Effects of methylprednisolone or immunoglobulin when added to standard treatment with intravenous azithromycin for refractory *Mycoplasma pneumoniae* pneumonia in children

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Background: **The prevalence of *Mycoplasma pneumoniae* pneumonia has increased considerably in recent years. To evaluate the efficacy of combined treatment of azithromycin with intravenous immunoglo-bulin (IVIG) or methylprednisolone in children with refractory *Mycoplasma pneumoniae* pneumonia (RMPP).**

Methods: **Children with RMPP were randomly allocated to group A [intravenous azithromycin (IA)+ methylprednisolone], group B (IA+IVIG) or group C (IA alone). Following a 7-day treatment, group C patients were randomly separated into two sub-groups: group C_1 (IA+methylprednisolone) and group C_2 (IA+IVIG). Temperature, respiratory symptoms and signs were examined. The average febrile period after treatment (F_2), average total febrile period (F_3), infiltration absorption, atelectasis resolution, pleural effusion disappearance were determined. The levels of C-reactive protein (CRP), D-dimer, and lactate dehydrogenase (LDH) were measured.**

Results: **Seven days after enrollment, the average F_2 after treatment of group A was the shortest. Compared with the control group C, the combined treatment group A and B showed higher rates of infiltration absorption, atelectasis resolution and pleural effusion disappearance, while lower levels of serum CRP, D-dimer and LDH. Fourteen days after enrollment, all children with combined therapy clinically improved, and presented better laboratory results. Group C_1 showed shorter F_3 and lower levels of CRP and LDH than those of group C_2. Overall, group A showed the shortest F_3, also has the lowest CRP and LDH.**

Conclusions: **Azithromycin with IVIG or methylprednisolone was better treatment for children with RMPP than azithromycin alone. IVIG treatment may be beneficial, especially when the efficacy of corticosteroids is insecure, thus could be considered as an alternative of primary therapeutic approaches.**

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Key words: **immunoglobulin; methylprednisolone; refractory *Mycoplasma pneumoniae* pneumonia**

Original article

Introduction

Mycoplasma pneumoniae (*M. pneumonia*, MP) is one of the common pathogens which causes children community-acquired pneumonia (CAP). More than 10%-40% CAP are caused by MP.[1] MP pneumonia (MPP) may develop into a severe life threatening pneumonia in some cases, although it is generally a benign self-limited disease. As the first-choice treatment for MP infections in children, macrolide antibiotics have been used for MP treatment for many years. However, many clinical isolates from MP cases showed resistance to macrolides. Recently, it was reported that mechanism of severe MPP is related to cell mediated immunity and corticosteroid treatment may be effective.[2-4] As we know, intravenous immunoglobulin (IVIG) has been used as an effective immune-modulator for Kawasaki disease and other immune-mediated diseases. More recently, the use of IVIG for adults with severe MP infection has been reported. However, available data are

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limited for children.[5-7] To investigate the therapeutic effects of immune-modulating therapy, in this study, we compared the treatment of combined IVIG to corticosteroids alone in the hospitalized children with MP caused community acquired pneumonia. This is the first study evaluating the efficacy of IVIG in hospitalized refractory *Mycoplasma pneumoniae* pneumonia (RMPP) children.

Methods

Subjects

The study was performed between May 2013 and May 2015 in children hospitalized in the Pediatric Pulmonology Department, Shengjing Hospital of China Medical University, and a total of 168 previously healthy children with RMPP were enrolled. Refractory pneumonia is defined as follows: 1) fever for 7 days or more (from start of appropriate antibiotic treatment) or 2) persistent consolidation of more than one lobe of the lung despite appropriate antibiotic treatment, including macrolides.[4] All these patients required the administration of intravenous macrolide antibiotics according to the Infectious Diseases Society of America guidelines.[8] The study protocol was approved by the University Hospital Ethical Committee (2013PS163K), and informed consent was obtained from the children's guardians.

Inclusion criteria

1) Male and female subjects aged ≥2 years and <14 years; 2) CAP were diagnosed by clinical manifestation, physical examination and radiology. All patients had fevers (>37.5°C), coughs, moist rales and other abnormal auscultations, and exhibited abnormal chest radiographic findings when they were admitted to our department. The consolidation, infiltration or pleural effusion on chest *X* rays could not be attributed to any other etiology; 3) the MP infection was determined by the serological test using MP immunoassay enzyme-linked immuno sorbent assay kits (SERODIA®-MYCO II) and polymerase chain reaction test of nasopharyngeal swabs. Other tests, including purified protein derivatives tuberculin test, tuberculosis-immunoassay test, respiratory virus tests (such as respiratory syncytial viruses, adenovirus influenza adenovirus, parainfluenza virus), nasopharyngeal swabs and blood cultivations were also recruited. These tests were negative for all of the subjects.

