Autoimmune cytopenias following alemtuzumab-induced renal transplant: clinical features and treatment outcomes

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Received: July 21, 2025.
Accepted: May 15, 2026.
Early view: May 28, 2026.

https://doi.org/10.3324/haematol.2025.288549

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Abstract

The anti-CD52 monoclonal antibody, alemtuzumab, is used as induction therapy for renal transplantation. Its use has been associated with autoimmune manifestations, particularly autoimmune cytopenias (AIC). Here, we report a single-center, retrospective analysis of patients who developed AIC after an alemtuzumab-induced renal transplant. Over a period of 8 years, 40 renal transplant patients developed immune thrombocytopenia (ITP) (N=28), autoimmune hemolytic anemia (AI-HA) (N=7) or Evans syndrome (N=5), with two peaks of incidence, at 18 and 36 months after alemtuzumab. Response and relapse rates to standard first-line ITP and AIHA therapy were comparable to primary forms, with two thirds requiring second-line agents. Most patients with ITP who failed to go into remission after steroids or intravenous immunoglobulin received either rituximab or a thrombopoietin receptor agonist (TPO-RA). Compared to primary ITP, a higher response rate (91.6%) and median duration of response (56 months) were achieved with rituximab; and a higher proportion of patients were able to discontinue TPO-RA and maintain remission (50%). Most patients experienced one or more adverse events, most commonly, infections (62.5%), cardiovascular diseases (27.5%) and deep vein thrombosis (25%). In conclusion, AIC are a significant complication following alemtuzumab-induced renal transplantation, typically occurring within the 5-year period of immune reconstitution. Both rituximab and TPO-RA show good efficacy, a few patients develop multi refractory disease, and the majority go into sustained remission off-treatment. Given that treatment is complicated by high rates of infections and thrombosis, supportive measures using anti-microbials as well as quick re-introduction of antiplatelet or anticoagulants in ITP and addition of anticoagulation in AIHA is recommended.

Introduction

Alemtuzumab is a humanized monoclonal antibody which targets CD52, a glycoprotein expressed on T and B cells causing their rapid, profound and long-lasting depletion.[1,2] It is approved in Europe and in the US for the treatment of relapsing-remitting multiple sclerosis,[3,4] and is used off-label for the treatment of chronic lymphocytic leukemia and in the context of solid organ transplantation, for the prevention and treatment of acute rejection.[5]

One of the side effects of alemtuzumab is the development of autoimmune diseases. This usually occurs within 5 years of therapy, with a peak incidence at 2 years. These have mostly been reported in patients with multiple sclerosis,[6] with a few case reports in patients treated for chronic lymphocytic leukemia,[7] and solid organ transplantation.[8] The most frequent autoimmune complications include thyroid disorders (both hypothyroidism and Graves' disease), occurring in up to 30%; immune thrombocytopenia (ITP) with an incidence of 1-2%; other autoimmune cytopenias (autoimmune hemolytic anemia [AIHA] and autoimmune neutropenia [AIN]) and autoimmune nephropathies (0.3%).[9,10]

ITP is an autoimmune disease characterized by immune-mediated destruction of platelets and impaired platelet production, leading to a decreased platelet count and an increased risk of bleeding.[11] The pathogenesis has

been attributed to the presence of auto-antibodies directed against platelets and megakaryocytes.[12,13] T-cell changes are also apparent with skewed Th1 T-helper cells,[14] reduced number and function of regulatory T cells,[15] and cytotoxic $CD8^+$ T cells.[16] In AIHA, autoantibodies are directed against erythrocyte membrane antigens, causing extravascular or intravascular hemolysis.[17,18] Evans syndrome (ES) is the combination (either simultaneous or sequential) of at least two autoimmune cytopenias: AIHA, ITP and AIN.[19,20]

Alemtuzumab has been used for over 20 years as induction therapy in kidney and simultaneous pancreas-kidney transplantation to reduce the risk of organ rejection and to prolong the survival of the graft.[21]

In this study, we describe the clinical features, management and outcomes of patients who developed autoimmune cytopenias (ITP and AIHA) after receiving a renal or SPK transplantation induced with alemtuzumab over an 8-year period.

Methods

Patients

All patients with post-alemtuzumab cytopenias in North West London are referred to the Hammersmith Hospital Immune Hematology service. In this report, we retrospectively analyzed 40 patients who developed an autoimmune cytopenia (ITP or AIHA) between January 2010 and March 2018.

Diagnosis of immune thrombocytopenia

Diagnosis of ITP was defined according to International Working Group (IWG) standardized criteria:[11] isolated thrombocytopenia (platelet count <100x10^9/L) in the absence of any cause other than previous exposure to alemtuzumab.

Diagnosis of autoimmune hemolytic anemia

Diagnosis of AIHA was defined as hemoglobin (Hb) level <100 g/L with a positive direct antiglobulin test and increased markers of hemolysis, with no known underlying etiology other than the administration of alemtuzumab.[22]

Diagnosis of Evans syndrome

Diagnosis of ES was defined as the coexistence of at least two autoimmune cytopenias, either simultaneous or sequential (ITP, AIHA or AIN).[23]

Definition of response to treatment

ITP response was evaluated according to IWG standardized criteria.[11] No response (NR): platelet count ≤30x10^9/L or less than doubling of the baseline count. Response (R): platelet count ≥30x10^9/L and at least doubling of baseline count in the absence of bleeding symptoms. Complete response (CR): platelet count ≥100x10^9/L. Sustained response off-treatment (SROT): proportion of patients able to discontinue treatment and maintain the response at last follow-up.

Automimmune hemolytic leukemia

CR: Hb >120 g/L and normalization of all hemolytic markers. Partial response (PR): Hb >100 g/L or at least 20 g/L increase in Hb and no transfusion requirement. Response duration: the time from the first documented response to the start of a subsequent treatment or the last follow-up. Overall response rate (ORR): the sum of CR and R. Relapse-free survival (RFS): the time between the achievement of response and relapse or death.

Ethics

This was retrospective data collection, with no identifiable patient data, and collected as a service delivery audit process. Audit registration number is ASM_HH_25.

Statistical analysis

Clinical, demographic and laboratory characteristics of subjects were summarized with descriptive statistics for both continuous and categorical variables. Survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. *P* value <0.05 was deemed statistically significant. Statistical analysis was performed using SPSS Version 24.0 and Jamovi v. 2.3.

