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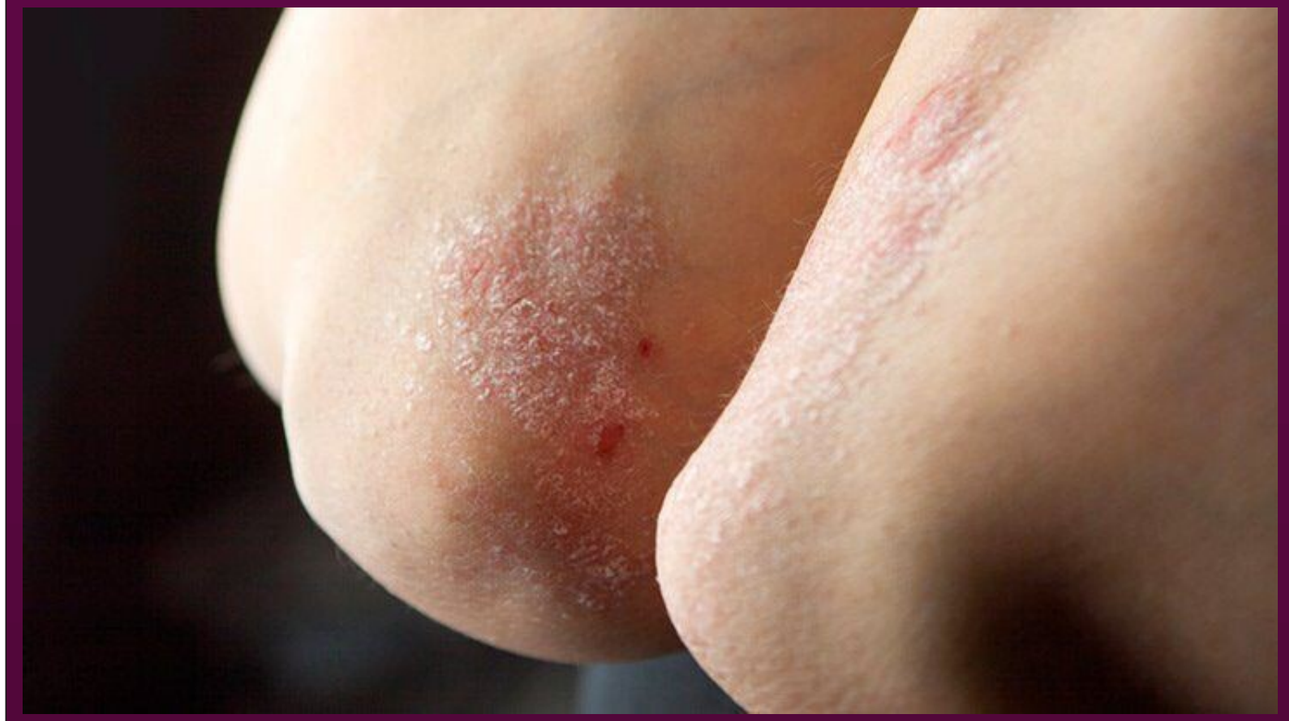
Azathioprine Compendium In Dermatology



EXECUTIVE SUMMARY

AZATHIOPRINE IN DERMATOLOGY

- Azathioprine helps to reduce prednisolone dose in long-run.
- Weekly azathioprine pulse appears to be an effective treatment for chronic plaque psoriasis, and can be used as an alternative therapy to other available therapeutic agents
- In particular narrowband ultraviolet B, was respondents' preferred first line treatment for adults with recalcitrant moderate to severe atopic eczema, perhaps reflecting access to, and clinical experience of, this approach. Azathioprine is widely used as a longer term maintenance treatment.
- Azathioprine 300 mg weekly pulse and 100 mg daily dose are equally effective and safe in the treatment of Parthenium dermatitis.
- Azathioprine helps to reduce prednisolone dose in long-run.
- MTX and AZA seem to be effective and safe as maintenance treatments in moderate-to-severe AD up to 5 years. Few patients in both groups survive on their originally allocated drug although some discontinued because of controlled AD.
- A strong clinical recommendation was given for azathioprine in atopic dermatitis. Conclusions regarding safety in an off-label setting could not be reached because of scarce and incomplete data (level C
- Evidence). Long-term registries and prospective studies could add to the existing evidence and provide legal support for off-label drug use in dermatology.

