ERS pocket guidelines

From the ERS task force on Severe Asthma

Management of Severe Asthma: a European Respiratory Society/American Thoracic Society Guideline

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It was prepared by Fernando Holguin and Andy Bush on behalf of all members of the Task Force

Question #1: Should a monoclonal anti-IL5 antibody be used in adults and children (for the purposes of this guideline, age >5 years) with severe asthma?

We suggest anti-IL5 strategy as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype

- **Conditional recommendation**
- **Very low to moderate quality of evidence (varied by treatment)**

Evidence on benefits and harms

There are three monoclonal strategies approved by the U.S. Federal Drug Administration (FDA)/European Medicines Agency (EMA). These are mepolizumab and reslizumab which target IL-5, and benralizumab which targets the IL-5 receptor.

- All three reduce exacerbations and hospitalizations in patients with severe eosinophilic asthma.
- Mepolizumab and benralizumab lead to reduction in dose in those prescribed maintenance oral corticosteroid
- The effects on asthma control, quality of life and FEV_1 did not achieve the minimally important difference
- There were fewer serious adverse events likely driven by the reduction in severe asthma exacerbations by these drugs.
- Drug-related adverse events were slightly higher in those assigned to mepolizumab and benralizumab, and lower in those assigned to reslizumab. We did not consider drug-related adverse events in the overall assessment because the outcome was not pre-defined.

Rationale of recommendation

The Task Force members placed a relatively higher value on reducing exacerbations, and acknowledged that biomarker (blood eosinophil) measurement was highly feasible. The Task Force placed a relatively lower value on cost and invasiveness. Due to the limited number of treated adolescents over aged 12 years, and the absence of studies in younger children, the TF was unable to provide a recommendation for the use of anti-IL5 and anti-IL5Ra antibodies in this age group.

Implementation considerations

The high cost of these drugs and its impact on cost effectiveness, equity and feasibility to implementation must be weighed by clinicians in relation to the benefits on asthma outcomes shown by all anti-IL5 and anti-IL5Ra strategy drugs.

Question #2: Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 antibody or anti-IL Rα in adults and children with severe asthma? (chosen biomarkers: exhaled NO, peripheral or sputum eosinophils, and serum periostin)

We suggest that a blood eosinophil count cut-off point of ≥ 150 /µL can be used to guide anti-IL5 initiation in adult patients with severe asthma and a history of prior asthma exacerbations

- **Conditional recommendation**
- **Low quality of evidence**

Evidence on benefits and harms

- The specific cut-off blood eosinophil count to predict benefit varies across anti-IL5 strategies (mepolizumab 150 /µL, reslizumab 400 /µL, benralizumab 300 /µL).
- There is very low quality evidence that mepolizumab may provide further benefit in reducing exacerbations in patients with baseline blood eosinophilia ≥ 500/µL compared to those with an eosinophil level < 300/µL and 300 to <500/ µL.
- There was no difference in adverse events amongst those with higher vs lower eosinophil counts for benralizumab.
- More recent studies have now shown that both benralizumab and mepolizumab, maintain an adequate safety profile during long term use for up to 2 and 4.5 years, respectively

Rationale of recommendation

The Task Force placed a relatively higher value on reducing exacerbations, and acknowledged that biomarker (blood eosinophil) measurement was highly feasible. The Task Force placed a relatively lower value on cost and invasiveness.

Implementation considerations

Blood eosinophils can be measured in any standard laboratory, but additional testing beyond the point of care maybe required to ascertain baseline levels, particularly among patients on or recently taking systemic corticosteroids. Sputum eosinophil levels are currently only performed in specialized centers. It should be noted that there may be causes other than atopy (e.g. parasitic infections) for peripheral blood eosinophilia especially in low and middle-income settings. Furthermore, determining baseline eosinophil count may require more than one measurement, as this biomarker is highly variable and significantly reduced by systemic and inhaled corticosteroids.

Question #3: Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (chosen biomarkers: exhaled NO, peripheral or sputum eosinophils, and serum periostin)

In adult and adolescent (>12 years) patients with severe asthma being considered for omalizumab we suggest using a blood eosinophil cut-off of ≥ 260 /µl to identify those more likely to benefit from anti-IgE treatment; and using a FeNO cut-off of ≥ 19.5 ppb to identify those more likely to benefit from anti-IgE treatment

- **Conditional recommendations**
- **Low quality of evidence**

Evidence on benefits and harms

- A baseline blood eosinophil count of greater or equal to 260/µl is associated with greater improvements in FEV_1, and a decreased rate of exacerbations and a longer time to first exacerbation, compared to a baseline blood eosinophil count less than 260/µl.
- A FeNO level of greater or equal 19.5 ppb is associated with improvements in AQLQ, reduced exacerbation rate and longer time to first exacerbation, compared to a FeNO level less than 19.5 ppb.
- A periostin level less than 50ng/ml was associated with improvements in AQLQ, compared to a periostin level greater than or equal to 50ng/ml.
- Periostin levels are influenced by age, skeletal growth and puberty, making it an unsuitable biomarker, especially in children and young people
- There were no differences in the adverse effects in patients treated with omalizumab versus placebo according to high or low FeNO, blood eosinophils or periostin.

Rationale of recommendation

The recommendation places a high value on an increased treatment response when blood eosinophil and FeNO are used to select patients, because they predict important outcomes, and a low value on the use of periostin, which has a much lower predictive value for the important outcome of asthma exacerbations.

