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ANCA ASSOCIATED VASCULITIS: CLINICAL COURSE AND OUTCOME OF 44 PATIENTS FROM A SINGLE CENTER IN TURKEY

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Abstract

Aim: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of disease characterized by necrotizing, granulomatous inflammation of small to medium-sized blood vessels. The classification of vasculitis is performed according to The International Chapel Hill Consensus Conference, which was held in 2012; a system that classifies the disease according to the vessel size. According to this classification, ANCA-AAV is classified as granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis polyangiitis (EGPA). Although AAV is a rare disease with an incidence of about 20 per million population per year in Europe and North America. There is a slightly male preponderance. The aim of our study aimed to reveal the clinical features of ANCA-AAVs and to compare the effects of related organ involvement on prognosis

Material and Methods: Forty-four patients who were followed up with the diagnosis of ANCA-AAV between 2006 and 2020 at the Rheumatology-Immunology Unit were included in our study. The data were analyzed retrospectively.

Results: In this retrospective study, 44 patients were included who were followed up with the diagnosis of AAV. The patients had 38 (86%) GPA, 4 (9%) MPA, 2 (4.5%) EGPA diagnoses. Forty-two patients were positive for ANCA (35 cytoplasmic-ANCA and 7 perinuclear-ANCA). ANCA test of two patients were negative. Ten of the patients with GPA had limited and 28 of them had severe disease. Forty-two patients were followed up for an average of 36 (3-168 months) months. The initial mean Birmingham vasculitis activity score (BVAS) of the patients was calculated as 19 (±7.512). The number of patients in clinical remission was 31 (71%), and the mean time to remission was 6 months. During the follow-up, 21 patients' disease relapsed, 2 patients quit followed up, and 3 patients died.

Conclusion: The variety of clinical symptoms of this curable disease may result as a delay for diagnose and treatment. The disease had a heterogeneous clinical presentation. Therefore, it is appropriate to make a patient-based decisions for management. In this study, we demonstrated the clinical diversity and the efficacy of cyclophosphamide and rituximab during induction therapy.

Keywords: ANCA-associated vasculitis (AAV), granulamatozis polyangitiis, BVAS

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INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a disease characterized by autoantibodies against the antigenic components of the neutrophilic cytoplasm and characterized by necrotizingand granulomatous inflammation of small to medium blood vessels. The most widely used classification system for systemic vasculitis is the International Chapel Hill Consensus Conference, which was held in 2012 that evaluates the disease according to the vessel size. According to this classification, ANCA-AAV is classified into 4 clinical groups: Granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis polyangiitis (EGPA), and renal limited vasculitis. Antineutrophil cytoplasmic antibodies are specific for proteinase 3 (PR3) or myeloperoxidase (MPO) and can be found in most patients with AAV (1). PR3 ANCA is most frequent in GPA (frequency 75%) whereas rarely found in EGPA (frequency 5%). MPO ANCA positivity is more frequent in patients with MPA (70% frequency) than GPA patients (20%). EGPA has different pathogenetic mechanisms, genetic features, and clinical findings than other diseases in this group (2). In AAVs, 10% of patients may reveal negative ANCA test. These patients are presented with a similar clinical course and comparable treatment response compared with the ANCA-positive group; however, but ANCA-negative patients are more likely to have kidney-limited disease or less severe systemic disease (3). Although AAV disease is rare with an incidence of 20 per million population per year in Europe and North America, it is the most common form of primary systemic vasculitis. There was a slight male preponderance. The incidence increases with age and has a peak in the 60-70 years (4). Constitutional symptoms (fatigue, weight loss, fever, joint-muscle pain) are evident and may occur several months before other symptoms have started. Respiratory symptoms are more common in GPA, and ground-glass densities, cavitation, or nodular lesions can be seen on thorax tomography. Upper respiratory tract involvement may present as rhinitis, sinusitis, otitis media, or granulomatous inflammation leading to septal perforation and nasal collapse (5). Upper airway involvement is less common in MPA, and lung involvement in MPA typically presents with alveolar hemorrhage and pulmonary fibrosis (6). Hearing loss, episcleritis/uveitis, purpuric rash in the lower extremities secondary to leukocytoclastic vasculitis, and peripheral neuropathy (mononeuritis multiplex) may be seen, but the central nervous system involvement is rare. Deep venous thrombosis may occur during the active phase of vasculitis (7,8). Renal involvement is common in AAV and is the most important cause of mortality. Patients with glomerular filtration rates (GFRs) <50 mL/min have a 50% risk of death or end-stage renal disease in 5 years. Renal involvement can be seen as a rapidly progressing glomerulonephritis (GN) with decreased kidney function accompanied by nephrotic proteinuria, microscopic hematuria, and, hypertension. Typically, pauci-immune focal necrotizing crescentric GN is seen on kidney microscopic examination. Higher proteinuria levels are associated with a higher percentage of crescent (9).

