Review Article

Anti-thyroid drugs in pediatric Graves' disease

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ABSTRACT

Graves' disease is the most common cause of hyperthyroidism in children. Most children and adolescents are treated with anti-thyroid drugs as the initial modality. Studies have used Methimazole, Carbimazole and Propylthiouracil (PTU) either as titration regimes or as block and replacement regimes. The various studies of anti-thyroid drug (ATD) treatment of Graves' disease in pediatric patients differ in terms of the regimes, remission rate, duration of therapy for adequate remission, follow up and adverse effects of ATD. Various studies show that lower thyroid hormone levels, prolonged duration of treatment, lower levels of TSH receptor antibodies, smaller goiter and increased age of child predicted higher chance of remission after ATD. A variable number of patients experience minor and major adverse effects limiting initial and long term treatment with ATD. The adverse effects of various ATD seem to more in children compared to that of adults. In view of liver injury including hepatocellular failure need of liver transplantation associated with PTU, the use has been restricted in children. The rate of persistent remission with ATD following discontinuation is about 30%. Radioactive iodine therapy is gaining more acceptance in older children with Graves's disease in view of the limitations of ATD. For individual patients, risk-benefit ratio of ATD should be weighed against benefits of radioactive iodine therapy and patient preferences.

Key words: Anti-thyroid drugs, Graves' disease, pediatric

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children and is due to the effect of thyroid stimulating hormone (TSH) receptor stimulating antibodies which stimulate the thyroid to produce excess hormones. The incidence of GD is believed to be between 0.1 and 3/100,000 children with a prevalence of 1 in 10,000 children in the United States.[1,2]

The other causes of hyperthyroidism like toxic nodular goiter, thyroiditis, and activating mutations of TSH receptor are uncommon in pediatric practice. The signs and symptoms of thyrotoxicosis are similar to that of adults, although features such as ophthalmopathy and dermopathy are uncommon.[3,4] Being a relatively rare disease in pediatric practice, there is a delay in diagnosis compared to that of adults. However, delayed diagnosis may be associated with impaired neurodevelopmental outcome, altered skeletal maturation, including craniosynostosis, advanced bone age, and reduction in school performance.[3,5]

The various options for treatment of GD in children include antithyroid drugs (ATD), radioactive iodine (RAI), and thyroidectomy. In most centers, the majority of children with GD are initiated on ATD with RAI and surgery being reserved for children who do not achieve sustained remission with ATD. Considering the adverse effects of ATD especially fatal liver injury with propylthiouracil (PTU) and the fact that <30% of children achieve sustained remission with ATD, there is increase in the number of children subjected to RAI.[6,7] Still, ATD forms the initial therapy for pediatric GD in a significant proportion of subjects. This review focuses on the current use of ATD in children.

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Anti-Thyroid Drugs

Anti-thyroid drugs are thionamides which contain a sulfhydryl group and a thiourea moiety within a

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heterocyclic structure. The common agents that are used as methimazole (MMI), carbimazole, and PTU. These agents are concentrated in the thyroid against a concentration gradient. These agents primarily act by inhibiting thyroid hormone synthesis by inhibiting thyroid peroxidase mediated iodination of tyrosine residues in the thyroglobulin, an important step in the thyroid hormone synthesis. In addition, PTU can block the conversion of T4 to T3 within the thyroid and in peripheral tissues. ATD can also have immunosuppressive effects with reduction in TSH receptor antibody, Intercellular Adhesion Molecule-1, soluble IL-2 and IL-6 receptors.[8]

Initiating and titrating therapy with anti-thyroid drugs

The recommended starting dose is 0.5–1.0 mg/kg/day for MMI and 5–10 mg/kg/day for PTU.[4] In a study comparing low and high dose MMI (<0.5 mg/kg vs. >0.5 mg/kg), more subjects (82%) responded to the higher dose than the lower dose (42%).[9] The medications are initiated at this dose and reduced every 4–8 weeks after documenting resolution of symptoms and thyroid function tests.[10] In most patients with GD, there is early reduction of T3 and T4 to normal levels correlating with resolution of symptoms. Recovery of suppressed TSH to normal levels occurs gradually. Continued suppression of serum TSH in patients with GD during ATD treatment is related to thyroid binding inhibiting immunoglobulin, pre-treatment severity of hyperthyroidism, and time to normalization of serum T_3 and T_4.[11]

The doses of ATD are progressively reduced and maintained at minimum doses required to maintain a clinical and biochemical euthyroidism (Normal T3 and T4) for a period of 12–24 months. Following that the ATD is discontinued, and patient kept under follow-up for recurrence of symptoms.

