



Short communication

Comparison of the novel CompEx asthma exacerbation endpoint to the ATS/ERS adapted moderate/severe asthma exacerbation definition used in the MITRA trial



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1. Background

One of the main goals of asthma treatment is the prevention of recurrent exacerbations that progressively increase the symptoms of the disease and require a change in treatment [1]. However, severe asthma exacerbations are not frequent events, and high numbers of patients are necessary to assess the clinical effect of a treatment aiming at minimizing or lowering the number of recurrent severe asthma exacerbations. A novel asthma exacerbation endpoint (CompEx) was recently suggested by Fuhlbrigge et al. [2] to enable shorter duration and/or smaller sample sizes in clinical trials assessing asthma exacerbations. It is proposed as a composite endpoint that can mirror the treatment effect on severe exacerbations, and is constructed based on data from 17,000 patients across 12 randomised controlled trials. The number of CompEx events should be significantly higher than for severe exacerbations and the hazard ratio (HR) for CompEx should closely match the HR for severe exacerbations. CompEx combines the occurrence of clinically relevant deteriorations as collected in diary records (diary events) and the occurrence of severe asthma exacerbations [3]. Diary records included in CompEx are based on peak flow, reliever use, and asthma symptoms, all assessed morning and evening, giving a total of 6 diary based variables included in the assessment. Composite endpoints are frequently used in other indications such as cardiovascular studies (e.g. MACE), and having such an endpoint for asthma studies would be a valuable tool.

In this study, the CompEx endpoint was applied post-hoc to data from a large phase III house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet allergic asthma trial to further explore the usability of this novel analysis tool (MITRA, EudraCT 2010-018621-19; [4]). The results achieved with CompEx were compared to results achieved during the MITRA trial using an adapted version of the American Thoracic Society and European Respiratory Society (ATS/ERS) definition of moderate/severe asthma exacerbations [5] to validate the CompEx endpoint and the primary results from the trial. The

ATS/ERS adapted definition of moderate/severe exacerbations was constructed to increase sensitivity in asthma trials, which was also the purpose of CompEx. Thus, the comparison of these 2 endpoints should provide useful information on the best approach for future trials.

2. Methods

The MITRA trial included 834 subjects randomised 1:1:1 to once-daily treatment for up to 18 months with placebo or the HDM SLIT-tablet (Dose: 6 SQ-HDM or 12 SQ-HDM, ALK, Denmark). The HDM SLIT-tablet is an immunotherapy for the treatment of allergic rhinitis and allergic asthma triggered by HDM allergens. Subjects had > 1 year history of HDM allergic asthma and associated rhinitis not well-controlled by inhaled corticosteroids (ICS), and positive tests of HDM sensitisation. Diary data on peak expiratory flow, reliever use, and asthma symptoms were recorded each morning and evening, and night-time awakenings were recorded each morning during the 6 months efficacy assessment period. The primary outcome for the MITRA trial was the HR for first moderate or severe asthma exacerbation during the efficacy assessment period starting > 7 months after randomisation and lasting 6 months (ICS reduction first 3 months and ICS withdrawal during the next 3 months). In the MITRA trial, severe asthma exacerbations were defined by the use of systemic corticosteroids or a hospital or emergency room visit due to asthma as described by ATS/ERS [3]. The definition of moderate asthma exacerbation was adapted from the ATS/ERS recommendations as described in Virchow et al. [3,5]. For exact definitions and further details, please refer to Virchow et al. [4]. According to CompEx, an exacerbation has occurred when an ATS/ERS defined severe asthma exacerbation occurs or when a diary event occurs. The algorithm for calculating diary events (based on daily records on peak flow, reliever use, and asthma symptoms) was described in Fuhlbrigge et al.

Data were analysed with SAS (SAS Institute) version 9.3. Treatment effect based on the 2 types of definitions was expressed as an HR after 3

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Table 1
Analysis of time to first asthma exacerbation.

