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Infection risk of Mycophenolate Mofetil and Sirolimus treatments in patients with Autoimmune Cytopenias and Primary Immuno-Regulatory Disorders.

Coordinatore: *Prof. Pasquale Striano*

Tutor: *Dr. Carlo Dufour*

Co-tutor: *Dr. Maurizio Miano*

Dottorando:

Dr. ssa Daniela Guardo

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Index

Abstract

Introduction. Autoimmune cytopenias are a group of disorders characterized by immune-mediated destruction of blood cells. In children they are often secondary to immune dysregulation which may require long-lasting immunosuppression. Mycophenolate mofetil and sirolimus represent two well tolerated options to treat these disorders, often used for steroid-dependent patients. However, no data are available on the infection risk for patients undergoing long-lasting treatments.

Patients and Methods. A retrospective data review of patients suffering from Primary Immuno-Regulatory Disorders, mainly ALPS/ALPS-like syndromes, and immune thrombocytopenia treated with Mycophenolate and Sirolimus at Haematology Unit of G. Gaslini Children's Hospital and Pediatric Hematology and Oncology Unit of the Policlinico of Catania have been performed on patients' clinical charts. Moreover, an exhaustive search was performed on the main scientific libraries including PubMed, Embase, Google Scholar and Cochrane.

Results. From January 2015 to May 2023, 13 out of 112 patients (11%) undergoing treatment with mycophenolate mofetil or sirolimus developed severe infections requiring hospitalization. No patients died. Infections involved 11 out of 69 (15%) and 2 of 91 (2%) patients treated with sirolimus and mycophenolate, respectively. The infection rate under sirolimus therapy was significantly higher in patients with ALPS-like syndromes (9, 13%) than in patients with ALPS and immune thrombocytopenia (2, 2%) (p=0.007); moreover, infection rate was higher in

patients who sequentially received both therapies (8, 61%) (p=0.03) and was significantly correlated with therapy duration (p=0.04). Infectious events free survival was 98%, over 12 months, 95% over 36 months, 93% over 60 months and 90% over 72 months.

Discussion To the best of our knowledge, this is the first study describing the infectious risk related to mycophenolate and sirolimus treatments in patients with autoimmune cytopenias and immune-dysregulation. It highlights that the infections rate is rather low and mainly related to the underlying condition.

Conclusions Mycophenolate and sirolimus represent a safe immunosuppressive therapy in autoimmune cytopenias and syndrome with immune dysregulation.

Introduction

Autoimmune cytopenias (AICs) represent a group of heterogeneous disorders defined by the presence of immune-mediated destruction of one or more hematopoietic lineage cells, which include immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), autoimmune neutropenia (AIN), and Evans syndrome (ES).

AICs can be idiopathic or secondary to other underlying diseases (autoimmune diseases, immunodeficiency, tumors, medications, or infections). In children, Primary Immuno-Regulatory Disorders (PIRDs) represent frequent underlying conditions who require immunosuppressive treatment in most cases: corticosteroids are used as first-line therapy. However, some patients do not respond or become steroid-dependent with severe side effects such as endocrine dysfunctions, osteoporosis, and avascular necrosis. Therefore, other long-term therapies are often required to control the disease without the risk of side effects. Mycophenolate mofetil (MMF) and sirolimus (SR) represent two efficient drugs, which are more manageable, safe and well-tolerated (Miano et al., 2015).

Immune thrombocytopenia purpura (ITP) is the most frequent AIC in children characterized by the destruction of platelets by autoantibodies: it is defined as a platelet count less than 100.000/mmq in the absence of any underlying etiology. Clinically, patients with ITP present with a new onset of petechiae, purpura and mucosal bleeding (epistaxis, gengivorrhagia, menorrhagia) at the time of diagnosis. In rare cases, life-threatening bleeding can occur such as

gastrointestinal and cerebral hemorrhages (Kochhar & Neunert, 2021a). According to the American Society of Hematology (ASH) guidelines, clinical manifestations of ITP are classified in minor, mild moderate and severe: in grade 1 probands develop minor bleeding, few petechiae (<100) and/or <5 small bruises (<3 cm in diameter), no mucosal bleeding, in grade 2, instead, they have mild bleeding, many petechiae (>100 total) and/or >5 large bruises (>3 cm in diameter), no mucosal bleeding. Grade 3 is described as moderate bleeding, overt mucosal bleeding, troublesome lifestyle and grade 4 as severe bleeding, mucosal bleeding leading to decrease in Hb > 2 g/dL or suspected internal hemorrhage (Provan et al., 2019). The evaluation of suspected ITP patient consists of a complete history, physical examination, full blood count, peripheral blood smear; moreover, a direct antiglobulin test (DAT) and baseline immunoglobulin levels are recommended to exclude coexistent autoimmune hemolytic anemia and immunodeficiency, especially prior to therapy. A bone marrow aspiration or biopsy is not recommended as initial evaluation of ITP and prior to treatment, expect for those patients in which abnormal or potentially malignant cells are visualized on peripheral smear, abnormalities of the hemoglobin and/or white cell count (except for microcytic anemia) are described in blood count or if there is hepatosplenomegaly and/or adenopathy. The indication for bone marrow aspiration prior to steroid therapy is still controversial (Russo et al, 2023). In patients with persistent ITP and no response to therapy or spontaneous platelet increase, a bone marrow aspiration should be performed. Additional investigations include molecular genetics, autoantibody screening (antiphospholipid antibody, ANA, anti-cardiolipin antibody and lupus anticoagulant), serology for chronic infections (hepatitis,