Treatment: AAV therapy includes a 2-step approach. The first step, an induction phase (first 6-12 months) with the aim of rapidly suppressing the inflammatory process and minimizing tissue and organ damage. The second is the maintenance step, which continues for 24-48 months aiming for remission (10). Standard therapy for induction in severe AAV includes a combination of glucocorticoids with cyclophosphamide (CYC) or rituximab (RTX). For refractory patients whom presented with no improvement within 4 to 6 weeks or with worsening disease activity, it is recommended that the initial induction agent may be ex changed with an alternative agent. CYC and RTX may be switched to each other (11). The 2-year mortality before effective treatment regimens in AAV (mostly due to kidney and lung involvement) was about 93%. Survival was improved with the introduction of glucocorticoids in 1948 and CYC in the 1960s (12). During remission induction therapy, treatment may have to be interrupted because of serious complications such as opportunistic infections and bone marrow suppression. Although long-term therapy is expected to control the disease, more than 50% of patients develop relapse during or after maintenance therapy. The heterogeneity of disease recurrency and ANCA positivity are the main factors affecting the treatment success. Therefore, it is appropriate to make a patient-based decision in treatment selection (13).

The aim of our study aimed to reveal the clinical features of ANCA-associated vasculitides and to compare the effects of related organ involvement on prognosis. The induction and maintenance treatments of 44 patients with ANCA-related vasculitis followed in our clinic were consistent with the literature. Genitourinary involvement, which is one of the rare sites of involvement, was present in 3 of our patients, and we wanted to share this rare involvement. In our study, we found that the majority of recurrence were renal and lower respiratory tracts.

MATERIAL AND METHODS

Forty-four patients who were followed up with the diagnosis of ANCA-AAV between 2006 and 2020 at the Rheumatology-Immunology Unit at the Research Hospital of Çukurova

University were included in our study. GPA, microscopic polyarteritis nodosa (MPAN), and EGPA patients were diagnosed according to the criteria published by the 1990 American College of Rheumatology. The data were analyzed retrospectively. On 05/04/2019, the approval of the Ethics Committee numbered 87 was received from Çukurova University. Birmingham Vasculitis Injury Index Version-3 was used to score the disease activity (14). ANCA test was determined by the indirect immunofluorescence method and was reported as cytoplasmic-ANCA (c-ANCA) and perinuclear-ANCA (p-ANCA) by subgroup analysis using enzyme-linked immunosorbent assay test. Respiratory and other system evaluations were evaluated using radiography and computed tomography. Biopsies were performed from the involved organs: Such as; lung, renal, skin, nasal septum, palate, and brain; histopathology examination and immunofluorescence staining were performed.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version 20 software package (released 2011, IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA). Demographic variables were analyzed using descriptive analyses. Te normality of the distribution of continuous variables was checked using the Shapiro-Wilk test. Continuous parameters were compared using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test. Results with p values less than 0.05 were regarded as statistically significant.