AZA: Azathioprine,
IBD: Inflammatory Bowel diseases,
MP: Mercaptopurine,
OR: Overall Response,
MTX: Methotrexate,
AD: Atopic Dermatitis,
ANCA: Antineutrophil cytoplasmic antibodies,
TPMT: Thiopurine methyltransferase,
MMF: Mycophenolate Mofetil,
ASyS: antisynthetase syndrome,
SNVs: Systemic necrotizing vasculitides,
EGPA: Eosinophilic Granulomatosis with Polyangiitis,
LN: Lupus Nephritis,
CsA: cyclosporine
CRR: Complete Renal Remission, prednisone (PRED)

AZATHIOPRINE IN DERMATOLOGY

REVIEW ARTICLES

CLINICAL TRIALS

RANDOMIZED CONTROLLED TRIALS

SYSTEMATIC REVIEWS

Review

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

Joy Yee, David Orchard

Australas J Dermatol. 2018 Feb; 59(1):31-40.

Background and Aims

Systemic oral Immunomodulators azathioprine, methotrexate and cyclosporine are widely used in paediatric dermatology. Routine blood tests are performed to minimise drug-related adverse events. However, the frequency of monitoring tests may lead to significant fearful experiences for patients. We reviewed haematological abnormalities and clinical side-effects in a paediatric clinic population commencing Immunomodulators for dermatological conditions, where haematological profiles are monitored less frequently than in current recommendations.

Method

A double blind randomized controlled study was conducted on 56 new patients, assigned to two therapeutic groups: (i) prednisolone plus placebo; (ii) prednisolone plus Azathioprine. Patients were checked regularly for 1 year. 'Complete remission' was defined as healing of all lesions after 12 months, and prednisolone <7.5 mg daily, (DAI = 1). Analysis was done by 'Intention to Treat' (ITT) and 'Treatment Completed Analysis' (TCA).

Result

Both groups were similar in age, gender, disease duration, and DAI. Primary endpoint: By ITT and TCA, the mean DAI improved in both groups with no significant difference between them. The difference became significant for the last trimester (3 months; ITT: P = 0.033, TCA: P = 0.045). Secondary endpoint: The total steroid dose decreased significantly in both groups, with no significant difference between them, except for the last trimester (ITT: P = 0.011, TCA: P = 0.035). The mean daily steroid dose decreased gradually in both groups becoming statistically significant in favour of azathioprine, in the last trimester, especially at 12th months (ITT: P = 0.002, TCA: P = 0.005). Complete remission was significant at 12 months only for TCA (AZA/Control: 53.6%/39.9%, P = 0.043).

Conclusion

Azathioprine helps to reduce prednisolone dose in long-run.

https://pubmed.ncbi.nlm.nih.gov/27435804/

Clinical Trials

Effectiveness of weekly azathioprine pulse in the treatment of chronic plaque psoriasis: an open-label study.

P Verma, et.al.

Clin Exp Dermatol. 2016 Oct; 41(7):717-22.

Background and Aims

Azathioprine is a potent immunosuppressive drug that has been used in many immune-mediated diseases. There are a few reports of its use in psoriasis; however, azathioprine weekly pulse doses have not been evaluated in this disease. The objective of this study was to evaluate the therapeutic effectiveness of weekly oral pulse doses of azathioprine for the treatment of chronic plaque psoriasis, and to determine the side effects of this regimen both clinically and biochemically.

Method

In this open-label clinical trial, a 300 mg bolus dose of azathioprine was given once every week orally for 24 weeks to patients with chronic plaque psoriasis having body surface area involvement of = 10% and Psoriasis Area and Severity Index (PASI) of = 10. Patients were evaluated every 4 weeks for 24 weeks to determine the response to treatment and any adverse effects (AEs), and then followed up for a further period of 12 weeks to determine any relapse of the disease.

Result

There were 50 patients in the study, of whom 28 (56%) completed the 24 weeks of treatment and 27 (54%) completed the 12-week post-treatment follow-up. Azathioprine 300 mg weekly pulse was effective in achieving PASI 75 in 42% of patients, PASI 90 in 36% of patients and PASI 100 in 22% of patients. In five patients (10%), the therapy had to be withdrawn due to Aes

Conclusion

Weekly azathioprine pulse appears to be an effective treatment for chronic plaque psoriasis, and can be used as an alternative therapy to other available therapeutic agents.

https://pubmed.ncbi.nlm.nih.gov/27663145/

AZATHIOPRINE IN DERMATOLOGY

Clinical Trials

Treatment of moderate-to-severe atopic eczema in adults within the U.K.: results of a national survey of dermatologists

K. Taylor D.J. Swan A. Affleck.et.al.

Br J Dermatol. 2018 Jun; 178(6):1288-1296.

