Quantitative comparison of different inhaled corticosteroids in the treatment of asthma in children aged 5-12

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Abstract

Objective: Inhaled corticosteroids (ICS) are recommended by the Global Initiative for Asthma for the treatment of steps 2-3 childhood asthma. However, the difference in efficacy between these different ICS drugs is not clear. The main purpose of this study was to compare the efficacy of different ICS drugs in the treatment of childhood asthma and to provide effective quantitative information for guiding their use.

Methods: We searched PubMed and EMBASE for randomized controlled trials of ICS in the treatment of childhood asthma. Using forced expiratory volume in the first second (FEV_1) as the efficacy index, a time-course model of ICS drugs was constructed. Related influencing factors were also investigated. Important pharmacodynamic parameters, such as maximum efficacy and onset time of each ICS, were calculated to reflect their differences in efficacy characteristics.

Results: A total of 6 studies involving 2237 children were analyzed, including five arms of BUD (456 subjects), three arms of CIC (876 subjects), two arms of FP (352 subjects), one arm of MF (197 subjects), and three arms of FF (356 subjects). Since the study was limited by the data collected, pharmacodynamic models could only be constructed for BUD and CIC. The results showed that there was no significant difference in the maximum efficacy between BUD and CIC, and that the E_{max} values of the percentage change in FEV_1 were 17.4 (95% CI: 16.9, 17.9)%. The ET_{50} of CIC and BUD was 1.23 (95% CI: 0.76, 1.70) weeks and 2.97 (95% CI: 1.8, 4.14) weeks, respectively. Compared with the 95% confidence intervals of BUD and CIC, FP had the highest efficacy, MF had the lowest efficacy, and the efficacy of FF was comparable to that of BUD and CIC.

Conclusion: In this study, the efficacy of five ICS drugs was quantitatively compared,

providing necessary information for the implementation of medication guidelines for steps 2-3 asthma in children.

Key words: Asthma, children, model-based meta-analysis, Inhaled corticosteroids, budesonide, ciclesonide

Introduction

Asthma is one of the most common chronic diseases in children [1]. Wheezing, shortness of breath, chest tightness, and cough are the primary symptoms seen in asthmatic patients. According to the Global Initiative for Asthma (GINA), asthma in patients aged 6-11 years is divided into five steps, with step 5 being the most severe. When the child has symptoms twice a month or more but less than daily, it was considered Step 2; when the child had symptoms on most days or waked up at least once a week, it was considered Step 3. Daily inhaled corticosteroids (ICS) were recommended by GINA as the first choice for the treatment of steps 2 to 3 asthma in children.

The ICS listed in GINA included budesonide (BUD), ciclesonide (CIC), fluticasone furoate (FF), fluticasone propionate (FP), and mometasone furoate (MF). However, GINA has not quantitatively compared the efficacy of these different ICSs. Although Kramer [2] and others have reviewed and compared the efficacy and adverse reactions of CIC and other ICS in the treatment of childhood asthma, this study only made a qualitative summary of the literature conclusions and lacked quantitative results, which could not fully guide clinical rational drug use.

Model-based meta-analysis (MBMA) is a combination of modeling and meta-analysis, which can fully utilize the information contained in multiple studies and reduce potential bias. It not only provides an important basis for decision-making in all key aspects of drug research and development, but also provides effective information for clinical practice and rational drug use [3-4]. At present, this method has gradually become an important method in the strategy of model-informed drug development (MIDD). In this study, the MBMA method was used to quantitatively analyze the efficacy characteristics and influencing factors of ICS in the treatment of children with step 2 to 3 asthma based on extensive literature data, so as to provide necessary quantitative information for medication guidelines. At the same time, the prediction results of ICS obtained by the model could also provide reliable external control for relevant clinical trials to save valuable clinical trial resources for children [5-6].

Methods

Data sources

Randomized controlled trials of ICS drugs used alone in the treatment of childhood asthma were retrieved from PubMed and EMBASE databases. The retrieval date was up to October 31, 2019, and the language was limited to English. The specific search strategy is presented in the Appendix.

