Rheumatology, 2023, **00**, 1–8
https://doi.org/10.1093/rheumatology/kead319
Advance access publication 24 June 2023
Original Article

Clinical science

Characteristics and outcome of ANCA-associated vasculitides induced by anti-thyroid drugs: a multicentre retrospective case-control study

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Received: 4 March 2023. **Accepted:** 11 June 2023

Abstract

Objective: Data on ANCA-associated vasculitis (AAV) induced by anti-thyroid drugs (ATD) are scarce. We aimed to describe the characteristics and outcome of these patients in comparison to primary AAV.

Methods: We performed a retrospective multicentre study including patients with ATD-induced AAV. We focused on ATD-induced microscopic polyangiitis (MPA) and compared them with primary MPA by matching each case with four controls by gender and year of diagnosis.

Results: Forty-five patients with ATD-induced AAV of whom 24 MPA were included. ANCA were positive in 44 patients (98%), including myeloperoxidase (MPO)-ANCA in 21 (47%), proteinase 3 (PR3)-ANCA in six (13%), and double positive MPO- and PR3-ANCA in 15 (33%). Main clinical manifestations were skin involvement (64%), arthralgia (51%) and glomerulonephritis (20%). ATD was discontinued in 98% of cases, allowing vasculitis remission in seven (16%). All the remaining patients achieved remission after glucocorticoids, in combination with rituximab in 11 (30%) or cyclophosphamide in four (11%). ATD were reintroduced in seven cases (16%) without any subsequent relapse. Compared with 96 matched primary MPA, ATD-induced MPA were younger at diagnosis (48 *vs* 65 years, $P < 0.001$), had more frequent cutaneous involvement (54 *vs* 25%, $P = 0.007$), but less frequent kidney (38 *vs* 73%, $P = 0.02$), and a lower risk of relapse (adjusted HR 0.07; 95% CI 0.01, 0.65, $P = 0.019$).

Conclusion: ATD-induced AAV were mainly MPA with MPO-ANCA, but double MPO- and PR3-ANCA positivity was frequent. The most common manifestations were skin and musculoskeletal manifestations. ATD-induced MPA were less severe and showed a lower risk of relapse than primary MPA.

Keywords: drug-induced vasculitis, antithyroid drugs

Rheumatology key messages

- ATD-induced ANCA-associated vasculitides (AAV) were mainly microscopic polyangiitis with MPO-ANCA.
- AAV were less severe and showed a lower risk of relapse than primary MPA.
- There were no cases of relapse when anti-thyroid drugs were reintroduced.

Introduction

Antithyroid drugs (ATD) have been used in the treatment of hyperthyroidism for over 70 years [1], with an excellent safety profile [2, 3]. Although patients with Graves' disease may have positive ANCA before any treatment in 0% to 13% of cases [4–10], it is now well established that ATD increases the risk of developing ANCA. One of the most common ANCA-inducing drugs is propylthiouracil (PTU), with a prevalence of ANCA-positivity under treatment that varies from 4% to 41% [4–6, 8–14]. Associations with carbimazole and thiamazole are less frequent but have also been described [7–9, 11–13, 15]. However, very few of these patients with positive ANCA will eventually develop ANCA-associated vasculitides (AAV). AAV are systemic necrotizing vasculitides affecting predominantly small vessels. They include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). ANCA are positive in 90% of GPA, targeting proteinase 3 (PR3) in three-quarters [16], while ANCA target mostly myeloperoxidase (MPO) in MPA [17].

Multiple pathogenetic hypotheses have been proposed to explain the link between ATD and AAV. It has been known since 1988 that interaction between PTU and MPO can lead to the induction of MPO-ANCA [18]. More recent data have suggested that the abnormal conformation of neutrophil extracellular traps (NETs) under PTU therapy could be implicated in the pathogenesis of ATD-induced AAV [19].

