# Treatment of inherited bone marrow failure syndromes beyond transplantation

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**Despite significant progress in transplantation by the addition of alternative hematopoietic stem cell sources, many patients with inherited bone marrow failure syndromes are still not eligible for a transplant. In addition, the availability of sequencing panels has significantly improved diagnosis by identifying cryptic inherited cases. Androgens are the main nontransplant therapy for bone marrow failure in dyskeratosis congenita and Fanconi anemia, reaching responses in up to 80% of cases. Danazol and oxymetholone are more commonly used, but virilization and liver toxicity are major adverse events. Diamond-Blackfan anemia is commonly treated with corticosteroids, but most patients eventually become refractory to this treatment and toxicity is limiting. Growth factors still have a role in inherited cases, especially granulocyte colony-stimulating factor in congenital neutropenias. Novel therapies are warranted and thrombopoietin receptor agonists, leucine, quercetin, and novel gene therapy approaches may benefit inherited cases in the future.**

**Learning Objectives**

- Describe the standard nontransplant treatment of inherited bone marrow failure syndromes
- Define which patients may benefit from treatment with androgens, corticosteroids, or growth factors
- Identify the most common side effects of currently available therapies
- Identify cases in which toxicity outweighs a hematologic response, requiring treatment discontinuation

## Introduction

Hematopoietic stem cell transplantation is the preferred therapy for most inherited bone marrow failure syndromes. However, many patients lack a suitable histocompatible hematopoietic stem cell donor or are excluded from transplantation due to comorbidities. Transplantation is costly, which limits its availability in many parts of the world. Inherited bone marrow failure syndromes often also affect nonhematopoietic organs (eg, the endocrine system, lungs, liver, and gastrointestinal tract) and confer a higher probability of developing leukemia and nonhematologic cancers. These conditions are not mitigated by hematopoietic stem cell transplantation. Conversely, transplantation appears to accelerate lung and liver dysfunction in dyskeratosis congenita.

Inherited and acquired bone marrow failure syndromes have been historically seen as very discrete entities, but the availability of more comprehensive sequencing has blurred this distinction. More patients initially diagnosed with apparent "acquired" aplastic anemia may carry pathogenic variants in genes involved in the regulation of stem cell maintenance. To improve the management of patients with aplastic anemia, molecular screening should be applied at diagnosis to identify cases of cryptic inherited marrow failure that may not benefit from immunosuppression. In addition, treatment should aim to restore hematopoiesis, prevent other organ damage, and reduce cancer risk.

This review summarizes new findings on the use of androgens in the treatment of telomere diseases and reappraises their use in other inherited aplastic anemias. It also discusses the use of novel molecules to treat inherited marrow failure syndromes.

## Diagnostic considerations

The higher precision in diagnosis at the molecular level has profound implications for treatment, because patients previously diagnosed with acquired aplastic anemia may have an underlying genetic defect that may contribute to pathogenesis. The observation several decades ago that patients with apparent acquired marrow failure responded to androgens may be secondary to an unrecognized constitutional etiology at the time.[1]

It is important to recognize some common pitfalls and technical limitations in the workup when evaluating the treatment decision for a patient with suspected inherited bone marrow failure. In the genomics era, more genetic variants are observed in patients, but assessing variant pathogenicity may be challenging (see West and Churpek, in this book[2]). Some patients with Fanconi anemia may have false-negative results on chromosome breakage tests due to hematopoietic reversion. A diagnostic test applying flow cytometry to identify mitomycin C sensitivity in skin fibroblasts can correctly identify these cases.[3] In dyskeratosis congenita and other telomeropathies, telomere length measurement is essential for diagnosis.[4] Several methods are available to determine telomere length in peripheral blood leukocytes, including flow-fluorescence in situ

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Off-label drug use: The off-label use of androgen formulations and eltrombopag in the treatment of bone marrow failure syndromes is discussed.

hybridization (FISH), Southern blotting, and quantitative polymerase chain reaction. Flow-FISH is superior in the clinical setting, with higher accuracy and reproducibility, although quantitative polymerase chain reaction achieves acceptable agreement with flow-FISH with similar intra-assay variability.[4] If available, flow-FISH should be used to measure telomere length in patients' peripheral blood samples.

