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Original Article

Adalimumab Combined with Methotrexate as the Initial Treatment for Active Noninfectious Uveitis in Chinese Children: A Pilot Study

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Abstract:

Objectives: To investigated the effectiveness, safety and corticosteroids-sparing effects of adalimumab (ADA) plus methotrexate (MTX) as initial treatment in active pediatric noninfectious intermediate uveitis, posterior uveitis or panuveitis (NIPPU).

Methods: This was a prospective open-label pilot trial in 30 patients (54 eyes) between three to seventeen years old diagnosed with new-onset active NIPPU. All of the patients were treated with ADA plus MTX. Main outcome measures were remission rate and the time to reach remission. Corticosteroids-sparing effects and other ocular parameters were recorded. Approval Number: 2020KYPJ104. ClinicalTrials.gov identifier: NCT04588818.

Results: The remission rate within 6 months was 76.67% (23/30) and reached to 90.0% (27/30) at 12 months. The average time to reach remission was 5.3±1.5 months with a follow-up time of 12.1±2.6 months. The initial dosage of oral corticosteroids was 0.43±0.34 mg/kg/day with a corticosteroid stopping time of 14.2 (IQR 3.50, 29.29) weeks. The cumulative corticosteroids dose was 456.25 (IQR 142.50, 1396.25) mg/per patient. All ocular parameters improved significantly during follow up.

Conclusions: ADA plus MTX as initial treatment shows great effectiveness and safety in active pediatric NIPPU patients, providing a satisfying corticosteroid-sparing effect. More aggressive ADA therapy as initial treatment might lead to better prognosis in these children.

Key Words: adalimumab, tumor necrosis factor-alfa inhibitor, pediatric non-infectious uveitis, initial treatment, corticosteroid-sparing effects.

Introduction

Noninfectious uveitis (NIU) is a spectrum of vision-threatening diseases characterized by devastating intraocular inflammation. NIU can be associated with a systemic disease or be eye limited and affects people of all ages. [1] Despite its rarity in the pediatric population, acute or persistent ocular inflammation may engender several ocular structural destructions and functional impairment on children.[2, 3]

The standard first-line treatment for initial NIU is corticosteroids (topical, systemic, and injections). However, high-dose and long-term use of

systemic corticosteroids carry a high risk of devastating ocular and systemic adverse effects especially irreversible growth retardation in children.[4, 5] Therefore, conventional disease-modifying antirheumatic drugs (DMARDs) are recommended for controlling the chronic ocular inflammation and provide a corticosteroid-sparing effect. Among these drugs, methotrexate (MTX) is a currently highly recommended and the most commonly prescribed drug in pediatric NIU for its safety and effectiveness.[6] However, despite the early intervention of conventional DMARDs and systemic corticosteroids, 33-43% of patients with NIU experienced a treatment failure and the corticosteroid-sparing effects of conventional DMARDs are still unsatisfactory.[7] Consequently, novel safe and effective therapies with anti-inflammatory properties are urgently needed to provide a more satisfying corticosteroid-sparing effect.

Adalimumab (ADA), a fully human monoclonal antibody specifically targeting tumor necrosis factor-a (TNF-α), is effective in the treatment of various rheumatic diseases as well as NIU.[8-10] ADA can control the ocular inflammation and was associated with a lower rate of treatment failure than placebo in NIU patients. However, ADA is not commonly used as initial corticosteroid-sparing treatments for uveitis, because of its more expensive price and the risks for serious adverse effects.[11-13] Nevertheless, early use of ADA may control the inflammation of uveitis more quickly with a good corticosteroid-sparing effects, which can avoid ocular damage of long-term inflammation and reduce corticosteroid related advert effects.

We conducted a prospective pilot study to investigate the effectiveness of ADA plus MTX as the initial treatment in active pediatric noninfectious intermediate uveitis, posterior uveitis or panuveitis (NIPPU). Meanwhile, the corticosteroids-sparing effects and safety of ADA plus MTX treatment was explored.

Methods

• Study Design and Patients

We performed a prospective single group treatment trial in Zhongshan Ophthalmic Center, an ophthalmic center in southern China, from February 2020 to February 2021. This study was conducted in compliance with the principles of the Helsinki declaration, with approval obtained from the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. Approval Number: 2020KYPJ104. All patients and their guardians agreed to the treatment and were given written informed consent. ClinicalTrials.gov identifier: NCT0458 8818.

