Treatment and Outcome in Deficiency of Adenosine Deaminase 2: A Literature Review

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J Investig Allergol Clin Immunol 2022; Vol. 32(1): 13-22
doi: 10.18176/jiaci.0748

Abstract

Objectives: Deficiency of adenosine deaminase 2 (DADA2) is a rare disease with varying phenotypes and disease outcomes. We evaluated the treatment of DADA2 and explored the factors associated with disease outcome.
Methods: A systemic literature review of DADA2 was conducted. Cases were included if they had documented detailed genotypes, phenotypes, treatment protocols, and outcomes. Patients were categorized as having uncontrolled and controlled disease. Factors associated with disease outcome were analyzed using logistic regression models.
Results: The study population comprised 242 DADA2 patients with data on treatment protocols and responses, of whom 17 required no treatment. Tumor necrosis factor α inhibitors (TNFi) were effective in 78.6% (103/131). Hematological abnormalities and increased acute phase reactants are independently associated with the effectiveness of TNFi (OR, 0.21 [95%CI, 0.07-0.661; *P*=.007] and 9.62 [95%CI, 2.31-40.00; *P*=.002, respectively). Among the 225 patients requiring active treatment, 157 (69.8%) had controlled disease and 68 (30.2%) uncontrolled disease. Neither age of disease onset nor genotype was associated with disease outcome. Increased acute phase reactant values, constitutional symptoms, neurological symptoms, and treatment with TNFi were independently associated with disease control, while recurrent infections and severe vascular events were the main causes of mortality (10/21 and 6/21, respectively).
Conclusion: In patients requiring treatment, symptoms of systemic inflammation and vasculitis and treatment with TNFi are associated with disease control. Recurrent infections and severe vascular events should be treated intensively, as they are the main causes of death. Hematological abnormalities should be monitored, as they decrease the effectiveness of TNFi.

Key words: Deficiency of adenosine deaminase 2. Treatment. Outcome. TNF-α inhibitor.

Resumen

Objetivos: El déficit de adenosina desaminasa 2 (DADA2) es una enfermedad rara con diferentes fenotipos y una evolución variable de la enfermedad. Nuestro objetivo es resumir los tratamientos de DADA2 y explorar los factores asociados con la evolución de la enfermedad.
Métodos: Se realizó una revisión bibliográfica sistémica de DADA2. Los casos que se incluyeron fueron aquellos que habían documentado el genotipo, fenotipos, protocolo de tratamiento y evolución. Los pacientes se clasificaron en grupos controlados y no controlados. Los factores asociados con la evolución de la enfermedad se analizaron con modelos de regresión logística.
Resultados: Se incluyeron un total de 242 pacientes con DADA2 con los protocolos de su tratamiento y la respuesta al mismo, 17 de los cuales no requirieron tratamiento. La eficacia general de los inhibidores de TNF-α (TNFi) fue del 78,6% (103/131). Las anomalías hematológicas y el aumento de los reactantes de fase aguda se asociaron de forma independiente con la eficacia del TNFi, OR = 0,21 (IC del 95%: 0,07 a 0,661, p = 0,007) y 9,62 (IC del 95%: 2,31 a 40,00, p = 0,002), respectivamente. Entre los 225 pacientes que requirieron tratamiento activo, 157 (69,8%) pacientes estaban en el grupo controlado y 68 (30,2%) en el grupo no controlado. Ni la edad de inicio de la enfermedad ni el genotipo se asociaron con la evolución de la enfermedad. El aumento de los reactantes de fase aguda (APR), el deterioro constitucional, los síntomas neurológicos y el tratamiento con TNFi, se asociaron de forma independiente con el control de la enfermedad, mientras que las infecciones recurrentes y los eventos vasculares graves fueron las principales causas de mortalidad (10/21 y 6/21, respectivamente).
Conclusión: Los síntomas de inflamación sistémica, la vasculitis y el tratamiento con TNFi se asociaron con el control de la enfermedad en aquellos pacientes con DADA2 que requirieron tratamiento. Las infecciones recurrentes y los episodios vasculares graves deben tratarse de forma rápida y adecuada, ya que fueron las principales causas de muerte. Asimismo, se deben controlar las alteraciones hematológicas, ya que disminuyen la eficacia de los TNFi.

Palabras clave: Déficit de adenosina desaminasa 2. Tratamiento. Evolución. Inhibidores de TNF-α.