## Monitoring bone marrow failure

Bone marrow failure may appear in the second decade of life or even later in some patients with inherited marrow failure syndromes, and marrow function should be assessed at least once a year. Bone marrow failure is defined as a persistent low blood count associated with a hypocellular-for-age bone marrow with <5% blasts.[5] The clinician should be mindful that myelodysplastic syndrome (MDS), infections, and drug toxicity may all cause pancytopenia in these patients. Bone marrow failure may be mild (hemoglobin normal for age or >8 g/dL, absolute neutrophil count [ANC] >1000/μL, or platelets > 50 000/μL), moderate (hemoglobin normal for age or >8 g/dL, ANC >500/μL, or platelets > 20 000/μL), or severe (hemoglobin <8 g/dL, ANC <500/μL, or platelets <20 000/μL).[5] A bone marrow biopsy, aspirate analysis, and cytogenetics should be performed annually to identify malignant clonal evolution for patients with some degree of marrow failure. Marrow function should be assessed every 4 to 6 months for patients with decreasing peripheral blood counts, those who are transfusion dependent, and those with abnormal cytogenetics.[5]

Allogeneic hematopoietic stem cell transplantation is usually recommended for patients with severe marrow failure or those who have progressed to MDS or acute myeloid leukemia (AML). Alternative therapies to transplantation, such as androgens, can be considered for patients who lack a suitable donor, are ineligible for a transplant, or have moderate aplastic anemia. Patients with inherited marrow failure do not respond to immunosuppressive therapy with antithymocyte globulin and cyclosporine, although a hematologic response in patients with telomere disease has been anecdotally reported.[1]

## Androgens

Steroids with androgenic and/or anabolic effects have been used to treat inherited and acquired bone marrow failure syndromes since the 1950s, with variable response rates. A variety of androgen formulations have been used, from testosterone propionate and nandrolone decanoate to oxymetholone, oxandrolone, and danazol.[6-8] Nandrolone, oxymetholone, and oxandrolone are anabolic-androgenic steroids, whereas danazol is a synthetic steroid with antigonadotropic, antiestrogenic, and androgenic activities.[9] These testosterone derivatives vary in biotransformation, anabolic effects, and toxicities.

Androgens improve hematopoiesis by at least 2 mechanisms. First, androgens increase the red blood cell mass by stimulating the production of erythroid progenitors in the bone marrow either by increasing erythropoietin (EPO) production in the kidneys or by directly activating the EPO receptor on progenitor cells.[10] Second, androgens also increase telomerase (*TERT*) gene expression in hematopoietic cells,[11] which appears to be mediated by the biotransformation into estrogen. The *TERT* promoter region contains at least 2 estrogen-binding regions (estrogen receptor elements) and exposure to either androgens or estrogens increases *TERT* messenger RNA levels in hematopoietic cells. This stimulation is abrogated by inhibitors of aromatase, the enzyme that catalyzes the conversion of androgens into estrogens. Similarly, in a mouse model of aplastic anemia, testosterone therapy upregulated telomerase expression, increased peripheral blood counts, and elongated telomeres in peripheral blood leukocytes over time.[12] In contrast, telomerase-deficient mice treated with sex hormones did not display the same results, indicating that androgen effects on telomeres and hematopoiesis are mediated by telomerase. Also in support of these findings, a large epidemiological study involving 980 men investigated the association between circulation hormone levels, functional aromatase polymorphisms, and telomere length.[13] Serum dihydrotestosterone and estradiol levels positively correlated with age-adjusted telomere length and functional aromatase polymorphisms were associated with lower estradiol levels and shorter telomeres, further implicating this pathway in telomere length regulation in humans. In a recent study, danazol treatment led to telomere elongation in humans with telomeropathies.[7] Finally, androgens ameliorate hematopoiesis by stimulating other cellular pathways in hematopoietic stem and progenitor cells or exert some effects on the marrow microenvironment.

