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Safety and efficacy of Yupingfeng granules in children with recurrent respiratory tract infection: A randomized clinical trial

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ABSTRACT

Importance: Recurrent respiratory tract infection (RRTI) is common in children. Inappropriate RRTI treatment will lead to asthma and other diseases, thereby seriously affecting the growth and physical health of children. Immune function modulation can prevent and alleviate childhood RRTI. Yupingfeng (YPF), a patented traditional Chinese medicine (TCM), has immunomodulatory effects and is widely used in China to treat children with RRTI.

Objective: To evaluate the safety and efficacy of YPF monotherapy in treating children with RRTI.

Methods: This multicenter, randomized, double-blind, double-simulation, noninferiority clinical trial was conducted from January 2015 to August 2017, with an 8-week treatment period and 52-week follow-up after the drug withdrawal. Children aged 2–6 years with RRTI meeting the inclusion and exclusion criteria were enrolled in 13 hospitals in China and divided randomly into three groups (2:2:1 ratio) to receive YPF, pidotimod, or placebo. The primary outcome was the proportion of RRTI returning to normal standard level during the follow-up. The secondary outcomes were reduction in the number of RRTI recurrences, effect on clinical symptoms (in accord with TCM practice), effect per symptom, and safety. The trial was registered at the Chinese Clinical Trials Registry (www.chictr.org.cn) under the unique identifier ChiCTR-IPR-15006847.

Results: Three hundred and fifty-one children were enrolled and randomly assigned to 3 groups; 124, 125, and 61 children in the YPF, pidotimod, and placebo groups, respectively, had completed the trial. During the follow-up, the proportion of RRTI returning to normal standard level was 73.13%, 67.15%, and 38.81% with YPF, pidotimod, and placebo, respectively ($P < 0.0001$). The proportion of cases who returned to normal

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standard level in the YPF group was 34.32% higher than that in the placebo group. The safety profile did not significantly differ among the groups.
Interpretation: YPF granules were noninferior to the active control drug pidotimod oral solution for the treatment of RRTI in children, and were superior to placebo, with a high safety profile.

KEYWORDS
Pidotimod, Recurrent childhood respiratory tract infection, Traditional Chinese medicine, Yupingfeng

INTRODUCTION

Recurrent respiratory tract infection (RRTI) is a common childhood disease in China,[1–4] with an incidence rate of 8.9%–18.7%. RRTI refers to the frequency of upper or lower respiratory tract infections exceeding a certain range within a year.[5]

An immature immune system, which is common during childhood,[6] may increase the risk of RRTI. Currently, there is no consensus on a treatment strategy for RRTI. Immunomodulators, including pidotimod, are commonly used against RRTI. Yupingfeng (YPF) is a traditional Chinese medicine (TCM) available as compounded granules. Recently, a number of basic studies have confirmed that YPF powder (mainly composed of *Astragalus* [Huangqi], *Atractylodes* [Baizhu], and *Saposhnikovia divaricata* [Fangfeng]) or its extract can significantly improve specific and nonspecific immune function.[7–10] It shows immunomodulatory and anti-inflammatory effects and is widely used in China to treat children with RRTI.[11–13] YPF is primarily used as an adjuvant therapy combined with other immunomodulators for treating children with RRTI.[14–16] Previous studies on YPF monotherapy for children with RRTI were mostly single-centered and limited by a small number of patients; additionally, the trial designs were not adequately detailed.[17,18] In this milieu, we performed a multicentered randomized, double-blind, noninferiority, three-arm study to evaluate the safety and efficacy of YPF monotherapy in treating children with RRTI.

METHODS

Ethical approval

This study was approved by the ethics committees of Beijing Children's Hospital, Capital Medical University (2014-Y-004-C), the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (TYLL2014-Y-016), Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-A-2015-001-2), Children's Hospital Affiliated to Zhejiang University School of Medicine (2014-IEC-017), Children's Hospital of Chongqing Medical University (2015-2), Guangdong Maternal and Child Care Hospital (2015-005), and Liaocheng People's Hospital (2015-008). All procedures were in accordance with Good Clinical Practice and Helsinki Declaration. Written informed consent was obtained from the guardians of the children. The trial was registered at the Chinese Clinical Trials Registry (www.chictr.org.cn) under the unique identifier ChiCTR-IPR-15006847. The trial was registered before the first case was enrolled.

