Poster TSP44

Rapid clinical and immunological improvement of persistent lymphoproliferative disease in a patient with activated PI3K delta syndrome (APDS1)

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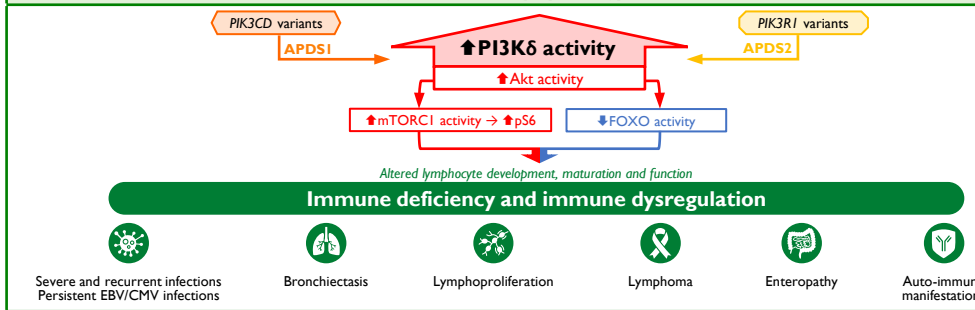
BACKGROUND

- APDS1 is a rare IEI caused by gain-of-function mutations in the *PIK3CD* gene encoding the PI3Kδ catalytic subunit, leading to PI3Kδ hyperactivity (**Fig 1**) [1,2]
  - This affects lymphocyte development, maturation and function, causing immune deficiency and immune dysfunction, which manifests (often from early childhood) as severe/recurrent infections, persistent EBV/CMV infection, and autoimmune and lymphoproliferation manifestations, with an increased risk of lymphoma over time
- The immunological profile of APDS is characterised by hypogammaglobulinemia with increased IgM, poor response to polysaccharide antigens, and accumulation of transitional B cells and senescent T/NK cells[1–3]
- Recently, clinical trials have demonstrated the efficacy of specific PI3Kδ inhibitors to treat APDS[4,5]
- Non-standardised, functional tests, assessing the activation status (phosphorylation) of proteins downstream of PI3Kδ (pAKT, pS6), can be utilised for APDS diagnosis as well as for therapy monitoring[6]

Figure 1: Pathophysiology of APDS[1,2]



CASE REPORT

- Here, we present a male patient with APDS1 and a history of lymphoma, treated with leniolisib, an investigational specific PI3Kδ inhibitor
- The patient history prior to starting leniolisib is summarised in **Fig 2.**[3] At 26 years old, lacking a compatible donor for HSCT, the patient started therapy with leniolisib 70 mg bid, through an early access programme
- At 12 months follow-up, he showed a clinical improvement with a reduction in chronic fatigue, infectious episodes and clinically assessable lymphadenopathies – abdominal CT images, taken immediately prior to and after 6 months of therapy, are shown in **Fig 3**
- Over the 12 months of follow-up, laboratory tests showed:
  - An increase in total lymphocytes and a decrease in IgM (**Fig 4**)
  - A decrease in CD38^{++}IgM^{++} transitional B cells with an increase in mature CD21^{+}CD24^{+} B cells (**Fig 5**)
  - A progressive decrease in phosphorylation of S6 (pS6), more evident in B-cell subsets **(Fig 5).** At 8 months, he exhibited a temporary rise in pS6 levels during an episode of urticaria
  - No significant improvements in T-cell phenotype **(Fig 6)**
  - A decrease in EBV viral replication from 31,570 to 17,101 copies/ml **(Fig 7)**

SUMMARY

- **Leniolisib proved to be well-tolerated and effective in a patient with APDS1**
- **Future follow-up will allow assessment of the long-term effectiveness of this treatment, including immunological parameters, and will enable the standardisation of markers (such as pS6) for diagnosis and follow-up**

Figure 2: Patient history prior to leniolisib treatment[3]

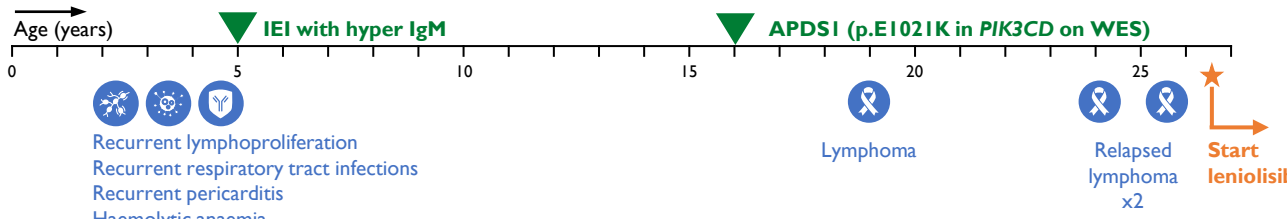


Figure 3: CT imaging of retroperitonal/visceral lymph nodes (A, B) and spleen (C–F) prior to, and during leniolisib treatment

