Does Immunosuppressive Therapy Improve Outcomes in Graves' disease?
A Systematic Review and Meta-analysis

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Introduction

Graves' disease is an autoimmune disorder and common cause of primary hyperthyroidism. The overall prevalence of Graves' disease varies but is ~ 0.5% (1). A standard treatment for Graves' disease includes use of thyrostatic drugs for a total duration of 12 to 18 months to treat overproduction of thyroid hormones. Yet, this treatment does not have an effect on the underlying autoimmune disorder, and risk of relapse is around 50% (2). Because of the autoimmune nature of Graves' disease, additional use of immunosuppressive drugs, in combination with standard thyrostatic drugs would be a logical treatment extension (3).

Methods

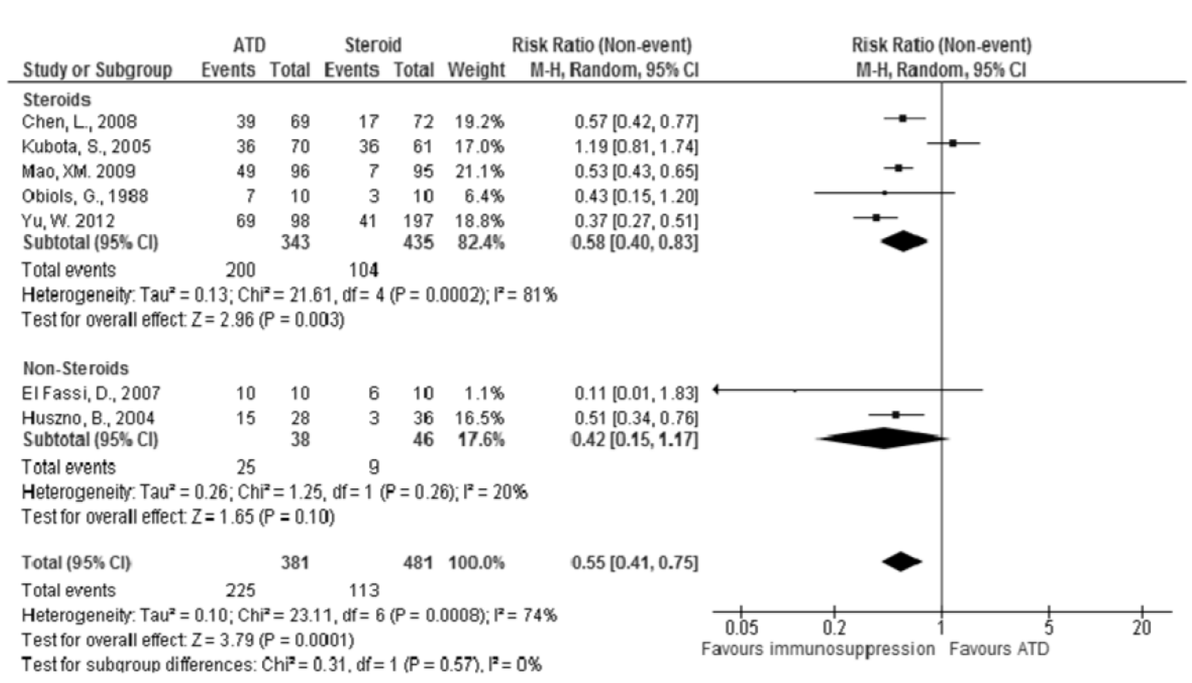
Based on a pre-specified protocol, we searched PubMed, EMBASE and Cochrane (all up to Jul 2015). We searched for (randomized)-controlled trials comparing immunosuppressive drugs with a control group. PRISMA and SIGN statements were used for reviewing data and assessing quality. Two reviewers extracted data on study characteristics, methods, and outcomes. Data were pooled using a random-effects model. The primary endpoint was relapse of disease until follow-up, secondary endpoints included reduction of thyroid volume and decrease in TSH-receptor-antibody [TRAb] levels.

