Title Page

(i) Title:

Monitoring recommendations for oral azathioprine, methotrexate, and cyclosporin in a paediatric dermatology clinic and literature review.

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(i) Abstract and Key Words

Background:

Systemic oral immunomodulators azathioprine, methotrexate, and cyclosporin, are widely used in paediatric dermatology. Routine blood tests are performed to minimise drug-related adverse events. However, the frequency of testing for monitoring may lead to significant fearful patient experiences.

Objectives:

We aim to review haematological abnormalities and clinical side effects in a paediatric clinic population commencing immunomodulators for dermatological conditions, where haematological profiles are monitored less frequently compared with current recommendations.

Methods:

A retrospective chart review of children starting on azathioprine, methotrexate, or cyclosporin for a dermatological condition between the years 2001-2015 from a primarily paediatric private Dermatology practice was performed. Blood tests were done at baseline, one month, two months, and then three-monthly for children on azathioprine. Children on methotrexate and cyclosporin had tests done at baseline, after one month, and then three-monthly.

Results:

A total number of 242 children were included in this study. Azathioprine, methotrexate, and cyclosporin cohorts had 95, 97, and 50 patients with mean duration of 656, 758, and 313 days, respectively. Isolated abnormal blood test indicated cessation of azathioprine in three of 95 (3.2%), methotrexate in five of 97 (5.2%), and cyclosporin in two of 50 (6.0%). Abnormal

blood test results were not associated with any reported clinical side effects in azathioprine group ($p=0.726$), methotrexate group ($p=0.06$) and cyclosporin group ($p=0.250$).

Conclusion: In our experience, less frequent monitoring did not result in any significant adverse events over a 15-year period. We suggest that haematological monitoring during immunosuppressants use can be safely reduced from current recommendations.

Key Words: azathioprine, methotrexate, cyclosporin, paediatric dermatology, blood test monitoring, adverse effects, immunomodulators

(ii) Text

Introduction

Azathioprine, methotrexate and cyclosporin are systemic immunomodulatory agents widely used in paediatric dermatology. They are cornerstones for treatment when topical treatments have been exhausted and inadequate in patients whose medical, physical, or psychological states are negatively influenced by their inflammatory or autoimmune dermatological condition.¹⁻³

Routine monitoring by blood tests is important to minimise drug-related adverse events. However, blood tests can be a fearful experience, being the most difficult part of a child's hospital experience.⁴ According to The European TReatment of severe Atopic eczema in children Taskforce (TREAT) survey, the necessity for blood test monitoring was identified as a barrier to the use of systemic agents in children with atopic eczema.³

The frequency of monitoring whilst on immunomodulators is generally determined by guidelines directed for both adults and paediatrics collectively. A comprehensive guideline for atopic dermatitis by Sidbury et al. discussed follow-up monitoring for azathioprine, methotrexate and cyclosporin.¹ Patients on azathioprine are advised to have complete blood count and differentials, liver function, and renal function twice per months for two months, monthly for four months, and then every other month.¹ Methotrexate follow-up monitoring includes complete blood count and differentials and liver function weekly for two to four weeks, two-weekly for one month, and then two to three monthly when dose is stable. Blood test should be repeated one week after any major dose increase. Renal function test should be done every 6 to 12 months.¹ Cyclosporin monitoring of renal function, liver function, lipid

profile, complete blood count and differentials, magnesium, potassium, uric acid is two-weekly for two to three months, then monthly. After an increase dose, blood test should follow after two to four weeks. If serum creatinine increases by 25%, dose should be reduced by 1mg/kg/day for two to four weeks followed by repeat creatinine test.¹

There are limited literature examining monitoring protocols in the paediatric population using immunomodulators azathioprine, methotrexate, and cyclosporin for dermatological indications. Recent studies have safe and less frequent monitoring in paediatric atopic dermatitis using azathioprine⁵ and juvenile idiopathic arthritis using methotrexate⁶. Efficacious results of cyclosporin have made it an attractive choice of treatment. However, the fear of toxicity in comparison to azathioprine and methotrexate have inflicted reservations in its use. Recent studies have found that children tolerate cyclosporin better than adults.⁷

Our aim is to review haematological abnormalities and clinical side effects in a paediatric clinic population commencing azathioprine, methotrexate, and cyclosporin for dermatological conditions, where haematological profiles are monitored less frequently compared with current recommendations.