Trial design and study participants

We conducted a multicenter, randomized, double-blind, double-simulation, noninferiority clinical trial to evaluate the safety and efficacy of YPF granules in treating children with RRTI (YPF-RRTI). The study period was from January 2015 to August 2017. Thirteen tertiary hospitals in East, North, South, and Central China participated in this trial.

TABLE 1 Criteria for determining recurrent respiratory tract infection (RRTI)

Age (year)	RRTI (times/year)	Recurrent lower respiratory tract infection (times/year)	
		Recurrent tracheobronchitis	Recurrent pneumonia
0∼2	7	3	2
∼5	6	2	2
∼14	5	2	2

(1) The interval between infections should be at least 7 days. (2) RRTI is divided into recurrent upper respiratory tract infection and recurrent lower respiratory tract infection. The diagnostic criteria number of RRTI can include both the number of upper and lower respiratory tract infections, while the diagnostic criteria number of recurrent lower respiratory tract infections only refers to the number of occurrences of lower respiratory tract infections. (3) The determination times should be observed continuously for 1 year. (4) Recurrent pneumonia refers to recurrent pneumonia twice within a year. Pneumonia must be confirmed by lung signs and imaging. During two diagnoses of pneumonia, the signs and imaging changes of pneumonia should completely disappear.

Eligible children with RRTI were prospectively assessed by a pediatrician in each hospital. The inclusion criteria (Table 1), based on guidelines published by the Subspecialty Group of Respiratory Diseases of the Chinese Medical Association,[5] were as follows: children diagnosed with RRTI; 2–6 years old; no acute infection, or having fully recovered from acute infection for no less than 1 week; and symptoms in accord with exterior deficiency syndrome category outlined in TCM (Table 2). The exclusion criteria were as follows: pediatric patients with primary immunodeficiencies, congenital lung and pulmonary airway malformation, gastroesophageal reflux disease, bronchopulmonary dysplasia, congenital heart disease, malnutrition, rickets, anemia, bronchial asthma, and/or other underlying diseases; immunosuppressants, immunopotentiators, or other methods used to treat RRTI within the last month; alanine aminotransferase level 1.5 times greater than the normal upper limit, or creatinine (Cr) level exceeding the normal upper limit; allergic to study drugs, or to more than one type of food or drug; not suitable for the trial or unable to complete the trial; and have participated in other clinical trials within past 3 months.

Three hundred and sixty-one pediatric patients meeting the inclusion/exclusion criteria were identified; 351 of these patients' guardians signed the informed consent and were enrolled in the study. The enrolled patients were randomly assigned to three groups: the YPF group, pidotimod group, and placebo group. A flowchart outlining the design of this study is shown in Figure 1.

Diagnosis of exterior deficiency syndrome

Exterior deficiency syndrome refers to *Guidelines for Diagnosis and Treatment of Common Diseases of Pediatrics in Traditional Chinese Medicine (2012)*.[19] Primary symptoms: 1) aversion to the wind, 2) spontaneous sweating, and 3) shortness of breath. Secondary symptoms: 1) pale complexion, 2) weak breathing and lazy to talk, 3) poor appetite, 4) thinness, and 5) sloppy stool. Images of tongue, pulse, and fingerprints: 1) pale tongue, 2) thin white tongue coating, and 3) weak pulse and pale fingerprints.