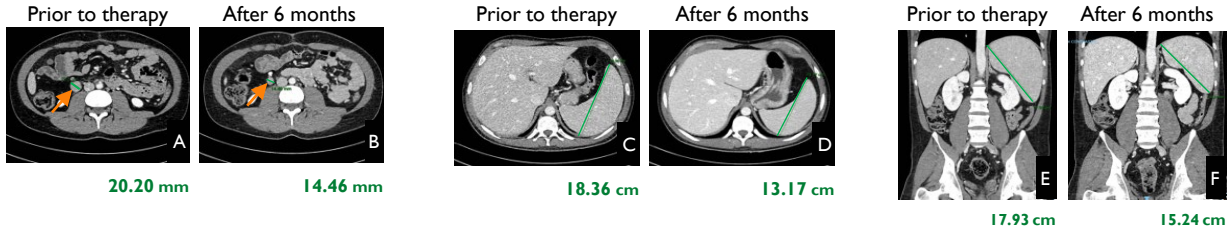


Figure 4: Lymphocyte counts and immunoglobulin levels during leniolisib treatment

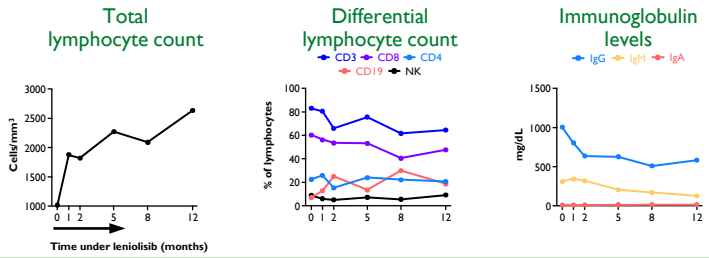


Figure 5: B cell phenotype during leniolisib treatment

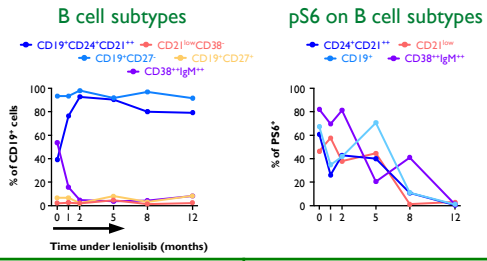


Figure 6: T cell phenotype during leniolisib treatment

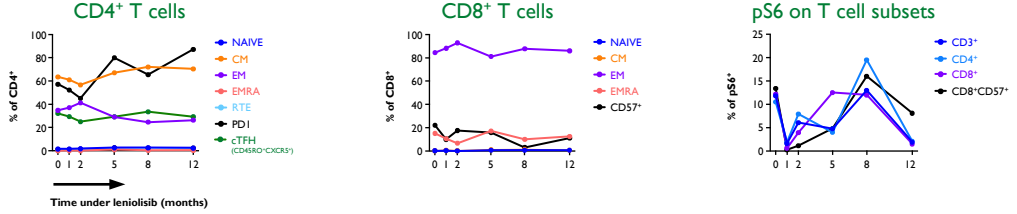
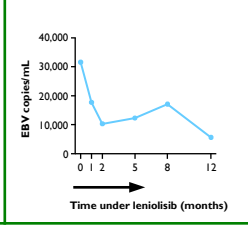


Figure 7: EBV titers



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ABBREVIATIONS

APDS, activated phosphoinositide 3-kinase delta syndrome; **CD**, cluster of differentiation; **CM**, central memory; **CMV**, cytomegalovirus; **cTFH**, circulation T-follicular helper cells; **CXCR5**, CXC motif chemokine receptor 5; **EBV**, Epstein Barr virus; **EM**, effector memory; **EMRA**, effector memory re-expressing CD45RA; **HSCT**, haemopoietic stem cell transplantation; **IEI**, inborn error of immunity; **Ig**, immunoglobulin; **mTORC1**, mammalian target of rapamycin complex 1; **NK**, natural killer; **pAKT,** phosphorylated AKT/protein kinase B; **PI3Kδ**, phosphoinositide 3-kinase delta; **pS6**, phosphorylated S6 ribosomal protein; **RTE**, recent thymic emigrants; **WES**, whole exome sequencing

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