Results

Patients' characteristics

Approximately 160 kidney or SPK transplants are performed per year with a male predominance (65%), at Imperial College NHS Trust, all induced with alemtuzumab. Between January 2010 and March 2018, 40 renal or SPK-transplant recipients were referred to the Immune Hematology service with autoimmune cytopenia: 28 ITP, seven AIHA and five ES. On average, five (range, 2-8) new cases of autoimmune cytopenia were diagnosed per year: 3.6 (range, 0-6) ITP and 1.4 (range 0-3) AIHA corresponding to an annual rate of 3.1% overall, 2.25% for ITP and 0.87% for AIHA.

Three patients in the ITP cohort and one patient in the ES cohort developed a transient neutropenia which was probably multifactorial (autoimmune, drug-related) and did not require any treatment. Baseline patient characteristics are reported in Table 1.

Most patients (67.5%) were male, and they were all still receiving post-transplant immunosuppressive therapy: 28 (70%) tacrolimus, nine (22.5%) tacrolimus and MMF, three (7.5%) tacrolimus and prednisolone. The median age at AIC diagnosis was 52 years (range, 21-76).

The median time between alemtuzumab administration and the onset of cytopenia was 33.5 months (range, 6-109) Figure 1. The median nadir platelet count was 6x10^9/L (range, 0-41) in patients with ITP; 17 ITP patients (51.5%) presented

with bleeding symptoms, in most cases skin or mucosal bleeding with no life-threatening bleeding; the remaining patients were identified through routine blood tests. The median nadir Hb was 53 g/L (range, 35-65) in patients with AIHA, all cases were warm antibody mediated (wAIHA).

Patients had significant comorbidities: 37.5% had type 2 diabetes and 65% had pre-existing cardiovascular comorbidities: 27 patients (67.5%) needed concomitant antiplatelet or anticoagulant medication before the cytopenia diagnosis - 42.5% aspirin or clopidogrel, 17.5% warfarin, apixaban or heparin, 7.5% had combined antiplatelet/anticoagulant treatment.

Diagnostic workup

Patients underwent physical examination, complete blood count with differential and peripheral blood smear, liver and kidney function, B12, folate and iron, coagulation panel, serum protein electrophoresis, immunoglobulins testing, Epstein-Barr virus (EBV) and Cytomegalovirus (CMV)-DNA polymerase chain reaction (PCR) blood titers, antiphospholipid antibodies (anti-β2-glycoprotein1 IgG and IgM, anti-cardiolipin IgG and IgM, lupus anticoagulant) and antinuclear antibodies. For patients presenting with anemia or with concomitant anemia and thrombocytopenia, hemolysis indices and DAT were performed. Patients with hemolytic anemia and negative DAT were screened for microangiopathy and paroxysmal nocturnal hemoglobinuria.

In patients with hepatomegaly or splenomegaly, lymphadenopathies, abnormalities in CBC or peripheral blood smear or failure to respond to first line therapy a bone marrow examination with flow cytometry and cytogenetics and a computed tomography-scan were performed.

A bone marrow examination was performed in 25 patients (62.5%). All were consistent with a diagnosis of ITP or AI-

Table 1. Patients' baseline characteristics.

Characteristics	ITP N=28	AIHA N=7	ES N=5
Sex, N (%) M F	 20 (71) 8	 5 (71) 2	 3 (60) 2 (60)
Median age at renal transplantation, years (range)	48 (20-69)	47 (29-67)	56 (32-58)
Median age at diagnosis, years (range)	52 (21-76)	49 (31-69)	59 (36-65)
Median time between alemtuzumab administration and diagnosis, months (range)	32 (6-109)	35 (19-89)	40 (18-94)
Median nadir (range) PLT count, x10^9/L Hb, g/L	 5.5 (0-41) -	 - 58 (35-65)	 4 (1-14) 56 (49-77)
Type of transplant, N (%) DDRT LRRT LURT AB0 incompatible	 13 (46) 8 (29) 6 (21) 1 (4)	 3 (42) 2 (29) 2 (29) 0	 2 (40) 2 (40) 1 (20) 0
Type of immunosuppression, N (%) Tacrolimus Tacrolimus + MMF Tacrolimus + Prednisolone +/- MMF	 1 (75) 6 (21) 1 (4)	 5 (72) 1 (14) 1 (14)	 2 (40) 2 (40) 1 (20)
Bone marrow examination, N (%)	16 (57)	4 (57)	5 (100)
Bleeding symptoms, N (%) Skin Mucosa Organ	16 (57) 6 (21) 6 (21) 4 (14)	- NA - -	1 (20) 0 1 (100) 0
Main comorbidities, N (%) Cardiovascular Diabetes	 18 (64) 12 (43)	 5 (71) 2 (29)	 3 (60) 2 (40)
Concomitant treatments, N (%) Antiplatelet Anticoagulant Combined	 12 (43) 3 (11) 3 (11)	 4 (57) 1 (14) 0	 1 (20) 3 (60) 0

AIHA: autoimmune hemolytic anemia; DDRT: deceased donor renal transplantation; ES: Evans syndrome; F: female; Hb: hemoglobin; ITP: immune thrombocytopenia; LRRT: living-related renal transplantation; LURT: living-unrelated renal transplantation; M: male; MMF: mycophenolate mofetil; NA: not applicable; PLT: platelet.

HA. Two patients had ITP and concomitant post-transplant lymphoproliferative disorder (PTLD) diagnosed via lymph node biopsy, with no bone marrow involvement in either case.

Seven patients (17.5%) had a detectable paraprotein at diagnosis which was too small for quantification without any other symptoms or laboratory results diagnostic for multiple myeloma. Twenty-four patients were tested for antiphospholipid antibodies: all were negative. Fifteen patients (37.5%) had positive EBV DNA PCR at the time of diagnosis: 13 in the ITP group and two in the AIHA group. There was no evidence of PTLD in this cohort.

Treatment

Immune thrombocytopenia

Thirty-three patients were managed for ITP, including the five patients with ES. Two patients had mild thrombocytopenia (nadir of platelet count $41x10^9$/L and $27x10^9$/L) which resolved without treatment: they were not included in further analysis. ITP treatments are reported in Figure 2.

