

Methotrexate for Severe Childhood Atopic Dermatitis: Clinical Experience in a Tertiary Center

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Abstract

Background/Objectives: Atopic dermatitis (AD) affects up to 20% of children. Although the majority of patients are adequately controlled using emollients, topical corticosteroids, topical calcineurin inhibitors, or phototherapy, children with moderate to severe AD may require systemic treatment for control. The objective of the current study was to evaluate the efficacy and safety of methotrexate in children with severe AD attending a tertiary referral center.

Methods: A retrospective chart review was undertaken of all children who received methotrexate for severe AD at our tertiary referral center from November 2010 to August 2015.

Results: Forty-seven children were started on methotrexate for AD during this period. The mean Investigator Global Assessment (IGA) at the 3- to 5-month follow-up improved from 4.25 to 2.8, with further improvement to 1.9 in the patients that continued therapy beyond 10 months. Changes in the Children's Dermatology Life Quality Index (CDLQI) mirrored changes in the IGA, with improvement in the mean CDLQI from 14.4 at the start of the treatment to 7.5 at the 3- to 5-month follow-up. Further improvement in the CDLQI to 6.6 in patients who continued methotrexate beyond 10 months confirmed continued improvement in disease control beyond medium-term therapy. The treatment was well tolerated.

Conclusions: Methotrexate appears to be an effective, safe treatment for severe pediatric AD. Its therapeutic effects continue beyond the medium-term treatment period, as reflected by further improvement in IGA and CDLQI scores in patients who continued methotrexate therapy beyond 10 months.

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Childhood atopic dermatitis (AD) is a common inflammatory skin disorder. Emollients, topical corticosteroids, and calcineurin inhibitors fail to adequately control moderate to severe disease in many cases and systemic therapy may then be required (1,2). Traditionally used immunomodulatory agents include cyclosporine and azathioprine. Cyclosporine has a rapid onset of response and continues to be the first choice of therapy in Europe, but adverse effects of nephrotoxicity and hypertension limit its long-term use (3). Azathioprine has a slower onset of response and recent reports of late-onset adverse effects, including skin cancer and hepatosplenic T-cell lymphoma, have discouraged its use in children.

Only a few reports of methotrexate use in children for treatment of AD have been published and include only one randomized controlled trial of low-dose cyclosporine versus low-dose methotrexate (4). Deo et al (5) published a retrospective review of 31 children with severe AD treated with methotrexate and Roberts et al (6) described a case series of 25 patients with discoid eczema who responded to methotrexate treatment.

Despite this small body of evidence, methotrexate is prescribed for severe AD in children, as reported in the European TReatment of severe Atopic eczema in children Taskforce (TREAT) survey of several European centers that treat large numbers of children with severe AD (3). Better evidence of short- and long-term efficacy and a safety profile of methotrexate in children with AD is needed.

METHODS

A retrospective review was undertaken of the treatment course of all patients 18 years of age or younger who had commenced methotrexate therapy for severe AD between November 2010 and August 2015 in our tertiary referral pediatric dermatology department. Local ethics committee approval was obtained. Demographic and clinical data, including sex, Fitzpatrick skin type, age of onset of AD, disease duration before methotrexate treatment, age at methotrexate commencement, comorbidities, and immunoglobulin E level were recorded. Previous hospital admissions for AD management, phototherapy, or systemic immunomodulator therapy were noted. The severity of AD at each visit was qualitatively recorded and subsequently quantified using an Investigator Global Assessment (IGA) tool (0 = clear, 1 = nearly clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe). The effect of AD on quality of life was documented with respect to sleep disturbance because of itching,

school absences, and self-reported effect on social life. The Childhood Dermatology Life Quality Index (CDLQI) was consistently recorded at each visit in approximately half of patients. Because the data were collected primarily for clinical management, SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) were not recorded. Our treatment regimen was to start on a full therapeutic dose of methotrexate (0.3–0.5 mg/kg single dose, once per week) after a successful trial of a test dose of 5 mg, with no further increments unless it was felt necessary for better control of AD. Methotrexate formulation and dose (in mg/kg), treatment duration, and follow-up period after treatment were noted for each patient in the study.