Background and Aims

Little is known about U.K. dermatologists' treatment approaches towards adult patients with recalcitrant moderate-to-severe atopic eczema. We wanted to learn about (i) treatment approaches used for this disease in the U.K.; (ii) factors that influence treatment decisions and (iii) perceived gaps in evidence on treatment safety and efficacy, and priorities for future trials

Method

We conducted an online survey of consultant-level dermatologists in the U.K.

Result

Sixty-one respondents from over 30 centres reported on management of moderate-to-severe atopic eczema in adults, out with the context of an acute flare. Phototherapy or psoralen–ultraviolet A was the most common therapeutic modality chosen first line (46%), and this was usually narrowband ultraviolet B. Systemic therapy was chosen as a first-line approach by 36% of dermatologists. Azathioprine was the commonest drug reported being used as first line followed by oral corticosteroids, cyclosporine and methotrexate. Methotrexate was the most common second-line treatment of respondents. The key factors that influenced decision making on the use of phototherapy and systemic agents were the respondent's clinical experience, results of baseline tests (systemic agents) and knowledge of both efficacy and acute and chronic side-effect profiles. The most important evidence gaps identified were the relative effectiveness of treatments, the alternatives to current approaches and the safety of long-term maintenance treatment. With regard to future trials, respondents suggested that priority should be given to studies involving methotrexate.

Conclusion

While survey study designs have limitations, we found that phototherapy, in particular narrowband ultraviolet B, was respondents' preferred first-line treatment for adults with recalcitrant moderate-to-severe atopic eczema, perhaps reflecting access to, and clinical experience of, this approach. Azathioprine is widely used as a longer-term maintenance treatment.

https://pubmed.ncbi.nlm.nih.gov/27943248/

RCT'S

Weekly azathioprine pulse versus daily azathioprine in the treatment of Parthenium dermatitis: A non-inferiority randomized controlled study.

Kaushal K Verma, et.al.

Indian J Dermatol Venereol Leprol. May-Jun 2015; 81(3):251-6.

Background and Aims
Azathioprine in daily doses has been shown to be effective and safe in the treatment of Parthenium dermatitis. Weekly pulses of azathioprine (WAP) are also effective, but there are no reports comparing the effectiveness and safety of these two regimens in this condition. The aim is to study the efficacy and safety of WAP and daily azathioprine in Parthenium dermatitis.

Method
Sixty patients with Parthenium dermatitis were randomly assigned to treatment with azathioprine 300 mg weekly pulse or azathioprine 100 mg daily for 6 months. Patients were evaluated every month to assess the response to treatment and side effects.

Result
The study included 32 patients in the weekly azathioprine group and 28 in the daily azathioprine group, of whom 25 and 22 patients respectively completed the study. Twenty-three (92%) patients on WAP and 21 (96%) on daily azathioprine had a good or excellent response. The mean pre-treatment clinical severity score decreased from 26.4±14.5 to 4.7±5.1 in the WAP group, and from 36.1±18.1 to 5.7±6.0 in the daily azathioprine group, which was statistically significant and comparable (P=0.366). Patients on WAP had a higher incidence of adverse effects (P=0.02).

Conclusion
Azathioprine 300 mg weekly pulse and 100 mg daily dose are equally effective and safe in the treatment of Parthenium dermatitis.

https://pubmed.ncbi.nlm.nih.gov/25851756/

AZATHIOPRINE IN DERMATOLOGY

RCT'S

Randomized double blind trial of prednisolone and azathioprine, vs. prednisolone and placebo, in the treatment of pemphigus vulgaris.

C Chams-Davatchi, et.al.

J Eur Acad Dermatol Venereol. 2013 Oct; 27(10):1285-92.

Background and Aims
The classic treatment for pemphigus vulgaris is prednisolone. Immunosuppressive drugs can be used in association. To compare the efficacy of Azathioprine in reducing the Disease Activity Index (DAI).