Introduction

Deficiency of adenosine deaminase 2 (DADA2) is an inherited autoinflammatory disease caused by mutations in the *ADA2* gene (adenosine deaminase 2, OMIM: *607575), formerly known as *CECR1* (cat eye syndrome chromosome region candidate 1) [1,2]. ADA2, predominantly expressed by monocytes, functions to regulate the innate immune response, maintain vessel integrity, and participate in endothelial cell and hematopoietic cell proliferation [3]. Loss of function in *ADA2* leads to chronic upregulation of neutrophil activity, dysregulation of neutrophil extracellular trap formation (NETosis), and reduction of M2 macrophage differentiation [4-6]. These pathophysiological changes reduce endothelial cell integrity and activate a bundle of inflammatory responses, including $CD14^+$ inflammatory monocytes, interferon (IFN), and nuclear factor-κB (NF-κB) signaling, as well as intracellular production of interleukin (IL) 1ß, IL-6, and tumor necrosis factor (TNF) cytokines [2,7,8]. TNF-α is the most important cytokine, as it penetrates involved vessels and is released into peripheral serum. Inhibition of this process could decrease both IFN and NF-κB inflammatory signatures, reduce perivascular TNF, resolve inflammatory myeloid cell infiltrates, and normalize blood vessels and endothelial layers [2,7,8]. Furthermore, abrogated B-cell proliferation and reduced secretion of IgM and IgA have been noted in patients with DADA2 [1].

Genetically, culprit mutations have been reported over the entire coding region of ADA2. These include missense mutations, nonsense mutations, deletions, and splicing variants (reviewed by Meyts et al [9]). Clinically, DADA2 contains 3 symptom domains: vasculopathy and inflammation, hematological abnormalities, and immunodeficiency [3,10]. The disease course varies greatly from asymptomatic to rapidly progressive. Some patients die before diagnosis [1,2,11], and other patients survive with major disability and irreversible organ damage [12,13]. It has been suggested that profound gene structure damage and undetectable ADA2 activity tend to be associated with disease severity [14], while studies on disease outcome are lacking. Tumor necrosis factor α inhibitors (TNFi) have significantly improved disease outcome, although some patients do not respond to TNFi or even die while taking them [15-17]. Our previous review showed that patients with DADA2 from different age groups (pediatric- and adult-onset) and genotypes had contrasting phenotypes but similar responses to corticosteroids and TNFi [18]. Thus, we aimed to evaluate the treatment options reported in DADA2 and identify the factors affecting the response to treatment.

Materials and Methods

Literature Review

We searched MEDLINE, EMBASE, and the Cochrane Library using the terms "DADA2" or "ADA2" or "CECR1" or "deficiency of adenosine deaminase 2" or "adenosine deaminase 2 deficiency" on Google Chrome (Google LLC. 90.0). The original searches were limited to articles in English and dated from 2014 to February 28, 2020. A manual search was performed from March 1, 2020 to December 31, 2020. Publications on other diseases, basic studies on the ADA2 protein/gene, and reviews without individual cases were excluded. Two unreported cases from our center were included.

We collected structured demographic data, symptoms, laboratory results, imaging findings, pathology findings, treatments, and prognosis. Missing data were recorded with a default value of 0. Cases reported in different publications were included only once, and clinical data were implemented from duplicated reports. We included cases that contained individual phenotypes and genotypes and excluded those where the disease was only suspected, the patient died before genotype confirmation, or there was no description of treatments or outcomes.

Definitions and Subgroups

The age at disease onset was recorded according to the literature report. In the case of asymptomatic patients who were diagnosed during screening, age at disease onset was the age at diagnosis. Patients with disease onset at <18 years were included in the pediatric group, while patients with disease onset at ≥18 years were included in the adult group. A positive family history was defined as having affected siblings or other family members. The genotypes of all patients were reviewed. Patients carrying only missense mutations were included in the missense mutation group, whereas those carrying at least 1 null mutation (ie, nonsense mutations, deletions, insertion-deletions, and frameshift mutations) were included in the null mutation group. ADA2% refers to the ratio of the tested ADA2 level to the lower limit of normal according to the literature report.

All phenotypes were collected according to the reports and were classified into 3 domains: vasculitic manifestations, hematological abnormalities, and immunodeficiency. Vasculitic manifestations included constitutional symptoms, neurological events, skin lesions, organ involvement, peripheral vasculopathy, and increased acute phase reactants (APRs). Peripheral vasculopathy referred to imaging-evidenced peripheral vascular stenosis or aneurysm, episodes of organ infarction, and biopsy confirmed vasculitis. Neurological events included cerebrovascular events, peripheral neuropathy, cognitive abnormalities, visual abnormalities, and hearing abnormalities. Organ involvement referred to musculoskeletal disease, cardiovascular disease (hypertension, cardiomyopathy, pulmonary hypertension), intestinal disease (hepatosplenomegaly, gastrointestinal bleeding, portal hypertension, and inflammatory bowel disease), kidney disease (urine abnormalities, nephritis, renal biopsy–confirmed glomerular nephritis), testicular disease, and others. The numbers of involved organs were summed. All the above symptoms were recorded as their original paper reported. APRs included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum TNF-α, IL-6, IL-8, and IL-10. Increased APRs were defined as reported APR levels higher than their normal range or levels that the paper reported as increased. Hematological abnormalities included anemia, leukopenia, thrombocytopenia, and pancytopenia as reported in the paper. Bone marrow hypoplasia was defined as bone marrow failure, pure red cell anemia, Diamond-

