Anti-IgE (Omalizumab) vs. Anti-IL5 (Mepolizumab and Reslizumab) for Asthma Patients: How to Decide

Indications

OMALIZUMAB	MEPOLIZUMAB	RESLIZUMAB
Asthma Omalizumab is indicated for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Omalizumab has been shown to decrease the incidence of asthma exacerbations in these patients.	**Asthma** Mepolizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.	**Asthma** Reslizumab is indicated for add on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype.
Limitations Of Use • Omalizumab is not indicated for the relief of acute bronchospasm or status asthmaticus. • Omalizumab is not indicated for treatment of other allergic conditions.	***Limitations of Use*** • Mepolizumab is not indicated for treatment of other eosinophilic conditions. • Mepolizumab is not indicated for the relief of acute bronchospasm or status asthmaticus.	***Limitations of Use*** • Reslizumab is not indicated for treatment of other eosinophilic conditions • Reslizumab is not indicated for the relief of acute bronchospasm or status asthmaticus.
Chronic Idiopathic Urticaria (CIU) Omalizumab is indicated for the treatment of adults and adolescents 12 years of age and older with chronic idiopathic urticarial who remain symptomatic despite H1 antihistamine treatment.		
Limitation Of Use Omalizumab is not indicated for treatment of other forms of urticaria.		

Dosage

OMALIZUMAB	MEPOLIZUMAB	RESLIZUMAB
Recommended Dosage Administer Omalizumab 75 to 375 mg by subcutaneous injection every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and by body weight (kg). Adjust doses for significant changes in body weight during treatment (see Table 1, 2 and 3). Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Omalizumab treatment cannot be used as a guide for dose determination. • Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination. • Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination using Table 1, 2, or 3 based on the patient's age. Periodically reassess the need for continued therapy based upon the patient's disease severity and level of asthma control. **Adult and adolescent patients 12 years of age and older:** Initiate dosing according to Table 1 or 2.	**Recommended Dosage** Mepolizumab is for subcutaneous use only. The recommended dose of mepolizumab is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.	**Recommended Dosage** Reslizumab is for IV infusion only. The recommended dose of reslizumab is 3mg/Kg once every 4 weeks by intravenous infusion over 20-50 minutes.

Table 1: Subcutaneous Omalizumab Doses Every 4 Weeks for Patients 12 Years of Age and Older with Asthma

PRE-TREATMENT	BODY WEIGHT			
SERUM IGE	30-60 KG	> 60-70 KG	> 70-90 KG	> 90-150 KG
≥ 30-100 IU/mL	150 mg	150 mg	150 mg	300 mg
> 100-200 IU/mL	300 mg	300 mg	300 mg	
> 200-300 IU/mL	300 mg			
> 300-400 IU/mL	SEE TABLE 2			
> 400-500 IU/mL				
> 500-600 IU/mL				

Table 2: Subcutaneous Omalizumab Doses Every 2 Weeks for Patients 12 Years of Age and Older with Asthma

PRE-TREATMENT	BODY WEIGHT			
SERUM IGE	30-60 KG	> 60-70 KG	> 70-90 KG	> 90-150 KG
≥ 30-100 IU/mL	SEE TABLE 1			
> 100-200 IU/mL				225 mg
> 200-300 IU/mL		225 mg	225 mg	300 mg
> 300-400 IU/mL	225 mg	225 mg	300 mg	
> 400-500 IU/mL	300 mg	300 mg	375mg	
> 500-600 IU/mL	300 mg	375 mg		
> 600-700 IU/mL	375 mg		DO NOT DOSE	

OMALIZUMAB	MEPOLIZUMAB	RESLIZUMAB

Table 3: Subcutaneous Omalizumab Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin Omalizumab Between the Ages of 6 to < 12 Years

Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight									
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg
		Dose (mg)									
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300	DO NOT DOSE	
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375	DO NOT DOSE			
>600-700		300	225	225	300	375	DO NOT DOSE				
>700-800	Every 2 weeks	225	225	300	375	DO NOT DOSE					
>800-900		225	225	300	375						
>900-1000		225	300	375	DO NOT DOSE						
>1000-1100		225	300	375							
>1100-1200		300	300	DO NOT DOSE							
>1200-1300		300	375								

*Dosing frequency:

Subcutaneous doses to be administered every 4 weeks

Subcutaneous doses to be administered every 2 weeks

Preparation and Administration

For information regarding preparation and administration, please visit: http://www.rxlist.com/xolair-drug/indications-dosage.htm

Preparation and Administration

Mepolizumab should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

Reconstitution Instructions

1. Reconstitute mepolizumab in the vial with 1.2 mL Sterile Water for Injection, USP, preferably using a 2-or 3-mL syringe and a 21-G needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab. Do not mix with other medications.

