Report of the Canadian Expert Committee on the management of ADA deficiency

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ABSTRACT

Adenosine deaminase (ADA) deficiency is a form of severe combined immunodeficiency. Aberrant mutations in the *ADA* gene result in loss of ADA activity and the toxic accumulation of metabolites that damage both immune and non-immune organs. While patients with complete ADA deficiency present during infancy with failure to thrive, recurrent bacterial, viral and fungal infections, those with incomplete (partial) deficiency may present at a later age with milder symptoms associated with reduced T, B, and NK cell subpopulations. Based on experience in Canadian centres, we provide management guidelines for patients with ADA deficiency, including a treatment algorithm for use of hematopoietic stem cell transplantation, gene therapy, and enzyme replacement therapy.

Statement of novelty: Herein, we define guidelines for the management and treatment of patients with ADA deficiency.

Introduction

Adenosine deaminase (ADA) is a ubiquitously expressed enzyme of the purine salvage pathway which catalyzes the irreversible deamination of adenosine and deoxyadenosine. It is essential for normal lymphoid development, with particularly high levels found in the thymus (Adams and Harkness 1976; Poliani et al. 2009). Deficiency of ADA, caused by mutations in the *ADA* gene and subsequent impairment of ADA activity, leads to an autosomal recessive form of severe combined immunodeficiency (SCID) (Sauer et al. 2012; Bradford et al. 2017). The toxic accumulation of ADA substrates and metabolites interferes with downstream metabolic pathways, including inhibition of ribonucleotide reductase and subsequent blockade of DNA synthesis, as well as S-adenosylhomocysteine hydrolase-dependent transmethylation (Flinn and Gennery 2018). The detrimental effects are most pronounced in pathways regulating lymphocyte

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maturation and function, although non-immunological organ systems, including the hepatic, renal, pulmonary, skeletal, peripheral and central nervous systems, can also be affected (reviewed by(Whitmore and Gaspar (2016)).

ADA deficiency affects 1:200 000 live births (Blackburn and Kellems 2005), with a higher frequency reported in Canadian Inuit and Mennonite populations (Grunebaum et al. 2013). Without treatment it is usually fatal within the first year of life. Genotype-phenotype correlations have revealed greater metabolic disturbance in those with more severe biallelic defects in *ADA* (Arredondo-Vega et al. 1998; Cagdas et al. 2018). By contrast, hypomorphic mutations result in somewhat reduced ADA activity and are associated with less severe or late-onset phenotypes. Prior to the advent of newborn screening, patients with complete ADA deficiency traditionally presented during infancy with recurrent bacterial, viral and fungal infections and failure to thrive, while laboratory evaluations revealed severe lymphopenia, hypogammaglobulinemia, and neutropenia. Skeletal abnormalities, cognitive impairment, and hearing loss are common (Albuquerque and Gaspar 2004; Titman et al. 2008; Sauer et al. 2009; Manson et al. 2013). Those with incomplete (partial) deficiency may present with milder but gradually worsening manifestations, associated with reduced populations of T, B, and NK cells (Santisteban et al. 1993; Shovlin et al. 1993). In either case, measurement of ADA enzyme activity and associated levels of ADA substrates/metabolites (adenosine, 2′deoxyadenosine (dAXP), deoxyadenosine triphosphate) is often the first step in identifying ADA deficiency.

The implementation of newborn screening for SCID in Canada (first introduced in Ontario in 2013 and now routine across Nova Scotia, New Brunswick, Prince Edward Island, and Alberta (Biggs et al. 2017; Reid et al. 2017)) has resulted in the early detection of ADA deficient patients as well as improved survival of this cohort (Scott et al. 2019). Management currently relies on immediate enzyme replacement therapy (ERT), immunoglobulin replacement, protective isolation procedures, and antibiotic prophylaxis until definitive treatment is initiated (Figure 1). Patients require close monitoring to reduce the risk of infectious and non-infectious complications (Table 1).

ERT using polyethylene glycol-modified bovine ADA has proved to be effective in correcting the immune and some non-immune abnormalities conferred by ADA deficiency, however, in some patients immune function declined over time (Booth et al. 2007). The bovine-derived ADA product was replaced in 2019 by a recombinant form of the enzyme (elapegademase) which has shown similar in-vitro and possibly better in-vivo activity compared to its predecessor (Murguia-Favela et al. 2020). ERT remains a costly treatment. Thus, it is considered a bridging modality before curative treatment is initiated. To date, hematopoietic stem cell transplantation (HSCT) is the treatment of choice when a human leukocyte antigen (HLA)-matched related donor (MRD) is available (Griffith et al. 2008). Another option that has been shown to correct for the absence of ADA is ex vivo-modified autologous hematopoietic stem cell gene therapy (HSC-GT) (Kohn et al. 1995; Aiuti et al. 2002; Ferrua et al. 2010; Cicalese et al. 2016). Experiences with HSCT with matched unrelated donors (MUD) or haploidentical donors have shown lower success rates (Hassan et al. 2012), although these options can still be considered if MRD HSCT or HSC-GT are not available.

