blood®
Letter to *Blood*

TO THE EDITOR:

Abatacept is useful in autoimmune cytopenia with immunopathologic manifestations caused by CTLA-4 defects

C. Dhunputh,[1,2] S. Ducassou,[1,2] H. Fernandes,[2] Capucine Picard,[3,4] Frédéric Rieux-Laucat,[4] J.-F. Viallard,[5] E. Lazaro,[5] O. Hermine,[6] M. Jouvray,[7] I. Machelard,[8] A. Lambilliotte,[9] M. Malphettes,[10] D. Moshous,[11] B. Neven,[11,4] A. Gauthier,[12,13] N. Garnier,[12] T. Leblanc,[14] J. Landman-Parker,[15] G. Leverger,[15] and N. Aladjidi[1,2]

[1]Pediatric Hemato-Immunology Centre d'Investigation Clinique (CIC) 1401, INSERM Plurithématique CIC (CICP), Bordeaux University Hospital, Bordeaux, France; [2]Centre de Référence National des Cytopénies Autoimmunes de l'Enfant (CEREVANCE), Bordeaux University Hospital, Bordeaux, France; [3]Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, Assistance Publique–Hôpitaux de Paris (AP-HP), University of Paris, Paris, France; [4]Laboratory of Immunogenetics of Pediatric Autoimmune Diseases, Institut Imagine, Unite Mixte de Recherche (UMR) 1163, INSERM, Paris, France; [5]Department of Internal Medicine and Infectious Diseases, Bordeaux University Hospital, Bordeaux, France; [6]Hematology Unit, Necker-Enfants Malades University Hospital, AP-HP, Paris, France; [7]Department of Internal Medicine, Hospital of Arras, Arras, France; [8]Department of Internal Medicine, Hospital of Bayonne, Bayonne, France; [9]Department of Pediatric Hematology, Lille University Hospital, Lille, France; [10]Clinical Immunology Department, Saint Louis University Hospital, AP-HP, Paris, France; [11]Pediatric Immuno-Hematology and Rheumatology Department, Necker-Enfants Malades University Hospital, AP-HP, Paris, France; [12]Pediatric Hematology and Oncology Institut, Hospices Civils de Lyon, Lyon, France; [13]Laboratoire Interuniversitaire de Biologie de la Motricité, EA7424, Team Vascular Biology and Red Blood Cell, University Claude Bernard Lyon 1, University of Lyon, Lyon, France; [14]Pediatric Hematology and Immunology Department, Robert Debré University Hospital, AP-HP, Paris, France; and [15]Pediatric Oncology Immunology Hematology Unit, Armand-Trousseau University Hospital, AP-HP, Paris, France

Autoimmune diseases can reveal underlying primary immune deficiencies (PIDs), among which are cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) pathway variants. From 2015, this pathway has become a classical clinical entity combining autoimmune cytopenia (AIC) and various immunopathologic manifestations (IMs).[1,2] The role of CTLA-4 in controlling lymphocyte activation can be disrupted in case of dominant heterozygous *CTLA-4* variants,[3,4] recessive homozygous mutations, or deletions of lipopolysaccharide-responsive beige-like anchor (LRBA)[5,6] or *DEF6* variants.[7] Abatacept, a CTLA-4 fusion protein labeled in rheumatoid arthritis,[8] is a logical targeted option for those patients.

In 2019, a preliminary study of the French OBS'CEREVANCE cohort of children with AIC identified CTLA-4 pathway pathogenic variants in 10 of 80 cases of pediatric-onset Evans syndrome (pES).[9] pES is now recognized as a severe long-lasting disease: numerous IMs appearing with increasing age in 78% of cases; high burden of second-line treatments to control severe bleeding or hemolytic flares or organ-specific IMs; and mortality rate reaching 10%.[10,11] Targeted therapies are urgently warranted to improve the outcome in those patients.

In May 2020, 19 of 1613 children from this national cohort were identified with CTLA-4 defects, and 9 of them were treated with abatacept. We aimed to describe the impact of this treatment on the course of their disease.