Because methotrexate has a slow onset of action, efficacy was assessed only in patients who had completed more than 3 months of treatment. Changes in IGA and CDLQI, improvement in sleep disturbance, and reduction in topical corticosteroid use were assessed, depending on the data available because of different follow-up frequencies, after 3 to 5 months of treatment (medium-term treatment) and at 10 to 14 months of treatment (long-term treatment). Adverse effects were analyzed for all patients who received at least one methotrexate dose, with particular emphasis on hematologic and biochemical profiles, gastrointestinal disturbances, infectious complications, and fatigue. Mean IGA scores and standard deviations were calculated and differences between two means were statistically analyzed using the Student *t* test. P-values <0.05 were considered statistically significant.

RESULTS

Patient Demographic Characteristics

Forty-seven patients started methotrexate treatment for AD between November 2010 and August 2015 (32 boys [68.1%], 15 girls [31.9%]). The mean age of onset of AD was 14.5 months (range 0 mos to 8 yrs, median 4 mos). Demographic and disease comorbidity details are summarized in Table 1.

Treatment with methotrexate was started at a mean age of 11.6 years (range 2–18 yrs). The mean disease duration at the start of methotrexate therapy was 10.3 years (range 20 mos–17.9 yrs), reflecting well-established chronic AD. Thirty-six (76.6%) children had undergone prior treatment with other modalities in addition to topical management with corticosteroids, calcineurin inhibitors, emollients, and baths (Table 2). Twenty-five children (53.2%) had

TABLE 1. Patient Demographic and Baseline Characteristics (*N* = 47)

Characteristic	Value
Sex, <i>n</i> (%)	
Male	32 (68.1)
Female	15 (31.9)
Fitzpatrick skin type, <i>n</i> (%)	
I, II	42 (89.4)
III	0 (0)
IV	1 (2.1)
V	2 (4.3)
VI	2 (4.3)
Eczema type, <i>n</i> (%)	
Generalized	44 (93.6)
Pompholyx	3 (6.4)
Age of atopic dermatitis onset, median (range)	14.5 mos (0 mos–8 yrs)
Comorbidities, <i>n</i> (%)	46 (97.9)
Asthma	27 (57.4)
Allergic rhinitis	15 (31.9)
Food allergy	27 (57.4)
Egg allergy	22 (46.8)
Ichthyosis vulgaris	15 (31.9)
Methicillin-resistant <i>Staphylococcus aureus</i> colonization	4 (8.5)
Recurrent herpes simplex infection	7 (14.9)
Other	
Recalcitrant mollusca	2 (4.3)
Achondroplasia	1 (2.1)
Vitiligo	1 (2.1)
Perinatal human immunodeficiency virus exposure with prophylaxis	1 (2.1)
Eosinophilic oesophagitis	1 (2.1)
Scoliosis	1 (2.1)
Hurler syndrome with bone marrow transplant	1 (2.1)
Anorexia nervosa	1 (2.1)
Atopic keratoconjunctivitis	2 (4.3)
Costochondritis	1 (2.1)
Autistic spectrum disorder	2 (4.3)
Obstructive sleep apnoea	1 (2.1)
Adrenal insufficiency	2 (4.3)
Visual impairment	1 (2.1)
Background of meningitis, epilepsy, and learning disability	1 (2.1)
Anxiety	1 (2.1)
Immunoglobulin E level, kU/L, mean (range)	10,761.7 (5.6–54,220)
Effect of atopic dermatitis, <i>n</i> (%)	
Sleep disturbance	43 (91.5)
Frequent school absence	27 (57.4)
Social life affected	33 (70.2)
Referral to psychology	13 (27.7)

previously been admitted for management of AD before considering systemic therapy. To minimize flare-up of AD when transitioning to methotrexate, 12 patients had no washout period between their previous therapy and methotrexate and had overlapping treatment with another systemic medication (7 oral corticosteroid, 3 prolonged course of an antibiotic, 2 overlap taper of previous systemic immunosuppressant [1 briefly maintained on methotrexate plus

TABLE 2. Treatment Characteristics (*N* = 47)