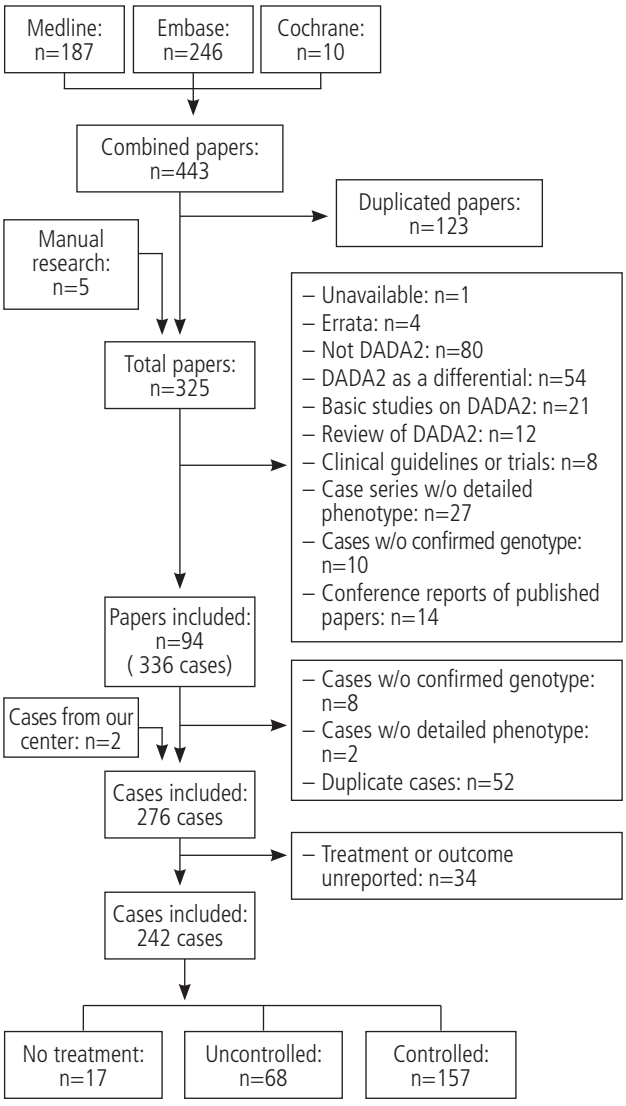

Figure. Flow chart of the literature review process. DADA2 indicates deficiency of adenosine deaminase 2 disease.

Blackfan anemia, and other types of decreased bone marrow proliferation. Immunodeficiency was defined as decreased levels of immunoglobulin and/or B cells. Recurrent infections were defined as documented infections before treatment.

Controlled disease was defined as freedom from symptoms after treatment, whereas uncontrolled disease was defined as sustained active disease during treatment or early relapses during tapering of treatment. Treatment was defined as effective if the disease responded to it and as ineffective if not.

Statistical Analysis

Continuous variables are described as the median (range) and were compared using the Wilcoxon rank sum test. Count variables are reported as whole numbers (frequencies) and were compared using the χ^2 test. Univariate and multivariate logistic regression analyses were performed to evaluate factors associated with well-controlled disease. Data were analyzed using Stata Statistical Software: Release 14 (StataCorp LP), and a 2-sided *P* value of <.05 was considered significant.

Results

Demographic Data

The literature review yielded 274 cases (Supplementary Table E1). Thirty-four cases were excluded because no disease outcomes were reported (Figure). Therefore, together with 2 patients from our center, a total of 242 patients were enrolled in the study (118 [48.8%] males and 124 [51.2%] females). The median age at disease onset was 4 years (range, 0-59 years). Fifty-eight patients (24.0%) reported a history of consanguinity, and 123 (50.8%) reported a positive family history. Seventeen patients had no symptoms or mild symptoms requiring no treatment. Compared with patients requiring active treatment, patients requiring no treatment had a higher age at onset (median 7.5 [range 5-18] years vs 4 [0-59] years; *P*=.047), were more likely to be in the adult group (35.3% vs 5.3%; *P*<.001), and more frequently had a positive family history (94.1% vs 47.6%; *P*<.001). Both groups had a similar frequency of null mutations (23.5% vs 27.6%) and history of consanguinity (29.4% vs 23.5%) (Table 1).

Among the remaining 225 patients receiving active treatment, vasculitic manifestations were the most common symptoms (215/225, 95.6%). Increased APRs were reported in 96 patients (42.7%) as follows: CRP (62/96, 64.6%), ESR (43/96, 44.8%), TNF-α (4/96, 4.2%), IL-6 (5/96, 5.2%), IL-8 (2/96, 2.1%), and IL-10 (4/96, 4.2%). Hematological symptoms were reported in 135 patients (60.0%), including 27 patients with pancytopenia. Among patients with hematological symptoms, 63 recorded bone marrow aspiration, and 49 of these reported bone marrow hypoplasia. Immunodeficiency was reported in 107 patients (47.6%). A total of 53 patients (23.6%) reported recurrent infections before treatment. Pathogens included bacteria, fungi, viruses, and mycobacteria.