Inclusion and exclusion criteria

The inclusion criteria of this study were (1) randomized controlled trials; (2) subjects were 5-12 years old children with asthma; (3) treatment drugs were ICS alone, including BUD, CIC, FF,

FP, MF, beclometasone dipropionate, and triamcinolone; and (4) forced expiratory volume in the first second (FEV_1).

Exclusion criteria: (1) the subjects had refractory asthma, (2) the subject had other diseases, (3) preventive administration, (4) treatment in acute exacerbation, (5) no baseline FEV_1 was reported, and (6) crossover trial and no data from the first cycle were reported.

Data extraction

Relevant data in the following categories were extracted from the included studies: (1) literature information (author, year of publication, clinical trial registration number, etc.), (2) trial information (drug name, dose, inhaler type, sample size, treatment duration, the blinding method, including the run-in period, etc.); (3) characteristics of subjects (average age, male ratio, baseline of FEV_1, etc.), and (4) outcome measures (the change rate of FEV_1 at each visit point compared with baseline).

The data were extracted independently by two researchers, and the dispute was resolved by a third researcher. When inputting graphics data, the software Engauge Digitizer (version 4.1) was used for data extraction. If the extraction errors of the two researchers are more than 2%, the data should be extracted again, and the average value should be taken as the final result.

Model building

The preliminary data exploratory analysis results showed that the change rate of FEV_1 compared with baseline increased with time and finally reached a plateau. This data feature conformed to the typical E_{max} model (Formula 1) [7], which contains two important parameters, E_{max} and ET_{50}.

$$E_{Typical} = \frac{E_{max} \times Time}{ET_{50} + Time} \qquad \text{formula 1}$$

In Formula 1, $E_{Typical}$ is the typical efficacy value, E_{max} is the maximum efficacy of the drug, and ET50 is the time when half maximal efficacy is achieved, which reflects the speed of drug onset.

The inter-study variability (η) of the model parameters was described by an exponential model

$$P_i = P_{TV} * \exp(\eta_i) \qquad \text{formula 2}$$

In formula 2, P_i is the model parameter of the i-th study, P_{TV} is the typical value of the model parameters, and η_i is the inter-study variability, which is assumed to be normally distributed with a mean of 0 and a variance of ω_1^2.

The residual error (ε) can be used to express the unexplained variations. In this study, an additive model is selected to explain the residual error (Equation 4):

$$E_{i,j} = E_{Typical,i,j} + \frac{\varepsilon_{i,j}}{\sqrt{N\,i,j/100}} \qquad \text{formula 3}$$

In Formula 3, $E_{i,j}$ is the observed efficacy of the i-th study at the j-th time point, $E_{predict,i,j}$ is the predicted efficacy of the i-th study at the j-th time point, and $\varepsilon_{i,j}$ is the residual error of the i-th study at the j-th time point. $N_{i,j}$ is the sample size of the i-th study at the j-th time point. The residual error $\varepsilon_{i,j}$ will be corrected by the sample size (the sample size is standardized to 100); that

is, the larger the sample size, the smaller the residual value. $\varepsilon_{i,j}$ is assumed to be normally distributed with a mean of zero and a variance of $\sigma^2/ N_{i,j}$.

The covariate model was established to investigate the potential influencing factors of model parameters, including age, type of drug, dose, and baseline FEV_1. For a covariate with a missing proportion of no more than 30%, the missing information was imputed using the median value of this covariate, while covariates with a missing proportion of more than 30% were not considered during covariate evaluation. Categorical covariates were modeled according to Formula 4, while continuous covariates were tested using formula 5-6.

$$P_i = P_{Typical} + COV \times \theta_{cov} \quad \text{formula 4}$$

$$P_i = P_{Typical} + (COV - COV_{median}) \times \theta_{cov} \quad \text{formula 5}$$

$$P_i = P_{Typical} \times \left(\frac{COV}{COV_{median}}\right)^{\theta_{cov}} \quad \text{formula 6}$$

In formula 4-6, P_i represents the model parameters at different covariate levels, and $P_{Typical}$ represents the typical values of the model parameters. COV is the value of the covariate, COV_{median} is the median of the continuous covariate, and θ_{cov} is the correction coefficient of the introduced covariate to the model parameters.