Methods

Study design

We performed a retrospective chart review of children, aged 18 years or younger, commencing azathioprine, methotrexate or cyclosporin through a single paediatric dermatologist clinic between the years 2001 to 2015. Subjects were excluded if treatment duration was not recorded. All patients followed the same protocol for dosage and blood test monitoring frequency (Table 1).

Target dose for azathioprine was 2.5mg/kg/day. Baseline test included full blood count (FBE), urea, electrolytes and creatinine (UEC), liver function test (LFT), IgE, and thiopurine methyltransferase (TMPT) activity. Subjects started at third dose for three weeks and then two-third dose for three weeks. Repeat tests were done after one month, whilst on two-third dose. If there were no issues, subjects advanced to full dose with another blood test one month after dose change. Further monitoring was done every three-monthly using FBE, UEC, and LFT. Lymphocyte count were used as a non-specific marker for toxicity. The aim was to maintain lymphocyte counts above $1.0 \times 10^9/L$ and dose increase could be considered if lymphocytes counts were $> 1.7 \times 10^9/L$. Slower dose increments and increased frequency of monitoring were performed if baseline TPMT activity was low.

Methotrexate dose ranged between 0.4-0.6mg/kg/week. Folic acid 5 mg was also prescribed weekly. Patients were commenced with half dose for two weeks and monitored for clinical side effects. Full dose followed if there were no issues. Baseline and monitoring tests (FBE, UEC, LFT) were done before treatment, one month after starting treatment, and three-monthly.

Cyclosporin was started at 5mg/kg/day in divided doses. If patients responded to treatment, dosage was reduced by 1mg/kg/day in divided doses. Baseline screening included FBE, UEC, LFT, magnesium, fasting lipid profile, and blood pressure (BP). Monitoring tests were identical to baseline screening tests with the addition of two-hour post-dose cyclosporin level. Tests were performed one month after commencing cyclosporin and then repeated three-monthly. The aim was to keep cyclosporin levels <1000 ng/mL. Cyclosporin levels were done to aid monitoring of long term toxicity and patient's compliance in taking cyclosporin. Test was repeated after any dose increase or if creatinine levels increased by >30% from baseline.

Outcome Measurements

The outcome variables were abnormal blood test, clinical side effects, and reason for ceasing immunomodulators. Abnormal blood test was defined as any result outside of the laboratory normal range. A "significant abnormal blood test" translated to change in dose, cessation of medication, or association with clinical side effects. Statistical analysis with Person's Chi Squared test and Fisher's exact test were used to identify associations. Cox proportional hazard model was used to analyse association between abnormal blood test and the time to side effect. Cases were censored at the final date of data collection.

Results

Azathioprine

We identified 101 patients aged 18 years old or under in our retrospective chart review. Six patients had no recorded duration on azathioprine, and were excluded. Of the excluded patients, one parent decided not to start their child on azathioprine and five patients were lost to follow-up. A total of 95 patients were included in our study. There were 42 (44.2%) females and 53 (55.8%) males, with the mean age 10.6 years (range 2-18 years). Mean duration was 656 days (range 4-2095 days). The indications for azathioprine included

eczema in 88 (92.6%), prurigo nodularis in four (4.2%), and alopecia areata in three (3.2%) patients.

Abnormal Blood Test

Mild abnormalities in baseline tests remained stable in six patients in their ongoing monitoring. Baseline TPMT activity was intermediate in two patients and low in three patients. One patient with intermediate activity of TPMT was found to have transient thrombocytopenia. He continued azathioprine without any complications or clinical side effects. One patient with low activity of TPMT stopped azathioprine because he had also developed elevated liver transaminase, but did not report clinical side effects.

New abnormal blood tests were found in 22 (23.4%) patients during follow up (Table 2). Nineteen (20.0%) patients had transient abnormal tests that normalised after repeat testing and did not have associated clinical side effects. Recorded cases of transient abnormal blood test included 12 cases of lymphopaenia (3 out of 12 were $<1.0 \times 10^9/L$), four elevated hepatic transaminase, four neutropenia, one thrombocytopenia, and one anaemia.

