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Secondary Autoimmune and Inflammatory Diseases after Allogeneic Hematopoietic Stem Cell Transplantation: A Retrospective Study from the EBMT Transplant Complications and Autoimmune Diseases Working Parties

Arsene Mekinian[1], Artem Oganesyan[2], Zinaida Perić[3], Myriam Labopin[4], Urpu Salmenniemi[5], José Antonio Pérez Simón[6], Anke Verlinden[7], Ioanna Sakellari[8], Mohsen Alzahrani[9], Massimo Martino[10], Baron Frédéric [11], John A. Snowden[12], Hakan Ozdogu[13], Alexander Kulagin[14], Edgar Jost[15], Anna Torrent[16], Fabio Benedetti[17], Anna De Becker[18], Sylvie François[19], Montserrat Rovira[20], Hans Christian Reinhardt[21], Alessandra Biffi[22], Mark Ringhoffer[23], Pascal Ambron[4], Jose Luis López Lorenzo[24], Nabil Yafour[25], Alexandre Galvagni[2], Manuela Badoglio[26], Ivan Moiseev[14], Tobias Alexander[27], Mohamad Mohty[26], Olivier Fain[28], [#]Raffaella Greco[29], [#]Olaf Penack[30 31]

[#]These authors contributed equally

[1]Sorbonne Université AP-HP, Hôpital Saint Antoine, Service de Médecine Interne et Inflammation-Immunopathology-Biotherapy Department (DMU I3), Faculté de Médecine Sorbonne Université, F-75012, Paris, France
[2]Department of Internal Medicine, Jefferson Abington Hospital, Abington, PA 19001, USA
[3]Division of Hematology, Department of Internal Medicine, University Hospital Center Rijeka, Rijeka, Croatia
[4]EBMT Paris study office, Department of Hematology, Saint Antoine Hospital, INSERM UMR 938, Sorbonne University, Paris, France
[5]Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
[6]Department of Hematology, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, (IBIS, CSIC) Universidad de Sevilla, Sevilla, Spain
[7]Department of Haematology, Antwerp University Hospital, Antwerp, Belgium
[8]Hematology Department and Bone Marrow Transplant (BMT) Unit, G. Papanicolaou Hospital, 57010 Thessaloniki, Greece
[9]Division of Adult Stem Cell Transplantation & Cellular Therapy, Department of Oncology, King Abdulaziz Medical City. Ministry of National Guard – Health Affairs, Riyadh, Saudi Arabia
[10]Hematology and Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", 89133 Reggio Calabria, Italy
[11]Department of Clinical Hematology, CHU of Liège, 1 Avenue de L'hôpital, 4000, Liège, Belgium
[12]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, S5 7AU, UK; Division of Clinical Medicine, School of Medicine and Population Health, The University of Sheffield, Sheffield, UK.
[13]Department of Hematology, Adana Adult Bone Marrow Transplantation Center, Baskent University, Adana, Turkey
[14]RM Gorbacheva Research Institute, Pavlov University, Saint Petersburg, Russia
[15]Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University, Medical Faculty & Center for Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf (CIO ABCD), Aachen, Germany
[16]Clinical Haematology Department, Catalan Institute of Oncology, Germans Trias i Pujol Hospital, Badalona, Spain; Josep Carreras Leukaemia Research Institute, Germans Trias i Pujol Hospital, Autonomous University of Barcelona, Barcelona, Spain
[17]Department of Medicine, Hematology, Bone Marrow Transplant Unit- AOUI Verona, Italy

[18]*Department of Haematology Universitair Ziekenhuis Brussel Jette Belgium*
[19]*Department of Clinical Hematology, Angers University Hospital, Angers, France*
[20]*BMT Unit, Department of Haematology, Institute of Haematology and Oncology, IDIBAPS, Hospital Clinic, Josep Carreras Leukaemia Research Foundation, University of Barcelona, Barcelona, Spain*
[21]*Department of Hematology and Stem Cell Transplantation, University Hospital Essen, University Duisburg-Essen, West German Cancer Center, German Cancer Consortium, Center for Molecular Biotechnology, Essen, Germany*
[22]*Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, University of Padua, Padua, Italy*
[23]*Department of Internal Medicine III, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany*
[24]*Hematology Department, Hospital Universitario Fundación Jiménez Díaz UAM, Madrid, Spain*
[25]*Department of Hematology and Cell Therapy, Establishment Hospitalier Universitaire 1st November, Oran, Algeria; Faculty of Medicine, Ahmed Benbella Oran 1 University, Oran, Algeria*
[26]*Department of Haematology, Saint Antoine Hospital, INSERM UMR 938, Université Pierre et Marie Curie, Paris, France*
[27]*Department of Rheumatology and Clinical Immunology-Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and the Berlin Institute of Health (BIH), Berlin, Germany*
[28]*Department of Internal Medicine, Sorbonne University, DMU i3D, Saint-Antoine Hospital, Paris, France*
[29]*Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy*
[30]*Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hematology, Oncology and Tumorimmunology, Augustenburger Platz 1, 13353 Berlin, Germany; University of Berlin and Humboldt University of Berlin, Berlin, Germany;*
[31]*National Center for Tumor Diseases (NCT), Partner Site, Berlin, Germany, Berlin Center for Translational Vascular Biomedicine, Berlin, Germany*

Corresponding author:
Arsène Mekinian
Assistance Publique-Hôpitaux de Paris
Service de Médecine Interne
Hôpital Saint Antoine, AP-HP
184 rue du Faubourg Saint Antoine
75012 Paris, France
arsene.mekinian@aphp.fr
+ (33) 1 49 28 21 04

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Abstract

Introduction: Secondary autoimmune and inflammatory diseases (SAIDs) are underrecognized and poorly described after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The standardization of management is hindered by the scarcity of data on epidemiology, pathogenesis, and clinical outcomes.

Methods: To improve the evidence base, we performed a retrospective multicenter EBMT database study of patients who underwent allo-HSCT between 2005 and 2019 for either hematological malignancy or severe aplastic anemia with available information on SAIDs.