Herein we, the Canadian Expert Committee, define guidelines on the management of ADA deficiency based on our collective experience and available literature in managing this group of patients.

Diagnosis of ADA deficiency

Complete deficiency

Mandatory findings[1]

(1) <1% of normal ADA activity in red blood cells or peripheral blood lymphocytes[2]
(2) Severe lymphopenia
(3) Low to absent responses to mitogens
(4) Biallelic pathogenic mutations in the ADA gene

[1]It is acknowledged that mandatory findings are ideal criteria to follow. However, in some circumstances where a sibling has been diagnosed with ADA deficiency or when all mandatory findings cannot be met but administration of treatment is urgent, criteria No. 4 plus one of the other findings could be sufficient.
[2]In patients who received blood transfusion, ADA level measurement in peripheral blood lymphocytes should be performed.

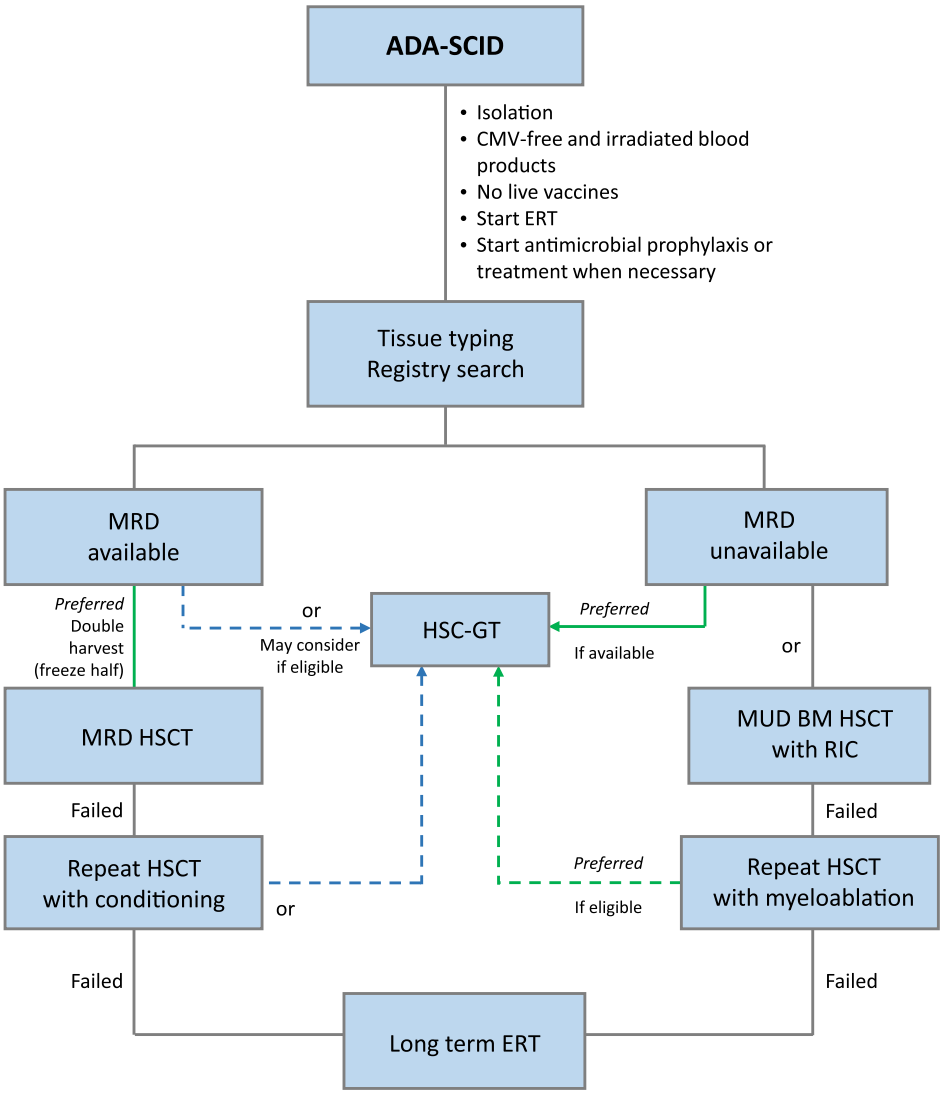

Figure 1: Algorithm for management of patients with ADA deficiency. ADA, adenosine deaminase; BM, bone marrow; CMV, cytomegalovirus; ERT, enzyme replacement therapy; HSC-GT, hematopoietic stem cell gene therapy; HSCT, hematopoietic stem cell transplantation; MRD, matched related donor; MUD, matched unrelated donor; RIC, reduced intensity conditioning; SCID, severe combined immunodeficiency.

