Mr. Shimon Rogoway

CTLA4 Deficiency Treatments & Pregnancy | 10/04/2024

Patient's Summary

A Woman in her 40s was diagnosed with CTLA4 Deficiency several years ago. She is treated with IVIG and lately added treatment with Abatacept. Still occasionally suffers from outbreaks of autoimmune inflammation.

Research Inquiry

1. Are there any other treatments available?
2. She would like to have another child is there an option that could enable that?

Conclusion

Research Inquiry #1

In managing CTLA-4 insufficiency, a personalized approach is essential. The heterogeneity in clinical presentations necessitates an individualized evaluation for each patient. The variable clinical phenotypes and the course of the disease significantly influence treatment decisions. Consequently, without comprehensive information, it is challenging to provide specific and customized recommendations. Key conclusions will vary based on the disease's manifestation, and further investigation may be required to refine the therapeutic strategy. By providing us with a more detailed description and manifestation of the patient's disease, we can better provide specific and patient-oriented information.

- **Evidence on the treatment of CTLA-4 insufficiency is limited, especially for refractory disease under abatacept treatment.**
- **Rituximab is often used as a second-line treatment for autoimmune cytopenias, such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA) when patients are refractory or relapsing after first-line treatments like high-dose steroids and intravenous immunoglobulin (IVIG).**
- **Abatacept, rituximab, mycophenolate, or sirolimus may be added as second-line agents for granulomatous-lymphocytic interstitial lung disease (GLILD) if there is no satisfactory response to first-line corticosteroids.**
- **For neurologic involvement, rituximab or cyclophosphamide are considered second-line strategies, used in combination with first-line high-dose corticosteroids and IVIG if there is no rapid response.**

- **In gastrointestinal involvement, sirolimus or vedolizumab are suggested as alternatives to abatacept, with sirolimus being recommended over anti-TNF-α agents as a second-line treatment.**
- **For severe or systemic skin involvement, agents like abatacept, sirolimus, or cyclosporine may be considered as second-line treatments, with or without systemic corticosteroids, depending on the extent and nature of the skin lesions.**
- **Allogeneic hematopoietic stem cell transplantation (alloHSCT) offers a potential cure for severe, treatment-refractory CTLA-4 insufficiency, with a 72% success rate in one study. However, it carries significant risks, including complications such as graft-versus-host disease and acute respiratory distress syndrome.**

Research Inquiry #2

- **Women with primary immunodeficiencies(as CTLA-4 insufficiency) can achieve successful pregnancies, as reported in the PREPI study- 2 patients with CTLA-4 insufficiency had 3 live births and 1 early fetal loss. However, a history of severe infection before pregnancy may increase the risk of poor outcomes.**
- **Optimal anti-infective prophylaxis during pregnancy and close monitoring by a clinical immunologist are essential measures to improve live birth rates and avoid complications.**
- **Most therapeutic agents for CTLA-4 insufficiency (abatacept, rituximab, sirolimus) carry potential fetal risks and should only be used if the benefits outweigh the risks. IgRT is considered safe during pregnancy.**

Important Note
Neither the services nor the research report constitute medical advice of any kind and are not intended to be a substitute for professional medical advice.

Introduction

inborn errors of immunity- According to the degree of immune dysregulation, IEI can be classified into **Primary Immune Regulatory Disorders (PIRD),** where immune dysregulation dominates the clinical picture, and **Primary Immune Deficiency Disorders (PID)**, where the clinical picture is dominated by immunodeficiency.

Primary immune regulatory disorders (PIRDs) are characterized by a predisposition to lymphoproliferation, autoimmune phenomena, and malignancies while exhibiting a lesser tendency toward recurrent infections.[1]

CTLA-4 insufficiency (also called *CTLA4 haploinsufficiency*, *CTLA4 deficiency* or *CHAI disease*- CTLA4 haploinsufficiency with autoimmune infiltration), is a complex PIRD characterized by a spectrum of immune dysregulation manifestations including autoimmunity, lymphoproliferation, early-onset malignancy, and severe atopy. This disorder arises from heterozygous germline mutations in the CTLA4 gene, leading to reduced expression or dysfunctional CTLA-4 protein. CTLA-4 plays a critical role in downregulating immune responses by outcompeting CD28 for binding to CD80/CD86 on antigen-presenting cells, thus preventing excessive T-cell activation. Since CTLA-4 insufficiency was first described in 2014, over 54

pathogenic variants have been identified.[6]