Results: We included 129 cases of SAIDs and 14,617 controls. The 5-year incidence of SAIDs was 0.9% (95% confidence interval (CI): 0.7-1.1), and the 10-year incidence was 1.1% (95% CI: 0.9-1.3). The median time from allo-HSCT to the diagnosis of SAIDs was 442 days [interquartile range (IQR): 242-1082]. Overall survival after the onset of SAIDs was 83.4% (95% CI 74.6-89.3) at 2 years and 73.4% (95% CI: 62-82) at 5 years. In multivariate analysis, risk factors significantly associated with SAIDs were bone marrow failure (Hazard Ratio (HR): 3.41 [95% CI, 1.55-7.52], p=0.002), female donor to male patient (HR 1.77 [95% CI, 1.15-2.73], p=0.009), and the presence of chronic GvHD (HR 1.61 [95% CI, 1.04-2.51], p=0.034).

Conclusion: SAIDs after allo-HSCT are rare but clinically significant entities requiring further investigations, exploring treatment and prevention strategies, as well as improving diagnostic approaches.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative procedure for patients with certain blood malignancies, non-malignant hematological conditions, and systemic inflammatory diseases. More than twenty thousand allo-HSCTs are performed in Europe annually, with a steady global increase of 7.8% per year (1).

Nonetheless, this procedure involves risks, including infections, graft-versus-host disease (GvHD), end-organ damage, graft failure, secondary malignancy and autoimmune or inflammatory diseases (SAIDs) (2,3). The latter is often poorly recognized and characterized due to many confounding factors, such as associations of the primary disease with autoimmune disorders. Based on data from smaller datasets, SAIDs is seen in only about 5-11% of people undergoing allo-HSCT, with a higher frequency in children compared to adults (4-7); however, data from larger cohorts are lacking.

Traditionally, post-transplant SAIDs are divided into main groups: hematologic and non-hematologic (8). The first group includes autoimmune cytopenias (i.e., autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), autoimmune neutropenia (AIN), and Evans syndrome). Non-hematologic SAIDs include rheumatologic conditions, autoimmune thyroiditis, cutaneous diseases, and neuromuscular manifestations (9). Risk factors are chronic GvHD (cGvHD), use of peripheral blood stem cells for transplant, mismatch between donor and recipient, minor histocompatibility antigen disparities, use of alemtuzumab or antithymocyte globulin in conditioning, T-cell replete grafts, underlying nonmalignant or metabolic disorders, as well as pre-existing autoimmunity or genetic predisposition (8,9). SAIDs usually occur within the first 2-3 years after allo-HSCT (6,7).

Data on survival outcomes in patients with post-transplant SAIDs is scarce and highly dependent on the type of condition as well as individual characteristics of patients (10). Although it is presumed that SAIDs can increase the morbidity and utilization of medical services, the impact on mortality has not been proven as of today (7). It is generally considered that if diagnosed and managed in a timely manner, favorable survival is expected in this patient population.

Although the precise mechanisms of secondary autoimmunity post-transplantation remain unclear, several theories have been proposed. Allo-HSCT may lead to impaired peripheral tolerance due to reduced number or function of T-regulatory cells with insufficient suppression of B-cell expansion (8). Alloreactive donor T-cells are also thought to trigger the autoimmune response cascade (9). B-cell hyperactivity and autoantibody production are also mentioned among possible pathways leading to loss of tolerance (8,9).

Due to a lack of data, the evidence base for management strategies is limited to anecdotal reports mostly. A myriad of different treatments has been suggested in the literature, with mixed efficacy, including corticosteroids, IV immunoglobulins, rituximab, bortezomib, and sirolimus.

The current study aims to evaluate the incidence and characteristics of SAIDs after allo-HSCT, as well as factors associated with these disorders and the impact on overall survival (OS).

Patients and Methods

This is a retrospective multicenter study based on the data collected from the EBMT registry. An initial survey to identify reported cases of SAIDs was conducted in all 696 EBMT centers. One hundred and twelve centers answered the survey. Subsequently, clinically relevant data were extracted from the EBMT database. For SAIDs cases, an additional inquiry was sent to fill out a specific questionnaire designed to gather further important information on patients, transplant characteristics, and outcomes.

The EBMT ensures that all personal data under its responsibility is processed according to the EU General Data Protection Regulation (GDPR). The data is stored in an electronic database located in a European country which is protected by safeguards that ensure security, including compliance with ISO27001 certification. EBMT centres are required to obtain signed informed consent from patients for transfer of de-identified data in accordance with data protection regulations. As per EBMT procedures, this study was formally approved by the ADWP and the TCWP.

Endpoints

The primary endpoint was the incidence of SAIDs after allo-HSCT in adult patients. Secondary endpoints were survival outcomes (including OS, non-relapse mortality (NRM), and event-free survival (EFS)), and risk factors of the occurrence of SAIDs (such as GvHD).

Inclusion and exclusion criteria

Inclusion criteria were adult patients (aged 18 years and older at the time of first allo-HSCT) transplanted between 2005 and 2019. All centers were asked to report the occurrence or not of SAID as defined by the following conditions after allo-HSCT: immune cytopenia (hemolytic anemia, immunological thrombocytopenia, neutropenia); connective tissue diseases (systemic lupus erythematosus, relapsing polychondritis, idiopathic inflammatory myopathy); systemic vasculitis (polyarteritis nodosa, giant cell arteritis, Behcet's disease, cryoglobulinemia vasculitis, unclassified forms); neutrophilic dermatosis (Sweet syndrome); inflammatory arthritis (rheumatoid arthritis, polymyalgia rheumatica, Remitting Seronegative Symmetrical Synovitis with Pitting Edema (RS3PE), or undifferentiated arthritis); undifferentiated systemic disease; auto inflammatory disease (Still's adult disease), hemophagocytic lymphohistiocytosis (HLH); autoimmune thyroiditis. Primary diagnosis and indication for allo-HSCT included hematological malignancies (acute and chronic leukemias, lymphomas, plasma cell disorders, myelodysplastic or myeloproliferative disorders) or severe aplastic anemia. The source of allograft cells was either bone marrow (BM) or peripheral blood (PB). Exclusion criteria were children, autoimmune disease as the primary indication for allo-HSCT, and the presence of autoimmune disease at the time of allo-HSCT.

Diagnoses for each SAIDs were made based on the established local protocols and guidelines from each medical center using standard diagnostic criteria for each specific autoimmune condition, similar to the approach in the non-transplant population. Depending on the disease, this normally included confirmation based on specialist evaluation and objective data, such as antibody titers or findings from corresponding imaging.