Exacerbation frequency (mean of active and placebo)		HR (95%CI)	p-value	N required per group*
MITRA primary endpoint (12 SQ-HDM versus placebo)				
3 months	19%	0.58 (0.39; 0.88)	0.010	221
6 months	23%	0.63 (0.49; 0.95)	0.025	300
CompEx endpoint (12 SQ-HDM versus placebo)				
3 months	25%	0.56 (0.39; 0.81)	0.002	151
6 months	34%	0.65 (0.48; 0.89)	0.006	199
MITRA primary endpoint (6 SQ-HDM versus placebo)				
3 months	19%	0.58 (0.39; 0.89)	0.011	220
6 months	29%	0.74 (0.53; 1.02)	0.069	452
CompEx endpoint (6 SQ-HDM versus placebo)				
3 months	25%	0.58 (0.40; 0.83)	0.003	160
6 months	35%	0.69 (0.51; 0.94)	0.018	264

*: Number of subjects needed for a significance level of 10% and 80% power.

months and after 6 months of ICS reduction/withdrawal, which was calculated using a Cox proportional hazards model for 6 or 12 SQ-HDM vs. placebo. Sample size was calculated based on 80% power and a statistical significance level of 10% (two-sided).

3. Results and discussion

To compare CompEx and the ATS/ERS adapted moderate/severe definition used in the MITRA trial, the primary outcome of the MITRA trial, i.e. time to first moderate/severe asthma exacerbation, was re-analysed to express the time to first CompEx event. Table 1 shows the results from the analysis of time to first asthma exacerbation during the MITRA trial using either the ATS/ERS adapted definition of moderate/severe exacerbations or CompEx. Results based on CompEx confirmed the primary outcome of the MITRA trial, thus cross validating both measures of exacerbations. CompEx resulted in a higher exacerbation frequency for 12 SQ-HDM and placebo combined compared to moderate/severe events, with event frequencies of 25% vs. 19% for the 3-month assessment period and 34% vs 28% for the 6-month assessment period. HRs were comparable between moderate/severe exacerbations and CompEx. Analyses comparing the time to first event for 12 SQ-HDM and placebo resulted in lower p-values for CompEx when compared to moderate/severe events. Similar results were seen with the lower dose of the HDM SLIT-tablet (6 SQ-HDM, Table 1). The increase in events and similarities in HR resulted in an approximately 30% reduction in the number of patients needed per group for CompEx compared with the moderate/severe definition. Overall, the increased event rate after 3 months of ICS reduction combined with the lower p-values imply that using CompEx could allow conduct of an allergic asthma trial with a shorter duration or fewer subjects, while still maintaining statistical power. The CompEx event frequencies calculated for the MITRA trial were generally higher than event frequencies found in Fuhlbrigge et al., which may be ascribed to the ICS reduction/withdrawal period included in the MITRA trial design. Reducing or withdrawing ICS from patients is likely to cause an increase in asthma exacerbations and therefore also increase sensitivity in a clinical trial seeking to assess prevention of asthma exacerbations. For this reason, asthma status was carefully monitored during the entire trial, and ICS was reinstated when necessary as judged by the investigator.

4. Conclusion

In the current study, we sought to investigate the usability of CompEx beyond the trials initially analysed, and compare CompEx results with the primary results obtained in the MITRA trial. We verified

that CompEx could be a valuable tool for assessing asthma exacerbations in clinical trials and establishing the therapeutic potential of a treatment. Furthermore, the results obtained mimicked and strengthened those originally obtained during the MITRA trial using the ATS/ERS adapted moderate/severe definition.

Conflicts of interest

GE has lectured or received honoraria from ALK, Airsonett and AstraZeneca, HN, CL and BR are employed by ALK, JCV has participated in advisory boards, lectured or received honoraria or grants from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed, Altana, Pfizer, Revotar, Sandiz-Hexal, Stalergens, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila, Regeneron, Roche, Sanofi-Aventis, Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern and possibly others.

Funding

The trial included in this study was sponsored by ALK.

Acknowledgements

The authors thank Maria Abildgaard Steffensen for medical writing assistance.

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