Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee.

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Raffaella Greco,[a,y,*] Tobias Alexander,[b] Nicoletta Del Papa,[c] Fabian Müller,[d,z] Riccardo Saccardi,[e] Fermin Sanchez-Guijo,[f] Georg Schett,[g,aa] Basil Sharrack,[h] John A. Snowden,[i] Karin Tarte,[j] Francesco Onida,[k,ab] Isabel Sánchez-Ortega,[l,ac] Joachim Burman,[m] Cristina Castilla Llorente,[n] Ricard Cervera,[o] Fabio Ciceri,[a] Andrea Doria,[p] Jörg Henes,[q] James Lindsay,[r,ad] Andreas Mackensen,[d,z] Paolo A. Muraro,[s] Elena Ricart,[t] Montserrat Rovira,[u,ae] Tsila Zuckerman,[v] Ibrahim Yakoub-Agha,[w,af] and Dominique Farge[x,ag,**]

[a]Unit of Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy
[b]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Department of Rheumatology and Clinical Immunology, Berlin, Germany
[c]Scleroderma Clinic, Rheumatology Department, ASST G. Pini-CTO, Università degli Studi di Milano, Milano, Italy
[d]Department of Internal Medicine 5 - Hematology and Oncology, University Hospital of Erlangen, Erlangen, Germany
[e]Cellular Therapies and Transfusion Medicine Unit, Careggi University Hospital, Florence, Italy
[f]Department of Hematology, IBSAL-University Hospital of Salamanca and Department of Medicine, University of Salamanca, Salamanca, Spain
[g]Department of Internal Medicine 3 - Rheumatology and Immunology, FAU Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany
[h]Department of Neuroscience and Sheffield NIHR Translational Neuroscience BRC, Sheffield Teaching Hospitals NHS Foundation Trust & University of Sheffield, Sheffield, England, United Kingdom
[i]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Division of Clinical Medicine, School of Medicine and Population Health, The University of Sheffield, Sheffield, UK
[j]SITI Lab, CHU Rennes, EFS Bretagne, University Rennes, Rennes, France
[k]Hematology & ASCT Unit, ASST Fatebenefratelli-Sacco, University of Milan, Italy
[l]Secretary of the Practice Harmonization and Guidelines Committee of EBMT, Barcelona, Spain
[m]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[n]Hematologie Department, Gustave Roussy, Villejuif, France
[o]Department of Autoimmune Diseases, Reference Centre for Systemic Autoimmune Diseases (UEC, CSUR) of the Catalan and Spanish Health Systems/Member of ERN-ReCONNET, Hospital Clínic, Barcelona, Catalonia, Spain
[p]Rheumatology Unit, Department of Medicine (DiMED), University of Padua, Padua, Italy
[q]Center for Interdisciplinary Rheumatology, Immunology and Autoimmune diseases and Department of Internal Medicine II (Haematology, Oncology, Clinical Immunology and Rheumatology, University Hospital Tuebingen, Germany
[r]Department of Gastroenterology, The Royal London Hospital, Barts Health NHS Trust, London, UK
[s]Department of Brain Sciences, Imperial College London, London, UK
[t]Gastroenterology Department. Hospital Clínic Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain
[u]BMT Unit, Haematology Department, Institute of Haematology and Oncology, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain
[v]Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion, Haifa, Israel
[w]CHU de Lille, University Lille, INSERM U1286, Infinite, 59000, Lille, France
[x]Internal Medicine Unit (04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire, Centre de Référence des Maladies auto-immunes systémiques Rares d'Ile-de-France, AP-HP, St-Louis Hospital Paris-Cite University, France
[y]Co-Chair of the Practice Harmonization and Guidelines Committee of EBMT and Chair of the ADWP of the EBMT, Barcelona, Spain
[z]Bayrisches Zentrum für Krebsforschung (BZKF) Erlangen, Germany
[aa]Deutsches Zentrum Immuntherapie, Universitätsklinikum Erlangen, Friedrich-Alexander University (FAU) Erlangen- Nürnberg, Erlangen, Germany
[ab]Co-Chair of the Practice Harmonization and Guidelines Committee of EBMT, Spain
[ac]EBMT Medical Officer, Executive Office, Barcelona, Spain

*Corresponding author. Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, via Olgettina 60, 20132, Milano, Italy.
**Corresponding author. Internal Medicine Unit (04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire, AP-HP, St-Louis Hospital, 1 avenue Claude Vellefaux, 75010, Paris, France.
E-mail addresses: greco.raffaella@hsr.it (R. Greco), dominique.farge-bancel@aphp.fr (D. Farge).

[ad]Centre for Immunobiology, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK
[ae]Josep Carreras Leukaemia Research Foundation, Spain
[af]Chair of the Practice Harmonization and Guidelines Committee of EBMT, Spain
[ag]Department of Medicine, McGill University, Montreal, QC, Canada

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Summary

Autoimmune diseases (ADs) are characterized by loss of immune tolerance, high chronicity, with substantial morbidity and mortality, despite conventional immunosuppression (IS) or targeted disease modifying therapies (DMTs), which usually require repeated administration. Recently, novel cellular therapies (CT), including mesenchymal stromal cells (MSC), Chimeric Antigen Receptors T cells (CART) and regulatory T cells (Tregs), have been successfully adopted in ADs. An international expert panel of the European Society for Blood and Marrow Transplantation and the International Society for the Cell and Gene Therapy, reviewed all available evidence, based on the current literature and expert practices, on use of MSC, CART and Tregs, in AD patients with rheumatological, neurological, and gastroenterological indications. Expert-based consensus and recommendations for best practice and quality of patient care were developed to support clinicians, scientists, and their multidisciplinary teams, as well as patients and care providers and will be regularly updated.

Keywords: Autoimmune diseases; Mesenchymal stem cells; Regulatory T cells; Chimeric antigen receptor (CAR) T cells

Research in context

Evidence before this study

Restoration of the immune tolerance with resolution of the auto-immune and inflammatory response provides durable remissions and foster tissue regeneration in AD patients.
Over the last 25 years, this has been successfully achieved with the use of hematopoietic stem cell transplantation (HCT), that became part of treatment algorithms for specific severe and refractory ADs patients and more recently, with the use of innovative CT, including MSC, CART and Tregs.
Because of the complexity of health care pathways and the number of innovative CT treatment options, there is a need for clinical practice recommendations, within the community, at the level of national and international organizations across relevant specialties.

Added value of this study

All available evidence on the use of MSC, CART and Tregs, based on the current literature and expert practices in AD patients with rheumatological, neurological, and gastroenterological indications was reviewed.
This European Society for Blood and Marrow Transplantation (EBMT) expert-based consensus and recommendations for best practice and quality of patient care were developed to promote patient safety and harmonization of procedures for CT in ADs, following Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP), and appropriate accreditation and regulatory requirements.
Detailed indications, contraindications, and areas for caution for each AD, together with comprehensive recommendations on diagnostic work-up, clinical management and immune monitoring protocols for these innovative CTs are provided.

Implications of all the available evidence

These recommendations aiming to support national and international stakeholders in the field of ADs and local clinical teams delivering innovative CTs will be regularly updated.
As previously with the clinical development of HCT for ADs, the EBMT, the International Society for the Cell and Gene Therapy (ISCT) and wider ADs specialist community should be central to coordination of retrospective registry-based analyses and prospective studies to evaluate the safety and efficacy of innovative CTs in patients with ADs. Areas of unmet need and future research questions are also highlighted.

Introduction

Autoimmune diseases (ADs) are a heterogeneous group of diseases affecting 8–10% of the Western population, characterized by loss of immune tolerance to auto-antigens,[1] although it is rare to identify a single antigenic epitope in some of the diseases. Consequent polyclonal activation of the immune system, with a defect of B or T lymphocyte selection and altered lymphocytic reactions, leads to the appearance of auto-reactive T and B cells and autoantibodies,[2] which together contribute to tissue damage and inflammation. Both T and B cells are central in the self-sustaining

autoreactive adaptive immune response and immune-mediated damage to target organs. The innate immune system and its tissue environment also play an important role to determine if exposure to a given antigen will induce an immune response or tolerance. Most of the classical ADs are polygenic diseases and share features of the broad spectrum of autoimmune and auto-inflammatory mechanisms.[3,4] Therefore, the optimal treatment of an AD should be discussed, in light of this specific pathological continuum between autoimmunity and auto-inflammation, which variably interacts in the ultimate phenotypic expression. They were traditionally classified as "organ specific" or "systemic" AD.[3] Examples for severe forms of ADs are systemic diseases such as Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SSc), neurological diseases, such as Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorder (NMOSD) and Myasthenia Gravis (MG) and other organ-centered conditions such as autoimmune Inflammatory Myopathy (IIM), Rheumatoid Arthritis (RA), primary Sjogren Syndrome (pSS) and Crohn's disease (CD).

The use of immunosuppressive or immunomodulatory drugs administered as monotherapies or in combinations are recommended by expert consensus as first-line or later treatment for ADs. However, not all AD patients respond to conventional systemic immunosuppression (IS) or to targeted disease modifying therapies (DMTs), with some patients being refractory or recurrently relapsing. Moreover, a prolonged use of these drugs, accounts for high morbidity and mortality in the AD population.

In this context, restoration of the immune tolerance with consequent resolution of the auto-immune and inflammatory response against self-antigens is one of the treatment goals to provide durable remissions and to foster tissue regeneration in AD patients. It can be achieved by the use of high dose chemotherapy followed by autologous, or less frequently allogenic, hematopoietic stem cell transplantation (HCT) which results in resetting of the immune response and induces tolerance *de novo* as developed for almost 3 decades.[5] Clinical application for HCT in AD has expanded as a treatment option for several specific ADs refractory to conventional therapy, or otherwise associated with poor prognosis and has become an integral and standard-of-care part of treatment algorithms in certain indications (e.g. subset of SSc or active Relapsing Remitting MS failing disease-modifying therapies [DMT]).[6–9] However, not all AD patients can undergo HCT and the use of different innovative cellular therapies (CT), that include mesenchymal stromal cells (MSC), Chimeric Antigen Receptors T cell therapy (CART), or regulatory T cells (Tregs) has progressively increased for severe ADs. Of importance, patients treated by HCT or innovative CT, are managed in services authorized for these procedures, within network of references for cell therapies in ADs, either at the national or European level, where AD experts work in tandem with hematologists in accordance with JACIE accreditation process and other regulatory requirements.