Although described since 1992 [20], with over 200 cases reported in the literature [21], ATD-induced AAV remain poorly studied. Because of its rarity, data are mainly retrospective, and mostly old, which is in contrast with the current management of AAV that dramatically improved during recent decades with the increasing use of rituximab. Also, requirement for immunosuppressive agents and the risk of relapse of ATD-induced AAV in comparison with primary AAV is poorly known.

We aimed to describe the clinical characteristics and outcome of patients with ATD-induced AAV in comparison to primary AAV.

Methods

Patients

We performed a retrospective multicentre international study of patients with ATD-induced AAV on behalf of the French Vasculitis Study Group (FVSG), including patients from patients from Europe and the Middle East, mainly France (45%), Turkey (29%) and the United Kingdom (9%).

ATD-induced AAV were defined as the development of AAV during treatment with ATD, the diagnosis of AAV being based on the 2012 revised Chapel Hill Consensus Conference [22].

Patients were classified as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) or unclassified vasculitides (UV) according to 2022 ACR/EULAR classification criteria [23–25]. However, classification of patients with double positivity for MPO-and PR3-ANCA, common in drug-induced vasculitis can be a difficult task [26, 27], as they can fulfil criteria of both GPA and MPA. Thus, we have chosen to revisit the European Medicines Agency (EMA) algorithm to definitively classify all patients [28] (Supplementary Fig. S1, available at *Rheumatology* online). Patients with a history that may mimic AAV (infections, malignancies, other vasculitis or autoimmune diseases), taking drugs known to induce AAV (hydralazine, levamisole, etc) or with insufficient data were excluded [26, 27].

Clinical and laboratory assessment

The characteristics of patients were collected using a standardized form. Physicians who participated in the study provided the following information: demographics, medical

history and treatments, initiation date of ATD and its dose, date of AAV diagnosis, clinical presentation at diagnosis, histological findings (biopsy location and result) and biological data. Biological data included C-reactive protein, serum creatinine, haematuria, proteinuria, ANCA positivity by immunofluorescence (IF) and ELISA, complement, ANA, anti-double stranded DNA and ENA. In addition, the use of immunosuppressive agents, their dosage and duration, the management of hyperthyroidism, duration of follow-up, outcomes (relapses, mortality), until last follow-up were also collected.

Minor and major relapses were defined according to the EULAR recommendations [29]. Disease activity was defined according to the BVAS version 3 [30]. BVAS and 1996 five-factor score (FFS) were calculated for all patients.

Case-control study of ATD-induced MPA

We further focused on MPA patients and compared patients with ATD-induced MPA and those with primary MPA. Each ATD-MPA was matched with four primary MPA on gender and year of diagnosis. Primary MPA were extracted from the French Vasculitis Study Group (FVSG) computerized database, which excluded drug-induced vasculitis [17].

Statistical analysis

Continuous variables were expressed as median (interquartile range [IQR]), while categorical variables were expressed as number (percentages). Baseline characteristics and treatments were compared with *t* tests for continuous variables, and χ^2 tests for categorical variables. Relapse-free survival was compared with Cox proportional hazard ratios models, adjusted on age at MPA diagnosis and on kidney involvement. Differences with a *P*-value <0.05 were considered statistically significant. Analyses were computed with R v4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This study was conducted in compliance with the Good Clinical Practices and principles of the Declaration of Helsinki. The Ethics Committee of Cochin University Hospitals approved this study (CLEP Decision No. AAA-2022–08029). According to French legislation, written consent was not necessary for this retrospective study.

Results

Of 56 eligible cases, 45 cases met the inclusion criteria and were included in the study (Fig. 1). Twenty-four (53%) fulfilled criteria for MPA, 11 (25%) for GPA, one (2%) for EGPA, and nine (20%) patients had unclassified AAV.

Hyperthyroidism and antithyroid drug

Thirty-four (76%) patients were treated for Graves' disease, and 11 (24%) for multinodular goitre. The most frequently AAV-inducing ATD was PTU (73%) followed by methimazole (18%). Median duration of PTU use at AAV diagnosis was 3 years (IQR 1–5). Nine patients (28%) developed PTU-induced AAV within one year (minimum duration 2 months), while the delay was >5 years for seven (22%), with a maximum interval of 14 years. The median daily dose of PTU was 150 mg.

