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THE ETIOLOGY, EEPIDEMIOLOGY AND MANAGEMENT OF IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS

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REVIEW

ABSTRACT. OBJECTIVE: To review the literature concerning idiosyncratic drug-induced agranulocytosis, a rare but life-threatening potential adverse event of most drugs. DATA SOURCES: Articles were identified through searches of MEDLINE (January 1966 to March 2005). Unpublished data from our cohort of drug-induced agranulocytosis in the University Hospital of Strasbourg, France were also considered. DATA EXTRACTION AND SYNTHESIS: All of the papers and abstracts were reviewed by at least two senior researchers that selected the data used in the study. The incidence of idiosyncratic drug-induced agranulocytosis remains stable in the past twenty years: 2.4 to 15.4 cases per million, despite the emergence of new causative drugs, mainly antibiotics, antiplatelet agents and antithyroid drugs. To date, drug-induced agranulocytosis remains a serious adverse event due to the frequency of severe sepsis with severe deep infections (such as pneumonia), septicemia and septic shock in around 2/3 of patients. In this setting, old age (>65 years), septicemia or shock, metabolic disorders such as renal failure, and a neutrophil count below $0.1 \times 10^9/L$ are poor prognostic factors. Nevertheless, with the aid of appropriate management using pre-established procedures, intravenous broad-spectrum antibiotic therapy and hematopoietic growth factors, the mortality rate is currently ~5%. CONCLUSIONS: Given the increased life expectancy and subsequent longer exposure to drugs, as well as the development of new agents, health care professionals should be aware of the adverse event associated with idiosyncratic drug-induced agranulocytosis as well as its management.

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1. INTRODUCTION

Schultz first proposed the term 'agranulocytosis' for cases of severe pharyngeal infectious symptoms, concomitantly with the lack of granulocytes in blood count [1]. Yet, agranulocytosis is marked by a profound decrease or an absolute lack of the number of granulocytes in circulating blood classically resulting in a neutrophil count of $<0.5 \times 10^9/L$ [2,3]. The criteria to assess causality are reported in TABLE 1 [4,5]. In the majority of patients, the neutrophil count is $<0.1 \times 10^9/L$. Patients with such severe neutropenia are likely to experience life-threatening and sometimes fatal infections. Most, but not all, instances of agranulocytosis result from exposure to drugs (idiosyncratic drug-induced agranulocytosis), and either the drug itself or a metabolite may be causative. Other common causes of agranulocytosis in adult patients are listed in TABLE 2 [2,6]. In the present paper, we report and discuss the current literature and our own experience of idiosyncratic drug-induced agranulocytosis.

2. SEARCH STRATEGY

A bibliographic search was performed on the PubMed database of the US National Library of Medicine for articles published from January 1966 to March 2005, using the following key words or associations: "agranulocytosis", "drug-induced agranulocytosis", and "idiosyncratic agranulocytosis." Restricted: English- or French-language publications from January 1, 1966 to March 1, 2005; human subjects; clinical trials; review or guidelines. All of the English and French abstracts were reviewed by at least two senior researchers in our working group. Two senior researchers (the authors of this paper) selected the papers used in the study. American Society of Hematology (ASH) educational books, textbooks of Hematology and Internal medicine, and information gleaned from international meetings, including those of the European Society of Hematology (ESH), the European Federation of Internal Medicine (EFIM) and the French Society of Internal Medicine (SNFMI) were also used. Additional not published data of our cohort of

drug-induced agranulocytosis in the University Hospital of Strasbourg, France were incorporated in this review.

3. PATHOPHYSIOLOGY

Clinical observations, studies in volunteers and patients, and laboratory experiments have suggested that idiosyncratic drug-induced agranulocytosis is mediated by immununo-allergic and toxic mechanisms [2,7]. However, the mechanisms that cause neutropenia are not completely understood. In many cases, neutropenia occurs after prolonged exposure, resulting in decreased granulocyte production by hypoplastic bone marrow. In other cases, repeated but intermittent exposure is needed. This suggests an immune mechanism, although this idea has not been completely established [8]. Direct damage to the bone marrow microenvironment or myeloid precursors plays a role in most other cases [9]. In immune-mediated drug-induced agranulocytosis (principally in case of antithyroid drugs and β -lactams), antineutrophil antibodies have been detected in all tested patients ($N = 13$) using ELISA for antibodies to autologous or normal granulocytes [10]. These antibodies binding to a target cell usually require the presence of the causative drug and the complement is often consumed [2,8]. The failure to reproduce such a mechanism experimentally may be due either to antibody specificity for a drug's intermediate metabolite or a low antibody titer [8]. In some cases, antibody binding to a myeloid progenitor cell has been inferred from the inhibition of colony-forming units-granulocyte macrophage (CFU-GM)-derived colony formation by the patient's serum [11]. Drugs can also damage myeloid precursors directly [2]. The complex metabolic pathways that detoxify drugs and chemicals are genetically regulated and genetic polymorphism is the probable basis for different levels of expression of genes encoding enzymes that generate or destroy toxic intermediate compounds [12,13]. Other mechanisms, involving cytotoxic T-cells, haptens, auto-immunity and oxidative modifications of drug have been invoked [2,7,14,15]. The impact of myeloperoxidase and NADPH-oxidase polymorphisms

