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Leniolisib and rapamycin in Activated PI3-Kinase-δ-syndrome: a retrospective ESID registry-based analysis

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Leniolisib and rapamycin in Activated PI3-Kinase-δ-syndrome: a retrospective ESID registry-based analysis

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Abstract

Background: Activated PI3K-delta syndrome (APDS) is a rare inborn error of immunity characterized by variable immune dysregulation, recurrent infections, and increased risk of malignancy. Clinical management is challenging. Rapamycin has been widely used off-label to control immune dysregulation, while the selective PI3Kδ inhibitor leniolisib has recently become available as a disease-specific targeted therapy. Real-world data on these treatment approaches remain limited.
Objective: To assess real-world treatment indications, clinical course, immunological changes, and tolerability in patients with APDS treated with rapamycin and leniolisib.
Methods: We performed a retrospective analysis of the ESID-APDS registry including 95 APDS patients treated with rapamycin (81) and/or leniolisib (28) through a Managed Access Program. Clinical manifestations, immunological parameters, and treatment-associated complications were assessed.
Results: Lymphoproliferation was the predominant indication (81% and 52% respectively) for treatment initiation. Overall responses (complete or partial) were observed in 67% of rapamycin- and 64% of leniolisib-treated patients. Across other disease manifestations, responses were documented in 35% and 50% of patients. Leniolisib was initiated for recurrent infections in 3 patients, whereas recurrent infections were not a primary indication for rapamycin. Treatment interruption due to adverse events occurred only in the rapamycin group. Lymphoma cases were observed during follow-up.
Clinical Implication: In this real-world registry cohort, both rapamycin and leniolisib were associated with improvement of lymphoproliferation in APDS. Treatment-limiting adverse events were reported

under rapamycin. Prospective long-term studies are needed to better define the role of these therapies and their long-term impact on disease outcome, including malignancy risk.

Clinical Implication

In a real-world APDS cohort, leniolisib and rapamycin reduced benign lymphoproliferation, with treatment-limiting adverse events reported only under rapamycin.

Capsule summary

In a real-world APDS cohort leniolisib and rapamycin reduced benign lymphoproliferation, which was the main reason to start treatment but not the only clinical manifestation. Treatment-limiting adverse events were reported only under rapamycin.

Key Words

Activated PI3K-delta syndrome; target treatment; PI3Kδ inhibitor; mTOR inhibitor; leniolisib; rapamycin; treatment response; immune dysregulation; infections.

Abbreviations

AID: Activation-induced cytidine deaminase
Akt: Protein kinase B
APDS: Activated phosphoinositide 3-kinase delta syndrome
APDS1: APDS caused by gain-of-function variants in PIK3CD
APDS2: APDS caused by loss-of-function variants in PIK3R1
ATE: Average treatment effect
DLBCL: Diffuse large B-cell lymphoma
ESID: European Society for Immunodeficiencies
EY0: Expected outcome if all patients had been treated with rapamycin
EY1: Expected outcome if all patients had been treated with leniolisib
FOXO1: Forkhead box O1
GOF: Gain-of-function
HSCT: Hematopoietic stem cell transplantation
IEI: Inborn error of immunity
ILD: Interstitial lung disease
IRB: Institutional review board
LOF: Loss-of-function
MAP: Managed Access Program
mTOR: Mammalian target of rapamycin
NA: not available
NLPHD: Nodular lymphocyte-predominant Hodgkin lymphoma
p110δ: Leukocyte-restricted catalytic subunit of PI3Kδ
p85α: Regulatory subunit of the PI3Kδ complex
PI3Kδ: Phosphatidylinositol 3-kinase delta
Tfh: T follicular helper
TMLE: Targeted maximum likelihood estimation

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Introduction

Activated PI3-kinase Delta Syndrome (APDS) is a rare inborn error of immunity (IEI) caused by the hyperactivation of the phosphatidylinositol 3-kinase delta (PI3Kδ) signalling. It results from gain-of-function (GOF) variants affecting the p110δ catalytic subunit (APDS1) or by loss-of-function (LOF) *PIK3R1* splice-site variants affecting the p85α regulatory subunit (APDS2) of the PI3Kδ complex.[1–4] Constitutive activation of PI3Kδ and its downstream pathways, including the Protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway, impairs lymphocyte development, metabolism, maturation, and function.

Immunologically, APDS patients show dysregulated/dysfunctional B and T cells[5] with progressive B-cell lymphopenia, expanded transitional and reduced switched-memory B cells[6], hypogammaglobulinemia, impaired specific antibody-response and elevated or normal IgM. Hyperactive PI3Kδ signalling also drives loss of naïve $CD4^+$ and $CD8^+$ T cells with expansion of terminally differentiated $CD8^+$ and circulating Tfh cells, producing a skewed, prematurely aged T-cell compartment. Functionally, these T cells show senescence and impaired proliferative responses associated with chronic activation, which compromises antiviral immunity and contributes to lymphoproliferation, and defective B-cell help.[7,8] Clinically, APDS patients present with early-onset, recurrent respiratory infections, impaired ability to control chronic viral infections, lymphoproliferation, enteropathy and autoimmunity, mainly cytopenia.[9–12] Chronic lung disease is a common manifestation, including bronchiectasis and small airway disease, often associated with lymphocytic infiltration and asthma-like features.[13] Hepatic involvement including hepatomegaly, elevated transaminases, non-cirrhotic portal hypertension, nodular regenerative hyperplasia, and primary sclerosing cholangitis may influence clinical outcomes, particularly in the hematopoietic stem cell transplantation (HSCT) setting, where liver disease can increase conditioning-related toxicity and affect peri-transplant morbidity and survival.[14–16] Patients also face an increased risk of malignancy, particularly lymphoma, which is one of the leading causes of death. Although the disease penetrance seems to be high,[12] clinical expressivity is highly variable, making treatment decisions difficult and resulting in heterogeneous therapeutic approaches. [17]

