



## OPEN ACCESS

## EDITED BY

Akira Sugawara,  
Tohoku University, Japan

## REVIEWED BY

Maria Laura Tanda,  
University of Insubria, Italy  
Natsuko Watanabe,  
Ito Hospital, Japan

## \*CORRESPONDENCE

Madhukar Mittal

✉ [mittalspace@gmail.com](mailto:mittalspace@gmail.com)

RECEIVED 22 November 2023

ACCEPTED 08 February 2024

PUBLISHED 21 February 2024

## CITATION

Mittal M and Rizvi A (2024) Commentary:  
Azathioprine as an adjuvant therapy in severe  
Graves' disease: a randomized controlled  
open-label clinical trial.  
*Front. Endocrinol.* 15:1342915.  
doi: 10.3389/fendo.2024.1342915

## COPYRIGHT

© 2024 Mittal and Rizvi. This is an open-access  
article distributed under the terms of the  
[Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).  
The use, distribution or reproduction in other  
forums is permitted, provided the original  
author(s) and the copyright owner(s) are  
credited and that the original publication in  
this journal is cited, in accordance with  
accepted academic practice. No use,  
distribution or reproduction is permitted  
which does not comply with these terms.

# Commentary: Azathioprine as an adjuvant therapy in severe Graves' disease: a randomized controlled open-label clinical trial

Madhukar Mittal \* and Azher Rizvi

Department of Endocrinology and Metabolism, All India Institute of Medical Sciences Jodhpur,  
Jodhpur, Rajasthan, India

## KEYWORDS

Graves' disease (GD), azathioprine (AZA), anti thyroid drugs, remission, TRAb  
thyroid antibodies

## A Commentary on

### Azathioprine as an adjuvant therapy in severe Graves' disease: a randomized controlled open-label clinical trial

by Allam MM, El-Zawawy HT, Kader Okda AA, Ali Alshaikh A and Ghazy RM (2023) *Front.  
Endocrinol.* 14:1168936. doi: 10.3389/fendo.2023.1168936

## 1 Introduction

We read the study by Allam and colleagues with interest, which studied the role of azathioprine as an adjuvant therapy to anti thyroid drugs (ATD) in patients with moderate and severe Graves' disease (GD) in a randomized controlled trial. The primary outcome of rate of remission after a follow up period of 2 years was compared among three randomized groups of patients, one on conventional therapy with ATDs and the other 2 on different doses of azathioprine in addition to conventional therapy (1). Currently recommended therapies for GD do not address the underlying immunopathogenesis of the disease and addition of immunosuppressives to standard treatment has been shown to improve relapse rates (2). Several immunotherapies including biologics, small molecule peptides and immunomodulators have shown efficacy in preliminary studies and could potentially transform the management of GD (3).

## 2 Inconsistencies in remission criteria

The results of the study are striking, with a high remission rate of 87.5% among patients taking adjuvant azathioprine therapy (1). The American Thyroid Association (ATA) uses a remission criteria of being euthyroid for at least 12 months after withdrawing ATDs (4). The authors here use a criteria for remission which includes complete (standard remission criteria) and partial remission (defined as being euthyroid while being on 5-15 mg/day of carbimazole for at least 12 months even with positive TSH receptor antibodies). There seems to be no explanation given for using an add-on partial remission criteria and this combined remission definition is inconsistent with previous literature including the guidelines by ATA and other thyroid associations (4, 5).

## 3 Unusually low remission rate among patients receiving conventional therapy with ATD

Considering the long term remission after a course of ATDs has been reported to be around 50%, with a range of 30-70% (6), it is certainly curious to note the extremely low remission rate of 7.4% observed among the group receiving ATDs alone, after 2 years of follow up. Interestingly enough, about 31% of patients with GD have been reported to have spontaneous remission even without ATDs (7). This remarkable divergence of the remission rate from not only previous studies but also our own clinical experience makes us wonder as to the basis of such low remission rates seen with ATD use in this study. The authors do report an additional 25.9% of patients which the authors consider to be in partial remission but with continued use of ATDs.