New insights are emerging in the complexity and power of innovative CT in this field. MSC, are a heterogeneous population of multipotent progenitor stromal cells that can be easily isolated, cultured, and expanded *ex-vivo* from the bone marrow (BM) stem cell niche[10] and from many other sources as adipose tissue (AT), umbilical cord (UC) or Wharton's jelly (WJ). These multipotent progenitor cells, as identified *in vitro* according to the 2006 ISCT criteria[11] and then extensively characterised *in vitro*,[12] have been investigated as treatment for several indications[13–15] based on their immunoregulatory, pro-angiogenic and anti-fibrotic properties.[12,16] MSC exert their immunomodulatory and trophic functions through a wide panel of mechanisms. MSC effects are mostly mediated through the production of soluble factors, which are induced by proinflammatory signals in the local milieu. Several growth factors, cytokines/chemokines, and enzymes [including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF1), angiopoietin-1 (ANGPT1), indoleamine 2,3-dioxygenase (IDO), prostanglandin-E2 (PGE2), tumor necrosis factor-inducible gene 6 (TSG-6), IL-10, transforming growth factor β (TGFβ), CXCL12, CCL2], with different profiles according to MSC tissue source and donor type, contribute to tissue regeneration in various AD, such as for SSc, SLE, MS and CD patients.[17,18] MSC also secrete neurotrophic growth factors, including glial cell-derived neurotrophic factor (GDNF), VEGF, and brain derived neurotrophic factor (BDNF), which neuroprotective effect in addition the immunomodulatory function of MSC support their use in progressive MS. MSC from various sources differ in terms of proliferation potential, multilineage capacities, transcriptional profile,[15] and functionality and standard functional markers of MSC potency as well as release potency assays have been defined for conducting advanced clinical studies.[16] Promising results and sustained safety[19] have been obtained with MSC of different tissue origin for cellular therapy in SSc, SLE, MS and with access to the market in CD (Supplementary Table S1).[17–23]

Tregs are a specialized subset of $CD4^+$ T lymphocytes with immune suppressive capacities, which are dysfunctional or decreased in some ADs. Adoptive Tregs therefore constitute an interesting therapeutic tool in AD. Despite high safety, polyclonal Tregs mediated suboptimal/controversial responses in clinical trials,[24–27] which was mainly attributed to low amount of disease relevant, antigen-specific cells (Supplementary Table S2).[28–31]

The CAR specifically redirects T cells to eradicate defined cell subsets. Current targets encompass the B cell antigen CD19 (broadly expressed from B cell

precursors up to plasmablasts) and the B cell maturation antigen (BCMA, expressed from plasmablasts up to long-lived plasma cells). Compared to monoclonal antibodies, CART aim to restore immune tolerance by depleting autoreactive B cells deeper than monoclonal antibodies, especially in inflamed tissues and within lymphoid organs (i.e. lymph node and spleen). Current available clinical data reveal that autologous CD19 CART effectively deplete B cells and plasmablasts in patients with SLE, leading to impressive short and longer term drug-free remission in patients refractory to standard therapies.[2] The clinical effect of CART appears to be associated with abrogation of autoreactive antibodies and effects persists even after B cell reconstitution.[32] Other early clinical reports with CD19 and BCMA CART have been reported in a variety of AD (anti-synthetase syndrome,[33,34] SSc,[35] NMOSD[36] and MG[37]), confirming that the generation and administration of CART in ADs is feasible and safe (Supplementary Table S3). Future studies on CART are warranted to elucidate the mechanism of action and to establish the sustained long-term duration of response.

Because of the rapidly growing field with numerous treatment options, there is a need for clinical practice recommendations to provide useful information and general principles on the use of these innovative cellular therapies in ADs, within the community, at the level of national and international organizations and local clinical teams across relevant rheumatologic, neurological and gastrointestinal specialties. This European Society for Blood and Marrow Transplantation (EBMT) consensus aims to promote patient safety and facilitate harmonization of procedures for AD patient selection, care and follow-up, clinical and immune monitoring before and after treatment delivery, and data collection, following Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP), and appropriate accreditation and regulatory requirements. As previously with the clinical development of HCT for ADs, the EBMT, the International Society for the Cell and Gene Therapy (ISCT) and wider ADs specialist community should be central to coordination of retrospective registry-based analyses and prospective studies to evaluate the safety and efficacy of innovative CTs in patients with ADs.

Methods

Methodology

This workshop was conducted according to the methodology published by the EBMT practice harmonization and guidelines committee.[38]

In April 2023, RG and DF proposed to set up a workshop to issue European recommendations regarding the indications and management of innovative cellular therapies (MSC, CART cells and Tregs) in ADs. Twenty-six experts from different countries belonging to the EBMT, including from the EBMT-Autoimmune Diseases Working Party (ADWP), and other disease-oriented specialist societies, from the International Society for the Cell and Gene Therapy (ISCT) and representatives from the Joint Accreditation Committee for ISCT and EBMT (JACIE) were invited to join the workshop. Several teleconferences took place to discuss and advance the first draft.

Search strategy and selection criteria

Data for this literature review were identified by searches of MEDLINE, Current Contents, Pubmed, and references from relevant articles using the search terms "Mesenchymal (stromal OR stem) cell", "cart-T-cell", "T-reg cells" and rheumatological diseases (SLE, SSc, IIM, RA and pSS), neurological diseases (MS, NMOSD and MG) and CD.

Only articles written in English from January 2010 until September 2023, including all clinical (single or randomized early phase I, phase II, or phase III randomized controlled) trials as well as retrospective or prospective case studies and key reviews were considered in the evaluation, and served as the basis for the discussions. Abstracts and reports from meeting were included only when they related directly to previously published work. As defined by the panel, the workshop together with literature search (Supplementary Material) included the use of MSC, CART and Tregs in AD patients with rheumatological (SLE, SSc, IIM, RA and pSS), neurological (MS, NMOSD and MG) and gastroenterological (CD) indications. The following records were excluded: metanalysis, protocols, preclinical and animal studies, studies that did not specify the stem cells type and/or origin. Best practice recommendations for management of adults and children undergoing CART from EBMT, JACIE and EHA[39,40] provided a model for discussions. HCT and MSC, CART or Treg experts in AD from various medical specialties (internal medicine, rheumatology, neurology, gastroenterology, immunology, hematology) assembled to draft recommendations during a two-day face-to-face meeting that took place in Lille, France on September 25th and 26th, 2023.

Objectives

These recommendations were created due to the growing number of MSCs and CART for patients with ADs. Although experience on Tregs is limited compared to MSC and CART, new Tregs-based approaches are currently under investigation (i.e. CAR Tregs). Given the current absence of high-quality evidence from randomized trials or large cohort studies in the field, the decision was made not to grade the recommendations. They therefore represent the consensus point of view of expert authors from international multidisciplinary teams (MDTs). These recommendations aim to cover indications, contraindications and areas of caution in patients with rheumatic, neurological, or gastroenterological ADs being considered for treatment with

innovative CTs, including: diagnostic work-up before CT and subsequent clinical administration, management of complications and follow-up according to each AD. They reflect current best practices in this new and rapidly evolving field, as mainly derived from MSC, CART, and HCT experience and research, and aim to help clinicians and other healthcare professionals in providing consistent, high-quality patient care. They will be inevitably updated according to newly emerging data and a growing evidence base.

These EBMT recommendations are intended to be general in scope and applicable to all mentioned diseases and types of innovative CTs adopted as standard clinical practice. When administering innovative CTs within clinical trials, physicians are advised to follow respective trial protocols.

Role of the funding source
This study was unfunded.

Results (consensus recommendations)

General considerations

Evidence for the feasibility, efficacy and toxicity of CT, such as MSC, CART and Tregs in ADs is summarized in each section of these recommendations. For some ADs, the effect of certain types of CT can be extrapolated from experience in HCT for this type of AD and/or in hematological cancers. Risks of serious toxicity vary between types of CT, the preparative and supportive care regimens required for their delivery, type and stage of AD and the associated co-morbidities.

Novel cellular therapies (MSC, CART, Tregs) are currently evaluated as a therapeutic option for patients with severe refractory ADs, and administration of any of these therapies may be delivered either for compassionate use or through an academic or industry-sponsored clinical trial. A severe and treatment-refractory AD course is considered a potential indication for CT as immunomodulatory or immunosuppressive intervention.

There is currently no unique definition nor guideline for refractory ADs, although these patients are at higher risk of morbidity and mortality due to sustained "moderate to severe" disease activity that is resistant to the currently available (biologic and non-biologic) immunesuppressive therapies. Furthermore, the AD can be complicated by recurrent disease activity flares that lead to progressive organ damage.

General considerations on the use of CTs:

- CT may be considered as a therapeutic option in patients with severe ADs being active or progressing despite the use of standard (guideline-based and/or regulatory approved) therapy.
- The selection of the approach of CT (MSC, CART, Treg) may vary depending on the specific indication and treatment target and expectations (e.g. suppression of inflammation, elimination of autoimmune cells). Depending on the half-life and efficacy of the cellular product, repeated application might be necessary as already shown for MSC and Tregs.
- Whenever possible, CT in ADs should be performed in the context of a clinical trial with well-defined end points and eligibility criteria in accordance with GCPs and appropriate regulatory requirements. If no study or clinical trial is available, patients should be considered for CT in documented multidisciplinary team (MDT) meetings, with clinical/research ethics committee review and/or external expert second opinions from both haematologists and relevant AD specialists, as mandatory.
- In patients for whom CT represents a treatment option, referral should be made to a centre with appropriate inter-disciplinary interaction using combined haematological and AD specialist experience to select and manage severe and refractory AD patients. Such expert centres should have a JACIE accreditation for Immune Effector Cells (IEC) administration and established multidisciplinary team meetings and/or similar processes for CT as for HCT, involving AD specialists and haematologists working in tandem in the same place to support thorough assessment, treatment and follow-up of these high-risk fragile patients.
- Appropriate clinical and laboratory monitoring that can assess efficacy and tolerability of CT should be available.
- Discussions should account for both the likelihood of AD response and the safety and risks of the specific CT, along with patient performance status, vital organ function, co-morbidities (including the presence of acute or chronic uncontrolled infections), AD respective indexes of activity and damage, and any other aspects that impact on risks of potentially serious complications and treatment-related mortality. AD bridging treatment before CT should also be an important part of these discussions.
- Alternative non-CT treatment options, including potential participation in other clinical trials, should be included in such assessment.