To date, allogeneic HSCT remains the only curative treatment. Refractory immune dysregulation and malignancies are the main indications for HSCT. Reversal of the clinical phenotype has been reported in 96% of patients, although mixed chimerism occurred in 17% of cases. Further, mortality after HSCT remains substantial, ranging from 14% to 22% across published cohorts.[16,18,19] Key HSCT-related challenges were reducing pre-transplant comorbidities, as well as the risk of graft failure, instability and poor graft function. In addition, HSCT is not feasible or appropriate for all patients, making it essential to carefully evaluate alternative therapeutic strategies that can either enable eligibility for transplantation or provide effective long-term disease control.

Since the identification of the pathogenic mechanism underlying APDS, the mTOR inhibitor rapamycin has been used as a potential immunomodulator, although it is neither licensed for APDS

nor studied in randomized controlled studies. *In vitro* experiments have demonstrated that rapamycin can partially restore the T cell phenotype by reducing T cell senescence, increasing the proportion of naive T cells, normalizing IL-2-mediated proliferation.[2,20,21] *In vivo*, ESID-APDS registry data from 26 rapamycin-treated patients confirmed a favourable response of lymphoproliferation in 2018. Notably, all patients receiving steroids at treatment initiation discontinued or reduced the steroid dose after starting rapamycin.[11] These findings were consistent with those of previous case series and cohort studies[9,10,20,23] and were further supported by data on 48 patients published in 2023.[12] However, response was limited in a significant proportion of APDS patients, mostly those with cytopenia and enteropathy. Isolated case reports have also shown an improvement in the T cell phenotype, IgG levels and reduction in transitional B cell.[2,20,22]

Recently, strategies directly targeting PI3Kδ signalling upstream of mTOR have been developed. Inhibiting PI3Kδ may not only impact mTOR dependent signalling but also address mTOR-independent effects of hyperactive PI3Kδ-AKT signalling, such as the phosphorylation and inactivation of FOXO1.[24]

Leniolisib is currently the only oral PI3Kδ inhibitor licensed in the USA, UK, Australia, Israel, and more recently in the EU (since July 2026) for treating APDS and the only therapy specifically approved for APDS. Data from the phase 3 randomized, blinded, placebo-controlled and subsequent extension studies (analysing a total of 37 patients over 12 years old and 21 aged 4–11 years) have shown that leniolisib effectively controls immune dysregulation (mainly lymphoproliferation) and improves the immunological phenotype. Reported adverse events were rare and mild and no patient withdrew due to adverse events. One patient with severe comorbidities died.[25–29] To date, no comparison has been conducted between patients managed with rapamycin versus leniolisib. Such an analysis may provide descriptive, hypothesis-generating information on observed outcomes.

Here, we used the ESID-APDS Registry to analyse retrospective, observational, real-world data of APDS patients treated with either rapamycin or leniolisib through the Managed Access Program (MAP). We assessed treatment indications, clinical and immunological evolution, treatment-associated adverse events, and patterns of treatment use to provide a descriptive overview of current real-world experience with these therapies.

Methods

ESID-APDS registry

The European Society for Immunodeficiencies (ESID) is a non-profit association promoting knowledge on IEIs. Its registry is an international, observational registry that collects clinical data on patients.[30] The APDS sub-registry includes patients with genetically confirmed APDS and collects disease-specific clinical and laboratory data. The registry is carried out in accordance with the section 15 of the Code of Conduct of the General Medical Council of Baden-Württemberg, Germany. The protocol was approved by the Ethics Committee of the University of Freiburg, Germany (IRB approval No. ESID registry: 493/14; IRB approval No. APDS registry: 458/15). Patient inclusion requires local ethics committee approval, agreement between the treating centre and ESID, and signed informed consent.

Leniolisib Managed Access Program (MAP)

The MAP provides access to investigational new drugs for patients with serious or immediately life-threatening conditions when no other standard treatment options are available. The leniolisib MAP, is sponsored by Pharming Technologies N.V. and managed by the Clinical Research Organization WEP Clinical. Patients enrolled in ongoing leniolisib trial or receiving commercial Joenja® in the UK were not included. Participation required adherence to local health authority regulations.

Patient selection and data collection

Data were collected from genetically confirmed APDS patients treated with rapamycin or leniolisib for at least 80 days. For patients who received rapamycin before switching to leniolisib outcomes were evaluated separately for each treatment. We collected information prior to treatment, at treatment start and last available follow up. For patients enrolled in clinical trial, data collection was restricted to time periods outside trial participation.

The study was approved by the ESID registry steering committee, APDS-ESID registry Principal Investigators and the participating centres. Written informed consent was obtained in accordance with the Declaration of Helsinki. Data collection closed in August 2025. Data cleaning and plausibility checks involved direct queries to treating physicians.