The incomplete penetrance of CTLA-4 insufficiency results in variable clinical phenotypes, even among individuals with the same genetic variant, making the prediction of disease course challenging.[2]

CTLA-4 insufficiency results in a phenotype similar to **CVID** with immunodeficiency, lymphoproliferation, and autoimmunity (Some studies describe CTLA-4 insufficiency as a Monogenic cause of CVID).[7] [8]

Common variable immunodeficiency disorders (CVID) are prevalent primary immunodeficiencies, affecting 1 in 10,000 to 50,000 individuals. Patients often experience recurrent respiratory infections and immune dysregulation, including autoimmune diseases and lymphoproliferation. While infections can be managed with immunoglobulin replacement therapy, immune dysregulation remains a significant challenge, leading to increased morbidity and mortality.[3]

Research Inquiry #1

Are there any other treatments available?

Meta Medical Findings

1. A 2022 retrospective study,[4] published in the *Journal of Allergy and Clinical Immunology* (IF 14.29; Q1), focused on therapeutic options for CTLA-4 insufficiency.

The trial included 173 carriers of the CTLA4 mutation, who were followed between 2014 and 2020 for a total of 2624 months from diagnosis. The therapeutic options evaluated included abatacept, rituximab, sirolimus, corticosteroids, and immunoglobulin replacement. The effectiveness of these treatments was assessed at an organ-specific level, with the primary study outcome being the characterization of the responsiveness of patients with CTLA-4 insufficiency to specific therapies.

Among the 173 CTLA4 mutation carriers, 123 (71%) had been treated for immune complications. Treatment with abatacept, rituximab, sirolimus, and corticosteroids ameliorated disease severity, especially in cases of cytopenias and lymphocytic organ infiltration of the gut, lungs, and central nervous system. Immunoglobulin replacement was effective in the prevention of infection.

- Abatacept: Used in 10 patients with granulomatous-lymphocytic interstitial lung disease (GLILD), with 5 showing full resolution and 2 showing partial response (70% effectiveness).
- Rituximab: Used in 30 patients with cytopenias, with 25 showing a positive response (83% effectiveness).
- Sirolimus: Used in 8 patients with GLILD, with 5 showing resolution of lesions (62% effectiveness).
- Corticosteroids: Used in 20 patients with inflammatory central nervous system (CNS) lesions, with 13 showing a symptomatic clinical response (65% effectiveness).
- Immunoglobulin replacement therapy (IgRT): Used in 59 patients with recurrent respiratory infections due to hypogammaglobulinemia, with 50 showing an improvement in susceptibility to infections (91% effectiveness).
- Splenectomy: Only 4 out of 16 patients (25%) with cytopenia who underwent splenectomy had a sustained clinical response.
- Stem Cell Transplantation: Cure was achieved with stem cell transplantation in 13 of 18 patients (72%).

Several side effects and adverse events were reported. IgRT led to side effects such as fever or rash in 11% of patients, which were managed with premedication or by switching to subcutaneous administration. Corticosteroids, used for various manifestations, required careful tapering to avoid dependence. While abatacept was effective for some, it worsened the condition in three patients, though specific side effects were not detailed. Adverse effects related to rituximab and sirolimus were not explicitly mentioned in the study. Notably, among the 18 patients who

underwent allogeneic hematopoietic stem cell transplantation, 5 died due to complications such as graft-versus-host disease (GVHD) and acute respiratory distress syndrome (ARDS).

The authors outline treatment strategies for CTLA-4 insufficiency based on the specific organ system involved:

- Hypogammaglobulinemia and Bone Marrow Abnormalities: Treatment for hypogammaglobulinemia includes immunoglobulin replacement therapy (IgRT) following the European consensus protocols, which recommend a dosage of 0.4-0.8 g/kg every 3-4 weeks. In cases of isolated deficiency of IgG1 and IgG2 subclasses, IgRT should be initiated if levels fall below certain thresholds.
  Symptomatic lymphoid infiltrations, particularly in organs like the gut, lung, and brain, are treated with corticosteroids, rituximab, or a combination of both. Asymptomatic cases are usually monitored without immediate treatment.

- Autoimmune Cytopenias: Such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia (AIHA), often have a chronic and relapsing course.
  First-line treatment for ITP includes high-dose steroids and intravenous immunoglobulin (IVIG). For AIHA, a combination of corticosteroids and rituximab is more effective than steroids alone.
  Refractory or relapsing cases may require rituximab. Thrombopoietin receptor agonists (TPO-RAs) are considered as second-line agents for ITP, although their effectiveness varies.
  HSCT may be necessary for severe, uncontrolled cytopenias, with a significant proportion of patients achieving a cure.

- Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD): Treatment starts with corticosteroids, with the dosage adjusted based on symptom severity and lung function.
  If there's no satisfactory response to steroids, **second-line agents like abatacept, rituximab, mycophenolate, or sirolimus may be added.** Abatacept has been shown to be safe and effective in some patients with CVID and GLILD.

- Neurologic Involvement: Treatment optimization includes the use of abatacept or sirolimus to control lymphocyte activation.
  High-dose corticosteroids are the first-line treatment for acute episodes, with IVIG as an additional option if there's no rapid response. **Second-line strategies include rituximab or cyclophosphamide**, continuing the first-line therapy.

- Gastrointestinal involvement: For enteropathy in CTLA4 mutation carriers, the authors suggest following gluten-free or lactose-free diets if sensitive. Otherwise, a stepwise approach: (1) topical corticosteroids (budesonide) or sulfasalazine; (2) systemic corticosteroids; (3) abatacept, anti-TNF-α, or sirolimus; or (4) a combination. Abatacept is recommended first-line. **Sirolimus or vedolizumab are alternatives. Sirolimus is suggested over anti-TNF-α as second line.** HSCT was performed in 9 patients with recalcitrant inflammation, curing 6 but causing 3 deaths.

- Skin Involvement: Skin lesions in CTLA-4 insufficiency require careful management due to the risk of infections. Topical corticosteroids are the first-line treatment, with topical tacrolimus or pimecrolimus as alternatives for facial lesions.
  For more severe or systemic skin involvement, agents like abatacept, sirolimus, or cyclosporine may be considered, with or without systemic

corticosteroids. The choice of treatment depends on the extent and nature of skin lesions.

Study limitations include the retrospective nature of data collection, which made it challenging to distinguish between treatment adverse effects and the natural progression of CTLA-4 insufficiency. Treatment decisions might have been influenced by the lack of a CTLA-4 insufficiency diagnosis at the time. Variability in concomitant steroid regimens and the absence of a study on the interaction between different drug regimens further complicate the comparison of treatment responses. Additionally, the multicenter approach without defined protocols makes it difficult to compare treatment outcomes. Despite these limitations, therapeutic success was observed in most patients, although multiple changes in immunosuppressants were often required due to adverse effects or steroid dependence. In contrast, untreated or inadequately treated patients typically experienced progression of CTLA-4-related symptoms, indicating the progressive nature of the disease.

The authors of the study concluded that systemic immunosuppressants and abatacept may provide partial control but require ongoing administration, while allogeneic hematopoietic stem cell transplantation offers a possible cure for patients with CTLA-4 insufficiency. They also note that splenectomy is not recommended due to the lack of a sustained response.

2. In a 2018 retrospective analysis,[5] published in the Journal of Allergy and Clinical Immunology (IF 14.11, Q1), The authors identified 133 subjects from 54 unrelated families carrying 45 different heterozygous CTLA4 germline mutations.

   The primary outcome was characterizing the penetrance, clinical features, and best treatment options in these CTLA4 mutation carriers. The results showed that 90

mutation carriers were considered affected, suggesting a clinical penetrance of at least 67%. The median age of onset was 11 years, and the mortality rate within affected carriers was 16% (n=15).

The main clinical manifestations included hypogammaglobulinemia (84%), lymphoproliferation (73%), autoimmune cytopenia (62%), respiratory (68%), gastrointestinal (59%), or neurological features (29%). Eight affected carriers developed lymphoma and three developed gastric cancer, with an EBV association found in six of the malignancies.

The study explored several targeted therapies for CTLA-4 insufficiency:

- abatacept or belatacept: 14 affected mutation carriers received this treatment, with eleven responding positively. Improvements were seen in enteropathy (n=6), granulomatous-lymphocytic interstitial lung disease (GLILD) (n=2), lymphadenopathy, platelet counts, and optic neuritis. Treatment was discontinued in six patients due to allogeneic hematopoietic stem cell transplantation (alloHSCT) (n=3), EBV reactivation (n=2), or severe respiratory infections, neutropenia, and agranulocytosis (n=1).

