Telomere Biology Disorders (TBD), including Dyskeratosis Congenita (DC) are complex, genetic, multi-system disorders that cause premature aging of cells and organs. The clinical symptoms of TBDs are varied and may require multi-disciplinary diagnosis and management

HAEMATOLOGY MANIFESTATIONS

Childhood or adult onset bone marrow hypoplasia or bone marrow failure resulting in cytopenias, raised MCV, raised HbF, Myelodysplasia, CML, Low urate.

Marena R. Niewisch & Sharon A. Savage (2019) An update on the biology and management of dyskeratosis congenita and related telomere biology disorders, Expert Review of Hematology, 12:12, 1037-1052, DOI: 10.1080/17474086.2019.1662720
Savage SA. Dyskeratosis congenita 2009 (updated 2019 Nov 21) in Adam MP, Ardinger HH, Pagon RA *et al.,* Eds. Gene Reviews® [internet] Seattle (WA): University of Washington Seattle; 1993-1019. Bookshelf URL https://ncbi-nlm.nih.gov/books/

INVESTIGATION / MONITORING

- Bone marrow examination as required
- Exclude and treat other/additional causes of high MCV/cytopenia
- Bone marrow cytogenetic analysis by G-banding
- Blood count with MCV and differential reticulocyte count at least annually
- Bone marrow fluorescence in situ hybridization (FISH) to detect 5q-, 7q-/monosomy 7, or trisomy 8 and 20q- if clinically indicated

TREATMENT CONSIDERATIONS

- **TBD expert Haematology referral**
- Attenuated androgens[1] Non attenuated androgens oestrogen [2]
- Referral to Geneticist
- Colony stimulating factors e.g. GCSF, erythropoietin Eltrombopag [3]
- Referral to TBD / MDT specialist based on clinical need

TREATMENT CONSIDERATIONS

- Transfusion-early treatment to prevent iron overload is required in view of pre-existing risk of liver involvement
- Immuno-suppression is usually ineffective and may be harmful in TBDs

- Minimise ionising radiation exposure
- Early consideration of bone marrow/ stem cell transplant + donors
- Use non-myeloablative /minimally myeloablative conditioning protocol [4,5]

Recommended minimum annual MDT surveillance and intervention to include:

- Liver function assessment inc. bloods and fibro/fat scan
- Respiratory spirometry and gas transfer
- Dental and optician review
- Annual flu vaccine for patient and household members

[1] Danazol (Oxandrolone, tibolone, stanozolol may be better tolerated- but less evidence of efficacy). Tolerability is dose- related. Townsley *et al* N Engl J Med 2016;374:1922-31. DOI: 10.1056/NEJMoa1515319
[2] Non-attenuated androgens: oxymetholone. Oestrogens in females not deleterious and may be beneficial
[3] Eltrombopag could be considered for thrombocytopenia and anaemia, but of unknown benefit
[4] Dietz *et al* Bone Marrow Transplantation (2011) 46, 98–104
[5] Nelson *et al* Biol Blood Marrow Transplant. 2016 May 22(5): 884-888

We value your feedback. Please contact us.

ADVOCACY EDUCATION SUPPORT

This information is based on reports from the medical literature. Please see your doctor if you have concerns about TBD.

Telomere Biology Disorders (TBD) affect progenitor stem cell production and cell replication in multiple organ systems. Dyskeratosis Congenita (DC) is a severe TBD presenting in early childhood with a clinical triad of nail dysplasia, oral leukoplakia, and abnormal skin pigmentation, associated with bone marrow failure. Other clinical features can include pulmonary fibrosis; emphysema; cryptogenic liver cirrhosis; lacrimal duct, oesophageal, and urethral stenosis; premature greying of hair; avascular necrosis of hips and shoulders; periodontal disease; and an increased predisposition to epithelial and hematologic malignancies. Classical DC is characterized by extremely short telomeres but different gene mutations in an array of telomere maintenance genes can produce variable phenotypes, differing in severity, in childhood or later into adulthood. Mutations in DKC1, TERC, TERT, CTC1, NHP2, NAF1, NOP10, WRAP53, TINF2, RTEL1, PARN, ACD, STN1 and ZCCHC8, all involved in telomere biology, have been identified in patients with a spectrum of clinical manifestations, from bone marrow failure (BMF) and myelodysplastic syndromes (MDS) to pulmonary fibrosis and cirrhosis. The symptoms of TBD can appear at any age and adult-onset bone marrow failure can be difficult to distinguish from idiopathic aplastic anaemia. [1,2,3]