Data collection

Patient and donor baseline characteristics included age, gender, underlying hematological diagnosis of the patient, indication for allo-HSCT with the date of diagnosis, blood group (per the ABO system and the Rh system), CMV status, and Karnofsky score (KS). Transplant data contained the date of allo-HSCT, type of donor (matched related donor/matched unrelated donors (MRD/MUD), mismatched unrelated donors (mMUD), mismatched related donors (mMRD), haploidentical) human leukocyte antigen (HLA) disparity, stem cell source, conditioning regimen, serotherapy, and GvHD prophylaxis. Follow-up of allo-HSCT included autoimmune or inflammatory disorders (see inclusion criteria), acute or chronic (aGvHD and cGvHD), relapse or progression status of the last follow-up, and cause of death. The sample size was determined by available registry data

Statistical analysis

Standard demographic and transplant-related characteristics were summarized using median, range, and inter-quartile range (IQR) for continuous variables and percentages for categorical variables. Comparisons between the 2 groups (SAIDs vs controls) were performed using Fisher's exact test, χ^2 test, or Mann-Whitney test, as appropriate.

The incidence of SAIDs was defined as the probability of having had SAIDs during follow-up. OS was defined as the probability of survival irrespective of the cause of death. EFS was defined as the probability of being alive without relapse or progression of disease. NRM was the time to deaths without relapse/progression.

The probability of OS and EFS were calculated using the Kaplan-Meier estimate. Survivors were censored at last contact. Cumulative incidence was used for the estimation of the incidence of SAIDs, GvHD, relapses, and NRM. Death without experiencing SAIDs was treated as a competing event for SAIDs. Death and relapse are competing together. Relapse and death were considered competing events for acute and chronic GvHD. The median follow-up was estimated using the reverse Kaplan-Meier method. We included in the Cox model all factors differing between the 2 groups (SAID or not) and those potentially influencing the outcome. A multivariate analysis adjusting for potential confounding factors (aGvHD, cGvHD, BM failure, patient age, positive CMV status of the patient, KPS≥90, unrelated donor, haploidentical/other relative donor, female donor to male recipient, reduced intensity conditioning, TBI, in vivo T-cell depletion, year of HSCT (after 2014), source of allogeneic transplant (PB stem cells vs BM)) was performed using a Cox's proportional-hazards regression model for SAIDs. These were thought to be factors differing between study groups and potentially influencing outcomes. Results were

expressed as a hazard ratio (HR) with a 95% confidence interval (CI). To measure the impact of the occurrence of SAIDs on OS, EFS, and NRM, we considered the occurrence of SAIDs as a time-dependent variable. All analyses were conducted with a two-sided α level of 5%, and analyses were performed using R (version 4.2.3).

Results

Among the 112 responding centers in 14 countries, 129 patients developed SAIDs and 14,617 controls did not. Cases of SAIDs were identified from 27 centers. Completed questionnaires with additional data were retrieved from 101 cases in 20 centers.

Baseline characteristics of transplant recipients

The median age of allo-HSCT recipients developing SAIDs was 45.9 years (IQR: 35.1-55.3) and 49.9 years (IQR: 36.0-59.1) in the control group (p=0.05). In the control group, 57.8% were male, while the SAIDs group consisted of 58.6% males (p=0.86). The median year of transplant was 2014 (IQR: 2010 -2017) in the control group and 2015 (IQR: 2012-2017) in the SAIDs group (p=0.003). Median follow-up was 60.6 months (IQR: 34-101) in the control group and 74.3 months (IQR: 47.3-102.2) in the SAIDs group (p=0.01). The CMV status of recipients was positive in 9,765 (71.6%) in the control group and 93 (75%) in the SAIDs group (p=0.4). KS was ≥ 90 for 9,618 controls (71.3%) and 96 cases (83.5%) (p=0.004). Acute leukemia was the main indication for 8,196 cases (56.1%) in the control group and 66 patients (51.2%) in the SAIDs group, lymphoma for 1,759 (12%) in the control group and 17 (13.2%) in the SAIDs group. Bone marrow failure accounted for 423 patients (2.9%) in the control group and 11 patients (8.5%) in the SAIDs group. No major differences were found between the two groups in terms of Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) or status at the time of transplant (Table 1).

Characteristics of HSCT and donors

Detailed characteristics of the allo-HSCT procedure are shown in Table 2. Successful allo-HSCT engraftment was seen in all patients in the SAIDs group (n=127, 100%) and the vast majority of patients in the control group (n=13,538, 97.1%) with no statistically significant difference (p=0.055). Complete remission was observed in 86.7% (n=10,723) of patients in the control group and 93.4% (n=113) of patients in the study group (p=0.075). No differences were found between the groups in terms of graft cell source, total number of infused CD34+ stem cells, intensity of conditioning, or total body irradiation (Table 2). Female donors represented 36.8% of the control group (n=5,321) and 47.2% (n=60) in the SAIDs group (p=0.015). Female-to-male matching was seen in 2,672 (18.5%) in the control group and 35 (27.6%) in the SAIDs group (p=0.008). The median donor age was 36.5 years (IQR: 27.2-48.1) in the control group and 37.9 years (IQR: 26.6-51.3) in the SAIDs group (p=0.22). Donor CMV status was positive for 7,768 donors (56.9%) in the control group and 75 donors (61%) in the SAIDs group. Syngeneic or matched sibling donors represented 36.7% (n=5,365) of controls and 40.9% of cases (n=52) (p=0.017).

For GvHD prevention, no differences were found for post-transplant cyclophosphamide, *ex vivo* or *in vivo* T-cell depletion. The most common combination was cyclosporine and methotrexate, which was used in 6,444 controls (45.8%) and 57 cases (45.2%). Cyclosporine combination with

mycophenolate mofetil was utilized in 2,612 controls (18.6%) versus 13 cases (10.3%). A combination of tacrolimus and sirolimus was applied in 219 controls (1.6%) versus 12 cases (9.5%).

According to Glucksberg's classification of aGvHD, Grade I was seen in 2,622 controls (18.9%) and 20 cases (15.9%), Grade II in 2,211 (16%) and 18 (14.3%), Grade III in 921 (6.6%) and 11 (8.7%), Grade IV in 546 (3.9%) and 3 (2.4%).