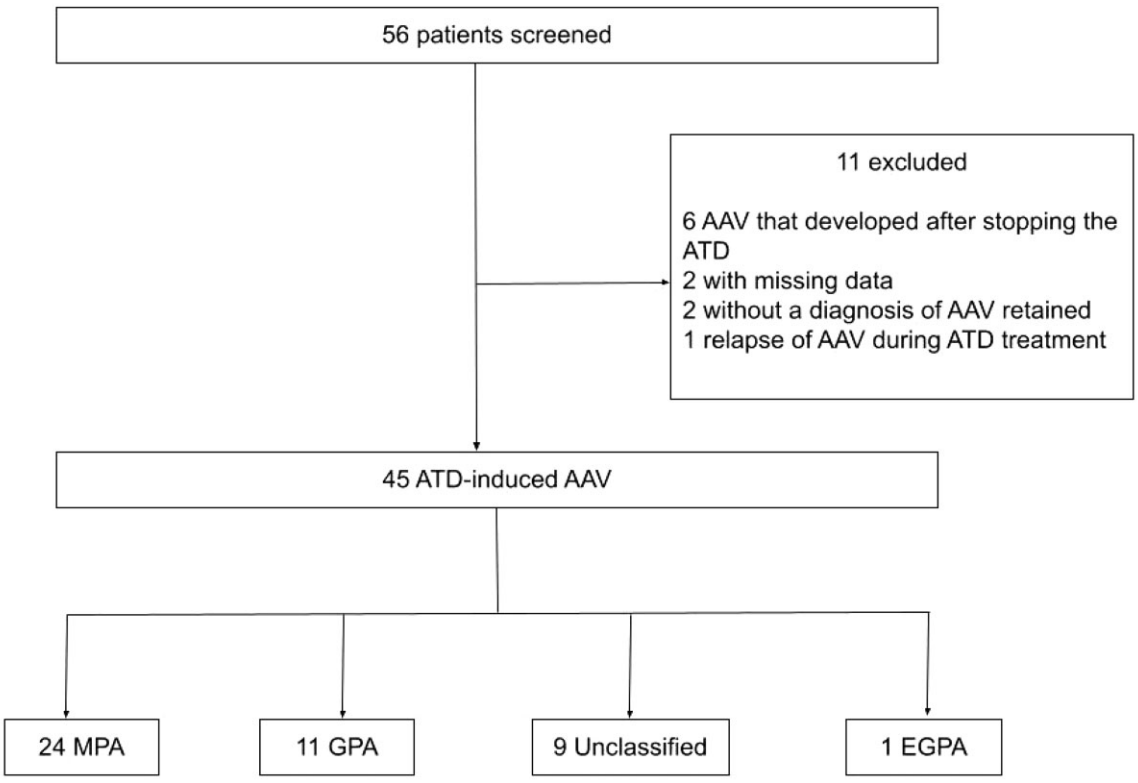

Figure 1. Flow chart of the study. AAV: ANCA-associated vasculitis; ATD: antithyroid drugs; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis

Clinical characteristics at ATD-induced AAV diagnosis

Baseline characteristics are summarized in Table 1. Median age was 44 years, and 80% were female. Diagnosis of ATD-induced AAV was made after 2010 in 37 (83%) patients. The most frequent organs involved were the skin (64%), joints and muscle (51%), the kidney (36%), and the lung (31%). Five patients (11%) had only skin involvement and 11 (24%) patients both cutaneous and joint involvement. At diagnosis, 1996 five-factor score was 0 in 80%, 1 in 4% and ≥2 in 16%. The median BVAS was 8 (IQR 4–14). There was no significant difference in clinical presentation and severity between ATD-induced MPA, GPA and unclassified AAV (data not shown).

