Aeromedical Decision Making for Military Aircrew with Graves' Disease

Edwin Hong-Teck Loh; Feng Wei Soh; Brian See; Benjamin Boon Chuan Tan

BACKGROUND: Graves' Disease (GD) is a common cause of hyperthyroidism. Although definitive treatment with radioactive iodine (RAI) is preferred for military aircrew, there are cultural and individual differences in receptivity toward RAI, and clinical guidelines that recommend antithyroid drugs (ATD) as the first line therapy. We examined a case series of Republic of Singapore Air Force (RSAF) aviators with GD treated with ATD and the impact of their condition on aeromedical disposition.

CASE SERIES: All RSAF aircrew diagnosed with GD and treated with ATD over a 15-yr period were retrospectively identified and analyzed to determine the impact on their fitness for flying duties. The mean age of the 13 aircrew was 33 ± 7.1 yr (range, 25–47 yr), with 11 (84.6%) being males. There were 10 (76.9%) who had ATD as the only treatment while 3 (23.1%) were initially treated with ATD but subsequently underwent RAI or surgery. Of the 10 treated with only ATD, 3 (30.0%) were returned to restricted flying, 6 (60.0%) were returned to unrestricted flying, and 1 (10.0%) is still undergoing ATD titration. There were 10 (76.9%) aircrew who were returned to some form of flying duties while on low doses of ATD.

DISCUSSION: This case series suggests that ATD is a viable treatment modality in the aeromedical management of military aviators with GD and it is possible to return military aircrew on a stable maintenance dose of ATD to flying duties. A framework is proposed to support the aeromedical decision-making process for military aircrew in the treatment of GD.

KEYWORDS: flight safety, fitness for flying, anti-thyroid drugs, hyperthyroidism.

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Graves' Disease (GD) is the most common cause of hyperthyroidism in areas with sufficient iodine intake, with a prevalence of 0.5%.[1] Treatment of GD may involve the use of antithyroid drugs (ATD), radioactive iodine (RAI) ablation, or surgery. These have been shown to be relatively safe and efficacious.[5] Definitive management with RAI or thyroidectomy induces a permanent hypothyroid state. The subsequent long-term thyroid replacement therapy is typically free of side effects and stable.[4]

Conversely, the recommended treatment duration with ATD (e.g., Carbimazole, Methimazole, Propylthiouracil) is 12–18 mo, with a high initiation dose that is subsequently tapered down to a lower maintenance dose until sustained normal levels of TSH and TRAb are achieved.[5] During treatment with ATD, frequent reviews are required to ensure the dosage is adjusted to an appropriate level to achieve euthyroid status. Furthermore, ATD usage is also associated with side effects such as rashes, arthralgia, and nausea in up to 13% of patients,[7] and more severe but rare adverse effects of agranulocytosis and hepatotoxicity.[5] The frequency of prolonged remission among patients treated with ATD for 1–2 yr varies from 15–80%, but is usually under 40%.[8] Disease recurrences can lead to repeated periods of grounding, with implications both on the individual's career and organizational resources. Undetected recurrences also affect flight safety.

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The presence of untreated GD is incompatible with flying duties due to aeromedical risks posed by the complications of thyrotoxicosis. The Medical Waiver Guides for the United States Air Force and United States Navy both state that definitive treatment with thyroid ablation followed by thyroid hormone replacement is the preferred treatment for aircrew with GD, and stipulate that ATD therapy is not waiverable for a return to flying duties.[9,10] Notwithstanding, the Republic of Singapore Air Force (RSAF) has returned military aircrew with GD to flying duties once they have achieved euthyroid status while remaining on stable and low doses of ATD. We understand that the United States Army, Royal Air Force and Royal Australian Air Force may waive aircrew on ATD treatment to return to flying duties on a case by case basis, albeit with varying restrictions.

This paper presents a case series of 13 RSAF aircrew with GD diagnosed over a 15-yr period and describes the impact of the condition and treatment on their fitness for flying duties. Based on the aeromedical management and disposition of this case series, we also propose a framework for aeromedical decision making for military aircrew with GD.