Table 1. Characteristics of DADA2 Patients

	Total	Requiring no treatment	Requiring active treatment	*P* Value
No.	242	17	225	
Male, %	118 (48.8)	9 (52.9)	109 (48.4)	.804
Median age at onset (range), y	4 (0-59)	7.5 (5-18)	4 (0-59)	.047
Adult group, %	18 (7.4)	6 (35.3)	12 (5.3)	<.001
Consanguinity, %	58 (24.0)	5 (29.4)	53 (23.5)	.564
Family history, %	123 (50.8)	16 (94.1)	107 (47.6)	<.001
Null mutations, %	66 (27.3%)	4 (23.5%)	62 (27.6%)	1.00
Median ADA2% (range)	1.3% (0%-63%)	1.3% (1%-63%)	1.28% (0%-50%)	.338

The detailed clinical features of these patients are shown in Table 2.

Treatment

Among the 225 patients requiring active treatment, most received more than 1 drug. A total of 131 (57.9%) patients received TNFi, including etanercept in 59.5% (78/131), adalimumab in 22.1% (29/131), and infliximab in 12.2% (16/131); 6.1% (8/131) did not report the type of TNFi. TNFi were effective in 78.6% of patients (103/131). The effectiveness of TNFi was associated with high APRs, the number of vasculitic manifestations, hematological symptoms, and recurrent infections (Table 3).

In the crude logistic analysis, high APRs and the number of vasculitic manifestations were positively associated with the effectiveness of TNFi (OR, 9.07 [95%CI, 2.932-28.08; *P*<.001] and 1.65 [95%CI, 1.216-2.237; *P*=.001], respectively), while hematological involvement and recurrent infections were associated with poor effectiveness of TNFi (OR, 0.35 [95%CI, 0.141-0.864, *P*=.023] and 0.24 [95%CI, 0.098-0.615, *P*=.003], respectively). In the multivariate analysis, high APRs and hematological involvement remained independently associated with the effectiveness of TNFi (OR, 9.62 [95%CI, 2.313-40.0, *P*=.002] and 0.21 [95%CI, 0.070-0.661, *P*=.007]). Furthermore, in patients with bone marrow hypoplasia, the effectiveness of TNFi was 29.4% (5/17).

Table 2. Clinical Characteristics of DADA2 Patients Requiring Treatment

	Total	Uncontrolled	Controlled	*P* Value
No.	225	68	157	
Male, %	109 (48.4)	31 (45.6)	78(49.7)	.573
Median age of onset (range)	4 (0-59)	2.5 (0-59)	4 (0-44)	.177
Consanguinity, %	53 (23.5)	12 (17.6)	41 (26.1)	.169
Family history, %	107 (47.6)	34 (50.0)	73 (46.5)	.629
Null mutations, %	62 (27.6)	22 (32.4)	40 (25.5)	.289
Median ADA2% (range)	1.28% (0-50%)	1.80% (0-17.4%)	0.8% (0-50%)	.063
Vasculitic manifestations, %	215 (95.6)	63 (92.6)	152 (96.8)	.164
No. vasculitic manifestations (range)[b]	4 (0-6)	3 (0-6)	4 (0-6)	.001[a]
Increased APRs, %	96 (42.7)	19 (27.9)	77 (49.0)	.003[a]
Constitutional symptoms, %	128 (56.9)	30 (44.1)	98 (62.4)	.011[a]
Dermatological symptoms, %	170 (75.6)	47 (69.1)	123 (78.3)	.139
Organ inflammation, %	175 (77.8)	52 (76.5)	123 (78.3)	.756
No. organ inflammation (SD)[c]	1 (0-5)	1 (0-3)	1 (0-5)	.048[a]
Neurological involvement, %	138 (61.3)	30 (44.1)	108 (68.8)	<.001[a]
Cerebrovascular events, %	87 (38.8)	15 (22.1)	72 (46.2)	.001[a]
Hematologic abnormalities, %	135 (60)	51 (75.0)	84 (53.5)	.003[a]
Pancytopenia, %	27 (12.0)	14 (21.0)	13 (8.3)	.008[a]
Immunodeficiency, %	107 (47.6)	35 (51.5)	72 (45.9)	.470
Recurrent infections, %	53 (23.6)	25 (36.8)	28 (17.8)	.002[a]
Treatment				
Other	40 (17.8)	25 (35.7)	15 (9.7)	
TNFi-based, %	99 (44.0)	15 (20.6)	85 (54.1)	
Corticosteroid-based, %	37 (16.4)	20 (29.4)	17 (10.8)	
TNFi+corticosteroid, %	25 (11.1)	6 (8.8)	19 (12.1)	
HSCT, %	24 (10.7)	3 (4.4)	21 (13.4)	

Abbreviations: ADA2%, ratio of tested ADA2 level to the lower limit of normal range; APR, acute phase reactants, including C-reactive protein, erythrocyte sedimentation rate, IL-6, IL-8, and IL-10; HSCT, hematopoietic stem cell transplantation; TNFi, tumor necrosis factor α inhibitors.
[a]*P*<.05.
[b]No. vasculitic manifestation is the cumulative number of high APR values, constitutional symptoms, dermatological symptoms, organ inflammation, neurological symptoms, and peripheral vasculopathy.
[c]No. organ inflammation is the cumulative number of cardiopulmonary events, intestinal inflammation, nephritis or urine abnormality, and musculoskeletal conditions.