Preparation and Administration

Reslizumab is provided as a solution in a single-use vial for intravenous infusion only and should be prepared by a healthcare professional using aseptic technique. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

Preparation of intravenous infusion

1. Remove reslizumab from the refrigerator. To minimize foaming, do not shake reslizumab.
2. Inspect visually for particulate matter and discoloration prior to administration. reslizumab solution is clear to slightly hazy/opalescent, colorless to slightly yellow liquid. Do not

	2. Direct the stream of Sterile Water for Injection vertically onto the center of the lyophilized cake. Gently swirl the vial for 10 seconds with a circular motion at 15-second intervals until the powder is dissolved. *Note: Do not shake the reconstituted solution during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the Sterile Water for Injection has been added, but it may take additional time.* 3. If a mechanical reconstitution device (swirler) is used to reconstitute mepolizumab, swirl at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1,000 rpm for no longer than 5 minutes is acceptable. 4. Visually inspect the reconstituted solution for particulate matter and clarity before use. The solution should be clear to opalescent and colorless to pale yellow or pale brown, essentially particle free. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, discard the solution. 5. If the reconstituted solution is not used immediately: • store below 30°C (86°F), • do not freeze, and • discard if not used within 8 hours of reconstitution. ***Administration instructions*** 1. For subcutaneous administration, preferably using a 1-mL polypropylene syringe fitted with a disposable 21-to 27-G x 0.5-inch (13-mm) needle. 2. Just before administration, remove 1 mL of reconstituted mepolizumab. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.	administer if discolored or if other foreign particulate matter is present. 3. Withdraw the proper volume of reslizumab from the vial(s), based on the recommended weight-based dosage. Discard any unused portion. 4. Dispense syringe contents slowly into an infusion bag containing 50 mL of 0.9% Sodium Chloride Injection, USP to minimize foaming of reslizumab (reslizumab is compatible with polyvinylchloride (PVC) or polyolefin infusion bags). Gently invert the bag to mix the solution. Do not shake. Do not mix or dilute with other drugs. 5. Administer immediately after preparation. If not used immediately, store diluted solutions of CINQAIR in the refrigerator at 2°C to 8°C (36°F to 46°F) or at room temperature up to 25ºC (77ºF), protected from light, for up to 16 hours. The time between preparation of reslizumab and administration should not exceed 16 hours. ***Administration instructions*** 1. If refrigerated prior to administration, allow the diluted reslizumab solution to reach room temperature. 2. Use an infusion set with an in-line, low protein-binding filter (pore size of 0.2 micron). reslizumab is compatible with polyethersulfone (PES), polyvinylidene fluoride (PVDF), nylon, and cellulose acetate in-line infusion filters.

	3. Administer the 1-mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.	3. Infuse the diluted solution of reslizumab intravenously, over a 20–50 minute period. Infusion time may vary depending on the total volume to be infused as based upon patient weight. 4. Do not infuse reslizumab concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of reslizumab with other agents. 5. Observe the patient over the infusion and for an appropriate period of time following infusion. 6. Upon completion of the infusion, flush the intravenous administration set with 0.9% Sodium Chloride Injection, USP to ensure that all reslizumab has been administered.

Side Effects

Omalizumab

ADVERSE REACTION	OMALIZUMAB (N = 738) %	PLACEBO (N = 717) %
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

Mepolizumab

ADVERSE REACTION	MEPOLIZUMAB 100 MG SUBCUTANEOUS (N = 263) %	PLACEBO (N = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	< 1
Muscle spasms	3	< 1

Reslizumab

ADVERSE REACTION	RESLIZUMAB (N=1131)%	PLACEBO (N=730)%
Myalgia	1	0.5
Musculoskeletal adverse reactions	2.2	1.5
Oropharyngeal pain	2.6	2.2

Time to Improvement

OMALIZUMAB	MEPOLIZUMAB	RESLIZUMAB
Up to 12 weeks for improvement of chronic idiopathic/spontaneous urticarial (3 doses at 4 week interval)	Significant improvement at around four months (4 injections).	Reslizumab demonstrated improvements as early as 4 weeks and through 52 weeks in lung function and asthma control (as measured by ACQ-7)

Please note: some patients may respond better to one agent versus another.
Further work is needed to determine better phenotypic discriminators of efficacy regarding specific agents.