CASE SERIES

RSAF aircrew who were diagnosed with GD and treated with ATD over the 15-yr period from January 1, 2005, to December 31, 2019, were retrospectively identified using the RSAF Aeromedical Centre's electronic database. A total of 11 pilots and 2 nonpilot aircrew were identified for inclusion in the case series. Institutional Review Board approval was not required for this review.

All 13 aircrew were comanaged by their endocrinologists and RSAF flight surgeons. Review frequencies began with 1- to 2-monthly reviews at the treatment initiation phase, followed by 3- to 6-monthly reviews after they achieved clinical and biochemically euthyroidism on a stable low dose of ATD. Patient education on the disease effects and treatment side effects was provided to all affected aircrew, to facilitate prompt recognition and reporting of symptoms experienced. They were subsequently assessed by an Aeromedical Board comprised of three aviation medicine specialists before waiver was granted.

The mean age of the 13 aircrew was 33 ± 7.1 yr (range, 25–47 yr), with 11 (84.6%) being males. A summary of the cases, including details such as their presenting laboratory results and thyroid antibody statuses is shown in **Table I**. Of the 13 aircrew, 10 (76.9%) had ATD as the only treatment modality while the remaining 3 (23.1%) were initially treated with ATD but subsequently underwent RAI ablation or surgery due to relapse or poor response to ATD. Of the 10 who were treated with only ATD, 6 (60.0%) had been safely returned to unrestricted flying; 3 (30.0%) were returned to restricted flying but were currently reviewed for a return to unrestricted flying; and 1 (10.0%) was still undergoing ATD titration with a tentative plan for definitive therapy. **Fig. 1** summarizes the aeromedical disposition with time for all 13 cases.

Case 1

A 28-yr-old male fighter pilot was diagnosed with GD in March 2005. He was initiated on Carbimazole 10 mg TDS (three times daily), which was gradually tapered to a maintenance dose of 5 mg OM in April 2007. He was returned to unrestricted flying in May 2007. However, he had a relapse after stopping his medications in July 2007 and was unable to achieve satisfactory control of his thyroid function. He eventually underwent thyroidectomy in October 2008 and was returned to unrestricted flying duties in May 2009 after achieving euthyroid state while on thyroxine replacement.

Case 2

A 41-yr-old male fighter pilot was diagnosed with GD in March 2010. He was started on Carbimazole 10 mg OM (once in the morning) in May 2010, which was tapered to a maintenance dose of 2.5 mg OM in June 2010. He remained clinically and biochemically euthyroid subsequently. Taking into account his flying experience and willingness to undergo frequent reviews, he was returned to unrestricted flying duties in July 2010 while on a stable low dose of Carbimazole of 2.5 mg OM and has since remained euthyroid. He eventually completed therapy in July 2011.

Case 3

A 35-yr-old male helicopter pilot was diagnosed with GD in August 2011. He was started on Thiamazole 20 mg OM and completed treatment in December 2012. He was returned to unrestricted flying duties in April 2013 and has since been euthyroid.

Case 4

A 27-yr-old male helicopter pilot was diagnosed with GD in April 2012 and was treated with Propylthiouracil 100 mg BD (twice daily) due to Carbimazole allergy. He was unable to achieve a stable euthyroid state despite 16 mo of Propylthiouracil treatment and had to undergo 2 cycles of RAI before achieving a hypothyroid state in December 2014. He was returned to unrestricted flying duties in March 2015 after achieving an euthyroid state while on thyroxine replacement.

Case 5

A 47-yr-old male weapon systems operator was diagnosed with GD in August 2013. He was started on Carbimazole 15 mg BD in August 2013, which was tapered to a maintenance dose of 5 mg OM d/wk in January 2014. He was returned to unrestricted flying duties in January 2014 on the maintenance dose. He completed treatment in April 2015 and has since been euthyroid.

Case 6

A 31-yr-old male transport pilot was diagnosed with GD in September 2014. He was started on Carbimazole 30 mg OM, which was tapered down to a maintenance dose of 10 mg OM in September 2015. He was allowed back to fly with an as-or-with copilot restriction in January 2016 while on Carbimazole maintenance therapy. However, he experienced an

Table I. Summary of Cases.