In the block and replace method, both ATD and thyroxine are supplemented in an attempt to maintain euthyroidism. However, this approach needs a higher dose of ATD and hence vulnerable to the adverse effects. The rate of remission in this approach is not superior to the traditional approach described above.[12,13]

Remission with anti-thyroid drugs in paediatric Graves' disease

A patient is considered to be in remission if T3, T4, and TSH remain normal 1 year after discontinuation of antithyroid therapy.[10] The remission rates in adults with GD seem to be variable with studies from US reporting it at 20–30% remission after 12–18 months of medication.[10] The remission rate appears to be higher in Europe and Japan; a long-term European study indicated a 50–60% remission rate after 5–6 years of treatment.[10,13]

The natural history of untreated GD in children is not well described. The remission rates in children seem to be lower than in adults. The remission rates in various studies are given in Table 1. These studies have used various drugs (PTU, MMI or Carbimazole), different drug schedules (titration vs. block and replace regimes), and variable duration of ATD. In various studies lower levels of thyroid hormones (T3 and T4), longer duration of treatment, age group, TSH Rab at presentation, ethnicity, and smaller goiter were associated with increased chances of remission with ATD therapy.

The relation between pubertal stages and rates of remission was discussed in various studies. In a study involving 40 patients, remission of GD with relation to puberty has shown that being pre, peri, or post pubertal did not have significant effects on the rate of remission, although the time to remission was longer in the pre pubertal children. During a median follow-up period of 4 years, remission was achieved in 10 of the patients receiving ATD (28%) after 3.76 ± 1.1 year of treatment. No significant associations were found between outcome and age or pubertal stage at diagnosis. Adverse effects were more in pre pubertal children.[22]

In another study of 143 patients, 38% of patients were prepubertal. 20 patients (7 prepubertal, 13 pubertal) reached remission on ATD. Duration of treatment needed to achieve remission was longer in prepubertal (4.2 years) than in pubertal patients (3.1 years) ($P = 0.02$). The rate of remission was not different between prepubertal (25.9%) and pubertal patients (33.3%) ($P = 0.59$). There was no difference between adverse effects to ATD between pubertal and pre- pubertal patients.[19]

In French Childhood GD Study Group, a multicenter prospective follow-up of 154 patients who were on MMI for a period of 24 months, followed by a follow-up of 2 years. The overall estimated relapse rate for hyperthyroidism was 59% at 1 year and 68% at 2 years after the end of treatment. The median time to relapse was 8 months. Multivariate survival analysis showed that the risk of relapse was higher for patients of non-Caucasian origin, with high serum thyroid-stimulating hormone receptor antibodies, and high free T4 levels at diagnosis. The risk of relapse decreased with increasing age at onset of disease and duration of the first course of ATD. There was no significant effect of pubertal age on chances of remission in subjects with hyperthyroidism.[17]

In an observational study involving 154 subjects, repeated courses of carbimazole each lasting 2 years were used. Remission was defined as a disease-free for at least 18 months

Table 1: Drugs, drug dosage, duration of therapy, remission rates and factors predicting remission in various studies