Nine patients had severe vasculitis as defined by a FFS >0. Compared with nonsevere patients, severe ATD-induced AAV had more constitutional symptoms (100 *vs* 47%, $P = 0.011$), less cutaneous involvement (22 *vs* 75%, $P = 0.012$), more frequently received induction regimen (100 *vs* 78%, $P = 0.007$) and maintenance therapy (78 *vs* 36%, $P = 0.043$) (Supplementary Table S1, available at *Rheumatology* online).

Biological data and histological findings of ATD-induced AAV

Main biological and histologic characteristics at diagnosis are reported in Table 2. Mean (S.D.) serum creatinine was 98 (80) μmol/l. Among the 45 ATD-induced AAV cases, 44 were ANCA-positive (98%), including MPO-ANCA in 21 (47%), PR3-ANCA in six (13%), and double positive MPO- and PR3-ANCA in 15 (33%). ANA status was available for 31 patients (69%) and was detected in 18 (58%), with a median titre of 1/320. None had anti-dsDNA antibody. Antiphospholipid antibodies were positive in 6/30 (20%), and all became negative during follow-up. No patient had hypocomplementemia.

Histological evidence of vasculitis was obtained in 31 (69%) patients. Skin biopsy was performed in 22 and showed leukocytoclastic vasculitis in 21 (95%). In immunofluorescence, 18 biopsies (81%) were pauci-immune, four (18%) showed C3 and two (9%) IgM deposits. Renal histology was available for seven patients showing necrotizing glomerulonephritis in six, with pauci-immune immunofluorescence in five and with mesangial IgA deposits in two.

Therapeutic management of ATD-induced AAV

Treatment was based on ATD discontinuation in 44 cases (98%), allowing vasculitis remission in seven (16%), with a median duration of 2 months (data available for three patients). One patient (2%) showed spontaneous vasculitis remission despite continuation of ATD. These eight patients not requiring glucocorticoids or immunosuppressive agents had skin involvement ($n = 7$), arthralgias ($n = 3$) and ENT manifestations ($n = 2$), but no acute kidney injury or pulmonary involvement. Compared with the 37 patients who received immunosuppressive therapy, these eight patients had a lower mean BVAS (5 *vs* 10, $P = 0.048$). Moreover, although it was not statistically significant, the mean time of ATD duration tended to be shorter (107 *vs* 184 months, $P = 0.26$).

Twenty-eight additional patients with non-severe vasculitis received systemic treatments: eight patients received short-term glucocorticoids alone for a median duration of 4 months (range 2–5); five patients received long-term glucocorticoids alone for a median duration of 2 years (range 0.6–4); and 15 patients received glucocorticoids in combination with immunosuppressive agents. Twelve patients received immunosuppressants as induction therapy (rituximab in six, azathioprine in three, methotrexate in two, cyclophosphamide in one) and 13 as maintenance treatment (azathioprine in five, rituximab in four, methotrexate in three and mycophenolate mofetil in one). Patients with severe disease ($n = 9$) received glucocorticoids, in combination with immunosuppressive agents in eight cases (rituximab in five and cyclophosphamide in three). Maintenance therapy was initiated in seven patients and consisted of rituximab in four, azathioprine in two and mycophenolate mofetil in one. Complete remission was achieved in all patients.