Deliverability of CTs is associated with substantial costs. At present, clinical trials provide the best means of delivering CT treatment, which may obviate the costs of clinical care. However, patients may be considered for individualized CT treatment outside of clinical trial settings (i.e. in case of life-threatening disease and no available clinical trial), and one should be mindful of costs and other healthcare resource limitations relevant to the feasibility of treatment.

Health economic assessments are necessary to determine whether CT-based treatments prove cost-effective by preventing, delaying or otherwise limiting the need for biological and other treatments. Studies using other sources of data (registry and established

Criterion	EBMT/EHA recommendations*	AD-specific recommendations
Performance status	ECOG <2, Karnofsky >60% or Lansky >60%	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs
Prior treatments, including prior immunosuppressive treatment	Relative contraindication. Any systemic immunosuppressive treatment may impair the efficacy of CART.	Consider balance of active disease, sequelae, damage and the possibility of withdrawing immunosuppressive therapies in the time window required to perform CTs. Specific wash out periods for CART cell process are described in table 10.
Infections	Active infection is a contraindication. In most cases, active infection requires only a temporary deferral. Nasopharyngeal PCR for SARS-CoV-2 before CT should be negative. Treatment should be delayed in cases of positive COVID-19 PCR.[41] Some latent infections e.g., HIV, are a contraindication to manufacturing for several (but not all) commercial and trial CART products. When proceeding to CART in cases of latent HBV, HCV or HIV infections, prophylactic anti-viral treatment is required.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs
CNS involvement	EBMT recommendations consider risk/benefit ratio. Anticonvulsant prophylaxis is mandatory in CNS involvement when using CART cell approaches.	There is no evidence suggesting substantially increased ICANS risk in AD patients receiving CART cells. However CNS involvement and peripheral neuropathy should be assessed at baseline and individual patient risk has to be considered, especially in CART.
Disease confirmation	Diagnosis should be confirmed using appropriate tests.	Activity, damage and organ involvement should be carefully assessed before CTs in ADs.
Bilirubin AST/ALT	<34 mmol/l in trials; higher limit acceptable (<43 mmol/l) with Gilbert's syndrome. <4 ULN a contraindication in some trials.	Specific AD involvement should be ruled out before CTs.
Creatinine clearance	>30 ml/min.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
Hepatitis B and C	As per national guidelines Serology/molecular testing.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
HIV	Leukapheresis for some CART cells as mentioned in SPC (e.g., tisagenlecleucel [Kymriah] manufacturing) will not be accepted from patients with a positive test for active HBV, HCV or HIV.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
Cardiac function	TTE to assess cardiac function and exclude significant pericardial effusions and structural abnormalities. LVEF <40% (via 4D EF or Simpson's biplane method) is a relative contraindication. ECG to exclude significant arrhythmias. Cardiac biomarkers (troponin and NT-proBNP) at baseline. CMR to assess extent of disease with cardiac involvement.	Extensive cardiac function assessment is mandatory in AD patients undergoing CTs (MSC, CART, Tregs).
CNS imaging and lumbar puncture	MRI not required except in those with a history of CNS disease or current neurological symptoms. Lumbar puncture not required except in those with a history of CNS disease or current neurological symptoms	In case of underlying diagnosis of SLE and neurological ADs, a detailed clinical examination, Montreal Cognitive Assessment (MOCA),[42] MRI ± EEG are strongly recommended.
Fertility	Females of childbearing potential must have a negative serum or urine pregnancy test. Test must be repeated and confirmed negative within 8 days of the CART cell infusion	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs. Fertility assessment and preservation should be proposed to AD patients before a CT.

*These EBMT recommendations were made for CART in hematologic malignancies and may differ to ADs.
Abbreviations: AD autoimmune diseases; Chimeric Antigen Receptors T cells (CART); CMR cardiovascular magnetic resonance; CNS central nervous system; COVID-19 Coronavirus disease 2019; CT cellular therapy; EBMT European Society for Blood and Marrow Transplantation; ECG electrocardiogram; EEG electroencephalogram; EHA European Hematology Association; HBV Hepatitis B virus; HCV Hepatitis C virus; HIV Human immunodeficiency virus; ICANS immune effector cell-associated neurotoxicity syndrome; LVEF left ventricular ejection fraction; MRI magnetic resonance imaging; MSC mesenchymal stromal cells; NT-proBNP N-terminal pro-brain natriuretic peptide; PCR polymerase chain reaction; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; SLE systemic lupus erythematosus; SPC summary of Product Characteristics; TTE transthoracic echocardiogram; Tregs regulatory T cells.

Table 1: **Recommendations for general screening and eligibility before CT (adapted from Hayden et al., 2022).[39,*]**

clinical trials) should be used in evaluating the potential cost-effectiveness of CT compared with alternative 'standard' treatment options in ADs.

Common recommendations for the application of CT in ADs:

- Active organ involvement that poses the patient at high risk for organ failure and/or damage needs to be present.
- AD needs to be resistant to at least two lines of immunosuppressive drug regimens, administered in an adequate dose and for a sufficiently long time to judge response. Type and number of drugs to have failed may vary among different forms of ADs.
- A 'refractory' disease course can be based on misdiagnosis rather than true resistance to treatment. Therefore, a critical evaluation of correct diagnosis of the respective AD fulfilling respective

disease criteria is of outmost importance before considering CT.
- Age should not be a specific limitation for CT treatment per se, but, given that fitness may decline, and co-morbidities may increase with age, should be considered as part of the biological fitness of the patient for the specific CT treatment.
- Impact of the lymphodepleting regimen (such as on reproductive function) are an important consideration in the planning of CT in ADs.
- Patient compliance and understanding of the procedure and expectations is essential, as a basis for providing informed written consent for compassionate based treatment or on a clinical trial.

Regarding the screening tests to be performed before the cellular therapy, we refer to current EBMT guidelines for CT (Table 1).[39]

Data reporting of all AD patients, who received CTs to the EBMT registry is strongly recommended. The EBMT registry has recently been upgraded to accommodate CTs (EBMT website: https://www.ebmt.org/). As a minimum, annual review and data reporting is mandatory to capture all outcomes, including late effects (i.e. secondary malignancies, insertional mutagenesis, secondary autoimmune diseases). Centers administering CTs for ADs should provide systems for long-term follow-up at least until 10 years after CT.

Annual simultaneous follow-up consultation of the AD specialist and the hematologists/CT specialists is recommended to facilitate assessments and data collection. If patients are discharged from the hematological center and followed by the referring specialist, their contact details should be available to the treatment center data managers so that data can be updated. Data managers should be adequately trained and supervised by relevant CT and AD specialists.

Considerations and recommendations for rheumatic diseases

Rheumatic and musculoskeletal diseases (RMDs) are chronic systemic diseases that can affect any organ of the body. Many of these diseases have a long-term relapsing course and worsen over time. In severe and refractory cases, RMDs can result in significant disability, with a major impact on both quality of life and life expectancy. Use of adequate tools to assess comorbidities at different organ levels and to differentiate AD activity and damage are required. MDT evaluation is highly recommended.

Experience in this setting is summarized in the Supplementary Tables S1–S3.[2,43] To ensure RMD patient eligibility to innovative CTs and fitness, the indications, contraindications and disease-specific assessments in Table 2A and B should be considered. This list is not exhaustive, and, in the trial setting, trial protocols should be followed. Regarding the screening tests to be performed before the CT, we refer to current EBMT guidelines for CT[39] and Table 1.

Considerations and recommendations for neurological ADs

Neurological autoimmune disorders may affect any part of the nervous system, including the brain and spinal cord, the peripheral nerves, neuromuscular junction and skeletal muscles.

There is limited evidence for the use of advanced CTs in autoimmune mediated neurological disorders (Supplementary Tables S1–S3).[62] At this stage, all patients should be treated in clinical trials.

Patients should be discussed in MDT meetings before offered any of these therapies. To ensure patient eligibility to receive innovative CTs, the indications, contraindications and relevant assessments are summarized in Table 3A and B. This list is not exhaustive, and, in the trial setting, study protocols should be followed.