Table 1: **Recommended immune evaluation while on ERT.**[a]

Time after starting ERT	First 6 mo or until immune reconstitution	6–18 mo	18–24 mo	>24 mo
Trough plasma ADA activity levels and deoxyadenosine levels[b]	At 3 and 6 mo	Q 6 mo	Q 6 mo	Q 12 mo
CBC, differential	At 2 wk, 1, 3, and 6 mo	Q 12 mo	Q 12 mo	Q 12 mo
Lymphocyte immunophenotyping	At 6 mo	Q 6 mo	Q 12 mo	Q 12 mo
IgG, IgA, IgM	At 6 mo	Q 6 mo	Q 12 mo	Q 12 mo
Mitogen stimulation	Q 6 mo	Q 6 mo	Q 12 mo	Q 12 mo
TCR-Vbeta—adjunct testing for consideration	Q 6 mo	Q 6 mo	Q 12 mo	Q 12 mo
CD45Ra/Ro—adjunct testing for consideration	Q 6 mo	Q 6 mo	Q 12 mo	Q 12 mo

[a]For elapegademase (Revcovi) naïve patients, guidelines in the product monograph may be followed.
[b]Testing for antibodies to elapegademase (Revcovi) should be performed if a persistent fall in plasma ADA activity trough levels below 15 mmol/h/L occurs.

Additional but not mandatory findings

(5) Increased deoxyadenosine in urine, plasma, or dried blood spots
(6) <1% of normal ADA activity in T cells

Additional clues to aid in diagnosis

(7) Recent/persistent infections consistent with SCID
(8) Neurological, skeletal, lung and liver anomalies, and
(9) Hematopoietic anomalies (most commonly neutropenia)

Incomplete (partial) deficiency

Mandatory findings

(1) Low ADA activity in red blood cells
(2) 20%–75% of normal ADA activity in lymphocytes
(3) T cell lymphopenia
(4) Low responses to mitogens

Additional but not mandatory findings

(5) Increased deoxyadenosine in urine, plasma, or dried blood spots

Additional clues to aid in diagnosis

(6) Can have delayed and (or) milder onset of clinical features listed under complete deficiency

Clinical and laboratory features

Non-immune features of ADA deficiency

Skeletal

- Rib and small bone anomalies

Neurological

- Developmental delay, hearing anomalies, seizures

Lungs

- Bronchiectasis, alveolar proteinosis

Liver

- Increased liver enzymes, autoimmune hepatitis, hepatic failure

Renal

- Hemolytic uremic syndrome

Hematopoietic and immune anomalies

Lymphoid cells

- Decreased number and function of T, B cells, NK cells

Lymphoid tissues

- Dysplastic thymus and lymph nodes

Hematopoietic

- Neutropenia, myeloid dysplasia

Management of patients with ADA deficiency

General

- Protective isolation at home or in hospital until reconstituted immune function[3]
- Immunoglobulin replacement
- Prophylaxis against *Pneumocystis jirovecii* pneumonia (trimethoprim-sulfamethoxazole) at 1 month of age
- Avoid breast feeding if CMV IgG is positive in the mother
- Use CMV negative and irradiated or leukoreduced blood products, when needed, discuss with local blood bank as per policy for immunosuppressed patients
- Avoid live vaccines (MMRV, rotavirus, BCG)

Specific treatment

Enzyme replacement (ERT)

- For newly diagnosed patients it is recommended to start recombinant PEG-ADA, elapegademase (Revcovi) at a total weekly dose of 0.4 mg/kg, divided and administered twice a week (0.2 mg/kg per injection) intramuscularly, as per product insert.
- Reassessment of dosing is recommended 6 months from treatment initiation and could be gradually reduced and (or) consolidated to 1 injection per week, based on immune reconstitution and (or) ADA activity of more than 30 mmol/h/L and dAXP level under 0.02 mmol/L.
- For patients already on pegademase (Adagen) treatment, we recommend changing to

[3]The decision to isolate at home or in the hospital usually depends on the patient's medical condition and home compliance.

elapegademase (Revcovi) with a starting dose of 0.2 mg/kg once a week while periodically increasing or decreasing doses by increments of 0.033 mg/kg weekly to monitor immune reconstitution; ADA activity above 30 mmol/h/L and (or) dAXP below 0.02 mmol/L.

Treatment duration

- For most patients ERT should be a temporary option until definitive treatment such as HSCT or HSC-GT are available.
- ERT should be stopped just prior or shortly after HSCT[4].
- Before HSC-GT, ERT should be administered according to the approved GT protocol used.
- Long term ERT can be used when HSCT or HSC-GT cannot be performed, and can be continued in patients who were treated for long durations (>10 years) and have no other option or where the risk of HSCT is deemed to be too high.
- Long term ERT can be effective in patients with partial ADA-deficiency

Dosing adjustment

- Doses should be adjusted over time according to ADA activity trough levels and dAXP levels.
- Antibodies to elapegademase (Revcovi) should be tested in cases where a persistent decline in plasma ADA activity is recorded.

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[4]Some suggest continuing ERT for 2 weeks.

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