Table 3. Factors Associated With Good Response to TNF-α Inhibitor Therapy

Factor	Crude				Multivariate analysis[a]		
	Total	Ineffective	Effective	*P* Value	OR	95%CI	*P* Value
Subgroup 1[b]							
Number	131	28	103				
High APRs	66 (50.4%)	4 (14.3%)	62 (60.2%)	<.001	9.62a	2.313-40.00	.002
No. vasculitic manifestations[c]	4 (0-6)	3 (0-6)	4 (1-6)	.005	1.19	0.821-1.736	.352
Hematologic abnormalities	68 (51.9%)	20 (71.4%)	48 (46.6%)	.032	0.21a	0.070-0.661	.007
Recurrent infections	28 (21.4%)	12 (42.9%)	16 (15.5%)	.004	0.98	0.302-3.175	.972
Subgroup 2[d]							
Number	106	22	84				
High APRs	51 (48.1%)	4 (18.2%)	47 (56.0%)	.002	10.39a	2.088-51.74	.004
No. vasculitic manifestations[c]	4 (0-6)	3.5 (0-6)	4 (1-6)	.056	1.10	0.746-1.648	.639
Hematologic abnormalities	50 (47.2%)	15 (68.2%)	35 (41.7%)	.032	0.15a	0.039-0.561	.005
Recurrent infections	21 (19.8%)	7 (16.7%)	14 (31.8%)	.136	2.04	0.479-8.708	.334

Abbreviation: APR, acute phase reactant.
[a] *P*<.05 in multivariate analysis
[b] Subgroup 1: All patients received TNF-α inhibitors.
[c] No. vasculitic manifestations is the cumulative number of the following symptoms: high APR, constitutional symptoms, dermatological symptoms, organ inflammation, neurological symptoms, peripheral vasculitis, or vascular events.
[d] Subgroup 2: To avoid confounding effects from corticosteroids, patients with both TNF-α inhibitors and corticosteroids at the outcome assessment were excluded.

In the subgroup analysis, effectiveness was similar in patients in the different age groups (78.5% vs 80.0%, *P*=.913) and mutation groups (81.4% vs 70.6%, *P*=.227). To avoid the confounding effect of corticosteroids, 25 patients who were taking both corticosteroids and TNFi at the outcome assessment were excluded. TNFi were effective in 79.2% of patients (84/106). In both the crude and the multivariate logistic analyses, after excluding the 25 patients taking both treatments, increased APRs and hematological involvement remained independently associated with the effectiveness of TNFi (OR, 10.39 [95%CI, 2.088-51.74; *P*=.004] and 0.15 [95%CI, 0.038-0.561; *P*=.005], respectively) (Table 3).

Corticosteroids were the most commonly used medicine before the diagnosis of DADA2. A total of 164 patients had received corticosteroids during their disease course. Among these, disease was controlled and therapy successfully tapered in 36 (22.0%) patients. Twenty-six patients (15.9%) were dependent on high corticosteroid doses, and 13 (7.9%) patients experienced a relapse after tapering. Therapy was partially effective in 21 patients (12.8%) and ineffective in 67 (40.9%). Forty-seven patients (28.6%) had to switch to TNFi owing to ineffectiveness of or dependency on corticosteroids.

Traditional immunosuppressive agents and anti-inflammatory agents were reported in few cases, with varying effectiveness (Table 4). Other biologic agents, including tocilizumab, IL-1 antagonists, and rituximab were reported in 10, 11, and 12 patients, respectively, and were effective in 20% (2/10), 9.1% (1/11), and 8.3% (1/12) of patients, respectively. Fresh frozen plasma was used in 12 patients for active ADA2 supplementation; temporary disease control was achieved for 8 months in only 1 case, after which the patient experienced another relapse [15]. Intravenous immunoglobulin (IVIG) was used mostly for immunoglobulin supplementation, and only 1 patient achieved disease control with high-dose IVIG [19]. Twenty-four patients (10.7%) underwent hematopoietic stem cell transplantation (HSCT), which, in 22 cases, was necessary to manage uncontrolled hematological abnormalities. One patient received HSCT owing to recurrent transient ischemic attack and hypoimmunoglobulinemia [20], and another patient received HSCT owing to a refractory cerebrovascular event [21]. Twenty-one patients achieved restoration of immunity and control of systemic inflammation, while 2 patients died after HSCT and 1 continued to have hematologic abnormalities [22].

