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ATG and other serotherapy in conditioning regimens for autologous HSCT in autoimmune diseases: a survey on behalf of the EBMT Autoimmune Diseases Working Party (ADWP)

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TO THE EDITOR:

Autologous hematopoietic stem cell transplantation (HSCT) is a therapeutic option for severe/refractory autoimmune diseases (AD) [1, 2] and is now considered standard of care for highly active relapsing-remitting multiple sclerosis (MS) failing disease modifying therapies and early severe diffuse-cutaneous systemic sclerosis (SSc) [3–5]. While multiple conditioning regimens exist, EBMT guidelines recommend Cyclophosphamide-anti-thymocyte globulin (Cy-ATG) and BEAM-ATG [1].

Polyclonal anti-thymocyte globulin (ATG) is commonly used in most conditioning regimens. Other monoclonal antibodies such as alemtuzumab and rituximab are also used, sometimes in combination with ATG [6, 7]. The use of ATG reflects a form of in vivo T-cell depletion, which concomitantly depletes host T-cells, along with other immune cells of lymphoid linage, that have survived the conditioning regimen while similarly depleting T-cells that are reinfused with the graft, contributing to the immune resetting [8] related to HSCT procedure.

To date, the choice of anti-T cell serotherapy largely depends on availability, center preference, and/or enrollment in clinical trials. Through a collaborative initiative of the ADWP, we evaluated the current real-word clinical practice among EBMT centers on the use of ATG and other serotherapy in conditioning regimens for HSCT in AD. Such information may allow to optimize and harmonize ATG administration schemes across centers, with the goal of maximizing benefits of HSCT while reducing adverse effects.

This study followed the EBMT study guidelines. All EBMT centers having performed more than 5 HSCT for AD in adult patients since 2015 were invited to the survey. A web-based limited/closed questionnaire (Supplementary Materials) has been developed and sent to leaders of centers for completion directly or by delegates. Data collection and statistical analysis were performed by the ADWP Data Office (Paris). The answers given by centers were summarized using descriptive statistics.

Forty-six EBMT centers (66%) from 18 countries responded to the survey. Among responding centers, 11 (23.9%) perform HSCT for neurological AD indications, 7 (15.2%) for rheumatological ADs, 1 (2.2%) for hematological ADs and 27 (58.7%) for multiple indications. All centers use ATG. Twelve centers (26.1%) use rituximab in addition to ATG, none of the centers currently uses alemtuzumab.

The conditioning regimens, serotherapy type and total dose (TD) used by centers are shown in Table 1.

Twenty-seven centers (58.7%) use the same conditioning regimen for all AD indications. Cy-ATG is the most frequently used regimen across EBMT centers, followed by BEAM-ATG, whereas reduced-intensity conditioning regimens like cyclophosphamide-fludarabine-ATG are used less frequently. Most centers (93.5%) use ATG for all AD indications. Only one center uses a serotherapy-free regimen (cyclophosphamide only), for neurologic indications.

Several types of ATG exist, including rabbit ATG of various brands (Thymoglobulin®/Sanofi-Genzyme and Grafalon®/Neovii), horse-ATG and goat-ATG [7]. Moreover, timing and dosage of administration of ATG in the conditioning scheme can vary considerably [7]. Thymoglobulin is the most commonly used ATG type (41 centers, 89.1%). Among centers using Thymoglobulin, 32.6% administer a TD of 7.5 mg/kg, while 53.6% administer <7.5 mg/kg and 4.3% >7.5 mg/kg. Four centers report using Grafalon, each center a with a different TD, and one center uses Atgam. ATG administration is always fractionated over multiple days, 3 days for 15 centers or 5 days for 17 centers; half of the centers divide the TD equally for each day of administration.

Twenty-nine centers administer ATG during chemotherapy (63%), especially if Cy-ATG is used, while rituximab is administered before chemotherapy in 3 centers, during chemotherapy in 1 center, after HSCT infusion in 2 centers, or before chemotherapy and after cell infusion in 6 centers.