### *Androgens for Fanconi anemia*

Several small retrospective clinical trials using various androgens have been reported in patients with Fanconi anemia. In a more recent report, 8 patients with Fanconi anemia and severe marrow failure were treated with danazol with a starting dose of 5 mg/kg per day; 7 showed a hematologic response at 6 months and maintained stable blood counts for up to 3 years.[14] Danazol was tapered over time, with a median dose of 2.6 mg/kg per day, without major side effects being reported. A phase 1/2 trial (clinicaltrials.gov NCT00243399) recently tested low-dose oxandrolone (0.1 mg/kg per day and 0.0625 mg/kg per day for male and female patients, respectively) to treat marrow failure in Fanconi anemia.[15] Of 9 patients, 7 (78%) achieved a hematologic response with a median follow-up of ~2 years. The drug was well tolerated and the main side effects were virilization and elevated liver function tests. A larger retrospective German study identified 70 patients who were treated with androgens over a period of 30 years; 37 patients were evaluable.[6] Most patients were treated with oxymetholone. Twenty-five patients (68%) had a hematologic response, with a median 6.5 g/dL increase in hemoglobin concentration (median time to response, 14 weeks), a 70 000/μL median increase in platelet counts (median time to response, 11.5 weeks), and a 1530/μL median increase in neutrophil counts (median time to response, 12 weeks). Although information on toxicity was not available for all patients, 78% of evaluable patients had some degree of virilization, with acne and deepening of voice. Grade 3 liver toxicity (elevated liver function tests) was observed in 5 of 26 patients (25%) and liver adenoma was observed in 12 patients (46%), causing treatment interruption in 6 patients. Nine patients (24%) developed abnormal cytogenetics (3q+, monosomy 7) and stopped therapy. Twenty-four patients (65%) eventually underwent allogeneic hematopoietic stem cell transplantation. The largest retrospective study on androgens for Fanconi anemia evaluated 66 patients with severe bone marrow failure treated with either oxymetholone (n = 49) or danazol (n = 17).[16] Oxymetholone was given at a starting dose between 0.5 and 1 mg/kg per day and danazol was given at a starting dose between 2 and 4 mg/kg per day. With a median treatment duration of 18 months, a hematologic response was observed in 52 patients (78%) and 30 patients (45%) displayed a trilineage response. Oxymetholone and danazol response rates were comparable. Grade 3 liver toxicity was observed in 7 patients (11%) and was more common in patients treated with oxymetholone.

Table 1. Androgen therapy for inherited bone marrow failure syndromes

| Study | Reference | Patients, N | Disease | Androgen | Median age, years | Median duration of therapy, years | Response, % | Toxicity |
|---|---|---|---|---|---|---|---|---|
| Scheckenbach et al. | 14 | 8 | Fanconi anemia | Danazol | 11 | 3 | 87 | — |
| Rose et al.* | 15 | 10 | Fanconi anemia | Oxandrolone | 9 | 2 | 70 | Virilization, liver, MDS |
| Paustian et al. | 6 | 37 | Fanconi anemia | Various | 8.8 | 4.2† | 68 | Virilization, MDS, hepatic adenoma |
| Ribeiro et al. | 16 | 66 | Fanconi anemia | Oxymetholone, danazol | 10.5 | 1.5 | 78 | Virilization, liver |
| Khincha et al. | 8 | 16 | Dyskeratosis congenita | Oxymetholone, fluoxymesterone, nandrolone decanoate | 11 | 2.2 | 69 | Bone fractures, virilization, splenic peliosis, liver |
| Townsley et al.* | 7 | 27 | Telomeropathy | Danazol | 41 | 2 | 83 | Liver, muscle |

MDS, myelodysplastic syndrome.
*Prospective study.
†For responders.

Peliosis hepatis was noted in 1 patient treated with oxymetholone, requiring drug discontinuation. Some degree of virilization was observed in most patients, including 7 of 18 female patients (39%) who developed voice hoarseness and 2 children who were bullied at school by classmates.

### *Androgens for dyskeratosis congenita and telomere diseases*

A retrospective case-control study evaluated 16 patients with dyskeratosis congenita and pathogenic variants mostly in *TINF2*, *RTEL1*, and *DKC1* treated with oxymetholone or fluoxymesterone for a median 2.2-year period. A hematologic response was observed in 11 patients (69%). Common side effects were hypercholesterolemia (54%) and dyslipidemia (38%). Although abnormal liver function tests were common (75%), the prevalence was not different from that observed in patients not treated with androgens, who were analyzed as "controls." A lesion suggestive of liver adenoma or fibrosis was found in 1 patient. Two patients received concomitant granulocyte colony-stimulating factor (G-CSF) and developed splenic peliosis causing a splenic rupture. Patients showed accelerated growth during treatment and all patients had some degree of virilization. In a phase 1/2 prospective study (clinicaltrials.gov NCT01441037), Townsley et al.[7] administered 800 mg of danazol per day to 27 patients with telomere diseases for 2 years. The primary end point was the mitigation of telomere attrition in peripheral blood leukocytes; the secondary efficacy end point was a hematologic response and the primary safety end point was toxicity. The study reached its primary end point early (all 12 evaluable patients demonstrated telomere elongation) and was stopped. Considering intention to treat, 12 of the 27 patients (44%) met the primary end point and almost all patients showed an increase in telomere length (mean 385 bp). A hematologic response was achieved by 19 of 24 patients (79%) at 3 months and by 10 of 12 evaluable patients (83%) at 6 months. The most common grade $\leq$2 adverse events were abnormal liver function tests in 11 patients (41%) and muscle cramps in 9 patients (33%).