cytomegalovirus, HIV, and/or H pylori), liver-spleen imaging, and other laboratory testing (genetic screening for inherited thrombocytopenia and bone marrow failure syndromes) (Provan et al., 2019). Generally, ITP resolves spontaneously. However, in some cases the disease persists (3–12 months) or becomes chronic (>12 months) (Rodeghiero et al., 2009). Steroids and/or intravenous immunoglobulin (IVIG) are first-line treatments, according to recent guidelines (Neunert et al., 2019; Russo et al., 2023). An incipient problem remains steroid-dependence patients, experiencing severe steroid-related side effects and no-responder patients. Although there are many available options (rituximab, splenectomy, thrombopoietin receptor agonists) for children with chronic/resistant ITP, the choice of the second-line treatment is not well established due to the lack of evidence-based studies. Immunosuppressors such as MMF and SR represent an effective choice for their safety (Miano et al., 2016): according to AIEOP (Italian Association of Pediatric Oncology and Hematology) guidelines, MMF or Eltrombopag (thrombopoietin receptor agonist) represent the suggested second-line therapy. Sirolimus is the third line treatment in those patients in which MMF or Eltrombopag fail (Ramenghi et al., 2017).

Autoimmune hemolytic anemia (AIHA) is a rare disease in children, in which red blood cells (RBC) are destroyed by immunomodulated mechanism. In most cases (60-70%) auto-reactive immunoglobulins G (IgG) destroy RBC, binding surface antigens through extra-vascular hemolysis; in few cases (20-30%), cascade complements are activated by immunoglobulins M (IgM) through an intra-vascular hemolysis. Sometimes, both mechanisms coexist (Miano et al., 2013). It can be idiopathic or secondary to infections, immunologic disease or malignancies.

Clinically, the onset is acute with anemia, pallor, jaundice, tachycardia with increased hemolysis signs (increased reticulocytes, lactate dehydrogenase, bilirubin and potassium) and positive DAT test: symptoms may be life-threatening, so rapid treatment is mandatory (Miano, 2016). According to AIEOP guidelines, first-line therapy is prednisone until remission of symptoms is achieved (Ladogana et al. 2017): if complete response or steroid-dependance are not achieved, it is necessary a second line therapy with Rituximab or a third line therapy with steroid-sparing agents, such as MMF and SR (Ladogana et al., 2018).

Evans Syndrome (ES) is a rare disorder traditionally defined as immune-mediated destruction of red blood cells and platelets but can also be described as involving at least two blood cell lineages. In 70% of cases, ES is secondary to autoimmune disease, ALPS and immunodeficiencies; in 30% of cases, it is idiopathic. Steroids represent first-line treatment, although no clinical trial validated their use; few data describe second and/or third line of therapy, so it was postulated a possible use of immunosuppressive drugs such as MMF and SR as steroid-sparing drugs or for relapsing/resistant disease (Miano, 2016). According to AIEOP recommendations, therapy is similar to AIHA treatment: steroids are the first-line therapy, but the association with IVIG can be useful if ITP occurs. Rituximab represents second-line treatment, but in ES secondary to ALPS, MMF and SR should be used to reduce immune dysregulation as long-term therapy (Ladogana et al., 2018). Recent reports have shown that ES is often a manifestation of an underlying Inborn Errors of immunity (IEI) that can benefit from specific treatments. Therefore, a molecular evaluation should be offered to all patients. (Miano, Guardo et al., 2022).

According to the European Society for Immunodeficiencies (ESID), PIRDs represent a large group of disease that can be divided into four categories: hemophagocytic lymphohistiocytosis (HLH), susceptibility to EBV, syndromes with autoimmunity and immune dysregulation with colitis. PIRDs with AICs are ALPS and ALPS-like syndrome (López-Nevado et al., 2021).

Autoimmune lymphoproliferative syndrome (ALPS) is a rare disorder of immune dysregulation characterized by lymphocytic dysfunctional apoptosis leading to chronic benign lymphoproliferation with hepato-splenomegaly and lymphadenopathy, autoimmune manifestations, such as autoimmune cytopenias, and an increased risk for lymphoma (Lambert, 2021). The etiology is to attribute to inheritable mutations of the FAS gene, leading to defective FAS-mediated apoptosis, or to mutations in other genes like FASLG and CASP10. These mutations cause dysregulation of FAS-mediated lymphocyte apoptosis, leading to defective activation-induced cell death (Bleesing et al., 2002). Physiologically, apoptosis of activated T cells is a defense mechanism for exaggerated immune responses and lymphoproliferation: mutations in FAS, FASL and CASP10 increase activation of T-cells with reduction of apoptosis leading to lymphoproliferation and organic lymphocytic infiltration (hepato-splenomegaly and adenomegaly) (Lambert, 2021). Although absolute numbers of lymphocytes are increased in most patients with ALPS, the pronounced lymphoproliferation has mainly been attributed to the pathognomonic accumulation of TCRαβ CD4-/CD8- double negative T (DNT) cells (Rensing-Ehl et al., 2016). Diagnostic criteria were suggested by National Institute of Health (NIH) in 2009 (see Table 1): 2 required criteria consist of chronic (>6 months) lymphadenopathy or splenomegaly (or both) and elevated CD3+TCRαβ+

CD4-/CD8- (DNT) cells >1.5% of total lymphocytes oR >2.5% of CD3+ lymphocytes (with normal or elevated lymphocyte count). Primary accessory criteria include defective lymphocyte apoptosis and somatic or germline mutation in FAS, FASLG, or CASP10 and secondary accessory criteria consist of AICs and elevated IgG levels (polyclonal hypergammaglobulinemia), elevated plasma sFASL (>200 pg/mL), IL-10 (>20 pg/mL), vitamin B12 (>1500 ng/mL), IL-18 (>500 pg/mL), family history of non-malignant/non-infectious lymphoproliferation with or without autoimmunity, typical immunohistology findings as reviewed by an expert hematopathologist. It is defined definitive ALPS when required criteria and one of the primary accessory criteria are fulfilled, instead probable ALPS is established when secondary criteria are met (Oliveira et al., 2010). The therapy of ALPS is challenging: corticosteroid is the first-line therapy, even if it is associated to related long-term side effects. Immunosuppression therapy with MMF and SR has a central role in treatment of ALPS, especially the latter, because it provides stabilization of cytopenias, improves lymphadenopathy and splenomegaly and decreases elevated biomarkers (Lambert, 2021).