This study enrolled children between three to seventeen years old diagnosed with new-onset NIPPU at Zhongshan Ophthalmic Center. New-onset patients were defined as those who suffer from an active ocular inflammatory disorder without systemic corticosteroids or conventional DMARDs treatment before consulting our clinic. Patients were required to visit a pediatrician to determine the concurrent systemic autoimmune disease. This study excluded patients with active infection, including hepatitis B or C infection, or tuberculosis. Patients with malignancy diseases, irreversible bilateral blindness, as well as those with previous exposure to another biological agent are also excluded.

• Sample Size Estimates

According to the existing literature, the effective rate of traditional MTX plus corticosteroids in the treatment of children NIPPU is 67%.[14] So, the objective performance criteria are set to 67%. Based on our previous research and clinical application, the expected effective rate of ADA plus MTX as first-line treatment in NIPPU children is set to 90%. A sample size of 27 was calculated using the method of single-arm objective performance criteria, with a one-sided type I error α of 0.025 and a type II error β of 0.1.

• Treatment Protocol and Study Visits

All eligible pediatric patients are treated with ADA plus MTX with oral corticosteroids as initial therapy and follow-up for at least one year. Patients over 30 kg weight receive a 40 mg ADA subcutaneously every two weeks continuing for the duration of the trial and those less than 30 kg receive a 20-mg dose. The dosage of MTX treatment is 10 to 20 mg per square meter of body-surface area, up to a maximum dose of 15 mg. In addition, systemic corticosteroids are prescribed based on the severity of vitritis, retinal vasculitis, papillitis, or macular edema, tapered slowly, and then suspended when inflammation is eliminated. Topical corticosteroids are applied

according to the severity of anterior chamber inflammation.

Demographic characteristics are collected at baseline. Trial visits are scheduled at 4, 8, and 12 weeks and then every 12 weeks until 12 months or until patients stop the trial regimen. The therapeutic management, ophthalmic assessments, systemic disorders, and adverse events (AEs) are evaluated for each patient at every visit. The ophthalmic assessments consisted of best corrected visual acuity (BCVA), intraocular pressure (IOP), anterior chamber cell (ACC) grade, vitritis grade, macular thickness (MT) and ocular complications. BCVA is evaluated using a LogMAR chart for statistical analysis. ACC grade and Vitritis grade are evaluated according to the SUN standard and Nussenblatt scale. [15, 16]

- **Outcomes**

The primary outcome is the remission rate within six months and the time to remission. The secondary outcomes are the corticosteroids-sparing effect, the improvement of ocular parameters and the number of relapses throughout the trial. The primary data was presented as follows.

Remission Rate Within Six Months: Clinical remission on medication of NIPPU was defined as a lack of inflammatory activity at ≥2 visits spanning ≥12 weeks on medication. Remission rate within six months refer to the percentage of enrolled patients who reach clinical remission on medication within 24±4 weeks (6 months ±4 weeks).

The Time to Reach Remission: The time from initiation of ADA to reach clinical remission is defined as the time to reach remission. The duration of remission is the time from remission to the first relapse.

Corticosteroids-sparing effect: The evaluation parameter of the corticosteroids-sparing effect is a reduction in systemic corticosteroids usage. The daily dosage, cumulative dosage and duration of corticosteroids using are recorded.

The number of Relapses: A relapse is defined as a new flare of uveitis (such as anterior or posterior chamber inflammation, retinal vasculitis, papillitis or macular edema) in a patient who was in remission. The number of relapses in remission patient during follow-up is recorded.

- **Statistical Analysis**

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 25.0 and GraphPad (GraphPad Software, San Diego, USA) version 9.0. Results were expressed as mean ± standard deviation (SD) for 'normal' data or as a median and interquartile range [IQR] [25th, 75th] for non-normally distributed data. The Kolmogorov-Smirnov test or Shapiro-Wilk test assessed the normality of data. Continuous variables were compared with the two-tailed Student's t-test or the Mann-Whitney U test. The Chi-square test or Fisher exact test and McNemar's tests were applied to compare dichotomous variables. Statistical significance was considered as a p-value <0.05 in all calculations.