			AT PRESENTATION											
CASE	VOCATION	AGE/SEX	Symptoms	Free T4 (9-25 pmol/L)	TSH (0.40-4.70 mIU/L)	Tr-Ab	Anti-TG	Anti-TPO	START ATD DOSE	MAINT-ENANCE ATD DOSE	TIME TO STABLE EUTHYROID (Months)	DEFINITIVE TREATMENT	TIME FLYING WHILE ON ATD (Months)	OTHER REMARKS
1	Pilot (FTR)	28/M	Y	111.0(↑)	0.01(↓)	-	Y	Y	10 mg TDS (Carbimazole)	5 mg OM	Nil	Surgery	2	
2	Pilot (FTR)	41/M	Y	21.0(↔)	0.02(↓)	Y	-	N	10 mg OM (Carbimazole)	2.5 mg OM	1	N	12	TED, Smoker
3	Pilot (Heli)	35/M	Y	81.7(↑)	0.01(↓)	Y	-	-	20 mg OM (Thiamazole)	Stopped	16	N	0	
4	Pilot (HELI)	27/M	Y	114.1(↑)	<0.01(↓)	Y	N	N	100 mg BD (PTU)	Unable to wean	Nil	RAI	0	
5	Weapon Systems Operator	47/M	Y	70.5(↑)	<0.02(↓)	Y	-	-	15 mg BD (Carbimazole)	5 mg OM	5	N	15	
6	Pilot (TPT)	31/M	Y	54.0(↑)	<0.01(↓)	Y	-	-	30 mg OM (Carbimazole)	5 mg OM	Nil	RAI	17	
7	Pilot (HELI)	28/M	Y	100.0(↑)	<0.1(↓)	Y	Y	Y	30 mg OM (Methimazole)	20 mg OM	13	N	30	
8	Pilot (TPT)	47/M	Y	35.0(↑)	<0.01(↓)	Y	Y	Y	20 mg OM (Methimazole)	2.5mg OM	4	N	2	
9	Pilot (FTR)	31/M	Y	31.2(↑)	<0.01(↓)	Y	-	Y	10 mg BD (Carbimazole)	2.5 mg OM	8	N	8	Smoker
10	Pilot (TPT)	30/F	Y	70.4(↑)	<0.01(↓)	Y	Y	Y	15 mg OM (Methimazole)	2.5 mg OM	9	N	20	
11	WSO (FTR)	25/M	Y	30.9(↑)	<0.01(↓)	N	Y	Y	15 mg OM (Carbimazole)	5 mg OM	13	N	13	
12	Pilot (TPT)	31/F	Y	-	<0.01(↓)	Y	Y	Y	5 mg OM (Methimazole)	5 mg OM	1	N	20	
13	Pilot (FTR)	28/M	Y	65.8(↑)	<0.01(↓)	Y	-	-	30 mg OM (Carbimazole)	2.5 mg OM	10	N	0	

Legend: FTR, fighter; Heli, helicopter; TPT, transport; WSO, weapon systems officer; M, male; F, female; Y, yes; N, no; -, unavailable; ↑, High; ↓, Low; ↔, Normal; PTU, Propylthiouracil; TrAb, TSH receptor antibodies; Anti-TG, antithyroglobulin antibodies; Anti-TPO, antithyroid peroxidase antibodies; TED, Thyroid Eye Disease.

