



Treatment outcomes of oral immunosuppressants in the treatment of atopic dermatitis

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1 Acknowledgement

I would first like to thank my supervisor, Dr Peter Arkwright for his continuous support and encouragement during this project. Secondly, the Manchester Medical School had provided me with the technical support that I needed. Lastly, I really appreciate that BAD recognised my project by choosing me as one the undergraduate project grant recipients.

2 Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory pruritic skin disease that affects more than 20% of children in many high-income countries. Most patients can be adequately managed with topical treatments. Children with recalcitrant AD have a poorer quality of life and may require alternative treatment modalities such as oral immunosuppressants. This retrospective study explored the treatment outcomes of ciclosporin (CsA) and azathioprine (AZA) in managing children with recalcitrant AD in a single tertiary paediatric eczema referral centre in Manchester, UK.

2 Methods

2.1 Setting

A retrospective survey recruited 58 children with severe atopic dermatitis (AD) who had received either oral CsA or oral AZA over a span of 15 years (From 2003 to 2017) at a specialised AD clinic. The tertiary referral AD clinic, which is part of the Department of Paediatric Allergy and Immunology, specialises in the management of children with AD that are not adequately managed with standard topical treatments.



Picture 1: With my project supervisor, Dr Peter Arkwright
in front of the Royal Manchester Children Hospital



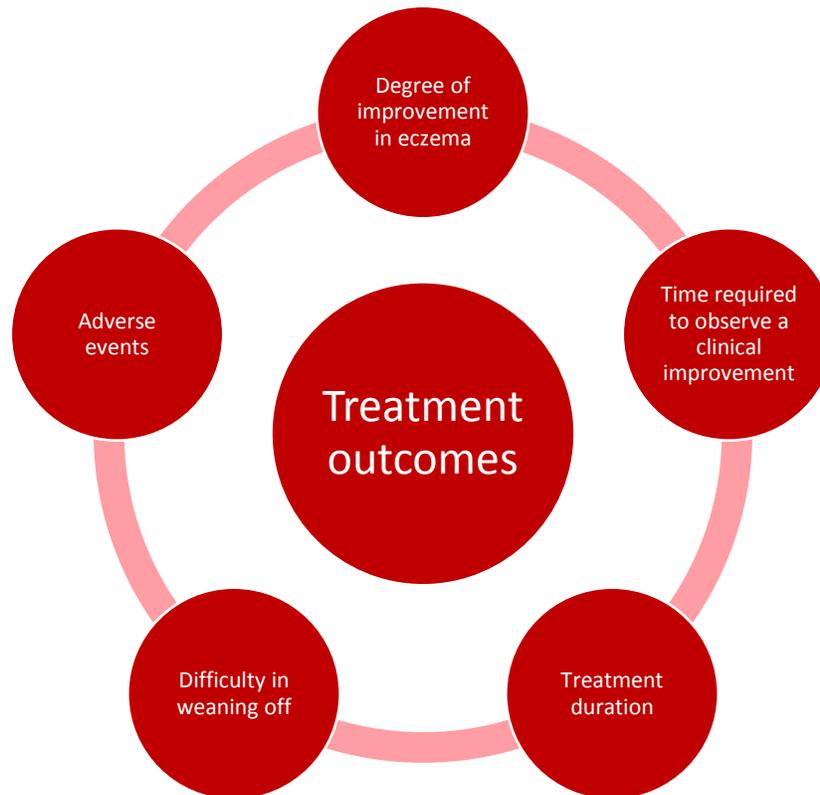
Picture 2 With the staffs working in the Paediatric Eczema clinic

2.2 Ethical approval and data collection

The hospital database (Medisec) was used to identify patients with severe AD who were under the age of 18 when either CsA or AZA were commenced. The treatment outcomes of both oral immunosuppressants were then compared using five parameters as illustrated by figure 1. The data collected was accurate and consistent as all patients were being monitored by one physician working in a single department.

The starting dose of oral CsA was always 5 mg/kg/day, while oral AZA was always commenced at a dose of 2 mg/kg/day. The dose of CsA was slowly weaned depending on patients' response to reduce the potential of developing side effects. Immunosuppressants were stopped if no improvement was noted after a month on CsA, or 3 months after commencing AZA. While on oral immunosuppressants, all patients were advised to continue with regular use of standard topical treatments.