First-line therapy

Of the 31 patients who received treatment, 28 were treated with standard first-line therapy (steroids or IVIG or steroids + IVIG), with an ORR of 61% (75% for steroids, 54% for steroids + IVIG, 40% for IVIG). Other treatment choices were rituximab (N=2), and romiplostim + IVIG (N=1), with an ORR of 100%.

Second-line therapy

Twenty-one patients (67.7%) required further treatment (due to relapse or failure to respond). Eleven received a repeated course of steroids, IVIG or combination as second-line therapy, with an ORR of 73%. Four patients received rituximab as second line therapy, with an ORR of 100%. Four patients received a TPO-RA (3 eltrombopag and 1 romiplostim), with an ORR of 75%. Two patients were treated with eltrombopag and rituximab in combination, ORR 100%.

Third-line therapy

Twelve patients (57%) relapsed, requiring three or more lines of therapy. Treatments used were steroids (N=1; ORR 100%), eltrombopag (N=10; ORR 70%), romiplostim (N=1; ORR 100%), rituximab (N=6; ORR 83%), a combination of rituximab and TPO-RA (N=5; ORR 60%), MMF (N=1; ORR 100%) and combinations (eltrombopag + romiplostim and eltrombopag + MMF + rituximab) (N=2; ORR 100%).

Fourth-line therapy and beyond

Twelve patients (38.7%) required four or more lines of treatments, including TPO-RA, rituximab, MMF and a combination of TPO-RA and rituximab. One patient with ES required eight lines of treatment, including combinations of multiple drugs (IVIG, eltrombopag, romiplostim, MMF, rituximab, plasmapheresis).

Epstein-Barr virus-positive patients

Three patients with high EBV PCR titers (26,500, 16,500 and 18,000 copies/mL) received rituximab for ITP and EBV treatment: one did not achieve a platelet response to

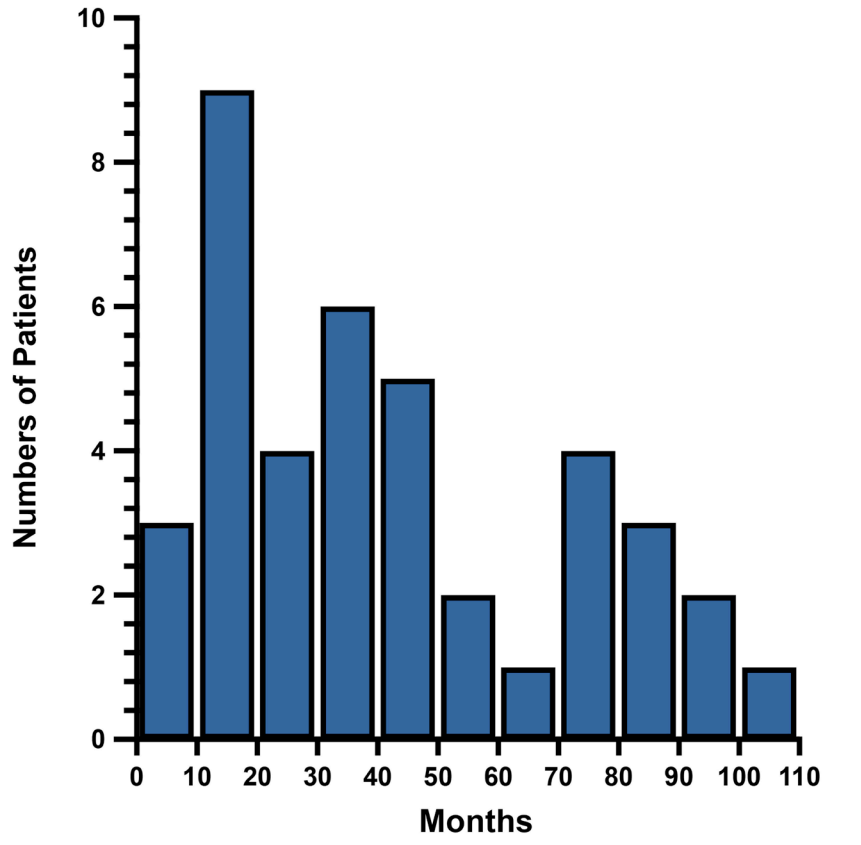


Figure 1. Incidence of autoimmune cytopenia in the months following alemtuzumab-induced renal transplant. The majority of patients (73%) developed an autoimmune disease within the first 5 years after alemtuzumab administration.