TABLE 1. CRITERIA OF IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS [4,5].

<p>DEFINITION OF IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS:</p> <ul style="list-style-type: none"> ▪ Neutrophil count $<0.5 \times 10^9/L \pm$ existence of a fever and/or any sign of infection (4)
<p>CRITERIA OF DRUG IMPUTABILITY:</p> <ul style="list-style-type: none"> ▪ Onset of agranulocytosis during treatment or within 7 days in case of previous intake of the same drug and complete recovery with more than $1.5 \times 10^9/L$ neutrophils in blood cell count, one month after drug-interruption [5]. ▪ Recurrence of agranulocytosis in case of the same drug administration (this latter criterion is usually not available because of the mortality rate). ▪ Criteria of exclusion: any history of congenital neutropenia or immune neutropenia, recent infectious disease (particularly recent viral infection), recent chemotherapy and/or radiotherapy and/or immunotherapy and existence of an underlying hematological disease (for detail, see TABLE 2).

TABLE 2. DIFFERENTIAL DIAGNOSIS OF IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS IN ADULTS [2,3,6].

<ul style="list-style-type: none"> • Normal variations: ethnic and familial neutropenia. • Splenic sequestration: cirrhosis and portal hypertension (alcoholism, etc), Gaucher’s disease. • Nutritional deficiencies: cobalamin and folate deficiencies, copper deficiency, cachexia (Kwashiorkor). • Infectious: bacterial (typhoid fever, brucellosis, tuberculosis, rickettsia, severe sepsis, etc), viral (Eptein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis virus, rubella, parvovirus B19, etc), protozoal and fungal (histoplasmosis, leishmaniasis, malaria, etc) • Immune neutropenia: isolated autoimmune neutropenia, collagen vascular autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis or Felty’s syndrome), T γ-δ lymphocytosis • Hematological diseases: such as myelodysplasia, pure white blood cell aplasia, and red cell aplasia, Marchiafava-Michelli disease. • Primary congenital or chronic neutropenia (e.g., familial and nonfamilial cyclic neutropenia).
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in drug-induced agranulocytosis was recently studied [16].

4. EPIDEMIOLOGICAL DATA

In Europe, the annual incidence of idiosyncratic drug-induced agranulocytosis is between 3.4 and 5.3 cases per million population [7,17]. In the USA, Strom et al. reported rates ranging from 2.4 to 15.4 per million per year [18]. In our experience (observational study), from 1996 to 2003, the annual incidence of symptomatic idiosyncratic drug-induced agranulocytosis remained stable, with approximately 6 cases per million population (FIG. 1A) [19]. It is to note that this incidence remains stable despite intensive development of pharmacovigilance. This incidence increases with age, as only 10% of cases are reported in children and young adults, and more than half of these episodes occur

in people over 60 years of age [20]. Similarly, in a cohort study (N = 91) followed in our hospital, 67% of patients were aged ≥ 65 years (FIG. 1) [19]. However, this is probably to be a biased data resulting from the number of drugs taken by the elderly since they are exposed to many more drugs than younger people are. The higher incidence of drug-induced agranulocytosis in elderly patients was also reported in the prospective International Agranulocytosis and Aplastic Anemia Study (IAAAS) [21,22]. Idiosyncratic drug-induced agranulocytosis is approximately twice as frequent among women as men, but this is likely to be a biased data resulting from women’s longer life expectancy [19].