Significant abnormal tests in three (3.2%) patients resulted in cessation of azathioprine. Two patients had consistently elevated hepatic transaminase (mean aspartate aminotransferase (AST) 62.5U/L and mean alanine aminotransferase (ALT) 65U/L), but no reported clinical side effects. The mean time at cessation was 42 days of treatment. One patient stopped azathioprine after 35 days of treatment due to significant abnormal blood test with elevated hepatic transaminase (AST 62U/L and ALT 52U/L) and drug hypersensitivity.

Clinical Adverse Events

Clinical side effects were reported in 13 of 95 (13.7%) patients and are outlined in Table 3. Seven (7.4%) patients discontinued azathioprine after experiencing clinical side effects. These included three cases of nausea and vomiting and separate single cases of infection, rash, headache, and hypersensitivity syndrome.

Statistical Analysis of Azathioprine

Baseline factors of age, sex and condition were not associated with side effects and abnormal blood tests. The finding of abnormal blood tests was also not associated with reported side effects ($p=0.726$) or termination of azathioprine due to side effects ($p=0.604$). Time to side effects analysis also showed no statistically significant association between number of abnormal blood test and time to side effects.

Methotrexate

Our retrospective chart review during the study period identified 104 patients, aged 18 years old or under, commencing methotrexate. Seven patients were excluded due to no recorded duration of methotrexate. Of the excluded patients, one had relocated, four patients' parent refused medication, and two were lost to follow up. Therefore, 97 total patients (35 males and 62 females) were included in our methotrexate cohort. The mean age of starting methotrexate was 9.0 years (range 2-18 years). The mean duration was 758 days (range 2-4447 days). The main indication for methotrexate for this cohort was eczema (59.8%) and psoriasis (30.9%). There were also four cases of morphea, two cases of prurigo nodularis, and separate single cases of lichen sclerosus et atrophicus, urticaria, and mid-dermal elastolysis.

Abnormal Blood Test

Twenty-four (24.7%) patients had abnormal blood tests during follow-up (Table 2). Nineteen of 24 (19.6%) patients' blood test abnormalities were transient and returned to normal range after repeat testing. One patient with transient mildly elevated hepatic transaminase also reported concomitant nausea at the same time. She did not stop methotrexate, and resolved her nausea by dose spitting and taking doses with meals.

Methotrexate was ceased due to significant abnormal blood tests in five (5.2%) patients. Four patients had recurrent elevated hepatic transaminase (mean AST 66U/L and mean ALT 111U/L; mean duration of treatment 282 days). One patient stopped methotrexate due to recurrent lymphopaenia (mean lymphocyte count of $0.4 \times 10^9/L$) and significant flu-like symptoms after 39 days of treatment.

Clinical Adverse Events

Twelve (12.4%) patients reported clinical side effects from methotrexate (Table 3). This included 5 (5.2%) patients, who stopped methotrexate due to clinical side effects. Two patients stopped due to nausea. There were separate single cases of lethargy, recurrent flu-like symptoms, and non-specific reason of "intolerance".

Statistical Analysis of Methotrexate.

Interestingly, we found transient abnormal tests to be more frequent in younger patients (mean 7.4 years, $p=0.03$) compared with the older patients (mean 9.76 years). Sex was not associated with abnormal blood test or side effects.

Abnormal tests were not associated with side effects ($p=0.06$), or with cessation due to side effects ($p=0.595$). No association was found in the time to side effects analysis.

Cyclosporin

The initial number of patients aged 18 years old or under in our cyclosporin cohort was 54 (28 males, 22 females). Four patients were lost to follow-up and had no recorded duration on cyclosporin. The mean age was 9.3 years (range 2-18). The mean duration patients were on cyclosporin was 313 days (range 4-1130 days). The most common treatment indication in this cohort was eczema in 42 (84%) cases, followed by psoriasis and urticaria, both having four (8%) cases.

Abnormal Blood Test

Nine (18%) patients developed abnormal follow-up blood tests from baseline. (Table 2) Abnormal tests was transient in seven (14.0%) patients and returned to normal range in subsequent testing. Two other patients with hypertriglyceridemia also reported gum hypertrophy with mean duration of treatment 387 days. Cyclosporin levels for both patients were below 1000ng/mL.