TABLE 2 Quantitative criteria of TCM syndrome grading

Symptoms	(−)	(+)	(++)	(+++)
Main Symptoms	0 point	2 points	4 points	6 points
Aversion to wind	–	Slightly aversion to wind, cuddling in arms	Fear of cold, and need more clothes and quilt	Aversion to cold, without alleviation even putting on more clothes and quilt
Spontaneous sweating	–	Profuse sweating after exercise	Sweating after exercise	Sweating even without exercise
Shortness of breath	–	Shortness of breath after exercise	Shortness of breath after slight exercise	Shortness of breath even without exercise
Secondary symptoms	0 point	1 point	2 points	3 points
Pallor complexion	–	Pale complexion	Lusterless complexion	Pale complexion (usually seen in shock patients)
Lazy to talk	–	Unwilling to talk	Lazy to talk	Reluctant to talk
Poor appetite	–	Unlike to take milk, and food intake 1/3 less than normal	Aversion to eating, and food intake 1/2 less than normal	Refusal to eat, food intake 2/3 less than normal
Thinness	–	Bodyweight loss less than 15% of children of the same age	Bodyweight loss between 15% and 25% of children of the same age	Bodyweight loss more than 25% of children of the same age
Sloppy stools	–	Sloppy stool	Slight watery stool	Watery stool

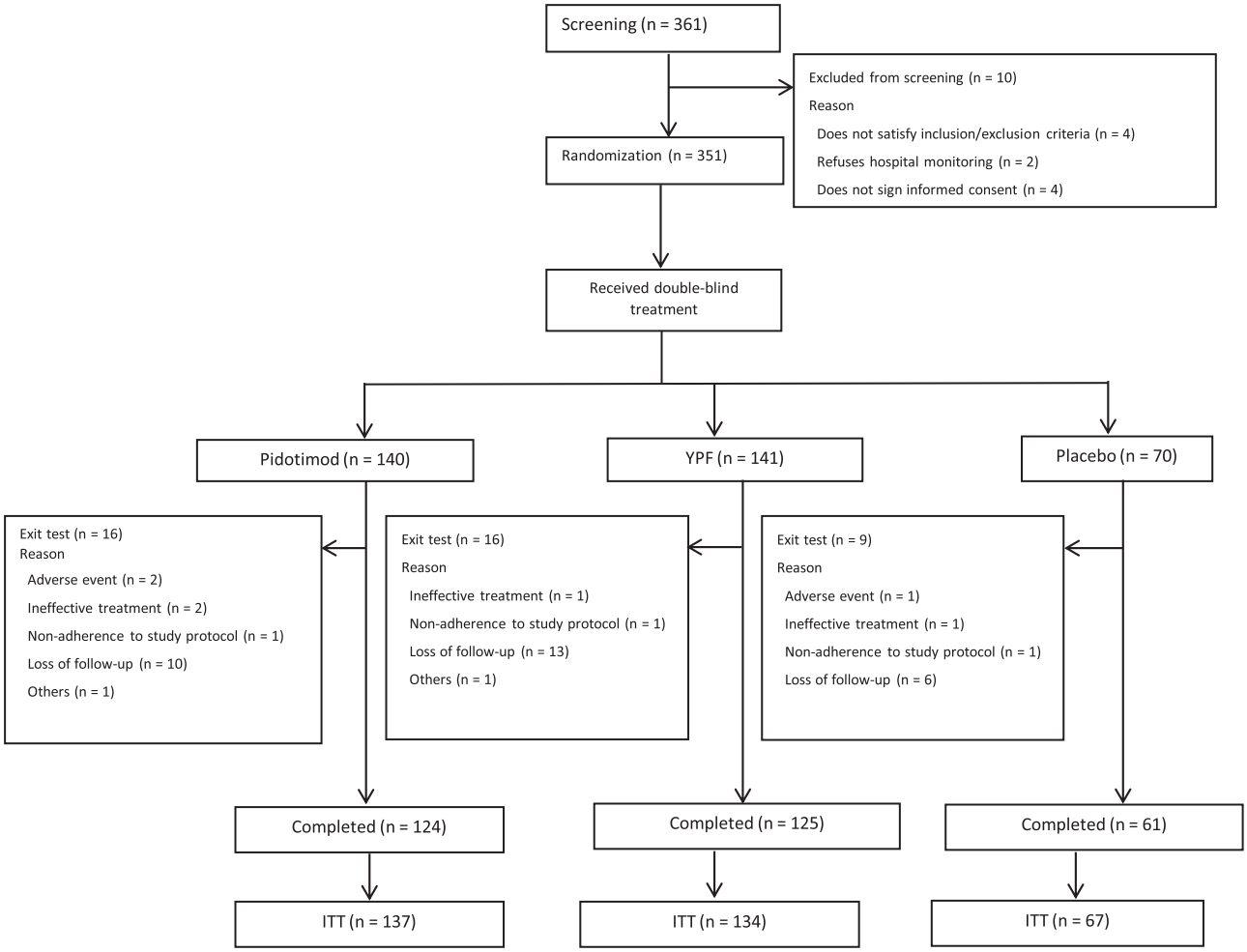

FIGURE 1 A flow chart of children recruited into the study. YPF, Yupingfeng; ITT, intention-to-treat.