Results

- **Demographic and Clinical Features at Baseline**

This study included a total of 30 Chinese children (54 eyes) aged 8.95±3.68 years old with NIPPU. Twenty-one (70.0%) were female, nine (30.0%) were male. Bilateral uveitis presented in 80.0% (24/30) of the patients. The main demographic characteristics, etiologies of uveitis, and previous therapies are exhibited in **Table 1**.

Table 1. Demographic characteristics of children with noninfectious uveitis.

Characteristics	**Value**
Age; mean ± SD years	8.95±3.68
Num. of children (eyes)	30(54)
Sex; Patients (%)	
Male	9(30.0%)
Female	21(70.0%)
Laterality; Patients (%)	
Unilateral	6(20.0%)
Bilateral	24(80.0%)

Uveitis type; eyes (%)	
Panuveitis	54(100%)
Systemic diagnosis; Patients (%)	
Behçet's Disease	13(43.4%)
Idiopathic uveitis	10(33.3%)
Juvenile idiopathic arthritis	7(23.3%)
Duration from disease onset to receiving treatment; mean ± SD weeks	10.3±8.8
Duration of follow-up; mean ± SD months	12.1±2.6
Duration of corticosteroid-using; median (IQR) weeks	14.2(3.5, 29.3)
Previous system therapy; (n %)	
No systemic medication	30(100%)
Immunosuppressive therapy	0(0.0%)
Biologic agent	0(0.0%)

Abbreviation: SD=standard deviation, IQR=interquartile range.

The etiologies of uveitis included idiopathic uveitis presented in 13 (43.4%) patients, followed by Behcet's disease (BD) in 10 (33.3%), and juvenile idiopathic arthritis associated uveitis (JIA-U) in 7 patients (23.3%). None had received systemic therapies before. All participants have completed the study. The mean duration from NIU onset to receiving treatment in our patients was 10.3±8.8 weeks and the mean follow-up time was 12.1±2.6 months.

- **Treatment Characteristic During Follow-Up**

Once diagnosed as NIPPU, all patients in our study were administered with MTX combined with ADA injections and 25 (25/30, 83.3%) patients received systemic corticosteroids. The initial dosage of oral corticosteroids was 0.43±0.34 mg/kg daily of prednisone, and the dose was tapered according to their inflammatory status. Twenty (20/30, 66.7%) patients received a 40 mg dose of ADA every two weeks, while ten (10/30, 33.3%) patients took 20 mg every two weeks. Meanwhile, all children received MTX at a mean dosage of 14.00 ± 2.33 mg per week without other conventional DMARDs. At 12 months, 29 patients (29/30, 96.7%) remained on the standard dose of ADA (40 or 20mg). ADA was optimized by decreasing the frequency to every 3 or 4 weeks in seven patients (7/30, 23.3%) and 22 patients (22/30, 73.4%) was still on the standard frequency. One patient changed the treatment from ADA plus MTX to cyclophosphamide (CTX) plus MTX because of treatment failure. Another two patients experienced treatment failure maintained in ADA plus MTX treatment and additionally received CTX and cyclosporine A (CsA) respectively. The therapeutic characteristics are given in **Table 2**.

- **Remission Rate and the Time to Reach Remission.**

In our cohort, half of the patients achieved remission at 4.87 months, and 23 (76.67%) patients reached remission within 24±4 weeks (6 months ± 4 weeks) (**Figure 1A**). At 12 months, 27 patients (27/30, 90.0%) achieved remission. Three patients (3/30, 10.0%) couldn't achieved remission during one year follow-up and experienced the treatment failure. Among the patients achieving remission, the average time to reach remission was 5.3±1.5 months. In idiopathic uveitis, BD and JIA-U, the time to reach remission was 5.7±1.6, 5.1±1.6, and 4.8±1.4 months respectively. No significant differences were found among the three subgroups (**Figure 1B**). During follow-up, six eyes (6/48, 12.5%) of three children (3/27,11.1%) in remission experienced one relapse but quickly under control when adding low-dose oral corticosteroids back.

