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Antithyroid DrugsInduced Neutropenia or Agranulocytosis: what is important and new for the clinician?

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Introduction

Synthetic antithyroid drugs (ATDs), prescribed for almost 50 years, include several molecules derivatives of thioureas. ATDs include carbimazole, methimazole, thiamazole (active form of carbimazole), benzylthiouracil, and propylthiouracil (PTU). Difference between the different molecules is minimal [1]. ATDsare used in the majority of hyperthyroid patients, either over the long term or before thyroid surgery or prescription of radioactive iodine [1, 2].They are selectively concentrated by the thyroid gland and decrease the synthesis of thyroxine (T4) and triiodothyronine (T3) by decreasing the iodine used in hormonogenesis [1]. Propylthiouracil has the well-known characteristic of inhibiting T4 deiodination, characterized by a decrease in T3 and an increase in T3 reverse, whose clinical importance is still debated. Similarly, thiamazol, or carbimazol (thiamazol prodrug) modulates the immune system in vitro under certain conditions, although it cannot be concluded that this drug has an influence on the development of hyperthyroidism related to Basedow's (Grave's) disease.ATDs have been associated with idiosyncratic neutropenia and agranulocytosis, respectively defined as an absolute blood neutrophil count (NC) ≤1.5 x 109/L and NC of ≤0.5 x 109/L with fever or NC of ≤0.1 x 109/L [3, 4]. In this setting, it seemed useful to carry out a review of the recent literature, because the literature on this topic is relatively limited, often analyzing small patient populations, and most often involving American, Chinese or Japanese populations treated mainly with methimazole [2].

A relative important risk of neutropenia and agranulocytosis!

Idiosyncratic neutropenia and agranulocytosis have been related to most classes of drugs (Table 1) [4-6]. For the majority of drugs, the risk is likely to be very small [1, 3]. However for several drugs, the risk may be much more important, as for example for ATDs [3, 4]. To date, the most important series devoted to ATD-induced severe neutropenia and agranulocytosis is a monocentric Japanese study, conducted from 1975 to 2001 [7]. Out of 30, 798 patients treated for Basedow's disease, 109 cases of severe neutropenia were reported with ATDs, representing an incidence of 0.35%. In the International Agranulocytosis and Aplastic Anaemia Study (IAAAS) involving seven European countries and Israel, 45 cases severe neutropenia with ATDs have been reported (cases with methimazole: n=33, with propylthiouracil: n=8, and cases with carbimazole: n=4) [8]. This study concluded that there is an excess risk of 6.3 cases of agranulocytosis per week per million users and an incidence of 3 per 1, 000 users per year. In this series, the relative risk (RR) for agranulocytosis use was determined to be 102 (95% CI: 38-275). The width of the confidence interval is explained by the fact that of the 1, 771 individuals in the control group, only five subjects were treated with ATD. In this setting, a Dutch study by Van der Klauw et al. had reported a RR for agranulocytosis of 115 (95% CI 90.5-218.6) [9]. The cumulative incidence of ATD-induced agranulocytosis and pancytopenia at 100 and 150 days after the initiation of ATD was 0.28 and 0.29%, respectively [10].

Table 1. Drugs related to idiosyncratic neutropenia and agranulocytosis [3-6].