Assessment of clinical response

The clinical response for each disease manifestation was assessed qualitatively by the treating physician based on routine clinical evaluation and classified according to predefined response categories (details in supplementary). Lymphadenopathy and hepatosplenomegaly were evaluated by recurrence and/or changes in size; cytopenia, enteropathy, and lung disease by recurrence and/or changes in clinical severity; malignancy by recurrence or new appearance/onset during treatment. Outcomes for infections, including upper and lower respiratory and gastrointestinal infections, were assessed according to changes in frequency and/or severity.

Statistical analysis

Data were organized using Microsoft Excel (Microsoft, Redmond, Wash). Data visualization and statistical analysis were performed using GraphPad Prism (San Diego, CA 92108) and R version 4.1.0 (R Foundation, Vienna, Austria). Time and duration variables were compared using the Mann–Whitney U test, with $p < .05$ (*) considered significant. Adjusted association between treatment and clinical and laboratory outcomes were estimated using Targeted Maximum Likelihood Estimation (TMLE), an advanced semiparametric method that provides efficient statistical association analysis. The analysis was possible only for variables with enough data available. Clinical outcomes were dichotomized as favourable (complete or partial remission) versus all other responses and analysed only in patients with the manifestation at treatment start. For laboratory outcomes, the limited sample size did not allow absolute values comparative analyses. Accordingly, measurements were classified as within the normal range, below, or above normal values for age [31–33] and dichotomized as normal (1) versus abnormal (0). We used the TMLE R package (version 4.3.3) for both the outcome (Q) and treatment (g) models. The ensemble included a generalized linear model and the mean-only model. The TMLE algorithm estimated the expected outcome if all patients had been treated with leniolisib (EY1), the expected outcome if all had been treated with rapamycin (EY0), the Average Treatment Effect (ATE) as the difference between these, and the Relative Risk (RR) as the ratio of EY1 to EY0. All analyses were adjusted for the sex, log-transformed age at onset, mutation type, family history, group dimension, log-transformed age at clinical diagnosis, and log-transformed age at treatment initiation. Results were reported with 95% confidence intervals and p-values. Separate analyses were performed for each clinical and laboratory outcome. Clinical and laboratory outcomes were also summarized using heatmaps, categorized by dominant response and color-coded accordingly (details in supplement to Figure 3A-B).

Results

Cohort description and disease burden

A total of 95 APDS patients were enrolled: 81 patients treated with rapamycin and 28 with leniolisib, including 14 who initially started on rapamycin and then switched to leniolisib. Data from 48 of the included patients treated with rapamycin have already been published.[11,12]
Overall, 65 patients (68%) carried heterozygous disease-causing variants in *PIK3CD,* (APDS1) and 30 patients (32%) in *PIK3R1* (APDS2). Genotype distribution was similar between treatment groups and consistent with previous studies [11,12] (Figure 1A-B).
Age at disease onset was consistently early in life whereas clinical and genetic diagnosis and age at treatment start were very variable, without significant differences between treatment groups (Figure 1C, E1A-D).
As expected from the more recent availability of leniolisib, treatment duration was significantly longer for the rapamycin cohort (median duration 28.6 months in the rapamycin vs 15.6 months in the leniolisib group, p=0.0009). Nevertheless, the leniolisib cohort included 16 patients treated for longer than a year (Figure 1C; E1E). At treatment evaluation the median age was 18.6 years (range 1.9-48.9 years) in the rapamycin group and 16.5 years (range 4.6-45.8 years) in the leniolisib group (Figure E1F).
Importantly, disease burden in the prior medical history and at treatment start was comparable between the two cohorts with a similar mean number of manifestations (leniolisib 6.64 [SD 2.26] vs rapamycin 5.78 [2.34]) (Figure 1D, E2, Table E1-2-3). The most frequent symptoms at treatment start were infections and lymphadenopathy (Figure 1D, Table E3).
Most patients showed similar and characteristic immunological alterations, including reduced total and naïve CD4 T cells and switched-memory B cells and increased IgM. (Figure 1E, Table E4). Hence, groups were largely similar with respect to their genetic, clinical and immunological characteristics.

Main target of treatment: chronic benign lymphoproliferation

In both groups, treatment was most often initiated because of symptomatic disease but more patients in the leniolisib group had previously failed other lines of therapy (32% in leniolisib vs 9% in rapamycin group) (Figure 2A). Both treatments were used to improve symptom control prior to planned HSCT. The primary treatment goal was reduction of lymphoproliferation (81% in rapamycin vs. 52% in leniolisib group) in both groups, followed by control of cytopenia (8%) and enteropathy (8%) in the leniolisib group and enteropathy (8%) in the rapamycin group. Rapamycin was started with the main objective of treating chronic lung disease in 5% of patients, whereas leniolisib was used more frequently with this indication (20% of patients). Moreover, three patients started leniolisib primarily to control recurrent infections, whereas no patient started rapamycin to control infections (Figure 2B). In summary, chronic benign lymphoproliferative disease was the main indication to start immunomodulatory treatment.