This was a national observational study. Of note, patients younger than 18 years of age with AIC are routinely included in real time in the OBS'CEREVANCE cohort, prospectively followed, and screened for an underlying diagnosis of IM and PID.[9,11,12] Written informed consent was obtained from parents and patients. Patients with underlying CTLA-4 pathway pathogenic variants who were treated with abatacept were analyzed in May 2021 with a more than 1-year follow-up for all. End points were the effect on AIC and IM according to standard definitions and the burden of further second-line treatments. Adverse events and their grades were recorded (CTCAE v5.0). Continuous variables were described as the median (range), and categorical variables were described as the number (percentage).

Eight patients with pES and 1 with isolated autoimmune hemolytic anemia (AIHA) were treated with abatacept within the context of *CTLA-4* (n = 5), *LRBA* (n = 3), and *DEF6* (n = 1) variants. The median time from AIC initial diagnosis to molecular identification of the CTLA-4 defect was 6.9 years (range, 0.3-20.1 years). Median time to abatcept introduction was 5.5 months (range, 0.6-19.2 months) after the molecular diagnosis. The median follow-up was 4 years (range, 1.6-5.2 years) after abatacept initiation (Table 1).

At the time of abatacept initiation, the median age was 18.5 years (range, 2.3-26.6 years). Six patients had immune thrombocytopenic purpura (ITP) and AIHA in complete remission (CR), 2 had ITP in partial remission (PR) or no remission (NR; patients 2 and 3), 1 had AIHA in NR (patient 9); and 8 of 9 patients had a median number of 3 active IMs (range, 1-5), mainly pulmonary and gastrointestinal. All patients had long-lasting hypogammaglobulinemia and received antibioprophylaxis and immunoglobulin replacement. All patients had received immunoglobulin or steroids for ITP or AIHA and a median number of 4 (range, 0-8) previous second-line treatments (rituximab, n = 7; splenectomy, n = 3). In 3 patients, hydroxychloroquine was started concomitantly; in 5 patients, ongoing treatment was steroids (n = 3), Rapamune (sirolimus; n = 2), everolimus (n = 1), or romiplostim (n = 1).

Table 1. Patients' characteristics and therapeutic responses

Patient, sex	AIC PID	Age at diagnosis (y)	Age at D1-A (y)	Number of IM	Active AIC and IM at D1-A	Number of second line before A	Previous second lines
1, Male*	pES CTLA-4	5.5	26	4	GLILD +++ Digestive +++ Arthritis ++ LP +	4	RTX ×8, SPX, AZA, Cy
2, Male*	pES CTLA-4	14.1	26.6	1	ITP PR GLILD +++ BD ++	6	CICLO, HCQ, SPX, RTX ×2, ELT, AZA
3, Male*	pES CTLA-4	12.6	19.7	3	ITP NR BD ++ Digestive +++ Arthritis ++	2	RTX ×4, ELT, ROMI
4, Male*	pES CTLA-4	15.2	18.5	4	GLILD ++ Digestive ++ Alopecia + Diabetes	0	—
5, Male	pES CTLA-4	7.1	8.7	3	GLILD ++ Digestive ++ Keratitis+	1	RTX ×2
6, Male†	pES LRBA	2.8	20	2	BD ++ Digestive +++	7	CICLO, AZA, RTX ×4, MMF, INF, ADA, TMS
7, Female*,†	pES LRBA	2.6	14.8	3	GLILD + Digestive + LP +++	7	Cy, RTX, 6MP, SPX, MMF, SRL, EVE
8, Male*,†	pES LRBA	2.2	9.7	5	GLILD, BD ++ Digestive ++ LP ++ Keratitis ++ Tubulopathy +	2	MMF, SRL
9, Female*,†	AIHA DEF6	1.4	2.3	0	AIHA: NR	5	RTX, Cy, AZA, BORTZ, SRL

Initial doses for abatacept were 10 (n = 4) or 20 mg/kg (n = 5). In patients receiving 10 mg/kg, doses were increased to 20 mg/kg because of gastrointestinal flare-up at month 2 (patient 8), progressive AIHA at month 4 (patient 9), progressive lung involvement at month 8 (patient 1), and ITP relapse at month 39 (patient 2). Initially, IV injections were repeated every 2 weeks and then progressively spaced out. However, injections had to be maintained more frequently in 3 patients: ITP flare-up (patient 2) and persistent pulmonary (patient 1) or gastrointestinal disease (patient 7). The median duration of abatacept was 3.2 years (range, 1.1-4.9 years).