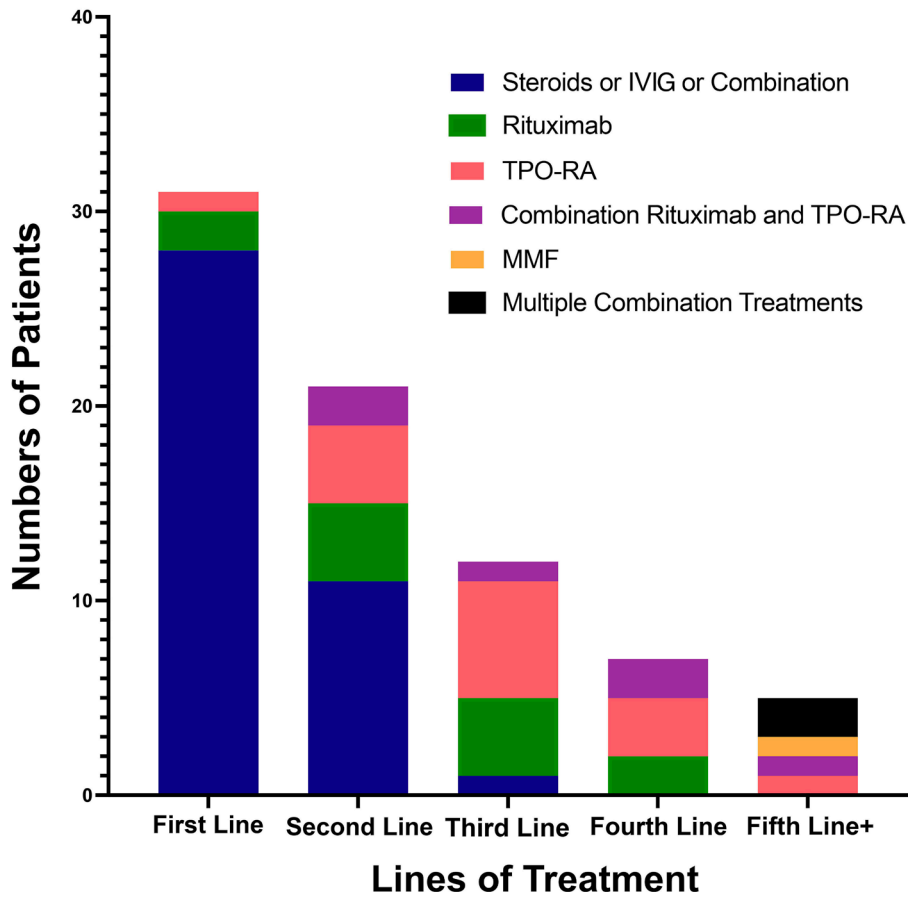


Figure 2. Treatment of immune thrombocytopenia. IVIG: intravenous immunoglobulins; MMF: mycophenolate mofetil; TPO-RA: thrombopoietin receptor-agonists.

rituximab but responded to eltrombopag; one responded and relapsed after 9 months; one stayed in remission for 15 months, with disappearance of EBV viral load, then relapsed and responded to rituximab again.

Patients with concomitant immune thrombocytopenia and post-transplant lymphoproliferative disorder

In two patients, the diagnosis of ITP was made shortly before the diagnosis of PTLD. One patient received steroids and IVIG for ITP, achieving a quick CR, and then was diagnosed with monomorphic PTLD, plasmacytoma type, and treated with four courses of R-CHOP chemotherapy. The other patient was treated with steroids for ITP, achieving a CR. A few weeks later, a diagnosis of marginal zone lymphoma with plasmocytic differentiation was made, and he received rituximab for both PTLD and relapsed ITP. Both were in complete remission for ITP and PTLD at last follow-up.

Response to rituximab or a thrombopoietin receptor agonists

Altogether, rituximab or a thrombopoietin receptor agonist (TPO-RA) were used in 16 instances (13 eltrombopag and 3 romiplostim), with an ORR of 75%. Among the patients who responded, ten of 12 (83%) were able to discontinue treatment after a median of 64.5 days (range, 7-528) on treatment, and five of ten (50%) remained off-treatment, achieving SROT, with a median duration of response at last follow-up of 50 months (range, 35-51).

Response to rituximab

Rituximab was used 12 times, with a response rate of 92%. Four patients relapsed (9, 11, 15, 27 months after treatment). The median duration of response at last follow-up of the remaining patients was 56 months (range, 5-95). The three patients with positive EBV PCR that received rituximab for ITP had a lower response rate compared to the other patients treated with rituximab (66% *vs*. 100%), but the numbers are too small to draw further conclusions.

There was no statistically significant difference (P=0.93) in RFS with TPO-RA and rituximab (Figure 3).

A combination of rituximab and TPO-RA was used eight times, with a response rate of 75%. Five patients discontinued the TPO-RA after a median of 173 days (range, 17-462), three of five patients (60%) were able to achieve SROT; median duration of response was 16 months (range, 6-55).

Immune thrombocytopenia overall response

After a median follow-up of 49 months (range, 8-105), 27 patients (87%) discontinued treatment. The remaining four patients were still taking eltrombopag (N=2), romiplostim (N=1) and rituximab (N=1). Twenty-eight patients (90%) were in CR, two patients (6%) in R, and one patient was not responding to treatment.

Autoimmune hemolytic anemia

AIHA treatments are reported in Figure 4. Twelve patients were treated for AIHA including the five patients diagnosed with ES. Ten of 12 patients received high-dose prednisolone (1 mg/kg/day) as first-line treatment, with a response rate of 60% and a relapse rate of 33%. One patient received first-line rituximab with CR. One patient had already received multiple treatments for ITP, when he developed AIHA. He had a very refractory ES treated with IVIG, steroids, plasma exchange, MMF; he was receiving eltrombopag and romiplostim in combination for ITP, having already completed a course of rituximab. Response to treatment in this patient was not available at last follow-up.

Seven of 11 patients (63.6%) required a second-line therapy: six of seven received rituximab (375 mg/m^2 weekly x 4) with an ORR of 50%. One patient received multiple courses of IVIG, with CR. Three patients needed subsequent lines of therapy: one was treated with splenectomy and re-