We recommend the following criteria (Table 3) to identify potential candidates for the use of innovative CTs in this group:

- Multiple Sclerosis (MS)
  - o Relapsing Remitting MS (RRMS)
    - Diagnosis of RRMS according to the McDonald and Lublin criteria[63,64]
    - Expanded Disability Status Scale (EDSS)[65] between 3 and 6
    - Active inflammatory disease (with at least one significant relapse or MRI disease activity over the previous 12 months) despite treatment with high efficacy DMTs[9,66,67] for at least six months
  - o Primary Progressive MS (PPMS) or Secondary Progressive MS (SPMS)
    - Diagnosis of progressive MS according to the McDonald and Lublin criteria
    - EDSS between 3 and 6
    - Documented evidence of disability progression over the previous 24 months
    - Evidence of intrathecal IgG production through oligoclonal bands present in the cerebrospinal fluid (CSF) or an elevated IgG index
    - Active inflammatory diseases (with at least one significant relapse or MRI disease activity over the previous 12 months), mainly for CART candidates;
- Neuromyelitis optica spectrum disorder (NMOSD)
  - Confirmed diagnosis based on the published diagnostic criteria[68]
  - Active disease despite the use of at least one biological agent (i.e. monoclonal antibodies against B-cells, the interleukin-6 receptor, or complement);
- Myasthenia Gravis (MG)
  - Confirmed diagnosed of generalized MG[69]

A) Patient eligibility

Type of disease	Indications	Contraindications	Concerns
Systemic Lupus Erythematosus	• Age: ≥18 yrs • EULAR-ACR classification criteria 2019[44] • Anti-DsDNA or anti-histone or anti-SM or anti-nucleosome antibody positive • With active disease (defined by not being in remission according to DORIS criteria or in low disease activity state [LLDAS])[45-47] • With at least one active organ system involvement[48] • With one BILAG A score (severe) or more than 2 BILAG B scores (moderate disease activity)[49] and with insufficient response to glucocorticoids and to at least 2 of the following treatments for at least 3 months each: cyclophosphamide, mycophenolate mofetil or its derivatives, belimumab, azathioprine, anifrolumab, methotrexate, rituximab, obinutuzumab, cyclosporin, tacrolimus or voclosporin.	• Life-threatening end-organ damage defined as: - FVC <45% and/or DLCO (corrected for Hb) <30% predicted - LVEF <40% cardiac echocardiography - Pulmonary hypertension: baseline resting systolic PAP >50 mmHg by echocardiography • Active liver disease: AST, ALT> 3 × N • History of malignancy, unless being free of the disease for ≥2 years (except basal or squamous cell carcinoma of the skin; carcinoma in situ of the cervix or breast), mainly for CART[39] • Neutropenia <0.5 × 10^9 ANC/L, Thrombocytopenia: <30 × 10^9 platelet cell count/L, Anemia: Hb < 8 g/dL, Lymphopenia: lymphocyte cell count <100 × 10^9/L • Uncontrolled infection • Unvaccinated against SARS-CoV-2 unless previous exposure • Psychological, sociological or geographical conditions precluding compliance	• Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production • Pre-existing irreversible kidney damage
Systemic Sclerosis	• Age: ≥18 yrs • SSc according to ACR/EULAR 2103 criteria[50] • Disease duration ≤5 yrs and i) mRSS of >20 and (ESR >25 mm and/or Hb < 11 g/dL), or ii) mRSS >15 and ≥1 major organ involvement: ✓ Lung: DLCO and/or FVC <80% + interstitial lung disease (chest X-ray and/or HRCT scan); ✓ Kidney: past renal crisis and/or stage 2 or 3 chronic kidney disease (Crcl: 30–89 ml/min); ✓ Heart: reversible congestive heart failure, atrial or ventricular rhythm disturbances and/or mild to moderate pericardial effusion. • Insufficient response to at least two of the following mycophenolic acid, methotrexate, tocilizumab, rituximab, nintedanib, methotrexate, cyclophosphamide for a minimum of 3 months, and Contraindication, inadequate response or unwillingness to undergo AHCT (determined by patient and physician judgement)	• As above	• As above • Pre-existing excessive and irreversible fibrotic damage • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation
Rheumatoid Arthritis	• Age: ≥18 yrs • RA according to 2010 ACR/EULAR classification criteria[51] - Moderate to severe disease activity (DAS28-ESR>3.2) - Failure to at least 3 different classes of previous DMARDs (targeted synthetic or biologic) for at least 3 months • Seropositivity for RF and/or anti-CCP antibodies or presence of B cells in synovial biopsies is recommended for cellular therapy targeting B cells	• As above	• Presence of "activity" based on non-inflammatory domains • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production
Sjögren's syndrome	• Age: ≥18 yrs • Sjögren's syndrome according to 2016 ACR/EULAR) with–persistent high activity defined by EULAR ESSDAI >5[52] - Presence of extra-glandular domains such as vasculitis, or hematologic, lung, kidney and neuronal involvement - Serological activity defined as hypocomplementemia or elevated CRP/eESR/IgG/RF level (excluding acute or chronic infection and other factors). - Poor response to previous treatments with glucocorticoids and at least 2 of the following drugs: cyclophosphamide, azathioprine, MMF, methotrexate, rituximab or belimumab.	• As above	• Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production • Pre-existing irreversible damage • Consider risk of concomitant lymphoma
Polymyositis	• Age: ≥18 yrs • Idiopathic Inflammatory Myopathy (IIM) according to EULAR/ACR criteria[53] • Active myositis on MRI or biopsy, with or without the presence of interstitial lung disease • In case of amyositic disease course, presence of interstitial lung disease (ILD) involvement is mandatory • Presence of myositis specific autoantibodies • Incomplete response to high doses of glucocorticoids combined with at least 2 of the following treatments: iv IGs, methotrexate, azathioprine, cyclophosphamide, tacrolimus, JAK inhibitors or rituximab.		• Challenge of rapid progressive disease especially in ILD • Consider risk of concomitant cancer • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production

(Table 2 continues on next page)

B) Disease assessment

Type of disease	Key measures	Response measures
Systemic Lupus Erythematosus	Overall disease activity (SLEDAI-2K)[48] Organ specific (skin CLASI,[54] joint CDAI, GFR Urine-protein/creatine ratio, urinary sediment analysis, urine culture) Serology (C3, C4 levels, dsDNA, ANA and APL antibodies)	DORIS remission or LLDAS criteria[a] which includes SLEDAI, PGA and concomitant treatments[a]
Systemic Sclerosis	Overall disease activity (SHAQ,[55] EUSTAR-AI)[56] Organ specific (Skin: mRSS[57]; Lung function: FVC, DLCO; Kidney function Crcl; Urine-protein/creatine ratio, urinary sediment analysis, urine culture) Laboratory: NT-ProBNP, Troponin, CK	Response to treatment, defined as decrease in mRSS >25%, increase in FVC >10% predicted and/or increase in DLCO >15% predicted, without need for further immunosuppression except low dose steroids[58] Progression-free survival, progression defined as any one of the following: decrease in FVC >10% predicted; decrease in DLCO >15% predicted; decrease in left ventricular ejection fraction on cardiac echocardiography >15%; decrease in weight >15%; decrease in creatinine clearance >30%; increase in mRSS >25%; and/or increase in Scleroderma-Health Assessment Questionnaire >0.5
Sjögren's Syndrome	Overall disease activity (ESSDAI)[53] Organ specific (Salivary flow test; Schirmer test; Lung function: FVC DLCO; Kidney function Crcl; Urine-protein/creatinine ratio, urinary sediment analysis, urine culture) Laboratory: CRP, ESR, IgG, and RF levels cryoglobulinemia	Rate of ESSDAI response, or MCII of ESSDAI,[59] which was defined as an improvement of ESSDAI at least three points Rate of ESSPRI response, or MCII of ESSPRI, which was defined as an improvement of ESSPRI at least one point or 15% Change of PGA score Change of salivary glands function including the salivary flow rate (unstimulated whole salivary flow: If score is > 0 at baseline: increase of ≥25% from baseline. If score is 0 at baseline: any increase from baseline.) and the Schirmer's test (increase ≥5 mm from baseline) Change of serological activity parameters including CRP, ESR, IgG (decrease of ≥10%.), and RF levels (decrease of ≥25%)
Rheumatoid Arthritis	Overall disease activity DAS28,[60] CDAI[52] Laboratory/serology CRP, ESR, RF, ACPA	EULAR-ACR Remission
Polymyositis	Overall disease Organ specific [Lung function test: FVC DLCO; Chest CT scan Muscle strength (MMT8)] Laboratory/serology: CK, Troponine, NT-ProBNP, myoglobine	EULAR-ACR major response 2016 criteria in TIS (ACR-EULAR myositis response criteria 2016)[61]

Abbreviations: ACPA anti-citrullinated protein/peptide antibody; ALT alanine aminotransferase; ANA antinuclear antibody; ANC absolute neutrophil count; anti-CCP cyclic citrullinated peptide; anti-DsDNA anti-double stranded deoxyribonucleic acid; APL antiphospholipid antibody; AST aspartate aminotransferase; BILAG British Isles Lupus Assessment; C3 complement 3; C4 complement 4; CDAI clinical disease activity index; Chimeric Antigen Receptors T cells (CART); CK creatine kinase; CLASI cutaneous LE disease area and severity index; Crcl creatinine clearance; CRP C-reactive protein; CT scan computerized tomography scan; DAS disease activity score; DAS28 disease activity score in 28 joints; DLCO diffusing capacity for carbon monoxide; DMARD disease-modifying antirheumatic drugs; DORIS definition of remission in SLE; dsDNA double stranded deoxyribonucleic acid; ESR erythrocyte sedimentation rate; ESSDAI EULAR Sjögren's syndrome (SS) disease activity index; ESSPRI EULAR primary Sjögren's syndrome (pSS) patient-reported index; EULAR-ACR European League Against Rheumatism/American College of Rheumatology; EUSTAR-AI European Scleroderma Trials and Research Group (EUSTAR) activity index (AI); FVC forced vital capacity; GC glucocorticoid; GFR glomerular filtration rate; Hb haemoglobin; HRCT high resolution chest tomography; IgG: immunoglobulin G; IS immunosuppressant; Iv intravenous; LLDAS Lupus Low Disease Activity State; LN lupus nephritis; LVEF left ventricular ejection fraction; MCII minimal clinically important improvement; MMT8 manual muscle testing in a subset of eight muscles; MRI magnetic resonance imaging; mRSS modified Rodnan skin score; NT-ProBNP N-terminal pro-brain natriuretic peptide; OR odds ratio; N normal; PAP pulmonary artery pressure; PGA physician's global assessment; RF rheumatoid factor; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; SCr serum creatinine; SLE systemic lupus erythematosus; SLEDAI Systemic Lupus Erythematosus Disease Activity Index; SHAQ Scleroderma Health Assessment Questionnaire; TIS Total Improvement Score; UPr urinary proteinuria. [a]In SLE, Complete remission (absence of clinical activity with no use of GC and IS drugs) is infrequent. To this end, the previously defined low disease activity LLDAS state (based on a SLEDAI score ≤4 with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity, PGA ≤1 with GC ≤7.5 mg of prednisone and well tolerated IS agents)[47] has shown comparable rates with remission, regarding halting of damage accrual (OR 0.5–0.7 for increase in damage index) and prevention of flares. Accordingly, treatment in SLE should aim at remission or, if this state cannot be achieved, at low disease activity state. In LN, therapy should aim at least partial response (defined as ≥50% reduction in UPr to sub-nephrotic levels and SCr within 10% from baseline) by 6–12 months; complete renal response (proteinuria <500 mg/24 h and SCr within 10% from baseline), however, may require longer treatment duration, often more than 12 and until 24 months.