Among patients with available data of aGvHD (50 cases), most of aGvHD (n=47) predated SAIDs. Out of these 50 patients, grade II and above were seen in 31 patients, with the most affected organs being skin, liver, and intestines (Table 3).

Incidence of SAIDs

By far, the most common SAIDs was hematological SAIDs (n=39, 30%), followed by autoimmune thyroiditis (n=22, 17%), and arthritis (n=16, 12.4%), psoriasis (n=6, 4.6%), and autoimmune encephalitis (n=6, 4.6%) (Table 4). The cumulative incidence of SAIDs was calculated for 122 cases (7 cases had missing dates of diagnosis). The median time from allo-HSCT to the diagnosis of SAIDs was 441.5 days [IQR: 242-1082]. The 5 and 10-year incidences were estimated at 0.926% (95% CI: 0.765-1.113) and 1.104% (95% CI: 0.905-1.335), respectively.

Risk factors for developing SAIDs

Results of univariate analysis are summarized in Table 5. In multivariate analysis, four factors were statistically significantly associated with a higher risk of SAIDs: bone marrow failure as allo-HSCT indication (HR 3.41 [95% CI: 1.55-7.52], p=0.002)), the year of transplantation after 2014 (median) (HR 1.12 [95% CI: 1.05-1.19], p=0.0003)), female donor to male patient (HR 1.77 [95% CI: 1.15-2.73], p=0.009), and chronic GvHD studied as a time-dependent variable (HR 1.61 [95% CI: 1.04-2.51], p=0.034).

Impact of SAIDs on outcomes

Two-year and 5-year OS of patients with SAIDs were 83.4% (95% CI: 74.6-89.3) and 73.4% (95% CI: 62-82), respectively (Table 6). No association was found between the presence of SAIDs and further disease relapses of the underlying hematological conditions (HR 0.63 [95% CI: 0.35-1.15], p=0.13), OS (HR 0.93 [95% CI: 0.64-1.34], p=0.68), and EFS (HR: 1.0 [95% CI: 0.7-1.44], p=0.98). No statistically significant association was found for NRM as well, despite an observed trend (HR: 1.52 [95% CI: 0.96-2.38], p=0.072) .

SAIDs treatment and outcomes:

In the SAIDs group, 7 (out of 129, 5.4%) patients developed additional SAID. Among these new cases, four were autoimmune cytopenias (3 ITP and 1 AIHA), 1 was vasculitis, 1 was arthritis, and 1 was myositis. Majority of SAIDs cases required treatment (84.4%). These treatments included systemic corticosteroids in 57 patients (64%), classical disease-modifying anti-

rheumatic drugs (DMARD) in 23 patients (25.8%) (most commonly cyclosporine in 11 patients, methotrexate in 4 patients, and mofetil mycophenolate in 4 patients), and biological targeted drugs in 26 patients (31.3%) (most commonly, rituximab in 19 patients). Other therapies were required in 31 cases (39.2%), such as intravenous immunoglobulin (IVIg) (7 patients), bortezomib (2 patients), autologous HSCT (1 patient), intense blood transfusion (seven units of packed red blood cells in 1 patient), thrombopoietin (TPO) agonist (2 patients), and hemodialysis (1 patient). Treatment for the 3 more frequent SAIDs are summarized in Table 7.

Of the 86 responses from complementary outcomes, 58 (67.4%) achieved complete remission with a median time of 161.5 days. Twenty-three patients (26.7%) still had active diseases. Only eight patients relapsed among the 58 who achieved remission (13.8%), with a median time from remission to relapse of 109.5 days.

Out of the 129 patients with SAIDs, 29 died. The most frequent cause of death was infections (9 patients) and GvHD (8 patients). Secondary neoplasms were responsible for two deaths (Table 8).

Discussion

It has been estimated that approximately 10% of the general population has autoimmune diseases, based on a large cohort study involving 22 million people from the UK (11). The most commonly seen conditions include autoimmune thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, psoriasis, inflammatory bowel disease, vitiligo, and pernicious anemia (11,12). Interestingly enough, data from our cohort somewhat mirrored the frequency seen in the general population, with thyroiditis being the most common autoimmune manifestation among SAIDs (Table 9).

Overall, the risk of SAIDs after allo-HSCT appeared to be small, with <1% at 5-year follow-up and only 1.1% at 10 years, with the median time from transplant to SAIDs diagnosis of 1.2 years. Data from previous studies showed comparably higher rates of SAIDs. For example, in children with primary immunodeficiency, there was a cumulative incidence of non-hematologic SAIDs of 7% (95% CI, 5–11%) at 5 years and 11% (95% CI, 7–17%) at 8 years after transplant, respectively (6). The median time from transplant to autoimmune conditions ranged from 6.5 months for autoimmune cytopenias (6) to 2.2 years for non-hematological autoimmune diseases (7). Another retrospective study of 530 patients with acquired aplastic anemia found a cumulative incidence of 4.6% (95% CI, 2.8–6.5%) at 5 years and 5.1% (95% CI, 3.1–7.2%) at 10 years, respectively. Among 445 adults with malignant hematopoietic conditions requiring allo-HSCT, there was a 4% (95% CI, 2.7–5.3%) incidence at 3 years post-transplant (4). Another multicenter study involving 1377 adult patients treated with allo-HSCT for blood malignancies found an incidence of 2.2% of hematologic SAIDs (13). The low rate of autoimmune conditions in our cohort may stem from underreporting, as many autoimmune diseases might have been

miscategorized as various manifestations of cGvHD, whereas the prevalence of cGvHD was high at 44.7%. In clinical practice, distinguishing autoimmune conditions from unusual presentation of cGvHD can be challenging, where overlaps in affected organ systems can make accurate diagnosis or categorization difficult.

Patients with SAIDs were likely to receive a transplant at a comparably younger age (45.9 vs 49.9 years old, p=0.05) and have a higher performance score (KS≥90: 83.5% vs 71.3%, p=0.004). Data from pediatric patients indicates that older age at transplant is associated with a higher risk and incidence of SAIDs (7). Previous studies showed that haploidentical related donors had a higher incidence of SAIDs in comparison to MRD and MUD (4,7). Although prior literature indicated that cord blood as a stem cell source was linked with an elevated risk, while T cell-depleted grafts were associated with a lower risk of post-transplant autoimmunity (4,9), the current cohort analysis could not confirm these findings.