## 4 Conflicting findings with different doses of azathioprine used

This was the first study to evaluate the effect of specific doses of azathioprine on outcomes as previous studies with azathioprine in patients with GD and Graves' orbitopathy (GO) have not evaluated it (8, 9). The authors however do not address the possible reasons for the discordant results seen with the different doses of azathioprine used. Complete remission was reported in 87.8% of patients in the group which received azathioprine at doses of 1mg/kg/day as adjuvant therapy to ATD with none of the patients reported to have partial remission. In contrast, complete remission rate in the group which received a higher dose of adjuvant azathioprine (2mg/kg/day) was 68.9% with an additional 24.4% of patients reported to have achieved partial remission. No explanation is provided for these observed differences.

## 5 No clarity regarding the duration of follow up in the study

In the article published, at several points in the text the authors mention that the follow up period was 12 months. Yet the data provided in table 2 as well as in the Kaplan Meier survival curve is for a follow up period of 2 years after remission. These varying follow up periods mentioned at different places need more clarification so as to remove any contradictions and bring out more clarity for the readers.

## 6 Discussion and conclusion

We appreciate the efforts of Allam and colleagues in studying a commonly used, well tolerated and economical immunosuppressive agent to complement the management of GD. Future comparisons of the frequency of exacerbations and new onset of Graves' ophthalmopathy would allow a better comparison of the immunosuppressive effects of additional azathioprine administration.

In this study, subjects were randomly assigned using a computer program, matched for age, sex and TRAb. However, thyroid volume varied considerably among the three groups, although the differences were not significant. It would be useful to perform a multivariate analysis, such as proportional hazards analysis or nominal logistic analysis, to eliminate the effects of confounding to determine the factors associated with recurrence. The statistical methods used in this study should also be mentioned.

The concerns emphasized in our commentary lead us to critique certain aspects of the study methods and seek certain plausible answers or explanations for the points raised above.

## Author contributions

MM: Conceptualization, Writing – review & editing. AR: Writing – original draft.

## Funding

The authors declare no financial support was received for the research, authorship and publication of this article.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Allam MM, El-Zawawy HT, Kader Okda AA, Ali Alshaikh A, Ghazy RM. Azathioprine as an adjuvant therapy in severe Graves' disease: a randomized controlled open-label clinical trial. *Front Endocrinol (Lausanne)* (2023) 14:1168936. doi: 10.3389/fendo.2023.1168936
2. Struja T, Guebelin L, Kutz A, Fehlberg H, Mueller B, Schuetz P. Does immunosuppressive therapy improve outcomes in Graves' Disease? A systematic review and meta-analysis. *Thyroid* (2016) 26:634–40. doi: 10.1089/thy.2015.0647
3. Lee ACH, Kahaly GJ. Novel approaches for immunosuppression in Graves' Hyperthyroidism and associated orbitopathy. *Eur Thyroid J* (2020) 9:17–30. doi: 10.1159/000508789
4. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* (2016) 26:1343–421. doi: 10.1089/thy.2016.0229
5. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of Graves' Hyperthyroidism. *Eur Thyroid J* (2018) 7:167–86. doi: 10.1159/000490384
6. Kim H-J. Long-term management of Graves disease: a narrative review. *J Yeungnam Med Sci* (2022) 40:12–22. doi: 10.12701/jyms.2022.00444
7. Codaccioni JL, Orgiazzi J, Blanc P, Pugeat M, Roulier R, Carayon P. Lasting remissions in patients treated for Graves' hyperthyroidism with propranolol alone: a pattern of spontaneous evolution of the disease. *J Clin Endocrinol Metab* (1988) 67:656–62. doi: 10.1210/jcem-67-4-656
8. Huszno B, Trofimiuk M, Gołkowski F, Plinta T, Szybiński Z. Assessment of early immunosuppressive therapy in the prevention of complications of Graves' disease. *Przegl Lek* (2004) 61:868–71.
9. Rajendram R, Taylor PN, Wilson VJ, Harris N, Morris OC, Tomlinson M, et al. Combined immunosuppression and radiotherapy in thyroid eye disease (CIRTED): a multicentre, 2 × 2 factorial, double-blind, randomised controlled trial. *Lancet Diabetes Endocrinol* (2018) 6:299–309. doi: 10.1016/S2213-8587(18)30021-4