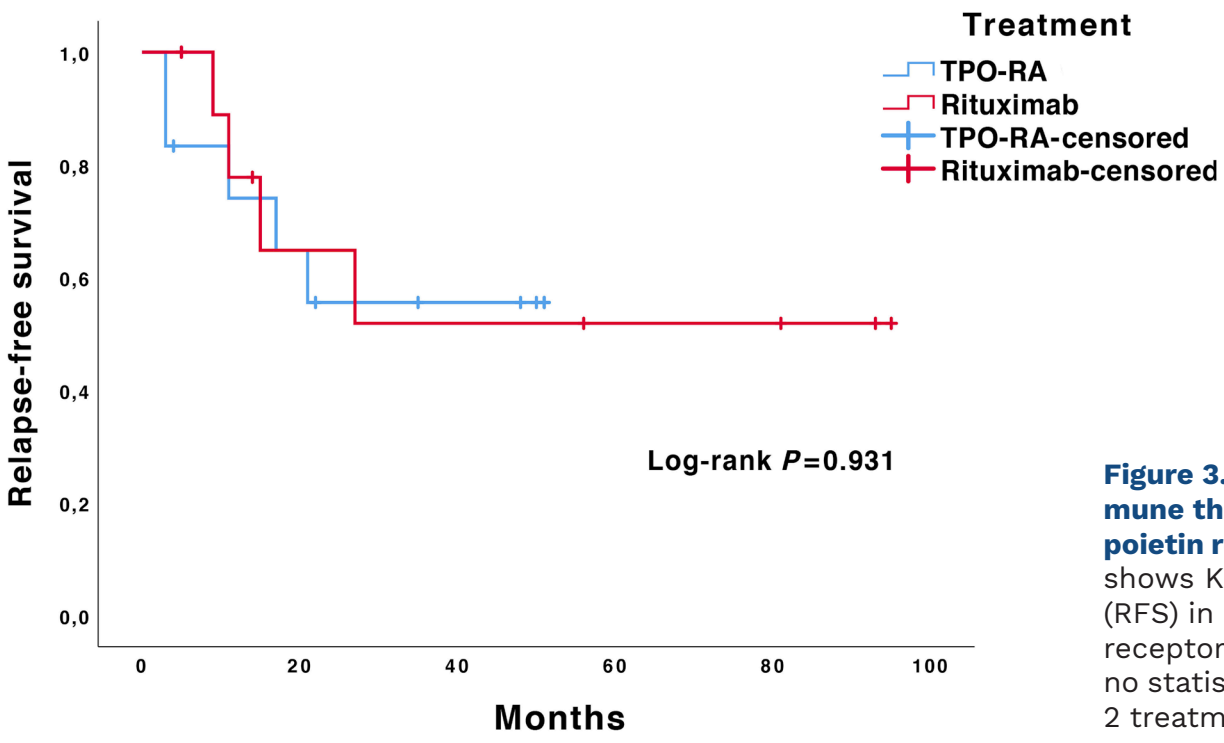


Figure 3. Relapse-free survival in patients with immune thrombocytopenia receiving either thrombopoietin receptor-agonists and rituximab. This figure shows Kaplan-Meier curves of relapse-free survival (RFS) in patients who responded to thrombopoietin receptor-agonists (TPO-RA) or rituximab. There was no statistically significant difference in RFS with the 2 treatments (P=0.93, log-rank).

sponded; one was retreated with rituximab and responded; the third patient had very refractory disease and received multiple lines of therapy (autologous mesenchymal stem cells, danazol, monthly IVIG) and eventually achieved remission 4 years after diagnosis. After a median follow-up of 65 months (range, 2-113), ten of 12 patients discontinued treatment: five (50%) were in CR, five in PR.

Evans syndrome

ES treatments are reported in Figure 5. Relapse rate after first-line ITP therapy was 100% in patients with ES. Most patients (3/5) responded to second-line therapy without relapse, while one particularly refractory patient needed eight lines of treatment. Most patients with ES (60%) needed a second-line therapy for AIHA, and rituximab was effective in 50%.

Adverse events

Adverse events (AE) are summarized in Table 2 and *Online Supplementary Table S1*. Thirty-five of 40 patients (87.5%) experienced one or more AE, 23 of 28 in the ITP group (82%), six of seven in the AIHA group (86%) and 100% in the ES group. The most common AE were infections (62.5%), cardiovascular events (27.5%) and deep vein thrombosis (DVT) (25%). Most infections were grade ≥3, and among the 19 patients who developed a grade ≥3 infection, eight had received rituximab.

Ten patients (25%) developed a total of 11 DVT. Five of 11 events occurred in patients with an indication for antiplatelet (N=3) or anticoagulant (N=2) treatment before the thrombosis onset. Three patients were still receiving an antiplatelet/anticoagulant treatment when DVT occurred. There was no difference in terms of median age between patients who developed DVT and those who did not (54 *vs*. 52 years; *P*=0.73).

Eleven patients (27.5%) developed 18 cardiovascular AE; atrial fibrillation (N=8), worsening heart failure (N=2), ventricular fibrillation (N=1), abdominal aortic aneurysm (N=1), transient ischemic attack (N=1), cardiac arrest (N=1), ischemic stroke (N=3), atrial thrombus (N=1).

Four patients (10%) experienced major bleedings: cerebrovascular bleeding (N=2), one in the AIHA group, one in CR for ITP; native kidney hematoma (N=1, in CR for ITP), melena (N=1) during acute ITP.

A significantly higher probability of experiencing a thrombotic event was seen in patients treated with a combination of rituximab and TPO-RA compared to TPO-RA alone, rituximab alone or steroid and IVIG treated patients (*P*=0.012) (Figure 6).

Other AE included diabetes (7.5%) and other steroid-induced side effects (17.5%), including adrenal insufficiency, visual hallucinations, irritability, weight gain and left knee

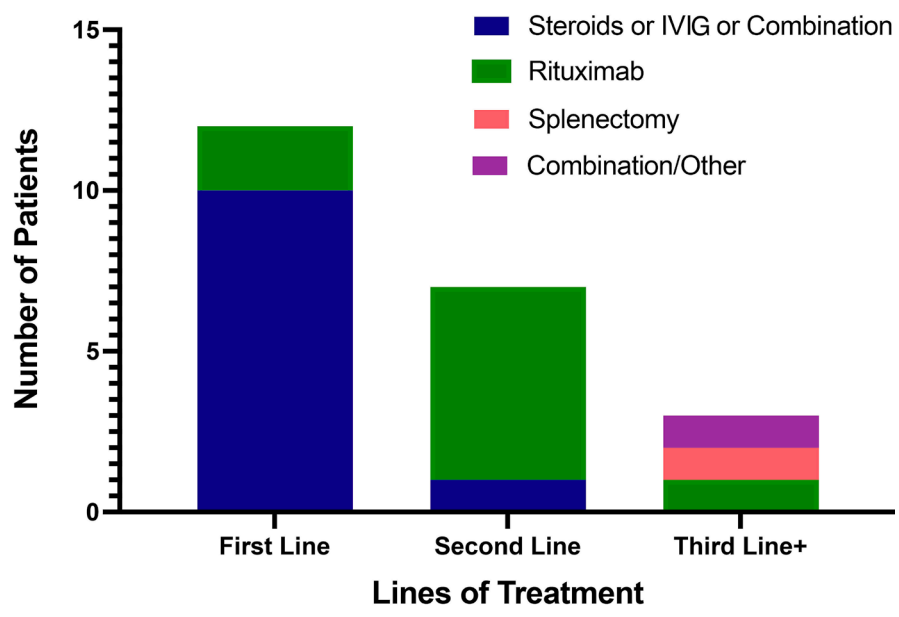


Figure 4. Autoimmune hemolytic anemia treatments. IVIG: intravenous immunoglobulins.

