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Stat of Art of Idiosyncratic Antithyroid Drugs Induced Neutropenia or Agranulocytosis

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Abstract

Introduction: Idiosyncratic drug-induced neutropenia and agranulocytosis is seldom discussed in the literature, especially for new data regarding synthetic antithyroid drugs. In the present paper, we report and discuss the clinical data and management of this relatively rare disorder, with a focus on these agents (carbimazole, methimazole, thiamazole, benzylthiouracil and propylthiouracil).

Materials and Methods: A review of the literature was carried out using the PubMed database of the US National Library of Medicine.

Results: Transient Grade 1 neutropenia (absolute neutrophil count [NC] from 1.5 to 1 x 109/L) related to antithyroid agents is relatively common with these drugs. Grade 2-4 neutropenia or agranulocytosis (absolute NC between 1.0 to less than 0.1 × 109/L) and clinical manifestations related to sepsis are less common, with a prevalence of 0.18 to 1.75%. In this setting, a relative risk associated for Grade 3-4 neutropenia (absolute NC from 0.5 to 0.1 and <0.1 x 109/L, respectively) and agranulocytosis of more than 100 had been estimated with antithyroid agents use. Idiosyncratic neutropenia should be managed depending on clinical severity, with permanent/transient discontinuation of the drug, switching from one drug to another (with possibility of cross-reactivity), broad-spectrum antibiotics in cases of sepsis, and hematopoietic growth factors (particularly G-CSF).

Conclusion: In recent years, significant progress has been made in the field of idiosyncratic antithyroid drug-induced neutropenia, leading to an improvement in their management and prognosis. Clinicians must continue their efforts to improve their knowledge of these adverse events.

Keywords: Drug; synthetic antithyroid agents; idiosyncratic; neutropenia; agranulocytosis; fever; infections; ticlopidine; clozapine; sulfasalazine; antibiotics as trimethoprim-sulfamethoxazole (cotrimoxazole), deferiprone; non-chemotherapy; hematopoietic growth factor; G-CSF

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Introduction

Drug-induced neutropenia or agranulocytosis is defined as a profound decrease or a complete lack of the number of neutrophils (granulocytes) in circulating blood [1]. This disorder is a potentially severe complication that may be fatal in approximately 5% of cases [1-3]. It has been related to most classes of drugs [1,3-6]. For the majority of drugs, the risk is likely to be very small [2]. However for several drugs, the risk may be much more important, as for example for synthetic antithyroid drugs (ATD) [1-3,6]. These drugs are used in the majority of hyperthyroid patients, either over the long term or before prescription of radioactive iodine or surgery [7,8]. ATD, prescribed for almost 50 years, are derivatives of thioureas. The difference between the different molecules as carbimazol, methimazol, thiamazol (active form of carbimazole), benzylthiouracil, and propylthiouracil

(PTU) is minimal [7]. 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 [7]. 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.

Because the literature on neutropenia and agranulocytosis due to ATD is relatively limited [8], often analyzing small patient populations, and most often involving American, Chinese or Japanese populations treated mainly with methimazole, it seemed useful to carry out a review of the literature on this subject, with a focus on severe neutropenia and agranulocytosis.

Search strategy

A literature search was performed via the PubMed database of the US National Library of Medicine. We searched for articles published between January 2010 and October 2019 using the following key words or associations: "antithyroid drug-induced neutropenia", "antithyroid drug-induced agranulocytosis", "carbimazole-induced neutropenia", "carbimazole-induced agranulocytosis", "methimazole-induced neutropenia", "methimazole-induced agranulocytosis", "thiamazole-induced neutropenia", "thiamazole-induced agranulocytosis", "benzylthiouracil-induced neutropenia", "benzylthiouracil-induced agranulocytosis", "propylthiouracil-induced neutropenia", "propylthiouracil-induced agranulocytosis", "idiosyncratic neutropenia" and "idiosyncratic agranulocytosis". Restrictions included: English-, Spanish-, or French-language publications; papers published from January 1, 2010 to September 31, 2019; human subjects; and clinical trials, review articles, or guidelines.

American Society of Hematology educational books, textbooks of Hematology, Endocrinology, and Internal Medicine, and information gleaned from international meetings were also reviewed.