Exterior deficiency syndrome can be diagnosed if containing at least two primary symptoms and one secondary symptom, together with the above-mentioned images of tongue, pulse, and fingerprints.

Randomization and blinding

Randomization was performed via a random-code table generated by the clinical-trial-data management and statistical unit. Patients were randomly divided into the YPF, pidotimod, and placebo groups at a ratio of 2:2:1. In this study, double simulation technology was used to make simulants of YPF granules and pidotimod oral solution. The simulants did not contain active ingredients but were consistent with the simulated drugs in terms of appearance, smell, and so forth. The participants in the YPF group were treated with YPF granules and mock pidotimod oral solution, and those in pidotimod group were treated with mock YPF granules and pidotimod oral solution, and the placebo group were treated with mock YPF granules and mock pidotimod oral solution.

If serious adverse events occurred during the trial, emergency unblinding was performed according to relevant procedures.

Sample size calculation

We evaluated the commercially available YPF granules in a randomized, double-blind, noninferiority, multicenter clinical trial. According to previous studies,[20–22] the 1-year follow-up the proportion of RRTI returning to the normal standard level of the control group (8 weeks of treatment) and placebo group was 77.0% and 33.0%, respectively; we hypothesized that these would be 75.0% and 35.0%, respectively. Based on the difference in the proportion of RRTI returning to the normal standard level of the control group and placebo groups, the noninferiority limit was set at 13%. Type I error (α) was set to 0.05 and the power of test $1-\beta$ was set at 80%. Participants, randomly assigned to the three groups at a ratio of 2:2:1, were treated with YPF granules and mock pidotimod oral solution, pidotimod oral solution, and mock YPF granules,

and mock pidotimod oral solution and mock YPF granules (placebo), respectively. We anticipated 118, 118, and 59 participants per group, respectively. Considering an exclusion rate of 20%, 360 participants were enrolled in this study. Intention-to-treat was used for efficacy evaluation, and the Safety Set principle was used for safety evaluation.

Procedures

Patients in the treatment groups were treated with YPF and sham pidotimod oral solution. Patients in the control group were treated with pidotimod and sham YPF granules. Patients in the placebo group were treated with sham YPF granules and sham pidotimod oral solution. YPF granules (or sham YPF granules) were orally administered at 2.5 g to children aged 2–3 years, or at 5 g to children aged 4–6 years; administration was performed once in the morning and once in the evening for 8 weeks. Pidotimod (or sham pidotimod) was orally administered at 400 mg once daily, 1 h after dinner for 8 weeks.

A 12-month follow-up was conducted for all patients after the end of treatment. A patient's diary was provided to the guardians to record any recurrence of respiratory infection. A monthly follow-up visit was performed for all pediatric patients over the phone. Patients with recurrent infections were recalled to the clinic, where the locale, severity, and course of infection were recorded.

Endpoint definition

The primary endpoint was the proportion of RRTI returning to the normal standard level (the normal standard level was defined as the number of respiratory tract infections per year falling below the diagnostic criteria). We hypothesized that the clinical proportion of RRTI returning to the normal standard level of YPF would not be lower than that of pidotimod; the noninferiority limit was set to 13%. The secondary endpoints were: (1) reduction in the number of respiratory tract infections; (2) according to the Guiding principles for clinical research on new drugs of traditional Chinese medicine,[23] the TCM syndrome classification quantitative standard was formulated. According to the severity of the symptom, the symptom was divided into four grades, with 0,2,4,6 points for the main symptom and 0,1,2,3 points for the secondary symptom. Improvement rate (post-treatment syndrome score decreased by ≥70%), assessed using the TCM model; (3) effect of treatment on separate symptoms assessed using the TCM model parameters of cure rate (symptom disappears, score decreases to 0). The TCM syndrome classification quantitative standard is shown in Table 2.