Characteristic	Value
Age at methotrexate commencement, years, mean (range)	11.6 (2–18)
Atopic dermatitis duration at methotrexate commencement, mean (range)	10.3 yrs (20 mos to 17.9 yrs)
Prior treatment, <i>n</i> (%)	36 (76.6)
Azathioprine	8 (17)
Cyclosporine	8 (17)
Narrowband ultraviolet light B	4 (8.5)
Intravenous immunoglobulin	1 (2.1)
Oral corticosteroid	16 (34)
Long-term antibiotic	18 (38.3)
Hospital admission	25 (53.2)
Parallel treatment at methotrexate commencement, <i>n</i> (%)	12 (25.5)
Oral corticosteroid	7 (14.9)
Long-term antibiotic	3 (6.4)
Azathioprine	1 (2.1)
Cyclosporine	1 (2.1)
Methotrexate formulation, <i>n</i> (%)	
Oral	40 (85.1)
Subcutaneous	1 (2.1)
Both	6 (12.8)
Treatment duration of first completed methotrexate course, months, mean (range)	17.2 (5–33)

azathioprine, 1 on methotrexate plus cyclosporine)). The remaining 24 patients had a washout period ranging from 0.5 to 60 months (mean 10.4 mos).

Methotrexate Dosing Schedule

The mean methotrexate dose was 0.34 mg/kg (0.2–0.5 mg/kg) as a single weekly dose. The predominant methotrexate formulation used was oral (*n* = 40 [85.1%]), with only one patient receiving subcutaneous methotrexate at treatment initiation. Six patients had used oral and subcutaneous formulations, in all cases transferring to subcutaneous methotrexate because of gastrointestinal intolerance of oral methotrexate. At the time of data collection, methotrexate treatment was ongoing in 33 patients (30 first course and 3 second course after relapse). One patient was lost to follow-up after 5 months of treatment. One patient experienced no clinical improvement before 3 months of treatment was completed; his treatment was stopped and he was subsequently lost to follow-up. One patient discontinued methotrexate after three doses because of chest tightness experienced with each dose; his treatment was changed to azathioprine. Fourteen patients successfully completed their first course of methotrexate

(clear or nearly clear when treatment discontinued) during the study period, with a mean treatment duration of 17.2 months (range 5–33 mos). Three patients subsequently received a second methotrexate course because of disease relapse (Fig. 1).

Medium- and Long-Term Efficacy

The 44 patients who completed at least 3 months of methotrexate treatment were included in the medium-term efficacy analysis (Table 3). Assessment timing ranged from 3 to 5 months depending on follow-up scheduling. Thirteen patients had completed 3 months, 22 had completed 4 months, and 9 had completed 5 months of treatment at the time of the assessment. The mean baseline IGA in this group was 4.25 ± 0.65 , improving to 2.8 ± 0.8 at the 3- to 5-month follow-up (Fig. 2). The mean treatment difference in IGA was 1.45 (95% confidence interval 1.25, 1.66; $p < 0.001$).

Thirty children who completed at least 10 months of treatment were included in the long-term efficacy assessment (Table 4). Assessment timing for this

TABLE 3. *Medium-Term Methotrexate Treatment Efficacy (3–5 mos) (n = 44)*

Factor	Value
Investigator global assessment, mean $\pm$ standard deviation (range)	
At commencement	4.25 ± 0.65 (3–5)
At 3–5 mos	2.8 ± 0.8 (2–5)
Treatment difference, mean (95% confidence interval), p-value	1.45 (1.25–1.66), <0.001

group ranged from 10 to 14 months, depending on scheduling. Six patients completed 10 months of therapy, 22 completed 12 months, 1 completed 13 months, and 1 completed 14 months. The mean IGA at 10 to 14 months of follow-up improved to 1.90 ± 0.84 , indicating further continued improvement achieved with long-term methotrexate treatment. The CDLQI was reliably recorded at the start of treatment and at the 3- to 4-month follow-up for 19 patients. The mean CDLQI at the start of the treatment was 14.4 (range 2–22) and improved to a mean of 7.5 (range 1–20) at the 3- to 4-month follow-up. Of this group, a further 12 patients had a recorded CDLQI at the 10- to 12-month follow-up; these also