A number of patients with AIC may fulfil some, but not all criteria required for the diagnosis of ALPS and are often defined as having ALPS-like syndromes (Miano et al., 2015). ALPS-like syndromes are defined as diseases with AIC plus at least one absolute or primary additional criterion for ALPS (Miano et al., 2015). To date, few genes have been related with ALPS-like syndrome in the literature: phenocopies of PID (NRAS and KRAS), susceptibility to EBV (MAGT1, PRKCD), regulatory T-cells defects (CTLA4, LRBA, STAT3 GOF), combined immunodeficiencies (ITK, STK4), defects in intrinsic and innate immunity and predisposition to infection (STAT1

GOF, IL12RB1) and autoimmunity/autoinflammation (ADA2, TET2). Clinically, common findings in ALPS-like are autoimmunity, lymphoproliferation and predisposition to infection: the last one is the main clinical feature that differentiates ALPS-like from ALPS. In ALPS-like not only AICs are common, but also other autoimmune manifestations are described such as autoimmune thyroiditis in PIK3R1 or STAT1 GOF patients, autoimmune polyarthritis in STK4 patients, autoimmune enteropathy in XIAP, STAT3 GOF, CTLA4, LRBA and IL2RB patients or autoimmune hepatitis in STAT1 GOF or LRBA patients. The diagnosis of ALPS-like is challenging because there is no specific exam and clinical and biochemical features (AICs, DNT and other findings of ALPS) can direct to diagnosis. Treatment, generally, is similar to ALPS, especially in patients without a conclusive genetic exam; in patients with specific mutation can benefit from target therapy (López-Nevado et al., 2021).

The characterization of autoimmune cytopenias as idiopathic or secondary to ALPS or ALPS-like syndrome, has treatment implications: secondary AICs, especially ALPS and ALPS-like syndrome, more likely benefit from MMF and rapamycin (Rao & Oliveira, 2011; Bride et al., 2016; Palmisani et al., 2018) or may deserve targeted treatments.

Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase in purine synthesis that targets B, T and NK cells. It has been shown to be effective in autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia in some retrospective studies on adult patients that occasionally included children with response rate ranged between 62% and 82%

(Howard et al., 2002; Hou et al. 2003; Zhang et al. 2005; Provan et al., 2006). Other studies reported efficacy in children with ALPS-associated cytopenia (Rao et al., 2005). In a study of primary and secondary autoimmune cytopenias, MMF was safe and effective, mainly as a second line treatment, in all 11 patients with Evans syndrome (ES) associated with an underlying diagnosis of ALPS (n = 9) or ALPS-like disorder (n = 2), defined as the presence of at least one absolute or primary additional diagnostic criterion for ALPS, suggesting a potential role in patients with ALPS, ALPS-like syndrome and AC (Miano et al., 2015). MMF is used at a dose of 600 mg/m^2 twice a day (maintaining serum levels between 1–3.5 ug/ml) and evaluate the response after 3 months. MMF treatment is usually given for 2 years with a period of tapering off over 6 months before stopping. Given that MMF needs long time to generate a response, ideally it should be overlapped with first-line therapy, such as high-dose steroids, immunoglobulins, or rituximab, to enable the achievement of therapeutic plasma levels, and given as a 'maintenance treatment'. In general, given the good results in patients with ALPS (Miano et al., 2015; Rao et al., 2005; Rao & Oliveira, 2011; Teachey et al., 2010) and the side effects of rituximab, MMF should be useful to children with ES secondary to ALPS in a more up-front approach soon after the failure of first-line treatment (Miano, 2016).

Sirolimus (SR) is an inhibitor of the mammalian (mechanistic target of rapamycin (mTOR), which increases T-regulatory cells (T-regs) and induces apoptosis in abnormal lymphocytes. The drug has been used for over 20 years (Hartford & Ratain, 2007) for autoimmune diseases, transplant and AIHA (Miano et al., 2014). Sirolimus has also been described as useful in ALPS patients with or without

cytopenia in which it reduced the count of double-negative T-cells (Teachey et al., 2010). In a study of Miano el al., sirolimus was effective in all five children with refractory AIHA, in 6/10 with ITP, and in the only patient affected with ES. All these children previously failed MMF, suggesting a potential role for sirolimus in patients with primary refractory cytopenias or with underlying defects other than ALPS. Sirolimus is given at the dose of 2–3 mg/m^2 once a day, maintaining serum levels between 4–12 ng/ml, with a target of 9 ng/ml, for at least 3 months before evaluating its efficacy. Similarly to MMF, sirolimus is given for a total of 2 years followed by another 6 months of tapering off before stopping. It may represent an effective rescue treatment after MMF failure in patients with ALPS, ALPS-like syndromes, refractory/resistant ITP and AC, and in those who need a steroid-sparing/maintenance treatment (Miano, 2016).

MMF and SR are immunosuppressive drugs because they act on lymphocyte to reduce immunological response: an increased infection rates correlated with their use, have been described in patients undergoing solid organ transplants. However, there are not studies in literature showing a correlation between their use and infections in haematological patients.