In summary, androgen therapy may result in durable hematologic responses in most patients with Fanconi anemia and dyskeratosis congenita (Table 1). However, in a minority of cases, the response may be transient. Androgen treatment may result in liver dysfunction, adenomas, and adenocarcinomas, and patients should have liver function tests performed every 3 to 6 months and hepatic lesions assessed by ultrasonography every 6 months. Hematologic responses to oxymetholone and danazol are comparable, but liver toxicity appears to be more common with oxymetholone.

## Corticosteroids

The use of corticosteroids in marrow failure syndromes is restricted for the treatment of Diamond-Blackfan anemia (DBA).[17] In DBA, the major aim of treatment is to maintain a stable hemoglobin concentration sufficient for adequate growth and development in children and for daily activities with minimal anemic symptoms in adults. Corticosteroids may achieve these goals in up to 80% of patients, but a significant proportion eventually become steroid refractory or halt therapy due to toxicity.[18,19] Side effects are common; nearly half of patients develop cushingoid features and approximately one-fourth develop cataracts or pathologic bone fractures.[18] In a large registry study, only 37% of patients responded to corticosteroids without dose-limiting toxicity.[18]

Data on the appropriate corticosteroid type, dose, or schedule are scarce and guidelines are not currently based on prospective clinical trials.[19] To mitigate toxicity, steroids should be prescribed cautiously. Prednisone and prednisolone are the most frequently used steroids, at a starting dose of 2 mg/kg per day. An increase in hemoglobin should be expected within 4 weeks. Patients with continued transfusion dependence after a 4-week trial are considered steroid refractory and the drug should be discontinued. If a response is obtained, corticosteroids may be slowly tapered to the minimal effective dose required to avoid transfusions. Consider discontinuing steroids if the dose cannot be titrated below the recommended maintenance dose of $\leq$0.5 mg/kg per day to avoid long-term toxicities. For some patients, a partial response may be acceptable if a clear benefit on transfusion reduction is obtained with a clinically tolerable dose. Steroids should be deferred until the age of 1 year to avoid potential effects on growth and neurocognitive development.

## Growth factors and agonists

### *EPO*

EPO was initially considered a logical treatment in DBA, but the very high EPO serum levels disproportionate to the anemia level reflect the relative EPO insensitivity, as confirmed by in vitro studies.[20] Small clinical trials failed to demonstrate any clinical benefit of EPO

in DBA. In other inherited marrow failures, EPO only produces transient and unsustainable hemoglobin responses.[21]

### G-CSF and granulocyte-macrophage colony-stimulating factor

Recombinant G-CSF increases neutrophil counts in congenital neutropenias.[22,23] In Shwachman-Diamond syndrome, in which neutropenia is the most prominent cytopenia, G-CSF is effective in improving neutrophil counts.[24]

The aim of long-term G-CSF treatment is to prevent infections, and G-CSF should be instituted when severe neutropenia develops or recurrent infections are present. Most patients respond to a G-CSF dose between 3 and 20 μg/kg per day, but ~25% of patients with congenital neutropenia require doses between 20 and 100 μg/kg per day.[25]

As life expectancy improves, long-term use of G-CSF in congenital neutropenia is associated with a risk of progression to MDS and AML. AML appears to derive from a multistep process involving the expansion of clones harboring acquired *CSF3R* gene mutations that confer autonomous proliferation.[26]

### Thrombopoietin receptor agonists

Eltrombopag is an oral nonpeptide small molecule that activates the thrombopoietin (TPO) receptor, MPL. Eltrombopag binds MPL at a site distinct from endogenous TPO. It can restore trilineage hematopoiesis in refractory acquired aplastic anemia. Its addition to standard immunosuppression as the first-line treatment yielded an impressive hematologic response of 94% (many being complete responses) and considerably restored the number of $CD34^+$ cells in the bone marrow.[27] Given the ability of eltrombopag to expand the hematopoietic stem and progenitor cell pool in cases with acquired marrow failure, eltrombopag may be speculated to have activity in inherited bone marrow failure syndromes. A case report by Winkler et al.[28] described the treatment of a single patient with steroid-refractory DBA who achieved transfusion independence with high doses of eltrombopag. There remains a legitimate concern that eltrombopag may increase the risk of clonal evolution to MDS/AML. Patients with inherited bone marrow failure syndromes should not receive eltrombopag outside the context of a clinical trial.