Definitions

Definitions of neutropenia and agranulocytosis

Neutropenia is defined as an absolute blood neutrophil count (NC) ≤1.5 x 109/L [2]. Severe neutropenia is defined as less ≤0.5 x 109/L. Neutropenia have been classified by the National Cancer Institute into several categories based on the severity of neutropenia (https://www.cancer.gov/). This classification includes several neutropenia categories with: "Grade 1": defined by an absolute NC from 1.5 to 1 x 109/L; "Grade 2": defined by an absolute NC from 1 to 0.5 x 109/L; "Grade 3": defined by an absolute NC from 0.5 to 0.1 x 109/L; and "Grade 4": defined by an absolute NC from ≤0.1 x 109/L. Severe neutropenia, also called agranulocytosis, is characterized by a profound decrease or an absolute lack of circulating granulocytes, classically resulting in an absolute NC of ≤0.5 x 109/L [1,3,5]. For several authors, a definition of "established" agranulocytosis requires the combination of an absolute NC ≤0.1 x 109 neutrophils per liter with fever or signs of sepsis [1,5]. The majority of hospitalized patients for such neutropenia have a NC ≤0.1 x 109/L, either initially or later in the hospitalization [2,3].

Criteria of drug imputability

In practice, most but not all cases of neutropenia occur as a result of exposure to drugs, either chemotherapy, defining the "chemotherapy" neutropenia, or other drugs, defining the "idiosyncratic" neutropenia (classically unexpected) [9,10]. Either the drug itself or one of its metabolites may be at the origin of the neutropenia [4]. This is the case for the ATD. In this setting, many causality assessment methods have been proposed to assess the relationship between a drug treatment and the occurrence of an adverse event, including neutropenia, in each patient [1,2,5,11]. The assessment methods roughly belong to three categories: "probabilistic approaches", "algorithms" and "expert judgments". For chemical drugs, the recommended criteria for blood cytopenias are derived from an international consensus meeting [1,5,11]. To date, these criteria remain valid for all chemical drugs and thus for ATD. These criteria, for assessing causality for implicating drugs in the etiology of neutropenia, are presented in Table 1 [11].

Table 1: Definition and criteria of drug imputability for idiosyncratic chemical drug-induced neutropenia and agranulocytosis [1,5,11].

Definition of neutropenia and agranulocytosis	Criteria of drug imputability
• Neutropenia is defined by a neutrophil count ≤1.5 × 10^9/L • Agranulocytosis is defined by a neutrophil count ≤0.5 × 10^9/L ± existence of a fever and/or any signs of infection	• Onset of agranulocytosis during treatment or within 7 days after exposure to the drug, with a complete recovery in neutrophil count of more than 1.5 × 10^9/L within one month of discontinuing the drug • Recurrence of agranulocytosis upon re-exposure to the drug (theoretically the gold standard method but ethically questionable) • Exclusion criteria: history of congenital neutropenia or immune mediated neutropenia, recent infectious disease (particularly recent viral infection), recent chemotherapy and/or radiotherapy, and existence of an underlying hematological disease

Differential diagnosis

In adults, the differential diagnosis of severe neutropenia and agranulocytosis includes a limited number of conditions [1,10,11]. 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 [10,11]. In the experience of Andersohn et al., idiosyncratic Grade 3-4 neutropenia or agranulocytosis was reported to be drug-related in 97% of cases [11]. In clinical practice, the main differential diagnoses of neutropenia in adults are listed in Table 2 [1,2,11]. Outside the context of chemotherapy and cancer, these differential diagnoses mainly include: (i) neutropenia secondary to viral infections or to severe sepsis, particularly in case of severe bacterial infections; (ii) neutropenia secondary to bone marrow disorders, such as myelodysplastic syndromes (particularly in elderly patients) or acute leukemia; and (iii) neutropenia associated with hypersplenism (Table 2) [1,2,11]. 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 LES. Nutritional deficiencies must also be considered because of the prevalence of the association of the thyroid disorders with coeliac disease.

Table 2: Differential diagnosis of antithyroid drug-induced neutropenia in adults [1,10,11].