Author	Number	Type of anti-thyroid medication	Initial dose of ATD	Duration of therapy	Rate of remission %	Comment
Hamburger 1985[14]	262	PTU/MMI	Not mentioned	1-3 years Variable	14	3.8% in remission <2 years. No definite predictors of remission
Glaser and Styne 1997[15]	191	PTU: 80% MMI: 20%	PTU: 7.7 mg/kg and MMI: 0.54 mg/kg	2 years	14	A total of 85/191 patients were excluded from the analyses
Glaser and Styne 2008[16]	70	Block and replace regime with PTU and MMI	PTU: 5-7 mg/kg/day	2 years	29	Predictors of remission include T3 and T4 and euthyrodism in 3 months. MMI dose was chosen at the discretion of the attending physician
Kaguelidou *et al.* 2008[17]	154	Carbimazole	0.7 mg/kg/day if FT4 is 3.9 ng/dl or greater or 0.5 mg/kg/day if FT4 is <3.9 ng/dl	2 years	28	Predictors relapse were age, serum FT4, TSH RAb at presentation, duration of treatment and non-Caucasian race
Léger *et al.* 2012[6]	154	Carbimazole	0.7 mg/kg/day if FT4 is 3.9 ng/dl or greater or 0.5 mg/kgd if FT4 is <3.9 ng/dl	10.4 years	20	20% remission rate at 4 years. 49% remission rate at 10 years. Remission predicted by FT4 levels and presence of other autoimmune diseases
Ohye *et al.* 2014[18]	1138	MMI and PTU	30 mg MMI or 300 mg PTU	3.8 years	46.2	Cumulative remission increased up to duration of 5 years
Poyrazoglu *et al.*[19]	143	PTU and MMI	0.5±0.2 mg/kg MMI and 5.6±2.1 mg/kg PTU	2 years minimum	14	BRT was used in 40% patients. No definite factors identified as markers of remission
Gruñeiro-Papendieck *et al.*[20]	116	MMI	MMI: 0.5-1 mg/kg/day	2-4 years	29	10 years of follow-up. No definite predictors of remission
Lippe *et al.*[21]	63	MMI and PTU	MMI: 30 mg/day in weight >38 kg and 15 mg if weight <38 kg PTU: 300 mg/day	Median: 4.3 years	25	75% of patients are predicted to be in remission in 10.9±2.3 year
Lazar *et al.* 2000[22]	40	PTU and MMI	PTU: 6.4±1.9 mg/kg/day MMI: 0.74±0.2 mg/kg/day	2-7.5 years	28	Remission associated with total T3 levels
Kon *et al.*[23]	42	MMI	0.5 mg/kg/day	4.3±2.5 years medication	52.4	25 percentile was remitted at 3.7 years, 50 percentile at 7.1 years, and 75 percentile at 9.2 years. Initial TSH levels (higher) predicted remission
Song *et al.*[24]	113	MMI (93.8%) or PTU (6.2%)	Not available	4.5 years of therapy and 6.6 years of follow-up	46	Age at diagnosis was a prognostic factor for remission
Bhadada *et al.*[25]	56	Carbimazole	0.6-0.8 mg/kg/day	34.4±22.6 months	47	Follow-up of 4.9±3.0 years. No factors achieved significance for remission
Gastaldi *et al* [26]	115	MMI	0.5-0.7 kg/kg/day	2 years	33	Relationship between the time required for TRAb normalization and the patient outcome. Visible goiter, mean TSH RAb also predicted remission

ATD: Antithyroid drug, PTU: Propylthiouracil, MMI: Methimazole, ANCA: Anti-neutrophil cytoplasmic antibody, FT4: Free T4, TSH: Thyroid stimulating hormone, RAb: Receptor antibody, BRT: Block and replacement therapy, TRAb: TSH-receptor antibody

after the completion of each course of ATD treatment. The median duration of follow-up in this study was 10.4 years. Overall estimated remission rates 18 months after the withdrawal of ATD treatment increased with time and were 20%, 37%, 45%, and 49% after 4, 6, 8, and 10 year follow-up, respectively. In a multivariate risk model, baseline high free T4 levels and the presence of other autoimmune disease at diagnosis was associated with a lesser chance of remission.[6]

In one of the largest series of 1138 patients with GD, of the 639 patients who discontinued ATD treatment, 334 (46.2%) achieved a remission, 247 (34.2%) experienced a relapse, and 58 (8.0%) dropped out. The cumulative remission rate increased with the duration of ATD treatment up until 5 years. No significant predictors of a remission were identified.[18]

In various studies, lower thyroid hormone levels, longer duration of treatment, lower levels of TSH receptor antibodies, and smaller goiter predicted higher chance of remission. There was a trend toward higher remission rates in older children with GD on treatment.