The aim of this study is to evaluate the infectious risk of MMF and sirolimus treatments in patients with hematological autoimmune disease.

Patients and methods

Medical records of patients suffering from PIRDs, such as ALPS/ALPS-like syndromes, and immune thrombocytopenia treated at Haematology Unit of G. Gaslini Children's Hospital and at Pediatric Hematology/Oncology Unit of Policlinico of Catania from January 2015 to May 2023 were reviewed.

Patient fulfilling the revised diagnostic criteria for either definitive or probable ALPS were classified as ALPS patients (Oliveira et al, 2010).

ALPS-like was defined as the presence of AIC associated with the presence of one absolute or primary additional criterion for ALPS. Patients classified with chronic ITP are defined with a low platelet count (<100.000/mmq) over 12 months. We established severe infection event (SIE) as an event with necessity of hospitalization and/or intravenous antibiotics.

A search strategy was developed to recognize the most significant literature on the topic. An exhaustive search was performed on the main scientific libraries including PubMed, Embase, Google Scholar and Cochrane. We used the following keywords: infection, infectious disease, mycophenolate mofetil, sirolimus, autoimmune lymphoproliferative syndrome (ALPS), ALSP-like, immune thrombocytopenia, ITP, autoimmune cytopenia, Evans syndrome. A combination of MeSH and associated terms with other methodological terms (mycophenolate and infection or infectious disease, sirolimus and infection or infectious disease, autoimmune lymphoproliferative syndrome and infection or infectious disease,

ALPS and infection or infectious disease, ALPS-like and infection or infectious disease, immune thrombocytopenia and infection or infectious disease, ITP and infection or infectious disease, autoimmune cytopenia and infection or infectious disease, Evans syndrome and infection or infectious disease).

The search was limited to articles published in English peer-reviewed journals between January 1990 and May 2023. For data processing, the document management tool Mendeley and the program Microsoft Excel were used. Descriptive statistics were produced for demographic and clinical characteristics of patients. Mean and standard deviation (SD) are presented for normally distributed variables, median and interquartile range (IQR) for non-normally distributed variables, number and percentages for categorical variables. For infectious events outcome, groups were compared with Pearson's chi-square test (or Fisher's exact where appropriated) and parametric or non-parametric tests according to data distribution. Survival analysis was performed by Kaplan-Meier estimate. Differences between treatments and diagnosis groups were assessed by log-rank tests and considered significative if $p<0.05$.

Results

Between 2015 and 2023, 114 patients, 60 (53%) females and 54 (47%) males, were treated with MMF (45, 40%) and Sirolimus (23, 20%) alone or with Sirolimus after MMF failure (46, 40%). Eighty-eight of 114 patients (77%) were treated for more than 5 months. The median age was 10.5 years (range 2-54 years); the median age at initial follow-up was 6 and 9 years in patients with SIEs and without SIEs, respectively. Twenty-two (19%), 55 (48%) and 37 out of 114 (32%) suffered from ALPS, ALPS-like syndromes and ITP, respectively. Forty-five of 114 (39%) patients developed infections during therapy, mostly mild upper respiratory infections. SIEs were documented in thirteen (12%) out of 112 evaluable patients who had a total of 16 SIE, mostly pneumonias (10 patients). The remaining ones consisted of abdominal infection (2), sepsis (2), cryptococcal meningitis (1), pyelonephritis (1). Data on SIE according to underlying disorders and type of therapy are shown in Table 2.

No statistically significant differences were found between ALPS, ALPS-like and ITP (Table 3): however, SIE were more frequent (10, 76%) in ALPS-like patients compared with others (3, 25%) (p=0.0078, with Yates correction p=0.016). Infection rate was higher in patients who received SR after failure of MMF (p=0.03) and was significantly related to therapy duration (p=0.04); data on patients with and without SIE are shown in Table 4. Event free survival (EFS) is described in Table 5. Figures 1a and 1b show EFS and cumulative hazard risk in the whole cohort of

studied patients; figures 2a, 2b, 3a and 3b describe EFS survival and cumulative hazard risk based on therapies and on diagnosis.

Discussion

Over the last decade, efficacy and safety of sirolimus and mycophenolate therapy in patients with ALPS, ALPS-like and other AICs have been reported (Howard et al., 2002; Rao et al., 2005; Zhang et al., 2005; Provan et al., 2006, 2019; Hartford & Ratain, 2007; Teachey et al., 2010; Rao & Oliveira, 2011; Ladogana et al. 2013; Miano et al., 2013, 2015, 2016; Taylor et al., 2015; Bride et al., 2016; Rensing-Ehl et al., 2016; Nocerino et al., 2018; Neunert et al., 2019; Weli et al., 2020; Bradbury et al., 2021; Kochhar & Neunert, 2021; Lambert, 2021; Goldberg & Levy, 2023); however, to the best of our knowledge, no one underlines the effective risks in terms of infections. This is the largest cohort of patients in which infection rate has been quantitatively evaluated and showed that only a minority of patients had severe infections requiring of hospitalization and/or intravenous antibiotics and none died.

In our records, only 2 patients treated with MMF developed severe infections. These data clearly confirm what suggested by the few previous available data on its safety. In fact, in adult patients with ITP, no one developed severe infections (Taylor et al., 2015, Bradbury et al., 2021,Goldberg & Levy, 2023) but no experience was described in hematological pediatric patients apart from two case reports which underlined the safety of MMF (Lim et al., 2013 and Weli et al., 2020). In two studies on children with rheumatological diseases and nephritic syndrome, severe infection rate during MMF was not significantly increased (Hassan et al., 2013; Barbati et al., 2022).