– **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

Epidemiological data

Idiosyncratic drug-induced Grade 3-4 neutropenia or agranulocytosis is a rare disorder. In Europe, the annual incidence of these hematological events is between 1.6 and 9.2 cases per million population [1-3,5]. In the USA, Strom et al. have reported rates ranging from 2.4 to 15.4 per million per year [3]. Geographic variability in incidence is related to both differences in reporting and medication usage but could also suggest genetic differences in susceptibility [1]. The prevalence of Grade 2-4 neutropenia and agranulocytosis due to ATD has been established to be between 0.18 and 1.75% [13,14]. To date, the most important series devoted to ATD-induced agranulocytosis is a monocentric Japanese study, conducted from 1975 to 2001 [15]. Out of 30, 798 patients treated for Basedow's disease, 109 cases of Grade 2-4 neutropenia were reported with ATD, representing an incidence of 0.35%. In the International Agranulocytosis and Aplastic Anaemia Study (IAAAS) involving seven European countries and Israel, 45 cases of Grade 3-4 neutropenia with ATD have been reported (cases with methimazole: n=33, with propylthiouracil: n=8, and cases with carbimazole: n=4) [16]. 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) [17]. 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 [19].

6. Phenotype of the patient

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 [13,20]. 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 [21]. 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 [18]. 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) [22].

To date, ATA are one of the drug classes most at risk of neutropenia, while the prevalence of hyperthyroidism is high (nearly 1% of the population) [7,8]. The different series of ATD-induced neutropenia and agranulocytosis includes 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 [15-18].

Drugs involved

The drugs most commonly associated with idiosyncratic Grade 1-4 neutropenia and agranulocytosis are shown in Table 3 [1-3,5,6,23]. Almost all non-chemotherapy classes of drugs have been implicated, as in recent years biotherapies, but for the majority the risk appears to be very small [1-3,6]. However, for drugs such as ATD, ticlopidine, clozapine, sulfasalazine, trimethoprim-sulfamethoxazole (cotrimoxazole), and dipyrone, the risk may be higher [1-3]. In our experience (observational study in a referral center), the first two drug classes involved which are also frequently prescribed were antibiotics (49.3%), especially ß-lactams and cotrimoxazole, and ATD, especially carbimazole and propylthiouracil (n=203) [3]. These findings are comparable to reports from several European research teams, except for antiviral drugs [14,26,27].

Table 3: Drugs related to idiosyncratic neutropenia and agranulocytosis [1-3,5,6].

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

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

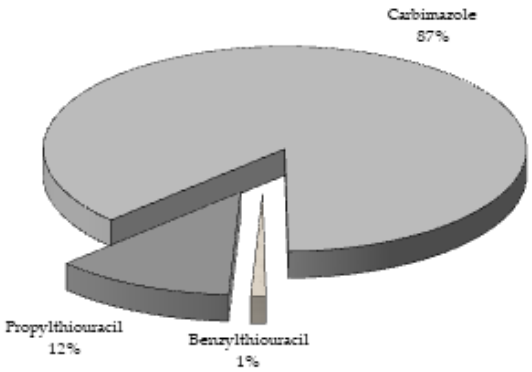
Anti-infective drugs Abacavir, acyclovir, amodiaquine, atovaquone, cephalosporins, chloramphenicol, chloroguanine, chloroquine, ciprofloxacin, clindamycin, dapsone, ethambutol, flucytosine, fusidic acid, gentamicin, hydroxychloroquine, isoniazid, levamisole, lincomycin, linezolid, macrolides, mebendazole, 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

ATD are responsible for 5 to 23% of drug-induced Grade 1-4 neutropenia depending on the series considered [3,16,28,29]. 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 [29]. In this study, the RR associated with ATD is estimated at 115 (95% CI: 60.5-218.6). In the aforementioned Japanese study, including 109 cases of Grade 2-4 neutropenia, 93 cases were related to methimazole (which represents an incidence of 0.35%) and 16 with propylthiouracil (incidence of 0.37%) [15]. Trotter had established a higher frequency of agranulocytosis with propylthiouracil compared to carbimazole (0.7% versus 0.3%) [30]. 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 Grade 3-4 neutropenia are more frequent with propylthiouracil, with an incidence for propylthiouracil 2.75 times higher than that for carbimazole [31]. Figure 1 shows the distribution of ATD involved in Grade 3-4 neutropenia cases, collected between 1980 and 2006, by the network of French Pharmacovigilance Centers [31]. 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.