- sirolimus: 13 affected carriers were treated with sirolimus, with a good response in 8. Improvements were seen in pure red cell aplasia, lymphadenopathy, splenomegaly, immunoglobulin consumption, and CMV viral load. Sirolimus was used in combination with other treatments, such as prednisolone, belatacept, rituximab, and steroids, leading to improvement in enteropathy (n=3). Treatment was discontinued in some patients due to ineffectiveness for cytopenia, increased blood pressure, worsening lymphopenia, sepsis, or serious respiratory infections.

- alloHSCT: 12 affected carriers underwent alloHSCT between 10 and 50 years of age, with the main indications being treatment-resistant cytopenia,

enteropathy, and Hodgkin lymphoma. 9 of these patients are alive, with 3 being more than five years post-HSCT and off all medication.

The retrospective nature of this study has some limitations. The involvement of multiple physicians and medical departments worldwide may lead to an incomplete understanding of the clinical phenotype. Moreover, single-time point data collection makes it difficult to determine if symptoms or immunological findings are due to immunosuppressive treatment or the natural course of the disease.

The study did not clearly define first- or second-line treatments, as the choice of therapy appeared to be based on individual patient characteristics and the severity of their condition.

Research Inquiry #2

She would like to have another child is there an option that could enable that?

Meta Medical Findings

- The PREPI study was a retrospective, observational, monocentric study, published in the Journal of Allergy and Clinical Immunology in 2023 (IF 14.290, Q1), conducted at a single medical center in Paris, France.[9]
  The study compared the pregnancy outcomes and characteristics of 93 women with primary immunodeficiencies (PID), including 27 with combined immunodeficiencies, 51 with predominantly antibody deficiencies, and 15 with innate immunodeficiencies. The primary study outcome was the rate of live births, which was 69% overall (154 of 222 pregnancies), with similar rates across the different PID groups. **There were 2 patients with CTLA-4 insufficiency with pregnancy outcomes being 3 live births and 1 early fetal loss**. The results also showed that a history of severe infection before pregnancy was significantly associated with poor pregnancy outcomes (fetal loss, ectopic pregnancy, or medical termination of pregnancy) (adjusted odds ratio 0.28, 95% CI 0.11-0.67, P = .005). Additionally, the study suggested that optimal anti-infective prophylaxis during pregnancy might improve the live birth rate, as pregnancies with optimal prophylaxis had a live birth rate of 82% (60/73) compared to 63% (20/32) in pregnancies with suboptimal prophylaxis.

- A 2018 case series,[10] published in *BMC Pregnancy and Childbirth* (IF 2.587, Q2), reported the outcomes of conception, pregnancy, and management in 9 families with PIDs.
  The study described various strategies used by these families, such as preimplantation genetic diagnosis, chorionic villus sampling, and using donor

eggs, to prevent passing on the disease to their offspring. It also highlighted the importance of close monitoring and management of these patients by a clinical immunologist during pregnancy and postpartum to ensure the best possible care and to avoid potential complications. The authors conclude that pregnancy in PID patients is more complex than in the normal population, and consultation with a clinical geneticist is crucial in order to choose the best available approach for each case.

List of possible therapeutic agents for CTLA-4 insufficiency and their teratogenicity:

- **Abatacept**: Abatacept is categorized as pregnancy category C by the FDA, which means that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks. There is limited data on the use of abatacept in pregnancy, and it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Rituximab:** Rituximab is classified as pregnancy category C by the FDA. There are no adequate and well-controlled studies in pregnant women. However, animal studies have shown reproductive toxicity, including potential teratogenic effects. Rituximab should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. It is recommended to avoid pregnancy for at least 12 months after treatment.
- **Sirolimus**: Sirolimus is classified as pregnancy category C by the FDA. Animal studies have shown teratogenic effects, including embryotoxicity and fetotoxicity. There are no adequate and well-controlled studies in pregnant women. Sirolimus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **Corticosteroids:** The teratogenicity of corticosteroids in humans is unclear. However, they are generally considered safe during pregnancy when indicated, as the potential benefits often outweigh the risks. Prolonged or high-dose corticosteroid use during the first trimester may be associated with a slightly increased risk of oral clefts in the newborn. It is important to use the lowest effective dose for the shortest duration.
- **Immunoglobulin Replacement Therapy (IgRT):** IgRT is generally considered safe during pregnancy. There is no evidence of increased risk of teratogenicity or adverse pregnancy outcomes associated with IgRT.