Table 2: **Recommendations for cell therapy in rheumatic ADs: A) patient eligibility criteria and specific concerns/contraindications; B) disease assessments for rheumatic ADs with disease-specific endpoints.**

- Fluctuating or inadequate clinical response to second line immunosuppressive treatment (i.e. azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, cyclophosphamide);
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Confirmed diagnosis based on the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) criteria[70]
  - Fluctuating or inadequate clinical response to second line immunosuppressive treatment.

The following disease-specific assessments are suggested at baseline, 3 and 6 month and yearly thereafter:

- MS
  - Clinical score: EDSS,
  - Brain and spinal cord magnetic resonance imaging (MRI),
  - Bladder ultrasound with search and quantification of post-void residue,
  - A baseline cardiac echography should be performed in all patients plus a myocardial MRI for

A) Patient eligibility

Type of disease	Indications	Contraindications	Concerns
MS	CART: ■ RRMS–Active disease despite the use of highly active DMTs (or patients who cannot receive autologous HCT because of co-morbidities) ■ PPMS–Treatment option for patients with clinical or radiological evidence of inflammation ■ Contraindication, inadequate response or unwillingness to undergo autologous HCT (determined by patient and physician judgement). MSC: ■ Progressive MS ■ Contraindication, inadequate response or unwillingness to undergo autologous HCT (determined by patient and physician judgement).	Stable disease (adequately treated or unrated)	Potential central or peripheral nervous system toxicity mainly with BCMA CART, although such AEs have not been seen in CAR-T trials for MG and NMOSD.[36,37] Prophylactic use of anticonvulsant is mandatory in CART.
NMOSD	CART: ■ AQP4+ disease failing at least one biological treatment	Stable disease	
MG	CART: ■ Ab + disease refractory to second line treatment	Stable disease	
CIDP	CART: ■ Disease refractory to conventional treatments	Stable disease	

B) Disease assessment

	Type of disease	Key measures
Neurological indications	MS and NMO	Brain and spinal cord MRI (mandatory to assess response in RRMS) Cerebrospinal fluid analysis (OCB, cytology in case of pleiocytosis; viral PCR and microbiological cultures; autoantibodies anti-MOG and AQP4; NF-L) OCT Cognitive and functional assessments +/− EEG in case of CART
	CIDP	Nerve Conduction Study
	All	Disease-related scores

Abbreviations: Ab antibody; AD autoimmune diseases; AE adverse events; AQP4 Aquaporin 4; BCMA B-cell maturation antigen; CART Chimeric Antigen Receptors T cells; CIDP chronic inflammatory demyelinating polyneuropathy; CT cellular therapy; DMT disease-modifying therapies; EEG electroencephalogram; EMG electromyography; HCT hematopoietic stem cell transplantation; MG myasthenia gravis; MOG myelin oligodendrocyte glycoprotein; MRI magnetic resonance imaging; MS multiple sclerosis; MSC mesenchymal stromal cells; NF-L Neurofilament-light chain; NMO neuromyelitis optica; NMOSD Neuromyelitis optica spectrum disorder; OCB oligoclonal band; OCT Optical coherence tomography; PCR polymerase chain reaction; PPMS primary progressive multiple sclerosis; RRMS relapsing-remitting multiple sclerosis; SPPMS secondary progressive multiple sclerosis.

Table 3: **Recommendations for CTs in neurological ADs: A) patient eligibility criteria and specific concerns/contraindications; B) disease assessments specifically for neurological ADs.**

those who have received previous cardiotoxic treatments (mitoxantrone or high cumulative dose cyclophosphamide), with follow-up evaluations according to clinical need, especially in CART.

- NMOSD
  - Clinical score: EDSS,
  - MRI of the brain, orbits and spinal cord,
  - Antibodies to aquaporin-4 (AQP4-Ab) or antibodies towards myelin oligodendrocyte glycoprotein (MOG),
  - Myocardial MRI in patients who have received cardiotoxic treatments, such as mitoxantrone or a high cumulative dose of cyclophosphamide.
- MG
  - Functional score: Garches score[71]; clinical severity score: Myasthenia Gravis Foundation of America (MGFA) score.[72]
- CIDP
  - Functional Scores: Overall Neuropathy Limitations Scale (ONLS), modified score Rankin score,[73]
  - Clinical scores: Medical Research Council (MRC),[74] Inflammatory Neuropathy Cause and Treatment (INCAT-ODSS),[75]
  - Nerve Conduction Study.

Regarding the screening tests to be performed before the CT, we refer to current EBMT guidelines for CT[39] and Table 1.

Considerations and recommendations for gastrointestinal diseases

Inflammatory bowel diseases (IBD) are immune-mediated inflammatory diseases. Experience in this setting is currently restricted to MSCs (Supplementary Table S1), able to modulate the immune response in individuals with CD.

MSCs have demonstrated their ability mostly to heal perianal CD fistulae in patients refractory to conventional or biologic therapy in several controlled trials to the point where darvadstrocel (Alofisel®, Takeda),[76] a

suspension of expanded human allogeneic adipose-derived MSCs extracted from the subdermal adipose tissue of healthy donors via liposuction, has been approved since 2018 for use in clinical practice. Darvadstrocel is indicated for the treatment of complex perianal fistulas in adult patients with non-active or mildly active luminal CD when fistulae have shown an inadequate response to at least one conventional or biologic therapy. We highlight that (i) patients should have mucosal healing of any rectal disease and (ii) a combination of the use of MSCs and expert surgical techniques are required for optimal results. Since its administration requires a multidisciplinary medical-surgical approach, it is recommended that its use be centralized in selected referral centers.

Ongoing research on MSCs for perianal fistulizing CD will determine the ideal cell number, optimal delivery, retreatment interval, tissue, source and donor choice. Additionally, studies with the goal of further optimizing the efficiency and effectiveness of local MSC therapy are ongoing with the investigation of novel techniques such as use of fresh adipose tissue, co-injection with adjunctive agents, and use of bio-absorbable plugs.

The data and safety profiles emerging from studies evaluating systemic infusion of MSCs in luminal CD suggest safety but equivocal efficacy. To address this issue, phase II and III studies using both clinical remission and endoscopic response as co-primary endpoints should be performed. Furthermore, the optimal origin and sources of MSCs, as well as dosage and modalities of administration, have still to be determined. Future trials should aim to resolve these questions in order to optimally recommend the potential use of MSCs to treat luminal CD.

It is worth noting that other CTs, like CART or Tregs for CD, lack sufficient evidence at this stage, making it unfeasible to provide recommendations for or against their use. These approaches require further clinical and mechanistic studies to establish their potential in CD treatment, given a more pronounced autoinflammatory background.[4] For this reason, the panels has decided to provide recommendations specifically for MSC, *e.g.* Darvadstrocel, use in refractory perianal CD:

- Indications
  - Complex symptomatic perianal disease refractory to anti tumour necrosis factor (TNF) therapy in which there is no evidence of active rectal disease only when used in specialist centers after MDT discussion;
- Contraindications
  - Undrained perianal sepsis.

Relevant disease-specific assessments in luminal and perianal CD should include:

- Standard screening tests prior to advanced CT[39] (Table 1),
- Endoscopy to assess disease activity,
- MRI of abdomen/pelvis to exclude penetrating disease and undrained sepsis.

This list is not exhaustive, and, in the trial setting, trial protocols should be followed.

Considerations and recommendations for immune monitoring

In recent years, remarkable advances have been made in cell-type phenotyping and the understanding of intercellular interaction mechanisms, intracellular signaling pathways, and genetic control of the immune system (Supplementary Tables S4 and S5).

We recommend specific immune monitoring protocols in patients with ADs, mainly rheumatological and neurological indications, undergoing innovative CTs, with successive time points performed before, during and after CT infusion depending on each CT's specific kinetic and its expected effects on the immune subpopulations during patient follow-up. Laboratory immune monitoring and biobanking should routinely be performed to refine our understanding of the underlying mechanisms of action and for investigational purposes, so as to optimize clinical HCT protocols.

The cellular product before infusion should be characterized in detail where possible and if allowed by the trial protocol (Table 4A).

Monitoring of the CART product after infusion is highly recommended (Table 4B). Tregs cannot be specifically tracked in the body, while MSCs do not persist in vivo after IV infusion (24 h–7 days).[77]

We recommend also to monitor the effects on the immune system (Table 4C) of the AD patients undergoing innovative CTs.

For safety profile, the following additional tests should be considered:

- Soluble factors related to cytokine release syndrome (CRS; i.e. IL-1, IL-6, TNF, IL-8, etc);
- Bone marrow aspirate sampling at baseline and after CART in case of prolonged cytopenia according to EBMT guidelines.[40]

Considerations and recommendations for clinical management of CT in ADs

This paragraph focuses mainly on the application of CART. The experience with MSC[19] is broad and there is little safety concern both in the short- and long-term follow up of patients nor risk of transformation.[78] In contrast, data on Treg usage are scarce.[28] However, there is little toxicity with mainly moderate infusion related side effects. In line, safety concerns are little in Treg to date.