Implementation considerations

The high cost of omalizumab and its impact on cost effectiveness, equity and feasibility to implementation must be weighed by clinicians in relation to the benefits on asthma outcomes. Since these recommendations have not been prospectively evaluated, treatment decisions should consider these biomarker thresholds cautiously, as patients with eosinophil or FeNO values below the proposed cutoffs can still benefit from omalizumab. In addition, these thresholds were largely determined by one particular study)

Question #4: Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?

For children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies, we recommend the addition of tiotropium

- **Strong recommendation**
- **Moderate quality of evidence**

Evidence on benefits and harms

- Long-acting muscarinic antagonist treatment in children, adolescents and adults with severe asthma may improve FEV_1 and reduce loss of asthma control.
- In adults, treatment with tiotropium 5 ug improves asthma control and increases time to first exacerbation.
- There was a lower frequency of adverse events in children, adolescents and adults treated with tiotropium 5 ug compared to placebo.
- The frequency of severe adverse events was low and nearly equal to placebo

Rationale of recommendation

Based on the estimated beneficial effects observed for the addition of tiotropium, the Task Force judged that these benefits outweigh the adverse effects, burdens, and costs associated with this treatment for the management of severe asthma. This recommendation places a high value on improving symptom control and reducing exacerbations. The evidence suggested with moderate certainty a large benefit and trivial harm with the balance of effects clearly favoring the intervention.

Implementation considerations

Tiotropium was considered probably acceptable and probably feasible to implement. This recommendation also accounts for the feasibility of this inhaled therapy compared to the cost and burden of alternative add-on biologic therapies for severe asthma. While the taskforce only found data on the efficacy of 5ug in adults with severe asthma, the effects on lung function were similar to the FDA-approved 2.5ug and 5mcg doses evaluated in parallel, placebo-controlled trials of adults with mild-moderate asthma. In addition, clinical trials in adolescents with moderate and severe asthma showed that the 2.5 and 5ug doses were similarly effective

Question #5: Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

We suggest a trial of macrolide treatment to reduce asthma exacerbations in adult asthmatics on GINA/NAEPP step 5 therapy who remain persistently symptomatic or uncontrolled

- **Conditional recommendation**
- **Low quality of evidence**

Evidence on benefits and harms

- Macrolides reduce the number of asthma exacerbations, and at least one study suggests that this effect is similar for participants with or without eosinophilia.
- There is no clinically significant effect of macrolides on asthma control and quality of life
- Chronic macrolide therapy has been associated with increased incidence of diarrhea; however, the number of serious adverse events or number of participants with at least 1 adverse event is not different to placebo.
- Macrolides have a potential risk for QT prolongation or hearing loss, but the frequency of these events was the same as in the placebo arm in patients whom at baseline had no hearing deficits or abnormally prolonged QTc.
- Relative to placebo, studies on the prevalence of nasal and oropharyngeal macrolide-resistant bacteria are conflicting.
- There was a lower rate of antibiotic use and clinically diagnosed infections in those treated with macrolides

Rationale of recommendation

The previous ERS/ATS guidelines made a conditional recommendation that long-term macrolide antibiotics should not be used in the treatment of adults or children with severe asthma, based on available evidence. However, new evidence from studies with varying definitions of asthma (none meeting ERS/ATS criteria for severe asthma) have led to a change in this Task Force. The current recommendation is conditional and based on the need to avoid exacerbations and reduce oral corticosteroid usage. The benefits and safety of using macrolides for asthma for more than one year have not been determined.

Implementation considerations

Clinicians should balance the risk of individual benefit with societal harm, because it is almost certain that the widespread prescription of macrolides will result in resistant strains becoming very common in the community.

Question #6: Should a monoclonal anti-IL4Rα be used in adults and children with severe asthma?

We suggest dupilumab as add-on therapy for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels

- **Conditional recommendation**
- **Low quality of evidence**

Evidence on benefits and harms

- Dupilumab, as add-on therapy in patients with asthma that is uncontrolled on medium-high dose ICS + LABA, may reduce exacerbations and improve asthma symptoms and lung function.
- The efficacy is greater in patients with type 2 biomarkers (blood eosinophils > 150 cells/mm3 or FeNO > 25 ppb)
- Dupilumab may allow reduction of OCS dose in patients with severe CS-dependent asthma.
- The risk of dupilumab therapy appears to be small with injection site reaction as the most common treatment related adverse effect.
- Frequency of serious and any side effects were similar with dupilumab when compared with placebo.
- The mechanisms and potential clinical significance of treatment-related transient blood eosinophilia are not fully understood and needs further elucidation. Because dupilumab-mediated eosinophilia has not been associated with adverse events, there are no specific monitoring recommendations.

Rationale of recommendation

The Task Force placed a relatively higher value on reducing exacerbations and a relatively lower value on cost and invasiveness. Due to limited number of adolescents treated with antiIL4/13, the TF was unable to provide a recommendation for this age group and no available evidence exists for children < 12 yrs.

Implementation considerations

As with anti-IL% monoclonal strategies, the high cost Dupilumab and its impact on cost effectiveness, equity and feasibility to implementation must be weighed by clinicians in relation to the benefits on asthma outcomes shown by all anti-IL5 and anti-IL5Ra strategy drugs.