5. DRUGS INVOLVED AND RISK FACTORS

The current drugs, most commonly, associated with idiosyncratic agranulocytosis are shown in

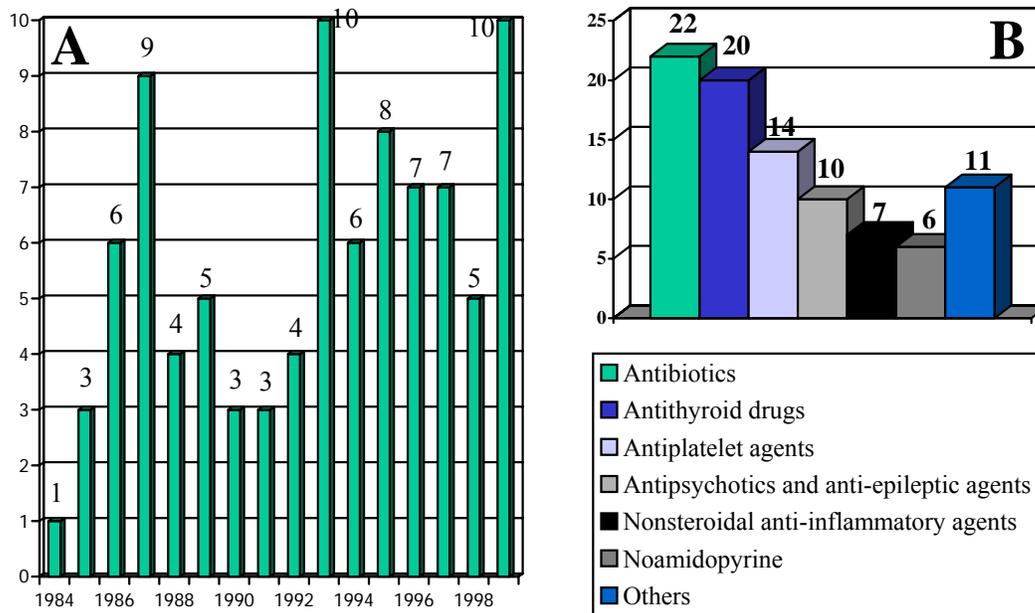


FIGURE 1. EPIDEMIOLOGICAL DATA FROM THE COHORT STUDY OF IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS IN THE UNIVERSITY HOSPITAL OF STRASBOURG, FRANCE (N = 91) [19]. A: Number of patients per year. B: Type of drugs involved.

TABLE 3 [2,3,7,19,23-25]. For the majority of these compounds, the risk appears to be very small. However, for drugs such as antithyroid drugs, ticlopidine, clozapine, sulfasalazine, gold salts, penicillamine and phenylbutazone, the risk may be higher [2,3,26,27]. For example, for antithyroid drugs, a risk of 3 per 10,000 users has been reported [28]. Nevertheless, inconsistent findings in terms of risk for a specific drug are usually found among different studies. Thus in our opinion, case-control studies are probably the best way to quantify an observed individual risk from a drug, but few such studies have been conducted [2]. In the previously mentioned cohort, the most frequent causative types of drugs were antibiotics (25%), particularly β -lactam and cotrimoxazole, antithyroid drugs such as neomercazole (23%), antiplatelet agents such as ticlopidine (16%), neuroleptic and antiepileptic agents (11%) and nonsteroidal anti-inflammatory agents (8%) (FIG. 1B) [19]. These findings are in accordance with recent reports of Shapiro et al. [22] and van der Klauw et al. [26,27]. In our cohort study, two thirds of patients received

more than two drugs with a mean of three drugs, accounting for the difficulty in relating the agranulocytosis to its causative agent. In this cohort, no case of self-medication was reported [19].

For a few drugs, specific risk factors, such as histocompatibility antigens (human leukocyte antigen [HLA]), have been identified [29,30]. For example, an association has been reported between HLA-B27 and HLA-B38 and clozapine [31,32]. Noteworthy, the occurrence of HLA-B35 might prevent patients from clozapine-induced agranulocytosis in the certain ethnic group [30]. Other risk factors include underlying autoimmune diseases such as rheumatoid arthritis for patients receiving captopril, with renal failure or concomitant treatment with probenecid [2,32].

6. CLINICAL MANIFESTATIONS

Historical case reports of idiosyncratic drug-induced agranulocytosis described edema, necrosis and obstruction of the pharynx, followed within

TABLE 3. DRUGS INCRIMINATED IN THE OCCURRENCE OF AGRANULOCYTOSIS [REF. 2,3,7,19,23,24].

