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Brief report

Patient-reported outcomes in HSCT for autoimmune diseases: Considerations on behalf of the EBMT ADWP, PAC, and Nurses Group

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Background: Over the last 3 decades, hematopoietic stem cell transplantation (HSCT) has been successfully used to treat severe and refractory autoimmune diseases (AIDs).
A multidisciplinary appraisal of potential benefits and risks by disease and transplant specialists is essential to determine individual suitability for HSCT.
Objective: Our aim was to observe that patient-reported outcomes (PROs) and health-related quality of life instruments can capture the unique patient perspective on disease burden and impact of treatment.
Methods: Herein, we describe the basis and complexity of end points measuring patient-reported perceptions of efficacy and tolerability used in clinical practice and trials for patients with AIDs undergoing autologous HSCT.
Results: PRO measures and patient-reported experience measures are key tools to evaluate the impact and extent of disease burden for patients affected by AIDs. For formal scientific assessment, it is essential that validated general instruments are used, whereas adaptations have resulted in disease-specific instruments that may help guide tailored interventions. An additional approach relates to qualitative evaluations, from carefully structured qualitative research to informal narratives, as patient stories. The patients' subjectively reported responses to HSCT may be influenced by their preprocedure expectations and investment in the HSCT journey.
Conclusions: The complexity of AIDs advocates for individualized and multidisciplinary approach to positively affect the patient journey. PROs and health-related quality of life need to be collected using validated instruments in clinical practice and trials to enable robustness of data and to ensure the impact of the intervention is comprehensively assessed, addressing the main questions and needs of the involved stakeholders. (J Allergy Clin Immunol Global 2024;3:100283.)

Key words: *Autoimmune diseases, autologous transplant, quality of life, patient-reported outcomes*

INTRODUCTION

Autologous hematopoietic stem cell transplantation (HSCT) is increasingly used for the treatment of severe/refractory autoimmune diseases (AIDs). Affected patients suffer from chronic diseases, usually requiring disease-modifying therapies (DMTs) for the rest of their lives, with deep impact in terms of comorbidity and quality of life (QoL).[1,2] Evidence suggests that AIDs are increasing worldwide, with a prominent higher burden in North America and Western Europe.[3,4] Autologous HSCT is an intensive "one-off" procedure associated with sustained responses in different severe/refractory AIDs (Table I),[1,5,6] incorporated as standard-of-care treatment in multiple sclerosis (MS) and systemic sclerosis (SSc), and frequently adopted also in Crohn disease (CD) and SLE.[1] In addition, with the increasing recognition of genetic risk variants contributing to the development of certain AIDs, it has become evident that allogeneic rather than autologous HSCT could be a promising approach for long-term disease control, particularly when there is overlap with autoinflammatory and immunodeficiency diseases in the pediatric setting.[7,8] A careful and multidisciplinary appraisal of potential benefits and risks by disease and transplant specialists, working

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Abbreviations used
AID: Autoimmune disease
CD: Crohn disease
DMT: Disease-modifying therapy
EBMT: European Society for Blood and Marrow Transplantation
HRQoL: Health-related quality of life
HSCT: Hematopoietic stem cell transplantation
MS: Multiple sclerosis
PRO: Patient-reported outcome
QoL: Quality of life
SSc: Systemic sclerosis

closely together in a multidisciplinary team with patients and carers, is strongly recommended to determine individual suitability for HSCT.[9]

The patient journey is a complex experience and challenge, including perceptions and experiences. Understanding this journey is crucial for optimizing patients' QoL and to understand their needs, especially in disease wherein manifestations may vary over time. Patient-reported outcomes (PROs) and health-related quality of life (HRQoL) instruments can capture the unique patient perspective on the burden of disease and impact of treatment arguably better than many established disease activity scores or study end points. However, the use of validated instruments to measure QoL is still suboptimal in patients with AIDs using biologic agents[10] and undergoing HSCT.

Irrespective of these approaches, it should be recognized that patients' subjectively reported responses to HSCT may be influenced by their preprocedure expectations and their investment in the HSCT journey. In addition, the increasing influence of social media on patient experience, behavior, and treatment assumptions needs to be recognized. Although effective in bringing together patient experiences and voices, it is a less regulated means of communication that can be associated with risks, especially when treatment abroad is considered in centers with limited experience. In this context, the medical and health care community, including international societies (ie, the European Society for Blood and Marrow Transplantation [EBMT]), may help in delivering clear recommendations.

Herein, we describe the basis and complexity of end points measuring patient-reported perceptions of efficacy and tolerability used in clinical practice and trials for patients with AIDs most commonly undergoing autologous HSCT (MS, SSc, CD, and SLE).