Figure 1: Distribution of the various antithyroid drugs involved in agranulocytosis cases collected by the network of French Pharmacovigilance Centers (n=203) [31].



The time of onset of agranulocytosis is most often less than three months with ATD treatment. Thus, 82% of cases occurred within the first 3 months in the IAAAS study [16] and 97% of cases occurred within 6 months in the Pearce study [32]. In the meta-analysis of Andersohn et al., the median of this time was 41 days for carbimazole and 36 days for propylthiouracil [2]. The mean duration of treatment with propylthiouracil, carbimazole and methimazole used to cause agranulocytosis was found to be 36, 41, and 42 days, respectively [33].

Risk factors and predisposing conditions

Several authors have searched for factors and conditions that expose patients to an increased risk of neutropenia and agranulocytosis related to ATD. The search for such predisposing factors and conditions is important, particularly in an attempt to prevent or detect them early [1-3,5]. In this setting, the phenotype of the patient, the conditions of use of the ATD, the existence of an underlying autoimmune diseases and the histocompatibility antigens (human leukocyte antigen [HLA]) have been extensively studied (Table 4) [1,2,34-45].

Table 4: Risk factors and predisposing conditions for antithyroid drug-induced neutropenia [1,2,34-45].

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%)

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 [36]. Cooper compared 50 patients with agranulocytosis related to ATD (14 patients on thiouracil) with a control group of the same size [37]. 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 ($p < 0.0001$) [22]. Cooper also had investigated the relationship between the dosage used and the occurrence of Grade 2-4 neutropenia [36]. 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 [38]. Similarly, the highest incidence of Grade 3-4 neutropenia under ATD (1.75%) has been reported in a population composed exclusively of patients with Basedow's disease [9]. 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 [39,40]. 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 [41]. 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 [42,43].

In the context of ATD-induced neutropenia, the existence of cross-reactions between ATD has been documented since 1983 [44,45]. In a retrospective study, cross-reactivity between carbimazole and propylthiouracil has been reported in 15.2% of cases, all adverse events combined [10]. Chemical groups common to several molecules probably explain the occurrence of these cross-reactions.

Pathogenesis

Clinical observations, studies in volunteers, and laboratory experiments have suggested that idiosyncratic drug-induced neutropenia is mediated by immune allergic and toxic mechanisms [4,5]. Direct damage either to the microenvironment of the bone marrow or to myeloid precursors may play a role [4,45,46]. In this setting, neutropenia associated with ATD are usually considered to respond to an immuno-allergic rather than toxic mechanism (Figure 2) [8,31]. Genetic polymorphism has been considered, given the heterogeneity of expression of the various enzymes that metabolize drugs and other chemicals, as well as oxidative modification of the drug [4,45,46]. In this setting, the impact of myeloperoxidase and NADPH-oxidase polymorphism in drug-induced agranulocytosis has been studied [4,46,47].

Immuno-allergic mechanism

Wall et al. have showed the existence of immunoreactivity, by lymphocyte transformation and leuco-agglutination tests, in the presence of propylthiouracil or carbimazole in 12 patients who developed agranulocytosis related to ATD being used for the treatment of Basedow's disease [47]. Guffy et al. have studied the cytotoxicity of anti-neutrophil antibodies. The study was performed on the serum of one patient with propylthiouracil-

induced agranulocytosis [48]. The serum collected in the acute phase showed a very high cytotoxic activity towards the patient's neutrophils, but also against the neutrophils of controls, which implies the notion of background environment predisposing to agranulocytosis with propylthiouracil via the antigens carried by the neutrophils. It should be noted that this cytotoxic activity due to immunoglobulin M (IgM) decreases as the number of circulating neutrophils increases. Weitzman et al. have found the presence of IgM anti-neutrophil antibodies with opsonizing complement-dependent activity in one methimazole-treated patient who developed agranulocytosis [49]. Finally, Fibbe et al. have studied the serum reactivity of one patient with propylthiouracil-induced agranulocytosis on circulating granular cells and progenitor myeloid cells [50]. They found antibodies reacting with these two cell populations in the presence of propylthiouracil. In the same study, anti-erythrocyte antibodies are also identified in addition to anti-neutrophil antibodies.