Exclusion criteria

1) Children who have a history of tuberculosis, bronchiectasis, lung tumor, or nosocomial pneumonia; 2) obvious malnutrition, unconsciousness, chronic pulmonary and cardiac disease, congenital disease, immunodeficiency; 3) mechanical ventilation indication; 4) discharge within 8 hours after enrollment; 5) other pathogens were found; and 6) children younger than 2 years were all excluded because of a high rate of respiratory viral infections. Children older than 14 years were not included as well.

Study design

This study was an open, randomized, controlled clinical trial. All patients included were given the standard intravenous azithromycin (IA) at a dose of 10 mg/kg/day once daily for 3 days, according to the hospital recommendations, and were randomly allocated to three groups (Fig.). Randomization was done according to a computer-determined allocation to groups A, B or C. The sequence was concealed in an envelope, and the next neutral envelope was opened each time the next patient was included in the study. In the first three days, group A (*n*=56) received the additional intravenous methylprednisolone (2 mg/kg/day, 3 days); group B (*n*=56) received IVIG 400 mg/kg/day, for 3 days; group C (*n*=56) received IA alone without additional therapy. All patients were followed for 7 days. Treatment

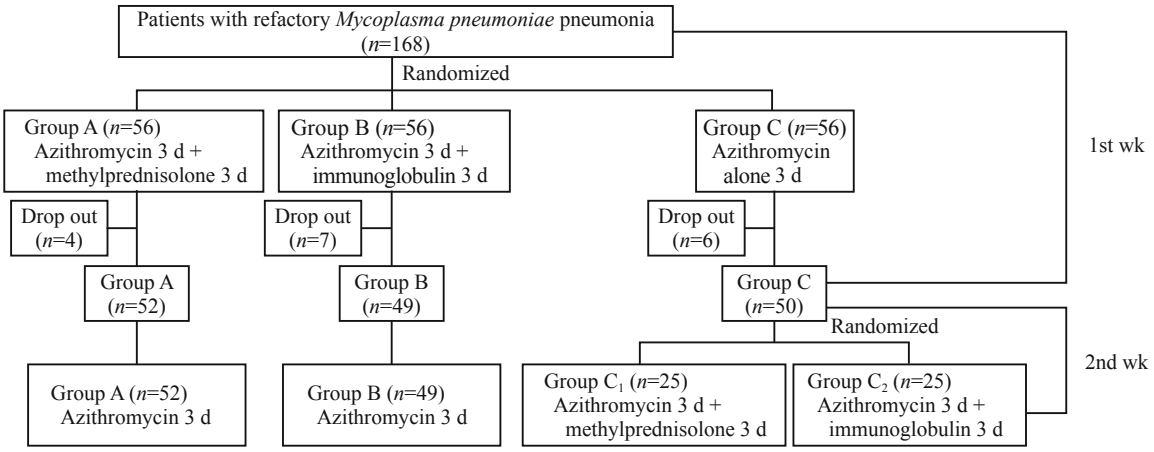

Fig. Study flow chart.

compliance was evaluated by the returning medication after the intervention period.

From the 2nd week, all patients were given IA for 3 consecutive days. Since all of the children in group C still had a fever, we randomly divided group C into two subgroups: group C_1 (methylprednisolone 2 mg/kg/day+IA, 3 days, *n*=25) and group C_2 (IVIG 400 mg/kg/day+IA, 3 days, *n*=25). All groups received water-electrolyte balance maintenance, sputum aspiration and other comprehensive treatments.

Body signs and laboratory testing

To evaluate the role of methylprednisolone and IVIG in the treatment of RMPP, the body temperature, respiratory symptoms and other signs were examined after enrollment and every 8 hours thereafter. This observation was terminated 2 weeks after the antibiotic therapy. The standard for assessing pneumonia severity and scores according to the Chinese Guidelines for the Management of Community-Acquired Pneumonia in Children by Pediatric Infectious Diseases Society of China are shown in Table 1. The criteria in the mild column score 0, those in the moderate column score 1, and those in the severe column score 2.

