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Extended Research Article

Establishing the best step-up treatments for children with uncontrolled asthma despite inhaled corticosteroids: the EINSTEIN systematic review, network meta-analysis and cost-effectiveness analysis using individual participant data

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Scientific summary

Establishing the best step-up treatments for children with uncontrolled asthma despite inhaled corticosteroids: the EINSTEIN systematic review, network meta-analysis and cost-effectiveness analysis using individual participant data

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Scientific summary

Background

In the UK, asthma remains a common medical condition affecting over 1 million children, one of the highest prevalence rates worldwide. Asthma is characterised by wheezing, breathlessness, chest tightness, cough and can affect the child's quality of life (QoL) by limiting daily activities and causing acute attacks. In the UK, it was estimated that one child is admitted to the hospital every 20 minutes because of an asthma attack. Following a diagnosis of asthma in a child, a stepwise approach to treatment should be taken. The initial level of treatment consists of using a low-dose inhaled corticosteroid (ICS) to prevent symptoms and a short-acting β_2-adrenoceptor agonist for relieving symptoms. However, around 10–15% of children have inadequate control of asthma symptoms with a low dose of ICS. The target of asthma management is to control the disease through complete control defined as (a) no daytime symptoms, (b) no night-time awakening due to asthma, (c) no need for rescue medication, (d) no asthma attacks, (e) no exacerbation, (f) no limitations on activity, including exercise, (g) normal lung function, (h) minimal side effects from medication. Hence, when asthma remains uncontrolled, a series of further steps are followed. These consist of a treatment step-up by including add-on preventer therapies, such as long-acting β_2-agonists (LABAs) or leukotriene receptor antagonists (LTRAs), an increase of the dose of ICS, or adding sustained-release theophylline.

Choosing the best step-up treatment becomes a crucial decision to prevent exacerbation occurrence and avoid poor asthma control, improve the QoL of patients and their families, and optimise the use of NHS resources. No clear preferential option for initial step-up exists. Moreover, there is substantial heterogeneity among individuals in the treatment response.

Objectives

The overall aim of the EINSTEIN study was to identify and synthesise all evidence from randomised controlled trials (RCTs) using individual participant data (IPD) to evaluate the clinical effectiveness of pharmacological treatments to use in children with uncontrolled asthma on ICS. A further aim was to identify and evaluate the potential for treatment effect modification to optimise treatment delivery and maximise patients' informed treatment choice. We assessed the cost-effectiveness of treatments by developing an economic model to estimate the incremental cost per quality-adjusted life-year (QALY) gained.

Methods

We carried out a systematic review and IPD network meta-analysis (NMA) – supplemented with aggregate data (AgD) – of RCTs in children (< 12 years) and adolescents (12–17 years) with asthma uncontrolled on ICS, and a Markov-based economic model. A comprehensive search strategy was developed with an information specialist. We searched MEDLINE, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, National Institute for Health and Care Excellence (NICE) Technology Appraisals, and the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) series for RCTs of interventions. The reference lists of existing clinical guidelines, along with included studies and relevant reviews, were checked to identify further relevant studies. Unpublished studies were located by searching across a range of clinical trial registries, including internal trial registers for pharmaceutical companies. Only articles in the English language were considered. Studies were eligible if they were parallel or crossover RCTs of any duration and level of blinding comparing at least one of the health technologies of interest; they included participants aged under 18 years with uncontrolled asthma on any dose ICS alone at the screening visit; they considered the following pharmacological treatments at any dose and with any inhaler device: ICS (beclometasone dipropionate; ciclesonide; fluticasone propionate and fluticasone furoate; budesonide; mometasone), LABA (formoterol; salmeterol; vilanterol), LTRA (zafirlukast; montelukast) and theophylline. Study screening was conducted independently by two reviewers using a consensus procedure for disagreements, and one reviewer

performed data extraction and risk-of-bias assessment (using the Cochrane Risk Of Bias tool), which was confirmed by a second reviewer for a sample of studies. We contacted the first author or sponsor of each included trial to request anonymised IPD, metadata and relevant documentation (protocol and blank case report forms) for the respective trial. When IPD was unavailable, we supplemented the missing data with AgD from publications where possible.