The incidence of adverse reactions was used as an indicator of drug safety; this referred to adverse reactions, irrelevant to treatment purpose, occurring during normal drug administration at normal doses.

Pharmacoeconomics evaluation

We performed a pharmacoeconomic analysis of direct medical costs (including hospital registration, laboratory tests, diagnosis and treatment, medicines, examination, hospitalization, nursing care, and adverse reaction treatment) associated with the use of YPF granules and pidotimod oral solution to treat children with RRTI. The cost-effectiveness analysis was conducted by analyzing the cost-effectiveness ratio and incremental cost-effectiveness ratio of the primary endpoints, respectively. Sensitivity analysis was performed on a 10% price increase of YPF and a 10% price decrease of pidotimod.

Statistical analysis

Quantitative data were described by mean ± standard deviation, and group comparisons were performed using analysis of variance or rank-sum test according to data distribution. Qualitative data were described by frequency and percentage, and the χ^2 test or Fisher's exact probability test was used to compare groups of disordered data, and the rank-sum test was used to compare groups of graded data. The comparison test level among the three groups is $\alpha = 0.05$, that is, $P \leq 0.05$ is considered to be statistically significant, and the pairwise comparison between the groups is corrected by the Bonferroni method, that is, $\alpha' = \alpha$/number of comparisons = 0.0167, that is, the pairwise comparison between groups is 0.0167. $P \leq 0.0167$ for comparison was considered statistically significant. All statistical analyses were performed using SAS v9.3 statistical analysis software (Version 9.3, SAS Institute, USA).

RESULTS

Patient

From January 2015 to August 2017, 361 pediatric patients meeting the inclusion/exclusion criteria were diagnosed at 13 research hospitals; 351 of these patients were enrolled in this study. Among these patients, 141 were randomly assigned to the YPF group, 140 to the pidotimod control group, and 70 to the placebo group. One hundred and twenty-four patients in the YPF group, 125 in the pidotimod group, and 61 in the placebo group had completed the trial.

Baseline demographics of the pediatric patients

The baseline data of the three groups were not significantly different. There were no significant differences in the vital signs, including body temperature, heart rate, respiration, and blood pressure, frequencies of respiratory tract

TABLE 3 Baseline characteristics of pediatric patients in each group

Variables	Group			*P*
	Pidotimod ($n = 137$)	YPF ($n = 134$)	Placebo ($n = 67$)	
Age (years)	4.5 ± 1.3	4.5 ± 1.3	4.4 ± 1.4	0.9201
Number of girls	51 (37.23)	55 (41.04)	30 (44.78)	0.5693
Physical examination				
Height (cm)	106.02 ± 13.31	106.31 ± 12.41	103.84 ± 13.35	0.4163
Weight (kg)	18.55 ± 4.44	19.10 ± 5.31	18.45 ± 4.96	0.6705
BMI (kg/m^2)	16.55 ± 2.93	16.82 ± 3.27	17.13 ± 3.55	0.5976
Body temperature (°C)	36.62 ± 0.25	36.59 ± 0.24	36.61 ± 0.21	0.3905
Heart rate (times/min)	96.13 ± 10.72	97.91 ± 11.04	98.52 ± 10.68	0.3658
Respiration (times/min)	23.61 ± 3.54	23.54 ± 3.44	24.01 ± 2.99	0.3557
SBP (mmHg)	89.77 ± 6.13	90.22 ± 6.48	91.14 ± 6.29	0.3010
Drug allergy	0 (0.00)	3 (2.24)	0 (0.00)	0.1629
STCMS	9.02 ± 3.17	8.65 ± 3.17	9.19 ± 3.12	0.2847
NRTI	9.82 ± 3.35	10.07 ± 3.94	9.31 ± 2.76	0.5905
NURTI	7.54 ± 2.33	7.78 ± 3.06	7.37 ± 2.33	0.8303
NLRTI	2.28 ± 2.30	2.29 ± 2.03	1.94 ± 1.43	0.7498
NBI	1.78 ± 2.10	1.77 ± 1.69	1.52 ± 1.25	0.8347
NLI	0.50 ± 0.72	0.52 ± 0.82	0.42 ± 0.70	0.7003