Regarding AIC, CR was obtained in patient 2, and sustained PR was obtained in patients 3 and 9. Moreover, no relapse was observed despite cessation or decrease in ongoing treatments in all 6 patients already in CR. Regarding active IMs, significant improvement was seen in 7 of 8 patients, particularly in lung disease. The benefit was enhanced when abatacept was infused every 2 weeks. Abatacept allowed steroid, Rapamune, or everolimus discontinuation (patients 2, 7, 8, and 9) and Rapamune or romiplostim sparing (patients 3 and 9). In patient 6, abatacept was replaced by vedolizumab after 3.1 years because of refractory enteropathy.

No severe adverse effects occurred. Three patients had recurrent mouth ulcers, which were attenuated by a reduction in abatacept dose and/or by increased immunoglobulin replacement therapy.

At the last follow-up, all patients were alive, and 8 patients were on continuous treatment. None of the 9 patients had presented with new ITP or AIHA flare-ups. Patient 9 was a candidate for hematopoietic stem cell transplantation (HSCT) because of initial extreme severity and persistent hemolysis. No patient, excluding patient 6, had been treated with additional immunosuppressive therapy or splenectomy.

AIC in patients with insufficient CTLA-4 often had a severe, chronic, and relapsing course.[13] We have herein reported a national prospective observational analysis of 9 children and

Table 1. (continued)

Ongoing and concomitant (+) treatments at D1-A	Number of doses of A in the first year	Total duration of A (y)	Efficiency on AIC and IM	Treatment sparing	Follow-up from diagnosis (y)	Age at last follow-up (y)
No	24	5.1 +	GLILD + Digestive 0 Arthritis + LP 0	NA	25.7	31.2
CS (0.07 mg/kg/d)	15	4 +	ITP CR GLILD + DDB +	CS STOP m36	16.5	30.6
Romiplostim (7.6 µg/kg/w)	11	1.6 +	ITP PR BD + Digestive 0 Arthritis 0	romiplostim STOP m12	8.7	21.3
No	22	3.6 +	GLILD 0 Digestive 0 Alopecia + Diabetes	NA	6.9	22.1
No	22	2.9 +	GLILD + Digestive 0 Keratitis 0	NA	4.5	11.5
+ HCQ m4 (4 mg/kg/d)	23	3.1 STOP	BD 0 Digestive +++	NA	21.3	24.1
Everolimus (0.06 mg/kg/d) +HCQ m0 (7 mg/kg/d)	14	5.1 +	GLILD + Digestive + LP 0	everolimus STOP m8	17.3	19.9
CS (0.1 mg/kg/2d) Rapamune (0.04 mg/kg/d) +HCQ m0 (4 mg/kg/d)	24	4 +	GLILD, BD 0 Digestive 0 LP 0 Keratitis 0 Tubulopathy +	CS STOP m35 Rapamune STOP m24	11.6	13.8
CS (0.4 mg/kg/d) Rapamune (0.24 mg/kg/d)	17	1.7 +	AIHA PR	CS STOP m14 Rapamune ↓ (0.11 mg/kg/d)	2.6	4

6-MP, 6 mercaptopurine; A, abatacept; ADA, adalimumab; AIC, auto-immune cytopenia; AZA, azathioprine; BD, bronchial dilatation; BORTZ, bortezomib; CICLO, cyclosporine; CR, complete response; CS, corticosteroids; Cy, cyclophosphamide; D1-A, first day of abatacept initiation; ELT, eltrombopag; EVE, everolimus; GLILD, granulomatous lymphoid interstitial lung disease; HCQ, hydroxychloroquine; IM, immunopathological manifestations; INF, infliximab; LP, lymphoproliferation; m, month; MMF, mycophenolate mofetil; Nb, number; NR, non response; PID, primary immune deficiency; PR, partial response; ROMI, romiplostim; RTX, rituximab; SPX, splenectomy; SRL, sirolimus; TMS, temsirolimus; y, years.

*A familial history of AIC or IM was in 7 of 9 patients.

†Parents of patients 6, 7, 8, and 9 were consanguineous.

young adults with refractory AIC and IM despite extensive treatments. The response to abatacept was excellent and so was the long-term benefit-risk ratio with treatment duration up to 4.9 years. A significant sparing of associated immunosuppressive therapies was also noted.