Response to treatment

Across all disease manifestations, complete or partial responses were documented in 35% of rapamycin-treated and 50% of leniolisib-treated patients (Figure 3A, E3A). Detailed information on patients who switched from rapamycin to leniolisib is reported in Figure E3. In both treatment groups, the highest response rates were observed for lymphadenopathy, lymphoid hyperplasia and splenomegaly (Figure 3A, Table E5,6). Enteropathy (defined as endoscopy-documented inflammatory bowel disease) was more challenging to treat with only 11% vs 14% of rapamycin-treated versus leniolisib-treated patients achieving partial/complete remission (Figure 3A, Table E5,6). New onset or worsening of enteropathy and chronic diarrhoea mainly occurred in the rapamycin group (Figure 3A) but this did not reach statistical significance (Figure 3B, Table E5-7). Recurrent infections improved predominantly in the leniolisib-treated (23/28 patients, 82%) vs

rapamycin-treated group (28/81 patients; 35%; Figure 3A, 3B and Table E5,6). Among the three patients who started leniolisib because of recurrent infections all showed a partial response in terms of frequency and severity over 2.5 -3.5 years of follow-up. Infections was the only clinical outcome that remained significant after targeted maximum likelihood estimation (TMLE) adjustment (ATE 0.299, 95% CI 0.108-0.489). Nevertheless, the number of hospitalizations due to infections or immune dysregulation improved under both treatments (Figure 4A-B). Within the available follow-up, no patient receiving leniolisib required more than one or two hospital admissions per year for either infections or immune dysregulation. These observations should, however, be interpreted cautiously because of the shorter follow-up and smaller cohort size in the leniolisib group, resulting in lower statistical precision and wider confidence intervals.
Overall, the benefit on pulmonary manifestations was modest regardless of treatment. Pulmonary manifestations were numerically more likely to improve under leniolisib than rapamycin (Figure 3A) with higher proportion of partial/complete remission across interstitial lung disease (ILD) (18% vs 7%) small airways disease (18% vs 12%) and asthma (14% vs 6%) while bronchiectasis mostly remained stable in both groups (43% vs 38%; Table E5, 6). However, none of these differences reached statistical significance.
The small number of patients with cytopenia and enteropathy precluded TMLE analyses for these manifestations (Figure 3A, Table E6). Complete response among other manifestations of immune dysregulation were uncommon and included skin rash in one rapamycin-treated patient and lichen nitidus and skin rash in two leniolisib-treated patients.

Given the retrospective, non-randomized study design, unequal follow-up duration, and the relatively small leniolisib cohort, these findings should be interpreted as descriptive and hypothesis-generating rather than evidence of comparative treatment efficacy.

Incidence of malignancy prior to and during treatment

Several patients in both groups had a history of malignancy before treatment initiation (Figure E2, Table E2,3). In the rapamycin group 7 patients (9%) had malignancy prior to treatment: 5 lymphomas, one breast cancer, and one thyroid cancer. Among the lymphoma patients three had relapsed before treatment, one of whom also developed a submandibular gland malignancy, one had Diffuse large B-cell lymphoma (DLBCL) and relapsed with Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHD) and started rapamycin at the time of NLPHD diagnosis. In the leniolisib group, 3 patients (11%) had malignancy prior to treatment, two relapsed with lymphoma and one had a dysgerminoma (Table E2).
While on rapamycin, 8 patients developed a new malignancy 6 lymphomas and 2 bilateral ovarian dysgerminomas/gonadoblastoma) whereas no malignancies were reported during the substantially shorter time of leniolisib treatment (28.6 [range 2.8-135.2] vs 15.6 [range 2.9-65.4] months) (Table E5-6, Figure E1E). No relapses of previously diagnosed malignancies occurred with either drug.

Immunological changes during treatment

Improvements in lymphocyte counts and subset were observed under both treatments. This effect was more pronounced under leniolisib (Figure 3C and D) but not significant in the TMLE analysis, which was also not possible with relevant cell subsets, such as naïve CD4 T cells and transitional B cells because of missing values (Figure 3D and Table E9). In contrast, some patients treated with rapamycin showed a progressive CD4 and B-cell lymphopenia with persistently elevated IgM (Figure 3C, Table E8). Three patients (13%) in the leniolisib group were able to reduce their immunoglobulin replacement therapy in comparison with 2 (5%) rapamycin-treated patients (Table E10).

Both rapamycin and leniolisib are steroid-sparing therapies

Initiation of both treatments allowed reduction or discontinuation of other immunosuppressive therapies, including rituximab and steroids (rapamycin: 14% pre- vs 8% post-treatment; leniolisib: 19% pre-vs 12% post-treatment). This trend was particularly evident among patients previously treated with rapamycin who subsequently switched to leniolisib (Figure 4C). Corticosteroids were discontinued or tapered in 24% of patients in leniolisib and 17% in rapamycin group. Conversely, steroid initiation or dose escalation was less frequent with leniolisib than rapamycin (8% vs 29%), mainly to manage cytopenia, enteropathy and lymphoproliferation (Figure 4D).

Both rapamycin and leniolisib were used as bridge to HSCT

Both drugs were used to improve symptom control prior to planned HSCT. In the rapamycin group, 19 patients received HSCT (24%): 9 due to insufficient disease control and the rest while disease was controlled. At the time of analysis, 7 HSCT were planned, including 4 due to insufficient disease control. In the leniolisib group, 2 patients received HSCT (7%): one was already scheduled before treatment initiation, and one was performed due to insufficient disease control. Furthermore, clinical improvement after leniolisib enabled HSCT planning in additional 2 patients and led to cancellation of a previously planned HSCT in another (Figure 4E).