Method
A double blind randomized controlled study was conducted on 56 new patients, assigned to two therapeutic groups: (i) prednisolone plus placebo; (ii) prednisolone plus Azathioprine. Patients were checked regularly for 1 year. 'Complete remission' was defined as healing of all lesions after 12 months, and prednisolone <7.5 mg daily, (DAI = 1). Analysis was done by 'Intention to Treat' (ITT) and 'Treatment Completed Analysis' (TCA).

Result
Both groups were similar in age, gender, disease duration, and DAI. Primary endpoint: By ITT and TCA, the mean DAI improved in both groups with no significant difference between them. The difference became significant for the last trimester (3 months; ITT: P = 0.033, TCA: P = 0.045). Secondary endpoint: The total steroid dose decreased significantly in both groups, with no significant difference between them, except for the last trimester (ITT: P = 0.011, TCA: P = 0.035). The mean daily steroid dose decreased gradually in both groups becoming statistically significant in favour of azathioprine, in the last trimester, especially at 12th months (ITT: P = 0.002, TCA: P = 0.005). Complete remission was significant at 12 months only for TCA (AZA/Control: 53.6%/39.9%, P = 0.043).

Conclusion
Azathioprine helps to reduce prednisolone dose in long-run.

https://pubmed.ncbi.nlm.nih.gov/23062214/

RCT'S

Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial.

L A A Gerbens.et.al.

Br J Dermatol. 2018 Jun;178(6):1288-1296.

Background and Aims
Systemic treatment is indicated for moderate-to-severe atopic dermatitis (AD) refractory to topical treatment. Long-term evidence, up to 5 years, of off-label prescribed methotrexate (MTX) and azathioprine (AZA) is lacking. To investigate long-term effectiveness, safety and drug survival of MTX and AZA.

Method
In an open-label follow-up phase of a clinical trial, patients were seen every 3 months for 5 years. MTX and AZA doses could be increased or decreased concurrent with daily clinical practice. Primary effectiveness outcomes were mean absolute and relative reduction in SCORing Atopic Dermatitis (SCORAD) index and Investigator's Global Assessment (IGA) after 5 years compared with baseline. To assess safety, the type, frequency, severity and relatedness to treatment of adverse events were investigated. Drug survival was analysed by Kaplan-Meier curves.

Result
Thirty-five of 43 originally included patients participated, of whom 27 completed the follow-up. At year 5, the mean relative reduction in SCORAD index was similar in the MTX and AZA groups: 53% and 54% using descriptive analysis. Twelve serious adverse events occurred in 5 years; for three there was a possible causal relationship. Drug survival demonstrated a longer survival for MTX, but survival in both groups was low after 5 years (MTXn = 5, AZAn = 1).

Conclusion
Based on this relatively small pragmatic study, MTX and AZA seem to be effective and safe as maintenance treatments in moderate-to-severe AD up to 5 years. Few patients in both groups survive on their originally allocated drug although some discontinued because of controlled AD.

https://pubmed.ncbi.nlm.nih.gov/29237228/

AZATHIOPRINE IN DERMATOLOGY

Systematic Review

Off-label use of azathioprine in dermatology: A systematic review

Mandy E Schram, et.al.

Arch Dermatol. 2011 Apr;147(4):474-88.

Background and Aims
To summarize evidence regarding the effectiveness, efficacy, and safety of off-label azathioprine use in dermatology.

Method
Randomized controlled trials, cohorts, and case series concerning the use of azathioprine in an off-label dermatologic setting were independently assessed for eligibility by 2 co-authors. The search retrieved 3870 articles, and 148 articles were selected for detailed review. Forty-three articles matching the inclusion and exclusion criteria were reviewed for methodologic quality by 2 reviewers independently, including an evaluation of components associated with biased estimates of treatment effect. High-quality evidence (level A) was found for a moderate therapeutic effect in severe atopic dermatitis. Evidence of moderate quality (level B) was found for efficacy in parthenium dermatitis (an airborne plant allergen contact dermatitis), bullous pemphigoid, chronic actinic dermatitis, and leprosy type 1 reaction. Furthermore, favorable therapeutic effects existed for erythema multiforme, lichen planus, and pityriasis rubra pilaris, although the quality of evidence was low (level C).

Conclusion
A strong clinical recommendation was given for azathioprine in atopic dermatitis. Conclusions regarding safety in an off-label setting could not be reached because of scarce and incomplete data (level C evidence). Long-term registries and prospective studies could add to the existing evidence and provide legal support for off-label drug use in dermatology.

https://pubmed.ncbi.nlm.nih.gov/21482898/