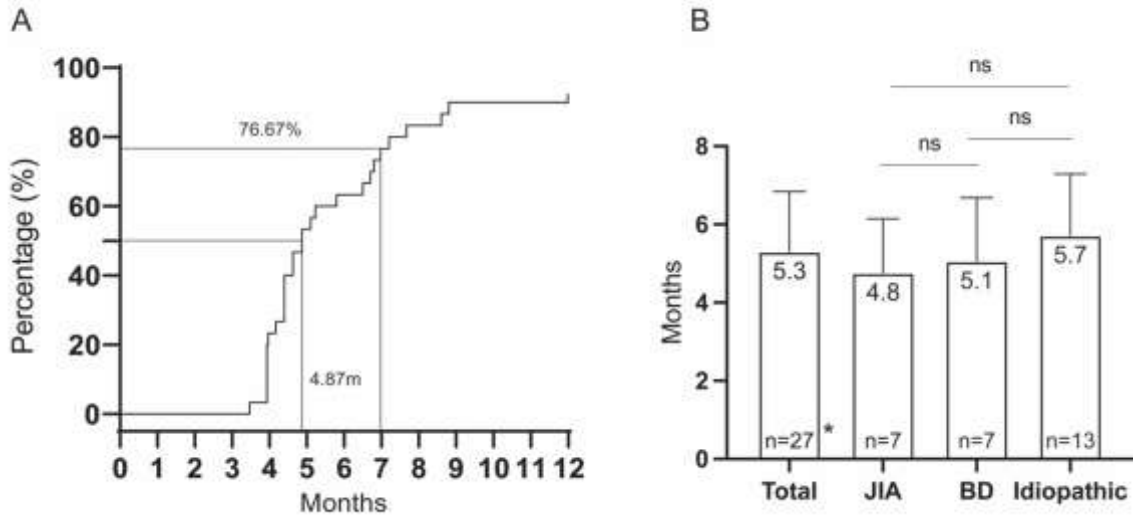

Figure 1. A: The change of remission rate during follow-up. B: The time to reach remission in pediatric noninfectious uveitis patients and subgroups. (n=patents, *Three children couldn't get remission at the 12 months)

- **Corticosteroid-sparing Effect**

During the follow-up period, the average daily dose of corticosteroids at each time point was shown in **Figure 2A**.