Effective duration of anti-thyroid drugs therapy in pediatric Graves' disease

In adults with GD, it is recommended that if MMI is chosen

as the primary therapy for GD, the medication should be continued for approximately 12–18 months, then tapered or discontinued if the TSH is normal at that time.[10] A meta-analysis shows the remission rate in adults is not improved by a course of ATDs longer than 18 months.[27]

However, in children, the duration of therapy is controversial. Most studies have used around 24 months of therapy. There are data to support improved remission rates with longer duration of therapy. In Glaser *et al*., series of 184 pediatric patients treated with ATDs for up to 4 years, remission rates progressively improved from 10% after 1 year to 20% after 3 years and 23% after 4 years of ATD.[16] In the multicenter French Childhood GD Study Group, 154 patients who were on MMI for a period of 24 months, followed by a follow-up of 2 years. In this study, relapse risk decreased with longer duration of the first course of ATD. Furthermore, the estimated relapse rate 2 years after the end of treatment was 83% in patients treated for no more than 24 months, and 60% in patients treated for more than 24 months.[17]

TRAb serves as a marker predicting remission in adults with GD. In a study of 86 children and adolescents with GD treated >3 years, mean TRAb levels decreased with duration of therapy, but even after 13–24 months, TRAbs had normalized in only 3/16 (18.8%) patients. The initial TRAb titer correlated significantly with severity of the initial hyperthyroidism but did not predict the response to therapy as indicated by the dosage of ATD required to control the hyperthyroidism at 6 and 12 months.[28] In another study of 115 children, 38 children (33%) achieved remission after 2 years of ATD therapy. Absence of goiter, lower median TSH receptor antibody levels and lower time required for TSH R Ab normalization were factors associated with a better outcome in pediatric GD.[26] In another small study (n = 17) of subjects with GD, TRAb (TBIAb) was the only factor associated with a lasting remission.[29]

Although it seems that the rates of remission in children are lower than that of adults, there is no definite duration of therapy proposed for children. In studies of pediatric GD, the risk of relapse is reduced with longer duration of therapy with ATD,[16,17] although 24 months can be considered reasonable before deciding to choose an alternate mode of definitive treatment.[12,30] Although not compared in the same centers, Asian ethnic patients seem to have a higher rate of remission with ATD.[18,24,25] Practitioners planning to continue medications for longer duration should weigh the benefits of ATD against the poor remission rates and adverse effects of ATD.

Does anti-thyroid drugs induced adverse effects occur more commonly in children?

Both PTU and MMI are associated with adverse effects in children and adults. Both medications may cause serious adverse effects such as agranulocytosis and hepatotoxicity. MMI causes cholestatic hepatitis, and PTU causes hepatocellular injury including fulminant hepatic failure. Other serious adverse effects include Steven Johnson Syndrome, thrombocytopenia, neutropenia, and vasculitis. Minor adverse effects include rash, pruritus, arthralgia, hives, nausea, and reduced taste.[2,3,8,10]

Side effects of MMI are dose-related, whereas those of propylthiouracil are less clearly related to dose.[8] In adults, the frequency of adverse effects associated with ATD are skin rash (4–6%), arthralgia (1–5%), gastrointestinal (1–5%), polyarthritis (1–2%), agranulocytosis (0.1–0.5%) with rest of the adverse events described as rare.[8]

In a prospective study of 70 children treated with PTU, 11 children (16%) developed adverse reactions to PTU including skin rash, arthralgia, arthritis with purpura and hematuria, elevated transaminases, and neutropenia. These children were treated with block and replace regimen with a daily dose of 5–7 mg/kg body weight of PTU.[16] In a group of 154 patients followed up for 10 years, only three patients had adverse reactions to ATD necessitating discontinuation of treatment. The incidences of minor reactions were not mentioned in this study.[6]

In a review that compiled the adverse effects of ATD in 500 children, there was an increased incidence of ATD related adverse effects in children: Mild increases in liver enzymes (28%), mild leukopenia (25%), skin rash (9%), granulocytopenia (4.5%), arthritis (2.4%), nausea (1.1%), agranulocytosis (0.4%), and hepatitis (0.4%). Other adverse effects were considered rare.[31] The risk of adverse effects associated with ATD in various studies is shown in Table 2.

There seems to be a difference in adverse reactions to ATD in relation to the pubertal status. In a study of 40 children by Lazar *et al*., the overall, adverse reactions to ATDs occurred in 35%, with a higher rate among the prepubertal children (71%) than the pubertal (28%) and post pubertal (25%) patients. Major adverse reactions were noted in two children, both prepubertal.[22]

The adverse effects of MMI seem to be dose related. The incidence of agranulocytosis in children is not known although it has been reported in about 0.3% of adult patients taking MMI or PTU.[8,31]