Drug Family	Drugs
Analgesics and non-steroidal anti-inflammatory drugs	Acetaminophen, acetylsalicylic acid (aspirin), aminopyrine, benoxaprofen, diclofenac, diflunisal, dipyrone, fenoprofen, indomethacin, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, tenoxicam, tolmetin
Antipsychotics, hypnosedatives, and antidepressants	Amoxapine, chlomipramine, chlorpromazine, chlordiazepoxide, clozapine, diazepam, fluoxetine, haloperidol, levomepromazine, imipramine, indalpine, meprobamate, mianserin, olanzapine, phenothiazines, risperidone, tiapride, ziprasidone
Antiepileptic drugs	Carbamazepine, ethosuximide, phenytoin, trimethadione, valproic acid (sodium valproate)
Antithyroid drugs	Carbimazole, methimazole, potassium perchlorate, potassium thiocyanate, propylthiouracil, benzylthiouracil
Cardiovascular drugs	Acetylsalicylic acid (aspirin), amiodarone, aprindine, bepridil, captopril, coumarins, dipyridamole, digoxin, flurbiprofen, furosemide, hydralazine, lisinopril, methyldopa, nifedipine, phenindione, procainamide, propafenone, propranolol, quinidine, ramipril, spironolactone, thiazide diuretics, ticlopidine, vesnarinone
Anti-infective drugs	Abacavir, acyclovir, amodiaquine, atovaquone, cephalosporins, chloramphenicol, chloroguanine, chloroquine, ciprofloxacin, clindamycin, dapsone, ethambutol, flucytosine, fusidic acid, gentamicin, hydroxychloroquine, isoniazid, levamisole, lincomycin, linezolid, macrolides, mebendazole, mepacrine, metronidazole, minocycline, nitrofurantoin, norfloxacin, novobiocin, penicillins, pyrimethamine, quinine, rifampicin, streptomycin, terbinafine, tetracycline, thioacetazone, tinidazole, trimethoprim-sulfamethoxazole (cotrimoxazole), vancomycin, zidovudine
Biotherapies	Anti-CD20 agents (rituximab), anti-CD52 (alemtuzumab), interleukin-1 inhibitors (anakinra, canakinumab), interleukine-6 inhibitors (tocizulimab), interferon-α, TNF-α inhibitors (adalimumab, etanercept infliximab)
Miscellaneous drugs	Acetazolamide, acetylcysteine, allopurinol, aminoglutethimide, arsenic compounds, bezafibrate, brompheniramine, calcium dobesilate, chlorpheniramine, cimetidine, colchicine, dapsone, deferiprone, famotidine, flutamide, gold, glucocorticoids, hydroxychloroquine, mesalazine, methapyrilene, methazolamide, metoclopramide, levodopa, octreotide, olanzapine, omeprazole, oral hypoglycemic drugs (glibenclamide), mercurial diuretics, penicillamine, ranitidine, riluzole, sulfasalazine, most sulfonamides, tamoxifen, thenalidine, tretinoin, tripelennamine

A potential role of the type of molecule used!

ATDs are responsible for 5 to 23% of drug-induced neutropenia and agranulocytosis depending on the considered series [8, 11-13]. In this setting, a 20-year Dutch case-control study has reported 17 cases of agranulocytosis related to carbimazole or methimazole (15.7%) out of a total of 108 cases [13]. In this study, the RR associated with ATDs is estimated at 115 (95% CI: 60.5-218.6). In the aforementioned Japanese study, including 109 cases of severe neutropenia, 93 cases were related to methimazole (which represents an incidence of 0.35%) and 16 with propylthiouracil (incidence of 0.37%) [7]. Trotter had established a higher frequency of agranulocytosis with propylthiouracil compared to carbimazole (0.7% versus 0.3%) [14]. A 40-year study (1963-2003), based on the records of the Great Britain National Pharmacovigilance Agency, also reports a risk of higher agranulocytosis with carbimazole, with 94 cases observed versus 12 with propylthiouracil. Based on the registers of the network of French Pharmacovigilance Centers, it also appears that severe neutropenia and agranulocytosis are more frequent with propylthiouracil, with an incidence for propylthiouracil 2.75 times higher than that for carbimazole [15]. Figure 1 shows the distribution of ATDs involved in severe neutropenia cases, collected between 1980 and 2006, by the network of French Pharmacovigilance Centers [16]. The explanatory hypotheses would include a higher toxicity of propylthiouracil, but also a higher rate of pharmacovigilance reporting by practitioners for this ATD that they are less familiar with, and the use of higher doses of propylthiouracil in some groups.

The time of onset of agranulocytosis is most often less than three months with ATD treatment. Thus, 82% of cases occurred within the first three months in the IAAAS study [8] and 97% of cases occurred within six months in the Pearce study [15]. In the meta-analysis of Andersohn et al., the median of this time was 41 days for carbimazole and 36 days for propylthiouracil [4]. In the Mutharasan's study, the mean duration of treatment with propylthiouracil, carbimazole and methimazole used to cause agranulocytosis was found to be 36, 41, and 42 days, respectively [17].

The phenotype of the "victim"!

In the literature, the median age of onset of neutropenia is between 51 and 54.4 years for carbimazole-induced agranulocytosis, with an increased frequency in people over 65 years of age [18, 19]. In this literature there is also a female predominance (e.g., 82% of the patients were female in the aforementioned IAAAS cohort). In this setting, a recent study showed a higher female-to-male ratio (10.4:1) and similar age of onset (41.7 ± 12.3 years) in 114 patient with ATD-induced agranulocytosis

[20]. A retrospective American study (cases treated with methimazole: n=19, with propylthiouracil: n=17, and cases with benzylthiouracil: n=14) also found a sex ratio of 1/7 in favor of women, with an average age of patients of 50.6 years [10]. To our opinion, these results may be mainly due to a higher prevalence of hyperthyroidism among women, particularly relatively young patients in cases of Basedow's disease, rarely of hyperthyroidism related to Hashimoto's disease. Nevertheless, in one of the largest published series of ATD-induced agranulocytosis (n=754 cases), the mean age of onset was 43.4 ± 15.2 years, nearly 45% of patients were aged in their 40s and 50s and females were more affected than males (6.3: 1 ratio) [21].The different series of ATD-induced neutropenia and agranulocytosis includes patients with hyperthyroidism related to: mainly, Basedow's disease (between 70 to 90%) and toxic adenoma or goiter; rarely, hyperthyroidism related to Hashimoto's disease; and exceptionally, hyperthyroidism during pregnancy [7-10].