The chest radiographic, serum C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer levels were assessed 7 days and 14 days after admission. If the results of the patient's X-rays showed that the areas of infiltration and atelectasis were 30% less than those of pre-treatment, we considered this patient to be a case of infiltration and/or atelectasis absorption. Next, the ratios of infiltration absorption, atelectasis resolution and pleural effusion disappearance were calculated on day 7 and day 14 after enrollment.

Statistical analyses

All of the data were analyzed using SPSS 13.0. Chi-squared test, to compare categorical variables and one-way analysis of variance (ANOVA) was used to compare continuous variables. The mean±standard deviation expresses the central tendency of the data. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics

A total of 168 patients were included in this study. On admission, all patients had pneumonic symptoms and signs, including fever (axillary temperature >37.5°C), cough, moist rales and other abnormal auscultation, and abnormal chest radiographic findings. All of the subjects were conformed to meet the diagnostic criteria of RMPP prior to the admission of this trial. In total, 17 (10.1%) patients were considered drop-outs [4 (7.1%) in group A, 7 (12.5%) in group B and 6 (10.7%) in group C, $P>0.1$]. The reasons for drop-outs were as follows: withdrawal of consent, antibiotic stop within 48 hours, non-compliance, and loss of follow-up. Therefore, data of 151/168 children were available: 52/151 in group A, 49/151 in group B and 50/151 in group C. Baseline demographics, clinical characteristics, initial chest radiographic findings, serologic tests, and clinical symptom scores did not differ significantly among these three groups (Table 2).

Therapeutic effect of methylprednisolone and IVIG on RMPP

After the first week of enrollment, the average febrile period after treatment (F_2) of group A (0.86±0.85 days) and group B (3.00±1.21 days) were shorter than that of the control group C (7.00±0.00 days, $P<0.001$), and the F_2 of group A was the shortest ($P<0.001$, Table 2). All the patients in group C still had a fever. The clinical symptom scores in group A [2 (0-5)] and B [2 (1-6)] were lower than that in group C [6 (3-9)] ($P<0.001$).

In the combined treatment, group A and B showed higher infiltration absorption rate [73.9% (17/23) and

Table 1. Determining severity through physical observations and score calculation

Variables	Mild	Moderate	Severe
General condition	Good		Poor
Apastia or dehydration	No		Yes
Disturbance of consciousness	No		
Respiratory rate	Normal or minimal-mild increase*		Increase obviously†
Cyanosis	No		Yes
Forced respiration (grunting, nasalalar breathing, retraction)	No		Yes
Extent of infiltration on chest X-ray examination	≤1/3 of one lung		≥2/3 of one lung
Pleural effusion	No		Yes
SpO_2	>0.96		≤0.92
Extrapulmonary complications	No		Yes
Criteria	All of the above criteria are met (point 0)	Not mild or extreme (point 1)	Any one of the above conditions are met (point 2)

Increase in respiratory rate (RR, breaths/min) by age. *: <2 months, RR ≥60; 2 months, RR ≥50; 1-5 years, RR ≥40; >5 years, RR ≥30; †: infant, RR >70; older child, RR >50. SpO_2: oxgen saturation.

71.4% (15/21)] than that in the control group C [25.0% (6/24), *P*=0.001]. The atelectasis resolution rates in groups A and B [74.1% (20/27) and 67.9% (19/28), respectively] were also higher than that in group C [34.6% (9/26), *P*=0.007], and the rate of pleural effusion disappearance in groups A [83.3% (15/18)] and B [72.2% (13/18)] were better than that in group C [33.3% (7/21), *P*=0.003]. Compared with the control (group C, 51.67±18.70 mg/L), the level of serum CRP in combined treatment groups (A: 20.02±6.66 mg/L and B: 33.48±17.01 mg/L) was also lower. The serum CRP of group A was only 20.02±6.66 mg/L. The levels of D-dimer and LDH in combined treatment groups A (D-dimer: 505.37±252.84 μg/L, LDH: 429.90±114.99 IU/L) and B (D-dimer: 506.22±245.37 μg/L, LDH: 416.27±103.66 IU/L) were lower than those in group C (D-dimer: 808.14±685.56 μg/L, LDH: 627.92±112.03 IU/L) (*P*<0.001).