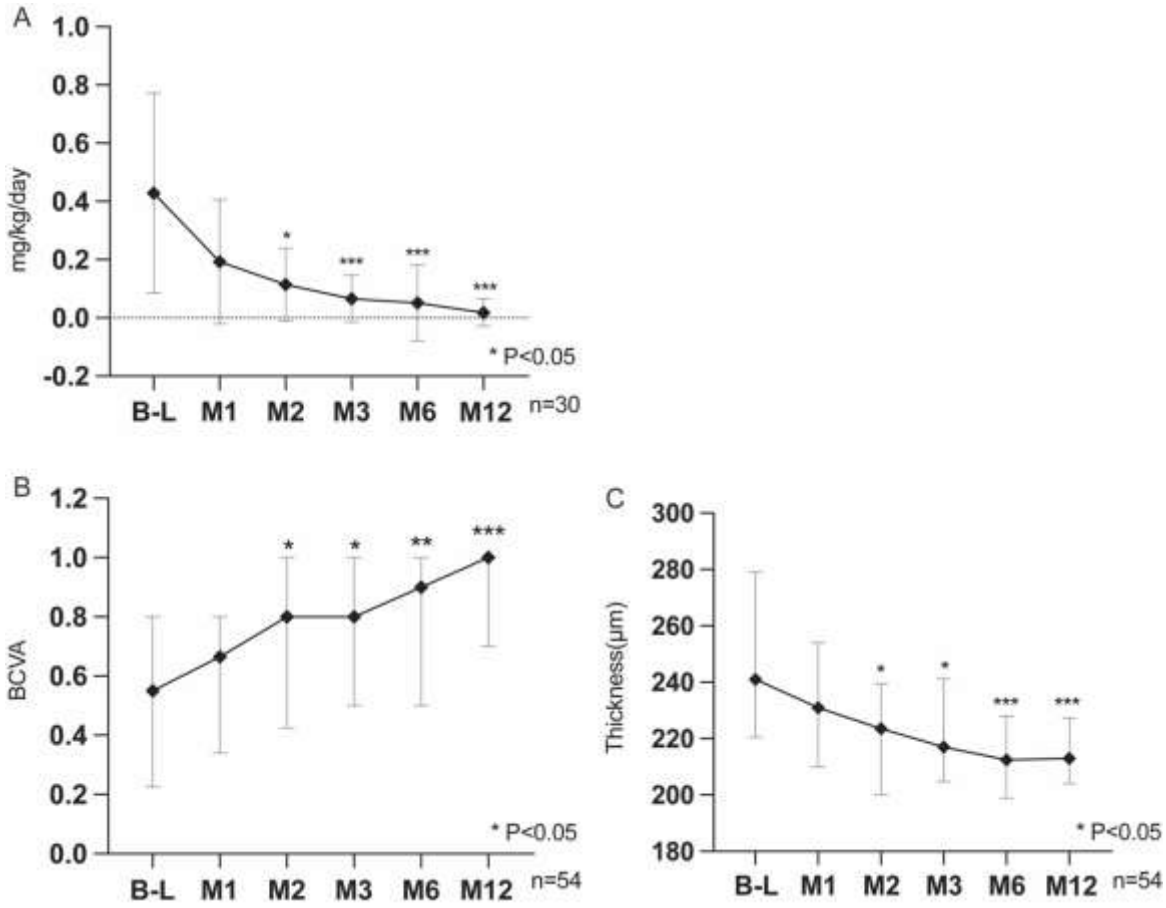

Figure 2. A: The corticosteroid-sparing effect during follow-up (n=patents). B: The change of Best corrected visual acuity (BCVA) during follow-up (n=eyes). C: The change of central macular thickness (CMT) during follow-up (n=eyes).

At 12 months, 20 patients (20/25, 80%) had their corticosteroids suspended, while only five (5/25, 20%) patients still needed oral corticosteroids to control their ocular inflammation. Of note, five patients (5/30, 16.7%) did not use any oral corticosteroids during follow-up, while two patients only received a periocular injection of triamcinolone acetonide (TA) for each of their eyes (2/54, 3.7%) in which one patient received twice, and one patient received once. The overall duration of corticosteroids-use was 14.2 (IQR 3.50, 29.29) weeks. The mean daily oral corticosteroids dosage decreased to 0.07±0.08 (mg/kg/day) at three months and 0.02±0.05 (mg/kg/day) at the 12 months. The cumulative corticosteroids dose was 456.25 (IQR 142.50, 1396.25) mg/per patient at the 12 months **(Table 2)**.

Table 2. Therapeutic characteristics of children with noninfectious uveitis.

Characteristics	Baseline	12 Months
Topical therapy, eyes (%)		
corticosteroid droplet	54(100%)	6(11.1%)
TA periocular injection	0	2(3.7%) †
Systemic treatments, patients (%)		
Oral corticosteroid	25(83.3%)	5(16.7%)
MTX	30(100%)	30(100%)
CTX	0	2(6.7%)
CSA	0	1(3.3%)
Dosage		
Oral corticosteroid (mg/kg/day, mean ± SD)	0.43±0.34	0.02±0.05 *
Cumulate Oral corticosteroid (mg/patient, median (IQR))	N/A	456.25(142.50, 1396.25)
MTX (mg/week, mean ± SD)	14.00 ± 2.33	14.00 ± 2.33
Adalimumab Dosage, patients (%)		
40 mg	20(66.7%)	19(63.4%)
20mg	10(33.3%)	10(33.3%)
0mg	0	1((3.3%)
Adalimumab Interval, patients (%)		
2 weeks	30(100%)	22(73.4%)
3 weeks	0	1(3.3%)
4 weeks	0	6(20.0%)
Stop	0	1(3.3%)

Abbreviation: TA= Triamcinolone Acetonide, MTX= methotrexate, CTX= cyclophosphamide, CSA= cyclosporine. †: During the follow-up, 1 eye in each of the 2 patients had received TA periocular injection, including 1 patient who received twice and 1 patient who received once. *: P<0.001

- **Ocular Parameter Improvement of the Eyes After Treatment**

The BCVA was increased from 0.55 (IQR 0.22-0.80) at baseline to 1.0 (IQR 0.7-1.0) (P<0.0001) at the 12 months (**Figure 2B**). Inflammatory activities, including the presence of ACC and vitritis at any degree, were both seen in 88.9% (48/54) eyes at baseline, decreasing to 13.0% (7/54) and 18.5% (10/54) respectively at 12 months (P < 0.001). ACC grade decrease from 1.2±0.7 to 0.1±0.3 at 12 months (Changed grade = -1.1, P < 0.001), while vitritis grade decrease from 1.4±0.7 to 0.2±0.5 (Changed grade = -1.2, P < 0.001). Changes in ACC and vitritis grades are presented in **Figure 3**.