Only 10% patients of our cohort developed severe infections under SR treatment. In literature, few studies showed the relation between SR therapy and infections in hematological patients: in ALPS patients, no increase was observed in infection frequency or severity (Tommasini et al., 2009; Bride et al. 2016; Nocerino et al., 2018). Interestingly, in the few articles analyzing the infection rate and treatment with SR for lymphatic malformations, a possible increased risk of infections or SIE was highlighted: in a study of a cohort of 39 patients with PIK3CA-related overgrowth spectrum (PROS) treated with sirolimus, the authors describe infections in 41% of cases, although the severity of infections was not reported. This data is comparable to our result of 39% of cases with mild events as upper respiratory infections. In other reports, 3 patients were shown to have SIEs but during the first months of SR treatment (Russell et al. 2017; Ying et al. 2018 and Parker et al., 2019) which can be hardly related to the immunomodulant which is well known to starts after 6-8 weeks of treatment. In our cohort, most patients developing SIEs under SR were affected with ALPS-like syndromes which are well known to have, per se, an increased risk to develop infections compared with ITP and ALPS. In fact, ALPS-like syndromes are often associated with hypogammaglobulinemia and/or lymphopenia defects. Our ALPS-like patients were affected by STAT3 GOF syndrome, TACI or NEMO deficiency, typically associated with a per se high infection risk and showed hypogammaglobulinemia in all cases (Lee et al., 2022; Leiding et al., 2023; Salzer & Grimbacher, 2021). Similarly, all our patients with diagnosis of Cartilage-Hair-Hypoplasia (CHH), IPEX and LRBA deficiency developed a complex phenotype with autoimmunity and immunodeficiency (Barzaghi et al., 2018; Kiykim et al., 2019).

Interestingly, the higher occurrence of SIEs during SR rather than during MMF seems in contrast with the knowledge that SR has a prevalent immunoregulatory than an immunosuppressive effect. However, this unexpected result can be also explained by the higher number and longer duration of previous therapies received by this setting of patients, already per se predisposed to infections risk. In fact, infection rate was higher in patients treated with SR after MMF failure and was significantly correlated with therapy duration. Nonetheless, no events required intensive care support in any patients and no death were described.

Conclusions

This is the first study of patients with hematological disorders treated with MMF and SR, in which infection rate was quantitatively evaluated. In conclusion, with the obvious limitations of a retrospective data review, our data suggest that MMF and SR represent safe and effective treatments which do not increase infectious risk in patients with haematological diseases, apart those who have an intrinsic risk due to the underlying disease. Nevertheless, clinical trials are needed to confirm these results.

Tables and Figures

Table 1: ALPS criteria (Oliveira et al. 2010)

Required
• Chronic (6 months), non-malignant, non-infectious lymphadenopathy or splenomegaly or both
• Elevated CD3 TCRαβ CD4-/CD8- DNT cells (1.5% of total lymphocytes or 2.5% of CD3 lymphocytes) in the setting of normal or elevated lymphocyte counts
Accessory primary
• Defective lymphocyte apoptosis (in 2 separate assays)
• Somatic or germline pathogenic mutation in FAS, FASLG, or CASP10
Accessory secondary
• Elevated plasma sFASL levels (200 pg/mL) OR elevated plasma interleukin-10 levels (20 pg/mL) OR elevated serum or plasma vitamin B12 levels (1500 ng/L) OR elevated plasma interleukin-18 levels 500 pg/mL
• Typical immune-histological findings as reviewed by an experienced hematopathologist
• Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia
• Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

A definitive diagnosis is based on the presence of both required criteria plus one primary accessory criterion. A probable diagnosis is based on the presence of both required criteria plus one secondary accessory criterion (Oliveira et al., 2010).

Table 2 Data on therapy duration and severe infectious events

Therapy duration (months)	median	range
Total	42,5	3-168
Mycophenolate	27,5	3-144
Sirolimus	31	6-132
Severe infectious events	n	%
Missing data	2	1
Episodes during follow up	99/112	88
Patients with at least 1 episode	13/112	11
Total episodes	16	

Table 3 Patients with severe infectious events

	Diagnosis	Genetic or associated disease	n. SIE	MMF (months)	SR (months)	Type of infection	Previous therapy	Drugs during SIE
Case 1	ALPS-like	SLE	2	53	31	Pyelonephritis and sepsis from E. coli	MTX, HCQ, azathioprine, CPM, tacrolimus, thalidomide, bortezomib, eculizumab, belimumab	MMF and SR
Case 2	ALPS		1	144	0	Pneumonia	/	MMF
Case 3	ALPS		1	0	22	Gastroenteritis	/	SR
Case 4	ITP		1	4	46	Pneumonia	/	SR
Case 5	ALPS-like		2	0	6	Pneumonia and sepsis	Steroid	SR
Case 6	ALPS-like	NEMO deficiency	1	0	72	Pneumonia	Steroid	SR
Case 7	ALPS-like	LRBA deficiency	1	24	100	Pneumonia	Steroid, Abatacept	SR
Case 8	ALPS-like	IPEX	1	15	73	Pneumonia	/	SR
Case 9	ALPS-like	ES+IBD	1	6	52	Sars-Cov2 Pneumonia	Steroid, IVIG	SR, steroid and thalido-mide
Case 10	ALPS-like	RMRP	2	0	98	Abdominal infection and meningitis (Cryptococcus)	IVIG	SR
Case 11	ALPS-like	STAT3 GOFS	1	11	40	Pneumonia	Steroid, IVIG, Rituximab	SR
Case 12	ALPS-like		1	0	35	Pneumonia	Steroid	SR
Case 13	ALPS-like	TACI deficiency	1	1	4	Viral pneumonia	/	SR