Serum creatinine levels in this cohort were all within normal range. Four patient had creatinine rise $>30\%$ above their baseline. Repeat levels of all four patients decreased to $<30\%$ above their baseline and cyclosporine treatment was continued without dose adjustment.

Clinical Adverse Events

Seven (14%) patients experience clinical side effects, of which four stopped cyclosporin due to side effects. (Table 3) One patient had nausea after 3 days, another had lethargy after 4 days, and two other had gum hypertrophy after 375 and 399 days of treatment.

Statistical Analysis of Cyclosporin

Baseline variables of age, sex and condition were not associated with side effects and abnormal blood tests. Abnormal blood test was not associated with side effects ($p=0.250$) or cessation due to clinical side effects ($p=0.089$). In the time to side effects analysis, no associations were obtained.

Discussion with Literature Review

Literature review, using PubMed and EMBASE, identified papers that have had similar objectives as our study. Our inclusion criterion included paediatric dermatology studies using azathioprine, methotrexate, or cyclosporin, describing blood test monitoring frequency, and conveying their rates of haematological abnormalities. Initial search resulted in 66, 140, and 92 articles for azathioprine, methotrexate, and cyclosporin, respectively. However, only four, six, and four studies fulfilled the inclusion criterion for azathioprine, methotrexate, and cyclosporin treatment in the paediatric dermatology populations, respectively.

Azathioprine

In our literature review, only four studies described frequency for blood test monitoring frequency and significant haematological findings. (Table 4) The dermatological condition in all four studies was atopic dermatitis. Dosage in studies ranged between 1.5 to 3 mg/kg/day. The monitoring frequencies in studies were different, ranging from weekly to monthly after baseline and one to three monthly when dose was stable.^{5, 8-10} Our study mean follow-up was 655.8 days (1.8 years) and was similar to Fuggle et al.⁵ and Murphy et al.'s¹⁰ retrospective studies of 2.14 and 2 years, respectively.

Blood test monitoring is important to detect azathioprine-related toxicity. Neutropenia, lymphopaenia, and deranged liver function may be relevant and indicate myelotoxicity, susceptibility to infection, and hepatotoxicity, respectively.² Our rate of cessation due to abnormal tests was three of 95 (3.2%) patients, which was slightly higher than Murphy et al. (2.1%)¹⁰ but lower than Fuggle et al. (9.8%)⁵. Similar to our findings, elevated hepatic transaminase was found to be the most common abnormal blood test resulting to azathioprine cessation.^{5,10} A prospective study done by Caufield et al.⁸ and a case report by Murphy et al.¹⁰ did not report any lab findings causing cessation.

Rates of abnormal tests that did not lead to azathioprine cessation were higher in Murphy et al.¹⁰ (not including eosinophilia) and Fuggle et al.⁵ (40.2% and 47.9%, respectively) compare to our study (20.0%). This may be difficult to compare, as abnormal blood test may be defined differently in each study. Similar to our study, lymphopaenia and elevated liver function were the most common abnormalities not requiring azathioprine termination.

Frequency of blood test monitoring in our study was similar to Murphy et al.'s suggestion to test FBE and LFT after four to 12 weeks of treatment and 12-weekly thereafter

(unless dose increased).¹⁰ We took a more conservative approach and started with one-third of full dose (2.5mg/kg/day) for three weeks and then two-third dose for three weeks. Prior to advancing full dose, patients were tested with FBE, LFT and UEC. Murphy et al. found that it was safe to start treatment as close as possible to full dose of 3mg/kg/day.¹⁰

Methotrexate

We found six studies using methotrexate in the paediatric population and discussing frequency of monitoring and haematological findings. (Table 5) The conditions treated with methotrexate included psoriasis,¹¹⁻¹³ atopic dermatitis¹⁴ and localised scleroderma^{15,16}. Weibel et al.'s study duration of treatment was similar to ours, but other studies were shorter.¹¹⁻¹⁶ Dose of methotrexate ranged between 0.03-0.9mg/kg/wk¹¹⁻¹⁶, similar to our dosing of 0.4 to 0.6mg/kg/wk. Our method of initiating methotrexate by starting half dose for two weeks and monitoring clinical side effects was not described by other studies. Monitoring frequency ranged between one week to three months from baseline, and four weeks to six months once treatment was stable.¹¹⁻¹⁶ Our study's rate of non-significant abnormal blood testing was more frequently found in the younger age group (mean 7.4 years). This was not described previously.