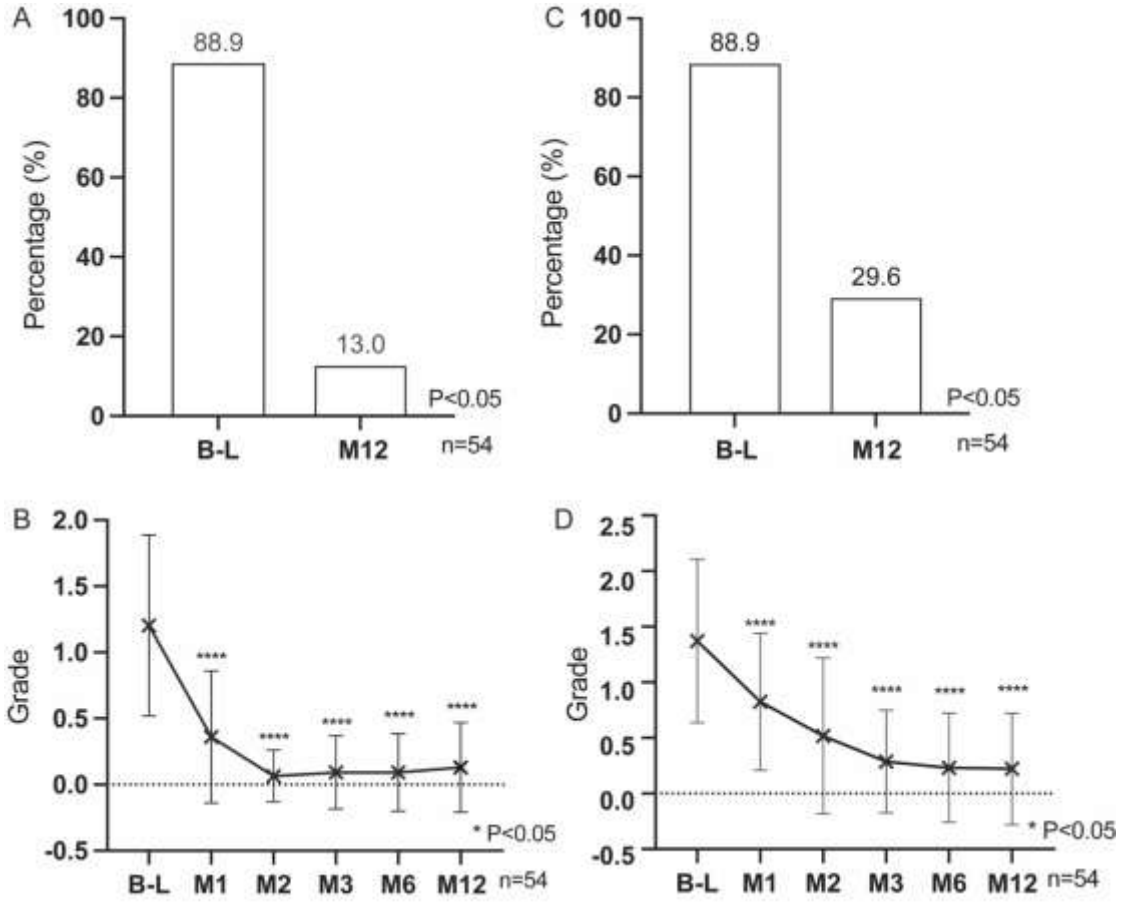

Figure 3. A-B: Changes on the anterior chamber cell (ACC) percentage and grade during follow-up; C-D: Change on the vitritis percentage and grade during follow-up. (n=eyes)

At baseline, cystoid macular edema (CME) was present in 25.9% (14/54) of the eyes. CME vanished in 85.7% (12/14) eyes at 12 months, while still persisted in the two eyes of patients failed to reach remission. The median MT at baseline was 241.00μm (IQR 220.50-279.00), which decreased to 213.00μm (IQR 204.00-227.25) at 12 months (P<0.001) (**Figure 2C**).

