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CLINICAL THYROIDOLOGY

The onset of MPO-ANCA–associated vasculitis with antithyroid drugs is both rare and unpredictable, but is more common with PTU

Noh JY, Yasuda S, Sato S, Matsumoto M, Kunii Y, Noguchi Y, Mukasa K, Ito K, Ito K, Sugiyama O, Kobayashi H, Nihojima S, Okazaki M, Yokoyama S. Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. J Clin Endocrinol Metab 2009;94:2806-11.

SUMMARY

BACKGROUND The presence of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) in a patient in whom respiratory failure developed while taking propylthiouracil (PTU) was first described in 1992. Since then, only a few reports of MPO-ANCA-associated vasculitis with PTU and methimazole (MMI) have been published, thus providing sparse clinical descriptions of this disorder. The aim of this study was to determine the incidence of MPO-ANCA-associated vasculitis in a large number of patients taking PTU or MMI and to analyze the clinical characteristics of this condition, including its symptoms, and the association of antithyroid drugs and their doses to clinically apparent MPO-ANCA-associated vasculitis.

METHODS The study subjects were 92 patients with Graves' disease who had MPO-ANCA-associated vasculitis as an adverse reaction to antithyroid drugs and thus were reported, as required by law in Japan, to Chugai Pharmaceutical, which makes PTU and MMI.

RESULTS Of the 92 patients, 23 (25%) were taking MMI from 1979 through December 2007, 68 were taking PTU (75%) from 1982 through December 2007, and 1 more patient was taking antithyroid drugs, but it was not clear which of the two had been taken. The median age at the onset of the adverse reaction was 46 years (range, 10 to 81), and the ratio of men to women was 20:72. The following data were collected: the type of MPO-ANCA-associated vasculitis, dose of antithyroid drug at the time of vasculitis onset, severity and outcome, duration of treatment from the time of onset, and MPO-ANCA

titer. Here and elsewhere, all percentages >1% are rounded to an integer.

The type and frequency of MPO-ANCA-associated vasculitis and its symptoms and organ involvement are shown in Figures 1 and 2. MPO-ANCA-associated vasculitis caused single-organ failure in 41 patients (45%), two-organ failure in 32 patients (35%), three-organ failure in 13 patients (14%), four-organ failure in 2 patients (2%), and was unknown in 4 patients (4%) (Figure 3). The most common combination of two-organ failure was kidneys and respiratory organs, and the most common threeorgan failure was kidneys, joints, and skin. Symptoms were severe in 79 patients (86%), moderate in 2 (2%), and mild in 2 (2%); the severity was unknown in 9 patients (10%). (Figure 4). MPO-ANCA-associated vasculitis resolved in 62 patients (67%), caused death in 2 (2%), and caused persistent sequelae in 21 (23%); the outcome was unknown in 7 patients (8%) (Figure 4). Of the two patients who died, one each had been treated with MMI and PTU, and had MPO-ANCA titers of 317 ELISA units (EU) and 489 EU, respectively, and both had kidney and respiratory organ failure. The median MPO-ANCA titer, which was known for 76 of the 92 patients (83%), was 230.5 EU (range, 33 to 5170); and for the remaining 16 patients was recorded only as positive. The MPO-ANCA titer was less than 100 EU in 22 patients (29%), which was considered weakly positive. At the onset of MPO-ANCA-associated vasculitis, the median dose of MMI was 15 mg/day (range, 2.5 to 45), and for PTU 200 mg/day (range, 50 to 450). The median time from starting an antithyroid drug to the onset of MPO-ANCA-associated vasculitis, for all 83 patients for whom these data were available, was 42 months



Figures 1 and 2. These figures show the type and frequency of symptoms and the organs involved with MPO-ANCA-associated vasculitis. GI = gastrointestinal.

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(range 1 to 372); it was 60 months (range, 1 to 372) for MMI and 39 months (range, 1 to 132) for PTU, a difference that was not statistically significant between the two drugs. The MPO-ANCA titers were not significantly different among patients with different extents of symptom severity or with multiple organ involvement. The MPO-ANCA titer after discontinuing antithyroid drugs, which was recorded in 50 of the 92 patients, decreased in 40 patients; it decreased to within the reference range in 9 patients, and decreased then increased in only 1 patient, who had crescentic nephritis and arthralgia. Intervention and treatment consisted of discontinuing antithyroid drugs in all patients, and treatment with steroids in 70 patients (76%) and of concurrent therapy with immunosuppressants (cyclosporine and cyclophosphamide) in 17 patients (18%); 6 patients (7%) required renal dialysis.