Our analysis did not show a significant association between aGvHD and SAIDs; nonetheless, grades II-IV GvHD were associated with a 58% risk of developing SAID (p=0.034) in this cohort. Chronic GvHD was linked to a higher risk of SAIDs (HR 1.61 [95% CI, 1.04-2.51], p=0.034). Chronic GvHD was shown to be a risk factor for SAIDs (both hematologic and non-hematologic) in several studies (4,14). Lv and colleagues found that cGvHD was linked to a HR of 3.76 (95% CI, 1.18–11.92; p=0.025) for SAIDs (4). On the other hand, data regarding links between aGvHD and SAIDs is limited. However, there have been possible implications from the former in causing thymic damage and loss of regulatory T-cell control, which can initiate chronic immune dysregulation leading to an ultimate autoimmune condition. Moreover, the evolution of aGvHD to chronic form requires expansion of autoreactive T-cells and B-cells from donors that will result in autoimmunity (15,16).

The SAIDs group had a higher prevalence of female donors (47.2% vs 36.8%, p=0.015). Female-to-male matching was associated with 77% higher risk of SAIDs (HR 1.77 [95% CI: 1.15-2.73], p=0.009). Prior data supported this finding (17). Female donor to male recipient is known to be a risk factor for cGvHD (18,19), which, as mentioned above, is itself linked to SAIDs. The mechanism behind such links is thought to be an upregulation of the immune response to male-specific antigens that may result in autoimmunity.

Bone marrow failure diagnosis was associated with a higher risk of SAIDs with an HR 3.41 ([95% CI: 1.55-7.52], p=0.002) compared to the control group in our cohort. Previous studies demonstrated that non-malignant conditions (such as autoimmune diseases or primary immunodeficiencies) as an indicator for allo-HSCT were associated with a higher risk of SAIDs (4,20,21).

Our study failed to find any association between occurrence of SAIDs and source of the graft, conditioning regimen intensity, or number of injected cells. This finding contradicts the results reported in the previous studies. In pediatric cohorts, cord blood was shown to be linked with a higher risk of SAIDs. Similarly, haploidentical donor transplants had a higher 3-year incidence

of SAIDs (8.7%, 95% CI, 5.7–11.7%) compared to matched sibling donors (3.5%, 95% CI, 0.9–6.1%, p=0.004) or matched unrelated donors (1.8%, 95% CI, 0.6–3.0%, p=0.012) (4).

SAIDs had no significant impact on the relapse of the underlying blood malignancy or overall survival in our study. Nonetheless, we observed a trend for better engraftment (100% vs 91.1%, p=0.075) and complete remission (93.4% vs 86.7%, p=0.055) in the SAIDs group. To the best of our knowledge, no previous investigation reported specific outcomes related to the incidence of SAIDs.

It is important to note that cGvHD and SAIDs share common risk factors, common pathophysiological pathways, and overlap in clinical manifestations, making diagnostic distinction challenging. SAIDs require the presence of disease-specific autoantibodies and biomarkers for confirmation. However, antibodies do not exclude cGvHD and can co-occur, representing a subclass called "*other features or unclassified entities*", especially in cases of ITP and AIHA (22). The latter complicates differentiation between cGvHD and SAIDs, potentially leading to higher risk of misclassification. To date, there is no established guidance on the distinction between cGvHD, post-transplant immune dysregulations, and SAIDs. This question remains an area of further investigation and clarification.

We did not find any associations between TBI and SAIDs. Buxbaum and colleagues discuss in their article that the absence of TBI in conditioning regimens can be a risk factor for autoimmune cytopenia after allo-HSCT, particularly in cases of AIHA and immune thrombocytopenia, in pediatric populations (8). Although seemingly counterintuitive, the protective effect of TBI against autoimmune cytopenias was demonstrated in a comprehensive review article by Neunert and Despotovic, where non-TBI-containing conditioning was associated with an odds ratio of 1.82 (95% CI: 1.01–3.26) of AIHA and immune thrombocytopenia (23). Potential mechanisms include a deeper immunosuppressive impact when compared to chemotherapy-only regimens, possibly due to the complete ablation of autoreactive lymphocytes through better penetration of residual tissues. These protective effects of TBI are less explored in adult populations (24). One of the potential reasons can be related to increased tissue toxicity, to which adult patients are less resilient compared to children.

Noticeable differences in the incidence of SAIDs between our cohort and those reported in the literature may stem from several reasons. Suboptimal ascertainment related to lack of clinical awareness and, most prominently, overall differentiation between cGvHD and SAIDs, leading to underdiagnosis, can be a significant contributor. As already mentioned, there is no standardized workup for SAIDs, and distinction from cGvHD remains an area of further clarification. Most of the present data originates from pediatric populations, whose immune regulations differ from those of adult patients. Our study also reports data from a registry, which is subject to bias as a limitation, especially when compared to prospective studies

The present study has several important limitations. First, bias inherent to the observational nature of the study restricts the generalizability of the findings. Second, it was difficult to

account for all missing data, which nonetheless represented a relatively small proportion of the study population. Third, there was a lack of strict standardization for the diagnosis and evaluation of the severity of all autoimmune conditions. Due to the retrospective nature of the study design, we were also unable to universally adjudicate against alternative etiologies, including infectious or drug related. These limitations are balanced by strengths. To our knowledge, this is one of the first studies to investigate associations of SAIDs in adult patients receiving allo-HSCT. Additionally, our study used multicenter referral across Europe, which enhances the generalizability of the results. Future prospective studies should aim to control these factors while implementing a universal protocol for participating sites to provide more reliable and specific diagnoses for SAIDs.

Conclusions

SAIDs remain a relatively rare complication of allo-HSCT with poorly described clinical characteristics, especially in the adult population. The present multicenter study demonstrated that female-to-male matching, cGvHD, and bone marrow failure as the indication of allo-HSCT were risk factors for SAIDs. Further research is needed to provide a better understanding of pathogenetic mechanisms of SAIDs, to develop screening tools, and to identify effective treatment strategies for SAIDs.