Fourteen days after enrollment, the children in every group clinically improved, and the chest X-rays and laboratory tests were back to normal. The combined treatment group A and B appeared to have a shorter average total febrile period (F_3: 9.93±1.81 days and 11.76±2.50 days, respectively) than those in groups C_1 and C_2 (16.60±2.78 days and 18.49±2.26 days, respectively; *P*<0.05, Table 3). The combined group had higher infiltration absorption rate [group A: 91.3% (21/23); group B: 90.5% (19/21)], higher atelectasis resolution rate [group A: 92.6% (25/27); group B: 89.3% (25/28)] and higher pleural effusion disappearance rate [group A: 100% (18/18); group B: 100% (18/18)]compared with those of groups C_1 and C_2 (all *P*<0.05). The CRP, LDH and the clinical symptom scores of combined treatment in groups A and B were lower than in group C_1 and C_2 (all *P*<0.05). The lowest level of CRP was found in group A (7.92±1.85 mg/L, *P*<0.001). Group C_1 has shorter F_3, lower levels of CRP and LDH than group C_2.

Initial chest X-ray findings of these RMPP patients

Table 2. Baseline demographics of the patients

Items	Group A (azithromycin+methylprednisolone)	Group B (azithromycin+immunoglobulin)	Group C (azithromycin alone, control)	*P* value
Sample size	52	49	50	
Age (y), mean±SD	7.36±2.33	7.36±2.32	7.29±3.03	0.990
Sex, male/total	26/52	25/49	26/50	0.980
F_1 (d), mean±SD	9.08±1.53	8.76±2.19	8.70±2.25	0.592
Respiratory symptom score, mean (min-max)	14 (12-17)	14 (12-17)	15 (12-17)	0.056
Lobar infiltration, ratio	23/52	21/49	24/50	0.867
Lobar atelectasis, ratio	27/52	28/49	26/50	0.836
Pleural effusion, ratio	18/52	18/49	21/50	0.732
WBC ($\times10^9$/L), mean±SD	8.64±3.50	9.75±3.16	9.37±3.14	0.226
CRP (mg/L), mean±SD	58.34±17.56	56.12±20.50	55.87±20.00	0.778
D-dimer (μg/L), mean±SD	1197.88±579.57	1220.92±709.24	1231.34±921.47	0.974
LDH (IU/L), mean±SD	921.90±235.52	901.24±130.90	911.78±96.42	0.824

F_1: average febrile period prior to admission; WBC: white blood cell; CRP: C-reactive protein; LDH: lactate dehydrogenase; SD: standard deviation.

Table 3. Primary and secondary outcomes in the patients

Items	Group A (*n*=52, azithromycin+methylprednisolone)	Group B (*n*=49, azithromycin+immunoglobulin)	Group C (*n*=50, azithromycin)	*P* value
F_2 (d)	0.86±0.85	3.00±1.21	7.00±0.00	<0.001
Score, mean (min-max)	2 (0-5)	2 (1-6)	6 (3-9)	<0.001
Infiltration absorption rate, %	73.9 (17/23)	71.4 (15/21)	25.0 (6/24)	0.001
Atelectasis resolution rate, %	74.1 (20/27)	67.9 (19/28)	34.6 (9/26)	0.007
Pleural effusion disappearance rate, %	83.3 (15/18)	72.2 (13/18)	33.3 (7/21)	0.003
CRP (mg/L)	20.02±6.66	33.48±17.01	51.67±18.70	<0.001
D-dimer (μg/L)	505.37±252.84	506.22±245.37	808.14±685.56	0.001
LDH (IU/L)	429.90±114.99	416.27±103.66	627.92±112.03	<0.001

F_2: average febrile period after treatment; CRP: C-reactive protein; LDH: lactate dehydrogenase; IU: international unit.