Risk factors and predisposing conditions to be known…

Several authors have searched for factors and conditions that expose patients to an increased risk of neutropenia and agranulocytosis related to ATDs. The search for such predisposing factors and conditions is important, particularly in an attempt to prevent or detect them early [3, 6, 11]. In this setting, the phenotype of the patient, the conditions of use of the ATDs, the existence of an underlying autoimmune diseases and the histocompatibility antigens (human leukocyte antigen [HLA]) have been extensively studied (Table 2) [1, 23-31]. Tamai et al. have looked for a correlation with age, the dose of ATD used, the duration of treatment, or the existence of one or more previous exposures, but only identified these factors in 12 patients [23]. Cooper compared 50 patients with agranulocytosis related to ATD (14 patients on thiouracil) with a control group of the same size [24]. In this study, the RR for agranulocytosis related to ATD was about six times higher in a subject over 40 years of age than in a younger subject. In the aforementioned study from Nakamura et al., when compared with untreated patients with Basedow's disease, those with agranulocytosis were older ($p < 0.001$) and more likely to be female ($p < 0.0001$) [21]. Cooper also had investigated the relationship between the dosage used and the occurrence of neutropenia [24]. Under methimazole, the RR of agranulocytosis appears approximately eight times higher with a daily dose greater than 40 mg (RR 8.6, CI: 95%, 1.7-44.1, $p < 0.001$). For propylthiouracil, the average dosage did not appear to be involved in the risk of agranulocytosis. A few rare data suggest the role of certain autoimmune diseases in the development of agranulocytosis. Thus, in Young's study, there is a higher incidence of agranulocytosis in patients who were positive for rheumatoid factor [25]. Similarly, the highest incidence of severe neutropenia under ATDs (1.75%) has been reported in a population composed exclusively of patients with Basedow's disease [4]. However, the total number of patients was 514, whereas a minimum of 1, 000 to 5, 000 patients would have been required to determine a reliable incidence when the adverse event studied is rare. In this setting, specific HLA phenotypes have been identified as markers of susceptibility to neutropenia and agranulocytosis for some molecules.

The histocompatibility antigen DRB1*08032 was associated with the occurrence of agranulocytosis with methimazole in a total of 24 Japanese patients with Basedow's disease [26, 27]. Genetic determinants of ATD-induced agranulocytosis have shown that the alleles HLA-B*38: 02 and HLA-DRB1*08: 03 are independent susceptibility loci for agranulocytosis [28]. Carrying both HLA-B*38: 02 and HLA-DRB1*08: 03 increases the odds ratio to 48.41 (95% CI 21.66–108.22). In Caucasians, a different HLA-B allele (B*27: 05; OR 7.3, 95% CI 3.81–13.96) and rare NOX3 variants have been tentatively associated [29, 30].In the context of ATD-induced neutropenia, the existence of cross-reactions between ATDs has been documented since 1983 [31]. In a retrospective study, cross-reactivity between carbimazole and propylthiouracil has been reported in 15.2% of cases, all adverse events combined [15]. Chemical

Figure 1. Distribution of the various antithyroid drugs involved in agranulocytosis cases collected by the network of French Pharmacovigilance Centers (n=203) [16].

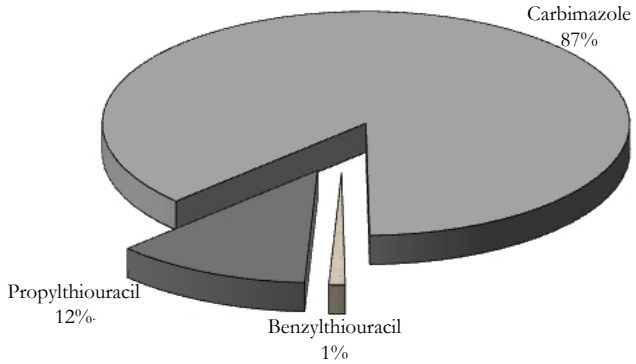

Table 2. Risk factors and predisposing conditions for antithyroid drug-induced neutropenia [1,2,34-41].