Conflicts of Interest Statements

JAS declares no COI directly relevant to study, but has undertaken consultancy for Sanofi, Jazz, Medac, Vertex and BMS in years of the study

OP has no COIs directly related to this work. OP has received honoraria or travel support from Alexion, Gilead, Jazz, MSD, Neovii, Novartis, Pfizer and Therakos. He has received research support from Incyte, Gilead and Priothera. He is member of advisory boards to Apogepha, Alexion, Equillium Bio, Jazz, Gilead, Novartis, MSD, Omeros, Orca Bio, Priothera, Sanofi, Shionogi and SOBI.

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Table 9: Clinical implications of SAIDs from the study cohort

Table 1: Baseline characteristics of study population

		Total (n=14746)	Controls (n=14617)	SAIDs (n=129)	P-value
Follow-up months (reverse KM)	median [IQR]	60.7 [34.1-101]	60.6 [34.0-101]	74.3 [47.3-102.2]	
Year transplant	median (min-max) [IQR]	2014 (2005-2019) [2010-2017]	2014 (2005-2019) [2010-2017]	2015 (2005-2019) [2012-2017]	**0.003**
	missing	1	0	1	
Patient age (years)	median (min-max) [IQR]	49.9 (18-78.7) [36-59.1]	49.9 (18-78.7) [36-59.1]	45.9 (18.6-68.6) [35.1-55.3]	**0.05**
	missing	1	0	1	
Patient sex	Male	8517 (57.8%)	8442 (57.8%)	75 (58.6%)	0.86
	Female	6217 (42.2%)	6164 (42.2%)	53 (41.4%)	
	missing	12	11	1	
Patient CMV	CMV negative	3910 (28.4%)	3879 (28.4%)	31 (25%)	0.4
	CMV positive	9858 (71.6%)	9765 (71.6%)	93 (75%)	
	missing	978	973	5	
HCT-CI	HCT-CI = 0	4326 (56.4%)	4277 (56.4%)	49 (55.7%)	0.14
	HCT-CI = 1 or 2	1533 (20%)	1509 (19.9%)	24 (27.3%)	
	HCT-CI ≥3	1812 (23.6%)	1797 (23.7%)	15 (17%)	
	Missing	7075	7034	41	
Karnofsky score	<90	3885 (28.6%)	3866 (28.7%)	19 (16.5%)	**0.004**
	≥90	9714 (71.4%)	9618 (71.3%)	96 (83.5%)	
	missing	1147	1133	14	
Diagnosis	Acute leukemia	8262 (56%)	8196 (56.1%)	66 (51.2%)	
	Chronic leukemias	997 (6.8%)	990 (6.8%)	7 (5.4%)	
	Lymphoma	1776 (12%)	1759 (12%)	17 (13.2%)	
	Plasma cell disorders	717 (4.9%)	714 (4.9%)	3 (2.3%)	
	MDS/MPN	2413 (16.4%)	2391 (16.4%)	22 (17.1%)	
	Bone marrow failure	434 (2.9%)	423 (2.9%)	11 (8.5%)	
	Hemoglobinopathies	147 (1%)	144 (1%)	3 (2.3%)	
Status at transplant	CR1/CP1	5723 (41%)	5668 (41%)	55 (44.7%)	0.29
	CR2/CP2	1701 (12.2%)	1688 (12.2%)	13 (10.6%)	
	CR3	279 (2%)	277 (2%)	2 (1.6%)	
	No CR	5690 (40.8%)	5646 (40.9%)	44 (35.8%)	
	CR unknown	549 (3.9%)	540 (3.9%)	9 (7.3%)	
	missing	804	798	6	

CR: Complete response; HCT-CI: Hematopoietic cell transplantation-specific comorbidity index; KM: Kaplan-Meier; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasms

Table 2: Transplants descriptions

		Total (n=14746)	Controls (n=14617)	SAID (n=129)	P-value
Type of donor	MSD/Syngeneic	5417 (36.7%)	5365 (36.7%)	52 (40.9%)	**0.017**
	Unrelated Donor	7718 (52.3%)	7665 (52.4%)	53 (41.7%)	
	Other relative	1609 (10.9%)	1587 (10.9%)	22 (17.3%)	
	Missing	2	0	2	
Type of donor	MSD	5359 (36.9%)	5307 (36.8%)	52 (40.9%)	
	UD 10/10	4480 (30.8%)	4449 (30.9%)	31 (24.4%)	
	UD 9/10	1360 (9.4%)	1348 (9.4%)	12 (9.4%)	
	UD >8/10	1 (0%)	0 (0%)	1 (0.8%)	
	UD HLA unknown	1877 (12.9%)	1868 (13%)	9 (7.1%)	
	Haploidentical	1337 (9.2%)	1322 (9.2%)	15 (11.8%)	
	Relative <2 mismatches	5 (0%)	0 (0%)	5 (3.9%)	
	Relative (unknown number of mismatches)	116 (0.8%)	114 (0.8%)	2 (1.6%)	
	missing	211	209	2	
Donor sex	Donor male	9193 (63.1%)	9126 (63.2%)	67 (52.8%)	**0.015**
	Donor female	5381 (36.9%)	5321 (36.8%)	60 (47.2%)	
	Missing	172	170	2	
Female-to-male transplant	Other	11931 (81.5%)	11839 (81.6%)	92 (72.4%)	**0.008**
	Female to male	2707 (18.5%)	2672 (18.4%)	35 (27.6%)	
	Missing	108	106	2	
Sex matching	Male to male	5714 (39.2%)	5675 (39.3%)	39 (30.7%)	**0.042**
	Male to female	3468 (23.8%)	3440 (23.8%)	28 (22%)	
	Female to male	2707 (18.6%)	2672 (18.5%)	35 (27.6%)	
	Female to female	2674 (18.4%)	2649 (18.3%)	25 (19.7%)	
	Missing	183	181	2	
Donor age	Median (min-max) [IQR]	36.5 (0.1-122.7) [27.2-48.1]	36.5 (0.1-122.7) [27.2-48.1]	37.9 (18.9-72.1) [26.6-51.3]	0.22
	Missing	4574	4562	12	
Donor CMV	CMV negative	5940 (43.1%)	5892 (43.1%)	48 (39%)	0.36
	CMV positive	7843 (56.9%)	7768 (56.9%)	75 (61%)	
	Missing	963	957	6	
Cell source	Bone marrow	2209 (15%)	2188 (15%)	21 (16.4%)	0.48
	Peripheral blood	12463 (84.5%)	12357 (84.5%)	106 (82.8%)	
	Bone marrow + Peripheral blood	73 (0.5%)	72 (0.5%)	1 (0.8%)	
	Missing	1	0	1	