A test dose is used by 16 centers before ATG administration (ranges 0.28–25 mg or 0.5–1 mg/kg). None of the centers uses a rituximab test dose. The variability of reported doses for ATG test dose shows that some centers administer a lower ATG dose in the first day of administration and reported it as "test dose". ATG administration is slow: 22 centers (48.9%) administer it over 12 h, 7 (15.6%) over 8 hours, 7 (15.6%) over 6 h. Rituximab is mainly administered over 4 hours (5 centers) or 6 h (5 centers).

Class-related adverse effects of serotherapy include acute infusion-associated reactions, consistent with cytokine-release syndrome, anaphylaxis and other allergic phenomena [9, 10]. Premedication is used to prevent serotherapy-related adverse events, including antihistamines (100% of centers), paracetamol (91.1%) and steroids (98%); details are shown in Table 1. Fifteen centers repeat the premedication at fixed times during a single infusion, typically every 4 h (7 centers) or 8 h (3 centers).

In 37 (80.4%) centers, the planned TD of ATG is successfully administered to all patients. Nine out of 12 centers administer the TD of rituximab to all patients. Our survey revealed that most centers experience transient disease-related symptoms during serotherapy and conditioning. Among 36 centers performing HSCT for neurological ADs, pseudo-relapse [11] was reported by 12 centers treating MS, by 4 centers treating neuromyelitis optica (NMO) and by 5 centers treating chronic inflammatory

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Table 1. Use in current practice of conditioning regimens, serotherapy and premedication in HSCT for AD indications.

Conditioning regimen and serotherapy	Dose (if applicable)	*N*[e] of centers (%)
Conditioning regimen		**46**
Cyclophosphamide-ATG		23 (50)
BEAM-ATG		3 (6.5)
Both Cyclophosphamide-ATG and BEAM-ATG		7 (15.2)
Use of RIC protocols[a] and Cyclophosphamide-ATG		9 (19.6)
Use of RIC protocols only		1 (2.2)
Various protocols (including ATG-free regimens[b])		3 (6.5)
ATG		**46**
Rabbit ATG - Thymoglobulin®	≤5 mg/kg	3 (6.5)
	6 mg/kg	19 (41.3)
	7.5 mg/kg	15 (32.6)
	>7.5 mg/kg	2 (4.3)
	Different doses[c]	2 (4.3)
Rabbit ATG - Grafalon®	7.5 mg/kg	1 (2.2)
	10 mg/kg	1 (2.2)
	15 mg/kg	1 (2.2)
	90 mg/kg	1 (2.2)
Horse ATG - Atgam®	40 mg/kg	1 (2.2)
Rituximab		**12**
Rituximab i.v.	500 mg	3 (25)
	500 mg for 2 days	6 (50)
	1000 mg	3 (25)
Alemtuzumab		**0**
Steroids[d]		**45**
Methylprednisolone (or equivalent, with or without taper)	1 mg/kg/day	17 (37.8)
	2 mg/kg/day	16 (35.6)
	1000 mg/day	4 (8.9)
	500 mg/day	2 (4.4)
	5 mg/kg/day (max 250 mg/day) or 250 mg/day flat dose	2 (4.4)
Other		3 (6.7)
None		1 (2.2)
Other premedication[d,e]		**45**
Paracetamol		41 (91.1)
Antihistamine		45 (100)

ATG anti-thymocyte globuline; *BEAM* Carmustine, Etoposide, Cytarabine, and Melphalan; *RIC* reduced-intensity conditioning; *IVIG* intravenous immunoglobulins.
[a]Reported RIC protocols included Cyclophosphamide-Fludarabine-ATG, Cyclophosphamide-Fludarabine-ATG-Rituximab (with or without IVIG), Cyclophosphamide-Thiotepa-ATG, Fludarabine-Melphalan-ATG.
[b]Reported ATG-free regimens included Cyclophosphamide alone, Cyclophosphamide-Rituximab, Cyclophosphamide-Fludarabine-Rituximab.
[c]According to clinical trial or different disease.
[d]One missing answer.
[e]Not mutually exclusive.