Similar results were reported in a first case report in 2016.[1] In 2020, 22 Turkish children with deficient LRBA received abatacept for a shorter median duration of 12.5 months, and regarding the IMs, the best response was observed in AIC.[14]

In our study, as previously reported in the context of rheumatoid arthritis, drug efficacy appears to be dose dependent, with a better response rate with 1-week or 2-week interval in comparison with 4 weeks. An initial dose of 20 mg/kg per 15 days until complete response of all target organs appears to be well tolerated and facilitates progressive spacing of infusions as proposed in juvenile arthritis.[15] The tolerance was excellent for treatment duration up to 5 years, assuming that optimal prevention of recurrent infections and nonmalignant lymphoproliferation is provided by immunoglobulin replacement and antibioprophylaxis. In the field of pediatric rheumatic diseases, with up to 5 years of follow-up, the long-term safety profile of abatacept is favorable, especially for the risk of malignancies.[16–19] The risk of relapse on abatacept discontinuation is not known. Thus far, HSCT is the only long-term cure for CTLA-4 insufficiency and LRBA deficiency,[20,21] and abatacept before HSCT may improve organ function and lead to superior outcomes.

A multidisciplinary approach is warranted in patients with AIC associated with hypogammaglobulinemia and/or severe multiorgan manifestations. It is essential to perform genetic studies looking for an underlying PID. Our results clearly demonstrate that patients with different CTLA-4 pathway defects, even young children, may benefit from early treatment with off-label new targeted treatment options to avoid heavy nonspecific immunosuppression and the development of severe multiorgan manifestations. National and international collaborative cohorts or registries will allow validation of therapeutic guidelines and standardization of evaluation criteria for the various organ manifestations in those diseases. Two ongoing prospective trials may answer questions raised by our work on the benefit-risk ratio of abatacept and on its specific impact in AIC (clinicaltrials.gov: #NCT03733067; ABACHAI: EudraCT 2019-000972-40).

Acknowledgments

The authors thank all the patients, families, and medical and paramedical teams involved in the CEREVANCE prospective cohort study from 2004 onward.

This work was supported from 2004 by the French Ministry of Health (Rare Disease Plan 2007 and 2017) and the O-CYTO patients' association. The genetic analyses were performed thanks to the financial support of the Institut National de la Santé et de la Recherche Médicale (INSERM) and French government grants from the Agence National de la Recherche (ANR) as part of the "Investment for the Future" program (ANR-10-IAHU-01 and ANR-18-RHUS-0010), the Ligue Contre le Cancer-Comité de Paris, Fondation ARC pour la Recherche sur le CANCER, the Centre de Référence Déficits Immunitaires Héréditaires (CEREDIH), the Agence National de la Recherche (ANR-14-CE14-0026-01 "Lumugene", ANR-18-CE17-0001 "Action"), and the Fondation pour la Recherche Médicale (Equipe FRM EQU202103012670).

Authorship

Contribution: C.D., S.D., H.F., G.L., and N.A. designed the research; C.D., S.D., H.F., and N.A. analyzed data and wrote the paper; and C.P., F.R.-L., J.-F.V., E.L., O.H., M.J., I.M., M.M., A.L., D.M., B.N., A.G., N.G., T.L., and J.L.-P. recruited the patients and performed the research.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: C.P., 0000-0001-8788-5056; F.R-L., 0000-0001-7858-7866; J.-F.V., 0000-0001-7500-9323; N.A., 0000-0003-0231-4460.

Correspondence: Nathalie Aladjidi, Pediatric Hemato-Immunology, CIC 1401, INSERM CICP, Centre de Référence National des Cytopénies Auto-Immunes de l'Enfant CEREVANCE, Hôpital des Enfants, Hôpital Pellegrin, Place Amélie Raba Léon, 33000 Bordeaux, France; e-mail: nathalie.aladjidi@chu-bordeaux.fr.

Footnotes

Submitted 28 July 2021; accepted 1 October 2021; prepublished online on *Blood* First Edition 29 October 2021.

There is a *Blood* Commentary on this article in this issue.