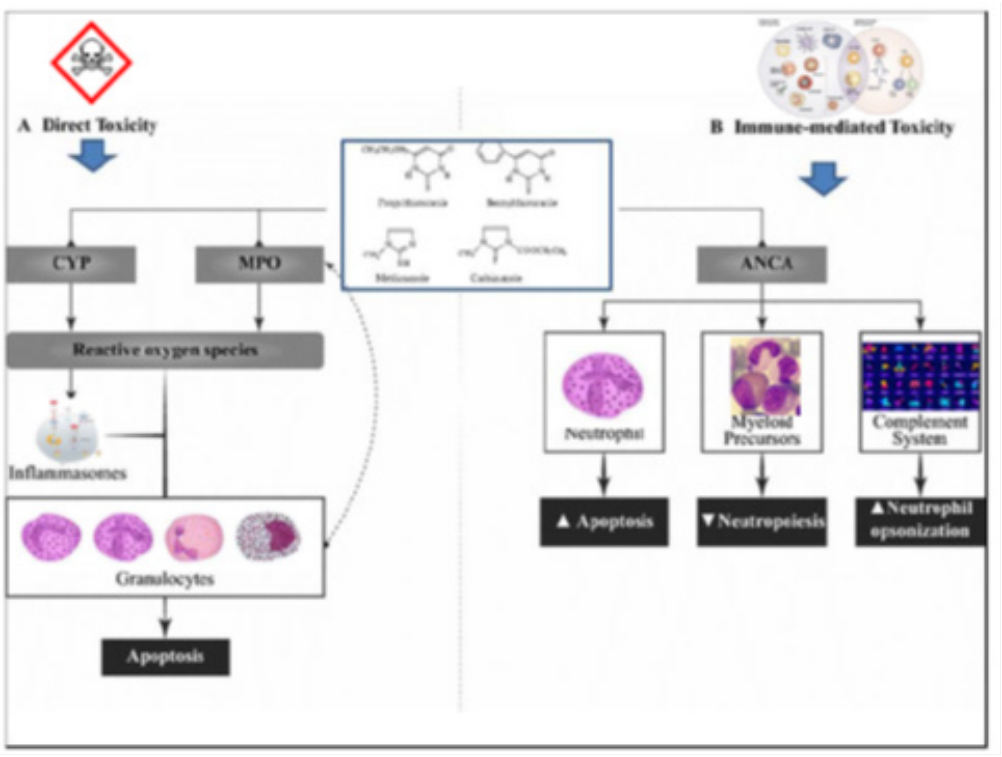


Figure 2: Mechanisms of antithyroid drugs -induced neutropenia (adapted from [4,45,46]).

Focus on neutrophil anti-cytoplasm antibodies

Anti-cytoplasmic antibodies of neutrophils (ANCA) have been identified in patients treated with long-term ATD use who have developed neutropenia [7]. Indeed, the antigenic targets of these antibodies can be expressed on the cell surface of neutrophils. However, at present neither the precise mechanism nor the target antigens are clearly established. Moreover, the detection of anti-neutrophil antibodies is not specific to agranulocytosis since these antibodies are found in very diverse diseases (e.g., vasculitis, rectal ulcerative hemorrhagic colitis) [30]. One hypothesis formulated by Lam is that the propylthiouracil accumulated in the neutrophil would damage the cell by binding myeloperoxidase (MPO). This would make this enzyme immunogenic in some patients [7]. The presence of MPO p-ANCA has been reported in 37.5% of patients with Basedow's treated with propylthiouracil [51]. The presence of these anti-neutrophil antibodies is correlated with the duration of treatment, but not with the presence of anti-TPO antibodies. In this series, 3 of 21 patients (14.3%) with ANCA developed neutropenia or agranulocytosis [52]. More recently, Akamizu et al. reported the case of one patient with Basedow's disease who developed severe and chronic neutropenia and ANCA after propylthiouracil treatment [53]. The case was positive for ANCA anti-PR3 and anti-MPO. Cytotoxicity tests have shown that these antibodies lysed neutrophils by a complement-mediated mechanism and not by dependent cell-antibody cytotoxicity. The discontinuation of propylthiouracil resulted in hematological recovery and the disappearance of ANCA.