Table 1. Main clinical data at diagnosis of 45 patients with ATD-induced AAV

Clinical characteristic	Results
Female, sex	36 (80%)
Age, years	44 [31–58]
Comorbidities	
Graves' disease	34 (76%)
Multinodular goiter	11 (24%)
Antithyroid drugs	
Propylthiouracil	33 (73%)
Dose, mg ($N = 26$)	150 [50–300]
Duration of therapy, months ($N = 32$)	36 [12–56]
Methimazole	8 (18%)
Duration of therapy, months ($N = 7$)	6 [4–17]
Benzylthiouracil	3 (7%)
Carbimazole	1 (2%)
Year of diagnosis	
<2010	8 (17%)
>2010	37 (83%)
Vasculitis manifestations	
Constitutional signs	26 (58%)
Fever	11 (24%)
Weight loss	18 (40%)
Cutaneous manifestations	29 (64%)
Purpura	19 (42%)
Urticarial lesions	5 (11%)
Ulcers	4 (9%)
Arthralgias	23 (51%)
Renal manifestations	16 (36%)
Urine sediment abnormality without acute kidney failure	7 (16%)
Serum creatinine >140 μmol/L	9 (20%)
Dialysis-dependent	2 (4%)
Lung manifestations	14 (31%)
Alveolar hemorrhage	8 (18%)
Pulmonary nodules, mass or cavitation	5 (11%)
Ear, nose and throat manifestations	9 (20%)
Crusting rhinitis	3 (7%)
Sinusitis	4 (9%)
Eye involvement	6 (13%)
Scleritis	5 (11%)
Gastrointestinal involvement	2 (4%)
Mononeuritis multiplex	2 (4%)
Cardiovascular manifestations	1 (2%)
1996 FFS at diagnosis	
= 0	36 (80%)
= 1	2 (4%)
≥2	7 (16%)
BVAS	8 [4–14]

Data are expressed as *n* (%) or median [interquartile range, IQR].
FFS: five-factor score.

Table 2. Main biological and histological parameters at diagnosis of 45 patients with ATD-induced AAV

Biological and histological parameters	Results
Serum creatinine, μmol/L ($N=44$)	98 (80)
Proteinuria, g/day ($N=34$)	0.6 (2.7)
Hematuria ($N=40$)	17 (43%)
ANCA specificity	44 (98%)
MPO-ANCA +/PR3-ANCA –	21 (47%)
MPO-ANCA –/PR3-ANCA +	6 (13%)
MPO-ANCA +/PR3-ANCA +	15 (33%)
MPO-ANCA –/PR3-ANCA –	2 (4%)
ANCA titers of	
MPO-ANCA, UI/mL, median [IQR] ($N=27$)	91 [46–135]
PR3-ANCA, UI/mL, median [IQR] ($N=18$)	41 [19–52]
ANA ($N=31$)	18 (58%)
DsDNA Ab	0
Anti-Sm Ab	1 (3%)
Antiphospholipid Ab ($N=30$)	6 (20%)
aCL IgM	2 (7%)
aCL IgG	1 (3.5%)
aβ2GPI IgM	2 (7%)
Lupus anticoagulant	1 (3.5%)
Hypocomplementemia ($N=20$)	0
Histological confirmation of vasculitis	31 (69%)
Skin	22 (49%)
Kidney	8 (17%)
Lung	1 (2%)
Sinonasal	1 (2%)
Skin biopsy ($N=22$)	
Leukocytoclastic vasculitis	21 (95%)
IF pauci-immune	18 (81%)
Kidney biopsy ($N=7$)	
Glomeruli with crescents	6 (83%)
Interstitial inflammation	4 (57%)
Mesangial hypercellularity	2 (29%)
IF pauci-immune	5 (71%)
IgA mesangial deposits	2 (29%)

Data are given as mean (S.D.) for continuous variables or *n* (%) for categorical variables, unless specified otherwise.
Ab: antibody; aβ2GPI: anti β_2Glycoprotein I; aCL: anticardiolipin; dsDNA: double-stranded DNA; IF: immunofluorescence; IQR: interquartile range; MPO: myeloperoxidase; PR3: proteinase 3.