Treatment-limiting adverse events under rapamycin

In the rapamycin cohort, 52 patients (64%) discontinued treatment: 12% because of adverse events (including arterial hypertension, cytopenia, aphthous stomatitis, gastrointestinal tract disease and abnormal renal/liver function), 17% to receive a HSCT (4 treated as bridge therapy to planned HSCT and 10 due to clinical worsening), 16% to switch to PI3K inhibitor (6 treated within clinical trials with no subsequent follow-up data available and 7 included in leniolisib group and still on treatment), 10% because of inefficacy, and 4% following lymphoma development (Figure 5A). In contrast, no patient in the leniolisib group discontinued treatment because of adverse events, and only 2 patients stopped treatment to proceed to a planned HSCT (Figure 5B). The most common adverse events were aphthous stomatitis (7 patients) and aplasia/cytopenia (3 patients) with rapamycin, and rash (2 patients) and infections (2 patients) with leniolisib (for details see supplement to Figure 5). Temporary interruptions occurred in 35% of rapamycin-treated and 19% of leniolisib-treated patients with comparable interruption duration (Figure 5D,E).

Mortality

8 out of 81 patients in the rapamycin group died, 5 patients after treatment suspension (1 intracranial hematoma in the context of thrombocytopenia, 1 lymphoma, 2 post-HSCT, 1 acute respiratory failure), 1 from sepsis shortly after rapamycin suspension, 2 patients from lymphoma that developed during treatment. No patients in the leniolisib group died.

Discussion

In this retrospective registry-based study we describe real-world treatment patterns and outcomes in patients with APDS receiving rapamycin or leniolisib. By integrating treatment indications, clinical and immunological outcomes, adverse events, and use as long-term therapy or bridge to HSCT, this analysis provides a contemporary overview of targeted treatment in routine clinical practice.

The patient cohort was clinically and immunologically homogeneous and consistent with previously reported data.[9–12] The longer exposure time in the rapamycin cohort reflects historical treatment

availability and limits direct comparison between therapies, particularly for outcomes that accumulate over time such as chronic lung disease or malignancy. The principal indication for treatment initiation was non-malignant lymphoproliferation, and this was also the manifestation with the most consistent clinical improvement under both therapies. Responses of other disease manifestations were considerably more heterogenous. Our analysis highlights that gastrointestinal and lung disease were more difficult to treat than lymphoproliferation. This could be relevant when assessing patients for HSCT and deciding if a treatment approach is needed as bridge to HSCT.
Both treatments enabled reduction or discontinuation of concomitant immunosuppressive therapies. This is clinically relevant because prolonged corticosteroid exposure contributes substantially to treatment-related morbidity.

Lymphoid malignancies are one of the leading causes of death in APDS patients.[9,10,34] Although most patients who developed lymphoma had previously exhibited benign lymphoproliferation, it remains unclear whether, and to what extent, early treatment with these agents may prevent lymphoma. In our cohort, new lymphoma diagnoses were recorded during follow-up in the rapamycin cohort, while no such events were observed during the available follow-up in the leniolisib cohort. Given the unequal duration of follow-up between the treatment groups, these observations should not be interpreted as evidence of a differential effect of treatment on lymphoma risk. Cases of lymphoma during leniolisib therapy have also been reported elsewhere.[35,36] These findings underscore the need for appropriate surveillance and screening, even in patients receiving these treatments. They also highlight the need for continuous critical evaluation of whether HSCT - currently the only curative treatment option - is indicated. Prospectively, emerging approaches such as gene editing could meaningfully expand the therapeutic landscape beyond current pharmacologic and transplant strategies.[37,38]
Immunologically, both treatments improved lymphocyte counts and distribution, however numbers were too low to assess detailed immunological changes. At present, immunological parameters cannot be considered reliable biomarkers for predicting clinical outcomes. The clinical relevance of these changes, including severe infections prevention or development of malignancies must be further explored prospectively in larger cohorts with longer follow-up.

Treatment-limiting adverse events were observed in the rapamycin but not in the leniolisib cohort; interpretation is limited by non-randomised design and differential follow-up. Moreover, the actual rapamycin blood levels were not collected and its worse tolerability in APDS than Autoimmune Lymphoproliferative Syndrome[39] may reflect the higher doses or target levels needed for clinical effect.

Finally, this study has several important limitations inherent to its retrospective registry-based design. Data were collected across multiple centres with heterogeneous clinical practice and follow-up strategies, resulting in non-uniform data collection and subjective physician-assessed outcome measures. Consequently, some outcomes, particularly lymphoproliferation, were assessed qualitatively rather than using standardized quantitative measures. Treatment exposure also differed substantially between cohorts because of the more recent availability of leniolisib through the Managed Access Program. The longer follow-up in the rapamycin cohort may have influenced the ascertainment of time-dependent outcomes, including malignancy and chronic lung disease, thereby limiting direct comparisons between treatments. Although TMLE was used to adjust for measured baseline confounders, residual confounding from unmeasured variables and confounding by indication remain inherent limitations. In addition, some patients received sequential treatment with rapamycin followed by leniolisib, and the potential influence of prior rapamycin exposure on subsequent treatment responses could not be evaluated. Missing data further limited several analyses, particularly for infection outcomes under rapamycin and for detailed immunological parameters and may have introduced additional bias. Finally, the absence of an untreated comparator prevented

assessment of the natural history of APDS and the extent to which treatment modifies disease progression.