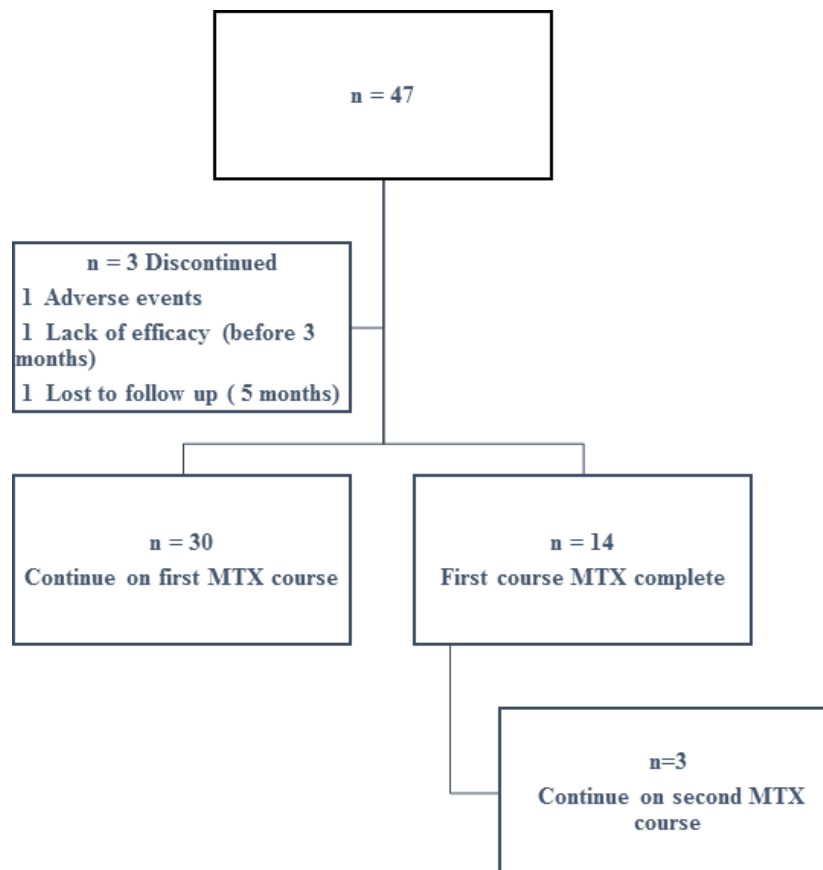


Figure 1. Summary of patients included in this study.

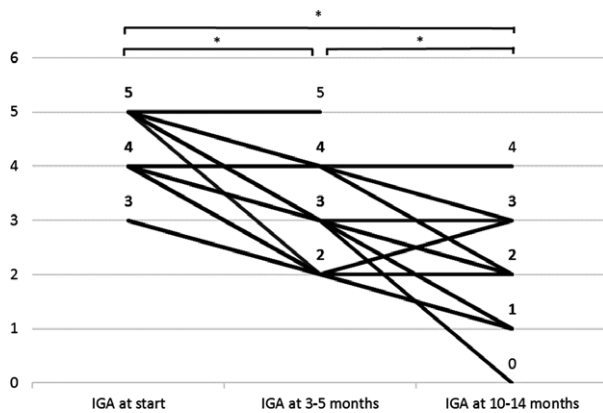


Figure 2. Improvement in investigator global assessment score with methotrexate treatment. * $p < 0.001$.

TABLE 4. Long-Term Methotrexate Treatment Efficacy (10–14 mos) ($n = 30$)

Factor	Value
Investigator global assessment, mean $\pm$ standard deviation (range)	
At commencement	4.37 $\pm$ 0.67 (3–5)
At 10–14 mos	1.9 $\pm$ 0.84 (0–4)
Treatment difference, mean (95% confidence interval), p-value	2.47 (2.12–2.82), <0.001

continued to improve (mean 6.6, range 1–14) with continued long-term methotrexate therapy (Tables S1 and S2).

The mean time to the first noticeable improvement that patients or their parents reported was 11.3 weeks (range 3–24 wks) after starting methotrexate. At the medium-term follow-up, 29 of 44 patients (65.9%) reported a reduction in itch and 33 (75%) reported a decrease in topical steroid use. Of 40 patients who initially complained of nocturnal sleep disturbance caused by pruritus, 29 (72.5%) reported improved sleep (Table S3).

Ten (22.7%) children experienced no flare-up during their methotrexate treatment and 31 (70.5%) experienced a mild flare-up treated with a topical corticosteroid, minor methotrexate dose adjustment, or both. Two patients were prescribed a short course of an oral corticosteroid for a flare-up during their methotrexate therapy and one patient was admitted for inpatient treatment of an AD flare (Table S4).