Figure 1: Parameters used to compare the treatment outcomes of CsA and AZA



2.3 Statistical analysis

The SPSS version 23 software was used to carry out statistical analysis relevant to the study. The relationship between two categorical variables was explored using the chi-squared test. As not all the data was normally distributed, Mann-Whitney U test was used to evaluate the relationship between two independent groups when the dependent variable were continuous variables. A p-value of less than 0.05 was considered statistically significant. Binary logistic regression was used to calculate the odds ratio with gender, ethnicity, atopic disease and allergy related triggers as covariates.

3 Results

3.1 Treatment outcomes of Ciclosporin (CsA) and Azathioprine (AZA)

In this study, both CsA and AZA were commenced in patients with a median age of 6 years old. Clinical characteristics of the two groups depending on the oral immunosuppressants they had are summarised in Table 1. Overall, more than 80% of the children experienced either a major improvement in their AD or their skin were completely cleared after taking one of these two oral immunosuppressants. (P-value = 0.8) Two-fifths of individuals treated with CsA (39%) and 61% of those on AZA had trouble weaning off their medications due to recurrent flares. (P-value = 0.1) 24% of children on CsA and 33% of the children on AZA experienced adverse events such as eczema herpeticum, molluscum infections and chickenpox. (P-value = 0.4) The adverse events associated with taking either oral immunosuppressants in this study are summarised in Table 2. Time required to observe a clinical improvement and treatment duration were statistically different between the treatment groups. Children taking CsA had a more rapid clinical improvement (3 weeks) compared with those taking AZA (9 weeks) (P-value < 0.001). Patients on CsA were also found to have a significantly shorter treatment duration (18 weeks) as compared to those treated with AZA (37 weeks) (P-value = 0.02).

3.2 Variables influencing outcomes of the Ciclosporin (CsA) and Azathioprine (AZA) treatment groups

Multi-variate analysis showed that gender, ethnicity, atopic disease, and allergy-related AD triggers, did not influence the degree of improvement in eczema. However, children treated with CsA who had allergy-related triggers were found to be 4.8 times more likely to experience difficulty weaning compared to those who did not have allergy-related triggers. On the other hand, having allergy-related triggers did not make it more difficult for those being with managed with AZA to be weaned off the medication (Table 3).

4 Conclusion and Recommendations

Both CsA and AZA were found to be highly effective in treating the majority of children with AD poorly responsive to topical therapy. The beneficial effect of CsA were usually observed with a month, while effects of AZA took a median of 2 months to be seen. CsA could usually be weaned off within 4 months, while AZA took a median of 9 months to wean. Multiple allergic triggers significantly retarded the rate at which patients on CsA could be weaned off this medication. One in ten patients suffered from cutaneous viral infections (particularly localised herpes simplex skin infections) while on these medications and therefore it is important to ensure that both patients and clinicians looking after them are aware of these complications and how to treat them.

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Appendix 1: Abstract

Background Ciclosporin and azathioprine are used to treat atopic dermatitis (AD) that are not adequately managed with standard topical treatments such as emollients and topical immunosuppressants.

Methods The aim of this study is to evaluate the treatment outcomes of using ciclosporin and azathioprine to manage children with severe AD. A retrospective survey was conducted involving a cohort of 58 children with recalcitrant AD. There were 47 participants on ciclosporin and 18 on azathioprine because seven participants who were initially treated with ciclosporin switched to azathioprine after no improvement was observed with ciclosporin. 5 parameters including degree of improvement in eczema, time required to observe a clinical improvement, treatment duration, difficulty in weaning off and adverse events were used to evaluate treatment outcomes.

Results Children treated with ciclosporin required a significantly shorter time to observe a clinical improvement (3 weeks) as compared to children on azathioprine (8 weeks). (P-value < 0.001) Treatment duration was also significantly shorter for children managed with ciclosporin (18 weeks) as compared to those on azathioprine (37 weeks). (P-value = 0.02) Participants on ciclosporin who have allergy-related triggers were found to be 4.8 times more likely to have difficulty in weaning off ciclosporin as compared to those who do not have allergy-related triggers. (95 % confidence interval)

Conclusion 82-85% of all patients had major improvements with oral immunosuppressants. in this cohort, ciclosporin induced a more rapid clinical effect and could be weaned off more quickly than azathioprine.