Complications had already occurred in 87.0% (47/54) eyes of 83.3% (25/30) patients at baseline, including band keratopathy (17/54, 31.4%), complicated cataract (27/54, 50.0%), ocular hypertension (OHT) (5/54, 9.3%), active choroidal neovascularization (CNV) (1/54, 1.8%), cystic macular edema (14/54, 25.9%), and synechia (12/54, 22.2%). No new complications occurred during follow-up and the active CNV in one eye had become stabilized at 12 months. In the five eyes with, the IOP was decreased to normal level at 12 months. The mean IOP decreased from 14.5±5.9 at baseline to 12.6±3.2 at 12 months (P<0.05). Two eyes from two patients underwent cataract phacoemulsification and intraocular lens (IOL) implantation surgery, with the BCVA of 0.8 and 0.9 respectively at 12 months. Changes in clinical parameters are displayed in **Table 3**.

Table 3. Ocular characteristics of children with noninfectious uveitis.

Characteristics	Baseline	12 Months
Lens status, eyes (%)		
Clear	27(50.0%)	27(50.0%)
Cataract	27(50.0%)	25(46.3%)
Pseudophakia	0	2(3.7%)
Clinical parameters		
BCVA, median (IQR)	0.55 (0.22-0.80)	1.0 (0.7-1.0) *
IOP (mmHg), mean ± SD	14.5±5.9	12.6±3.2*

MT(μm), median (IQR)	241.00(220.50-279.00)	213.00(204.00-227.25) *
ACC Grade (mean ± SD)	1.2±0.7	0.1±0.3 * (Changed = -1.1)
ACC Percentage	88.9%	13.0% *
Vitritis Grade (mean ± SD)	1.4±0.7	0.2±0.5*(Changed = -1.2)
Vitritis Percentage	88.9%	18.5% *
Ocular complications, eyes		
Band keratopathy	17(31.4%)	17(31.4%)
Ocular hypertension	5(9.3%)	0
Active CNV	1(1.8%)	0
Cystic macular edema	14(25.9%)	2(3.7%)
Synechia	12(22.2%)	12(22.2%)
Type of adverse event, patients		
Skin redness and itching	N/A	3(10.0%)
Varicella virus infection	N/A	1(3.3%)
Gastrointestinal discomfort	N/A	6(20.0%
Alopecia	NA	1(3.3%)

Abbreviation: BCVA=best corrected visual acuity, IOP=intraocular pressure, MT=macular thickness, ACC=anterior chamber cell, CNV=choroidal neovascularization, SD=standard deviation, IQR=interquartile range. *: P<0.001.

- **System Disorder Monitoring and Adverse Events**

Three patients had localized skin redness and itching during the follow-up period due to ADA injection, which dissipated spontaneously in one or two days. There were no other adverse events except one case of varicella virus infection and one case of mild alopecia. In addition, six patients complained of gastrointestinal discomforts like nausea after taking MTX orally. No patient discontinued ADA and MTX treatment due to severe adverse events. (**Table 3**).

Discussion

Uveitis is one of the leading causes of ocular morbidity and blindness.[1] Systemic corticosteroids, in combination with conventional DMARDs, are recognized as the first-line treatment for NIPPU in children.[4, 17-19] However, most NIPPU children initially treated with corticosteroids and conventional DMARDs often fail to achieve control of their inflammation or would require a very long time to reach remission with high relapse rate.[14, 20] During this period, the cumulative use of corticosteroids may have a significant impact on the growth and development of children, including growth restriction, behavior change, osteonecrosis, muscle weakness, increased appetite, acne, thrush, stomach upset, or trouble sleeping.[4, 5] Moreover, long-term ocular inflammation may also cause irreversible visual impairment.[21, 22] ADA has been proven to have ideal efficacy in a series of rheumatic diseases including NIU. In the adult population, treatment of NIPPU with ADA, either active or inactive at baseline, has been demonstrated to reduce disease relapse and maintain visual acuity, as shown in the VISUAL I and II clinical trials.[12, 23] ADA has also been proved to be a good treatment option in children with JIA-U. ADA can control the ocular inflammation and was associated with a lower rate of treatment failure than placebo in JIA-U patients.[9] However, no studies explored the remission rate and corticosteroid-spring effects of ADA as initial treatment for active pediatric NIPPU. Thus, this is the first study to present these data and evidence while providing a reference for future pediatric NIPPU treatment.

The time to reach remission of traditional MTX plus corticosteroids therapy is 16.6 to 35.2 months with a remission rate range from 60% to 76.6%.[14] In contrast, most patients in our study (23/30, 76.67%) attained ocular inflammation remission within six months, and 90.0% of our patients (27/30) reaching remission at 12 months, with a shorter to reach remission (5.3 months). This suggests a much superior efficacy of the ADA plus MTX treatment regimen.