RESULTS AND DISCUSSION

PRO measures and patient-reported experience measures are key tools to evaluate impact and extent of disease burden for affected patients. For formal scientific assessment, it is essential that validated general instruments are used, whereas adaptations have resulted in disease-specific instruments that can help guide tailored interventions (Table II).[11-15] An additional approach relates to qualitative evaluations. These can range from carefully structured qualitative research to informal narratives, as exemplified by the patient stories reported in the book *Everyday Miracles.*[2]

People with MS may access HSCT thanks to official indications and specific guidelines.[1] Despite solid evidence, HSCT is not yet universally accepted by neurologists as a treatment option alongside modern DMTs. Accordingly, many people with MS refer to publicly available scientific outputs, collectively and individually, to access appropriately skilled clinical services and the required financial resources for HSCT in their country or abroad. Patient-reported HSCT outcomes cover all spheres of QoL: physical functioning with stable or improved neurological functions (walk, balance, fatigue, continency, pain, etc); psychological functioning (having one's life back, faith in the future, etc); and social functioning (improved independency and social and leisure interactions, capacity to go back to work and earn a living, etc). HSCT being most of the time a persons with MS–driven treatment, sense of health responsibility and accomplishment permeate patient experience before, during, and after this heavy single one-off treatment. The latter is massively perceived as physically and psychologically less harsh than the chronic condition of living with MS under endless drugs. Their second expectation is to experience symptomatic improvements. In this context, people with MS have recently helped to drive improvement in the access to HSCT, sharing their experience of HSCT compared with previously applied DMTs.[16] Two studies have investigated the impact of HSCT on both clinical status and HRQoL.[11,12] With primary end points, both studies show that HSCT can induce sustained clinical stabilization and significant HRQoL improvements.

In addition to receiving and maintaining remission, improvement in HRQoL is a central treatment goal in all rheumatic and musculoskeletal diseases, which can greatly affect the everyday life and overall well-being of patients. HRQoL assessments have been included in several trials, but only a few studies have specifically addressed this aspect (Table II). A retrospective study comparing Scleroderma Health Assessment Questionnaire—Disability Index scores from 41 patients with SSc who underwent HSCT and 65 conventionally treated patients with different baseline characteristics found considerably lower scores with better function in patients treated with HSCT.[17] Similarly, results from a prospective EBMT study demonstrated significant improvements in Scleroderma Health Assessment Questionnaire–Disability Index scores.[18] The largest evidence in HSCT recipients with SLE demonstrated a highly significant improvement in all the 36-item Medical Outcomes Study Short-Form score domains (Table II), including the physical and mental component summary scores.[19] This is remarkable in view of the fact that improvements of the 36-item Medical Outcomes Study Short-Form domains in trials of targeted biologic drugs (ie, belimumab) are usually modest.[20,21]

CD can have a negative impact on QoL.[2] Most patients with CD respond to conventional treatments and biological therapies. However, a group of patients with refractory courses of their disease presents with decreased QoL and an increase in the costs of care associated with the disease for whom HSCT is a therapeutic option.[22] HSCT is currently indicated as a clinical option in those patients with objective evidence of inflammatory activity, severe course of the disease over the years, inadequate response to different therapies, and when surgery is not a viable option or is accompanied by significant risks.[23]

TABLE I. Transplant indications for adult patients with AIDs (adapted from current EBMT guidelines developed according to the strength of evidence based on clinical trials, registry data, and the opinion of EBMT experts)[5]

Disease	Disease status	Autologous transplant
MS	Highly active RR-MS failing DMT	S/I
	Progressive MS with AIC, and aggressive MS[6]	CO/II
	Progressive MS without AIC	GNR/III
Systemic sclerosis		S/I
SLE		CO/II
CD		CO/II
Rheumatoid arthritis		CO/II
JIA		CO/II
Monogenic AID		GNR/II
Vasculitis	ANCA positive, BD, Takayasu, others	CO/II
PM-DM		CO/II
Autoimmune cytopenia		CO/II
Neuromyelitis optica		CO/II
CIDP, MG, and SPS		CO/II
Type 1 diabetes		D/II
RCD type II		CO/II
Primary ID		NA

AIC, Active inflammatory component; *ANCA*, anti-neutrophil cytoplasmic antibodies; *BD*, Behcet disease; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *CO*, clinical option (can be carried after careful assessment of risks and benefits); *D*, developmental (further trials are needed); *GNR*, generally not recommended; *ID*, immunodeficiency; *JIA*, juvenile idiopathic arthritis; *MG*, myasthenia gravis; *NA*, not applicable; *PM-DM*, polymyositis-dermatomyositis; *RCD*, refractory coeliac disease; *RR-MS*, relapsing-remitting multiple sclerosis; *S*, standard of care (generally indicated in suitable patients); *SPS*, Stiff person syndrome.