RESULTS

Forty-four patients with ANCA-AAV who were followed up in our clinic were included in the study. The patients were diagnosed as: GPA in 38 (86%) patients, MPA in 4 (9%) patients and EGPA in 2 (4.5%) patients. Demographic and clinical data of the patients are given in Table 1. The mean age of 44 patients was 49 (± 12.3) years. Twenty patients were (45%) female and 24 were (55 %) male. Forty-two (42) patients were followed up for an average of 36 (3-168) months. Two patients quit follow-up after the first dose of remission induction therapy. Three patients died during follow-up. Forty-two patients were positive for ANCA (35 c-ANCA, and seven p-ANCA). ANCA test of two patients was negative. Patients with a negative ANCA test were diagnosed with GPA after a transthoracic lung biopsy. Ten patients were diagnosed with limited GPA (non-renal limited lung involvement). Systemic involvement of the patients was as follows: Upper respiratory tract 25 (57%), lung involvement 36 (82%), renal involvement 31 (71%), skin 16 (36%), mononeuritis multiplex 16 (36%), articular 18 (41%), eyes 10 (23%), testis 2 (5%), prostate 1 (%2.5) (Table 2).

Table 1. Demographic and general characteristics of patients with ANCA-associated vasculitis

Sex n (%)	
Female	20 (45%)
Male	24 (55%)
Age (mean) (SD)	49 (±12.3)
BMİ (mean) (SD)	28 (±5.3)
Tobacco n (%)	13 (30%)
Diagnosis n (%)	
GPA	38 (86%)
MPA	4 (9%)
EGPA	2 (4.5%)
Disease age (mean) (mounth)	36 (37.11-65.44)
The number of histopathological samples n, (%)	33 (75%)
Nose	17 (39%)
Lung	5 (11%)
Renal	9 (21%)
Skin	1 (2%)
Brain	1 (2%)
Comorbidity n (%)	27 (61%)
Organ involvement	
Upper respiratory tract n (%)	25 (57%)
Lower respiratory tract n (%)	36 (82%)
Renal n (%)	31 (71%)
Skin n (%)	16 (36%)
Mononeuritis multiplex n (%)	16 (36%)
Articular n (%)	18 (41%)
Eye n (%)	10 (23%)
Testicular n (%)	2 (5%)
Prostate n (%)	1(2.5%)
ANCA during diagnosis	
c-ANCA n (%)	35 (80%)
p-ANCA n (%)	7 (16%)
ANCA negative	2 (4%)
BVAS (mean, during diagnosis) (SD)	19 (±7.512)
Remission n (%)	31 (71%)
Remission time (mean)	6 (5.08-7.93)
Relapses	21 (47%)
Relapses time (mean)	10.5 (11.74-28.25)
Regions of relapses	
Renal n (%)	6 (14%)
Upper respiratory tract n (%)	2 (6%)
Lower respiratory tract n (%)	13(30%)
Retinal artery trombosis n (%)	1 (2%)

ANCA: Antineutrophil cytoplasmic antibody, BMI: Body mass index, EGPA: Eosinophilic granulomatosis polyangiitis, GPA: Granulomatous polyangiitis, MPA: Microscopic polyangiitis, BVAS: Birmingham vasculitis activity score, c-ANCA: Cytoplasmic-ANCA, p-ANCA: Perinuclear-ANCA

Lung involvement patterns were as follows: 19 of 36 patients had nodular lesions, and 17 had cavitary lesions. Biopsy was taken from 34 organs: Nose 17 (50%), lung 6 (17%), renal 9 (26%), skin 1 (3%), and brain 1 (3%). The initial mean Birmingham vasculitis activity score (BVAS) score of the patients was calculated as 19 (±7.512). The number of patients in clinical remission was 31 (71%) and the mean time to remission was six months.