In reviewed studies, abnormal tests that were not significant and significant (requiring cessation) had a wide range from 0 to 69.2% and 0 to 15.4%, respectively.¹¹⁻¹⁶ Perhaps the variable rate of abnormal test findings may be influenced by the variable frequency in blood test monitoring. However, our rate (19.6%) of transient abnormal tests not requiring cessation was similar to the Deo et al. study rate of 19.4%.¹⁴ Deo et al. performed monitoring every three months and then every six months.¹⁴ This was half the frequency in comparison to our protocol (one month after starting and then every three months).

Our rate (5.2%) of significant abnormal blood tests requiring cessation of methotrexate was within the range of reported literature. Similar to other studies, the predominant abnormal test was deranged liver function. There has been a controversial suggestion regarding the role of liver biopsy in children. Some have suggested routine liver biopsy according at specific cumulative doses, while others have not.¹ In rheumatology literature, similar dosing in paediatric patients does not suggest liver biopsies unless indicated by abnormal blood test and physical examination.¹⁷

Methotrexate is generally a well-tolerated drug. Side effects commonly resolve by decreasing dosage or temporarily ceasing methotrexate.^{1,17} It is widely used in dermatology as well as rheumatology. Dosage ranges in juvenile idiopathic arthritis (JIA) are similar to

ranges used for dermatological conditions. The American College of Rheumatology guidelines for JIA includes monitoring (LFT, complete blood count, renal function) monthly after starting or changing dose and every three to four months when the dose is stable.¹⁸ This monitoring frequency is similar to our protocol and perhaps can be considered as safe guidelines for dermatological conditions.

Cyclosporin

In our literature review for cyclosporin, we found four relevant studies that fit inclusion criteria. Two were case reports^{19,20} and two were prospective studies^{21,22}. (Table 6) Only one case report had a longer duration of 12 months compared with our study (mean 10.3 months).²⁰ Prospective studies observed duration of cyclosporin for six and eight weeks.^{21,22} All studies had different doses ranging from 0.5 to 5 mg/kg/day.¹⁹⁻²² Monitoring frequency ranged between two to six weeks from baseline and two-weekly to monthly when dose was stable.¹⁹⁻²²

Few abnormal haematological findings have been reported in literature. One study reported a single case of creatinine greater than 30% baseline.²¹ All patients in our cyclosporin cohort had serum creatinine within normal range throughout their treatment. Four patients had increased creatinine greater than 30% from baseline, but this was safely resolved by repeating blood test within two weeks and reducing dose if indicated. All patients were able to continue cyclosporin safely without associated side effects. Proposed mechanism of reduced nephrotoxicity in children may be due to higher clearance or decreased bioavailability.²³ The four reviewed studies did not report significant blood test abnormalities requiring cessation of cyclosporin. Two percent of our cohort had significant blood test requiring termination of cyclosporin due to hypertriglyceridemia. The level of hypertriglyceridemia was not life-threatening, but we felt that it was more appropriate to switch treatment rather than introduce lipid-lowering therapy in children.

Conclusion

Azathioprine, methotrexate, and cyclosporin were safely used and monitored in our study. Similar rates and types of significant and non-significant abnormal blood tests were found in comparison to previous literature. There were no statistically significant associations between abnormal tests and side effects in all subgroups. In our time to side effects analysis, there was no overall association between time to side effects and abnormal blood tests. Each case with abnormal test result was reviewed for clinical relevance. The only case that was

significant was a single case of hypersensitivity syndrome and elevated hepatic transaminase in our azathioprine subgroup. Our patients with abnormal tests and clinical side effects that required cessation of immunomodulators had fully normalised parameters after cessation and had no residual clinical effects. In our experience, less frequent monitoring did not result in any significant adverse events over a 15-year period. We suggest that haematological monitoring during immunosuppressants use can be safely reduced from current recommendations.