ANALGESICS AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS: Aspirin (Acid Acetylsalicylic), Aminophenazone, Benoxaprofen, Diclofenac, Diflunisal, Dipyron, Fenopropfen, Indomethacin, Ibuprofen, Phenylbutazone, Piroxicam, Sulindac, Tenoxicam, Tolmetin.
ANTIPSYCHOTICS, HYPNOSEDATIVES AND ANTIDEPRESSANTS: Amoxapine, Chlordiazepoxide, Clozapine, Diazepam, Haloperidol, Imipramine, Indalpin, Meprobamate, Mianserin, Phenothiazines, Risperidone, Tiapride.
ANTI-EPILEPTIC DRUGS: Carbamazepine, Ethosuximide, Phenytoin, Trimethadione, Valproic Acid (Valproate Sodium).
ANTITHYROID DRUGS: Carbimazole, Metamizole (Thiamazole), Potassium Perchlorate, Potassium Thiocyanate, S ³⁵ Thiouracil.
CARDIOVASCULAR DRUGS: Acid Acetylsalicylic, Aprindine, Captopril, Flurbiprofen, Furosemide, Hydralazine, Lisinopril, Methyldopa, Nifedipine, Phenindione, Procainamide, Propafenone, Propanolol, Quinidine, Spironolactone, Thiazide Diuretics, Ticlopidine.
ANTI-INFECTIVE AGENTS: Acyclovir, Cephalosporins, Chloramphenicol, Chloroquine, Ciprofloxacin, Clindamycin, Cotrimoxazole, Dapsone, Ethambutol, Flucytosine, Gentamicin, Hydroxychloroquine, Isoniazid, Levamisole, Lincomycin, Mebendazole, Mepacrine, Metronidazole, Nitrofurantoin, Novobiocin, Penicillins, Pyrimethamine, Quinine, Rifampicin, Sulfamethoxazole, Streptomycin, Terbinafine, Tetracycline, Thioacetazone, Tinidazole, Vancomycin, Zidovudine.
MISCELLANEOUS DRUGS: Acetazolamide, Allopurinol, Aminoglutethimide, Arsenic Compounds, Benzafibrate, Brompheniramine, Chloropheniramine, Cimetidine, Colchicine, Deferiprone, Famotidine, Flutamide, Gold, Metapyrilène, Methazolamide, Metoclopramide, Levodopa, Olanzapine, Oral Hypoglycemic Agents (Glibenclamide), Mercurial Diuretics, Penicillamine, Ranitidine, Most Sulfonamides, Tamoxifen, Thenalidine, Tretinoid, Tripeleminamine.

days by prostration, coma, and death [1,6]. Presently, patients usually present high fever, sore throat, several deep infections and a general sensation of malaise, often including chills, myalgia and/or arthralgia [2,7,19,23]. Most patients (>60%) develop septicemia while some have evidence of severe pneumonia as well as anorectal, skin or oropharyngeal infection and septic shock [2,6,23,24, 32,33]. As in cancer chemotherapy patients, the occurrence of infection depends on the degree and duration of neutropenia [6]. It is to note that when antibiotics are preemptively administered, both the patient's complaints and the physical findings may be attenuated and fever may be the only symptom [7,34]. The clinical manifestations in our previously mentioned cohort study are presented in FIG. 2 [19]. In this cohort of life-threatening idiosyncratic drug-induced agranulocytosis, clinical features include septicemia and septic shock in approximately 35% of patients and severe documented infection in 25% of patients [19]. A causative pathogen, typically Gram-negative bacilli or Gram-positive cocci (mainly Staphylococcus spp.), has been isolated in 30% of cases [2]. Fungi are also commonly involved as secondary infective agents (<10%) [2,6]. It is noteworthy, that in elderly patients, clinical manifestations were generally

more severe, with septicemia or septic shock in at least two-thirds of them [20,35]. However, some patients (<20%) remained at least transiently asymptomatic, supporting the routine close monitoring of blood count in individuals receiving high risk medication such as antithyroid drugs or ticlopidine [36,37].