Table 3. ATD-induced MPA *vs* matched primary MPA on gender and year of diagnosis

Variables	ATD-induced MPA ($n=24$)	Primary MPA ($n=96$)	*P* value
Demography			
Female	17 (71%)	64 (67%)	0.88
Age at diagnosis, years	48 (17)	65 (15)	<0.001
Vasculitis manifestations			
Constitutional signs	13 (54%)	52 (54%)	1
Cutaneous manifestations	13 (54%)	24 (25%)	0.012
Arthralgia	14 (58%)	49 (51%)	0.68
Renal manifestations	9 (38%)	70 (73%)	0.002
Lung manifestations	7 (29%)	43 (44%)	0.25
ENT manifestations	3 (13%)	8 (8%)	0.81
Eye involvement	4 (17%)	3 (3%)	0.041
Mononeuritis multiplex	1 (4%)	33 (34%)	0.007
1996 FFS at diagnosis			0.004
= 0	17 (75%)	36 (38%)	
= 1	2 (8%)	38 (40%)	
≥2	4 (17%)	22 (23%)	
BVAS	9 (7)	13 (7)	0.011
Laboratory features			
Serum creatinine, μmol/L	115 (99)	213 (217)	0.037
ANCA positivity	24 (100%)	96 (100%)	
MPO-ANCA	24 (100%)	95 (99%)	1
PR3-ANCA	8 (33%)	2 (2%)	<0.001
Treatments			
Induction therapy			<0.001
No treatment	4 (17%)	0 (0%)	
GCs alone	7 (29%)	17 (18%)	
Rituximab	5 (21%)	15 (16%)	
Cyclophosphamide	3 (13%)	47 (49%)	
Maintenance therapy			0.49
Rituximab	6 (25%)	33 (34%)	
Azathioprine	3 (13%)	20 (21%)	
Duration of follow-up, years	3.9 (3.5)	3 (2.6)	0.15
Relapse	1 (4%)	21 (22%)	0.087
Minor	1 (4%)	10 (10%)	
Major	0	11 (12%)	
Death	1 (4%)	6 (6%)	1

Data are given as mean (S.D.) or *n* (%).
ATD: antithyroid drug; FFS: five-factor score; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3.

Outcome of ATD-induced AAV and hyperthyroidism

Median follow-up of patients was 3 years (IQR 1–6). During follow-up, five patients (11%) had a relapse, all minor, after a median time of 5 years. Among these relapsing patients, two had GPA, one had EGPA, one had MPA and one had unclassified AAV. None of them had a severe disease at diagnosis. No predictive factor was identified (data not shown).

At last follow-up, 16/35 patients (46%) were ANCA-negative, with a median time from AAV diagnosis to ANCA negativity of 6 months (IQR 3–19). Fifteen patients had disease sequelae, including chronic kidney disease in seven cases, and complications of corticosteroid therapy in five. One patient (2%) died during follow-up, unrelated to vasculitis.

To treat hyperthyroidism, 13 (29%) patients underwent thyroidectomy, 12 (27%) monitoring only and eight (18%) radioactive iodine. ATD were reintroduced in seven cases (16%), including derivatives of thiouracil in three, and none of them experienced a relapse.

Case-control study of ATD-induced MPA compared with primary MPA

First, by comparing ATD-induced MPA ($n=24$) with primary MPA ($n=378$), and although the result is not significant due to a probable lack of statistical power, there was a trend towards a higher proportion of women (70.8% *vs* 52.6%, $P=0.128$).

Then, we compared patients with ATD-induced MPA ($n=24$) with 96 matched primary MPA (Table 3). The time from onset of the first symptom to diagnosis was similar in both groups. Compared with primary MPA, ATD-induced MPA were significantly younger at diagnosis (48 *vs* 65 years, $P<0.001$), had less frequent kidney (38 *vs* 73%, $P=0.02$) and peripheral nervous system involvement (4 *vs* 34%, $P=0.007$). In contrast, ATD-induced MPA had more frequently cutaneous (54 *vs* 25%, $P=0.012$) and ocular involvement (17 *vs* 3%, $P=0.041$). ATD-induced MPA had a lower mean BVAS (9 *vs* 13, $P=0.011$) at diagnosis. Finally, despite a less aggressive treatment, the risk of relapse was lower in ATD-induced MPA than in primary MPA with an adjusted HR for relapse of 0.07 (95% CI 0.01, 0.65, $P=0.019$) (Table 4). Relapse-free survival for ATD-induced MPA and primary MPA are shown in Fig. 2.