REFERENCES

1. Lo B, Fritz JM, Su HC, Uzel G, Jordan MB, Lenardo MJ. CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency. *Blood*. 2016;128(8):1037-1042.
2. Gámez-Díaz L, Seidel MG. Different apples, same tree: visualizing current biological and clinical insights into CTLA-4 insufficiency and LRBA and DEF6 deficiencies. *Front Pediatr*. 2021;9:662645.
3. Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. *Science*. 2014;345(6204):1623-1627.
4. Schubert D, Bode C, Kenefeck R, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat Med*. 2014;20(12):1410-1416.
5. Moser von Filseck J, Čopič A, Delfosse V, et al. Intracellular transport. Phosphatidylserine transport by ORP/Osh proteins is driven by phosphatidylinositol 4-phosphate. *Science*. 2015;349(6246):432-436.
6. Gámez-Díaz L, August D, Stepensky P, et al. The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency. *J Allergy Clin Immunol*. 2016;137(1):223-230.
7. Serwas NK, Hoeger B, Ardy RC, et al. Human DEF6 deficiency underlies an immunodeficiency syndrome with systemic autoimmunity and aberrant CTLA-4 homeostasis [published correction appears in *Nat Commun*. 2019;10:4555]. *Nat Commun*. 2019;10(1):3106.
8. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med*. 2003;349(20):1907-1915.
9. Hadjadj J, Aladjidi N, Fernandes H, et al; Members of the French Reference Center for Pediatric Autoimmune Cytopenia (CEREVANCE). Pediatric Evans syndrome is associated with a high frequency of potentially damaging variants in immune genes. *Blood*. 2019; 134(1):9-21.
10. Aladjidi N, Fernandes H, Leblanc T, et al. Evans syndrome in children: long-term outcome in a prospective French national observational cohort. *Front Pediatr*. 2015;3:79.
11. Pincez T, Fernandes H, Leblanc T, et al. Long term follow-up of pediatric-onset Evans syndrome: broad immunopathological manifestations and high treatment burden [published online ahead of print 14 January 2021]. *Haematologica*. doi:10.3324/haematol.2020.271106.
12. Aladjidi N, Leverger G, Leblanc T, et al; Centre de Référence National des Cytopénies Auto-immunes de l'Enfant (CEREVANCE). New insights into childhood autoimmune hemolytic anemia: a French national observational study of 265 children. *Haematologica*. 2011;96(5):655-663.
13. Schwab C, Gabrysch A, Olbrich P, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. *J Allergy Clin Immunol*. 2018;142(6):1932-1946.
14. Kiykim A, Ogulur I, Dursun E, et al. Abatacept as a long-term targeted therapy for LRBA deficiency. *J Allergy Clin Immunol Pract*. 2019; 7(8):2790-2800.
15. Hara R, Umebayashi H, Takei S, et al. Intravenous abatacept in Japanese patients with polyarticular-course juvenile idiopathic arthritis: results from a phase III open-label study. *Pediatr Rheumatol Online J*. 2019;17(1):17.
16. Harigai M, Ishiguro N, Inokuma S, et al. Safety and effectiveness of abatacept in Japanese non-elderly and elderly patients with rheumatoid arthritis in an all-cases post-marketing surveillance. *Mod Rheumatol*. 2019;29(5):747-755.
17. Genovese MC, Pacheco-Tena C, Covarrubias A, et al. Long-term safety and efficacy of subcutaneous abatacept in patients with rheumatoid arthritis: 5-year results from a phase IIIb trial. *J Rheumatol*. 2018; 45(8):1085-1092.
18. Ozen G, Pedro S, Schumacher R, Simon TA, Michaud K. Safety of abatacept compared with other biologic and conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: data from an observational study. *Arthritis Res Ther*. 2019;21(1):141.
19. Randell RL, Becker ML. Safety updates in novel therapeutics for pediatric rheumatic disease. *Curr Opin Rheumatol*. 2021;33(5):403-408.

20. Slatter MA, Engelhardt KR, Burroughs LM, et al. Hematopoietic stem cell transplantation for CTLA4 deficiency. *J Allergy Clin Immunol*. 2016; 138(2):615-619.

21. Seidel MG, Böhm K, Dogu F, et al; Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation. Treatment of severe forms of LPS-responsive beige-like anchor protein deficiency with allogeneic hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2018;141(2):770-775.

DOI 10.1182/blood.2021013496