Table 4. Efficacy of methylprednisolone/immunoglobulin in children

Items	Group A (*n*=52)	Group B (*n*=49)	Group C_1 (*n*=25)	Group C_2 (*n*=25)	*P* value
F_3 (d)	9.93±1.81	11.76±2.50	16.60±2.78	18.49±2.26	<0.001
Score, mean (min-max)	0 (0-1)	0 (0-2)	1 (0-2)	1 (0-3)	<0.001
Infiltration absorption rate, %	91.3 (21/23)	90.5 (19/21)	71.4 (10/14)	70.0 (7/10)	0.201
Atelectasis resolution rate, %	92.6 (25/27)	89.3 (25/28)	72.7 (8/11)	93.3 (14/15)	0.309
Pleural effusion disappearance rate, %	100 (18/18)	100 (18/18)	88.9 (8/9)	83.3 (10/12)	0.045
CRP (mg/L)	7.92±1.85	10.61±5.78	15.43±8.12	21.52±8.24	<0.001
D-dimer (μg/L)	220.23±58.83	214.49±50.22	252.76±182.95	265.12±62.14	0.064
LDH (IU/L)	239.94±33.00	221.57±41.30	271.20±58.65	327.12±55.70	<0.001

F_3: average total febrile period; CRP: C-reactive protein; LDH: lactate dehydrogenase; IU: international unit.

showed lobar infiltrates or atelectasis combined pleural effusion. After combined treatment of methylprednisolone or IVIG, all patients had clinically improved, with improved radiographic findings and laboratory items (Table 3&4). All patients were followed up with a month after their discharge. There were no adverse reactions to methylprednisolone or IVIG and no cases of drug discontinuation (neither methylprednisolone nor IVIG) have been reported.

Discussion

RMPP and macrolide-resistant MP (MRMP) has been increasing in recent years.[9-12] Refractory or severe MP infections usually share similar laboratory findings to severe acute respiratory syndrome: increased serum CRP, LDH (which are non-specific markers of inflammation) and D-dimer.[13] In MRMP children, serum CRP can predict the curative effect of macrolides thus helping pediatricians make good clinical decisions.[14] In our study, the significant elevated serum CRP suggested the severity of systemic inflammatory responses to MP infections. Also, the elevated D-dimer should be noted during the clinical course of severe MP pneumonia.[15-17] Children with MPP, especially those with lobar pneumonia, showed increased plasma levels of thrombomodulin and D-dimer. Some studies demonstrated that damages to vascular endothelial cells and blood hypercoagulability might be involved in the pathogenesis of MPP, and might reveal that the prothrombotic state is related to systemic infection.[18] The results of this trial suggested that CRP, LDH and D-dimer may partly indicate the severity of the infection and then drop back when undergoing the recovery of RMPP. There were no significant adverse reactions in all treatment groups. These results suggested that both methylprednisolone and IVIG offer an appropriate and safe therapeutic intervention to treat MPP.

The prevalence of MRMP has increased to 10%-30% worldwide.[19-21] The macrolide-resistant strains are known to cause severe refractory MP.[19] Although we did not perform the macrolide-resistant test, the unresponsiveness to macrolide in these patients is likely associated with macrolide resistance.

The host innate and adaptive immune systems work together against injury from the MP infection. However, when the inflammatory response was excessively amplified, the clinical course of pneumonia might have worsened. In RMPP, host immune responses may cause pulmonary injury rather than direct microbial damages.[22] Therefore, to some extent, RMPP is an immune mediated disease and therefore immune suppressive therapy might be a rational approach. Some studies reported that immunosuppressant drugs, such as corticosteroids or IVIG, were used in the selected patients.[6,23]

It has been demonstrated that cell-mediated immunity plays an important role in the MP infection progress. Interleukin (IL) 2, IL8, IL5, IL6, IL18 and other cytokines might be involved in the MP infection, and induce the inflammatory response.[24] The hyper immune reaction of T-cells might cause the destruction to the lung tissue. Immunological reactions produced many inflammatory mediators, which may induce more severe lung injury.[25-27] The excessive cell-mediated immunity and cytokine responses play an important role in RMPP.[28] RMPP is not only a kind of infection, but also an immune-mediated disease. Corticosteroids can regulate immunity against inflammation reactions. It has been certified that corticosteroids could improve clinical manifestation and lung injury effectively in children and adults with MP infection, reduce lung histopathologic score and decrease mortality in severe pneumonia by decreasing cytokines and reducing the inflammatory response.[2,21,29,30] Even though there are no treatment guidelines for corticosteroid therapy for RMPP, clinicians have been using the corticosteroid in some children.[2,4,21] However, the treatment protocols were variable from oral prednisolone of 1 mg/kg/day to intravenously methylprednisolone 30 mg/kg/day for three days. Based on these reports, we initially gave intravenous methylprednisolone 2 mg/kg/day with IA for 3 days at the beginning (group A) or after a 3-day IA treatment (group C_1). Our study also demonstrated that the dose of methylprednisolone 2 mg/kg/day for 3 days was valuable for RMPP. Various extra-pulmonary manifestations (such as skin rash, MP-associated Stevens-Johnson syndrome and central nervous system disorders) in MP infection may be the result of host immune responses to MP.[24,31,32] Immunoglobulins are considered as an effective immune-modulator for various immune-mediated diseases. IVIG has been used in MP-associated central nervous system diseases, and the results showed a rapid recovery.[6] This improvement from some reported cases may be the result of IVIG-induced provision of anti-idiotypic antibodies, which can block the immune-mediated response.[33] It was reported that IVIG had significant activity against MP and provided an extra protection, especially in using antibiotic therapy patients with sub-optimal responses.[34] IVIG has been reported to be effective in the treatment of many autoimmune and systemic inflammatory diseases. Immunomodulation mechanisms of IVIG are not fully understood. The Fc-dependent and/or F(ab0)2-dependent mutually non-exclusive effects might be involved.[35] The well-recognized anti-inflammatory effects of IVIG can