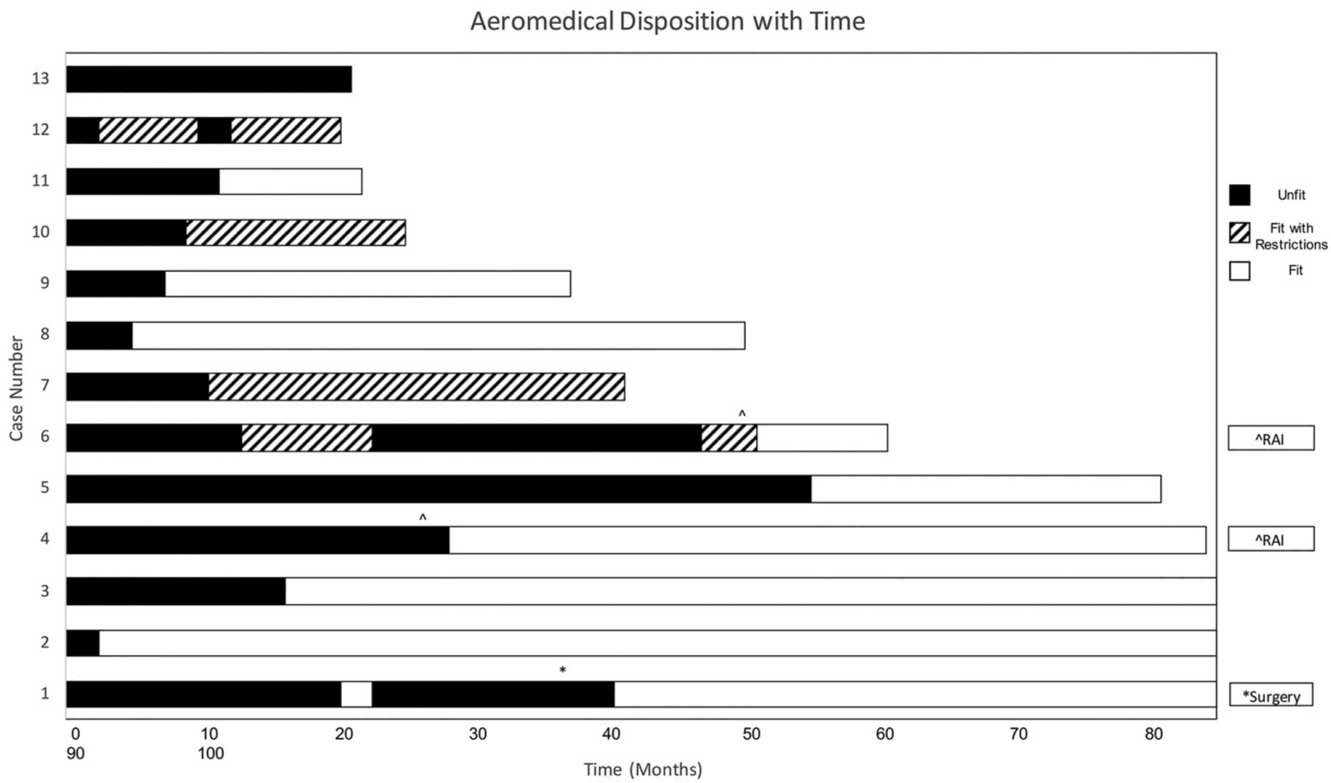

Fig. 1. Variation of Aeromedical Disposition with Time for Cases.

episode of hyperthyroidism requiring Carbimazole dosage adjustment to 30 mg OM in January 2017. This was tapered to a maintenance dose of 5 mg OM and he was returned to as-or-with copilot restriction in July 2019. He had another relapse in December 2019 and eventually underwent RAI in June 2020. He is currently being monitored for thyroid function stability before being returned to unrestricted flying duties.

Case 7

A 28-yr-old male helicopter pilot was diagnosed with GD in March 2014. He was started on Methimazole 30 mg OM, which was tapered to 20 mg OM in March 2015. In consultation with his endocrinologist and noting that he displayed both clinical and chemical euthyroidism with expected good response to thionamide therapy, he was returned to as-or-with copilot flying duties while still on a stable maintenance dose of 20 mg OM in April 2015. He was eventually weaned off medications in October 2017 and has since been euthyroid. He is currently undergoing review to be returned to unrestricted flying duties.

Case 8

A 47-yr-old male transport pilot was diagnosed with GD in October 2015. He was started on Methimazole 20 mg OM initially and his medication was stepped down to a low maintenance dose of 2.5 mg OM in February 2016. He was returned to unrestricted flying duties in April 2016 on this low maintenance dose. He eventually stopped treatment in June 2016 and has since been euthyroid.

Case 9

A 31-yr-old male fighter pilot was diagnosed with GD in February 2017. He was started on Carbimazole 10 mg BD, which was tapered to a maintenance dose of 2.5 mg OM in October 2017. He was returned to unrestricted flying duties in November 2017 on the maintenance dose which was eventually stopped in July 2018. He has since been euthyroid.