Risk factors and predisposing conditions	Documented
Age/Sex	Age ≥40 years; female
Conditions of treatment use	Methimazole ≥40 mg/day
Underlying diseases	Rheumatoid factor (Sjögren's syndrome?); Basedow's (Grave's) disease?
Human leukocyte antigen (HLA)	HLA-B*38: 02 and HLA-DRB1*08: 03
Cross reactions	Cross-reactivity between carbimazole and propylthiouracil (>15%)

groups common to several molecules probably explain the occurrence of these cross-reactions.

Clinical manifestations to which the clinician should expect!

Transient neutropenia (NC between 1.5 to 1 x 109/L) is relatively common with ATDs. In this setting, ATD-induced neutropenia may often be asymptomatic [16]. This neutropenia discovery is kinked to the routine follow-up of the patient under ATD as recommended by several endocrinology societies [3, 16]. In 30% of the cases, ATD-induced neutropenia may be revealed by an "isolated" fever, an oropharyngeal lesion (historically of a necrotic nature), or a localized infections, most often pulmonary [3, 6, 11]. It is notable that when antibiotics are administered prophylactically in cases with isolated fever, both the patient's complaints and the physical findings may be "masked" and fever may be the only clinical sign detected [4, 11]. It should be noted that the follow-up of the patients potentially (with blood NC follow-up in case of ATD intake) modifies the mode of discovery of the neutropenia, with asymptomatic patients or patients with isolated fever, but without necessarily modifying the evolution of this hematological event [3, 11]. For severe neutropenia (NC of ≤0.5 x 109/), most patients (>60%) who do not receive medical intervention develop septicemia, while some have clinical signs of pneumonia as well as anorectal, skin, or oropharyngeal infections or septic shock [1,3,5,6]. In a cohort study of 203 cases of severe neutropenia and agranulocytosis, the main clinical presentations during the immediate follow-up have been:"isolated" fever or fever of unknown origin (26.3%), septicemia (13.9%), documented pneumonia (13.4%), sore throat and acute tonsillitis (9.3%), and septic shock (6.7%) [3]. While in hospital, 19.2% of the patients worsened clinically and exhibited features of severe sepsis, septic shock, or systemic inflammatory response syndrome (SIRS) [11].

Do not miss another diagnosis…

In adults, the differential diagnosis of severe neutropenia and agranulocytosis includes a limited number of conditions [3, 32]. Indeed, neutropenia with an absolute NC ≤0.5 x 109/L has been shown to be attributable to drugs in 70 to 90% of cases [32]. In the experience of Andersohn et al., idiosyncratic neutropenia or agranulocytosis was reported to be drug-related in 97% of cases [33].In clinical practice, the main differential diagnoses of neutropenia in adults are listed in Table 3 [3, 32]. In the context of ATD use, the autoimmune disorders must be particularly considered as a possible cause of the neutropenia because of the prevalence of the association: Basedow's and Hashimoto's disorders with Sjögren's syndrome and systemic lupus erythematosus. Nutritional deficiencies must also be considered because of the prevalence of the association of the thyroid disorders with coeliac disease.

A better prognostic and a falling mortality…

Over the past 20 years, the mortality rate for idiosyncratic drug-inducedagranulocytosisis 10-16% in European studies [3, 4, 6, 11]. This is likely due to improved recognition, management, and treatment of the condition. In this setting, the literature from the last 30 years related to ATD-induced severe neutropenia and agranulocytosis shows a progressive decrease in mortality every decade. A Swedish study conducted in 1966-1975 has reported 5 deaths among 29 cases of agranulocytosis induced by ATD (17%); the risk appeared similar for carbimazole, methimazole, and propylthiouracil [31]. Cooper's study (1953-1981) and IAAAS (1980-1986) each found a mortality rate of about 2% [24]. Finally, Pearce's retrospective study from 1963 to 2003 has shown a mortality rate of 18% [15]. No significant difference in mortality is found between patients taking carbimazole and those exposed to propylthiouracil. Mortality appears more pronounced in subjects over 65 years of age: 13.8% versus 1.2% (RR: 12.9, 95% CI: 1.45-114.9). The improvement in knowledge of the pathophysiology and the optimization of treatment, particularly with regard to the use of antibiotic combinations, are probably at the root of this significant reduction in mortality [3, 11]. For example, there were no deaths in 109 cases of agranulocytosis related to ATD, managed in a Japanese endocrinology reference center, where this pathology is known (numerous publications from this center), diagnosed early and treated in a codified manner, with in particular the systematic use of hematopoietic growth factors (e.g., Granulocyte-Colony Stimulating Factor (G-CSF)[7].

A codified management!

The management of drug-induced neutropenia and agranulocytosis begins with the immediate withdrawal of any medications which may potentially be responsible, here the ATD [3, 4, 11].

Table 3. Differential diagnosis of antithyroid drug-induced neutropenia in adults [3, 32].

