Treating eosinophilic exacerbations of asthma and COPD with benralizumab: Do we have a magic bullet (ABRA-CADABRA)?

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The Acute exacerbations treated with BenRAlizumab trial (ABRA) was a multicenter, phase 2, double-blind, double-dummy, active placebo-controlled trial that showed benralizumab was an effective treatment for eosinophilic exacerbations of asthma and COPD, performing better outcomes than the current standard of care with prednisolone alone[1]. At the time of an acute eosinophilic exacerbation of asthma or COPD, patients with ≥300 blood eosinophils/μL were randomly assigned to three treatment arms: prednisolone 30 mg once daily for 5 days and a single 100 mg benralizumab subcutaneous injection (BENRA+PRED group); placebo tablets once daily for 5 days and a single 100 mg benralizumab subcutaneous injection (BENRA group); or prednisolone 30 mg once daily for 5 days and placebo subcutaneous injection (PRED group). At 90 days, treatment failures occurred in 39 (74%) of 53 in the PRED group, and 47 (45%) of 105 in the pooled-BENRA group (OR=0.26; 95% CI: 0.13–0.56; p=0.0005). The 28-day total VAS mean difference was 49 mm (95% CI: 14–84; p=0.0065), favoring the pooled-BENRA group.

Although this is a breakthrough study, there are certain clinical implications that need to be considered.

Sample

The sample size critically affects the hypothesis and the study design, and in this study 158 patients with eosinophilic exacerbation of asthma or COPD were randomized. Although that the sample size is sufficient to provide a powered study, an imbalance regarding the different diagnosis is noted, as the majority of patients (56%) were suffering from asthma and only one-third of randomized patients were suffering from COPD. The ABRA trial was not powered to investigate asthma and COPD exacerbations separately, and this is a certain limitation of the study. Another critical point, is that only a minority of patients had exacerbations requiring systemic glucocorticoids in the previous year, which possibly reflects that most patients recruited were well-controlled asthma patients or non-frequently exacerbating COPD patients. This could affect the impact of benralizumab in treating eosinophilic exacerbations in a group of patients suffering from 'more severe' airways disease.

Primary outcomes

An interesting strategy by the researchers was the selection of two co-primary outcomes: treatment failures over a 90 days period and total symptoms evaluated by a visual analogue scale (VAS) at day 28. This innovation results in a clinically valuable approach as it equalizes the importance of a 'measurable' outcome such as treatment failure to a 'subjective' outcome such as patient symptoms recovery.

Exacerbations

Another consideration is the 'physiognomy' of the events analyzed as eosinophilic exacerbations of asthma or COPD. A very small minority (one in eight) of exacerbations were recruited from the emergency department and could be considered as severe exacerbations. It is probable, as authors

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discussed, that benralizumab treatment in severe exacerbations is likely to reduce the healthcare burden associated with re-admissions, but that must be investigated in future studies.

Although patients were randomly assigned in three treatment arms (BENRA+PRED group, BENRA group and PRED group), the primary endpoint was met when comparing the PRED and the pooled-BENRA treatment groups. The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together. Thus, the Kaplan–Meier plot of time to first treatment failure event showing that benralizumab can be used as a treatment of acute eosinophilic exacerbations, includes patients who received not only benralizumab but (half of them) also prednisolone. In fact, prevention of events was slightly more effective with BENRA+PRED compared to MENRA alone (Supplementary file Figure 2).

Do we have a new targeted treatment for airway diseases exacerbations (ABRA-CADABRA)?

Despite the aforementioned considerations, this is the first study showing that using a monoclonal antibody at the time of an acute exacerbation of asthma or COPD could prevent treatment failures and achieve better outcomes than the current standard of care with prednisolone alone.

Current recommendations (GINA, GOLD)[2,3] for acute exacerbations of asthma and COPD are limited to bronchodilators, systemic glucocorticoids, antibiotic therapy, or both. The 'ABC approach', an acronym that reflects the three classes of drugs (Antibiotics, Bronchodilators and Corticosteroids) is still used for exacerbations of COPD[4], and similar therapeutic strategies for the initial treatment of an asthma exacerbation are followed.

The ABRA study, shows that the use of benralizumab, an antibody which rapidly depletes eosinophils, reduces treatment failure in eosinophilic exacerbations with an unadjusted risk reduction of 74% and a number needed to treat of 4. Prior to any further recommendations, we also need to consider that the dose of benralizumab used in the ABRA trial was 100 mg, different from the dose of 30 mg approved for severe eosinophilic asthma. Additionally, the increased dose of 100 mg of benralizumab is not practically feasible, as 4 syringes of 30 mg each should be used, with the fourth one not to be fully used and even 3 syringes of 30 mg increase rapidly the total cost for the treatment of one exacerbation, for which the administration of the classical prednisolone treatment is still needed according to the results of the study.

Nevertheless, the ABRA results need to be prospectively evaluated in future studies to define whether this monoclonal antibody therapy is the magic bullet for the ABRA-CADABRA management of airway diseases exacerbations ('abracadabra' is used as an apotropaic incantation on amulets and is common today in stage magic. It is of unknown origin)[5].

CONFLICTS OF INTEREST

The authors have each completed and submitted an ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declare that they have no competing interests, financial or otherwise, related to the current work. G. Hillas reports receiving consulting fees and payment or honoraria from AstraZeneca, Alector Pharmaceuticals, Boehringer Ingelheim, Chiesi, ELPEN, GILEAD, GSK, Guidotti, Menarini, Sanofi and Specialty Therapeutics. He also reports receiving support for attending meetings and/or travel from AstraZeneca, Chiesi, ELPEN, GILEAD, Guidotti and Menarini. A. Gogali reports receiving consulting fees from Boehringer Ingelheim, Chiesi, and Menarini, payment or honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK and Menarini. She also reports receiving support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Chiesi and Menarini. K. Kostikas reports receiving grants from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK and Menarini, receiving consulting fees and payment or honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GSK, Guidotti, Menarini, Pfizer and Sanofi. Furthermore, he reports receiving support for attending meetings and/or travel from AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, Pfizer and Sanofi, participating on a Data Safety Monitoring Board of Chiesi, leadership role for Member of GOLD Assembly and also receiving other financial or non-financial interests from AstraZeneca as an employee from 2 September to 29 November 2024.

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DATA AVAILABILITY

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