demyelinating neuropathy (CIDP). Only one center treating MS reported Uhthoff's phenomenon, ie short-term and stereotyped worsening of neurological function among MS patients in response to increases in core body temperature. Centers treating myasthenia gravis reported various symptoms typical of this disease: ptosis (2 centers), respiratory failure (2 centers), dysphagia (1 center), limb weakness (1 center). Among fourteen centers treating gastroenterological ADs, 3 centers reported clinical signs of disease activity during serotherapy when treating Crohn's disease. Among twenty-nine centers performing HSCT for rheumatological diseases, in particular SSc, cardiac toxicity was reported by 14 centers, renal crises by 8, interstitial pneumonitis by 10 and pulmonary failure by 10. Few centers have performed HSCT in systemic lupus erythematosus, but 2 of them reported disease relapse involving a vital organ during serotherapy. Steroids have been associated with renal crises, however, with the limits of a survey-based study, we found no difference in steroid dose used by centers treating rheumatological diseases reporting renal crises and centers not reporting them.

Interestingly, some centers reported no experience of neurological disease-specific complications (4 centers treating MS, 2 centers treating NMO, 2 centers treating CIDP) while all centers treating SSc reported complications during serotherapy and conditioning. This may reflect the complexity of performing HSCT in SSc patients, whose fitness is crucial for the safety of the procedure [12].

In the management of serotherapy-related adverse events, 28 (62.2%) centers collaborate with Intensive Care, most frequently transferring some patients to the ICU and managing other patients in the Transplant Ward with Intensive care staff assistance (21 centers).

Serotherapy, most commonly including ATG, is a key component of conditioning regimens, contributing to the restoration of immunologic self-tolerance and to induce long term-remissions [7, 8]. This survey reveals a high degree of consistency across EBMT centers regarding the choice of rabbit ATG and Cy-ATG regimen. There is still a high variability in doses, both TD and schemes to fractionate the doses, in current practice, with a general trend towards low ATG-TD. Moreover, different medications, in particular different types of ATG, are not equally available in different countries. Supportive care measures, including slow infusion and premedication with high dose steroids, allow most centers to infuse the planned TD to all patients, although the optimal premedication and infusion scheme allowing to maximize the number of patients receiving the planned TD is still open to debate. Even though ATG dosing is based on ATG type, body weight and schedule of administration, ATG pharmacokinetics also depends on the number of lymphocytes in the blood, lymph nodes, and bone marrow at the time of treatment. In the setting of allogeneic transplant for hematologic malignancies, suboptimal ATG exposure has been associated with the main transplant outcomes [13]. Similarly, ATG exposure in SSc patients treated with autologous HSCT was shown to be higher in HSCT responders than in non-responders, even with the same weight-based ATG dose and administration schedule [14]. How to modulate ATG administration schemes in order to optimize ATG exposure, also according to the specific disease indication, is still an open research question.

Few centers use rituximab, all in addition to ATG, mainly in rheumatological diseases (75% of centers), though not exclusively. Interestingly, alemtuzumab is currently not used by centers in the context of HSCT for ADs.

In conclusion, these results suggest the need for improved reporting and communication between centers performing HSCT in ADs to foster collaborative and comparative research studies in the future, including patient-level studies starting from the EBMT

registry and expanding to multicenter, prospective trials, detailing serotherapy administration schemes in relation to serotherapy-related adverse events and patient outcomes, including ATG pharmacokinetics. These include a larger heterogenous cohort of treated patients allowing more robust statistical analysis, wider generalization and pooling of protocols and costs. The aim is to identify commonalities and opportunities to reduce variations and inequalities in practice across healthcare systems, with the goal of offering similar treatment schemes to similar patients. The results of these studies may translate into consensus guidelines (developed in cooperation between transplant and disease specialists) to best standardize practice on serotherapy administration and improve patients' outcomes.

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DATA AVAILABILITY

The final analysis dataset will be available upon specific request to the Working Party chair.

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AUTHOR CONTRIBUTIONS

AI, RN, JAS and RG led on concept and design, provided expert and analytical feedback, and worked as a writing committee. MB and PA prepared and conducted survey and prepared data. ML analyzed the data. All authors contributed to the analysis and interpretation of data. All authors critically reviewed first a preliminary and then the final version of the manuscript.

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ADDITIONAL INFORMATION

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