Data are shown as *n* (%) or mean ± standard deviation. YPF, Yupingfeng; BMI, body mass index; SBP, systolic blood pressure; STCMS, scores of Chinese medicine syndrome; NRTI, number of respiratory tract infections; NURTI, number of upper respiratory tract infections; NLRTI, number of lower respiratory tract infections; NBI, number of bronchus infections; NLI, number of lung infections.

infections, treatment, and the allergic status of the three groups at baseline (Table 3).

The proportion of RRTI returning to normal standard level

With respect to the primary treatment endpoint, the proportion of RRTI returning to normal standard level after 1 year of treatment (total effective rate) of the three groups was as follows: 73.13% for the YPF group, 67.15% for the pidotimod group, and 38.81% for the placebo group ($P < 0.0001$). Pairwise comparisons indicated a significant difference between the YPF group and placebo group and between the pidotimod group and placebo group ($P < 0.0167$). However, the difference between the YPF group and the pidotimod group was not significant (73.13% *vs*. 67.15%, $P > 0.0167$). The difference in the proportion of RRTI returning to the normal standard level between the groups was 5.98% (95% confidence interval [*CI*] 0.0489–0.1685); this did not exceed the pre-established noninferiority limit (13%), indicating that the efficacy of YPF was not inferior to that of pidotimod. Furthermore, the clinical proportion of RRTI returning to the normal standard level of YPF was 34.32% (73.13% *vs*. 38.81%) higher than that of the placebo.

Follow-up situation

During the follow-up, the reduction value of respiratory infections frequency of the YPF and pidotimod groups was substantially higher than that of the placebo group (6.43 times/year *vs*. 6.39 times/year *vs*. 4.38 times/year; $P = 0.0006$) (Table 4). Pairwise comparison of the YPF and pidotimod groups did not show significant differences ($P = 0.9993$).

The curative effect and efficacy of TCM for a single symptom

After 8 weeks of treatment, the improvement rate of the three groups, evaluated using the TCM model, was as follows: 60.45% for the YPF group, 49.64% for the pidotimod group, and 35.82% for the placebo group. YPF granules were superior to pidotimod oral solution in alleviating separate symptoms, as defined by TCM, including aversion to wind and spontaneous sweating (Table 5).

Safety

During the study, 58 adverse events occurred in 43 pediatric patients: 21 adverse events occurred in 17 patients in the YPF group, 23 adverse events occurred in 16

TABLE 4 Reduction value of respiratory tract infection frequency in different groups

Variables	Group			χ^2	*P*
	Pidotimod	YPF	Placebo		
Reduction in the number of respiratory tract infections from baseline to flow-up	6.39 ± 4.67	6.43 ± 4.49	4.38 ± 3.48	14.9108	0.0006†
Reduction in the number of upper respiratory tract infections from baseline to flow-up	4.52 ± 3.72	4.58 ± 3.76	3.21 ± 2.99	12.5789	0.0019‡
Reduction in the number of lower respiratory tract infections from baseline to flow-up	1.87 ± 2.35	1.84 ± 1.94	1.16 ± 1.55	4.8346	0.0892
Reduction in the number of bronchial infections from baseline to flow-up	1.45 ± 2.09	1.34 ± 1.66	0.87 ± 1.35	5.4800	0.0646
Reduction in the number of pneumonia from baseline to flow-up	0.42 ± 0.77	0.50 ± 0.80	0.30 ± 0.76	2.1828	0.3358

Data are shown as mean ± standard deviation. YPF, Yupingfeng.
†Pidotimod group *vs*. YPF group, $P = 0.9993$; Pidotimod group *vs*. Placebo group, $P = 0.0007$; YPF group *vs*. Placebo group, $P = 0.0007$.
‡Pidotimod group *vs*. YPF group, $P = 0.9231$; Pidotimod group *vs*. Placebo group, $P = 0.0014$; YPF group *vs*. Placebo group, $P = 0.0010$.