Case 10

A 30-yr-old female transport pilot was diagnosed with GD in May 2018. She was started on Methimazole 15 mg OM, which was tapered to a maintenance dose of 2.5 mg OM in February 2019. She was returned to flying duties with an as-or-with copilot restriction in April 2019 with close follow-up and has since been euthyroid while on the low maintenance dose of Carbimazole. She is currently undergoing review to be returned to unrestricted flying duties.

Case 11

A 25-yr-old male weapon systems officer (fighter) was diagnosed in September 2018 with GD. He was started on Carbimazole 15 mg OM, which was tapered to a maintenance dose of 5 mg OM in October 2019. He was returned to unrestricted flying duties in November 2019 and has since been euthyroid.

Case 12

A 31-yr-old female transport pilot was diagnosed with GD in September 2018. She was started on Methimazole 5 mg OM and achieved an euthyroid state in October 2018. She was returned to flying duties with as-or-with copilot restriction in January 2019. She suffered a relapse in October 2019 due to noncompliance and had her medication dosage increased to 10 mg OM. This was tapered back to 5 mg OM and she was subsequently returned to as-or-with copilot restriction in January 2020 after achieving stable euthyroidism while on this maintenance dose. She is currently undergoing review to be returned to unrestricted flying duties.

Case 13

A 28-yr-old male fighter pilot was diagnosed with GD in October 2018. He was started on Carbimazole 30 mg OM in October 2018, which tapered to a maintenance dose of 2.5 mg OM by August 2019. He experienced a relapse of hyperthyroidism when his Carbimazole was stopped in February 2020 and is in discussion to undergo RAI. He remains on a maintenance dose of 2.5 mg OM and will likely be returned to unrestricted flying duties once he completes RAI and thyroxine replacement dose adjustment.

DISCUSSION

This case series of 13 RSAF aircrew who were diagnosed with GD revealed that over three quarters of them were returned to some form of flying duties while on low maintenance doses of ATD.

The American Thyroid Association recommends the use of ATD as a first-line therapy for patients with high likelihood of remission, such as patients with mild disease, small goiters, and negative or low-titer TRAb.[5] Furthermore, studies have shown that continued long term use of ATD in excess of 10 yr is effective and safe for patients.[3] Hence, there has been an increasing trend for ATD to be used as the initial treatment modality in the United States.[6]

It has been established that there are geographical, cultural, and individual differences in the preferred modality of initial treatment for GD worldwide. In Europe, Latin America, and Asia, there has been a greater patient and physician preference for ATD as the first line mode of treatment.[2] In Asia, a key reason for this has been due to the concerns surrounding exposure to radiation during RAI therapy.[12] Among the RSAF aircrew with GD, the majority were in their child-bearing years and were not keen to undergo RAI treatment despite appropriate counseling on the side effect profile of RAI. Some also had reservations about requiring lifelong thyroid hormone replacement at a relatively young age.

Given the cultural differences in patient receptivity toward RAI therapy, coupled with published clinical guidelines which recommended ATD as the first line therapy for those with a high likelihood of remission, the feasibility of ATD use in the aeromedical management of military aviators with GD should be further examined.

The aeromedical concerns over the use of ATD include flight safety implications from undetected thyroid function fluctuations and resultant need for frequent monitoring, medication side effects, uncertainty of the period of treatment, and the longer-term risk of disease recurrence following completion of therapy. In addition, the aircrew's personal treatment preference, career aspirations, compliance, and insight to their condition should also be taken into consideration when deciding on the initial treatment modality.

In view of the risks of undetected thyroid function fluctuations and side effects associated with the use of ATD, aircrew require close observation with regular clinical and laboratory reviews while on ATD. This would impact the deployability of aircrew to austere environments without access to medical care. Hence, definitive treatment is preferred due to the stability and predictability of thyroid hormone replacement.

