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Are Biweekly Granulocyte Counts Effective in Forecasting the Onset of Agranulocytosis in Patients with Graves' Disease Who Are Receiving Antithyroid Drugs?

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SUMMARY

Background

The rare complication of agranulocytosis remains at the back of the physician's mind when prescribing antithyroid drugs (ATDs) for Graves' disease. It appears that the mortality rate of this disorder has improved, in association with better therapy for sepsis and with increased awareness that a "trivial URI" can be an ominous sign in such patients. However, there is a persistent dichotomy of opinion about the value of performing routine granulocyte counts to monitor for the development of agranulocytosis. The American Thyroid Association's management guidelines for hyperthyroidism specifically state that routine monitoring of white-cell counts is not recommended, whereas in contrast, the Japanese package insert for MMI gives a strong warning to check blood counts every 2 weeks for the first 2 months of therapy.

Methods

Japanese Pharmaceutical Affairs Law states that physicians should report to the drug manufacturer any adverse drug reaction, including details on age, sex, dose at onset, time to onset, test results, treatment, and outcome. Over the 30-year period up to April 2011, a total of 754 patients with serious hematologic disorders associated with MMI or PTU use were reported to Chugai Pharmaceutical Co., the only Japanese manufacturer of MMI (1). (Chugai is also one of the two Japanese manufacturers of PTU.) The authors accepted a diagnosis of agranulocytosis if a granulocyte count under 500 per microliter had been documented in the report, whereas diagnoses of pancytopenia or aplastic anemia were accepted based on the reporting physician's diagnosis. Insurance reports submitted to the Japan Medical Data Center were used along with results from the 2010 Japanese census data to estimate the incidence of patients with newly diagnosed Graves' disease who were treated with MMI or PTU within a month of diagnosis; patients given a diagnosis of Graves' disease or a prescription for an ATD in the preceding 12 months were excluded, as were patients older than 64 because very few were insurance subscribers. Data obtained from Kuma Hospital between 2005 and 2012 were used to estimate the current sex and age distribution of new/untreated Graves' disease.

Results

Between 1981 and 2011, the Chugai Company received reports on major hematologic disorders in 754 patients: 670 had agranulocytosis and 84 had pancytopenia or aplastic anemia. MMI had been prescribed for 725 patients, and PTU for 28. Over the first two decades studied, the number of reports submitted each year tended to increase, while over the decade from 2001 to 2010, about 40 cases per year were reported. The authors estimated that about 33,500 patients 10 to 64 years of age were taking ATDs between April 2010 and March 2011, indicating that the annual incidence of major blood disorders was about 0.12% (40 of 33,500). The patients with

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these disorders were about 3 years older than the average patient with newly diagnosed Graves' disease seen at Kuma Hospital. The exact interval between the day ATD treatment started and the day the disorders appeared was available in 461 reports. In about 70%, the disorders had appeared within 60 days, and in about 85% the disorders had appeared within 90 days of the start of treatment. A granulocyte count above 1000 per microliter had been documented within 90 days of the onset of disorders in 221 patients. In about 20% of these cases, a granulocyte count above 1000 per microliter had been documented within a week of the onset of the disorder, and in 50% of cases it had been "normal" within 2 weeks of the onset of the disorder. In 20 case reports, multiple granulocyte counts had been documented over the 30 days before the onset of the disorder. When viewed in retrospect, over the 15 days before the disorder occurred, there seemed to be some decline in the granulocyte counts. In about half these cases, at least one count had been below 1500 per microliter.

Over the 30 years studied, 30 patient deaths were associated with ATD administration (30 of 754, or about 4%). On average, they were about 9 years older than patients with newly diagnosed Graves' disease seen at Kuma Hospital. All the patients who died had been taking MMI, although in one patient who had been switched to PTU because of urticaria, pancytopenia developed 26 days later. Apparently no white-cell/granulocyte data were available on any of the 30 cases of fatality within 90 days before agranulocytosis appeared. In 24 reports with sufficient data to establish a diagnosis, agranulocytosis was present in 17 cases and pancytopenia in 7. Nine patients were admitted on the day of or the day after symptoms began, while it took 3 days for 6 patients, 4 days for 1 patient, and 5 days for 2 patients to receive the diagnosis. Four patients did not visit a medical institution. Despite intensive care, 5 patients died within 3 days and 10 died within a week. The delay in diagnosis commonly reflected insufficient patient concern for symptoms, but in 5 cases, physicians had not obtained a granulocyte count, presumably because they did not know that the patient was taking an ATD.