Remission Induction and Maintenance Therapies

Remission induction treatments of 38 GPA patients were: 25 (65%) patients CYC [500 mg/m^2/month, intravenous (IV)] , 10 (26%) patients RTX (375 mg/m^2/week, 4 weeks) , 1 (2%) patient mycophenolate mofetil (2 g/day) and 2 (5%) patients methotrexate (MTX) (15-25 mg/week/sc). Two EGPA patients received pulse methylprednisolone (250-500 mg/day three doses) and MTX (15 mg/week/sc) treatments. Four MPAN patients received pulse steroid and IV CYC treatment. Plasmapheresis was applied ten times to 10 patients and for several indications. IV immünglobulin (0.4 gr/kg/day) treatment was given to 4 patients. Pulse methylprednisolone (250 mg-1000 mg/day/IV route) was given to 33 patients (Table 2). No statistically significant difference was observed between CYC and RTX treatments when evaluated for remission (p=0.409). There was no significant difference in the duration of remission between patients who were given CYC treatment and those who received RTX (p=0.281). Remission periods were similar in patients who received pulse steroids and who did not receive pulse steroid (p=0.801). There was a moderate positive correlation between baseline BVAS and remission periods (r=0.37, p=0.02). The number of patients who were given mycophenolate mofetil, MTX, and azathioprine (AZT) treatment was not eligible for statistical evaluation.

Thirty-nine patients received remission maintenance therapy: 15 (38%) patients AZT, 6 (15%) patinet MTX, 6 (15%) patients mycophenolate mofetil and 12 (30%) patients RTX.

Recurrence Data

Recurrence occurred in 21 (47.72%) patients during follow-up. The median time to relapse (median, 95% confidence interval) was 10.5 (11.7-28.2) months. Regions of recurrence were lung 13 (56%) renal 6 (26%) upper respiratory tract 2 (8%) retinal artery thrombosis 1 (4%). There was no statistically significant relationship between ANCA positivity and recurrence (p=0.267). No statistically significant relationship was found between tobacco use and relapse (p=0.380). There was no significant relationship between gender in recurrence frequency (p=0.567). There was no significant difference in patients who were given CYC or RTX treatments as remission induction therapy regarding recurrence and infection secondary to treatment (p=0.141, p=0.26).

Renal Involvement

In 31 patients with renal involvement, the initial median creatinine value was 1.32 mg/dL (0.24-7.41), and the mean GFR value was 66.93 mL/min/1.73 m^2 (±37.89). Hematuria was present in 23 (74%) patients and >1-g proteinuria was present in 22 (71%) patients. Five patients (16%) had proteinuria at the nephrotic level. Patients with renal involvement were similar in terms of remission and recurrence with the patients without renal involvement. There was no significant difference in remission and recurrence in patients who received CYC or RTX treatment (p=0.315, p=0.115). End -stage renal disease developed in two patients during follow-up.

Table 2. Features of treatment modalities and treatment-related complications

Pulse metilprednisolon (n,%)	33 (75%)
Remission induction (n, %)	
Cyclophosphamide (n, %)	29 (65%)
Rituximab (n, %)	10 (22%)
Mycophenolate mofetil (n, %)	1 (2%)
Methotrexate	2 (4.5%)
Remission maintenance (n, %)	39 (88%)
Azathiopurine (n,%)	15 (38%)
Methotrexate (n,%)	6 (15%)
Rituximab (n,%)	12 (30%)
Mycophenolate mofetil (n,%)	6 (15%)
Plazmapheresis(n,%)	10 (23%)
Complications during treatment n (%)	33 (75%)
Steroid myopathy	3 (10%)
Steroid induced diabetes	6 (18%)
Osteoporosis	3 (10%)
Hypogammaglobulinemia	1 (3%)
Deep vein thrombosis	3 (10%)
Avascular necrosis	1 (3%)
Severe infection n (%)	16 (46%)
Bacterial pneumonia	8 (50%)
Fungal infection	3 (19%)
Herpes zoster	2 (12.5%)
Tuberculozis	2 (12.5%)
Skin infection	1 (6.25%)
Trimethoprim-sulfamethoxazole prophylaxis n (%)	24 (55%)