7. HEMATOLOGICAL DATA

Besides a granulocyte blood count under $0.5 \times 10^9/L$, the hemoglobin (Hb) and platelet (Pla) counts are usually normal [6]. However, in elderly patients, associated hematological abnormalities are frequent: anemia (Hb <120 g/L) in at least 30% of patients and thrombocytopenia (Pla < $150 \times 10^9/L$) in 10% of patients [19,20]. Thus, especially in elderly, bone marrow examination is routinely required to exclude an underlying pathology [20]. The bone marrow typically shows a normal or mildly reduced total cellularity contrasting with the absence of myeloid precursor cells [2,20,38]. In some cases, lack of any mature myeloid cells is observed, whereas immature forms from the myelocyte stage remain preserved. This aspect is described as the "myeloid blocking", which may be a consequence of either a drug/antibody effect spe-

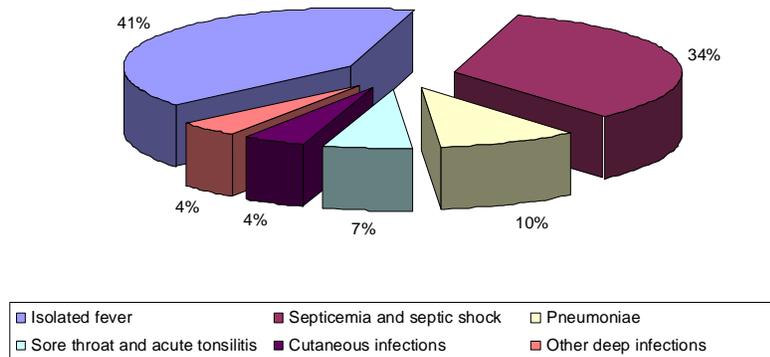


FIGURE 2. CLINICAL MANIFESTATIONS IN THE 91 PATIENTS WITH IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS INCLUDED IN THE COHORT FROM THE UNIVERSITY HOSPITAL OF STRASBOURG, FRANCE [19].

cifically on mature cells or may represent an initial stage of recovery [6]. Important clinical data can be inferred from the bone marrow findings, as, in the case of a lack of myeloid precursors, blood count recovery is unlikely before 14 days [2,32,38]. The picture of myeloid blocking is generally associated with a recovery within 2 to 7 days [38]. In the aforementioned cohort of idiosyncratic drug-induced agranulocytosis, these bone marrow examination profiles are not associated with delay to recovery (by using uni- and multivariate analysis) [39].

8. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of idiosyncratic drug-induced agranulocytosis in adults includes a limited number of conditions (TABLE 2) [2,3,6]. The most relevant differential diagnoses include: (i) nutritional deficiencies (cobalamin and folate deficiencies); (ii) neutropenia secondary to severe sepsis (especially viral); (iii) neutropenia appearing as the first manifestation of a bone marrow failure such as myelodysplastic syndromes; or (iv) neutropenia associated with hypersplenism [2,3,6]. Other differential diagnoses rarely include neutropenia secondary to the peripheral destruction of polymorphonuclear cells, such as Felty's syndrome or systemic lupus erythematosus (which is also often drug induced) [40].

9. PROGNOSIS AND MORTALITY RATE

Until the last twenty years, the mortality rate for idiosyncratic drug-induced agranulocytosis was 10–16% in European studies [2,7,32,33], but this rate has recently dropped to 5–10%, probably due to the improvements in recognition, management and treatment of this condition [2,41,42]. The highest mortality rate is observed in older patients (>65 years), as well as in those experiencing renal failure (defined as serum creatin level >120 $\mu\text{mol/L}$), bacteriemia or shock at diagnosis [2,20,32,35]. We have recently confirmed these data in an uni and multivariate analysis of factors affecting outcome in our cohort study (N = 91) [39]. Particularly, we have established that a neutrophil count $<0.1 \times 10^9/\text{L}$ at diagnosis, septicemia and/or shock were variables significantly associated with a longer time to neutrophil recovery. In contrast, the use of hematopoietic growth factors is associated with a shorter time to neutrophil recovery (see the next section).

10. MANAGEMENT WITH FOCUS ON THE USEFULNESS OF HEMATOPOIETIC GROWTH FACTORS

The management of idiosyncratic drug-induced agranulocytosis begins with the immediate withdrawal of any potentially causative drug [2,7]. The patient's medication history must be carefully and

TABLE 4. RECENT STUDIES ON HEMATOPOIETIC GROWTH FACTORS USE IN IDIOSYNCRATIC DRUG-INDUCED AGRANULOCYTOSIS.