In conclusion, this registry study provides a contemporary description of the real-world use of rapamycin and leniolisib in APDS. Both therapies were mostly used to treat benign lymphoproliferation and were associated with improvement of this manifestation, whereas responses of other disease features were more heterogeneous. These findings highlight the importance of defining treatment goals according to the predominant clinical manifestation and provide a framework for future prospective studies. Standardized longitudinal assessments in larger cohorts will be required to better define treatment selection, long-term safety, HSCT timing and indication, and whether earlier targeted intervention can delay or mitigate disease progression and improve long-term disease control.

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Figure Legends

Figure 1:
A) Frequency of the different disease-causing variants in the whole cohort. (Demographic characteristics are resumed in Table E1)
B) Distribution of disease-causing variants in rapamycin (blue) and leniolisib (green) groups.
C) Lexis diagram showing each patient as a horizontal timeline from birth to the last follow-up. Symptom onset is marked by a black dot, clinical diagnosis by an orange square, and genetic diagnosis by a red triangle. rapamycin treatment is shown as a thicker blue line, and leniolisib treatment as a green line; HSCT is indicated by a red cross. A grey background highlights patients who received rapamycin first and were subsequently switched to leniolisib.
D) Symptoms observed at the start of treatment in rapamycin (blue) and leniolisib (green) groups. Other immune-dysregulation (ID) includes rapamycin: 3 thyroiditis, 1 glomerulonephritis, 1 kidney vasculitis, 1 conjunctivitis, 1 celiac disease, 1 autoimmune hepatitis and thyroiditis, 1 LES, 1 skin rash, 1 erythema nodosum; In leniolisib: 1 lichen nitidus, 1 thyroiditis, 1 skin rash. (Statistics in Table E3).
E) Immunological phenotype at the start of treatment in rapamycin (blue) and leniolisib (green) groups.

Figure 2:
A) Main reason to start treatment in rapamycin group (n=79, 2 NA) and leniolisib group (n=28).
B) Main target manifestation in rapamycin group (n=79, 2 NA) and leniolisib group (n=25, 3 NA). Chronic lung disease includes bronchiectasis, interstitial lung disease (ILD) and small airways disease. HSP: Henoch-Schönlein purpura. In leniolisib infections include upper and lower tract infections, cutaneous abscess and BCGitis.

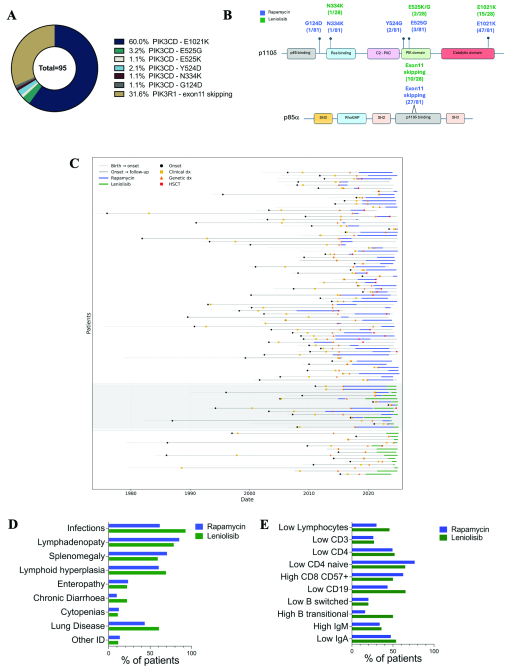
Figure 3:
A) Heatmap summarizing treatment responses for each clinical manifestations (row) across patients (column). Responses are color-coded as indicated. The columns were grouped by dominant response category and then ordered according to residual disease burden. The percentage of patients in each response group out of the total treated with rapamycin or leniolisib is shown in parentheses.
B) Targeted maximum likelihood estimation (TMLE) analysis of binary clinical outcome. For each outcome, TMLE was used to estimate the average treatment effect (ATE), with corresponding 95% confidence intervals.

C) Heatmap summarizing laboratory responses for each lymphocyte subset, IgA or IgM (row), across patients (column). Responses are color-coded as indicated. Columns were ordered using a response-dominance score, defined as the difference between the number of non-normalized and normalized parameters.
D) Targeted maximum likelihood estimation (TMLE) analysis of laboratory values. For each parameter, TMLE was used to estimate the average treatment effect (ATE), with corresponding 95% confidence intervals. IgG level was evaluated irrespective Ig substitution.

Figure 4:
A) Infection-related hospital admission rate per year (n=49 rapamycin and n=28 leniolisib).
B) Immune dysregulation–related hospital admission rate per year (n=45 rapamycin and 26 leniolisib).
C) Therapies received before and after the initiation of rapamycin and leniolisib. Each line represents one patient with treatment combination color-coded as indicated. Other therapies pre-rapamycin (11 patients, 14.0%, 10 NA), other therapies pre-leniolisib (5 patients, 19.2%, 2 NA). Other therapies post-rapamycin (4 patients, 8.2%, 32 patients NA of whom 4 had received other therapies prior to rapamycin), other therapies post-leniolisib (3 patients, 12.0%, 3 NA). See supplementary for the list of other therapies.
D) Rates of corticosteroid discontinuation/tapering and initiation/dose escalation following treatment with rapamycin or leniolisib. Corticosteroids were discontinued/tapered in 17,3% of rapamycin (n=13, 6 NA) and 24% of leniolisib (n=6, 3 NA) treated patients, whereas steroid initiation/dose escalation was required in 29.3% (n=22, 6 NA) and 8.0% (n=2, 3 NA) of patients, respectively. Steroid requirements remained unchanged in 4% (n=3) of rapamycin and in none of the leniolisib treated patients. Therapy duration is not available.
E) Rate of patients with planned and completed HSCT before and after starting rapamycin or leniolisib. During treatment, HSCT was performed in 19 rapamycin (24.1%) and 2 leniolisib (7.1%) treated patients.