Treatment Complications and Mortality

Thirty-four complications related to medications have occurred. These were: Severe infection in 16 (46 %) patients, steroid myopathy in 3 (10%) patients, secondary diabetes mellitus in 6 (18%) patients, osteoporosis 3 (10%) patients, skin infection in 1 (6.25%) patients, hypo-gammaglobulinemia in 1 (3%) patient, catheter-related deep vein thrombosis in 3 (10%) patients, steroid-related avascular necrosis in 1 (3%) patient. A total of 16 patients had treatment-related severe infections: Bacterial pneumonia in 8 (50%) patients, pulmonary fungal infection in 3 (19%) patients, herpes zoster in 2 (12.5%) patients, pulmonary tuberculosis in 2 (12.5%) patients, and skin infections in 1 (% 6) patient. Malignancy developed in 2 patients during follow-up. These were lung adenocarcinoma and basal cell carcinoma of the skin. A total of 3 patients died: Two patients died due to sepsis secondary to opportunistic lung infection. The other was due to acute renal failure based on chronic renal disease.

DISCUSSION

ANCA-AAV is a heterogeneous group of diseases characterized by chronic, necrotizing, and granulomatous inflammation of small to medium blood vessels. GPA typically presents with upper respiratory tract, lung, and renal involvement. MPAN is characterized by rapidly progressive GN and alveolar capillaritis (1,2). EGPA is systemic necrotizing vasculitis characterized by migrating infiltrates in the lung accompanied by allergic asthma, nasal polyposis, and eosinophilia (3). AAV is a rare disease with about 20 per million population per year in Europe and North America. There is a slight male dominance. Although GPA is more common in Northern Europe and Australia, there are geographic differences (4). In our retrospective review, GPA had numerical superiority in patients with total ANCA-AAV. In the literature, PR3-ANCA is most commonly associated with GPA (75%), MPO-ANCA is more commonly associated with MPA (60%) and EGPA (50-60%) (2). Similar to the data in our study, there were 89% PR-3 ANCA positivity in GPA, MPO-ANCA positivity in all patients in MPAN, 50% p-ANCA positivity in 50% c-ANCA in EGPA. This 100% p-ANCA positivity in MPAN may be due to the low number of patients. Ear, nose and throat manifestations can occur in patients with either GPA or MPA. However, they were higher in patients with GPA (estimated frequency is 90 percent versus 35 percent in MPA). Parenchymal lung nodules and cavities are a well-recognized manifestations in AAV (6). In our study, upper and lower respiratory tract involvement was founded 57% and 82%, respectively. These data were similar to those in the literature. The comparison of ANCA-AAV patients with other citations is presented in Table 3.

Renal involvement is more common in GPA and MPA, than in EGPA. In previously reported studies, GN was present in only 18 percentage of patients at presentation. However, GN developed in 77-85% of patients, usually within the first two years of disease onset (15). In our study, 31 (71%) patients had renal involvement at the time of diagnosis. In AAVs, varying subnephrotic-nephrotic proteinuria rates, microscopic hematuria, and active urinary sediment can be seen at the beginning and during the disease (16). Hematuria was presented in 23 (74%) patients, and subnephrotic proteinuria was presented in 22 (71%). Five patients (16%) had proteinuria at the nephrotic level. Urogenital manifestation is a rare feature of GPA that is present in <1 % of reported cases (16). In our series, two patients had testicular involvement, and one patient had prostate abscess.

Ocular involvement was present in 10 GPA patients (23%) included in the study. These were 4 episcleritis, 5 uveitis, and one retinal artery thrombosis. Considering the literature data, patients with AAV may develop episcleritis/scleritis, conjunctivitis, corneal ulceration, optic neuropathy, uveitis, and retinal vasculitis (17).

Patients with AAV may develop clinical manifestations involving the peripheral and central nervous systems, including mononeuritis multiplex, sensorial neuropathy, cranial nerve abnormalities, central nervous system lesions and sensorineural hearing loss (18). In our series, 16 patients had peripheral nervous system involvement and one patient had involvement in the form of a solid mass in the left cerebral hemisphere. The two-stage treatment of AAV consists of remission induction followed by a more extended period of maintenance of remission as soon as the treatment goal is achieved. The standard regimen for induction therapy in AAV includes a combination of glucocorticoids with CYC or RTX. CYC can be used in oral or IV regimens. There are several advantages of IV CYC, including lower cumulative dose, reduced exposure, bladder protection, and increased compliance (19).