Generally, operational restrictions should be imposed on aircrew who returned to vocational duties while on ATD to safeguard against the aeromedical risks posed by undetected thyroid derangement and medication adverse reactions. The ability to impose such restrictions would be dependent on the aircrew's platform type and individual factors. For helicopter and transport pilots operating in multicrew cockpits, they would typically be initially restricted to as-or-with copilot flying status, as seen in three of our aircrew. However, such restrictions would not be appropriate for fighter pilots operating alone, and for those performing instructional duties. Our case series included three fighter pilots who were allowed back to unrestricted duties while on stable low doses of ATD after careful deliberation by the Aeromedical Board. For these individuals, risk mitigating considerations included their individual flying experience, disease insight, compliance to therapy and stability of thyroid function. The requirement for frequent reviews was also imposed.

For nonpilot vocations, it was important to have a thorough understanding of their operating environment to assess if adequate risk mitigation measures were built into their operating procedures. Nonpilot aircrew are generally not in direct flight control and usually operate with another aircrew present, allowing cross-checking and supervision. These safeguards allowed two nonpilot aircrew in our case series to be returned to unrestricted flying duties while on low dose maintenance ATD.

With ATD, there is uncertainty in both the success and duration of treatment. Studies have shown that around 37–53% of patients would experience disease recurrence after completing ATD therapy.[7,11] For such individuals, repeated episodes of medical grounding or operational flying restrictions would place a strain on both organizational resources and personal career advancement. This was exemplified by Cases 1, 6, and 12 of our case series who had multiple changes to their aeromedical disposition while on ATD therapy. These uncertainties should, therefore, be clear to both the aircrew and their commanders prior to commencing ATD treatment. Conversely, definitive treatment with RAI or surgery, exemplified by Cases 1, 4, and 6 was associated with a low risk of disease recurrence and the duration required to induce a permanently hypothyroid state was less variable. Such definitive treatments are therefore preferred if a quick return to unrestricted duties was operationally required.