Appendix 2: Data tabulation and statistical analysis

Table 1 Treatment outcomes of Ciclosporin and Azathioprine

		Ciclosporin (n = 47)	Azathioprine (n = 18)	P value
Age (years) when oral immunosuppressant was started (median, range)		5 (1 - 17)	6 (2 - 13)	0.5
Improvement in eczema number (%)	Little improvement	7 (15%)	3 (18%)	0.8
	Nearly cleared	39 (85%)	14 (82%)	
Time (weeks) to clinical improvement (median, range)		3 (1 - 15)	8 (2 - 16)	0.001
Treatment duration (weeks) (median, range)		18 (2 - 109)	37 (12 - 100)	0.02
Difficulty weaning		18 (39%)	11 (61%)	0.1
Adverse events		11 (24%)	6 (33%)	0.4

Statistics: Discrete variables Chi squared test; Continuous variables Mann-Whitney U test

Table 2 Adverse events associated with Ciclosporin and Azathioprine

		Ciclosporin (n = 47)	Azathioprine (n = 18)
Cutaneous viral infections	Eczema herpeticum	4 (9%)	2 (11%)
	Warts	4 (9%)	0
	Molluscum	1 (2%)	2 (11%)
	Chickenpox	1 (2%)	1 (6%)
GI symptoms		2 (4%)	0
Deranged liver function tests		1 (2%)	0
Erythema multiforme		0	1 (6%)

Table 3 Variables associated with difficulty in weaning off the oral immunosuppressant

	Ciclosporin (n = 47)		Azathioprine (n = 18)	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Gender	1.0	1.0	0.8	0.9
Ethnicity	0.3	0.1	0.3	0.5
Asthma	0.7	0.7	-	1.0
Rhinitis	2.0	0.3	-	1.0
Allergy-related triggers	4.8	0.03	-	1.0

Statistics: Binary logistic regression: Odds ratio (95 % confidence interval)

Appendix 3: Patient information leaflets used in RMCH



HEALTHY SKIN	ECZEMA – A DAMAGED SKIN BARRIER	RESTORING THE SKIN BARRIER USING AN EMOLIENT*
<p>In healthy skin, moisturising factors help skin cells swell and fats and oils fill spaces between plump skin cells to form a natural skin barrier – keeping moisture in and irritants out.</p> <p>Skin cells and the surrounding fats and oils are often shown as a brick wall. The skin cells are the 'bricks' and the fats and oils the 'mortar'.</p>	<p>In atopic eczema there is a shortage of fats and oils surrounding the skin cells. The skin cells shrink, opening cracks which allow moisture to escape quickly and irritants to enter.</p> <p>The skin reacts causing redness, inflammation and is very itchy. Scratching damages the skin further. This leads to more irritation, itching and further scratching.</p>	<p>Emollients rehydrate dry skin by forming a layer of oil which traps moisture in the skin allowing cells to swell and close the cracks.</p> <p>Emollients should be applied at least twice a day, or more frequently if needed, in large amounts to moisturise and soften the skin. This makes the skin supple and less itchy. It is important to continue using emollients even when the skin appears to be better.</p>
<p>What causes inflammation?</p> <p>If irritants cross the skin barrier the skin reacts causing inflammation. This is the body's natural defence system to protect against its enemies (irritants and bacteria).</p> <p>In atopic eczema, the body can overreact and 'flare up' in response to irritants and bacteria which would usually be harmless.</p>	<p>Reducing inflammation</p> <p>When the skin 'flares up' additional creams and ointments will be used (e.g. topical steroids), to reduce the inflammation and redness. Continue using emollients when the eczema flares as they will help the other eczema treatments, but apply them alternately, leaving sufficient time to allow the first cream, gel or ointment to soak in.</p> <p>If the skin is red and itchy it may be due to the reaction of the skin to bacteria (e.g. Staph aureus) which is more common on atopic skin. The doctor may prescribe a treatment to reduce the number of these bacteria and help remove the cause of irritation.</p>	<p>Avoiding irritants</p> <p>There are many factors in the environment that can make eczema worse, some only apply to certain individuals but common ones include soap, detergents, changes in temperature and dust.</p> <p>More information about eczema is given overleaf with some helpful suggestions about avoiding irritants or trigger factors that can make eczema worse.</p>
<p>Presented with the compliments of Dermal www.dermal.co.uk</p>		