and Asthma Control Questionnaire (ACQ) scores. For further research on this topic standardization of asthma control therapy should be utilized. Expanding the trial population to determine if this treatment has any effect on other types of asthma or asthma with lower eosinophil counts.

Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J. Reslizumab for poorly controlled asthma: a randomized placebo-controlled study. American Journal of Respiratory and Critical Care Medicine. 2011; 184(10): 1125-32

Study Design: Double-blind, randomized, placebo-controlled study between 25 sites in the United States and Canada

Description of Study: *Methods*: A total of 106 patients were randomized and equally divided between the treatment and placebo arms of the trial. Inclusion criteria were confirmed asthma, receiving treatment with high-dose inhaled corticosteroids (more than 440 micrograms of fluticasone 2x/day) used in combination with at least on other agent, ACQ score of more than 1.5, and induced sputum eosinophils above 3%. Patients taking systemic corticosteroids were excluded along with those with a significant comorbidity (not described), or had hypereosinophilic syndrome. Infusions were given on weeks 0, 4, 8, and 12. The final assessment was taken during week 15 or at the time of early withdrawal, if applicable. The primary outcome was change in ACQ score from baseline to final assessment. Also measured were spirometry, blood and sputum eosinophil count,

and percentage with asthma exacerbations. *Outcome Results:* The average change in ACQ score during therapy was -0.7 and -0.3 for reslizumab and placebo, respectively (p=0.0541). In terms of patients who had an improvement of at least 0.5 in ACQ, there were 59% of patients in the treatment group and 40% in the placebo group with an odds ratio of 2.06 (p=0.0973).

Limitations: The small number of participants enrolled in this trial is a limitation. The investigators did not achieve their predicted power of 90% due to dropouts, but it cannot be assumed that the study fell below the accepted level of power at 80%. The main study objective did not have a p-value that indicated statistical significance. The result of improvement by at least 0.5 was not statistically significant either. These are limitations because without statistical significance, the results cannot be extrapolated to the general population.

Conclusion: This study showed that the patients experienced an improvement in airway function and eosinophil production. However, the results do not demonstrate an improvement in asthma control. The decrease in the ACQ score would not be considered clinically significant. A larger study population may potentially result in more positive results. These results do not suggest against using reslizumab, but they do make result in questions and hope for more data to show the benefit of the medication.

Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016; 150(4): 799-810.

Study Design: Randomized, double-blind, placebo-controlled trial at 66 study sites throughout the United States

Description of Study: *Methods*: Participants were randomly assigned to receive reslizumab or placebo in a 4:1 ratio. 398 were in the reslizumab arm, and 98 were in the placebo arm of the trial. 82 placebo patients, and 340 reslizumab patients completed the trial. Patients included were between 18 and 65 years-of-age, had ACQ scores above 1.5, and controlled by at least 440 micrograms of fluticasone or equivalent. Patients were excluded if they were taking oral corticosteroids. No limit was placed on FEV1 or blood eosinophil counts for the patients. The primary outcome was FEV1 change from baseline. Short-Acting Beta-Agonists (SABA) rescue use in the past 3 days before a visit were also measured. FVC and blood eosinophils were the final outcomes. Patients underwent a 3-week screening period, a 16-week treatment period, and finally a 12-week follow-up period. Visits were conducted every 4 weeks during the treatment period. *Outcome Results*: The between group difference between the two groups was a 68 ml increase in the FEV1 of the treatment patients over the placebo patients (p=0.17). The relationship between eosinophils and treatment also did not achieve statistical significance.

Limitations: The study was funded by Teva Pharmaceuticals the manufacturer of Cinqair, and Teva employees were involved in all aspects of the study.

Conclusion: No statistically significant results for the benefit of reslizumab were discovered. The patients did show some benefit from the medication although it is not clinically significant. Since the drug would apply to a specific subset of patients with asthma, more data would need to be returned to make a confident and clinically significant recommendation.

Contraindications [1, 2, 3, 4, 8]:

Contraindication to the use of reslizumab would be hypersensitivity to reslizumab or any of its components.

Precautions [4, 8]:

Anaphylaxis (Black Box Warning): Reslizumab has resulted in some cases of anaphylaxis within the first 20 minutes following the infusion. It may occur as early as the second dose. This would result in discontinuation of the drug.

Concomitant Medications: Do not abruptly stop any steroids, either systemic or inhaled, while receiving treatment with reslizumab.

Immunologic: If a patient has a helminth infection, it must be treated prior to treatment with reslizumab. If the patient develops a helminth infection during therapy, it must be treated. If the infection does not respond to therapy, then reslizumab must be stopped until the infection resolves.

Malignancies: Reports exist of malignant neoplasms in various tissues.

Respiration: This medication should not be used to treat any acute symptoms.

Adverse Effects (incidence in parentheses) [1, 2, 4]:

- Musculoskeletal Effects
  - Increased creatine kinase levels (0.8-20%)
  - Myalgia (1%)
- Immunologic Effects
  - Antibody Development (4.8-5.4%)
  - Anaphylaxis (0.3%)
- Respiratory Effects
  - Throat pain (2.6%)
- Oncogenic Effects
  - New cancers (0.6%)

Drug Interactions: [4, 8]

Reslizumab does not appear to have any CYP450 interactions. No studies

Dosing/Administration[1-4, 8]

Adult Dosing

3 mg/kg IV infusion given over 20-50 minutes every 4 weeks

Pediatrics (≥4 years of age)

No data have been obtained regarding use in pediatric populations.

Elderly

No dosage adjustment is necessary

Renal impairment

Specific guidelines do not exist at this time; however, dosage adjustments do not appear necessary.

Hepatic impairment

Specific guidelines do not exist at this time; however, dosage adjustments do not appear necessary.

Use in special circumstances:

Overdosage: No antidotes for reslizumab at this time. If the patient should become toxic on the medication, symptomatic therapy is indicated. Symptomatic therapy may include oxygen replacement, bronchodilators, diphenhydramine, steroids, epinephrine, and other vasopressors. [(4)]

Conclusion:

Reslizumab would be an add-on therapy option for uncontrolled asthmatic patients who have high eosinophil counts. Other indications may currently be in the pipeline for this medication in which the disease state revolves around the presence or activity of eosinophils. Based on current data from clinical trials, it does appear that reslizumab would provide benefit for these patients' asthma. However, this is a very specific patient population. If more studies are completed that show a benefit, then this medication could potentially be recommended in uncontrolled patients with this form of asthma. Currently no studies compare this medication to an active control [(9).] This would be necessary to make a strong recommendation for its use in this patient population. At this point it can be stated that this medication may have some utility, but more data will need to be obtained for this statement to become fact.

References:

1. Cinqair [package insert]. Frazer, PA: Teva Respiratory, LLC: 2016
2. Reslizumab. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: November 18, 2016.
3. Reslizumab. Lexi-Drugs [database online]. Lexi-Comp, Inc.; November 18, 2016.
4. Reslizumab. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: November 22, 2016.
5. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG Bardin P, et. al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel, double-blind, randomized, placebo controlled, phase 3 trials. Lancet Respiratory Medicine. 2015; 3(5): 355-66

6. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J. Reslizumab for poorly controlled asthma: a randomized placebo-controlled study. American Journal of Respiratory and Critical Care Medicine. 2011; 184(10): 1125-32
7. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. Chest. 2016; 150(4): 799-810.
8. Reslizumab. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: November 22, 2016.
9. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, et. al.Comparison of anti-interleukin-5 therapies in patients with severe asthma: Global and indirect meta-analyses of randomized placebo-controlled trials. Clin Exp Allergy. 2016.

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