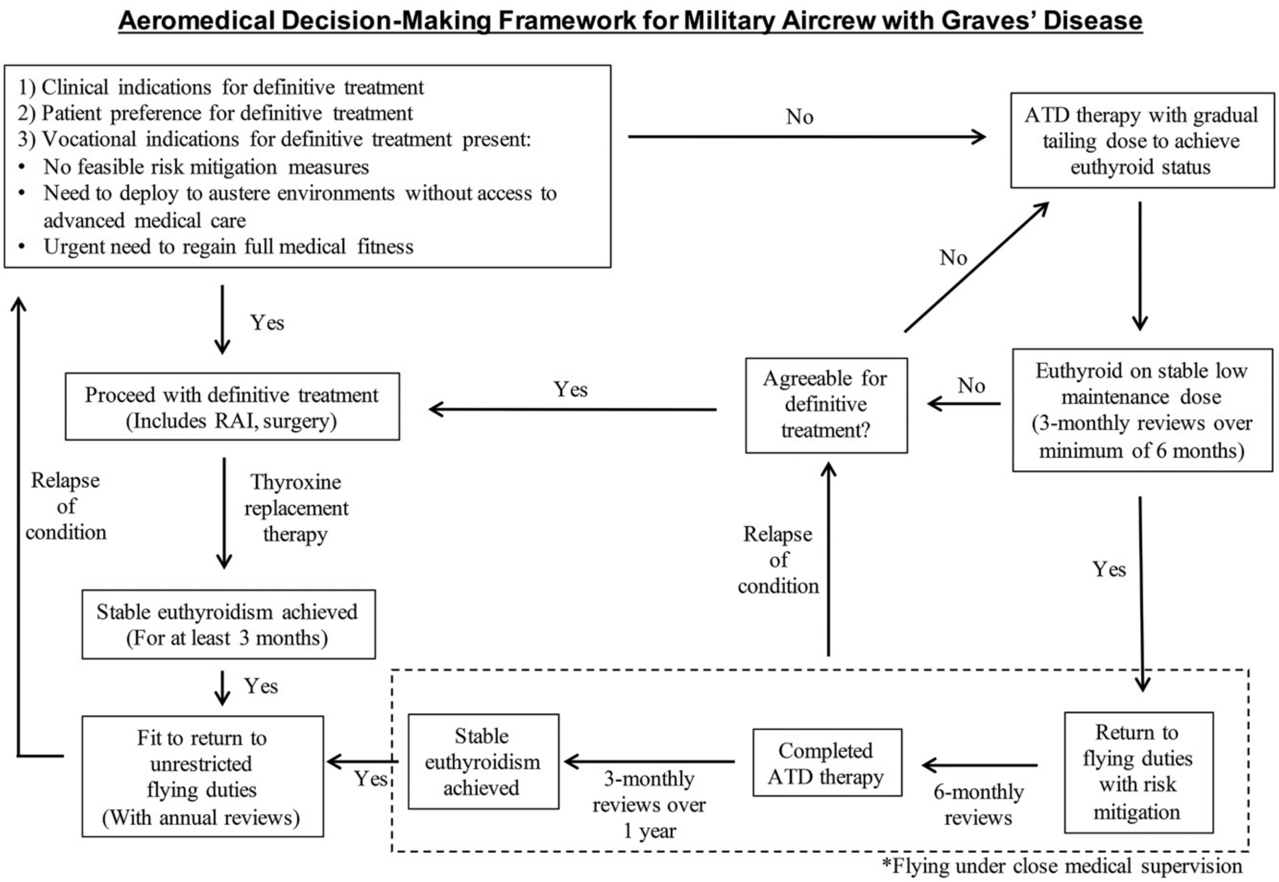

Fig. 2. Aeromedical Decision-Making Framework for Military Aircrew with Graves' Disease.

Finally, individual factors play an important role in the choice of therapy for aircrew with GD. ATD was the only option if the aircrew was strongly opposed to radiation exposure or surgery. The aircrew's career aspirations, desire to maintain vocational fitness and deployability, as well as other personal considerations may also result in preference for a certain treatment over the other.

It is our view that clinical indications for disease management should take precedence over vocational factors. Due to the small sample size, our study did not reveal any observable patterns with regard to the effect of factors such as presenting symptoms, laboratory results, thyroid antibody statuses, or smoking status on the eventual failure of ATD therapy or need for definitive therapy.

Based on the analysis of the aeromedical management of our case series, we propose an aeromedical decision-making framework for military aircrew with GD (**Fig. 2**). After considering both clinical indications and patient preference, aircrew with strong vocational indications could proceed directly for definitive treatment with RAI or surgery. In the absence of such vocational indications, and subject to appropriate patient education and consent, ATD can be employed as the first-line therapy. Following ATD initiation, the aircrew should be monitored closely for treatment response and adverse drug reactions. The ATD dosage can then be gradually tapered to a low maintenance dose (e.g., 2.5 mg–5.0 mg OM for Carbimazole or Methimazol). Once euthyroid (based on 3-monthly testing over a minimum of 6 mo) and on a low maintenance dose of ATD, the affected aircrew can be considered for a return to vocational duties with appropriate risk-mitigation measures and a 6-monthly review frequency. Care should be taken to educate them on disease and ATD side effect symptoms, with instructions to report to their flight surgeon if any of these symptoms are experienced. Following 12–18 mo of ATD therapy, ATD treatment can cease but with continued close observation including 3-monthly thyroid function testing. Aircrew who continuously remain euthyroid without ATD treatment after 1 yr can have their review frequency reduced to annually and be returned to unrestricted flying duties. Aircrew who are unable to achieve or maintain a euthyroid state, require high doses of ATD persistently for disease control, experience disease recurrence shortly after ATD cessation, or experience side effects of ATD should be advised to proceed with definitive therapy as the long-term likelihood of treatment success with ATD would likely be poor.

With the following: 1) guidelines recommending the use of ATD as the first-line treatment of GD for individuals with a high likelihood of remission; 2) preference for ATD over RAI ablation in certain patient and physician populations; and 3) data supporting the clinical safety of long-term low-dose ATD use, we are of the view that aircrew with GD should not be limited from ATD treatment. This case series suggests that ATD is a viable treatment modality, with the majority of aircrew on ATD returned to some form of flying duties while on low maintenance doses. A holistic assessment of the aircrew's individual characteristics, vocational requirements and the aeromedical considerations of both the disease and treatment modality, and a shared decision-making process, involving the aircrew, commanders and the flight surgeon would be critical in ensuring the awareness of all parties of the benefits and trade-offs of the various treatment modalities.

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