− **Normal variations:** Ethnic and familial neutropenia
− **Infections:** Especially viral infections (Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis virus, rubella, parvovirus B19); bacterial infections (typhoid fever, brucellosis, tuberculosis, rickettsia, severe sepsis); rarely in industrialized countries, protozoal and fungal (histoplasmosis, leishmaniosis, malaria)
− **Hematological disease:** Acute leukemia, myelodysplasia (especially in elderly patients), pure white blood cell aplasia and red cell aplasia, Marchiafava-Michelli's disease (paroxysmal nocturnal hemoglobinuria)
− **Immune neutropenia:** Isolated autoimmune neutropenia, collagen vascular autoimmune disease (systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis or Felty's syndrome), T γ-δ lymphocytosis
− **Nutritional deficiencies:** B9 and B12 deficiencies (related to coeliac disease, maldigestion and malabsorption syndromes)
− **Other drugs:** Potentially all drugs, especially ticlopidine, clozapine, sulfasalazine, trimethoprim-sulfamethoxazole (cotrimoxazole), and dipyrone

The patient's medication history must be carefully obtained in chronological order so that the suspected drug(s) may be identified. Importantly, the appropriate pharmacovigilance center must be notified of all cases of drug-induced neutropenia [3]. Essential drugs are being replaced by drugs from other therapeutic classes, not known to be the origin of severe neutropenia [3, 4, 11].In the context of hyperthyroidism, stopping an ATD is not a major endocrine problem in the short term, since the inhibitory effect on thyroid function is prolonged [1]. In patients with rhythmic and/or ischemic heart disease or with life-threatening hyperthyroidism, a substitution of an ATD with another antithyroid molecule may be necessary. However, the existence of cross-reactions between ATD has been documented particularly between carbimazole and propylthiouracil [25, 31]. A cross-reaction between carbimazole and propylthiouracilhas been observed in 15.2% of patients [18].In the setting of ATD-induced neutropenia, the occurrence of sepsis requires prompt management, including administration of antibiotics and hospitalization [3, 4, 6, 11]. Asymptomatic patients at high risk of infection should also be admitted to the hospital [3, 4, 11]. To our opinion, even patients with a low risk of infection, with none of risk factors (listed in Table 3) and good general health, should be treated in the hospital, unless adequate and comprehensive medical follow-up can be provided in an ambulatory setting or at home [3].

In the setting of drug-induced neutropenia, the occurrence of sepsis requires prompt management, including hospitalization and the administration of broad-spectrum intravenous antibiotic therapy (after blood, urine, and any other relevant samples have been cultured) [3, 4, 6, 11].To date, there are no official recommendations on antibiotic therapy to be used in this specific context of non-chemotherapeutic drug-induced neutropenia, particularly if ATD are causative. To our knowledge, only one study specifically reports microbiological data in the context of idiosyncratic ATD-induced neutropenia [34]. This is a study of 17 cases of agranulocytosis (a grouping of personal cases and case reports published in the English literature and supported from a microbiological data perspective). Of the 23 documented infections, the majority are related to Gram-negative bacillus infection. The most common was Pseudomonas aeruginosa (n=7, [30%]) [34]. In view of these date, empiric, broad-spectrum antibacterial therapy is generally the best choice, with an association of cephalosporins (e.g., ceftazidime) or piperacillin/tazobactam) and aminoglycosides or fluoroquinolones [3, 6, 11]. However, the choice of antibiotic used may need to be adapted depending on the nature of the sepsis, the clinical status of the patient, local patterns of antibiotic resistance, and previous antibiotic use [3, 4, 6, 11]. Preventive measures include good hygiene and infection control, paying attention to high-risk areas such as the mouth, skin, and perineum [1-3]. Patient isolation and the use of prophylactic antibiotics (e.g., for the gastrointestinal tract) have been proposed, but their usefulness in limiting the risk of infection has not been clinically proven [3].

In all chemical drug-induced agranulocytosis, therapeutic measures, such as transfusions of granulocyte concentrates, should only be used in exceptional circumstances, and only then for the control of life-threatening infections with antibiotic resistance such as perineal gangrene [3, 4, 11]. Corticosteroids are also to have an effect on the exit of cells from bone marrow and their migration into the circulatory stream. This led a Chinese team to evaluate their effectiveness in the treatment of severe neutropenia and agranulocytosis related to ATDs. However, no benefit was shown from their use [35].