A) CT product characterization upon release

	Focus	Markers	Material/Technique	Other comments
CART[a]	Proportion of CART	CAR	Cell product/Cytometry	Commercially available reagents.
	Differentiation	CD3, CD4, CD8, CD45RA, CCR7/CD27, CD69, CD25, CD137, CD127, Foxp3	Cell product/Cytometry	
	Exhaustion and coinhibitory receptors	CD57, PD-1, LAG3, TIM3, TIGIT	Cell product/Cytometry	
MSC[f]	Phenotype/viability	CD45, CD31, CD73, CD90, HLA-DR,	Cell product/Cytometry	
	Alloreactivity	HLA I and II typing	Cell product/molecular biology	Only for allogeneic MSC
	Function/potency assays	Capacity to produce immunosuppressive and trophic factors	Cell product/quantification of soluble or membrane markers in steady state and in response to inflammatory stimuli at protein or at RNA levels Cell product/inhibition of T-cell proliferation	
Tregs	Phenotype and activation status	CD3, CD4, CD127, CD25, FoxP3, Helios, (GARP, LAP, CTLA-4)	Cell product/Cytometry	
	Function	T-cell suppression and/or suppressive cytokine production	Cell product/*in vitro* stimulation assays	

B) CART product monitoring after administration

	Focus	Marker	Technique	Time-points[e]
CART[d]	Cell Count/viability	CAR (commercial reagents)	PBMC/Cytometry (done the day of blood collection)	d7, d10, d14, d28, mo3, mo6, mo9, mo12, mo18, mo24[e]
	Basic characterization	CD4/CD8 $T_N/T_{EM}/T_{CM}/T_{EMRA}$	PBMC/Cytometry	
	Extended phenotype	Treg (Foxp3, CD25, CD127) Activation (CD69, CD137, etc) Exhaustion (PD-1, LAG3, etc)	PBMC/Cytometry	

C) CTs effects on immune system

		Focus	Marker	Technique	Time-points[c]
Minimal	Serology	Ig Autoantibodies DSA (allogeneic MSC)	Total levels of IgG, IgM, IgA AutoAb relevant to the AD Anti-donor HLA Ab	Serum/ELISA +electrophoresis Serum/ELISA, IF Serum/Luminex	Baseline[b], d28, mo3, mo6, mo9, mo12, mo18, mo24 Baseline[b], d28, mo3, mo6, mo9, mo12, mo18, mo24 Baseline and at mo3
	Immune status	Blood count Lymphocyte, NK cell, monocyte count	WBC CD3, CD4, CD8, CD19, CD14, CD56/CD16	Blood count PBMC/Cytometry	For CART: Baseline[b], Day of infusion (pre), d7, d10, d14, d28, mo3, mo6, mo9, mo12, mo18, mo24 For MSC: Day of infusion (pre), d28, mo3, mo6, mo12. For Tregs: Day of infusion (pre), d7, d14, d28, mo3, mo6, mo12.
Extended	B cells	Differentiation	IgD, IgG, CD19, CD20, CD21, CD24, CD27, CD38, CXCR5, CD95, CD11c	PBMC/Cytometry	For CART: Baseline[b], day of infusion (pre), d7, d10, d14, d28, mo3, mo6, mo9, mo12, mo18, mo24 For MSC: Day of infusion (pre), d28, mo3, mo6, mo12 For Tregs: Day of infusion (pre), d7, d14, d28, mo3, mo6, mo12
	Non-CART	Differentiation	CD3, CD4, CD8, CD45RA, CCR7, CD28, CD57, CXCR5, PD-1	PBMC/Cytometry	
	Tregs	Differentiation	CD3, CD4, CD8, CD25, FoxP3, Helios, Ki-67	PBMC/Cytometry	
	Myeloid cells	Differentiation	CD14, CD16, HLA-DR, CD123, CD1c, CD141, CD15	PBMC/Cytometry	
	MAIT cells	Differentiation	CD3, CD4, CD8, CD161, TCRVa7.2, CCR6 and IL-18 R	PBMC/Cytometry	
	ILCs	Differentiation	CD45, lin (CD3, CD14, CD19), CD94, CD127, c-kit, CRTh2	PBMC/Cytometry	
	Immune system reprogramming	Cell activation & differentiation	Soluble factors involved in AD activity (such as TGFb) and/or cell therapy product activity (such as inflammatory factors, BAFF, IL-7 ...)	Plasma/ELISA or LUMINEX or PEA	

(Table 4 continues on next page)

C) CTs effects on immune system

		Focus	Marker	Technique	Time-points[c]
(Continued from previous page)					
Exploratory	Transcriptome and BCR/TCR repertoire	Renewal vs. Persistence	NA	PBMC/scRNAseq/TCRseq/BCRseq directly or frozen −80 °C or whole repertoire analysis (RACE PCR)	Baseline[b], mo6, mo12
	Microbiome	Changes in microbiota profile	NA	Stool/salivary Instantly frozen −80 °C	Baseline[b], d14 (upon discharge), mo3, mo12
	Tissue-resident or infiltrating cells	Number and Phenotype	NA	Biopsy of bone marrow, skin, lymph node, CSF, or gut/RNASeq and/or scRNASeq	Baseline[b], mo3, mo12

Abbreviations: Ab antibody; AD autoimmune diseases; BAFF B-cell activating factor; BCR B cell repertoire; BCRseq B Cell Repertoire sequencing; CART chimeric antigen receptors T cells; CD cluster of differentiation; c-kit tyrosine kinase receptor; CRTh2 chemoattractant receptor-homologous molecule expressed on Th2 cells; CSF cerebrospinal fluid; CT cellular therapy; CTLA-4 cytotoxic T-lymphocyte-associated protein 4; d day; DSA donor specific antibodies anti HLA; ELISA enzyme-linked immunosorbent assay; FoxP3 forkhead box P3; GARP glycoprotein A repetitions predominant; HLA human leukocyte antigen; IF immunofluorescence; Ig immunoglobulin; IL interleukin; ILC innate lymphoid cells; LAG lymphocyte-activation gene; LAG3 lymphocyte-activation gene 3; LAP LAG-3-associated protein; MAIT mucosal-associated invariant T cells; mo month; MSC mesenchymal stromal cells; PBMC peripheral blood mononuclear cells; PCR polymerase chain reaction; PD-1 programmed cell death protein 1; PEA proximity extension assay; RACE rapid amplification of cDNA ends; RNA ribonucleic acid; RNASeq RNA-sequencing; scRNASeq single-cell RNA-sequencing; TCM naïve central memory T cell; TCR T cell repertoire; TCRseq T cell repertoire sequencing; TEM effector memory T cell; TEMRA effector memory T cells re-expressing CD45RA; TGFb transforming growth factor-β; TIGIT T-cell immunoreceptor with Ig and ITIM domains; TIM3 T-cell immunoglobulin and mucin-domain containing-3; TN naïve T cell; Tregs regulatory T cells; WBC white blood cells. Biobanking should be performed, when possible, at the same time-points than phenotypic follow-up (frozen PBMC, serum, plasma). [a]This may be performed for any academic cell product. Commercial products may be measured according to local and national policy and in accordance with company regulations. [b]Baseline = before treatment and lymphodepletion. [c]To be repeated in case of repeated cell infusions. [d]CART and non-CAR T cells can be studied using the same flow cytometry panel. [e]Recommended time points (± 1 day up to day +14) but additional time points could be explored depending on specific scientific questions. [f]The preferred analytic methods for matrix assays evaluating the immunosuppressive and immunomodulatory capacities of MSC currently include[12,15,16]: a) flow cytometry analysis of functionally relevant surface markers; b) quantitative RNA analysis of selected gene products; c) protein-based assay of secretome; d) combination of transcriptome and secretome analyses. These parameters should be evaluated in steady-state and MSC activated by inflammatory stimuli.

Table 4: **Recommendations to: A) investigate CT product (upon release); B) monitor CART product after administration; C) investigate effects of CTs on immune system (efficacy).**

Type of therapy	Specific recommendations in ADs[a]	Comments
Steroids	May be administered at dosages ≤10 mg/day prednisone (or equivalent), by 7 days before leukapheresis and before LD; after leukapheresis and before LD, steroids may be administered at higher doses as needed for bridging therapy.	Depending on the patient's clinical picture; topic/inhaled steroids permitted.
Hydroxychloroquine	No specific need for a washout period	Individualized decision
Mycophenolate Mofetil, Azathioprine, Calcineurin inhibitors, mTOR inhibitors JAK inhibitors	Discontinued at least 2 weeks before leukapheresis	Tapering can be considered based on individual disease
Dimethyl fumarate, Fingolimod	Discontinued at least 6 weeks before leukapheresis	
Bortezomib/Proteasome inhibitors[b]	Discontinued at least 3 weeks before leukapheresis	
Cladribine	Discontinued at least 6 months before leukapheresis	Try to avoid if T cell therapy is planned
Cyclophosphamide Methotrexate	Discontinued at least 3 weeks before leukapheresis	The washout period is recommended to ensure T-cell activity at time of collection and to reduce potential toxicity for patients
Belimumab, B cell targeting antibodies (e.g. anti CD20)	Discontinued at least 1 week before leukapheresis	Irrelevant for T cell apheresis and CART production;
Anti-cytokine antibodies Natalizumab (humanized anti α4-integrin)	Discontinued at least 1 month before leukapheresis discontinued at least 6 weeks before leukapheresis	The washout period is recommended to reduce toxicity (ie. infections, such as PML) for patients and impact on B-cell, while preserving disease control, especially for CART
Alemtuzumab (anti CD52 mAb) Daratumumab (anti-CD38 mAb)[b] ATG[b]	Discontinued at least 6 weeks before leukapheresis	Try to avoid anti T cell directed antibody therapy (CD52, ATG, CD38) if B cell targeted CART is considered as next treatment

Abbreviations: ADs autoimmune diseases; ATG anti-thymocyte globulin; CART chimeric antigen receptors T cells; CT cellular therapy; JAK Janus kinase; LD lymphodepleting conditioning; mAb monoclonal antibody; mTOR mammalian target of rapamycin; PML progressive multifocal leukoencephalopathy. [a]Suggested wash out period vary according to AD type and activity, manufacturing recommendations, individual decisions and trials, mostly no data available. Suggestions are based on pharmaceutical wash out periods, sometimes lasting effects on T cells, associated risks of infections (such as viral reactivation), available recommendations[9,80] and loss of disease control. [b]None approved drugs frequently used in off-label.