Legend: ALPS: autoimmune lymphoproliferative syndrome, CPM: cyclophosphamide, ES: Evans syndrome, HCQ: hydroxychloroquine, IBD: inflammatory bowel disease, IPEX: immune dys-regulation, polyendocrinopathy, enteropathy, X-linked, ITP: immune thrombocytopenia, IVIG LRBA: lipopolysaccharide-responsive and beige-like anchor protein, MMF: mycophenolate mofetil, MTX: methotrexate, NEMO: NF-kb essential modulator, RMRP: RNA component of the mitochondrial RNA-processing endoribonuclease, SIE: severe infectious event, SLE: systemic lupus erythematosus, SR: sirolimus, STAT3 GOFS: signal transducer and activator of transcription 3 gain-of-function syndrome, TACI: transmembrane activator and calcium-modulator and cyclophilin ligan interactor

Table 4 Data on patients with and without severe infectious events

	Patients with at least 1 SIE (n = 13)	No SIEs (n = 99)	p
Sex (n, %)			**0.035**
Female	3, 24%	57, 58%	
Male	10, 76%	42, 42%	
Diagnosis (n, %)			0.082
ALPS	2, 15%	20, 20%	
ALPS-like	10, 77%	45, 46%	
ITP	1, 8%	34, 34%	
Therapy (n, %)			**0.033**
Only mycophenolate	1, 8%	42, 42%	
Only sirolimus	4, 31%	19, 19%	
Both	8 (7 during SR, 1 during MMF) 61%	38, 39%	
Therapy duration (months - median, IQR)			
Total	54, 71	36, 69.5	**0.043**
Mycophenolate	18, 37	30, 60	0.764
Sirolimus	44.5, 46.8	23, 42.5	0.102

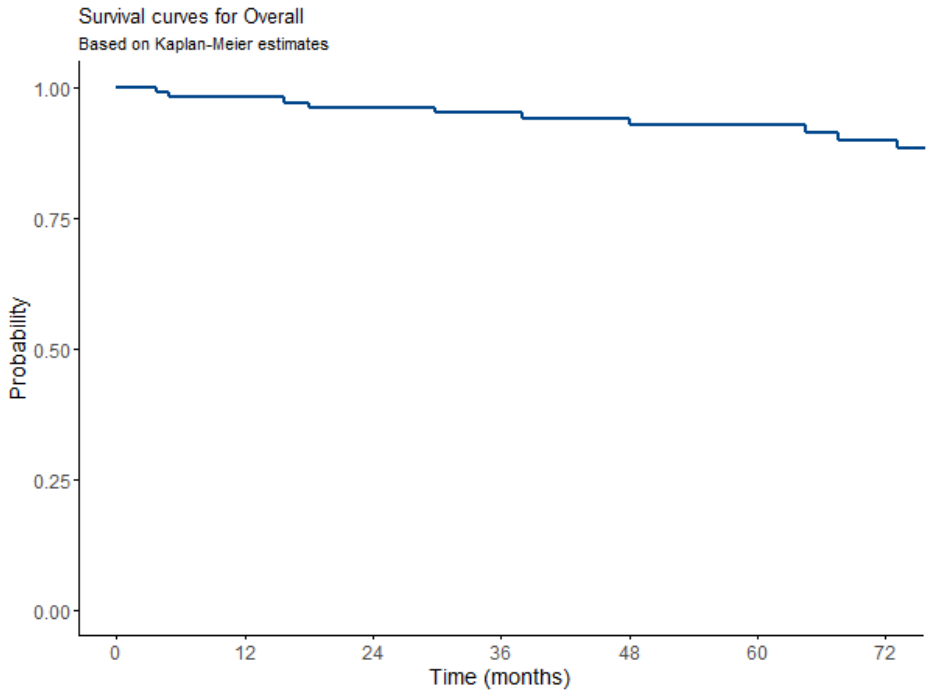
Legend: ALPS: autoimmune lymphoproliferative syndrome, IQR: interquartile range, MMF: mycophenolate mofetil, SIE: severe infectious event, SR: sirolimus

Table 5 Infectious events free survival

1, 3, 5, 6-year infectious events free survival

				95% Confidence Interval	
Months	Number at Risk	Number of Events	Survival	Lower	Upper
12	98	2	98.1 %	95.5 %	100.0 %
36	86	3	95.0 %	90.8 %	99.4 %
60	70	2	92.7 %	87.5 %	98.1 %
72	62	2	89.9 %	83.7 %	96.5 %

Figure 1a and 1b: Infectious events free survival plot and cumulative hazard overall