Each covariate was screened in a stepwise manner based on differences in the objective function value (OFV) between hierarchical models. A difference in the OFV of 3.84 (χ^2, $\alpha = 0.05$, df = 1) and 6.63 (χ^2, $\alpha = 0.01$ df = 1) during the forward inclusion and backward deletion steps were considered statistically significant.

Model evaluation

During model establishment, the choice between alternative models was based on the plots of goodness of fit [8], changes in OFV, and relative standard errors (RSEs) of the model parameters. The bootstrap [9-10] method is used to evaluate the stability of the model by comparing the distribution of model parameters obtained after 1000 repeatable samplings with the original model parameters. A visual predictive check (VPC) [11-14] was used to validate model prediction performance. VPC was plotted using a 95% confidence interval based on 1000 times using Monte Carlo simulation of the final model.

Analysis software

The modeling and simulation process was performed by NONMEM (Version 7.4, Icon Inc, PA, USA), and first-order conditional estimation (FOCE) was used to estimate the model parameters. R software (version 4.0.2) was used for the statistical analysis and visualization of results.

result

Data characteristics

Finally, 6 articles including 16 arms of 2237 subjects were included in the analysis [15-20], namely: five arms of BUD (sample size 456), one arm of MF (sample size 197), three arms of CIC (sample size 876), two arms of FP)(sample size 352), and three arms of FF (sample size 356). Beclomethasone dipropionate and triamcinolone acetonide were not included in the analysis. The literature selection process is illustrated in Figure 1.

In the included studies, the sample size per arm was 17-416 (median, 118), and the median treatment duration was 12 weeks. All trials were blinded. All patients had mild to moderate asthma, and all inhalers were pressurized metered-dose inhalers (pMDIs).The average age of the subjects was 7.9-9.7 years, the male ratio was 58.2%–67.7%, and the average baseline FEV_1 was 1.31-1.77L. Detailed trial information are shown in Table 1.

Model establishment and evaluation

Owing to the lack of data regarding FP, FF, and MF, modeling and analysis could not be done for these ICS. This study only built models for BUD and CIC. Upon covariant screening, only the type of drug (BUD or CIC) had a significant impact on ET_{50}, while age, baseline FEV1, and dose using model parameters found no significant impact on ET_{50}. The results show that the typical value of Emax of the final model was 17.4%, the typical value of ET50 of BUD was 2.97 weeks, and that of CIC was 1.23 weeks.

The goodness-of-fit plots for the final model are presented in Figure B. Generally, there was good agreement between the observed (OBS) and population model-predicted (PRED) values as well as between OBS and individual model-predicted (IPRED) values. The conditional weighted residual (CWRES) magnitude was small and randomly distributed around a straight line through 0, and

located within ± 4 °from the center. The above results suggest that there is no obvious bias in the final model. A 1000 bootstrap repeated sampling was used for internal verification, and 999 times of parameter estimations were successful. By analyzing the 999 results, the median of parameter estimation obtained by bootstrap was consistent with that of the original dataset (Table 2), which reflects the stability of model parameter estimation. The VPC results showed that the 97.5% quantile and 2.5% quantile of the model covered most of the observed values well, indicating that the prediction performance of the model was good.

Comparison of typical efficacy

Based on the final model, the typical efficacies of BUD and CIC at 2, 4, 8, and 12 weeks (Table 3) was simulated. The results showed that due to the rapid onset of CIC, the efficacy of CIC was obviously higher than that of BUD at the same time point. At 2 weeks, there was a 3.8% difference in the rate of change in FEV_1. However, with prolonged treatment duration, the difference in efficacy between CIC and BUD decreased, and the rate of change in FEV1 was reduced to 1.9% at 12 weeks.

Because of the few data points of FP, FF, and MF, the measured values of their efficacy were directly compared with the typical values of BUD and CIC. The results showed that the efficacy of FP (DPI) and FP (pMDI) was better than that of BUD and CIC. The efficacy of FF (DPI) was similar to that of BUD but lower than that of CIC, while the efficacy of MF (DPI) was significantly lower than that of BUD and CIC.

Discussion

At present, ICS are the first-line treatment for children with Steps 2 to 3 asthma. However, there are as many as seven kinds of ICS in the market yet there is no comprehensive study to compare the efficacy of these drugs, which confuses clinicians. Due to the limited resources of clinical trials in children, it is not realistic to conduct a comprehensive head-to-head comparison of different ICS through RCT studies. In this study, based on a wide range of literature data, MBMA was used to analyze the efficacy characteristics of different ICS drugs indirectly.