Table 5: **Recommendations on washout period before CT, leukapheresis, LD specifically for ADs.**

Criterion	EBMT/EHA recommendations[a39,40]	AD-specific recommendations
Lymphodepletion before CART	Fludarabine- cyclophosphamide Dose-reduced LD as per local approved label of fludarabine (i.e. 50%) in case of renal impairment	LD generally consists of cyclophosphamide and fludarabine.[b] Use of standard supportive care (such as Mesna) is highly recommended
CART product	LD should be administered following receipt of CART product on site Exceptional situations may necessitate the administration of LD following confirmation of successful CART manufacture, but before receipt	LD should be administered in AD following the receipt of CART product on site.
Clinical conditions	Active infections should be ruled out before starting LD Active or chronic infection is a contraindication Patient should be medically fit to proceed to LD	Referral should be made to a center with appropriate on site inter-disciplinary interaction using combined haematological and AD specialist experience to select and manage AD patients. If patient develops fever in presence of active infection after LD but before CART infusion, the latter must be postponed until 48 h without fever.
Cardiac function	Repeat TTE, ECG and cardiac biomarkers (troponin and NT-proBNP)	Detailed cardiopulmonary assessment is required at time of patent selection for CT in AD including ECG and echocardiography for all AD patients. MRI and MUGA can be necessary depending on the underlying AD and on patient comorbidities.
Lung function/Blood oxygen saturation	92% on ambient air Chest X ray	Lung function (i.e. FVC, DLCO) and chest CT scan should have been carefully assessed at time of patent selection for CT in ADs; detailed cardiopulmonary assessment from less than 3 months is required before CTs (CART, MSC, Treg).
WBC	Administer LD to all patients irrespective of WBC or ALC The SPC for tisagenlecleucel (Kymriah) state that patients with low WBC ($<1 \times 10^9$/l) 1 week before CART infusion may not require LD. use LD with caution when unexplained neutropenia pre-dates CART admission. LD is important to CART activity and proceeding with CART without LD is not generally recommended	Acquired neutropenia, usually mild and often intermittent, lymphopenia and thrombocytopenia may accompany ADs (SLE, SS, SSc, RA, IBD). LD should be considered for all patients regardless of blood cells counts. In severe cytopenia, LD dose may be reduced based on an individual patient risk assessment.
Infections markers (C-reactive protein, ferritin, LDH, metabolic profiling, fibrinogen level)	Required to rule out ongoing infection Baseline assessments of risk for CRS and ICANS	Inflammatory/ADs may account for abnormalities in routine laboratory studies (i.e. serum proteins, produced in response to inflammation and referred as inflammatory markers). In AD patients, a complete metabolic profile (e.g. protein electrophoresis, pre-albumin, HbA1c) is recommended.
Liver function (Bilirubin/AST/ALT)	Bilirubin <34 mmol/l; higher limit acceptable (>43 mmol/l) with Gilbert's syndrome criteria AST/ALT ≤4 × ULN or trial-specific criteria should be met Identify cause of liver derangement, e.g. infection, drug toxicity including antifungals, etc.	Clear identification of the cause of liver derangement is mandatory before starting the CT program in ADs. MDT evaluation is recommended to assess the risk benefit of CT in case of AD specific liver function abnormalities. An increase in muscle enzymes (creatinine kinase and AST, while ALT are normal) can be seen in autoimmune inflammatory myopathies; In SLE, lupoid hepatitis is frequent (3–4 ULN liver enzymes, in presence of anti-nuclear, anti-ASMA antibodies, and rheumatoid factor). Primary cholangitis can be associated with SSc in case of Reynolds syndrome, with Goujerot-Sjogren or be observed in other mixed connective tissue diseases. Drug-induced hepatotoxicity related to azathioprine can account for high liver enzymes (3–4 ULN).
Renal function (Crcl)	Crcl >30 ml/min Physicians should consider appropriate dose reductions in cyclophosphamide and fludarabine when Crcl is <60 ml/min and potentially an increased interval between LD and CART return to permit clearance of fludarabine metabolites	Comprehensive urine analysis, including culture, is recommended before LD to assess renal injury (glomerulonephritis, interstitial nephritis) and may show proteinuria, hematuria or active urinary sediment. Patients with severe renal insufficiency should be carefully evaluated by MDT to assess risk/benefit ratio, adapting LD dose (see above) and medications/dialysis.
CNS involvement	EBMT recommendations consider risk/benefit ratio. Anticonvulsant prophylaxis is mandatory in CNS involvement for CART.	There is no evidence suggesting substantially increased ICANS risk in AD patients, however CNS involvement and peripheral neuropathy should be assessed before treatment and individual patient risk has to be considered.

LD refers only to CART. Abbreviations: AD autoimmune diseases; ALC absolute lymphocyte count; ALT alanine aminotransferase; AST aspartate aminotransferase; ASMA anti-smooth muscle antibody; CART chimeric antigen receptors T cells; CNS central nervous system; Crcl creatinine clearance; CRS cytokine release syndrome; CT cellular therapy; CT scan computerized tomography scan; DLCO diffusing capacity for carbon monoxide; EBMT European Society for Blood and Marrow Transplantation; ECG electrocardiogram; EHA European Hematology Association; FVC forced vital capacity; HbA1c hemoglobin A1C; IBD inflammatory bowel diseases; ICANS immune effector cell-associated neurotoxicity syndrome; LD lymphodepleting conditioning; LDH lactate dehydrogenase; MSC mesenchymal stromal cells; MUGA multigated acquisition scan; NT-proBNP N-terminal pro-brain natriuretic peptide; RA rheumatoid arthritis; SLE systemic lupus erythematosus; SPC summary of product characteristics; SS Sjögren syndrome; SSc systemic sclerosis; TTE transthoracic echocardiogram; Tregs regulatory T cells; ULN upper limits of normal; WBC white blood cells. [a]These EBMT recommendations were made for CART in hematologic malignancies and may differ to ADs. [b]RNA-based CART did not use LD at all.[37]

Table 6: **Recommendations before starting LD for CART cells (adapted from EBMT/EHA recommendations: Hayden et al., 2022,[39] Rejeski/Subklewe et al., 2023)[40] and before infusion of other CTs (MSC, Tregs).**

	EBMT/EHA recommendations[a39,40]	Specific recommendations in ADs
pRBC/platelet transfusions in CART	As per institutional standards, based on patient risk profile For pRBC: consider using 1 product per time to reduce iron overload Irradiation of blood products; Start 7 days prior to leukapheresis until at least 90 days post CAR-T	As for hematological patients; monitoring of blood counts is mandatory in ADs (e.g. at every visit and as clinically indicated, including long-term follow up to evaluate risk of ICAHT).[39,40]
G-CSF in CART	**Prophylactic G-CSF:** On day +2 in patients with a high–risk profile for ICAHT (e.g. high CAR-HEMATOTOX score[82] and risk profile) In patients at low risk for ICAHT,[40] G-CSF not necessary Reduced risk of febrile neutropenia (without increasing the risk of severe, or grade ≥3, CRS nor ICANS). No detrimental effect on CART expansion kinetics or treatment outcomes	The CAR-HEMATOTOX score[82] is not validated in ADs. With only few patients reported so far, no prolonged hematotoxicity has occurred in AD. Administration of G-CSF may induce disease flare in ADs. Prophylactic use of G-CSF is not recommended.
	Therapeutic G-CSF: Severe neutropenia (ANC <500/mcl) neutropenia with or without infectious complications Patients with intermittent neutrophil recovery often rapidly respond to G-CSF stimulation, while aplastic patients are often G-CSF unresponsive	HLH can be causally related to underlying ADs and should be considered as differential diagnosis in case of prolonged cytopenia. In case of prolonged grade 3–4 neutropenia, the use of G-CSF should be considered according to the risk/benefit evaluation and EBMT guidelines.[39,40] Use of G-CSF may potentially favour an AD flare.
Antibacterial prophylaxis	In patients with a low risk for ICAHT, not recommended. In patients with a high–risk profile for ICAHT, prophylaxis may be considered once ANC <500/mcl. As per institutional standards (e.g. levofloxacin or ciprofloxacin). Look at local bacterial epidemiology. Warning in case of colonization by MDR pathogens.	As hematological patients Pre-exisiting humoral immune responses appear to be only marginal impacted by CD19 CART in SLE patients, but probably reduced more dramatically following BCMA CART.[83] The risk of infection depends on the AD and degree of immunosuppression, and management should be carefully discussed upfront by a multidisciplinary team meeting (disease specialist, infection-disease specialist, hematologists and CART experts). A follow-up of potential infectious complications should be considered mandatory. Sufficiently long anti-viral and antibacterial prophylaxis should be maintained according to patient individual risk and in line with institutional guidelines and current EBMT guidelines.[40]
Anti-viral	All patients Start from LD conditioning until 1-year post-CART infusion AND/OR until CD4+ count >0.2 × 10^9/l Valaciclovir 500 mg bid or aciclovir 800 mg bid	
Anti-pneumocystis	All patients To start from LD conditioning until 1-year post-CART infusion AND/OR until $CD4^+$ count >0.2 × 10^9/l Co-trimoxazole 480 mg once daily or 960 mg three times each week In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month) are recommended, dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered	
Systemic primary anti-fungal prophylaxis	Anti-fungal prophylaxis should be considered in severe neutropenia (ANC <500/mcl) with a high–risk profile for ICAHT (e.g. CAR HEMATOTOX score[82] and risk profile) and/or prolonged neutropenia Mold-active prophylaxis for 1–3 months (depending on the duration of neutropenia and use of steroids): posaconazole (300 mg/day) or micafungin (50 mg i.v./day) In patients with prior allogeneic HCT, prior invasive aspergillosis and those receiving corticosteroids after CAR- T cells (long-term >72 h, or high dose), prophylaxis is recommended	As for hematological patients. The risk of infection may depend on the AD and degree and duration of immunosuppression before CTs. Management should be carefully discussed upfront by a multidisciplinary team meeting (disease specialist, infection-disease specialist, hematologists and CART experts). A follow-up of potential infectious complications should be considered mandatory.
Vaccine strategy in CART	*Influenza vaccine* Pre-CART: preferably vaccinate 2 weeks before LD. In B-cell aplasia low likelihood of serological response. Post-CART: >3 months after CART patients should be vaccinated irrespective of immunological reconstitution. Comments: where there is incomplete immune reconstitution or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery. *SARS-CoV-2* Pre-CART: Preferably vaccinate before CART; in B-cell aplasia low likelihood of serological response. Post-CART: >3 months after CART infusion. Comments: Limited data is available on vaccine response after	Vaccinations status should be assessed and updated before LD. Vaccination is a balance between reducing the risk of infection but comes with a theoretical risk of triggering immune events, which is a concern in the setting of ADs. Measurements of specific antibody titers may be helpful in deciding whether to vaccinate or not.[9] Recently, ADWP has also provided specific COVID-19 vaccine recommendations in patients with ADs.[41] Vaccination after CART therapy is effective and risk consideration should guide the decision to vaccinate before the procedure.[84] In AD patients, as per hematological patients, re-vaccinations can be started from >3 months after CART therapy in fully immune reconstituted, defined as absolute CD4 T cells >0.2 × 10^9/l, CD19 or CD20 positive B cells >0.2 × 10^9/l, no concomitant immunosuppressive or cytotoxic therapy in line