TYPE OF STUDY AND TARGET POPULATION	MAIN RESULTS
Meta-analysis (N = 118); all patients with idiosyncratic drug-induced agranulocytosis [44].	G-CSF or GM-CSF (100 to 600 µg/day) reduced the mean time to neutrophil recovery (neutrophil count >0.5 × 10 ⁹ /L) from 10 to 7.7 days, in case of neutrophil count <0.1 × 10 ⁹ /L, and reduce the mortality rate from 16 to 4.2%.
Case control study, retrospective analysis (N = 70); all patients with idiosyncratic drug-induced agranulocytosis [43].	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 [42].	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 [41].	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.
Prospective randomized study (N = 24); all patients with antithyroid drug-induced agranulocytosis [47].	G-CSF (100 to 200 µg/day) did not significantly reduce the mean duration for hematological recovery.

chronologically obtained in order to focus on the suspected agent(s). In our opinion, for drugs with a known but rare association with agranulocytosis, the rarity and unpredictability of the reaction does not make routine monitoring worthwhile [2]. However, routine monitoring for agranulocytosis is required in some high-risk drugs, such as clozapine, ticlopidine and antithyroid drugs [2,7,36,37]. Measures to be undertaken concomitantly include the aggressive treatment of any diagnosed or potential sepsis, as well as the prevention of secondary infections [2,7,20]. Preventive measures require good hygiene maintenance with special attention to high-risk areas such as the mouth, skin and perineum [2,7]. Patient isolation and empirical prophylactic antibiotherapy (e.g., digestive decontamination) have been proposed, but their usefulness in limiting the infectious risk is far from validated [2]. The occurrence of sepsis in this life-threatening disorder requires prompt management, including intravenous broad-spectrum antibiotic therapy after blood, urine and any other relevant samples have been cultured [2,7,20,41,42]. Empiric broad-spectrum antibacterial therapy is generally the best choice, but may be adapted, depending on the nature of the sepsis, the clinical status of the patient and local patterns of antibiotic resistance [2,7,20].

When an antibiotic is suspected of having induced the agranulocytosis, one should keep in mind potential antibody cross-reactivity, and choose the antibiotics to be administered carefully. In our hospital, we commonly combine new cephalosporins or quinolones and aminoglycosides [19,41,42]. Therapeutic measures such as transfusions of granulocyte concentrates should only be used in exceptional circumstances, and only for the control of life-threatening antibacterial-resistant infections such as perineal gangrene [2,20].

In life-threatening idiosyncratic drug-induced agranulocytosis, the usefulness of hematopoietic growth factors: Granulocyte- and Granulocyte-Macrophage-Colony Stimulating factor (G-CSF and GM-CSF) has been previously reported [41-46]. The main recent studies on hematopoietic growth factor use in drug-induced agranulocytosis are reported in TABLE 4 [41-44,47]. In our experience, G-CSF and GM-CSF (at a mean dosage of 300 µg/day) were found useful in shortening the duration to blood count recovery without major toxicity or adverse effects [41,42]. In a multivariate analysis of all our patients with idiosyncratic drug-induced agranulocytosis patients (N = 91), we have demonstrated that G-CSF was an independent variable positively affecting the duration of hemato-

logical recovery [39]. However, it is to note that the only prospective randomized study available did not confirm the benefit of G-CSF [47]. A total of 24 patients with antithyroid-related drug-induced agranulocytosis were enrolled, and one may think that both the small size of the study and an inappropriate G-CSF dosing (100 to 200 µg/day) negatively impacted the results [45]. In the previously mentioned cohort study, we have established the long-term (mean follow-up >52 months) safety of hematopoietic growth factors, with the absence of hematological adverse effects such as myelodysplasia or hematological proliferative disorders [48]. To date, no experience of pegfilgrastim (a long-acting recombinant G-CSF) has been available in idiosyncratic drug-induced agranulocytosis [49].

10. CONCLUSIONS

Last twenty years, the annual incidence of life-threatening idiosyncratic drug-induced agranulocytosis remains stable (about 3 to 16 cases per million) despite the emergence of new causative drugs, especially antibiotics, antiplatelet agents, antithyroid drugs, neuroleptics, anti-epileptic agents and nonsteroidal anti-inflammatory agents. Idiosyncratic drug-induced agranulocytosis is often a serious adverse event due to the frequency of severe infections (such as deep infections, septicemia and septic shock), but modern management with broad-spectrum antibiotics and hematopoietic growth factors, is likely to improve the prognosis. Importantly, all cases of idiosyncratic drug-induced agranulocytosis must be included in a database of adverse effect for pharmacology vigilance. Given the increased life expectancy, increasing use of medications as a therapeutic modality and subsequent longer exposure to drugs, as well as the development of new agents, health care professionals should be aware of this adverse event and its management.

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