Table 2: Recorded adverse effects of anti-thyroid drugs in children

Author	ATD	Risk of adverse effects	Type of adverse effects
Hamburger 1985[14]	PTU and MMI	17%	Cutaneous-6%; neutropenia-0.55%; rheumatological-1.1%; hepatic-1.1%; neutropenia-2.2%; nausea-1.1%; multiple infections without neutropenia-2.75%
Rivkees *et al.*[32]	MMI	19%	Pruritus and hives 8%, diffuse arthralgia, muscle pain, and/or joint pain-5%; lymphopeniaand eosinophilia-1%, neutropenia 2%, Stevens-Johnson syndrome-3%, mild liver injury-1%
Glaser and Styne 2008[16]	PTU and MMI	16%	Skin rash (1 patient), rash with arthralgias (2 patients), arthritis with purpura and hematuria (1 patient), mild elevation in liver enzymes (3 patients), marked elevation in liver enzymes (2 patients), and neutropenia (2 patients)
Kaguelidou *et al.* 2008[17]	Carbimazole	6%	Urticaria (*n*=6), arthralgia (*n*=2), leukoneutropenia (*n*=1), thrombopenia (*n*=1)
Léger 2012[6]	Carbimazole	3 patients	Allergic reaction (n=1), neutropenia (*n*=1), arthralgia (*n*=1)
Ohye *et al.* 2014[18]	MMI and PTU	MMI: 21.4%, PTU: 18.8%	No fatal side effects. Cutaneous (16%), liver dysfunction (1.5%), agranulocytosis (*n*=7), neutropenia (*n*=6), ANCA (*n*=5)
Poyrazoglu *et al.*[19]	MMI and PTU	12%	Mild reactions include cutaneous reactions, mild liver enzyme elevations, leucopenia, arthralgia. Major toxicity in 3 patients including immune hemolytic anemia, autoimmune hepatitis, and Vasculitis-arthritis-hepatitis syndrome
Gruñeiro-Papendieck *et al.*[20]	MMI and PTU	12.9%	Cutaneous reactions, skin rashes and pruriticeruptions, urticaria and angioedema, (10/15), mild arthralgia (*n*=2), severe leucopenia (*n*=3)
Lippe *et al.*[14]	MMI and PTU	1.6%	Arthritic reaction (*n*=1)
Lazar *et al.* 2000[22]	PTU and MMI	35%	Major in 5% patients and minor in 30% patients. Minor (namely, fever, rash, arthralgia, transient leucopenia, and major (agranulocytosis and severe toxichepatitis)
Kon *et al.*[23]	PTU and MMI	4 patients	Transient neutropenia (*n*=1), hair fall (*n*=3)
Song *et al.*[24]	MMI and PTU	11%	Not mentioned
Bhadada *et al.*[25]	Carbimazole	1.8%	Agranulocytosis (*n*=1)
Gastaldi *et al.*[26]	MMI	Not mentioned	Not mentioned

ATD: Antithyroid drug, PTU: Propylthiouracil, MMI: Methimazole, ANCA: Anti-neutrophil cytoplasmic antibody

However, there is little evidence to show that regular routine monitoring of hematological profiles or liver function tests will identify subjects early in the course of illness. The recommendation is to stop MMI and PTU and monitor blood counts if children develop fever, mouth sores, pharyngitis, or feel ill.[8,30] In 95% of subjects who develop agranulocytosis, it develops within the first 100 days of therapy.[8,33] While routine monitoring of white blood counts may detect early agranulocytosis, it is not recommended since it is rare and not cost effective.

Most studies show that the incidence of adverse effect of ATD is more common in children than in adults. There is a trend to higher adverse effects in prepubertal children compared to pubertal children. This relative risk benefit ratios should help prioritize treatment options of RAI in children as primary therapy or as a definitive treatment after first cycle of medical treatment.

Propylthiouracil in children

Propylthiouracil (6 propyl-2-thiouracil) was introduced for clinical use in July 1947. It acts by inhibiting the enzyme thyroid peroxidase which adds iodine to the tyrosine residue on thyroxine hormone precursor thyroglobulin. PTU also inhibits the enzyme tetraiodine 5'deiodinase, which converts T4 to T3.[7,8]