The annual incidence of MPO-ANCA-associated vasculitis was estimated to be between 0.53 and 0.79 patients per 10,000 $\,$



COMMENTARY

Vasculitis associated with PTU has been recognized for some time (1-5). Although it has been well known that PTU is associated with MPO-ANCA-associated vasculitis that could spontaneously resolve after cessation of antithyroid drugs with or without immunosuppressive therapy, the treatment strategy for patients with MPO-ANCA-associated vasculitis has remained inconclusive (6), and large studies and longterm outcomes for patients with this complication have been lacking. A recent study by Gao et al. (7) of 15 patients with PTUinduced MPO-ANCA-associated vasculitis who were treated with immunosuppressive agents for less than 12 months and had follow-up for a mean of 55 months (range, 25 to 98) concluded that the long-term outcomes of patients with PTUinduced MPO-ANCA-associated vasculitis were relatively good. The authors recommended that PTU should be discontinued immediately after the diagnosis of MPO-ANCA-associated vasculitis and that immunosuppressive therapy should be used

in Japan, where the number of patients with Graves' disease is estimated to be between 92,400 and 138,600. Based on the annual shipments of MMI and PTU, the authors believe that the incidence of MPO-ANCA-associated vasculitis for PTU would be 39-fold that of MMI. In the present study, the onset of MPO-ANCA-associated vasculitis occurred within 2 months in 6 patients (7%) and within 1 year in 7 patients (8%) of the 83 patients for whom the time of onset was available, which means that it is impossible to predict when MPO-ANCA-associated vasculitis will occur. Moreover, the dependence of antithyroiddrug dose on MPO-ANCA-associated vasculitis is uncertain.

CONCLUSION The timing of antithyroid drug–induced MPO-ANCA–associated vasculitis is both rare and unpredictable, is increased with PTU, but is not correlated with the dose of antithyroid drugs or the duration of therapy or MPO-ANCA titers, and the symptoms of this complication range from minimal to severe, with multiple organ failure and death in some patients.



only in patients with vital organ involvements, and that longterm maintenance therapy may not be necessary. However, this was a relatively small study that lacked information concerning the relationships of the dose and duration of antithyroid drugs, and whether MPO-ANCA-associated vasculitis occurs exclusively with PTU was not addressed.

The study by Noh et al. is the largest study of this problem in which data on 92 patients with MPO-ANCA–associated vasculitis were available on key issues concerning this disorder. The symptoms of vasculitis stemmed from involvement of the kidneys, lungs, skin, joints, eyes muscle, gastrointestinal tract, and brain. Of the 92 patients in the study, 45% had single-organ failure, 35% had two-organ failure, most commonly kidneys and respiratory organs, and 14%, had four-organ failure. The most common three-organ failure was the kidneys, joints, and skin. Symptoms were severe in most of the patients (86%), and moderate to mild in the others. MPO-ANCA–associated vasculitis

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resolved in 62 patients (67%), caused death in 2 patients (2%), and produced persistent sequelae in 21 patients (23%) in whom the data were known.

The onset of vasculitis occurred within 2 months in 7% of the patients and within 1 year in 8% of the patients in whom a record of the time of onset was available, indicating that it is impossible to predict when vasculitis might occur. Moreover, the type and dose of the antithyroid drug did not correlate with the onset of MPO-ANCA–associated vasculitis. A total of 61 patients had been treated with PTU, and 20 with MMI. The appearance of MPO-ANCA and the onset of MPO-ANCA–associated vasculitis did not always occur together, nor did it correlate with the dose of PTU or MMI. Vasculitis did not necessarily occur in patients

who were positive for MPO-ANCA nor did the titer of MPO-ANCA correlate with the severity of vasculitis. Although PTU was calculated to be 39-fold that of MMI among patients with MPO-ANCA–associated vasculitis, the ratio of annual shipments of MMI to those of PTU was about 4 to 1 that might account for the higher ratio of PTU in patients with vasculitis. The authors of this study concluded that there is a need for vigilance in patients being treated with PTU or MMI because the severity and number of organs involved were not correlated with MPO-ANCA titer, and the time of onset of MPO-ANCA–associated vasculitis is so variable, and vasculitis can occur when MPO-ANCA titer is only weakly positive.

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