Primary outcomes of interest were *exacerbation* and *asthma control* measured by a validated test [asthma control test (ACT), asthma control questionnaire (ACQ)]. Secondary outcomes included *quality of life*, *mortality*, *forced expiratory volume in 1 second (FEV_1)*, *adverse events (AEs)*, *hospital admissions*, *costs*, *resource use* and *utilities* to inform the economic model. We had initially planned to include the outcome '*symptoms*'. Still, we abandoned this before conducting any analyses because it can be challenging to interpret symptoms in isolation. It was likely that many of the individual symptoms would have contributed to the asthma control outcome, with the rationale of a control score being to provide a summary of these symptoms.

We categorised ICS dose as 'Low', 'Medium' and 'High' according to Global Initiative for Asthma guidelines and conducted three separate analyses, subject to data availability: (a) comparison of treatment classes with ICS dose grouped when combined with LABA; (b) comparison of treatment classes with ICS dose stratified (Low, Medium, High) when combined with LABA; (c) comparison of individual treatment compounds. We used odds ratio (OR) as the measure of treatment effect for binary outcomes and mean difference (MD) as the measure of treatment effect for continuous outcomes.

We carried out pairwise meta-analyses (MAs), NMA and network meta-regression (NMR) analyses [fixed-effect (FE) and random-effects (REs) models] in a Bayesian framework using the R package (The R Foundation for Statistical Computing, Vienna, Austria) 'multinma' based on Stan. We examined model fit by the posterior mean of the residual deviance and the deviance information criterion to select models. Pairwise MA and NMA were also carried out with a frequentist framework using the R functions 'netmetabin' and 'netmeta'. An inverse variance model was used with a generalised methods of moments estimate of the between-studies variance. NMA models were multilevel models that combined IPD and AgD and accounted for correlation between treatment effects from multiarm trials. The between trial variance was assumed to be constant across all comparisons in the network. Inconsistency models and sensitivity analyses to explore the impact of exacerbation data collection approach and data availability bias were carried out, and we created dev–dev plots. To explore whether participant characteristics modify the treatment effects, we fitted Bayesian NMR models that included treatment by covariate interactions for the outcomes: *exacerbation*, *asthma control* and *FEV_1*. The following covariates were studied: age, sex, ethnicity, eczema, baseline severity (based on baseline FEV_1% predicted) and eosinophilia. We applied one NMR model for each outcome and covariate combination in turn.

A cost–utility analysis with a 12-month time horizon, which adopted the perspective of the NHS and Personal Social Services in the UK, was undertaken to compare alternative treatments for children with uncontrolled asthma despite ICSs. A literature review was performed to identify a suitable model structure and data requirements for a decision analysis to simulate resource use and health outcomes associated with asthma treatment. A Markov state transition model was developed, with probabilities of transitioning among four health states representing asthma being controlled, uncontrolled, asthma exacerbation and death from asthma exacerbation. Transition probabilities pertaining to low-dose ICS were adjusted by relative risks for asthma control and exacerbations for alternative treatments, derived from a NMA. Health state utilities were identified from literature sources. Costs comprised direct medical expenditures based on patients' use of primary and secondary care services and personal and social services. The model was based on weekly cycles with a half-cycle correction to account for events and transitions occurring at any point of the cycle. Cost-effectiveness was based on incremental costs per QALYs gained. One-way sensitivity analyses were conducted to assess the stability of the incremental cost-effectiveness ratio (ICER) to different assumptions or ranges of parameter estimates. A number of analyses were undertaken to assess the impact of structural uncertainty on the base-case ICER. A probabilistic sensitivity analysis was performed with Gamma distributions specified for utility scores; log-normal distributions for items of resource use and beta distributions to FE and RE Bayesian probabilities. The joint uncertainty in costs and QALYs was assessed using a Monte Carlo simulation with 10,000 replicates. A cost-effectiveness curve was generated to depict the probability of each intervention being cost-effective at different willingness-to-pay thresholds.

Results

We identified and screened 4708 publications from the search and retrieved 508 full-text articles for eligibility assessment. We confirmed 144 RCTs as meeting the eligibility criteria for this review and attempted to contact the trial owner for all studies. We could not identify a contact for 4 studies; 46 did not reply; 41 refused access to IPD; 24 agreed to provide IPD, but the legal terms of the data-sharing contract could not be agreed upon between the NIHR and the trial sponsors. We obtained IPD from 29 (20%) of the eligible trials contributing data for 5494 eligible participants and were able to extract limited AgD from a further 19 (13%) of the trials without IPD. The majority of trials included in the analyses had a low risk of bias overall.