TABLE 5 Traditional Chinese medicine symptom disappearance rate in different groups

Symptoms	Group			χ^2	*P*	*P1*†	*P2*‡	*P3*§
	Pidotimod	YPF	Placeco					
Aversion to wind	58 (51.79)	74 (67.89)	22 (40.00)	12.7583	0.0017	0.0147	0.1519	0.0006
Spontaneous sweating	59 (43.38)	77 (58.33)	23 (34.85)	11.3692	0.0034	0.0144	0.2467	0.0018
Shortness of breath	50 (60.24)	52 (63.41)	15 (39.47)	6.4858	0.0391	0.6748	0.0335	0.0140
Pale complexion	70 (63.64)	68 (66.67)	24 (42.11)	10.1136	0.0064	0.6437	0.0078	0.0026
Weak breathing and lasy to talk	26 (38.81)	31 (43.06)	10 (25.00)	3.6659	0.1599	/	/	/
Poor appetite	57 (61.96)	55 (63.22)	16 (39.02)	7.6303	0.0220	0.8616	0.0141	0.0102
Thinness	26 (53.06)	23 (56.10)	10 (40.00)	1.7163	0.4239	/	/	/
Sloppy stool	35 (77.78)	41 (89.13)	13 (50.00)	14.0892	0.0009	0.1445	0.0160	0.0002

Data are shown as *n* (%). YPF, Yupingfeng. Disappearance rate = proportion of symptom-free patients after treatment to those with such symptoms at baseline.
†Pidotimod group *vs*. YPF group; ‡Pidotimod group *vs*. Placebo group; §YPF group *vs*. Placebo group.

patients in the pidotimod group, and 14 adverse events occurred in 10 patients in the placebo group. Among these adverse events, three cases were judged to be adverse reactions by the investigator; of these, two occurred in the pidotimod group (epistaxis, rash) and one in the placebo group (nausea and vomiting). Other adverse events were not associated with treatment drugs. No drug-related adverse events occurred in the YPF group, and no serious adverse events occurred during the study period (Table S1).

Pharmacoeconomic analysis

The pharmacoeconomic analysis showed that the total direct medical cost per capita of the total research process in the YPF group was 552.73 ± 173.05 yuan and 956.56 ± 274.32 yuan in the pidotimod group. The difference between the two groups (403.83 yuan) was significant ($P < 0.0001$). The previous results showed that YPF granules were noninferior to the active control drug pidotimod oral solution for the proportion of RRTI returning to normal standard level, and the pharmacoeconomic analysis showed that the YPF group has lower costs per patient (Table 6). Therefore, cost-minimization analysis was adopted, and it showed that YPF granules have obvious economic advantages over pidotimod oral solution in the treatment of children with RRTI. Incremental cost-effective ratio analysis showed that the therapeutic effect of adding one unit in the YPF group was 67.53 yuan less than that in the pidotimod group.

The results of the univariate sensitivity analysis suggested that even if the price of YPF granules was increased by 10% or if the price of pidotimod oral solution was decreased by 10%, the results of the pharmacoeconomic analysis would remain unchanged.

TABLE 6 Total direct medical costs per capita of the total research process (in RMB yuan) for the two groups of pediatric patients

Monitoring indicator	Pidotimod group ($n = 137$)	YPF group ($n = 134$)	Z	P
Drug cost (yuan)	608.31 ± 136.31	151.22 ± 39.88	−12.5910	<0.0001
Examination cost (yuan)	319.30 ± 147.32	321.82 ± 147.99	0.2443	0.8070
Total cost (yuan)	956.56 ± 274.32	552.73 ± 173.05	−10.8399	<0.0001

Data are shown as mean ± standard deviation.