For a suggested diagnostic algorithm for germline telomere diseases see: Townsley DM *et al*. Bone marrow failure and the telomeropathies. *Blood*. 2014;124(18):2775–2783. doi:10.1182/blood-2014-05-526285

Medical Management of Bone Marrow Failure

Significant peripheral cytopenia should be managed with supportive therapy (blood and platelet transfusions). Khincha *et al* describe the use of the anabolic steroid oxymetholone to treat bone marrow failure.[4] Also Danazol was found to be effective in preserving and elongating telomeres in association with a haematological response in patients with telomere diseases. [5,6] A personal observation by Prof Inderjeet Dokal suggests patients with TBDs can respond to a dose as low as 0.25 mg oxymetholone/kg per day which can be increased, if necessary, to 2-5 mg/kg per day.[7] However a 2018 retrospective observational study found that telomere length for age shortened over time in patients with Dyskeratosis Congenita, irrespective of treatment with androgens and recommend that prospective long-term research is needed. [8] NB: No androgen therapy is licensed for treatment of TBD.

Stem Cell Transplantation and conditioning regimens

At the present time, allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for progressive marrow failure, myelodysplastic syndrome, or leukaemia related to DC and TBDs. Underlying chromosomal instability and sensitivity to chemotherapy and radiation preclude traditional conditioning regimens. Reduced intensity conditioning regimens are recommended. [9,10]

1. Mangaonkar AA *et al*. Short Telomere Syndromes in Clinical Practice: Bridging Bench and Bedside. Mayo Clin Proc. July 2018;93(7):904-916 https://doi.org/10.1016/j.mayocp.2018.03.020
2. Niewisch MR & Savage SA (2019) An update on the biology and management of dyskeratosis congenita and related telomere biology disorders, Expert Review of Hematology, 12:12, 1037-1052, DOI: 10.1080/17474086.2019.1662720
3. Savage SA. Dyskeratosis congenita 2009 (updated 2019 Nov 21) in Adam MP, Ardinger HH, Pagon RA *et al.,* Eds. Gene Reviews® [internet] Seattle (WA): University of Washington Seattle; 1993-1019. Bookshelf URL https://ncbi-nlm.nih.gov/books/
4. Khincha PP *et al*. Response to Androgen Therapy in Patients with Dyskeratosis Congenita. Br J Haematol. 2014 May; 165(3): 349–357.
5. Townsley DM *et al*. Danazol treatment for telomere diseases. N Engl J Med 2016;374:1922-31.
6. Islam A *et al*. Haematological recovery in dyskeratosis congenita patients treated with Danazol. British Journal of Haematology, 2013, 162, 842–862.
7. Chapter 11 Dyskeratosis congenita by Inderjeet Dokal in K.E. Sullivan and E.R. Stiehm (Eds): Stiehm's Immune Deficiencies. DOI: http://dx.doi.org/10.1016/B978-0-12-405546-9.00011-X
8. Khincha PP *et al*. Blood Adv. 2018 Jun 12;2(11):1243-1249. doi: 10.1182/bloodadvances.2018016964
9. Dietz AC *et al*. Disease-specific hematopoietic cell transplantation: nonmyeloablative conditioning regimen for dyskeratosis congenita. Bone Marrow Transplantation (2011) 46, 98–104
10. Nelson AS *et al*. A Reduced-Intensity Conditioning Regimen for Patients with Dyskeratosis Congenita Undergoing Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016 May 22(5): 884-888.

See also Chapter 7 Medical Management of Bone Marrow Failure in Dyskeratosis Congenita. Neelam Giri, MD, Neal S. Young, MD. In Savage, S. A. & Cook, E. F. Eds. (2015) DC &Telomere Biology Disorders: Diagnosis & Management Guidelines. TeamTelomere.org