Safety and Tolerability

All 47 patients who received at least one methotrexate dose were included in the adverse event analysis. Thirty-nine (83%) children experienced at least one adverse event (Table S5). The most frequently

encountered laboratory abnormalities included mild and mostly transient elevation of transaminases, mild isolated hyperbilirubinemia, and transient hematologic abnormalities (mild lymphopenia, neutropenia, normocytic anemia). None necessitated a dose reduction or discontinuation of therapy. Gastrointestinal side effects of nausea, vomiting, and abdominal pain after a methotrexate dose occurred in 29.8% of children and were managed using antiemetic medication (ondansetron at an age- and weight-appropriate dose, given three times over the 24 hours preceding the methotrexate dose), methotrexate dose adjustment, or a switch to subcutaneous delivery of medication. Seventeen percent of children experienced mild fatigue 24 to 48 hours after methotrexate administration. There were four serious adverse events (Table S6). A 12-year-old girl with Hurler syndrome who had had a previous bone marrow transplant was hospitalized for community-acquired pneumonia; methotrexate treatment was withheld for the duration of this illness. Several months later, she again developed community-acquired pneumonia while not taking methotrexate, and methotrexate was subsequently restarted with no further infectious episodes. A second patient developed post-streptococcal glomerulonephritis after having group A streptococcal pharyngitis. His methotrexate was withheld for 2 months and successfully restarted. Another 12-year-old boy was admitted with bullous impetigo 12 weeks into methotrexate treatment, which was continued throughout this episode. Finally, a 9-year-old boy with inadequately controlled asthma experienced chest tightness and wheezing after each of his first three methotrexate doses. He was evaluated in the emergency department after the third methotrexate dose and no abnormalities were detected on clinical examination or electrocardiogram. He was discharged home and his systemic therapy was switched to azathioprine.

DISCUSSION

AD is the most common inflammatory pediatric skin condition and, when moderate to severe, is associated with a significant effect on quality of life for patients and their families. The American Academy of Dermatology guidelines and European consensus guidelines for severe refractory cases recommend a trial of a systemic immunomodulatory agent in the form of cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil (7,8). Cyclosporine is the only product licensed for severe AD in Europe. Many studies of systemic immunomodulatory treatment of

AD in adults have been published but evidence of efficacy and safety in the use of these agents in children is lacking. As a result, there is wide variation in prescribing practices for refractory AD, as demonstrated by the European TREAT survey (3).

An early case series of 27 children treated with cyclosporine demonstrated good short-term effects, with reasonable tolerability, with a subsequent long-term use study showing more durable remission with continuous use of cyclosporine than with one or more 12-week courses of cyclosporine (9,10). A study by Sibbald et al (11) also suggests that a longer duration of low-dose cyclosporine may help decrease the risk of relapse in children with refractory AD, although prolonged use of cyclosporine is associated with renal dysfunction and hypertension, which are particularly concerning in children, and therefore some physicians use a short-term course of cyclosporine to achieve initial disease remission with a subsequent switch to one of the other systemic immunomodulatory agents for long-term disease control. A potential strategy to reduce cumulative cyclosporine dose using intermittent short-course weekend cyclosporine therapy was recently explored in a small case series (12).

A small prospective study and two retrospective studies in children and young adults indicated that azathioprine may be suitable for medium-term use in pediatric AD (13–15), but azathioprine has a malignancy black box warning based on the risk of hepatosplenic T-cell lymphoma, not just in a previously identified risk group of boys with inflammatory bowel disease, but also in patients with rheumatoid arthritis and older adults receiving a combination of a tumor necrosis factor alpha inhibitor and immunomodulators (16).

Mycophenolate mofetil is another potential immunomodulator for treatment of AD in children, with good efficacy demonstrated in two small retrospective pediatric case series (14,17). Recent phase 1 and 2 studies investigating a targeted approach with the interleukin-4 receptor-alpha antibody dupilumab for the treatment of AD in adults have been published with promising results (18,19).

