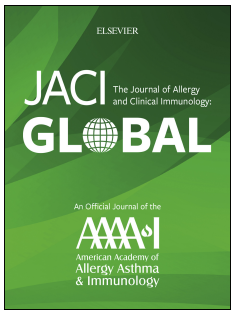


# Patient-reported-outcomes in HSCT for autoimmune diseases: considerations on behalf of the EBMT ADWP, PAC and Nurses Group

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

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**Abstract**

**Background:** Over the last three 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.

**Objectives:** Patient-reported outcomes (PROs) and Health-related Quality of Life (HRQoL) instruments can capture the unique patient perspective on disease burden and impact of treatment.

**Methods**: Herein, we describe the basis and complexity of endpoints measuring patient-reported perceptions of efficacy and tolerability used in clinical practice and trials for patients with ADs undergoing autologous HSCT.

**Results**: Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREM) are key tools to evaluate the impact and extent of disease burden for patients affected by ADs. For formal scientific assessment, it is essential that validated general instruments are used, while adaptations have resulted in disease specific instruments that may help guiding 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 pre-procedure expectations and investment in HSCT journey.

**Conclusions**: The complexity of AIDs advocates for individualized and multidisciplinary approach to impact positively the patient journey. PROs and HRQoL need to be collected using validated instruments in clinical practice and trials to enable robustness of data, ensure the impact of the intervention is comprehensively assessed, addressing the main questions and needs of the involved stakeholders.

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

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

**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 1**),(1, 5) incorporated as standard-of-care treatment in multiple sclerosis (MS) and systemic sclerosis (SSc), and frequently adopted also in crohn's disease (CD) and systemic lupus erythematosus (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 where there is overlap with autoinflammatory and immunodeficiency diseases in the paediatric setting.(6, 7) A careful and multidisciplinary appraisal of potential benefits and risks by disease and transplant specialists, working closely together in a multidisciplinary team with patients and carers, is strongly recommended to determine individual suitability for HSCT.(8)

The patient journey is a complex experience and challenge, including perceptions and experiences. Understanding this journey is crucial for optimizing the patient´s quality of life and to understand their needs, especially in disease where 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 endpoints. However, the use of validated instruments to measure QoL is still suboptimal in AID patients undergoing biologic agents (9) and HSCT.

Irrespective of these approaches, it should be recognised that patients' subjectively reported responses to HSCT may be influenced by their pre-procedure expectations and their investment in HSCT journey. In addition, the increasing influence of social media on patient experience, behaviour and treatment assumptions needs to be recognised. 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 centres with limited experience. In this context the medical and healthcare community, including international societies (ie. European Society for Blood and Marrow Transplantation, EBMT), may help in delivering clear recommendations.

Herein, we describe the basis and complexity of endpoints 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).

**Patient-reported outcomes in main diseases indications and Discusson**:

Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREM) 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, while adaptations have resulted in disease specific instruments that can help guiding tailored interventions (**Table 2**). An ~~alternative~~ 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 (pwMS) 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 pwMS 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. Patients reported HSCT outcomes cover all spheres of quality of life: 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); social functioning (improved independency and social and leisure interactions, capacity to go back to work and earn a living, etc). Being HSCT most of the time a pwMS-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, pwMS have recently helped to drive improvement in the access to HSCT procedure, sharing their experience of HSCT compared to previously applied DMTs.(10) Two studies have investigated the impact of HSCT both on clinical status and HRQoL.(11, 12) With primary endpoints, both

studies show that HSCT can induce sustained clinical stabilization and significant HRQoL improvements.

In addition to receiving and maintaining remission, improvement of HRQoL is a central treatment goal in all rheumatic and musculoskeletal diseases (RMDs), which can greatly affect the everyday life and overall wellbeing of patients. HRQoL assessments have been included in several trials, but only few studies have specifically addressed this aspect (**Table 2**). A retrospective study comparing Scleroderma Health Assessment Questionnaire–Disability Index (sHAQ) from 41 patients with SSc who underwent HSCT and 65 conventionally treated atients with different baseline characteristics, found considerably lower scores with better function in patients treated with HSCT.(13) Similarly, results from a prospective EBMT study, demonstrated significant improvements in sHAQ scores.(14) The largest evidence in HSCT-recipients with SLE demonstrated a highly significant improvement in all SF-36 scores domains (**Table 2**), including the physical and mental component summary.(15) This is remarkable in view of the fact that improvements of the 36-item Medical Outcomes Study Short-Form (SF36) domains in trials of targeted biologic drugs (ie. belimumab) are usually modest.(16, 17)

CD can negatively impact on quality of life.(2) Most CD patients 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.(18) HSCT is currently indicated as 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.(19) Clinicians need to consider that patients with refractory CD, referred to HSCT as 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 IBD compared with the general population.(20)

PROs have been acknowledged as useful measures (**Table 2**), complementary to and correlating with the Crohn's Disease Activity Index (CDAI), to produce a comprehensive disease assessment in clinical trial and real-life settings.(20) 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 prior 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 event normalises the overall wellbeing 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 impact positively the patient journey. However, for broader statements about the impact of HSCT (versus DMTs) and 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. CAR [Chimeric Antigen Receptor] T cell therapies).(21, 22)