(Table 7 continues on next page)

	EBMT/EHA recommendations[a39,40]	Specific recommendations in ADs
(Continued from previous page)		
	CART, and early reports suggest impaired serological responses in patients treated for haematological malignancies. SARS-CoV-2 vaccine-induced protection relies heavily on T-cell-mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; no T-cell threshold has been defined. Postvaccination response monitoring is desirable. Guidance on re-vaccination post- CART and frequency/dosing of booster vaccines will vary between countries. National guidelines should be followed in this area of rapidly evolving clinical practice. *Killed/inactivated vaccines:* Post-CART: >6 months after CART and >2 months after immunoglobulin replacement. Comments: Contraindications include concurrent immunosuppressive or cytotoxic therapy. *Live and non-live adjuvant vaccines* Post-CART: 1 year after CAR-T and fully immune reconstituted, defined as absolute CD4 T cells >0.2 × 10^9/l, CD19 or CD20 positive B cells >0.2 × 10^9/l, no concomitant immunosuppressive or cytotoxic therapy. Comments: contraindications include, <8 months after completion of immunoglobulin replacement.	with EBMT guidelines.[39,40] Vaccinations before full immune reconstitution can be effective and must be based on an individualized risk-assessment. Live vaccines are contraindicated in AD patients.
CRS, ICANS and ICAHT in CART	To be monitored and managed according to EBMT/EHA guidelines.[39,40]	As hematological patients. The early and prompt treatment of these complications is highly recommended in AD setting. Anticonvulsive prophylaxis according to institutional guidelines; mandatory in case of CNS involvement. Higher-grade toxicities were not observed in the patients with ADs already treated with CART. MDT clinical monitoring of AD patients after CART is strongly recommended.
WBC, biochemistry panel, AST, ALT, bilirubin, LDH, fibrinogen, CRP	Standard follow-up At every visit and as clinically indicated	As hematological patients.
CMV, EBV, adenovirus, COVID-19	Viral reactivation/infection (post-allogeneic HCT) As clinically indicated	As hematological patients; quarterly evaluation at least during the first year after CT, in consideration of past immunosuppression. MDT evaluation recommended.
Quantitative immunoglobulins	Consider i.v. (or s.c.) immunoglobulin replacement Consider in adults with serious/recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	As hematological patients; consider to replace immunoglobulins in case of hypogammaglobulinemia (<4 g/l) in AD patients, due to the risk of recurrent infections. Quarterly MDT evaluation is recommended.
Endocrine function and other standard late effects testing appropriate to age	Standard follow-up Yearly or as clinically indicated	As hematological patients. The occurrence of secondary ADs[85] should be investigated.

Abbreviations: AD autoimmune diseases; ALT alanine aminotransferase; ANC absolute neutrophil count; AST aspartate aminotransferase; CART chimeric antigen receptors T cells; CMV cytomegalovirus; CNS central nervous system; COVID-19 Coronavirus disease 2019; CRP C-reactive protein; CRS cytokine release syndrome; CT cellular therapy; EBMT European Society for Blood and Marrow Transplantation; EBV Epstein–Barr virus; EHA European Hematology Association; FBC full blood counts; G-CSF granulocyte colony-stimulating factor; HLH hemophagocytic lymphohistiocytosis; HCT hematopoietic stem cell transplantation; ICAHT immune effector cell-associated hematotoxicity; ICANS immune effector cell-associated neurotoxicity syndrome; LD lymphodepleting conditioning; LDH lactate dehydrogenase; MDR multidrug resistant; MDT multidisciplinary team; pRBC packed red blood cell; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; SLE systemic lupus erythematosus; WBC white blood cells. [a]These EBMT recommendations were made for CART in hematologic malignancies and may differ to ADs.

***Table 7*: Recommendations on supportive care, and management of short/medium term complications and long-term follow-up (adapted from EBMT/EHA recommendations: Hayden et al., 2022,[39] Rejeski/Subklewe et al., 2023).[40]**

Compared with their use in malignant diseases, the use of CART in AD seems to be well tolerated. Despite chronic immune suppression for years, production of a CART has been feasible and achieved high yields.[79] To achieve a good product, drug-specific washout periods before leukapheresis have to be considered to optimize T cell fitness as listed in Table 5. Usual recommendations for a successful CART production advice for 200/mcl CD3+ T cell counts, but CD3+ T cell counts >50/mcl can be sufficient. Secure venous access has to be guaranteed in ADs, when planning leukapheresis and lymphodepleting conditioning (LD).

For hospitalization and distance to the accredited treating center, we refer to current EBMT guidelines for CT and ideally up to 14 days for AD patients without severe reactions. Patients should be located within 60 min of the center with the continuous presence of a caregiver educated to identify the potential complications maintained for a year.[39] Given the intrinsic frailty of AD patients, related to both the underlying disease and prolonged immunosuppressive

treatments, a case by case evaluation is recommended by MDT.

LD acts to allow homeostatic CART cell expansion by modulating cytokine and immune pathways. Considerations before LD in CART cells and before infusion of other CTs are outlined in Table 6, adding relevant points in ADs. Of note, repeated dosing of BCMA CART has been efficacious in MG without LD[37] and CD19 CART was effective in a case of SLE with only half the dose. If and at what dose LD is needed for effective CART in AD is currently not established. As such, LD follows oncological guidelines.

Due to the complexity of the treatment in combination with the underlying AD, we recommend a joint follow-up period in a multidisciplinary team composed of disease specialist and a CART expert (hematologist) for at least 6 months after which, individual decisions can be made. General guidance for the management of short/medium term complications and long-term follow-up after CART and other CTs are listed in Table 7. Hematologists should be continued to be involved in monitoring of side effects according to EBMT handbook recommendations with a quarterly MDT assessments during the first year, and yearly thereafter with data collection and reporting in the EBMT registry.[81]

Discussion

There is evolving rationale, experience and forward vision of clinical experience of innovative CTs in patients with ADs. As with HCT, the field is bringing together fruitful multidisciplinary collaborations to address one of the most challenging groups of patients in clinical practice. In parallel, scientific studies will be important to elucidate mechanisms of clinical improvement and control of dysfunctional immune systems in ADs, alongside consideration of short-term toxicities and long-term risks.

Assessment of safety and efficacy need to be further demonstrated in controlled clinical studies. Long-term outcomes of safety, efficacy and 'late effects' are also of major importance, and data reporting to the national registry as for HCT and to the EBMT registry, as recently upgraded to include dedicated follow up of AD patients treated by HCT and CT, will be essential for long-term outcomes. Of note both the EHA and FDA agencies request long term follow up of all patients treated with CT before releasing any market authorization. Health economic considerations will also be central to the deliverability of these therapeutic strategies. High-quality, long-term data reporting will be essential for all of these aspects.

These recommendations reflect currently available evidence, coupled with expert opinion, and will be revised according to necessary modifications in practice. For the present, it is intended that this position statement and initial recommendations will promote patient safety and facilitate harmonization of procedural aspects, patient selection, data collection, retrospective analyses, prospective studies and mechanistic research for innovative CTs in each AD.

Outstanding questions

More clinical studies are warranted to properly evaluate the positioning of these innovative CTs within the treatment algorithms for each disease, including monoclonal and bispecific antibodies.

MSCs therapies have achieved tremendous advancements over the past decade, however substantial challenges remain to be overcome, including the CT product stability, heterogeneity, differentiation, and migratory capacity and, in case of repeated injections of allogeneic MSCs, immuno-compatibility. More and more studies are focusing on the attempts to overcome these shortcomings.

CAR-based therapies are projected to offer significant promise in the near future for several types of AD. However, some limitations must be addressed before the CARs become universally acceptable, especially in the setting of ADs. Research in this context focuses on the safety profile (i.e. CRISPR-Cas9 and suicide gene editing), development of allogeneic CART (ready to use and administered to patients), novel CAR designs, and various engineered immune cells (i.e. NK and Treg cells).

Experience with Tregs is limited in comparison. Despite safe, polyclonal Tregs mediated suboptimal responses in clinical trials, mainly due to low amount of disease-relevant antigen-specific cells and low level of Treg-cell persistence in vivo at least in peripheral blood. CARs can be employed to redirect the suppressive capacities of Tregs, thus increasing the number of antigen-specific cells that can be transferred to patients. CAR-Tregs proved very effective in controlling inflammatory conditions in pre-clinical studies.[28,86] Clinical trials in this setting are warranted in the next future.

Contributors

Conceptualization: RG, DF; Investigation and creation of recommendations: all authors; Final Analysis and Visualization: RG, DF, TA, NdP, FM, FSG, GS, BS, JAS, KT; Methodology: RG, DF, ISO, FO, IYA; Writing Original Draft: RG, DF; Writing Review and Editing: all authors. All authors read and approved the final manuscript.

Declaration of interests

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Appendix A. Supplementary data

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