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(iv)Tables

Table 1: Study Protocol

	Azathioprine	Methotrexate	Cyclosporin
Dosing	2.5mg/kg/day. Start 1/3 dose for 3 weeks, then 2/3 dose for 3 weeks, then full dose if no issues	0.4-0.6mg/kg/week Start ½ dose for 2 weeks and monitored clinical side effects	5mg/kg/day in divided dose If patients were doing well, reduce dose by 1mg/kg/day in divided dose
Baseline Test	FBE, UEC, LFT, TPMT, IgE	FBE, UEC, LFT	FBE, UEC, LFT, Magnesium, Lipids. BP done by paediatrician or general practitioner
Monitoring Test and Frequency	FBE, UEC, LFT after 1 month (on 2/3 dose), 2 months (on full dose), and then 3-monthly	FBE, UEC, LFT after 1 month and then 3-monthly.	FBE, UEC, LFT, Magnesium, Lipids and cyclosporin level after 1 month and then 3-monthly BP done by paediatrician or general practitioner.
Specific Consideration for further blood test	<ul style="list-style-type: none">Lymphocytes counts was used as a non- specific marker for toxicity and aimed		<ul style="list-style-type: none">Aimed Cyclosporin level <1000 ng/mLRepeat blood test within 2 weeks if creatinine level

	above $1.0 \times 10^9/L$ <ul style="list-style-type: none"> • Slower increments and more bloods test for patients with baseline low TPMT activity 		increased by >30% from baseline
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Blood pressure (BP) full blood count (FBE), liver function test (LFT), urea, thiopurine methyltransferase (TPMT), electrolytes, urea, and creatinine (UEC),

Table 2: New blood test abnormalities during study follow up

Blood test description	Azathioprine number of event(s)	Methotrexate number of event(s)	Cyclosporin number of event(s)
Transient abnormal blood, did not indicate termination of immune modulatory drug			
Lymphopaenia	12	2	1
Elevated hepatic transaminase	4	13	1
Neutropenia	4	1	1
Thrombocytopenia	1	5	0
Anaemia	1	2	0
Serum Creatinine	0	0	0

Lipid Profile	Not measured	1	2
Cyclosporin level	Not measured	Not measured	3
Abnormal blood test, indicated termination of immune modulatory drug			
Elevated hepatic transaminase	3	4	0
Lymphopaenia	0	1	0
Lipid Profile: Hypertriglyceridemia	0	0	2
Neutropenia	0	0	0

Table 3: Clinical adverse events reported during study follow up

Clinical Adverse Events Description	Azathioprine number of event(s)	Methotrexate number of event(s)	Cyclosporin number of event(s)
Nausea ± vomiting	4	7	4
Infection	2	2	
Lethargy	1	1	1
Headache	2		
Pruritus	2		
Alopecia	1		
Hypersensitivity syndrome	1		

Non-specific reason of “intolerance”		1	
Flu-like symptoms		1	
Gingival Hypertrophy			2

Table 4: Literature review of azathioprine monitoring frequency and haematological findings

Study	Disease	Patient Demographics	Dosing	Duration	Haematological Monitoring Frequency	Haematological Findings
Fuggle et al, ⁵ 2015 RCS	AD	Total: 82 (54 M, 28 F) Age: Mean 8.3 years (SEM 0.4)	2.0- 3.5mg/ kg/d	Mean 2.14 years	Baseline: FBE, hepatic transaminases, TPMT level, Vit D, VZV, Hep B and C, HIV, HHV-8 serology, Mantoux in high risk Monitoring frequency: Weeks 1, 3, 7 and then 3-monthly FBE, hepatic transaminases	Not indicating cessation: Total = 33 patients (40.2%), 37 events <ul style="list-style-type: none"> Leukopenia, lymphopaenia, neutropenia = 24 Elevated LFT = 11 Abnormal FBE and elevated LFT = 2 Indicating cessation: Total = 8 patients (9.8%) <ul style="list-style-type: none"> Neutropenia = 1