DISCUSSION

To the best of our knowledge, this YPF-RRTI study is the largest multicenter, randomized, double-blind, three-arm trial to evaluate the safety and efficacy of the commercially available YPF granules in treating pediatric patients with RRTI. This was also the first randomized controlled trial to evaluate a patented Chinese medicine for treating children with RRTI. This study was registered at the Chinese Clinical Trial Registry, a first-level registration authority of the International Clinical Trial Registration Platform of the World Health Organization, and was subjected to public scrutiny.

We used a treatment period of 8 weeks and a follow-up period of 52 weeks after the drug withdrawal with good compliance and low loss to follow-up rate. With respect to the preventive treatment outlined in TCM, our results indicate that YPF was effective in preventing RRTI in children. Treatment with YPF was not inferior to that with pidotimod, and superior to that with placebo, in children with RRTI.

After 1 year of treatment, the proportion of RRTI returning to normal standard level, as defined by TCM, was 73.13% and 67.15% in the YPF and pidotimod groups, respectively; these rates were higher than the rate in the placebo group ($P < 0.0001$). Treatment with YPF granules substantially reduced the frequency of RRTI occurrence. These observations agree with those of a recent meta-analysis, indicating that YPF adjuvant therapy increases the total effective rate ($R = 1.44$, 95% CI 1.196–1.75, $I^2 = 87.0\%$, $P < 0.001$) and significantly reduces the average number of RRTI occurrences compared with the effects of conventional treatment.[16] The independent effects of YPF in children with RRTI have been evaluated previously, and the results of these studies agree with those obtained in our study;[17,18,24] however, our study involved a higher number of patients and a longer follow-up period than previous studies.

Our study included the TCM model diagnosis as a part of the study design; this was done to reduce the risk of bias in patient selection. With respect to the TCM model, our results suggest that treatment with YPF was superior to that with pidotimod in alleviating aversion to wind and spontaneous sweating, which highlights the advantages of YPF.

No serious adverse events occurred during this clinical trial. In the YPF group, no adverse events related to the drug were observed. In the pidotimod and placebo groups, we recorded two and one possibly drug-related adverse event, respectively. These results further substantiate the safety of YPF granules in the treatment of children.

The pharmacoeconomic analysis showed that treatment cost in the YPF group was substantially lower than that in the pidotimod group. We found no difference in efficacy between YPF and pidotimod, but treatment with YPF was more economically advantageous than that with pidotimod for children with RRTI. The sensitivity analysis indicated that a 10% fluctuation in the cost of these two drugs would not affect the results of the pharmacoeconomic analysis.

The YPF granule instructions do not indicate a specific dosage for children. Therefore, the dosage of YPF granules for children was based on clinical experience and expert consensus reached before the study. In our study, we verified the safety and efficacy of this dosage in children with RRTI; our results can be used to improve the YPF dosing instructions. We focused on children aged between 2 and 6 years as preschool children are most likely to develop RRTI due to immune system immaturity and cross infections occurring in kindergartens.

We selected pediatric patients with nonacute RRTI primarily because YPF is an invigorating drug. Applying symptomatic treatment in acute conditions and radical treatment in nonacute conditions,[25] treating excess syndrome with purgative methods and deficiency syndrome with tonifying methods[26] are both included in the diagnosis and treatment principles of TCM. Pediatric patients with the acute disease are subject to remaining pathogenic factors that must be fully eliminated before strengthening the vital *qi* (healthy *qi*) of these patients. Conversely, if a tonifying method is used in patients with acute disease, it causes retention of pathogenic factors, thereby aggravating the disease. Consequently, based on the characteristics of YPF, pediatric patients with the nonacute disease were deemed suitable for this study.

Our study had some limitations. Legal guardians of pediatric patients show relatively low acceptance for using a placebo; this can affect patient compliance. Therefore, in this study, we used a 2:2:1 ratio instead of the more efficient 1:1:1 ratio, among the three groups. Additionally, we did not evaluate immunological indicators such as immunoglobulin levels and T-lymphocyte subsets. Last, the enrolled pediatric patients were aged between 2 and 6 years; therefore, our results cannot be extrapolated to evaluate children with RRTI of all ages. However, this study can be used as a reference for the use of YPF in children of other ages.

In conclusion, this YPF-RRTI study has shown that YPF granules are effective and safe for the treatment of children with RRTI.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

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