Toxic mechanism

The evidence of an accumulation of carbimazole and propylthiouracil in neutrophils (nearly 10 times the concentrations measured in other cell lines) leads to the presumption of a toxic phenomenon [7]. Tsuboi and Cooper have found that agranulocytosis most often occurred with high initial doses of thio-imidazoles [7,14]. Tsuboi et al. have conducted a study of 9 cases of agranulocytosis in 514 patients with Basedow's disease. In this

study, 4.11% of patients initially treated with 30 mg methimazole per day developed agranulocytosis, compared to 0.31% for patients who received 15 mg per day or less of this molecule, the difference being statistically significant [14]. Cooper, in a case-control study (n=19), has determined the existence of a threshold dosage for methimazole (40 mg per day) beyond which the RR for agranulocytosis is 8.6 (CI =1.7-44.1, p <0.001). The control group was representative of the general population but not matched to cases [17]. The finding of global, and therefore non-specific, bone marrow damage in some cases of agranulocytosis with ATD leads to the assumption of a mechanism of toxicity for all lines or towards bone marrow stem cells.

Clinical manifestations

The clinical presentation and evolution of Grade 1-4 neutropenia and agranulocytosis associated with ATD are not known to be different from to other drug-related neutropenia and agranulocytosis [1,6,15,31]. Patients with drug-induced Grade 1-4 neutropenia usually are asymptomatic or present with fever (often the earliest sign), associated with general malaise (often including chills, myalgia, and/or arthralgia) with a non-specific sore throat, and other localized infections [1-3,5,6,54-56]. For Grade 3-4 neutropenia and agranulocytosis, 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 (Figure 3) [1,3,5,6].

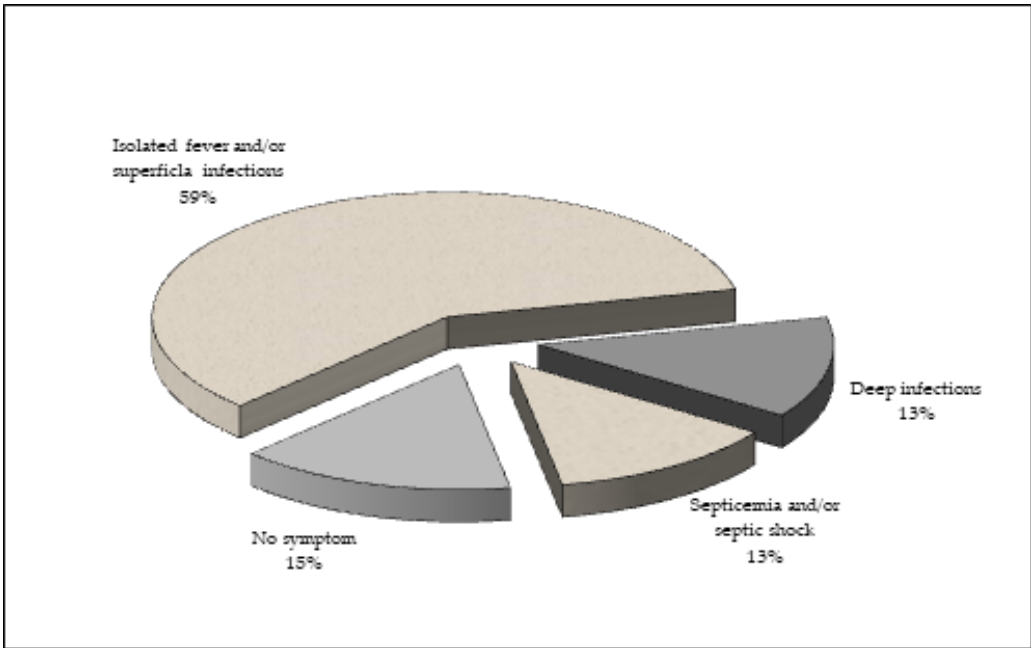


Figure 3: Clinical manifestations of drug-induced Grade 3-4 neutropenia and agranulocytosis (n=203) [3].