						<ul style="list-style-type: none"> Elevated LFT = 1 Temporary cessation due to CBC (2), LFT (4) = 6
Caufield and Tom, ⁸ 2013 PSS	AD	Total: 12 (4 M, 8 F) Age: Median 9.0 years, Range 2.6-18.1 years	1.5 - 3.4mg/kg/d	Range 7-12 months	Type of blood test not specific mentioned Monitoring frequency: Week 0, 2,4,8, 12, and then 4- 8 weeks	Not indicating cessation: Total = 10 patients (83.3%) <ul style="list-style-type: none"> Elevated transaminase = 6 Neutropenia = 4 Reported no lab findings indicated cessation
Murphy and Atherton, ⁹ 2003 CR	AD	14-year-old male	1.25mg/kg	10 months	BL: TPMT, FBE, UEC, LFT Monitoring frequency: Weeks 2,4,8	No significant lab findings
Murphy and Atherton	AD	Total: 48 (28 M, 20 F)	2.0-3.5mg/kg	Kept patients on for ~ 2	BL: TPMT, FBE, serum urea, Cr, and LFT	Not indicating cessation: Total = 23 patients (47.9%) <ul style="list-style-type: none"> Macrocytosis = 3

, ¹⁰ 2002		Age of entire screened group: Mean 82.5 months, Range 6-16 years		years	Monthly for 6 months and approximately 6-weekly thereafter	<ul style="list-style-type: none"> • Lymphopaenia = 15 • Thrombocytopenia = 1 • Abnormal LFT = 4 <p>Indicating cessation: Total = 1 patient (2.1%)</p> <ul style="list-style-type: none"> • Abnormal LFT = 1
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Adverse event (AE), atopic dermatitis (AD), baseline (BL), case report (CR), creatinine (Cr), full blood count (FBE), hepatitis B (HepB), hepatitis C (HepC), human herpesvirus -8 (HHV-8), human immunodeficiency virus (HIV), liver function test (LFT), prospective study (PSS), retrospective case series (RCS), urea, thiopurine methyltransferase level (TPMT), urea, electrolytes, and creatinine (UEC), varicella zoster virus (VZV)

Table 5: Literature review of methotrexate monitoring frequency and haematological findings

Study	Disease	Patient Demographics	Dosing	Duration Mean (range)	Haematological Monitoring Frequency	Haematological Findings
Van Geel et	Plaque-like Ps	Total: 25 (13 M, 12 F)	0.2 - 0.63mg/kg/wk	Mean 60.4 weeks	BL: haematological analysis, serum chemistry, hepatitis B and C serology	Did not report haematological findings that were abnormal and did not require cessation

al ¹¹ ,2015	PSS	Age: Mean 15 years, Range 6-17 years		(12.6-163.4 weeks)	Monitoring frequency: Week 1, 3, 6, 9, 12. 12-weekly after	Indicating cessation: Total = 2 patients (8%) <ul style="list-style-type: none"> • Raised LFT = 1 • Raised Cr = 1
Deo et al ¹⁴ ,2014	AD RCS	Total: 31 (14 M, 17 F) Age: Mean 10 years, Range 3-18 years	According to age 5-15mg/kg/wk	Median 9.5 months (2-38 months)	BL: FBE, LFT, renal function Monitoring frequency: 3-monthly and decreased 6-monthly if parameters were stable	Not indicating cessation: Total = 6 patients (19.4%) <ul style="list-style-type: none"> • Elevated LFT = 4 • Normocytic anemia = 2 Reported no lab findings indicated cessation
Collin et al ¹² , 2009	Plaque Ps RCS	Total: 13 (4 M, 9 F) Age: Mean 12.1 years, Range 5-6 years	0.03-0.41mg/kg/wk	Mean 71 weeks (2-267 weeks)	BL: FBE, UEC, Cr, LFT Monitoring frequency: Weekly and decreased 4-6-weekly once treatment was stable	Not indicating cessation: Total = 9 patients (69.2%) <ul style="list-style-type: none"> • Raised LFT = 9 Indicating cessation: Total = 2 patients (15.4%) <ul style="list-style-type: none"> • Raised LFT = 2