Potential interest of hematopoietic growth factors…

To date, there are three published clinical studies specifically dedicated to ATD-induced neutropenia and agranulocytosis treated with hematopoietic growth factor (HGF) [7, 36, 37]. The study by Fukata et al. is a prospective, randomized, Japanese study involving 24 patients with documented agranulocytosis related to ATD. In Fukata's study, there was no significant reduction in the average duration of agranulocytosis [36]. However, certain limitations must be pointed out that make it difficult to interpret the results of this study. First, the number of patients studied was small, and more importantly, the dosage of G-CSF (<200 µg/day) was lower than that currently considered effective [38]. In this setting, Andrès et al. have reported a study involving 20 patients with agranulocytosis related to ATDs [37]. Statistically significant differences in favor of the use of HGFshave been observed for hematological recovery times (6.8 versus 11.6 days; p=0.046) and hospitalization times (7.3 versus 13 days; p=0.038). As no fatal cases were observed, the benefit on mortality could not be studied. Tajiri et al., out of a total of 109 patients with agranulocytosis, also showed a 2-day shortening of the duration of agranulocytosis with HGFs (34 cases treated with G-CSF) [7]. In this study as well, since no fatal cases have been observed, the benefit on mortality could not be studied. It should be noted that in this work, the matching criteria were met but the daily dosage of G-CSF used (75 µg) was very low compared to the current recommended dosage.

Prevention and follow-up to be implemented!

Routine monitoring of blood NC in the general population is not indicated for all drugs [3, 6]. However, routine monitoring for neutropenia is at least recommended, and perhaps strictly required, in the use of some high-risk drugs such as clozapine, ticlopidine, and for ATDs [39, 40, 41]. In this setting, a standardized approach with blood NC examination at each visit when prescribing ATD was recently shown to correctly diagnose 64% and 94% of patients with agranulocytosis with no or minimum infection symptoms, respectively [37]. Despite this, to date, this recommendation continues to be debated because of the absence of impact on mortality and morbidity [11]. This may explain current attitudes towards routine monitoring of blood counts even in individuals receiving high risk medications such as antithyroid drugs or ticlopidine [3, 4, 41]. At this level, it is imperative to highlight the importance of patient education in preventing the most serious accidents.

Conclusions

Although it is a known adverse drug reaction, many questions remain in the study of idiosyncratic drug-induced neutropenia and agranulocytosis, including cases related to synthetic ATDs. The studies to date concerning the latter are based on rare series, of low numbers, mainly concerning non-European populations, and treated mainly with methimazole, a drug not used in France and rarely in Europe. Today, ATD-induced neutropenia

remains a potentially serious adverse event due to the frequency of severe sepsis, particularly those with severe neutropenia (NC of ≤0.5 x 109/). Knowledge of the commonly-implicated drugs and a high index of suspicion are essential in diagnosis. Physicians must be vigilant in identifying ATD-induced neutropenia because early detection can decrease the severity and prevent mortality if the drug is discontinued. Given the advancing age of the population, the increasing use of medications as a therapeutic modality, and the subsequent increased exposure to drugs, as well as the development of new drugs, health care professionals should be aware of this adverse event and its management.

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References

[1]. Cooper DS. Antithyroid drugs. New England Journal of Medicine. 2005 Mar 3;352(9):905-17.

[2]. Vicente N, Cardoso L, Barros L, Carrilho F. Antithyroid drug-induced agranulocytosis: state of the art on diagnosis and management. Drugs in R&D. 2017 Mar 1;17(1):91-6.

[3]. Andrès E, Zimmer J, Mecili M, Weitten T, Alt M, Maloisel F.. Clinical presentation and management of drug-induced agranulocytosis. Expert Rev Hematol. 2011 Apr;4(2):143-51. doi: 10.1586/ehm.11.12 PMID:21495924

[4]. Andersohn F, Konzen C, Garbe E. Non-Chemotherapy Drug-Induced Agranulocytosis: A Systematic Review of Case Reports: 108. Pharmacoepidemiology and Drug Safety. 2007 Jul;16., 146, 157-165.

[5]. Curtis BR. Non–chemotherapy drug–induced neutropenia: key points to manage the challenges. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):187-193. doi: 10.1182/asheducation-2017.1.187. PMID:29222255

[6]. Andrès E, Villalba NL, Zulfiqar AA, Serraj K, Mourot-Cottet R, Gottenberg AJ. State of art of idiosyncratic drug-induced neutropenia or agranulocytosis, with a focus on biotherapies. J Clin Med. 2019 Sep 1;8(9). pii: E1351. doi: 10.3390/jcm8091351. PMID:31480527

[7]. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: how has granulocyte colony-stimulating factor changed therapy?. Thyroid. 2005 Mar 1;15(3):292-7.

[8]. Retsagi G, Kelly J.P, Kaufman D.W. IAAAS: International Agranulocytosis and Aplastic Anaemia Study. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. BMJ: British Medical Journal.1988 Jul 23:262-5.