Anti-IgE (Omalizumab) vs. Anti-IL5 (Mepolizumab and Reslizumab)

"If you are deciding between [mepolizumab] vs [omalizumab], if the eosinophil count is very high, [mepolizumab] may be a better option. For [omalizumab], if the IgE count is very high along with very elevated perennial allergens (i.e. dust mites, cats, dogs, mold) and those are the major triggers of your asthma, [omalizumab] may work better. Although for [omalizumab] the upper limit of the IgE level is 700 IU/ml, if your IgE level is above that, you would not qualify for [omalizumab]. For [mepolizumab] there is no upper limit of the eosinophil count to qualify for the medication."
http://allergylosangeles.com/allergy-blog/new-asthma-drug-[mepolizumab]-mepolizumab-for-severe-eosinophilic-asthma/

Although not in quote: reslizumab can be added to mepolizumab.

"An indirect comparison versus omalizumab found trends in favor of mepolizumab in reducing the rate of clinically significant exacerbation among treatment-eligible severe asthma patients."
Funding: GSK (HO-13-9058).
http://www.jacionline.org/article/S0091-6749(15)02139-9/pdf

"…the newest light on biologic factors in asthma appears to illuminate better the path to further research rather than provide solutions to the challenge of improving outcomes in patients with difficult-to-treat asthma."
http://www.jmcp.org/doi/pdf/10.18553/jmcp.2009.15.3.289

In a poster presented by Mountford et al at the ACAAI meeting in San Francisco, an indirect comparison of patients treated with reslizumab versus omalizumab and mepolizumab found that treatment with reslizumab was associated with a significantly lower rate of severe exacerbations (severe exacerbation where the study definition required use of systemic corticosteroids) compared to omalizumab. For exacerbations meeting Definition 2 (use of systemic corticosteroids; doubling the baseline dose of beclomethasone dipropionate; or ≥20mg increase in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid) and Definition 3 criteria (any outcome in study with the term 'exacerbation'),non-significant trends were observed towards lower rates with reslizumab versus either omalizumab or mepolizumab.
http://www.epostersonline.com/acaai2016/node/673

Lastly, since approval of both drugs, there are data for better phenotype stratification of these biologics:

a. Hanania et al. demonstrated that those with FeNO >19.5 ppb (p<0.001)and/or peripheral blood eosinophil counts >260/ul (p<o.005) were more likely to respond (reduction in exacerbation rate)to omalizumab (Hanania Am J Respir Crit Care Med 2013;187(8):804-811).

b. Ortega et al. demonstrated the exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% (0·48, 0·39–0·58) in patients with a baseline blood eosinophil count of at least 150 cells per µL to 70% (0·30, 0·23–0·40) in patients with a baseline count of at least 500 cells per µL (Ortega Lancet Respir Med 2016; 4: 549–56).

c. Brusselle et al. demonstrated that reslizumab reduced clinical asthma exacerbations by 75% versus placebo in patients with late-onset asthma (age ≥ 40 years) who had a baseline blood eosinophil count of at least 400 cells per µL (Brusselle Eur Respir J 2015;46:OA287)

d. The following year Brusselle et al. also demonstrated that for patients in GINA step 4 and GINA step 5 vs placebo, reslizumab consistently improved the rate of asthma exacerbations (G4 [53% reduction] rate ratio 0.47[95% CI: 0.36,0.62]; G5 [72% reduction] 0.28[0.15,0.52]) and lung function (FEV_1: G4 difference 103mL[52,154]; G5 difference 237mL[68,407]) over 52 wks. RES also improved AQLQ, ACQ-7 and ASUI scores vs PBO for both G4 and G5 pts (Brusselle Eur Respir J 2016;48:PA4107)