CYCLOPS and CORTAGE studies evaluated the reduction in CYC-associated toxicity in AAV using IV pulse regimens instead of daily oral therapy. Although the total IV CYC dose was lower, the remission rates of both formulations were found to be clinically comparable (19). We also prefer the IV form in our patients because of its lower cumulative dose. Thus, we rarely met complications such as hematological malignancy and bladder pathologies associated with cumulative dose. Information from RTX in ANCA-associated vasculitis and rituximab versus cyclophosphamide in ANCA-associated renal vasculitis randomized controlled trials in 2010 supported the consideration of RTX as an option for induction therapy in AAV. The success of RTX and CYC in the induction of remission was similar (19). A total of 29 patients

received IV CYC (500 mg/m^2), and ten patients were treated with RTX (375 mg/m^2). Once remission induction goals are reached (usually within 3-6 months), maintaining remission reduces disease recurrence risk.

Withdrawal of glucocorticoid therapy has been identified as a strong predictor of relapse; therefore, it is common practice to keep patients on low doses of prednisone (or equivalent) as part of the maintenance regimen. AZT, MTX, and mycophenolate mofetil have proven to be as effective as CYC for AAV maintenance therapy in randomized trials (20-28) (Table 3).

Study Limitations

First, the number of patients is not enough. In particular, the induction treatment distributions were not homogeneous, and treatment comparisons could not be clearly demonstrated.

CONCLUSION

Patients with GPA and MPA still have a higher mortality rate than the general population. Untreated patients have an approximately 90 percent mortality rate within two years (21).The long-term survival in patients with GPA and MPA has improved dramatically since the additions of CYC and RTX to the therapeutic regimen (12). Patients with GPA and MPA reported a 2.7-fold increased risk of death in patients than the general population. Pulmonary hemorrhage and end-stage renal disease (ESRD) are the most common causes of death in ANCA-AAV (22). In our study, 3 patients died. Looking at the causes of death, two patients died from sepsis secondary to opportunistic lung infection. The other died from acute renal failure developed on the basis of chronic renal failure. AAVs are a group of diseases with high mortality without treatment, so that diagnosis and treatment should not be delayed.

Table 3. General demographics of some ANCA-associated vasculitis studies. Comparison of clinical involvement sites

	Shobha et al. (23)	Kim et al. (24)	Holle et al. (25)	Kumar et al. (26)	Koldingsness and Nossent (27)	Reinhold-Keller et al. (28)	Present series (Turkey)
Number (n)	60	45	445	25	55	155	44
Age (mean)	44	51	51	33.5	50	48	49
M/F	1.4/1	1/1.3	1/1	1/1.7	1.6/1	1/1.04	1.2/1
Duration of analysis (years)	14	26	36	12	15	27	14
Clinical features (%)							
Upper respiratory	21	91	98	84	80	93	57
Lung	63	66	60	84	60	55	82
Renal	70	40	60	72	76	54	71
Articular	27	35	73	44	64	61	41
Ocular	11	40	40	64	38	40	23
Periferic nervous system	25	37	33	4	35	21	36
Skin	48	29	26	32	31	21	36
Testis	-	-	-	-	-	-	5
ANCA positivity	93	65	81	70	88	84	c-ANCA 80% p-ANCA 16%
BVAS-3 score	21.5 (17-44)	13.1 (4-22)	-	-	23 (4-46)	-	19 (7-42)
Mortality	18	22	10		0.2	14	6

M: Male, F: Female, ANCA: Antineutrophil cytoplasmic antibody, BVAS-3: Birmingham Vasculitis Injury Index Version-3, c-ANCA: Cytoplasmic-ANCA, p-ANCA: Perinuclear-ANCA

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Çukurova University Clinical Research Ethics Committee (no: 87, date: 05/04/2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Design: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Data Collection or Processing: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Analysis or Interpretation: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Literature Search: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö., Writing: E.K., M.A.A., E.K.E., D.A., S.Ö., H.T.E.Ö.

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