In comparison to MMI and Carbimazole, PTU causes serious liver-related problems. PTU causes hepatocellular necrosis leading to liver transplantation and death.[7] In a review of US FDS Adverse Drug Reporting system, dissimilar hepatotoxicity profile of PTU and MMI in children was analyzed, PTU had a high adjusted reporting ratio for severe liver injury in a group less than 17 year of age. There were 23 cases of severe liver injury with PTU in less than 17 years of age and none with MMI. 4 subjects required liver transplantation. There were 4 cases of mild liver injury with PTU and 1 with MMI. In the same study, a major vasculitis signal was also observed with PTU in comparison to MMI.[34]

In the NICHD, OPPB Workshop in 2008 convened to evaluate PTU safety in children; it was observed that the risk of PTU associated liver transplantation was about 1 in 2000–4000 children. The liver failure associated with PTU was rapidly progressive with a low chance of reversibility. Children are at higher risk of liver failure than adults. The number of children developing reversible PTU-related liver toxicity is 10 fold greater than the number of children who develop liver failure requiring transplantation. Since PTU-induced liver injury is of rapid onset and can be rapidly progressive, serial testing of liver function will not be useful in identifying these subjects.[35] PTU is associated with higher risk of ANCA development and Vasculitis than MMI. PTU and MMI have comparable rates of agranulocytosis which are dose-dependent with MMI and not with PTU.[7]

Propylthiouracil hepatotoxicity has been reported to cause a variety of histological changes including portal and periportal inflammation with eosinophilic, lymphocytic, and plasmacytic infiltration in varying combinations, chronic active hepatitis, and submassive or massive hepatic necrosis.[36] These histological features resemble autoimmune hepatitis type 1 (AIH-1) and is referred to as drug-induced AIH-1. The various postulated for PTU-induced liver damage include inhibition of glucuronyltransferase, reduced bile acid synthesis, and increased oxygen consumption by the hepatocytes.[37,38]

If PTU is used, it is recommended that PTU should be stopped immediately and liver function be assessed in children who experience anorexia, pruritus, rash, jaundice, light colored stool or dark urine, joint pain, right upper quadrant pain or abdominal bloating, nausea or fatigue.[34] In 2010, FDA added a boxed warning to the drug label for PTU about reports of liver injury and acute liver failure.[39,40]

Alternatives to anti-thyroid drug therapy: Radioactive iodine and thyroidectomy

Radioactive Iodine therapy is a viable alternative to ATD therapy in children. Introduced more than 60 years back, RAI therapy leads to remission rates in excess of 95%. The aim of RAI therapy is to achieve hypothyroidism. Rare adverse effects include tenderness of the thyroid gland, thyroid storm, and worsening of ophthalmopathy. Experience with RAI is limited in children <5 years.[3,12,30] Thyroidectomy (near total or total) is another alternative mode of treatment for pediatric GD. Surgery should be done by high-volume thyroid surgeons and is indicated in children <5 years and those with thyroid gland >80 g in volume.[12,30,41]

Role of anti-thyroid drugs in the treatment of Graves's disease in children

Despite the fact that ATD achieves sustained remission in only a third of patients, has longer duration of treatment and the risk of adverse events, ATD still forms the initial treatment modality in a vast majority of children and adolescents of GD. PTU should not be used in children unless in a special situation as bridge therapy for short duration to control hyperthyroidism before surgical treatment in a patient intolerant to MMI.[12,30]

- Children *et al*. has proposed the following as guidance to choosing therapy in subjects with GD.[12,30] Children <5 years: MMI should be used as first-line treatment till the patient goes into remission. A prolonged duration of therapy may be needed. RAI may be considered when the child is older or if developing adverse effects to ATD. Thyroidectomy is a viable option in experienced hands
- Children 6–10 years: MMI should be considered as first-line treatment. RAI is a viable option as the child approaches 10 years or if there is a relapse on adequate course of ATD
- Children >10 years: MMI or RAI therapy can form the first-line treatment. Patients with small goiter and low titer of TSH- R-Ab would be the right candidates for MMI therapy. After 1–2 years of ATD therapy, RAI or a repeat course of ATD would be an option.

Conclusion

Most children and adolescents with GD are treated with ATD as the initial modality. The rate of persistent remission with ATD following discontinuation is in the tune of 30%. ATD are associated with adverse reactions in a minority of subjects including rare but severe adverse effects such as agranulocytosis, liver cell failure, Steven Johnson syndrome, and Vasculitis. The routine use of PTU in children has been restricted due to hepatotoxicity. In patients with relapse after ATD, radio RAI therapy or surgery should be considered as a viable option.

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