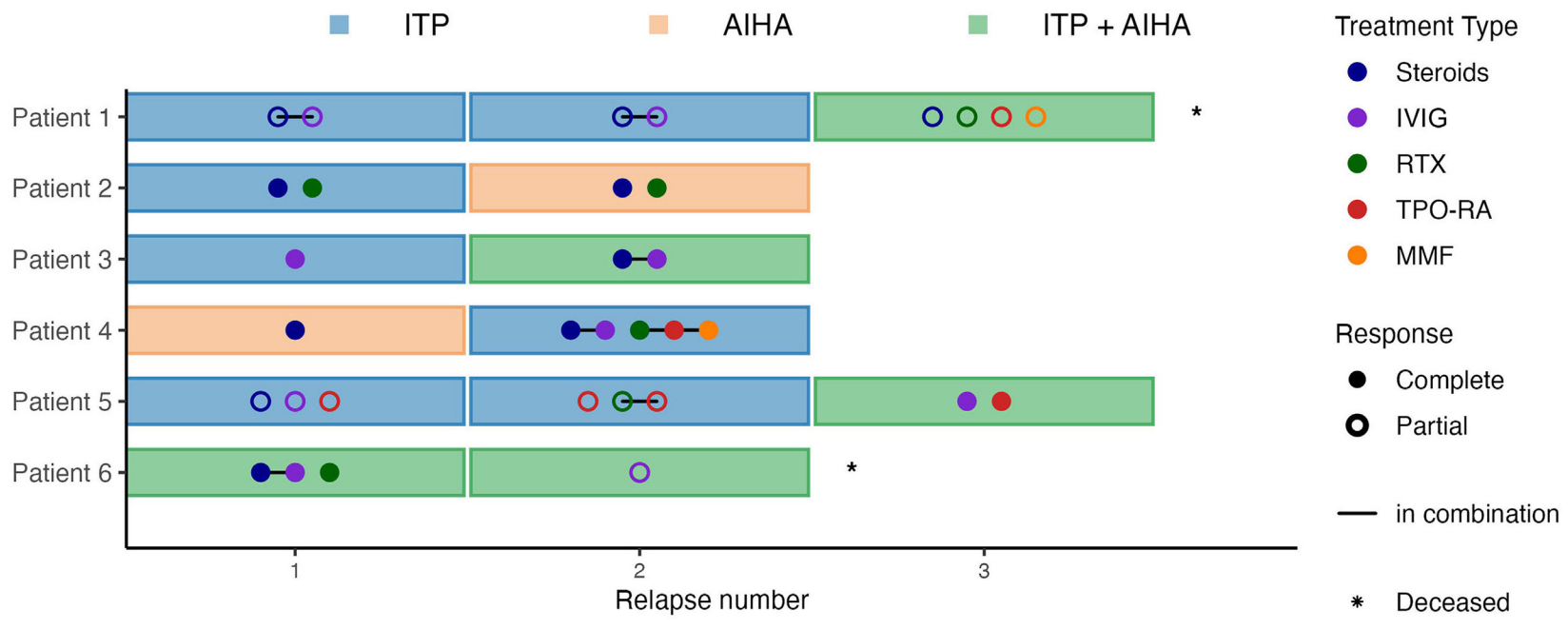


Figure 5. Description of patients with Evans syndrome and treatment received. AIHA: autoimmune hemolytic anemia; elt: eltrombopag; ITP: immune thrombocytopenia; IVIG: intravenous immunoglobulins; MMF: mycophenolate mofetil; RTX: rituximab; TPO-RA: thrombopoietin receptor-agonists.

osteonecrosis. Three patients (7%) developed renal graft failure.

Four patients (10%) developed neutropenia of uncertain origin, most likely autoimmune but possibly drug-induced, which resolved spontaneously without treatment.