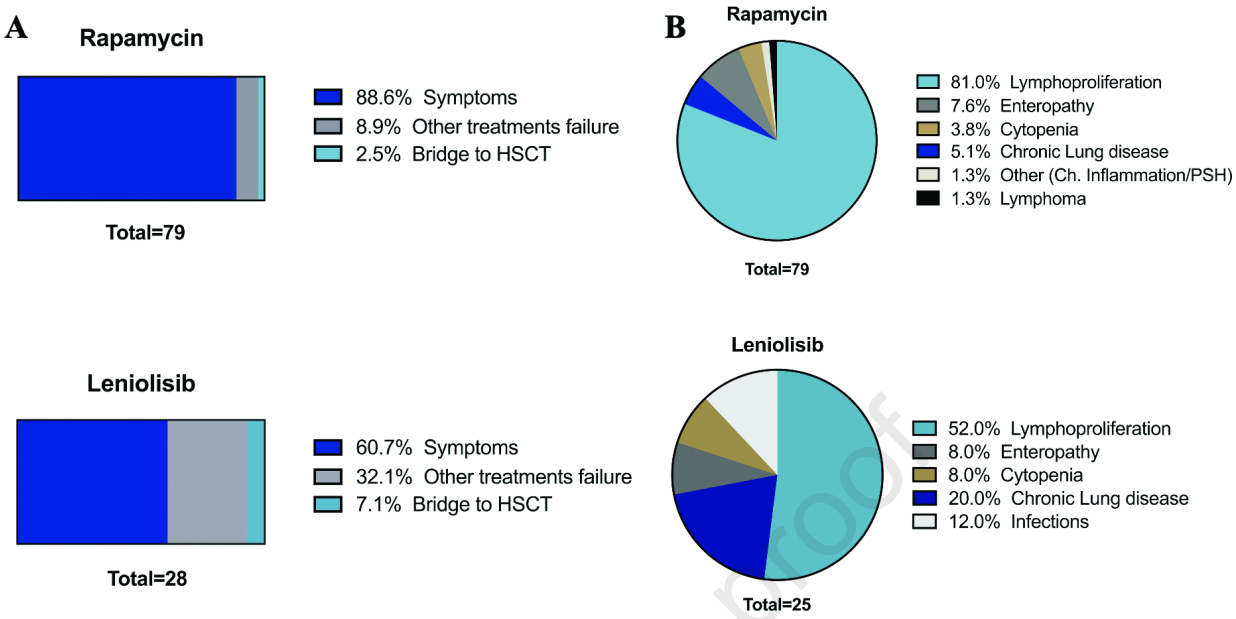
Figure 5:
A) Reasons for rapamycin discontinuation: Adverse events in 10 patients (12.4%; including 1 hypertension, 1 thrombocytopenia, 1 EBV reactivation, 1 increase ALP, 2 aphthous stomatitis, 1 aplasia, 1 osteomyelitis, 1 kidney disease, 1 vomiting and uncontrolled diabetes), HSCT in 14 patients (17.3%; 4 treated as bridge therapy to planned HSCT and 10 due to clinical worsening), switch to PI3K inhibitor in 13 patients (16.1%; 6 treated within clinical trials with no subsequent follow-up data available and 7 remaining on treatment), inefficacy in 8 patients (9.9%; 6 switched to PI3K inhibitors and remain on treatment, 1 underwent planned HSCT and subsequently started a PI3K inhibitor due to graft failure, and 1 patient no follow-up data available), 4 no compliance (4.9%), 3 lymphoma (3.7%), 29 ongoing (35.8%).
B) Reason for leniolisib discontinuation: HSCT in 1 patient (3.6%), 27 ongoing (96.4%).
C) Adverse events developed during rapamycin (33.3%, 26 patients, 3 NA) and leniolisib (32.1%, 9 patients).
D) Temporary therapy suspension in rapamycin (34.6%, 19 patients, 33 NA) and leniolisib (18.5%, 5 patients) groups.
E) Time to treatment suspension in rapamycin group (median 1 months, range 0.23-60.8) and leniolisib group (median 0.5 months, range 0.2 -1) (Mann-Whitney test, p=0,24).