Comparison of methimazole-induced AAV to propylthiouracil-induced AAV

Patients with methimazole-induced AAV ($n=8$) were compared with 33 propylthiouracil-induced AAV. Methimazole-induced

Table 4. Hazard ratios (95% CI) for the risk of vasculitis relapse for the 24 ATD-induced MPA and 96 primary MPA

	Univariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Antithyroid drug	0.15 (0.02, 1.09)	0.06	0.07 (0.01, 0.65)	0.019
Age at diagnosis	1.00 (0.98, 1.02)	0.99	0.98 (0.96, 1.01)	0.22
General signs	0.72 (0.31, 1.67)	0.45	—	—
Lung manifestations	1.55 (0.67, 3.58)	0.31	—	—
Kidney manifestations	1.01 (0.41, 2.49)	0.98	0.49 (0.18, 1.31)	0.16
Kidney involvement requiring dialysis	1.66 (0.38, 7.19)	0.5	—	—
Ear, nose and throat manifestations	1.95 (0.66, 5.77)	0.23	—	—
Arthralgias	0.55 (0.23, 1.29)	0.17	—	—
Cutaneous manifestations	0.89 (0.35, 2.30)	0.81	—	—
Eye involvement	0.67 (0.09, 4.96)	0.69	—	—
Mononeuritis multiplex	1.90 (0.77, 4.72)	0.17	—	—
Cardiovascular manifestations	1.64 (0.22, 12.25)	0.63	—	—
BVAS	1.01 (0.95, 1.08)	0.69	—	—
1996 FFS	1.29 (0.79, 2.12)	0.31	—	—

ATD: antithyroid drug; FFS: five-factor score; HR: hazard ratio; MPA: microscopic polyangiitis; 95% CI: 95% confidence interval.

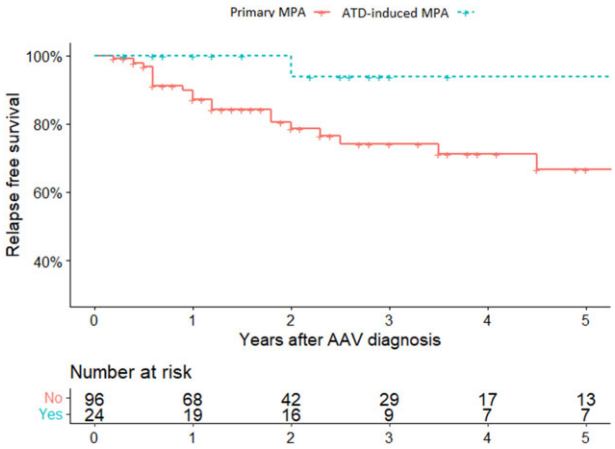

Figure 2. Kaplan–Meier curves showing relapse-free survival by the time of AAV diagnosis in the two groups. AAV: ANCA-associated vasculitides; ATD: antithyroid drugs; MPA: microscopic polyangiitis

AAV were significantly older (56 *vs* 42 years, $P = 0.042$), more severe (FFS ≥ 1 for 75 *vs* 12%, $P < 0.001$) and with a shorter onset time under ATD (43 *vs* 191 months, $P = 0.031$)

Discussion

In this retrospective, multicentre study, we report 45 patients with ATD-induced AAV, making it one of the largest series. The detailed description of these patients, associated with most cases diagnosed after 2010 and a mean follow-up of 4.5 years allow a better understanding of ATD-induced AAV in the era of biologics.