Kaur et al ¹³ , 2008	Ps	Total: 24 (20 M, 4 F) Age: Mean 11.3 years, Range 2.5-14	0.2-0.4mg/kg/wk	Mean 4.97 months (2-16 months)	BL: FBE, LFT, Renal function, Serological test of HIV and Hep B Monitoring frequency: FBE 2-weekly LFT 2-monthly Renal function 3-monthly	No significant alterations in the laboratory parameters
Weibel et al ¹⁵ , 2006	Localised Scleroderma (morphea)	Total: 34 Female to male ratio 2:1 Age Mean 8.2 years (SD 3.5)	Initial pulsed IV methylprednisolone, followed by oral prednisolone MTX 10 +/- 3.5mg m ⁻² /wk - mean maximum dose 12.4 +/- 4.3mg m ⁻² /kg	Mean 2.9 +/- 2.0 years	BL: ESR, ANA, smooth-muscle antibodies Monitoring frequency: Every 4-6 weeks FBE, electrolytes, urea, creatinine and LFT	Not indicating cessation: Total = 10 patients on MTX (29.4%) <ul style="list-style-type: none"> Elevated LFT = 5 Lymphopaenia <1500/uL = 3 Neutropenia <1500/uL = 2 Indicating cessation: Total = 2 patients (5.9%) <ul style="list-style-type: none"> Elevated LFT = 1 Lymphopaenia = 1

Fitch et al ¹⁶ , 2006 RCS	Localised scleroderma	Total: 17 (6 M, 11 F) Age disease onset: Mean 7.3 years, Range 2-14 years	0.3-0.9mg/kg/wk	Mean MTX alone 1.9 years. MTX + corticosteroids 1.3 years. (4 months to 5 years)	BL: FBE, LFT ANA, Urinalysis, ESR only for Baseline Monitoring frequency: Monthly for 2 months, then 2- monthly	Not indicating cessation: Total =1 patient (5.9%) • Increase LFT =1 Reported no lab findings indicated cessation
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Adverse event (AE), atopic dermatitis (AD), baseline (BL), case report (CR) creatinine (Cr), full blood count (FBE), hepatitis B (HepB), hepatitis C (HepC), human immunodeficiency virus (HIV), liver function test (LFT), methotrexate (MTX), prospective study (PSS), psoriasis (Ps), retrospective case series (RCS), urea, electrolytes and creatinine (UEC)

Table 6: Literature review of cyclosporin monitoring frequency and haematological findings

Study	Disease	Patient Demographics	Dosing	Duration	Haematological Monitoring Frequency	Haematological Findings
Kim et al ¹⁹ ,	Pustular Ps	8 year old male	0.5mg/kg/d - 1mg/kg/day	2 months	BL: FBE, LFT, Cr	Transient rise of ALT without cessation of cyclosporine

2006					Monitoring frequency: 2 weekly	
CR						
Perrtt et al ²⁰ , 2002	Severe Psoriasis	3 Cases CR 1: 9 year old male CR 2: 7 year old male CR 3: 11 year old male	CR 1: 0mg/kg/day - 3mg/kg/day CR 2: 3mg/kg/day - 3.5mg/kg/day CR 3: 3mg/kg/day	CR 1: 12 months CR 2: 4 months CR 3: 8 weeks	BL: FBE, LFT, renal function, Blood pressure. Lipid profile was only done at BL. Monitoring frequency: Fortnightly for 1 month, monthly for 2 months, then 2 every 2 months	All cases had no significant findings reported
Bunik owski et al ²¹ , 2001 PSS	Atopic Dermitis	Total: 10 (5M, 5F) Age: Mean 106 months, Range	Range: 2.5 - 5 mg/kg/day	8 weeks	BL: haematological and biochemical parameters, Blood pressure Monitoring frequency: 2-weekly	Not indicating cessation: <ul style="list-style-type: none"> • Cr > 30% from baseline but had low baseline = 1 (10%) • Elevated bilirubin = 2 (20%) • Cholesterol, triglycerides, hepatic transaminases, GGT, ALP, potassium,

		22-189 months)				and uric acid, did not show significant increase. Number cases not discussed. Reported no lab findings indicated cessation
Berth-Jones et al ²² , 1996 PSS	AD	Total: 27 13 M 14 F Age: Mean 9years Range 2-16 years	5mg/kg/day in divided dose	6 weeks	BL: FBE, Cr, LFT, Blood pressure Monitoring frequency: Week 6	No clinically significant rise in serum creatinine and Blood pressure. Liver function remained within normal range.

Adverse events (AE), alanine aminotransferase (ALT), atopic dermatitis (AD), baseline (BL), case report (CR) creatinine (Cr), full blood count (FBE), hepatitis B (HepB), hepatitis C (HepC), human immunodeficiency virus (HIV), liver function test (LFT), methotrexate (MTX), prospective study (PSS), psoriasis (Ps), urea, electrolytes, and creatinine (UEC)

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