One patient developed subclinical hypothyroidism and

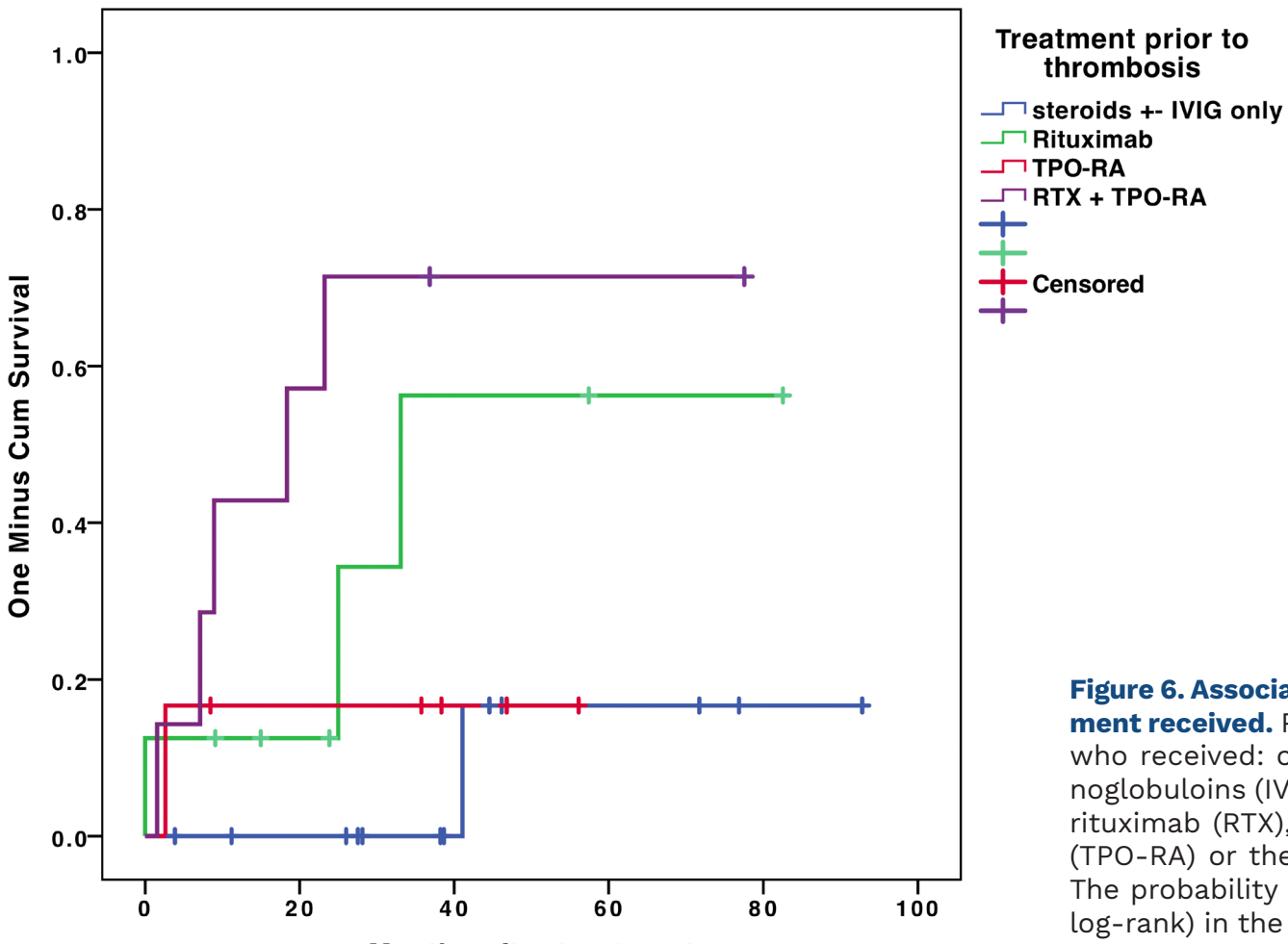


Figure 6. Association between thrombosis and treatment received. Probability of thrombosis in patients who received: only steroids or intravenous immunoglobuloins (IVIG), or an additional treatment with rituximab (RTX), thrombopoietin receptor-agonists (TPO-RA) or the combination of RTX and TPO-RA. The probability of thrombosis was higher (P=0.012, log-rank) in the latter group, even though it is confounded by additional comorbidities.

Table 2. Adverse events.

Type of AE	ITP, N=28 N (%)	AIHA, N=7 N (%)	ES, N=5 N (%)
N of patients with AE	23 (82)	6 (86)	5 (100)
DVT	6 (21)	2 (28)	2 (40)
Cardiovascular events (other than thrombosis)	7 (25)	1 (14)	3 (60)
Infections Grade ≥3	18 (64) 12 (66.6)	4 (57) 4 (100)	3 (60) 3 (100)
Bleeding	2 (7)	1 (14)	2 (40)
Diabetes	3 (10.7)	0 (0)	0 (0)
Other steroid-induced AE	5 (17.8)	2 (28.6)	0 (0)
Graft failure	1 (3.6)	3 (42.8)	1 (20)
Graft dysfunction	3 (10.7)	0 (0)	0 (0)
PTLD	4 (14)	0 (0)	1 (20)
Other malignancies	5 (18)	2 (28)	1 (20)
Neutropenia	3 (10.7)	0 (0)	1 (20)
Thyroid autoimmunity	1 (3.6)	0 (0)	1 (20)
Death	4 (14)	0 (0)	3 (60)

AE: adverse event; AIHA: autoimmune hemolytic anemia; DVT: deep vein thrombosis; ES: Evans syndrome; ITP: immune thrombocytopenia; PTLD: post-transplanted lymphoproliferative disease.

one Graves' disease: autoimmune manifestations likely related to alemtuzumab.

Five patients (12.5%) had a diagnosis of PTLD, two concomitants with ITP diagnosis and three subsequently. Eight patients (20%) developed a subsequent solid tumor (9 tumors in total): prostate cancer (N=1), anal squamous cell carcinoma (N=1), clear cell renal cell carcinoma (N=1), papillary renal cell carcinoma (N=1), squamous cell carcinoma of the skin (N=2), basal cell carcinoma (N=2), breast carcinoma (N=1).

Seven patients died (17.5%), four in the ITP group and three in the ES group. Four patients died due to infectious complications, one due to cardiac arrest and two due to PTLD, after a median of 114 months (range, 30-152) from transplantation, 57 months (range, 8-97) after cytopenia diagnosis, 39 months (range, 0-95) from the last treatment. None had received more than three lines of therapy.

Discussion

Here we report a distinctive type of secondary autoimmune disorders that arise in patients who received alemtuzumab as induction therapy for renal transplantation. The rate of post-alemtuzumab autoimmune cytopenias (around 3% per year, 2.25% ITP and 0.87% AIHA) is in line with previous reports in patients who received alemtuzumab for MS.[6,9,10] The higher frequency in males reflects the epidemiology of renal-transplanted patients at the Hammersmith Hospital.

Most patients developed autoimmunity within 5 years of alemtuzumab, with a first peak at 18-24 months and a second peak at 36 months confirming previous observations.[24-26] Although the pathogenesis of post-alemtuzumab autoimmunity is not completely understood, it appears to occur at a particular time point of immune recovery, when B cells have reached normal values and are hyper-proliferating, while CD4 cells are still markedly below normal values. Autoimmune manifestations could therefore be driven by the escape of autoreactive B cells in the absence of T-cell regulation,[27] or by the homeostatic proliferation of a clonally restricted population of T cells that survived the depletion.[28] However, only a small proportion of patients develop autoimmunity,[29] suggesting that other factors, including genetic predisposition and/or a "second hit" such as infection are necessary.

Both response and relapse rates to first-line therapy are different from those observed in patients with primary ITP[30] and AIHA.[22] Over two thirds of this patient cohort required further lines of therapy, with some having a protracted and multirefractory clinical course. This contrasts with alemtuzumab-treated MS patients who achieved SROT following standard first-line ITP therapy.[6] Despite the more refractory course, most patients were still able to discontinue TPO-RA treatment and achieve SROT,[31,32] or to achieve sustained responses with rituximab,[33,34] when compared to primary forms. This suggests that the vulnerable period for autoimmunity continues until T cells fully recover and that either TPO-RA can be used to maintain a normal platelet count, or rituximab can be used to remove the antibody-producing cells while T cells are reconstituting.

As with primary disease,[19,35] the five patients diagnosed with ES were more difficult to treat, with a 100% relapse rate.

Most patients (87.5%) experienced one or more AE attributable to their concomitant diseases, and in part, to the treatment received. While renal transplant recipients have a higher risk of cardiovascular disease-related death (50-fold higher)[36] and thromboembolic events (TE) (8-fold higher)[37-39] compared to the general population, patients who develop AIC appear to have a considerably higher rate of thrombosis. Both AIHA and ITP are also associated with an increased risk of TE compared with the general population: around two times higher in ITP and around three times higher in AIHA[40,41] perhaps compounding this existing background risk.