In an attempt to protect pediatric patients from acquiring too many deleterious side-effects associated with corticosteroids use, Heiligenhaus

has advocated that the pediatric corticosteroids dose (typically 1 to 2 mg/kg/day) should be tapered to under 0.15 mg/kg/day within 4 weeks and the duration limited to 3 months only.[19] Our study's average initial corticosteroids dose (0.43 mg/kg/day) was lower than the typical recommended dose, with most children withdrawing from corticosteroids use in a short time (14.2 weeks). To our knowledge, no previous study has counted the cumulative corticosteroids use in pediatric NIU patients. The median total amount of corticosteroids use in our study was 456.25 mg. In conclusion, compared with conventional DMARDs treatment, ADA plus MTX treatment can provide a good corticosteroid-sparing effect and reduce the dependence on oral corticosteroids.

During the 1-year follow-up, all ocular inflammatory parameters improved rapidly and continuously. Visual function and retina structure also improved greatly in our study. Of note, cystic macular edema (CME) is a significant cause of visual loss in patients with uveitis. In the present study, 25.9% of the eyes (14/54) had visible cystic changes in macula at baseline. After one year treatment, the central MT experienced a significant decrease. CME was only detected in two eyes of BD patients who failed to respond to ADA treatment. The complete resolution rate of CME in this study was 85.7% (12/14), higher than 54.5% observed in the previous pilot study of 19 patients.[24] In conclusion, using ADA in the early stage of uveitis can effectively reduce ocular inflammation and mitigate macular edema, showing a good protective effect on the anterior and posterior segment of the eye.

Recurrent uveitis greatly harms children's eyes. As inflammation relapses each time, the entire course of treatment restarts with high-dose corticosteroids, which indicates greater risk correlated with corticosteroids. What's more, resistance to previous immunosuppressants usually develops after relapse, requiring a change in the treatment regimen.[25] In this study, only 11.1% patients (3/27) in remission had a recurrence of ocular inflammation during the follow-up period. Compared with a previous study,[26] our remission rate is much lower than MTX plus corticosteroids, indicating that ADA plus MTX therapy in pediatric NIU can effectively maintain the remission state and avoid any sequalae due to recurrence.

As we know, corticosteroid-induced IOP elevation and cataract formation remain the most significant local risks following topical as well as systemic corticosteroid administration.[27] In the present study, due to the lower doses and shorter duration time of topical and systemic corticosteroids, IOP controlled well in all patients during follow-up without new OHT developed. What's more, no new complicated cataracts occurred during follow-up. Of note, after the stabilization of inflammation and oral corticosteroid withdrawal for at least 6 months, two eyes from two patients underwent cataract phacoemulsification and intraocular lens (IOL) implantation surgery with carefully operation. Topical corticosteroids were intensified during the postoperative period. Both eyes achieved good BCVA at 12 months without complications such as OHT, posterior capsular opacification, retrolental membranes, IOL capture and dislocated IOL.[28] This suggests that under the comprehensive management of topical corticosteroids and ADA plus MTX, cataract surgery is safe and effective in pediatric NIU patients with stable ocular inflammation for a long enough time.

In previous study, ADA showed a good safety and efficacy profile in elderly and young patients.[29, 30] Low incidence of AE has been proved in different age groups. Our study also confirmed the safety of ADA and MTX in children with active NIPPU. The most common adverse events during the follow-up period were local skin redness and itching due to ADA injection and gastrointestinal discomfort due to oral MTX.

One limitation of this pilot study is no control group. Another limitation is the small sample size and heterogeneity of uveitis etiology. A future prospective RCT is needed to confirm the superiority of ADA plus MTX treatment as initial treatment for pediatric NIPPU. Regardless, to the best of our knowledge, this is the first study to investigate the efficacy and safety of ADA plus MTX as initial treatment on Chinese children with NIPPU, while also confirming a good corticosteroid-sparing effect of ADA.

Conclusion

In summary, more aggressive ADA therapy as initial medication might lead to better prognosis and provide a good corticosteroid-sparing effect in

children with NIPPU.

Conflict of Interest Statement: The authors declare that they have no competing interests.

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