In addition, 28 (12.6%) patients received aspirin, 9 (4.0%) received anticoagulants, and 6 (2.7%) received both. Nineteen of these 43 patients (44.2%) experienced refractory stroke and 5 (11.6%) had hemorrhagic events after antiplatelet and/or anticoagulation therapy. Of those who received concurrent corticosteroids, 14/16 patients (87.5%) experienced new ischemic events, while in those who received concurrent TNFi, 4/15 (26.7%) experienced new ischemic events. Of the 5 patients who had hemorrhagic events, 3 were receiving concurrent corticosteroids and none concurrent TNFi.

Disease Control

Disease was controlled in 157 of the 255 patients who had received active treatment (69.8%) and uncontrolled in 68 (30.2%) at the time of the report. A total of 21 patients died for the following reasons: infections, 10; intracranial hemorrhage or intestinal perforation, 6; both vascular events and severe infection, 2; refractory hematological manifestations, 1; and complications once the disease had been controlled, 2. Four patients died before diagnosis of DADA2.

Table 4. Treatments Used in DADA2 Patients (Excluding Corticosteroids and TNFi)

Treatment	No. (%)	Effective control with monotherapy, No. (%)	Effective control with corticosteroids and/or TNFi, No. (%)
Cyclophosphamide	49 (21.8)	0	11 (22.4)
Mycophenolate mofetil	28 (12.4)	3 (10.7)	4 (14.3)
Methotrexate	25 (11.1)	2 (8.0)	6 (24.0)
Cyclosporine	13 (5.8)	1 (7.7)	0
Azathioprine	47 (20.9)	5 (10.6)	14 (29.8)
Colchicine	25 (11.1)	3 (12.0)[a]	0
Thalidomide	8 (3.5)	6 (75)	0
Sirolimus	6 (2.7)	1 (16.7)	0
Tocilizumab	10 (4.4)	2 (20.0)	1 (10.0)
IL-1 antagonists	11 (4.9)	1 (9.1)	0
Rituximab	13 (5.8)	1 (7.7)	3 (23.1)
Intravenous immunoglobulin	32 (14.2)[b]	1 (3.1)	0
Fresh frozen plasma	12 (5.3)	1 (8.3%)[c]	0

Abbreviation: TNFi, TNF-a inhibitors.
[a]Only effective in treating cutaneous manifestations.
[b]Seventeen patients received intravenous immunoglobulin because of a low immunoglobulin level.
[c]The patient remained stable with monthly fresh frozen plasma of 10 mL/kg but had constitutional symptoms 8 months later.

Age at onset, ADA2%, and frequency of null mutations were similar for both groups. Patients with controlled disease had significantly more vasculitic manifestations and organ involvement, and more frequent increased APRs, constitutional symptoms, and neurological symptoms, although they less frequently had hematological abnormalities or recurrent infections. Treatment with TNFi or HSCT was reported more often in patients whose disease was controlled (Table 2).

In the crude analysis, the number of patients with vasculitic manifestations, organ inflammation, constitutional symptoms, neurological symptoms, and increased APRs was associated with disease control, whereas hematological manifestations and recurrent infections were associated with uncontrolled disease. Receiving TNFi with or without corticosteroids—but not receiving corticosteroids alone—was more associated with disease control than receiving neither corticosteroids nor TNFi. HSCT also improved the odds of disease control (Table 5).

In the multivariate analysis of the clinical factors and treatment protocols set out above, constitutional symptoms, neurological events, and increased APR remained independently associated with disease control (OR, 7.17 [95%CI, 2.398-21.47, *P*=.007], 4.56 [95%CI 1.587-13.10, *P*=.005], and 5.00 [95%CI, 1.668-15.00, *P*=.004], respectively). The number of vasculitic manifestations and recurrent infections, on the other hand, were independently associated with poor disease control (OR, 0.49 [95%CI, 0.287-0.822, *P*=.007] and 0.35 [95%CI, 0.144-0.869], *P*=.024], respectively). TNFi with concomitant corticosteroids (OR, 8.81 [95%CI, 2.144-36.19], *P*=.003) or without concomitant corticosteroids (OR, 10.1 [95%CI, 3.780-26.98], *P*=.001), and HSCT (OR, 29.2 [95%CI, 6.177-138.0], *P*=.001) were associated with disease control, whereas corticosteroids were not (OR, 0.94 [95%CI, 0.333-2.647], *P*=.904) (Table 5).

Discussion

Since DADA2 is a rare disease with diverse clinical presentations, high mortality, and no suitable treatment, designing an effective therapeutic approach is very challenging. Despite consensus in recent years, the effectiveness of therapy varies, and studies focusing on factors associated with outcome of treatment are scarce. In the present review, we evaluated treatments and outcomes to determine the factors associated with good response to therapy.

Clinical profile can vary with genetic background and age at disease onset [18]. In the present study, although patients requiring no treatment tended to be older at onset, we found that neither age at onset nor genetic background impacted disease outcome in those requiring treatment. Therefore, we investigated other factors that might be associated with clinical outcome.