TPO-RA monotherapy was not associated with an increased incidence of thrombosis, confirming the safety of this treatment. Thrombosis was instead associated with rituximab and TPO-RA treatment in combination. This may reflect patients with more refractory and active disease but also suggests caution in giving combination treatment.

Post-transplant patients are at high risk of infections,[42] and 47% in this cohort experienced grade ≥3 infections. Corticosteroid therapy may have contributed to such a high percentage,[43] while infection risk after a single course of rituximab appears negligible.

The mortality observed in this cohort (17.5% with a median follow-up of 52 months; range, 8-113) is slightly higher than that expected in post-transplant patients that do not develop an autoimmune cytopenia: 16% at 5 years in the Hammersmith Hospital cohort[44] and 20-25% at 10 years in the extended literature.[45,46] The development of an autoimmune cytopenia after a renal transplantation therefore appears to be a poor prognostic factor.

How we manage autoimmune cytopenias following alemtuzumab-induced renal transplant?

Baseline investigations/workup is summarized in *Online Supplementary Table S2*. Anemia and thrombocytopenia presenting after renal transplantation require the exclusion of other causes of cytopenia (*Online Supplementary Table S2*), as well as investigation for PTLD and infections that can complicate the recovery from ITP and AIHA (including EBV, CMV, parvovirus, hepatitis A, B, C, E, and atypical infections), especially for those on continued immunosuppression.

Immune thrombocytopenia treatment

In patients who require treatment, we use a short course of high dose prednisolone (1 mg/kg for 4 days, followed by 40 mg/day for 2 weeks, 20 mg/day for 2 weeks, 10 mg/day

for 2 weeks, 5 mg/day for 2 weeks, then stop),[47] avoiding "low-dose maintenance" or repeated courses, due to the severity of steroid-related AE. In patients for whom steroids are contraindicated, IVIG monotherapy is a valid option.

For second line treatment, both rituximab (we use 1 g x 2 doses; given 2 weeks apart) and TPO-RA are highly effective, with higher SROT than that observed in primary ITP. Although the number of patients is small, there was no difference in the thrombotic or infectious risks following treatment with either TPO-RA or rituximab. As such, the choice should be driven by individual risk factors and availability. The choice of TPO-RA should be driven by the patient's preferences, comorbidities and interactions with other drugs. Once a response has been achieved, and is stable for 3-6 months, TPO-RA can be tapered and stopped if the platelet response is sustained.

Of note, three patients received TPO-RA and rituximab monotherapy upfront with 100% ORR. Given the significant morbidity associated with steroid use, we advise early consideration of steroid-sparing agents if patients do not show a good response to steroids.

The combination of TPO-RA and rituximab is an effective option, but it should be reserved for very refractory patients or in emergency situations, due to high thrombosis risk. MMF can be added in patients who are refractory, or who have fluctuating platelet counts on TPO-RA and, given the good responses in refractory patients, may have use as earlier-line therapy. Fostamatinib,[48] given its immunomodulatory activity and the fact that it does not increase the risk of thrombosis, may be a valid alternative for this cohort. The neonatal Fc receptor (FcRn) inhibitor, efgartigimod, which enhances the clearance of circulating autoantibodies without increasing thrombotic risk, may also have a role in the treatment of these patients; however, it has not yet been approved for the treatment of ITP.[49] All treatment should be tapered as soon as the platelet count has stabilized.

Given the high thrombotic risk in this population, it is important to re-introduce antiplatelet or anticoagulation treatment as soon as possible, ideally single antiplatelet or prophylactic anticoagulation when platelet count is >30x10^9/L and dual antiplatelet agents or full anticoagulation with platelet count is >50x10^9/L.

Because of the high response rates, the peculiar pathogenesis of this secondary ITP and the high comorbidity burden; more definitive options such as splenectomy are reserved for very refractory, fit patients.

Autoimmune hemolytic anemia treatment

We recommend using short courses of steroids and using rituximab early as a steroid-sparing agent. Further studies are needed to explore the use of rituximab as first-line therapy, as investigated in primary AIHA.[50] MMF is a useful adjunct in patients refractory to rituximab.

We recommend antimicrobial prophylaxis in patients who have received multiple immunosuppressive agents, particularly if they continue steroids. We also recommend short-term anticoagulant prophylaxis during hemolytic crisis due to the high risk of thrombosis and the high morbidity and mortality rates.

Due to its retrospective nature, this study has several limitations. Mild autoimmune cytopenias that resolved spontaneously may not have been referred to our service, with possible selection bias. The association between thrombosis and certain treatments should also be interpreted with caution, because other confounding factors might have contributed, including disease refractoriness, cardiovascular comorbidities, other concomitant treatments, devices or lifestyle. The small numbers and the retrospective nature of this report precluded further analysis.

Additionally, the absence of a control group prevents direct comparison, especially of adverse events - such as thrombosis and mortality.

In conclusion, hematological autoimmune complications after alemtuzumab occur in approximately 3% of renal-transplant recipients. ITP and AIHA arise similarly to the primary forms but have higher rates of SROT. Management is challenging due to patients' comorbidity burden including elevated thrombotic risk and chronic immunosuppression. Because corticosteroids exacerbate these risks, they should either be used in only short courses or avoided. Both rituximab and TPO-RA are effective and well tolerated. Antiplatelet agents and anticoagulation (if previously required) should be reinstated as soon as the platelet count has stabilized. The development of autoimmune cytopenias during T and B cell reconstitution sheds important light on the possible pathogenesis of ITP and AIHA and warrants further exploration.

Disclosures

NC is partly funded by the Imperial College NIHR Bioresources, and has received research grants from Grifols, Novartis, and Argenx; she has also received honoraria for advisory boards for Sanofi, Novartis, Sobi, Argenx, Amgen, Takeda, and Rigel. EL received honoraria from Amgen. All other authors have no conflicts of interest to disclose.

Contributions

EL, LK, SG, RC and NC designed the study and wrote the manuscript. RS provided statistical advice on data analysis. CA, MA, AL, SD, ML, AH, MS, SO, CV, DP, RS, AK, SG, and RC contributed to data collection, reviewed and approved the final version of the manuscript.

Data-sharing statement

Data is available on request to the corresponding author.

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