In contrast to a traditional meta-analysis, which only analyzes end-point efficacy, MBMA can analyze the entire time-course of drug efficacy. This study found that although the maximum efficacy of both CIC and BUD was 17.40%, the onset speed of CIC was 1.23 wk, which is faster than that of BUD.

At 5 weeks, CIC can reach 80% of its maximum efficacy, while BUD takes 12 weeks to achieve 80% of its maximum efficacy. CIC reached 80% of its maximum efficacy in 5 weeks, while it took at least 12 weeks for BUD. Due to the rapid onset of CIC, the efficacy of CIC is obviously better than that of BUD for the same treatment duration. However, as the treatment duration increased, this difference gradually narrowed.

It has been reported that the oral bioavailability and affinity to glucocorticoid receptors of CIC metabolites (desisobutyryl-ciclesonide) are higher than those of BUD and that the clearance of CIC is lower than that of BUD, which may be the reason why CIC has a faster onset than BUD [21-22]. Previous studies have shown that although the incidence of adverse events of CIC is similar to that of BUD, the main adverse events of CIC are infection and asthma deterioration. BUD, on the other hand, may cause slower height growth in children [23]. As reported by Von Berg et al., after 12 weeks of medication, the growth of children's height in the BUD group was 0.481 cm lower than that in the CIC group. The above results suggest that CIC is better than BUD in terms of onset and safety, but whether the difference in benefits and risks between CIC and BUD has clinical significance still needs to be determined by clinicians in medical practice.

Due to the limitation of the included data, our study failed to quantitatively analyze the time courses of FP, FF, and MF, and only analyzed the end-point efficacy at 12 weeks. The results showed that the efficacy of the above three drugs at 12 weeks could be roughly divided into three grades. Among them, the efficacy of FP was better than that of BUD and CIC, the efficacy of FF was between that of BUD and CIC, and the efficacy of MF was the lowest. The dose ratio of FP and BUD included in this study was approximately 1:2. A previous study found that the efficacy of FP and BUD in the treatment of adult asthma is almost the same under the above dose ratio [24]. Similarly, another study found that the efficacy of MF (100-200 μg / day) in the treatment of adult asthma is equivalent to that of BUD (400 μg/day) [25]. The conclusions of these trials are contrary to the results of this study, which may have been caused by different populations. FP may be more effective in children, whereas MF may be less effective in children.

This study investigated factors affecting the efficacy of BUD and CIC. However, because of the high homogeneity of the included studies; that is, all the trials were blinded, had a run-in period, and the drug inhalers were pMDI, the influence of the above factors could not be found in

this study. Some studies have pointed out that the impact of MDI with spacers is better [26]. Due to the lack of data, the differences in efficacy caused by different inhalers still need to be further evaluated. In addition, because the included studies were mainly from European and American countries, any racial differences in efficacy need to be further investigated. In terms of dose, BUD doses were 320 μg/day and 400 μg/day, while CIC doses were 80 and 160 μg/day, respectively. The results showed that there was no obvious dose-effect relationship between BUD and CIC within this dose range and that increasing the dose did not significantly improve efficacy. Although GINA guidelines classify the age of children as 6-11 years old, there are only a few studies in the literature having subjects strictly in this age range. Therefore, this study extended the age range of the subjects to 5-12 years of age. Due to the lack of trials involving children, this study only included five arms of BUD and three arms of CIC data for analysis. Nevertheless, homogeneity between the studies was good, and the parameter estimation of the model was stable.

conclusion

In this study, the efficacy characteristics of BUD and CIC in the treatment of children aged 5-12 years and having step 2-3 asthma were quantitatively analyzed. There was a significant difference in onset between BUD and CIC. This study also compared the efficacy of the five ICS drugs at 12 weeks. FP had the best efficacy, whereas MF had the lowest efficacy. The efficacies of CIC, FF, and BUD were between those of FP and MF. The above information provides the necessary quantitative information for the implementation of medication guidelines for steps 2-3 asthma in children.

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