Among patients receiving active treatment, having recurrent infections and more vasculitic manifestations was associated with uncontrolled disease. This is consistent with the finding that recurrent infections and severe vascular events were the main causes of death. Therefore, recurrent infections and severe vascular manifestations warrant intensive treatment, as they pose a high risk for poor disease outcome. Interestingly, recurrent infections in patients with congenital conditions are multifactorial. Clinical presentations are highly heterogeneous, and management requires multidisciplinary cooperation [23].

Table 5. Multivariate Analysis of Factors Predicting Disease Control

Factor	Crude			Multivariate analysis		
	OR	95%CI	*P* Value	OR	95%CI	*P* Value
No. vasculitic manifestations[a]	1.37	1.143-1.640	.001	0.49[c]	0.287-0.822	.007
Constitutional symptoms	2.10	1.181-3.748	.012	7.17[c]	2.398-21.47	<.001
No. organ inflammation[b]	1.37	1.010-1.860	.043	1.44	0.930-2.222	.103
Neurological involvement	2.79	1.555-5.015	.001	4.56[c]	1.587-13.10	.005
High APRs	2.48	1.342-4.592	.004	5.00[c]	1.668-15.00	.004
Hematologic abnormalities	0.38	0.204-0.722	.003	0.46	0.201-1.058	.068
Recurrent infections	0.37	0.197-0.708	.003	0.35[c]	0.144-0.869	.024
Treatment						
Other	1			1		
TNFi-based	10.12	4.308-23.77	<.001	10.1[c]	3.780-26.98	<.001
Corticosteroid-based	1.42	0.570-3.519	.453	0.94	0.333-2.647	.904
TNFi+corticosteroid	5.28	1.724-16.16	.004	8.81[c]	2.144-36.19	.003
HSCT	11.67	2.969-45.85	<.001	29.2[c]	6.177-138.0	<.001

Abbreviations: APR, acute phase reactant; HSCT, hematopoietic stem cell transplantation; TNFi, TNF-α inhibitors.
[a]No. vasculitic manifestation is the cumulative number of the following symptoms: high APRs, constitutional symptoms, dermatological symptoms, organ inflammation, neurological symptoms, and peripheral vasculopathy.
[b]No. organ inflammation is the cumulative number of the following types of organ involvement: cardiopulmonary events, intestinal inflammation, nephritis or urine abnormality, and musculoskeletal conditions.
[c]*P* value <.05 in the multivariate analysis.

In contrast, increased APR values, constitutional symptoms, and neurological symptoms were independently associated with controlled disease. Increased APR values and constitutional symptoms are signs of systemic inflammation, while neurological symptoms are signs of vasculitis. After evaluating 13 genetically confirmed DADA2 patients along with 53 patients with a clinical suspicion of disease, Rama et al [24] found that fever with neurological symptoms, along with either increased CRP or cutaneous manifestations, was highly predictive of disease (OR, 13.9 [95%CI, 1.86-172.87] and 17.72 [95%CI, 1.53-955.70], respectively). These symptoms would promote early diagnosis and early intervention. Furthermore, Schnappauf et al [25] reported the case of a patient who was asymptomatic but had increased APRs when diagnosed and then experienced an ischemic stroke 10 months later. Therefore, APRs might be used as a guide for treatment, even in asymptomatic patients. Insalaco et al [26] suggested increased interferons as biomarkers of disease activity; however, the APRs in the present study were mainly CRP and/or ESR, which are more readily available at most institutions and widely used in clinical practice.

Various studies recently demonstrated the effectiveness of TNFi in controlling the disease [7,27-29]. These agents have been shown to reduce the Pediatric Vasculitis Activity Score from 20/63 (IQR 13.0-25.8/63) to 2/63 (IQR 0-3.8/63) [30] and the incidence of stroke from 55 per 2077 patient-months to 0 per 733 patient-months [31]. The present review found that TNFi were administered in 78.6% of patients, and the use of TNFi, with or without corticosteroids, is significantly associated with disease control. Thus, factors associated with the effectiveness of TNFi are of clinical importance for forecasting the response to treatment with this agent.

We found that increased APR values were associated with the effectiveness of TNFi, probably owing to the increased production of TNF-α in both peripheral serum and affected tissues [2,7]. Preliminary studies have reported that treatment with TNFi reduced tissue and serum inflammatory mediators, such as IL-1ß, IL-6, and TNF, and improved small vessel endothelial integrity [8]. In contrast, we found that hematological manifestations were associated with decreased effectiveness of TNFi. This finding was consistent with previous observations that TNFi were ineffective in correcting hematological symptoms [22,30], and patients with refractory hematological abnormalities were the main reason for having to resort to HSCT. Ombrello et al [31] reported that anemia had resolved in 4 patients who were given TNFi and that hepatomegaly had resolved in 5. We noticed that TNFi were more likely to fail in patients with bone marrow hypoplasia, whereas those with healthy bone marrow might still respond to TNFi, probably because systemic inflammation could also cause hematologic symptoms without affecting the bone marrow. Thus, we recommend bone marrow aspiration in patients with DADA2 and hematological abnormalities. In patients with healthy bone marrow, TNFi might still be effective, while in those with bone marrow hypoplasia, other treatment should be considered, since even HSCT and TNFi treatment might not be effective.