Total infused CD34⁺ cells (10e5/kg)	Median (min-max) [IQR]	474 (1-1208) [326-700]	475 (1-1208) [326-700]	467 (67-1206) [331-700.5]	0.7
	Missing	9504	9486	18	
Intensity of conditioning	Myeloablative conditioning	8302 (56.8%)	8227 (56.8%)	75 (59.5%)	0.53
	Reduced-intensity conditioning	6317 (43.2%)	6266 (43.2%)	51 (40.5%)	
	Missing	127	124	3	
Total body irradiation	No	10783 (73.5%)	10688 (73.4%)	95 (74.8%)	0.73
	Yes	3897 (26.5%)	3865 (26.6%)	32 (25.2%)	
	Missing	66	64	2	
Ex vivo TCD	No ex vivo TCD	14253 (97.8%)	14130 (97.8%)	123 (97.6%)	0.76
	Ex vivo TCD	327 (2.2%)	324 (2.2%)	3 (2.4%)	
	Missing	166	163	3	
In vivo TCD	No in vivo TCD	6904 (48.6%)	6836 (48.6%)	68 (53.5%)	0.26
	In vivo TCD	7301 (51.4%)	7242 (51.4%)	59 (46.5%)	
	Missing	541	539	2	
Post-transplant cyclophosphamide	No	11862 (84.5%)	11752 (84.5%)	110 (87.3%)	0.38
	Yes	2179 (15.5%)	2163 (15.5%)	16 (12.7%)	
	Missing	705	702	3	
GvHD prevention	Steroids	1363 (9.6%)	1352 (9.6%)	11 (8.7%)	
	MTX + Cyclosporine	116 (0.8%)	116 (0.8%)	0 (0%)	
	Tacrolimus	208 (1.5%)	207 (1.5%)	1 (0.8%)	
	MMF	124 (0.9%)	122 (0.9%)	2 (1.6%)	
	Steroids + MTX	6501 (45.8%)	6444 (45.8%)	57 (45.2%)	
	MTX + Tacrolimus	413 (2.9%)	407 (2.9%)	6 (4.8%)	
	Steroids + MMF	2625 (18.5%)	2612 (18.6%)	13 (10.3%)	
	Steroids + Tacrolimus	117 (0.8%)	116 (0.8%)	1 (0.8%)	
	Steroids + MTX + MMF	168 (1.2%)	167 (1.2%)	1 (0.8%)	
	MMF + Tacrolimus	1668 (11.7%)	1651 (11.7%)	17 (13.5%)	
	MMF + Sirolimus	66 (0.5%)	66 (0.5%)	0 (0%)	
	Steroids + MMF + Tacrolimus	58 (0.4%)	57 (0.4%)	1 (0.8%)	
	Tacrolimus + Sirolimus	231 (1.6%)	219 (1.6%)	12 (9.5%)	
	Steroids + MMF + Tacrolimus + Sirolimus	1 (0%)	1 (0%)	0 (0%)	
	Other	546 (3.8%)	542 (3.8%)	4 (3.2%)	
	Missing	541	538	3	
Best response	Complete response	10836 (86.8%)	10723 (86.7%)	113 (93.4%)	0.075

	No response or progression	1374 (11%)	1368 (11.1%)	6 (5%)	
	Partial response	278 (2.2%)	276 (2.2%)	2 (1.7%)	
	Missing	2258	2250	8	
HSCT engraftment	No	409 (2.9%)	409 (2.9%)	0 (0%)	0.055
	Yes	13665 (97.1%)	13538 (97.1%)	127 (100%)	
	Missing	672	670	2	
Acute GvHD	Grade I	2642 (18.9%)	2622 (18.9%)	20 (15.9%)	Not done
	Grade II	2229 (15.9%)	2211 (16%)	18 (14.3%)	
	Grade III	932 (6.7%)	921 (6.6%)	11 (8.7%)	
	Grade IV	549 (3.9%)	546 (3.9%)	3 (2.4%)	
	Grade unknown	128 (0.9%)	127 (0.9%)	1 (0.8%)	
	No GvHD (Grade 0)	7499 (53.6%)	7426 (53.6%)	73 (57.9%)	
	Missing	767	764	3	

CMV: cytomegalovirus; GvHD: Graft-versus-Host Disease; HSCT: hematopoietic stem cell transplantation; IQR: interquartile range; MMF: mycophenolate mofetil; MSD: matched sibling donor; MTX: methotrexate; TCD: T-cell depletion; UD: unrelated donor.

Table 3: **Acute Graft-versus-host-Disease (GvHD) in SAID group, N=129**

Any Grade		**N**	**Median time Day** (min-max)
	None	74	
	Before SAID	47	343 (2-3912)
	After SAID	3	2, 73 and 194 days
	Total	124	
	Missing	5	
Grades II-IV		**N**	
	None	95	
	Before SAID	29	384 (2-2586)
	After SAID	2	2 and 73 days
	Missing	3	
Acute GvHD (n=50)	**Organ involved**	**Grade per OMS**	**N**
	Skin	0	6
		1	15
		2	20
		3	9
	Liver	0	42
		1	2
		2	3
		3	1
		4	1
		Missing	1
	Lower GI tract	0	33
		1	5
		2	5
		3	1
		4	2
		Missing	4
	Upper GI tract	0	40
		1	4
		2	2
		Missing	4
	Intestines	0	30
		1	7
		2	6

		3	2
		4	3
		Missing	2
	Other organs	Eosinophilia	1
		Eyes	1
		Joints	1
		Mouth	1

GI: gastrointestinal; GvHD: graft-versus-host disease; OMS: oral mucosal score

Table 4: **SAID diagnoses**

Type of SAID	Total number (n=129)	Completed cases (n=101)
Hematological SAID	39	35
Autoimmune thyroiditis	22	19
Arthritis	16	11
Autoimmune encephalitis	6	6
Psoriasis	6	5
Myasthenia	4	2
Vasculitis	4	3
SSc	3	
Guillain-Barre	3	2
Inflammatory pneumonitis	3	
Hepatitis	3	2
Myositis/Polymyositis	3	3
MS	2	2
Coeliac-RA	1	
DLE (Discoid lupus)	1	
Subacute myeloradiculopathy	1	
Panceatitis	1	1
Colitis ulcerosa	1	1
Immunolog/ synovitis	1	1
Antiphospholipid syndrome	1	1
SLE	1	1
Sjogren	1	
Cauda equine syndrome (CES)	1	1
Immunolog/ myelitis	1	1
Antinuclear Antibodies positivity (not specified)	1	1
Glomerulosclerosis	1	1
Raynaud	1	1
Dermatitis numular	1	1