Results

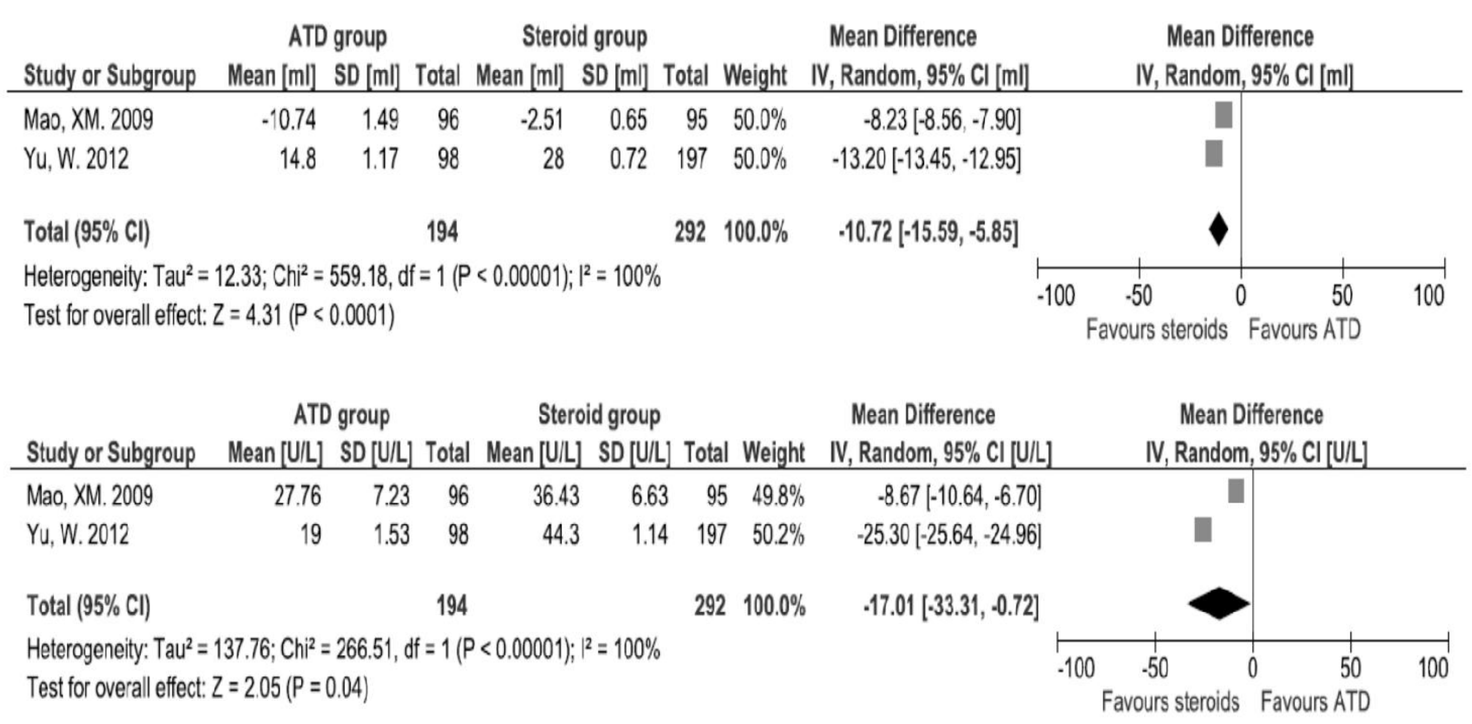
Primary endpoint					
	Intervention group	Control group	Risk ratio (95% CI)	Heterogeneity (I^2)	Subgroup diff. (I^2)
Overall analysis	113/481 (23.5%)	225/381 (59.1%)	0.55 (0.41, 0.75), (p < 0.001)	74%	
Subgroups - Type of immunosuppressive drug used					
Corticosteroid	104/435 (23.9%)	200/343 (58.3%)	0.58 (0.40, 0.83)	81%	0%
Other immunosuppressives	9/46 (19.6%)	25/38 (65.8%)	0.42 (0.15, 1.17)	20%	
Subgroups- Type of study					
Randomized trials	65/364 (17.9%)	157/263 (59.7%)	0.49 (0.38, 0.62)	58%	0%
Controlled trials	48/117 (41.0%)	68/118 (57.6%)	0.62 (0.31, 1.23)	75%	
Secondary endpoints - mean difference (95% CI)					
Thyroid volume	292 (60.1%)	194 (39.9%)	-10.72ml (-15.59, -5.85)	100%	
TRAb levels			-17.01 U/L (-33.31, -0.72)	100%	

1. Forest Plot for Relapse Risk

We included 7 trials with 862 participants. Most trials were small with moderate to high risk of bias. There were 113 relapses in 481 (23.5%) patients receiving immunosuppressive drugs compared to 225 relapses in 381 (59.1%) control patients (risk ratio for recurrence 0.55, 95% confidence interval [CI] 0.41, 0.75). Subgroup analyses showed similar effects for randomized trials and controlled trials (I2 0%), as well as for trials using corticosteroids (hydrocortisone, dexamethasone, methyl-prednisolone, prednisolone) and non-corticosteroids (azathioprine, rituximab, cyclophosphamide) immunosuppressive drugs (I2 0%). Immunosuppressive drug-related adverse effects were not systematically reported and thus not included in the quantitative analysis. They included leucopenia, rash, minor infections, chills and fever during infusion of rituximab. There were no reports on serious adverse effects.



2. Forest Plots for Reduction of Thyroid Volume (upper) and TRAb (lower)



Use of immunosuppressive drugs also resulted in significant reductions in thyroid volume (-10.72ml, 95% CI -15.59, -5.85) and TRAb levels (-17.01 U/L, 95% CI -33.31, -0.72).

Conclusion

Current evidence suggests a relevant reduction in relapse risk when immunosuppressive drugs are added to standard treatment of Graves' disease. The small number of trials with high heterogeneity and the lack of systematic reporting of adverse effects calls for larger, conclusive trials.

References

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