Clinicians need to consider that patients with refractory CD, referred to HSCT as a therapeutic option, have often gone through long years of disease and failed treatments, with many faced with, or have already, a permanent stoma. Literature reports more depression, anxiety and fatigue, sleep disturbance, and pain interference and less social satisfaction in patients affected by inflammatory bowel disease compared with the general population.[15]

PROs have been acknowledged as useful measures (Table II), complementary to and correlating with the Crohn's Disease Activity Index, to produce a comprehensive disease assessment in clinical trial and real-life settings.[15] The reported outcomes in CD are similar to the ones presented by HSCT recipients. In this scenario, it is fundamental to consider that the complications associated with HSCT will be related not only to the procedure but also to the underlying disease and previous treatments.

Collectively, these data demonstrate that HSCT not only provides long-term progression-free survival and/or remissions in AIDs but also significantly improves or even normalizes the overall well-being and disease-related impact in HRQoL. As reflected by the patient stories reported in *Everyday Miracles*,[2] the complexity of AIDs advocates for an individualized approach and a multidisciplinary effort to positively affect the patient journey. However, for broader statements about the impact of HSCT (vs DMTs) and to ensure a comprehensive assessment for the impact of the intervention, PROs and HRQoL need to be collected in clinical trials and real-life studies using validated instruments in adequate numbers to enable robustness of statistical power and conclusions. Including PROs in a clinical trial requires careful thought regarding the specific research questions to be addressed and the needs of all stakeholders, including patients, clinicians, and regulatory authorities. These aspects will also be relevant for the application of innovative cellular therapies (ie, chimeric antigen receptor T-cell therapies).[24,25]

Moreover, PROs should receive more attention in trials and clinical practice as important indicators for outcomes because they reflect the patient's perspective and evaluate how patients are affected by the procedure in the context of their daily lives, including work, family, and social life. Symptoms and PROs often do not correlate well with the actual inflammatory burden. The discrepancy between patient-reported symptoms and objectively assessed disease activity can indeed be instructive for the treating physician to draw an integrative picture of an individual's disease course. This poses a challenge for the design of novel and more comprehensive disease assessments, including PROs that correlate better and more consistently with disease activity. Future research should comprehensively focus on PROs in the entire population with AIDs potentially eligible for HSCT, including the testing and possible refinement of these tools for this population, which remains a current critical gap in the existing literature and may deeply contribute to design and delivery of treatments.

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TABLE II. Examples of PROs and HRQoL tools used for patients with AIDs undergoing HSCT

General HRQoL instruments

SF-12 and SF-36 generically cover 3 spheres of HRQoL with chronic disease:

- Physical functioning
- Psychological functioning (anxiety, depression, emotional control, etc)
- Social functioning (encompassing need for human and technical assistance, range and levels of activities and of interpersonal relations, and income)

Tools evaluating clinical status and HRQoL in MS[11,12]

- Multiple Sclerosis Quality of Life 54, which is a 54-item measure of HRQoL consisting of the SF-36 along with 18 additional items specific to MS
- Combination of SF-36, Fatigue Descriptive Scale, and Hospital Anxiety and Depression Scale

PROs commonly used to evaluate the HRQoL in SSc[13]

- Scleroderma Health Assessment Questionnaire—Disability Index
- Functional Assessment of Chronic Illness Therapy—Dyspnea questionnaire
- Baseline Dyspnea Index
- Cambridge Pulmonary Hypertension Outcome Review
- Raynaud Condition Score

HRQoL measures in SLE[14]

- Disease-specific questionnaires
  - Lupus QoL tool
  - Lupus Impact Tracker
  - Lupus Patient-Related Outcome
- Generic tools
  - SF-36
  - European Quality of Life 5 Dimension

PROs in CD[15]

- Crohn's Disease Activity Index is a complex composite score for disease activity, which includes as subscores patient-reported 2-item and 3-item, reporting stool frequency, presence of abdominal pain, and patient's general well-being;
- IBD-control questionnaire, including more comprehensive PROs, which covers both perceived disease activity and classical patient-reported functionality, through 13 items with the 4 core domains physical, social, and emotional functioning and treatment, as well as a visual analog scale;
- Other disease-specific PROs
  - Disease-specific QoL (IBD-Q), considering intestinal symptoms, systemic symptoms, social aspects, and emotional aspects
  - Fatigue (IBD-F)
  - Disability (IBD disability index), covering body function, body structures, activities and participation, and environmental factors
- A range of generic PROs
  - Instruments that measure depression and anxiety (BDI, HADS, and PHQ-9)
  - Instruments that measure sleep quality (PSQI)

BDI, Baseline Dyspnea Index; *HADS*, Hospital Anxiety and Depression Scale; *IBD*, inflammatory bowel disease; *PHQ-9*, Patient Health Questionnaire 9; *PSQI*, Pittsburgh Sleep Quality Index; *SF-12/36*, 12-/36-item Medical Outcomes Study Short-Form.

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Clinical implications: PROs should receive more attention in trials and clinical practice as important indicators for outcomes because they reflect the patient's perspective and evaluate how patients are affected by HSCT.

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