Patients with ATD-induced AAV were young with a median age of 44 years and mainly women, reflecting the epidemiology of Graves' disease [2]. The most common ATD associated with AAV was PTU, which was involved in three-quarters of our cases, as commonly reported in the literature. One of the aspects making the diagnosis challenging is the extremely variable duration of appearance under PTU therapy. In our study, interval between ATD initiation and AAV diagnosis ranged from 2 months to 14 years with a median interval of 3 years. The clinical presentation in our cohort was noticeably different from the previous studies. The two most affected organs were skin (64%) and joints (51%), with a quarter of patients having an isolated cutaneous and joint involvement, which is consistent with the literature on drug-induced vasculitis [31]. Furthermore, skin involvement was a good prognostic feature, patients with severe forms showing less frequent skin involvement than non-severe forms (22 *vs* 75%). However, the strong predominance of skin involvement was not previously described, with a proportion ranging from 17% to 29% in the main retrospective studies [32–35]. In addition, kidney involvement was only present in a third of our patients, a much lower rate than in the literature. These data explain the low proportion of kidney biopsies in our study (16%), skin biopsy being more accessible to confirm the diagnosis of vasculitis. Although roughly 20% of cases were severe with patients presenting with rapidly progressive glomerulonephritis, the majority of cases were non-severe.

ANCA detection was positive in 98% of cases, 47% displaying MPO-ANCA and 33% both MPO- and PR3-ANCA. This proportion of double positivity was greater than in the study by Chen *et al.* (11%) [36], but closer to the rate in hydralazine-associated AAV and levamisole-induced vasculopathy (39 and 43%, respectively) [26, 27]. Although some data suggest that drug-associated AAV are associated with elevated ANCA titres, we were unable to obtain enough samples for centralized analysis and statistical analysis [37]. As with hydralazine-induced AAV, in which ANA were detected in 89.2% compared with 18.7% in primary AAV, we found an increased frequency in ATD-induced AAV, with 58% of our patients having ANA [26]. However, none of them had anti-dsDNA, anti-histone antibodies, or hypocomplementemia. The vast majority of skin and kidney biopsies showed pauci-immune immunofluorescence, suggesting that, unlike other types of drug-induced AAV, ATD-induced AAV does not seem to overlap with drug-induced lupus [26].

Our cohort is also the first to individualize the phenotype of AAV and classify them between MPA, GPA, EGPA and UV. This approach allowed us to obtain a more homogeneous and well-defined group of ATD-induced MPA and to perform a

more relevant case-control study with primary MPA. Therefore, we highlighted some differences between ATD-induced MPA and primary MPA, especially a different clinical presentation with more frequent skin and eye involvement and less kidney involvement, a less severe disease and a lower risk of relapse. These results are in line with those of Chen *et al.* who also highlighted the better prognosis of this disease [36].

We next analysed the therapeutic management of ATD-induced AAV. All patients but one benefitted from ATD discontinuation. ATD discontinuation resulted in remission in seven patients and eight additional patients only required a short course of GCs and achieved sustained remission. These data suggest that in patients with mild-to-moderate disease, especially those with skin or skin and joint involvement, ATD discontinuation, possibly combined with short-term GCs, could be sufficient to achieve remission. Two-thirds of patients required more conventional induction therapy based on GCs alone or in combination with rituximab or cyclophosphamide. Maintenance therapy was initiated in only 54% patients, mainly based on rituximab or azathioprine. All patients achieved remission, and only five patients (11%) relapsed. These data illustrate that ATD-induced AAV could benefit from less toxic or shorter treatments, and suggest that rituximab could probably be used in severe cases as in primary AAV.

Finally, this study has some limitations. First, because of its retrospective design, data on the effectiveness of therapeutic management should be interpreted with caution. Also, the relatively small number of patients may have led to a lack of power for statistical analysis, especially to identify risk factors for severe disease or relapsing disease. Finally, because we collected patients from vasculitis networks, we cannot exclude a selection bias.

In conclusion, ATD-induced AAV were mainly induced by PTU with extremely variable durations of treatment. They were mainly MPA with MPO-ANCA, but double MPO- and PR3-ANCA positivity was frequent. ATD-induced MPA were less severe and showed a lower risk of relapse than primary MPA. ATD-induced AAV seemed to require less aggressive treatments than primary MPA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data are available on reasonable request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement: The authors have declared no conflicts of interest.

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