The Bayesian NMA suggests that ICS Medium + LABA reduces the odds of exacerbation [OR 95% credibility interval (CrI): 0.44 (0.19 to 0.90); 40 studies, 8168 patients] and increases FEV_1 [MD 95% CrI: 0.71 (0.35 to 1.06); 23 studies, 2518 patients] compared to ICS Low and also compared to ICS Medium [MD 95% CrI: 0.69 (0.33 to 1.05); 23 studies, 2518 patients] and ICS High [MD 95% CrI: 0.54 (0.24 to 0.81); 23 studies, 2518 patients]. LTRA is the least preferred. We could not find clear differences between treatments for asthma control measured by the ACT/ACQ test (16 studies, 3027 patients). Sensitivity analyses did not change conclusions.

We could not conduct NMA for any other outcome due to data limitations. Direct pairwise MA of a limited subset of two trials suggests a reduction in the mean QoL score, measured by the paediatric asthma QoL questionnaire (PAQLQ), for ICS + LABA compared to ICS medium [MD 95% confidence interval (CI) −0.91 (−1.53 to −0.29)], although the upper limit of the 95% CI includes values that would not be considered clinically important. There is insufficient evidence to conclude any further differences in QoL amongst the pairs of treatment classes for which we had sufficient data available.

The hospitalisation rate due to an asthma attack ranged from 0.5% of patients to 2.7% of patients across five trials, but data were too limited to perform MA.

There was considerable heterogeneity in the recording and coding of AEs data across studies. Slightly fewer patients reported neurological disorders (graded as mild or moderate) on ICS + LABA [one patient (4.3%)] compared to ICS + LTRA [seven patients (33.3%)] in one study [OR, 95% CI: 0.09 (0.01 to 0.82)], and a greater number of patients reported neurological disorders for ICS Medium compared to placebo in three studies [OR, 95% CI: 4.8 (1.12 to 20.60)]. There were no other notable differences in AEs, but analyses were limited by data availability and heterogeneity. There were no deaths recorded in any of the trials. We did not find convincing, consistent evidence to suggest that any of the patient characteristics (*age*, *sex*, *ethnicity*, *eczema*, *eosinophilia*, *asthma severity*), which we examined in exploratory NMR analyses, would be regarded as an effect modifier that is adequately supported by robust statistical evidence and clinical rationale. We cannot rule out the possibility of data availability bias but have tried to mitigate this risk by including both IPD and AgD in analyses wherever possible.

In the base-case analysis, ICS Low was the cost-effective option; ICS Medium (alone or + LABA) were not cost-effective, with ICERs of £232,500 and £310,000 per QALY gained, respectively. ICS High, ICS + LTRA and LTRA monotherapy were dominated by alternatives which were less costly and associated with more QALYs. Sensitivity analyses indicated that changes in utilities had an inconsequential effect on the ICERs, while varying the transition probabilities associated with the controlled and exacerbation states by ± 50% concurrently for all treatments resulted in ICS Medium becoming cost-effective at £15,102 per QALY gained. When the costs of branded inhalers were reduced individually by 50%, potentially reflecting a generic alternative, the ICER for ICS Medium + LABA reduced considerably but remained non-cost-effective. All the comparators to ICS Low remained non-cost-effective in the analysis of structural uncertainty. At willingness-to-pay thresholds of £20,000 and £30,000 per QALY, ICS Low had 0.45 and 0.44 probabilities of being cost-effective, respectively. ICS Medium had lower probabilities of 0.20 at £20,000 and 0.21 at £30,000 per QALY; while ICS Medium + LABA was the least likely of being cost-effective, with probabilities of 0.07 and 0.09 at the £20,000 and £30,000 per QALY thresholds, respectively.

Conclusions

Overall, we conclude that ICS Medium + LABA would be the recommended step-up treatment for children with asthma that is not well controlled on ICS and that LTRA alone should be avoided. There is very little evidence available on which to make conclusions regarding ICS + Theophylline and insufficient evidence at this time to suggest that treatment effect is modified by patient characteristics (age, sex, ethnicity, eczema, eosinophilia, asthma severity), although further research is recommended. The economic analysis indicated that ICS Low was the most cost-effective treatment, while ICS Medium (alone and + LABA) were associated with the highest number of QALYs; however, they did not meet the criteria to be cost-effective.

Study registration

This study is registered as PROSPERO CRD42019127599.

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