Transient Grade 1-2 neutropenia is relatively common with ATD. However, these hematological events are often responsible for acute and severe neutropenia (e.g., Grade 3-4 neutropenia), at diagnosis or in progress, with an acute and sometimes life-threatening infection [1-3,5,6,31]. However, ATD-induced neutropenia may be asymptomatic in 30% of the cases [31], identified during the routine follow-up of the patient as recommended by several endocrinology societies [1,31]. The latter is manifested either by an "isolated" fever, an oropharyngeal lesion (historically of a necrotic nature), by localized infections, most often pulmonary, or even septicemia (historically, by necrotic and extensive perineal abscesses) [1-3,5]. 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 [2,3]. 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 [1,3].

Prognosis and mortality rate

Over the past 20 years, the mortality rate for idiosyncratic drug-induced Grade 1-4 neutropenia is 10-16% in European studies [1-3,5,6]. This is likely due to improved recognition, management, and treatment of the condition. Grade 3-4 neutropenia and agranulocytosis are the most likely to cause death as seen in oncology where the severity of neutropenia has a documented impact on prognosis. To date, no robust data are available in the context of idiosyncratic ATD-induced neutropenia and agranulocytosis. This is due to the low number of documented cases available and the small number of patients in each series. Table 5 presents factors influencing the prognosis (hematological recovery, duration of hospitalization and antibiotic therapy, and mortality) with all chemical drugs [3,54-57].

Table 5: Impact factors for the prognosis* of idiosyncratic drug-induced agranulocytosis [1,3,54,56].

• Age: ≥65 years	Negative impact on duration of hematological recovery**, duration of hospitalization and antibiotherapy
• Neutrophil count at diagnosis: ≤0.1 × 10^9/L	Negative impact on duration of hematological recovery, duration of hospitalization and antibiotherapy
• Clinical status: Deep severe infections or bacteremia or septic shock (versus isolated fever)	Negative impact on duration of hospitalization and antibiotherapy and of mortality
• Severe underlying disease or severe co-morbidity: renal failure, cardiac or respiratory failure, systemic auto-inflammatory diseases	Negative impact on duration of hematological recovery and hospitalization
• Management with pre-established procedures and hematopoietic growth factor for use in severe conditions	Positive impact on duration of hematological recovery, duration of hospitalization and of mortality

*Prognosis: hematological recovery, duration of hospitalization and antibiotherapy, mortality.

**Hematological recovery: absolute neutrophil count >1.5 × 109/L

In this setting, the literature from the last 30 years related to ATD-induced Grade 2-4 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 [44]. Cooper's study (1953-1981) and IAAAS (1980-1986) each found a mortality rate of about 2% [7,37]. Finally, Pearce's retrospective study from 1963 to 2003 has shown a mortality rate of 18% [32]. 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 [1-3]. 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) [15].

Management

General measures

The management of drug-induced Grade 1-4 neutropenia and agranulocytosis begins with the immediate withdrawal of any medications which may potentially be responsible, here the ATD [1-3]. The discontinuation of ATD should be systematically carried out in this context with regard to the frequency of the association between neutropenia and these drugs. 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 [1]. Essential drugs are being replaced by drugs from other therapeutic classes, not known to be the origin of severe neutropenia [1-3]. 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 [7]. 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 [38,44,45]. A cross-reaction between carbimazole and propylthiouracil has been observed in 15.2% of patients [13]. In the setting of ATD-induced Grade 2-4 neutropenia, the occurrence of sepsis requires prompt management, including administration of antibiotics and hospitalization [1-3,5,6]. Asymptomatic patients at high risk of infection should also be admitted to the hospital [1-3]. To our opinion, even patients with a low risk of infection, with none of risk factors (listed in Table 5) 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 [1].

Management of patient with fever

In the setting of drug-induced Grade 1-4 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 [1-3,5,6,54]). 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 [59]. 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%]) [59]. 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 [1-3,5]. 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 [1-3,5,6]. 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 [1].