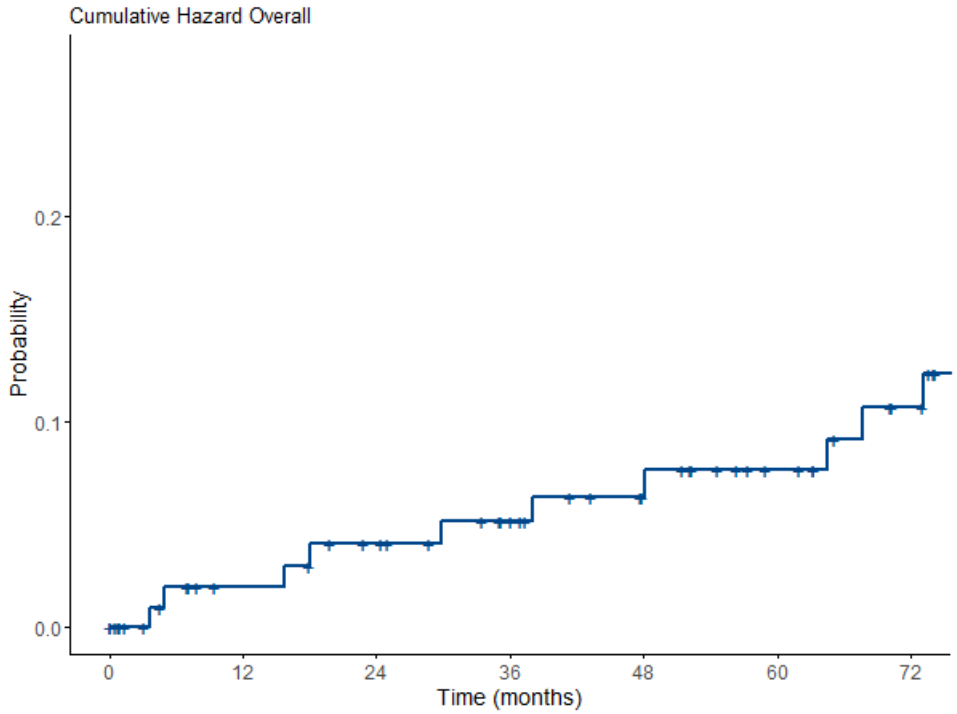
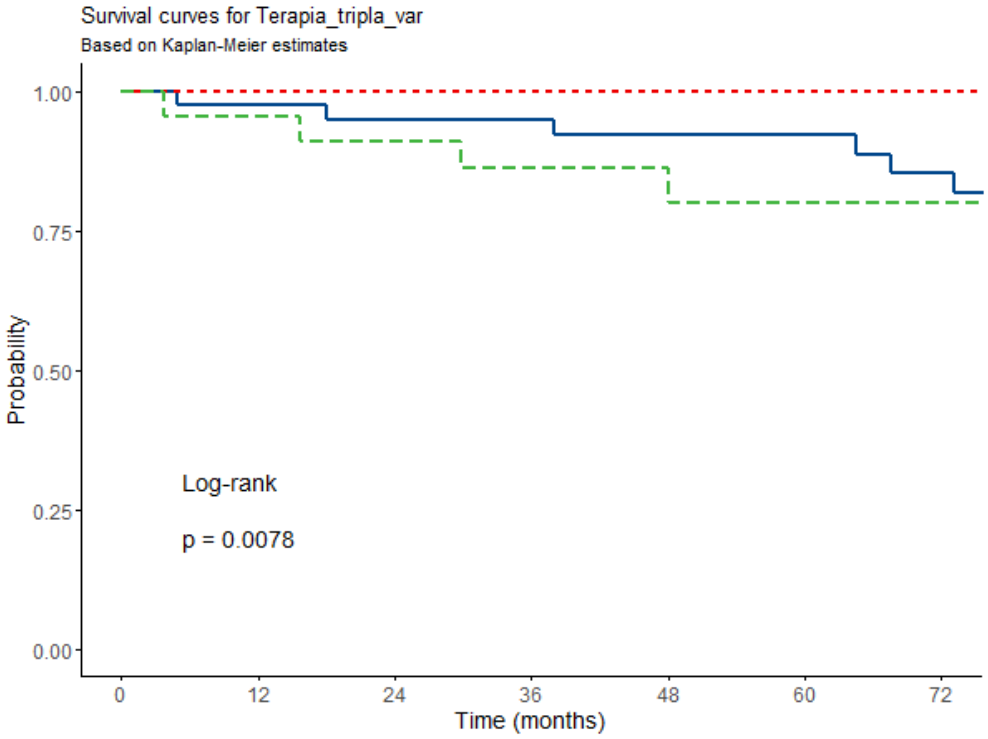
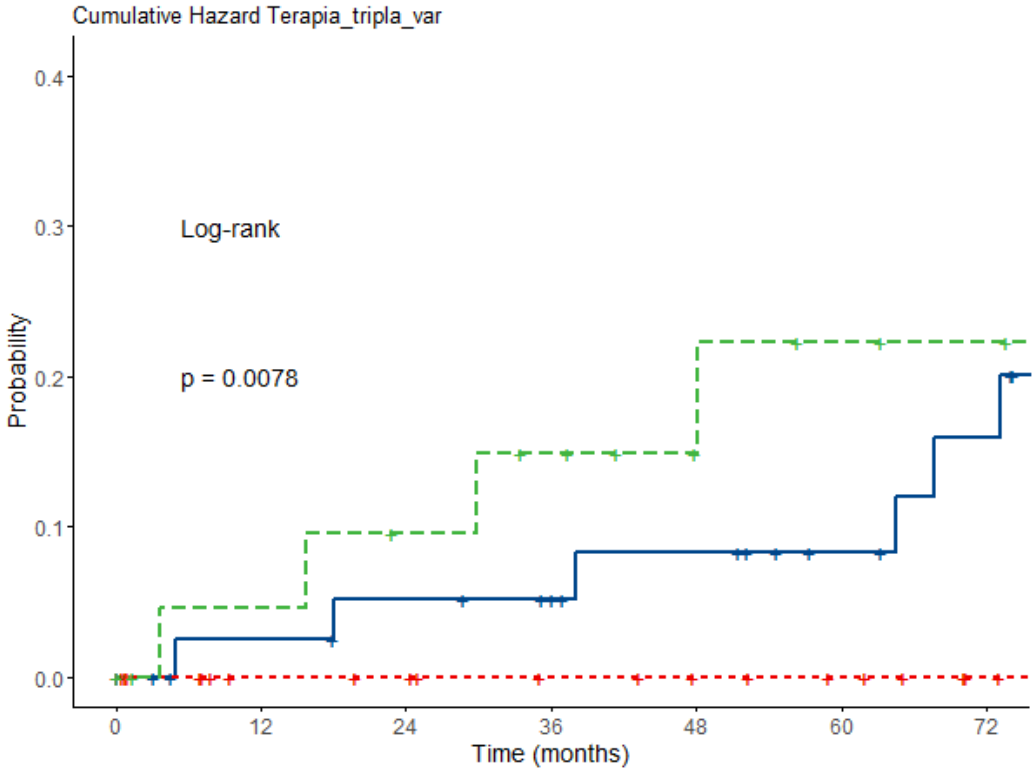