[9]. van der Klauw MM1, Goudsmit R, Halie MR, van't Veer MB, Herings RM, Wilson JH, et al.. A population-based case-cohort study of drug-associated agranulocytosis. Arch Intern Med. 1999 Feb 22;159(4):369-74. PMID:10030310

[10]. Watanabe N, Narimatsu H, Noh JY, Yamaguchi T, Kobayashi K, Kami M et al. Antithyroid drug-induced hematopoietic damage: a retrospective cohort study of agranulocytosis and pancytopenia involving 50, 385 patients with Graves' disease. J Clin Endocrinol Metab. 2012 Jan;97(1):E49-53. doi: 10.1210/jc.2011-2221. PMID:22049174

[11]. Andrès E, Mourot-Cottet R, Maloisel F, Séverac F, Keller O, Vogel T et al. Idiosyncratic drug-induced neutropenia & agranulocytosis QJM. 2017 May;110(5):299-305. doi: 10.1093/qjmed/hcw220. Epub 2017 Jan 9. PMID:28069912

[12]. Shapiro S, Issaragrisil S, Kaufman D.W, Anderson T, Chansung K, Thamprasit T, et al. Agranulocytosis in Bangkok, Thailand: a predominantly drug-induced disease with an unusually low incidence. Aplastic Anemia Study Group. Am J Trop Med Hyg. 1999 Apr;60(4):573-7. DOI:10.4269/ajtmh.1999.60.573 PMID:10348230

[13]. van der Klauw MM, Wilson JH, Stricker BH. Drug-associated agranulocytosis: 20 years of reporting in the Netherlands (1974-1994). Am J Hematol. 1998 Mar;57(3):206-11. DOI:10.1002/(sici)1096-8652(199803)57:3<206::aid-ajh4>3.0.co;2-z. PMID:9495370

[14]. Trotter WR. The relative toxicity of antithyroid drugs. The Journal of new drugs. 1962 Nov 12;2(6):333-43.

[15]. Weitten T, Alt M, Decker N, Andrès E. National Network of Pharmacovigilance Centers. Agranulocytosis with synthetic antithyroid drugs: epidemiological and clinical data. Study of 203 cases from the national pharmacovigilance database. Rev Med Int. 2009; 30 (Suppl 4): S347-8.

[16]. Pearce SH. Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. Clin Endocrinol (Oxf). 2004 Nov;61(5):589-94. PMID:15521961

[17]. Mutharasan P, Oatis W, Kwaan H, Molitch M. Delayed antithyroid drug-induced agranulocytosis. Endocr Pract. 2012 Jul-Aug;18(4):e69-72. doi: 10.4158/EP11339. PMID:22297058

[18]. Meyer-Gessner M, Benker G, Lederbogen S, Olbricht T, Reinwein D. Antithyroid drug-induced agranulocytosis: clinical experience with ten patients treated at one institution and review of the literature. J Endocrinol Invest. 1994 Jan;17(1):29-36. DOI:10.1007/BF03344959 PMID:7516356

[19]. Yang J1, Zhu YJ1, Zhong JJ2, Zhang J1, Weng WW1, Liu ZF, et al. Characteristics of antithyroid drug-induced agranulocytosis in patients with hyperthyroidism: a retrospective analysis of 114 cases in a single institution in China involving 9690 patients referred for radioiodine treatment over 15 years. Thyroid. 2016 May;26(5):627-33. doi: 10.1089/thy.2015.0439. PMID:26867063

[20]. Cooper, D.S.; Goldminz, D.; Levin, A.A.; Ridgway, E.C. Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. Ann Intern Med. 1983 Jan;98(1):26-9. PMID:6687345

[21]. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab. 2013 Dec;98(12):4776-83. doi: 10.1210/jc.2013-2569. Epub 2013 Sep 20 PMID:24057289

[22]. Dettling M, Cascorbi I, Roots I, Mueller-Oerlinghausen B.. Genetic determinants of clozapine-induced agranulocytosis: Recent results of HLA subtyping in a non-Jewish Caucasian sample. Arch Gen Psychiatry. 2001 Jan;58(1):93-4. PMID:11146763

[23]. Tamai H, Takaichi Y, Morita T, Komaki G, Matsubayashi S, Kuma K, et al. Methimazole-induced agranulocytosis in Japanese patients with Graves' disease. Clin Endocrinol (Oxf). 1989 May;30(5):525-30. PMID:2605789

[24]. Cooper DS, Goldminz D, Levin AA, Ridgway EC. Agranulocytosis associated with antithyroid drugs. Effects of patient age and drug dose. Ann Intern Med. 1983 Jan;98(1):26-9. PMID:6687345

[25]. Young, N.S. Drug-related blood dyscrasias. Eur J Haematol. 1996, 60 (suppl), 6-8.