attribute to the interactions between the IgG Fc domains and FccR, also they can modulate the production of cytokines.[35] In addition, IVIG has a remarkable impact on different immune system effector cells (such as B and T lymphocytes, dendritic cells, etc.), and regulates a wide range of genes.[35] Although only a few studies reported the IVIG use for severe MP,[5,7] our trial indicated that combined immune-modulating therapy of IVIG is an effective therapy. It should be mentioned that some severe patients might not be excluded from tuberculosis combined infection even though MP-IgM or MP-DNA results were positive. In these cases, IVIG would be safer than corticosteroids. IVIG is extracted from the blood, which should also be noticed on some occasions.

In this study, we demonstrated that combined treatment improved clinical manifestations faster, lowered clinical symptom score and relieved radiographic and laboratory items earlier than azithromycin therapy alone. The combined macrolides with steroid and IVIG used to treat MP showed a positive outcome without any adverse events. Even though there were no case-controls, the improvement of clinical symptoms and chest X-rays in RMPP children showed the usefulness of the combined treatment. Furthermore, double blind control trails would be needed to determine the best choice of combination therapy. Our study indicated that both methylprednisolone and IVIG were beneficial in children with RMPP. However, their clinical improvements and laboratory results were different. The investigation of their mechanism(s) might be the direction of our further study.

This study indicated the efficacy of methylprednisolone and IVIG in RMPP treatment. The dosage that we used was safe, and there were no adverse events during pulse therapy. Moreover, our study is very important for the future clinical trials design, especially for sample size and study cohorts planning. Further exploration randomized trial clinical study should be done to certify the benefits of systemic IVIG therapy. A better understanding of the IVIG action may help us to know its mechanisms in the pathogenesis of autoimmune and inflammatory diseases.

A major limitation of this trial is its "open" design. Because there is no placebo control group, a placebo effect cannot be excluded. Also, a potential of co-infections should be considered. In addition, due to the limitations of the individuals enrolled and the duration of our study, we collected all the qualified children rather than calculated the sample size in the study period. Therefore, it might lead to selective bias and reduce the test efficiency. Another limitation is that macrolide resistance was not tested. Some mycoplasmal strains may have been resistant to the antibiotic used. In addition, serum CRP, LDH and D-dimer levels were not compared with non-RMPP children. Further study might be focused on the macrolide resistance, the serum CRP, LDH and D-dimer as parameters for corticosteroid or IVIG selection.

In conclusion, this is the first clinical trial suggesting that the beneficial effects of methylprednisolone or IVIG combined treatment in children with RMPP. The azithromycin with IVIG or methylprednisolone therapy revealed better and more rapid clinical improvement without any adverse events. Our study suggests that the levels of serum CRP, LDH and D-dimer might relate to the severity of RMPP. In this prospective cohort study, adjunct systemic methylprednisolone or IVIG resulted in shorter average febrile period, and lower levels of CRP, LDH and D-dimer. Methylprednisolone therapy could significantly shorten the fever duration and decrease the level of serum CRP. While IVIG might be safer for the severe patients who could not exclude from the tuberculosis. We suggest that prompt IVIG combined therapy in children with severe RMPP may be beneficial. Also, IVIG can be considered as an alternative therapeutic approach, especially when it is insecure to use corticosteroids.

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