Use of hematopoietic growth factors

Since 1985, two-thirds of reported cases have been treated with HGF, first and foremost G-CSF and more rarely Granulocyte Macrophage-Colony Stimulating Factor [55]. The most recent major studies on HGF use in drug-induced agranulocytosis are described in Table 6 [2,5,60-66]. In this setting, G-CSF (at a mean dose of 5 µg/kg/day) has been found to be useful in shortening the duration of blood count recovery time, without inducing any major toxic or adverse effects, particularly in patients with poor prognostic factors [1,3,56,60].

Table 6: Recent studies on the use of hematopoietic growth factors in idiosyncratic chemical drug-induced agranulocytosis [2,5,60-66].

Type of Study and Target Population	Main Results
Systematic review of all published cases (n=492); All patients with idiosyncratic drug-induced agranulocytosis [2]	Treatment with hematopoietic growth factors was associated with a statistically significantly lower rate of infectious and fatal complications, in cases with a neutrophil count <0.1 × 10^9/L.
Meta-analysis (n=118); All patients with idiosyncratic drug-induced agranulocytosis [62]	G-CSF or GM-CSF (100 to 600 µg/day) reduced the mean time to neutrophil recovery (neutrophil count >0.5 × 109/L) from 10 to 7.7 days, in cases with a neutrophil count <0.1 × 10^9/L, and reduced the mortality rate from 16 to 4.2%.
Case control study, retrospective analysis (n=70); All patients with idiosyncratic drug-induced agranulocytosis [63]	G-CSF and GM-CSF (100 to 600 µg/day) reduced the recovery of neutrophil count from 7 to 4 days, particularly in patients with a neutrophil count <0.1 × 10^9/L.
Cohort study, retrospective analysis (n=54); Patients with idiosyncratic drug-induced agranulocytosis >65 years of age, with poor prognostic factors [54]	G-CSF (300 µg/day) significantly reduced the mean duration for hematological recovery from 8.8 to 6.6 days (p <0.04). G-CSF reduced the global cost.
Cohort study, retrospective analysis (n=20); Patients with antithyroid drug-induced agranulocytosis and poor prognostic factors [66]	G-CSF (300 µg/day) significantly reduced the mean durations of hematological recovery, antibiotic therapy and hospitalization from: 11.6 to 6.8 days, 12 to 7.5 days and 13 to 7.3 days, respectively (p <0.05 in all cases). G-CSF reduced the global cost.
Cohort study, retrospective analysis (n=145); All patients with idiosyncratic drug-induced agranulocytosis [61]	G-CSF shortens time to recovery in patients with agranulocytosis.
Cohort study, retrospective analysis (n=201); All patients with idiosyncratic drug-induced agranulocytosis [5]	G-CSF (300 µg/day) reduced the mean durations of hematological recovery for 2.1 days (p =0.057).
Prospective randomized study (n=24); All patients with antithyroid drug-induced agranulocytosis [63]	G-CSF (100 to 200 µg/day) did not significantly reduce the mean duration for hematological recovery.

G-CSF: Granulocyte-colony stimulating factor. GM-CSF: Granulocyte Macrophage-colony stimulating factor.

To date, there are only three published clinical studies specifically dedicated to ATD-induced neutropenia and agranulocytosis [15,63,64]. The study by Fukata et al. is the only one that meets the Evidence Based Medicine criteria for the study of HGF in agranulocytosis [62]. This 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 (Table 5) [63]. 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 [60]. In this setting, Andrès et al. have reported a study involving 20 patients with agranulocytosis related to ATD [66]. Statistically significant differences in favor of the use of HGF have 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 HGF (34 cases treated with G-CSF) [15]. 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.

Others measures

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 [1-3]. Corticosteroids are known for their immunosuppressive effect and interference with neutrophil function [67]. These molecules are also known 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 ATD. However, no benefit was shown from their use [67].

Prevention

Routine monitoring of blood NC in the general population is not indicated for all drugs [1, 2, 54]. 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 ATD [2,68,69]. 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 [64]. Despite this, to date, this recommendation continues to be debated because of the absence of impact on mortality and morbidity [3]. This may explain current attitudes towards routine monitoring of blood counts even in individuals receiving high risk medications such as antithyroid drugs or ticlopidine [1-3]. 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 ATD. 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 Grade 3-4 neutropenia. 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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