References:

1. Kolukısa B, Barış S. Primary Immune Regulatory Disorders and Targeted Therapies. Turk J Haematol. 2021 Feb 25;38(1):1-14. doi: 10.4274/tjh.galenos.2021.2020.0724. Epub 2021 Jan 14. PMID: 33442967; PMCID: PMC7927447.
2. Westermann-Clark E, Ballow M, Walter JE. The new quest in CTLA-4 insufficiency: How to immune modulate effectively? J Allergy Clin Immunol. 2022 Feb;149(2):543-546. doi: 10.1016/j.jaci.2021.11.020. Epub 2021 Dec 13. PMID: 34915039.
3. Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VASH, Ho HE, Hurst JR, IJspeert H, Prevaes SMPJ, Robinson A, van Stigt AC, Terheggen-Lagro S, van de Ven AAJM, Warnatz K, van de Wijgert JHHM, van Montfrans J. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. Front Immunol. 2021 Apr 15;12:606099. doi: 10.3389/fimmu.2021.606099. PMID: 33936030; PMCID: PMC8086379.
4. Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VASH, Ho HE, Hurst JR, IJspeert H, Prevaes SMPJ, Robinson A, van Stigt AC, Terheggen-Lagro S, van de Ven AAJM, Warnatz K, van de Wijgert JHHM, van Montfrans J. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. Front Immunol. 2021 Apr 15;12:606099. doi: 10.3389/fimmu.2021.606099. PMID: 33936030; PMCID: PMC8086379.
5. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, Hoshino A, Kobayashi M, Imai K, Takagi M, Dybedal I, Haddock JA, Sansom DM, Lucena JM, Seidl M, Schmitt-Graeff A, Reiser V, Emmerich F, Frede N, Bulashevska A, Salzer U, Schubert D, Hayakawa S, Okada S, Kanariou M, Kucuk ZY, Chapdelaine H, Petruzelkova L, Sumnik Z, Sediva A, Slatter M, Arkwright PD, Cant A, Lorenz HM, Giese T, Lougaris V, Plebani A, Price C, Sullivan KE, Moutschen M, Litzman J, Freiberger T, van de Veerdonk FL, Recher M, Albert MH, Hauck F, Seneviratne S, Pachlopnik Schmid J, Kolios A, Unglik G, Klemann C, Speckmann C, Ehl S, Leichtner A, Blumberg R, Franke A, Snapper S, Zeissig S, Cunningham-Rundles C, Giulino-Roth L, Elemento O, Dückers G, Niehues T, Fronkova E, Kanderová V, Platt CD, Chou J, Chatila TA, Geha R, McDermott E, Bunn S, Kurzai M, Schulz A, Alsina L, Casals F, Deyà-Martinez A, Hambleton S, Kanegane H, Taskén K, Neth O, Grimbacher B. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol. 2018 Dec;142(6):1932-1946. doi: 10.1016/j.jaci.2018.02.055. Epub 2018 May 4. PMID: 29729943; PMCID: PMC6215742.
6. Duke S, Maiarana J, Yousefi P, Burks E, Gerrie S, Setiadi A; BC Children's and St Paul's Hospital Members; Hildebrand KJ, James E, Turvey SE, Markle JG, Biggs CM. Expanding the molecular and phenotypic spectrum of CTLA-4 insufficiency. Pediatr Allergy Immunol. 2024 Feb;35(2):e14077. doi: 10.1111/pai.14077. PMID: 38351878.

7. Sun, Di; Heimall, Jennifer. Disorders of CTLA-4 expression, how they lead to CVID and dysregulated immune responses. Current Opinion in Allergy and Clinical Immunology 19(6):p 578-585, December 2019. | DOI: 10.1097/ACI.0000000000000590
8. Hoshino A, Toyofuku E, Mitsuiki N, et al. Clinical Courses of IKAROS and CTLA4 Deficiencies: A Systematic Literature Review and Retrospective Longitudinal Study. Frontiers in immunology. 2022;12. doi:https://doi.org/10.3389/fimmu.2021.784901
9. Mallart E, Ugo Françoise, Driessen M, et al. Pregnancy in primary immunodeficiency diseases: The PREPI study. ˆThe ‰journal of allergy and clinical immunology/Journal of allergy and clinical immunology/˜The œjournal of allergy and clinical immunology. 2023;152(3):760-770. doi:https://doi.org/10.1016/j.jaci.2023.05.006
10. Sheikhbahaei, S., Sherkat, R., Camacho-Ordonez, N. et al. Pregnancy, child bearing and prevention of giving birth to the affected children in patients with primary immunodeficiency disease; a case-series. BMC Pregnancy Childbirth 18, 299 (2018). https://doi.org/10.1186/s12884-018-1927-6