Figure 1. Baseline characteristics and disease burden



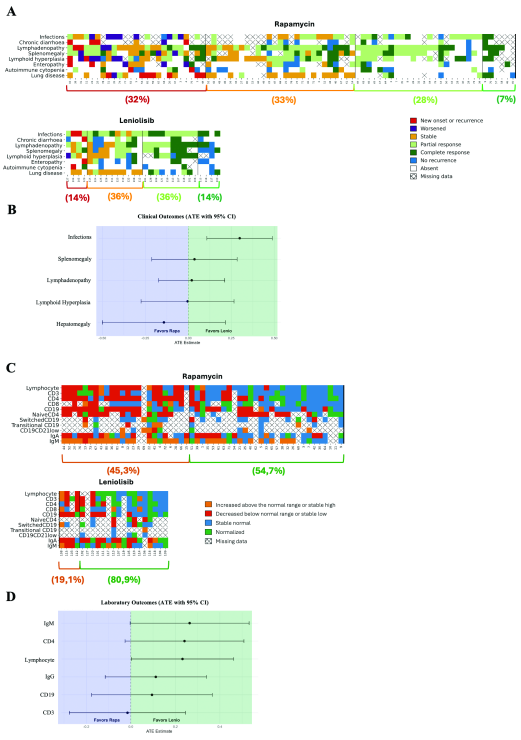
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Figure 2. Treatment initiation was primarily driven by chronic benign lymphoproliferation



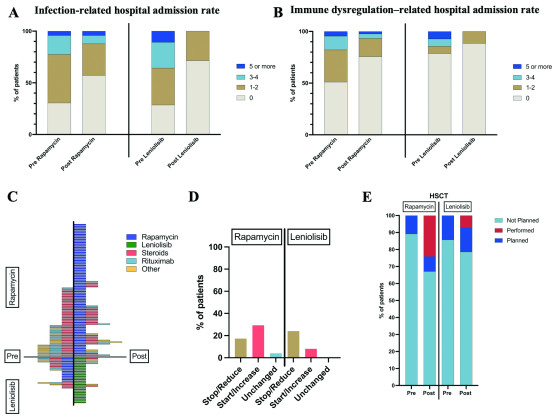
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Figure 3. Treatment outcome



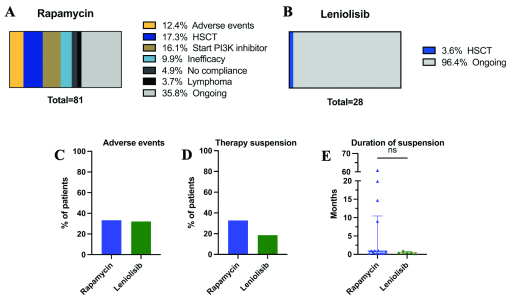
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Figure 4. Treatment response



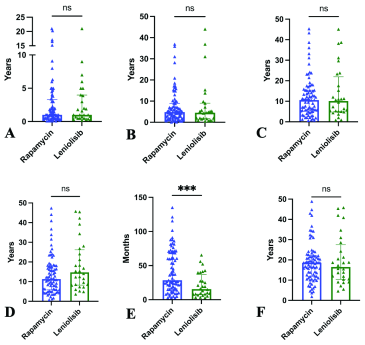
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Figure 5. Treatment discontinuation and side effect frequency across groups



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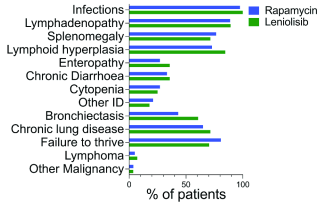
Figure E1: Clinical characteristics were comparable between the two groups, except for therapy duration



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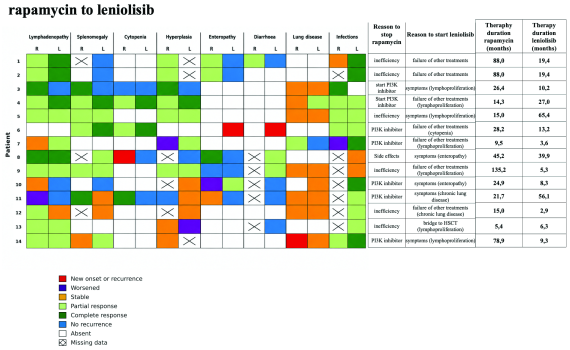
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Figure E2: Symptoms before starting treatment



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Figure E3: Treatment response to Rapamycin and Leniolisib in patients switched from rapamycin to leniolisib



	Reason to stop rapamycin	Reason to start leniolisib	Therapy duration rapamycin (months)	Therapy duration leniolisib (months)
1	inefficiency	failure of other treatments	**88,0**	**19,4**
2	inefficiency	failure of other treatments	**88,0**	**19,4**
3	start PI3K inhibitor	symptoms (lymphoproliferation)	**26,4**	**10,2**
4	Start PI3K inhibitor	failure of other treatments (lymphoproliferation)	**14,3**	**27,0**
5	inefficiency	symptoms (lymphoproliferation)	**15,0**	**65,4**
6	PI3K inhibitor	failure of other treatments (cytopenia)	**28,2**	**13,2**
7	PI3K inhibitor	failure of other treatments (lymphoproliferation)	**9,5**	**3,6**
8	Side effects	symptoms (enteropathy)	**45,2**	**39,9**
9	inefficiency	failure of other treatments (lymphoproliferation)	**155,2**	**5,3**
10	PI3K inhibitor	symptoms (enteropathy)	**24,9**	**8,3**
11	PI3K inhibitor	symptoms (chronic lung disease)	**21,7**	**56,1**
12	inefficiency	failure of other treatments (chronic lung disease)	**15,0**	**2,9**
13	inefficiency	bridge to HSCT (lymphoproliferation)	**5,4**	**6,3**
14	PI3K inhibitor	symptoms (lymphoproliferation)	**78,9**	**9,3**

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