[26]. Tamai H1, Sudo T, Kimura A, Mukuta T, Matsubayashi S, Kuma K, et al. Association between the DRB1*08032 histocompatibility antigen and methimazole-induced agranulocytosis in Japanese patients with Graves disease. Ann Intern Med. 1996 Mar 1;124(5):490-4. DOI:10.7326/0003-819-124-5-199603010-00005 PMID:8602707

[27]. Chen B, Lang R, Jutrin Y, Ravid M. Recurrent agranulocytosis-induced by two different antithyroid agents. Med J Aust. 1983 Jul 9;2(1):38-9. PMID:6865827

[28]. Chen PL, Shih SR, Wang PW, Lin YC, Chu CC, Lin JH, et al. Genetic determinants of antithyroid drug-induced agranulocytosis by human leukocyte antigen genotyping and genome-wide association study. Nat Commun. 2015 Jul 7;6:7633. doi: 10.1038/ncomms8633. PMID:26151496

[29]. Hallberg P, Eriksson N, Ibañez L, Bondon-Guitton E, Kreutz R, Carvajal A, et al. Genetic variants associated with antithyroid drug-induced agranulocytosis: a genome-wide association study in a European population. Lancet Diabetes Endocrinol. 2016 Jun;4(6):507-16. doi: 10.1016/S2213-8587(16)00113-3. Epub 2016 May 3.PMID:27157822

[30]. Plantinga TS, Arts P, Knarren GH, Mulder AH, Wakelkamp IM, Hermus AR, et al. Rare NOX3 variants confer susceptibility to agranulocytosis during thyrostatic treatment of Graves' disease. Clin Pharmacol Ther. 2017 Dec;102(6):1017-1024. doi: 10.1002/cpt.733. Epub 2017 Jul 10.PMID:28486791

[31]. Ostlere S, Apthorp GH. Recurrent agranulocytosis following carbimazole and propylthiouracil therapy. Br J Clin Pract. 1988 Nov;42(11):474-5. PMID:3256337

[32]. Palmblad J, Dufour C, Papadaki HA. How we diagnose neutropenia in the adult and elderly patient. Haematologica. 2014 Jul;99(7):1130. -1133.

[33]. Andersohn F, Bronder E, Klimpel A, Garbe E.. Proportion of drug-related serious rare blood dyscrasias: Estimates from the Berlin Case-Control Surveillance Study. Am J Hematol. 2004 Nov;77(3):316-8. DOI:10.1002/ajh.20176 PMID:15495238

[34]. Sheng WH1, Hung CC, Chen YC, Fang CT, Hsieh SM, Chang SC, et al. Antithyroid-drug-induced agranulocytosis complicated by life-threatening infections. QJM. 1999 Aug;92(8):455-61. DOI:10.1093/qjmed/92.8.455 PMID:10627862

[35]. Dai WX, Zhang JD, Zhan SW, Xu BZ, Jin H, Yao Y, et al. Retrospective analysis of 18 cases of antithyroid drug (ATD)-induced agranulocytosis.

Endocr J. 2002 Feb;49(1):29-33. PMID:12008747
[36]. FUKATA S, KUMA K, SUGAWARA M. Granulocyte colony-stimulating factor (G-CSF) does not improve recovery from antithyroid drug-induced agranulocytosis: a prospective study. Thyroid. 1999 Jan;9(1):29-31.
[37]. Andrès E, Kurtz, J.E, Perrin, A.E, Dufour, P, Schlienger, J.L, Maloisel F. The use of haematopoietic growth factors in antithyroid-related drug-induced agranulocytosis: a report of 20 patients. QJM.2001, 94, 423-428.
[38]. Andrès E, Weitten T, Mourot-Cottet R, Keller O, Zulfiqar AA, Serraj K, et al. Agranulocytosis with synthetic antithyroid drugs: review of the literature. The Journal of Internal Medicine. 2016 Aug 1; 37 (8): 544-50.
[39]. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. Arch Intern Med. 1990 Mar;150(3):621-4. PMID:2310281
[40]. Nakamura H, Ide A, Kudo T, Nishihara E, Ito M, Miyauchi A. Periodic Granulocyte Count Measuring Is Useful for Detecting Asymptomatic Agranulocytosis in Antithyroid Drug-Treated Patients with Graves' Disease. Eur Thyroid J. 2016 Dec;5(4):253-260. doi: 10.1159/000448586. Epub 2016 Sep 6. PMID:28101490
[41]. Tsuboi K1, Ueshiba H, Shimojo M, Ishikawa M, Watanabe N, Nagasawa K et al. The relation of initial methimazole dose to the incidence of methimazole-induced agranulocytosis in patients with Graves' disease. Endocr J. 2007 Feb;54(1):39-43 PMID:17053291