Moreover, PROs should receive more attention in trials and clinical practice as important indicators for outcomes, as they reflect the patient's perspective and evaluate how patients are affected by the procedure in the context of their daily lives, including working, 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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**AUTHOR CONTRIBUTIONS**

The authorship group includes active representatives of the EBMT ADWP, Nurses Group and PAC. RG, TA and JAS led on concept, design and coordination of the project, and provided expert and analytical feedback. All authors contributed to the review of data and interpretation of information, writing sections of the manuscript. All authors were involved in drafting the paper, revising it critically, and approval of the submitted and final versions.

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## Tables

Table 1. 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 | Auto |
|---|---|---|
| Multiple Sclerosis | Highly active RR-MS failing DMT | S/I |
| | Progressive MS with AIC, and Aggressive MS (23) | CO/II |
| | Progressive MS without AIC | GNR/III |
| Systemic sclerosis | | S/I |
| SLE | | CO/II |
| Crohn's disease | | CO/II |
| Rheumatoid arthritis | | CO/II |
| JIA | | CO/II |
| Monogenic AID | | GNR/II |
| Vasculitis | ANCA+ve, BD, Takayasu, others | CO/II |
| PM-DM | | CO/II |
| Autoimmune cytopenias | | 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 |

*Abbreviations*: AIC = Active inflammatory component; AIDs = autoimmune diseases; Auto = Autologous transplant; BD= Behcet's 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); DMT = Disease modifying treatments; EBMT = European Society for Blood and Marrow Transplantation; GNR = Generally not recommended; ID = Immunodeficiency; JIA = Juvenile Idiopathic Arthritis; MG = Myasthenia gravis; MS = Multiple sclerosis; 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); SLE = Systemic lupus erythematosus; SPS = Stiff person syndrome.

Table 2. Examples of PROs and HRQoL tools in AIDs undergoing HSCT.

| |
|---|
| **General HRQoL instruments:**<br>Short-Form 12 and 36 (SF-12/36) generically cover three spheres of HRQoL with chronic disease:<br>(I) physical functioning;<br>(II) psychological functioning (anxiety, depression, emotional control, etc.);<br>(III) social functioning (encompassing need for human and technical assistance, range and levels of activities and of interpersonal relations, income). |
| **Tools evaluating clinical status and HRQoL in MS:**(11, 12)<br>▪ Multiple Sclerosis Quality of Life 54 (MSQOL-54) which is a 54-item measure of HRQoL consisting of the Short Form 36 (SF-36) along with 18 additional items specific to MS;<br>▪ combination of SF-36, Fatigue Descriptive Scale (FDS), Hospital Anxiety and Depression Scale (HADS). |
| **PROs commonly used to evaluate the HRQoL in SSc:**(24)<br>▪ Scleroderma Health Assessment Questionnaire–Disability Index (sHAQ);<br>▪ Functional Assessment of Chronic Illness Therapy (FACIT)–Dyspnea questionnaire;<br>▪ Baseline Dyspnea Index (BDI);<br>▪ Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR);<br>▪ Raynaud's Condition Score (RCS).<br>**HRQoL measures in SLE:**(25)<br>▪ disease-specific questionnaires:<br>-Lupus QoL Tool (LupusQoL),<br>-Lupus Impact Tracker (LIT),<br>-Lupus Patient Related Outcome (LupusPRO);<br>▪ generic tools:<br>- 36-item Medical Outcomes Study Short-Form (SF36),<br>- European Quality of Life-5D (EQ-5D). |
| **PROs in CD:**(20)<br>▪ Crohn's Disease Activity Index (CDAI) is a complex composite score for disease activity which includes also as sub-scores patient reported 2-item (PRO2), and patient reported 3-item (PRO3), reporting stool frequency, presence of abdominal pain and patient's general well-being;<br>▪ IBD-control questionnaire, including more comprehensive PROs which covers both perceived disease activity and classical patient-reported functionality, through 13 items with the four core domains physical, social, and emotional functioning, and treatment as well as a visual analogue scale (VAS);<br>▪ Other disease-specific PROs:<br>-disease-specific quality of life (IBDQ), considering intestinal symptoms, systemic symptoms, social aspects, and emotional aspects,<br>-fatigue (IBD-F),<br>-disability (IBD disability index), covering body function, body structures, activities and participation, and environmental factors;<br>▪ A range of generic PROs:<br>-instruments that measure depression and anxiety (BDI, HADS, PHQ-9),<br>- instruments that measure sleep quality (PSQI). |

*Abbreviations*:
AIDs autoimmune diseases; CD Crohn's disease; HRQoL Health-related Quality of Life; HSCT hematopoietic stem cell transplantation; IBD inflammatory bowel disease; MS multiple sclerosis; PROs patient-reported outcomes; SLE systemic lupus erythematosus; SSc systemic sclerosis.