Table 5: **Risk factors for SAIDs (univariate analysis)**

Parameters		Cumulative incidence of SAID (5 years)	p-value
Patient age	age< 50 years (median)	1.19% [0.93-1.51]	**0.003**
	age≥ 50 years	0.65% [0.48-0.87]	
Patient sex	Male	0.94% [0.73-1.20]	0.55
	Female	0.88% [0.65-1.17]	
CMV status	CMV negative	0.81% [0.55-1.17]	0.25
	CMV positive	1.001% [0.80-1.24]	
Karnofsky score	<90	0.50% [0.30-0.79]	**0.003**
	≥90	1.04% [0.83-1.29]	

Type of donor	MSD/syngeneic	1.004% [0.74-1.34]	0.029
	UD	0.73% [0.55-0.97]	
	Haploidentical / other relative	1.37% [0.84-2.13]	
Donor sex	Donor male	0.77% [0.59-0.99]	**0.019**
	Donor female	1.16% [0.87-1.52]	
Female-to-male transplant	Other	0.81% [0.65-1.01]	**0.006**
	Yes	1.36% [0.93-1.92]	
Intensity of conditioning	MAC	0.86% [0.66-1.10]	0.72
	RIC	0.96% [0.71-1.26]	
TBI	CT	0.97% [0.78-1.20]	0.33
	TBI	0.75% [0.50-1.09]	
In vivo T-cell depletion	No	1.04% [0.79-1.34]	0.25
	Yes	0.86% [0.65-1.11]	
Year of BMT	year<2014	0.45% [0.31-0.64]	**0.001**
	year>=2014	1.42% [1.12-1.77]	
Cell source	Bone marrow	0.98% [0.58-1.55]	0.37
	Peripheral blood	0.90% [0.73-1.10]	
Diagnosis	Acute leukemia	0.82% [0.62-1.06]	**<0.001**
	Chronic leukemia	0.78% [0.35-1.54]	
	Lymphoma	0.91% [0.50-1.54]	
	Plasma cell disorders	0.30% [0.06-1.02]	
	MDS/MPN	1.01% [0.64-1.53]	
	Bone marrow failure	3.85% [1.97-6.70]	
	Hemoglobinopathies	2.12% [0.57-5.62]	
Bone Marrow failure	No	0.85% [0.69-1.03]	**<0.001**
	Yes	3.85% [1.97-6.70]	

CT: chemotherapy alone; MAC: Myeloablative conditioning; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasms; MSD: match sibling donor; RIC: reduced intensity conditioning; TBI: total body irradiation; UD: unrelated donor.

Table 6: Multivariate analysis of 107 cases with complete data

Parameters	HR (95% CI)	p-value
Acute graft-versus-host disease, grades II-IV	1.38 (0.87-2.17)	0.17
Chronic graft-versus-host disease	**1.61 (1.04-2.51)**	**0.034**
Bone marrow failure	**3.41 (1.55-7.52)**	**0.002**
Patient age (per 10 years)	0.89 (0.77-1.03)	0.12
Positive CMV status of the patient	1.19 (0.76-1.86)	0.44
Karnofsky Performance Status (KPS) ≥90	1.42 (0.85-2.37)	0.18
Unrelated donor	0.99 (0.63-1.56)	0.97
Haploidentical/other relative	1.36 (0.76-2.44)	0.3
Female donor to male recipient	**1.77 (1.15-2.73)**	**0.009**
Reduced intensity conditioning (RIC)	1.12 (0.75-1.68)	0.58
Total body irradiation (TBI)	0.8 (0.5-1.26)	0.33
In vivo T-cell depletion	0.78 (0.51-1.21)	0.27
Year of allogeneic hematopoietic stem cell transplantation (after 2014)	**1.12 (1.05-1.19)**	**0.0003**
Source of allogeneic transplant: peripheral blood stem cells vs bone marrow	1.23 (0.7-2.17)	0.47

Table 7: Treatment for SAID patients

		RMD	Hematological	Neurological	Gastrointestinal
Nr treatment / Total number of SAID (completed data)		n=9/12	n=30/35	n=11/13	n=4/4
Steroids	No	4 (36.4%)	5 (15.6%)	3 (27.3%)	0
	Yes	7 (63.6%)	27 (84.4%)	8 (72.7%)	4 (100%)
	missing	10	7	6	2
DMARD	No	6 (50%)	22 (68.8%)	7 (58.3%)	3 (75%)
	Yes	6 (50%)	10 (31.3%)	5 (41.7%)	1 (25%)
	missing	2	0	0	
SAID Biological targeted drugs	No	9 (100%)	13 (40.6%)	7 (63.6%)	3 (100%)
	Yes	0	19 (59.4%)	4 (36.4%)	
	missing	3	0	0	

DMARD: disease modifying anti-rheumatic drug, RMD rheumatoid musculoskeletal diseases

Table 8: Causes of death in SAIDs group, n=29

Causes of death	N
Infection/Sepsis	16
Graft-versus-Host Disease	4
Hemorrhage	1
Pulmonary embolism	1
Central nervous system toxicity with thrombotic microangiopathy	1
Multiorgan failure	1
Lung cancer	1
Relapses or progression of original disease	2
Secondary malignancy	1
Unknown	1

Table 9: Clinical implications of SAIDs from the study cohort

Typical time-to-onset from allo-HSCT	442 days
Common SAIDs types	Hematological SAIDs (35%) Autoimmune thyroiditis (19%) Arthritis (11%)
Risk factors	Chronic GvHD Female-to-male transplant Bone marrow failure
Commonly used treatments	Steroids (53%) Biologicals/targeted drugs (28%) DMARDs (19%)
Allo-HSCT: allogeneic hematopoietic stem cell transplantation; DMARDs: disease-modifying antirheumatic drugs; GvHD: graft-versus-host disease; SAIDs: secondary autoimmune diseases.	