Conclusions

The major blood disorders associated with ATDs generally have an abrupt onset and commonly occur within 3 months of initiating treatment; however, in about 15% of cases, the disorder appears after a longer period. It is critically important that each patient given an ATD also be given sufficient information about clinical signs that might suggest agranulocytosis. The urgency of discontinuing the drug and of obtaining a granulocyte count must be emphasized.

ANALYSIS AND COMMENTARY

Even when a granulocyte count was performed biweekly, it often provided no warning. Furthermore, fewer than 30% of the reports indicated that more than one granulocyte count had been performed within the 90 days before the disorder appeared, which suggests that biweekly counts often were not being performed (one cannot tell how many cases reflected patient noncompliance vs. physician noncompliance). This study excluded patients over 64 years of age, but even so, the patients who died were substantially older than the average age of the total group of afflicted patients. The data could be somewhat deficient if a physician forgot to report a case or missed the diagnosis in a case of sudden death. If, as it appears, no granulocyte counts had been performed within a week or two of the disorder in the 30 cases of fatality, it might be argued that had such a granulocyte count been done, it might have allowed the disorder to be discovered earlier, and thus some of the patients might have had a better outcome. Data that seem to bear on this issue were recently reported from Ito Hospital, where all patients with Graves' disease treated with ATDs do get routine biweekly complete blood counts (2). Nonetheless, of 39,149 patients given ATDs between 1983 and 2002, a major

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hematologic disorder developed in 55 (a frequency of 0.11%), and there was one fatality, in a 38-year-old woman (1 of 55, or about 2%). Assuming the Ito study patients were reported to Chugai Co., most cases would have been included in the current study, but despite the duplicated reports, the data indicate that the frequency of major blood disorders over the past 30 years apparently was under 0.15%. Similar comments apply to a study of children under the age of 15 years (1). The frequency of these disorders thus appears to be substantially less than the 0.3% to 0.6% previously reported for Japan (2,3).

It is not clear at what point a decline in the granulocyte count is sufficiently worrisome to discontinue ATD treatment. Of the 20 patients who had multiple granulocyte counts performed in the 30 days before agranulocytosis occurred, there were 9 in whom the count had dropped below 1500 per microliter. In patients with cancer, the risk for infection begins to increase at this level, although the effects of chemotherapeutic drugs on bronchoalveolar and gastrointestinal integrity may not permit these findings to be directly applied to ATD-related marrow disorders.

There is another side to the question: How many (if any) patients were saved from agranulocytosis because a decline in a biweekly granulocyte count prompted a physician to discontinue ATD therapy? Unfortunately, authors' databases could not provide information on this facet of the subject.

Clearly there are good reasons for obtaining a complete blood count—including a white-cell differential count—prior to beginning ATD therapy. For example, some patients normally have a lower granulocyte count, some patients with untreated Graves' disease have mild leukopenia (4), and patients with Graves' disease can have deficiencies in iron, folate or vitamin B12, and can have other autoimmune disorders, such as pernicious anemia.

The most important message is that physicians must carefully explain (and document) all the side effects of the antithyroid drugs, both to the patient as well as to a friend or relative of the patient, if possible. In addition, printed information detailing the side effects should be provided. Special emphasis should be given to possible symptoms of infection. The patient must understand that upon any suggestion of onset of a sore throat, URI, fever or other sign of infection, she must stop taking the ATD immediately and obtain a CBC, explaining to emergency medical personnel her previous use of an ATD.

References

1. Minamitani K, Oikawa J, Wataki K, et al. A report of three girls with antithyroid drug-induced agranulocytosis; retrospective analysis of 18 cases aged 15 years or younger reported between 1995 and 2009. Clin Pediatr Endocrinol 2011;20:39-46.
2. Watanabe N, Narimatsu H, Noh JY, 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;97:E49-E53.
3. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. Thyroid 2004;14:459-62.
4. Irvine WJ, Wu FC, Urbaniak SJ, Toolis F. Peripheral blood leucocytes in thyrotoxicosis (Graves' disease) as studied by conventional light microscopy. Clin Exp Immunol 1997;27:216-21.