A 12-week randomized controlled trial comparing methotrexate (at lower-than-usual therapeutic doses) with cyclosporine, with further follow-up of 12 weeks, demonstrated comparable efficacy (4). In keeping with our clinical experience, methotrexate had a longer onset of action than cyclosporine but a more durable relapse-free period after discontinuation of the drug. The remaining evidence for the use of methotrexate in severe childhood AD comes from retrospective case series (5,6,20). The use of methotrexate in children for

neoplastic and inflammatory disease, including linear morphea, psoriasis, inflammatory bowel disease, and juvenile idiopathic arthritis, has become more widespread and has a reasonable safety profile with well-known, predictable adverse effects. Our retrospective study offers further evidence that methotrexate is effective in treating childhood AD in the medium term, with continued improvement for up to 12 months of treatment, as demonstrated by continued improvement in IGA and CDLQI beyond 3 to 5 months of treatment. Adverse effects experienced were consistent with known methotrexate adverse effects and were mild in the majority of cases.

Its retrospective design, reflecting clinical experience with global outcomes recorded in the context of a busy clinical service instead of the preferred validated scoring measures, such as EASI or SCORAD, as would be used in the setting of a clinical trial, limited our study. CDLQI scores were consistently recorded in only approximately half of the patients. Nevertheless, these clinical data add significantly to the body of experience with methotrexate in AD.

In summary, the results suggest that methotrexate is an effective option for severe, recalcitrant childhood AD, with an acceptable adverse event profile when used in medium- to long-term management of AD, with continued improvement in severity of disease extending beyond 3 to 5 months of treatment. Further studies in the form of a large-scale randomized controlled trial are required to compare the efficacy and long-term safety of methotrexate with those of cyclosporine in the management of severe childhood AD.

ETHICAL APPROVAL

Local ethics committee approval was obtained for this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Medium-Term Children's Dermatology Life Quality Index Improvement ($n = 19$) (3–4 mos).

Table S2. Long-Term Children's Dermatology Life Quality Index Improvement ($n = 12$) (10–12 mos).

Table S3. Other Medium-Term Self-Reported Outcomes ($n = 44$) (3–5 mos).

Table S4. Treatment of Flare-Up During Treatment ($n = 44$).

Table S5. Adverse Events ($n = 47$).

Table S6. Serious Adverse Events.

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Table 1. Medium-Term Children's Dermatology Life Quality Index Improvement (n=19) (3–4 Months)

Score	Mean (Range)
At commencement	14.4 (2–22)
At 3–4 months	7.5 (1–20)

Table 2. Long-Term Children's Dermatology Life Quality Index Improvement (n=12) (10–12 Months)

Score	Mean (Range)
At commencement	13.8 (3–22)
At 10–12 months	6.6 (1–14)

Table 3. Other Medium-Term Self-Reported Outcomes (n=44) (3–5 Months)

Outcome	Value
Reduction in pruritus, n (%)	29 (65.9)
Reduction in topical steroid use, n (%)	33 (75.0)
In patients that reported sleep disturbance (n=40)	
Improvement in sleep, n (%)	29 (72.5)
Weeks to first noticeable improvement, mean (range)	11.3 (3–24)

Table 4. Treatment of Flare-Up During Treatment (n=44)

Treatment	n (%)
No flare	10 (22.7)
Topical corticosteroid, methotrexate dose adjustment, or both	31 (70.5)
Short oral corticosteroid course	2 (4.5)
Hospital admission	1 (2.3)

Table 5. Adverse Events (n=47)

Adverse Event	n (%)
Any	39 (83.0)
Biochemical	16 (34.1)
Hematologic	11 (23.4)
Gastrointestinal	14 (29.8)
Fatigue	8 (17.0)
Stomatitis	1 (2.3)
Infection	7 (14.9)
Miscellaneous	4 (8.5)

Table 6. Serious Adverse Events

Patient (Comorbidity)	Serious Adverse Event	Outcome
12-year old girl (Hurler syndrome with previous bone marrow transplantation)	Community-acquired pneumonia requiring hospital admission	Methotrexate temporarily held and successfully restarted
11-year old boy (autism spectrum disorder, obstructive sleep apnoea)	Post-streptococcal glomerulonephritis	Methotrexate temporarily held and successfully restarted
12-year old boy	Bullous impetigo	Methotrexate continued
9-year old boy (inadequately controlled asthma)	Chest tightness and wheezing	Methotrexate discontinued after 3 doses