A recent treatment guideline based on an international Delphi survey suggested TNFi as first-line therapy and potentially for indefinite use [32]. Long-term use of TNFi raises the concern of antidrug antibody, which was reported in 20.8% of patients with rheumatoid arthritis and 27.7% of patients with inflammatory bowel disease during the first 12 months of treatment [33]. On the other hand, Verboom et al [34] reported that 8/9 patients with Behcet disease received adalimumab for up to 5 years without generating antidrug antibodies. Thus, generation of antidrug antibody might be multifactorial. DADA2 is a rare autoinflammatory disease that does not involve antibody generation. Treatment with TNFi was recently implemented in this disease. Therefore, the problem of antidrug antibody would require long-term surveillance. Immunogenicity is more common in patients treated with infliximab (a murine-human chimeric monoclonal antibody) than adalimumab (a fully human monoclonal antibody) and is a major cause of low anti-TNF drug level, infusion reactions, and nonremission outcomes [35,36].

In the present study, corticosteroids were not associated with disease outcome, and their effectiveness was low. However, we found that corticosteroids were effective at high dosages (0.5-2 mg/kg/d). Thus, high-dose corticosteroids might be used for quick disease control during acute flares but could not be used for long-term disease control. The response to thalidomide, previously reported in only 8 cases [7], was good (6/8, 75%), probably due to its anti-TNFi effect, although its adverse effects should be borne in mind. HSCT is the only therapy that can cure the disease, restore serum ADA2 levels, and reconstruct the immune system [20]. However, complications of HSCT, including early infections, graft-versus-host disease, and post-HSCT autoimmune phenomena (reviewed by Kendall et al [3]), have restricted its clinical application. Intriguingly, Carmona-Rivera et al [4] revealed that recombinant ADA2 could ameliorate NETosis, which is one of the main pathophysiological changes in DADA2. Thus, further gene therapy aimed at reconstructing exogenous ADA2 might be promising.

Antiplatelet and/or anticoagulation therapies are frequently used after vascular events. Nevertheless, the present study indicated that they failed to prevent ischemic events, even with concurrent corticosteroids, and posed risks for hemorrhagic events. Given the high risk of both ischemic and hemorrhagic events in DADA2, the use of these agents is not recommended before disease is controlled [32]. The application of antiplatelet and/or anticoagulant agents in patients after disease has been controlled might require further investigation.

This study is subject to a series of limitations. First, DADA2 is a rare disease, which makes large cohort studies and well-designed clinical trials difficult. Data from case reports might be incomplete. A literature review based on previous case reports is highly heterogeneous and therefore subject to systemic bias. Second, the actual treatment of previous real-world cases is complicated. Some patients had received more than 1 regimen, and their regimen changed constantly during disease course, thus hampering the investigation of individual treatment. Finally, we only performed a qualitative analysis and could not construct the survival curve owing to the heterogeneity of the case reports. Nevertheless, the results of this study might still shed some light on the clinical management of the disease and on the underlying mechanisms.

In conclusion, we found that although the clinical profile can vary with genetic background and age at disease onset, neither was involved in disease outcome. Increased APR values were associated with better disease control and effectiveness of TNFi and could be used as a marker for monitoring disease activity. Constitutional symptoms and neurological symptoms could facilitate an early diagnosis and, therefore, early treatment, while recurrent infections and severe vascular events pose risks for uncontrolled disease and mortality. Treatment with TNFi was highly effective in controlling systemic inflammation and vasculitic manifestations, but not hematological abnormalities. Bone marrow aspiration might be useful for guiding the use of TNFi, as patients with bone marrow hypoplasia might not respond to TNFi.

DADA2 is a multisystem disease requiring multidisciplinary management involving more than just treatment with TNFi. Clinical therapeutic strategies are complicated and individualized, depending on the time of diagnosis, complications during treatment, expert experience of the medical center, availability of appropriate treatment, and cost considerations. Future bench and bedside studies might help to resolve outstanding issues in DADA2, including treatment duration, monitoring of TNFi and anti-TNFi antibodies, anticoagulation regimen, and the feasibility of genetic therapies. Multidisciplinary management might be crucial for long-term disease control.

Funding

This work was supported by the Fundamental Research Funds for the Central Universities (Grant No.3332020013), Natural Science Foundation of Beijing (Grant No.7192170), the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) (Grant No. 2017-I2M-3-001), the National Key Research and Development Program of China (Grant No.2016YFC0901500; 2016YFC0901501), Capital Medical Development Research Fund (2018-1-4012), and the Clinical and Translational Medical Research fund of the Chinese Academy of Medical Sciences (No. 2019XK320013).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received May 12, 2021; accepted for publication August 13, 2021.

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