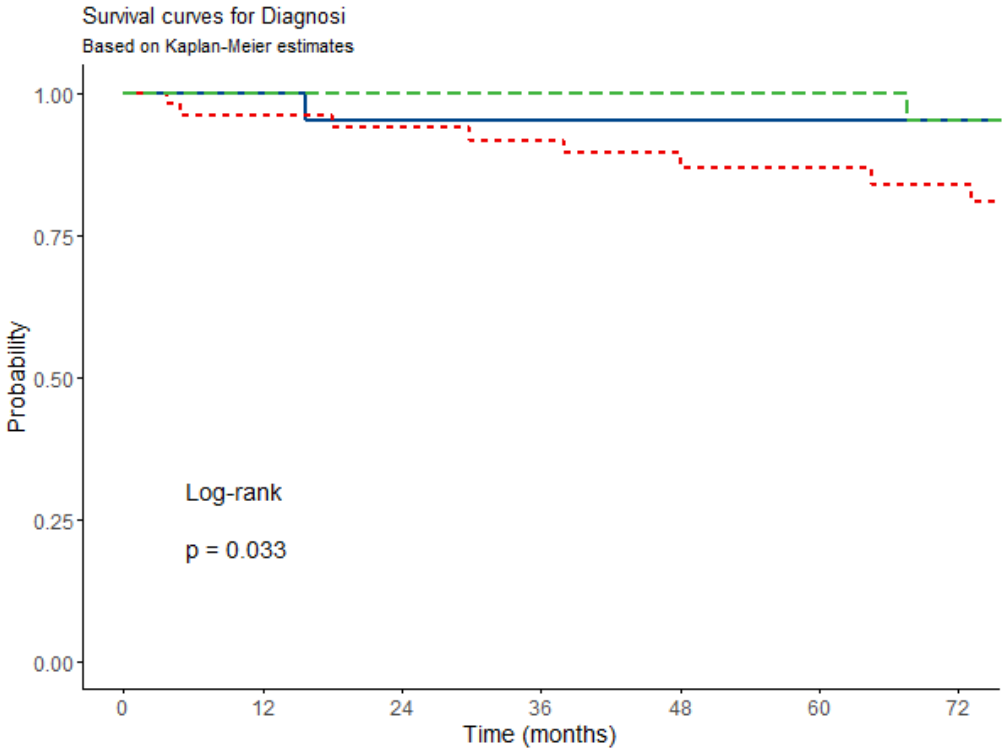
Figure 2a and 2b: Infectious events free survival and cumulative hazard risk based on therapies.

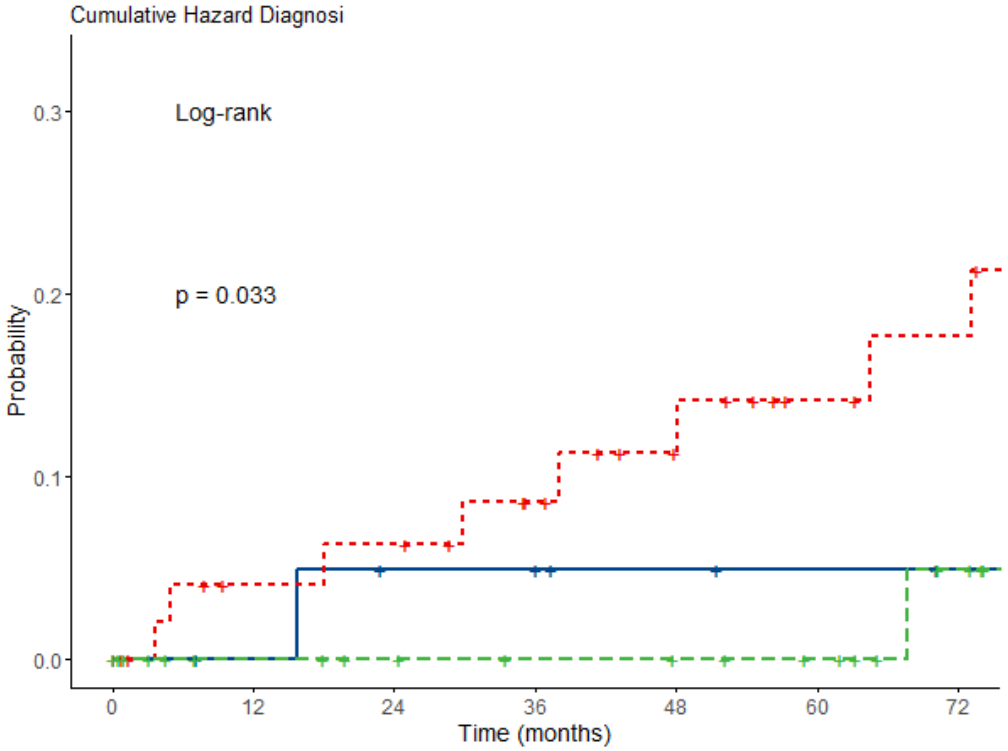




Legend: red (mycophenolate), green (sirolimus) and blue (both therapies)

Figure 3a and 3b: Infectious events free survival and cumulative hazard risk based on diagnosis.





Legend: green (ITP), blue (ALPS), red (ALPS-like syndrome)

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