## Nonhematopoietic complications

The development of cancer is a complication common to almost all types of inherited bone marrow failure syndromes.[29] Patients with either Fanconi anemia or dyskeratosis congenita have a similar risk of cancer, with high incidences of AML, tongue cancer, and cervical squamous cell carcinoma.[30] Gynecological cancers, especially in the vulva and cervix, are also common in Fanconi anemia. Although the risk of AML and MDS may be reduced with an allogeneic hematopoietic stem cell transplant, nonhematologic cancers are not prevented by transplantation. Importantly, patients with Fanconi anemia who undergo transplantation appear to have a higher incidence of head and neck cancer, which has been attributed to the development of graft-versus-host disease.[31,32]

Thus, patients with constitutional bone marrow failure syndromes should be screened for head and neck cancers every 6 months after age 10 years and suspicious lesions should be investigated. Patients should also be encouraged to refrain from alcohol consumption and tobacco use, because these are known risk factors for head and neck cancers. Although human papillomavirus is not directly linked to cancer in Fanconi anemia, guidelines recommend that patients should be vaccinated.[29]

Pulmonary and hepatic complications are common in dyskeratosis congenita. Pulmonary fibrosis and liver cirrhosis are common manifestations of telomere diseases with no effective available therapy.[1,33] Comorbidities including marrow failure and cirrhosis often exclude patients from lung transplantation. Patients with dyskeratosis congenita who undergo lung transplantation have high rates of renal complications, immunosuppression intolerance, and respiratory infections.[34] Cirrhosis is another feature of telomere diseases without effective treatment. In a prospective study of danazol for the treatment of telomere diseases, the diffusion capacity of the lungs for carbon monoxide and the forced vital capacity remained stable during therapy in a subset of patients with lung disease, suggesting that lung function did not deteriorate.[7] However, lung function was not the primary end point and these results should be further investigated with proper controls. Similarly, liver fibrosis, as measured by ultrasonic transient elastometry, was available for 6 patients in the same study. Fibrosis was significantly reduced in 3 patients and deteriorated in 1 case.[7]

Chronically transfused patients will develop iron overload and require chelation, which should be started when the volume of transfused red cells reaches 200 mL/kg, the hepatic iron level is >5 mg/g dry weight, or the serum ferritin level is persistently >1000 μg/L. Deferasinox is well tolerated and effective in reducing iron overload in children with Fanconi anemia.[35] The starting dose is 20 mg/kg per day and renal and hepatic toxicities are common.

## Future directions

There is currently no direct comparison of responses and toxicities with each androgen formulation to better guide clinical choices. New trials are warranted to determine the minimal effective dose to minimize virilization and liver adverse events observed with oral formulations. An ongoing trial is currently assessing this issue (clinicaltrials.gov NCT02055456) by evaluating the effects of nandrolone decanoate, a parenteral androgen without first liver passage, in patients with telomeropathies.

Currently, there are several ongoing trials for inherited marrow failure syndromes based on innovative translational research. In DBA, there is haploinsufficiency of a ribosome protein gene (*RPS19* is most frequently mutated), which interferes with ribosome function. The amino acid L-leucine enhances protein synthesis by activating messenger RNA translation. In DBA models, leucine improves anemia by activation of the mechanistic target of rapamycin pathway.[36,37] These findings encouraged the development of a phase 1/2 clinical trial (clinicaltrials.gov NCT01362595), in which patients with transfusion-dependent DBA receive leucine at a dose of 2100 mg/m$^2$ per day for 9 months. The primary end point is hemoglobin response.

The efficacy of eltrombopag in acquired aplastic anemia raises the possibility that TPO agonists may be effective in inherited marrow failure disorders as well. Because of the uncertainty regarding whether eltrombopag promotes clonal evolution, patients with inherited bone marrow failure syndromes should only receive TPO agonists in the clinical trial setting.

In Fanconi anemia, bone marrow failure is induced by increased transforming growth factor (TGF)-β signaling and TGF-β blockade rescues hematopoietic stem cell function.[38] Quercetin is a flavonoid

polyphenol with antioxidant properties and cellular effects, including TGF-β inhibition. An ongoing phase 1 trial (clinicaltrials.gov NCT01720147) addresses the safety of administering quercetin to patients with Fanconi anemia and its effects on hematopoiesis.

Currently, there are 2 clinical trials addressing the toxicity and efficacy of gene therapies for the treatment of bone marrow failure in patients with Fanconi anemia (clinicaltrials.gov NCT01331018 and NCT03157804). In both studies, hematopoietic stem cells are harvested, genetically corrected by lentiviral transduction, and reinfused to the patient.[39]

Patient-specific induced pluripotent stem (iPS) cells have been derived from cases with dyskeratosis congenita,[40] Fanconi anemia, and DBA,[41] mimicking the deficient hematopoietic phenotype. In a recent study, an unbiased drug screen platform using iPS cells found a molecule that induces autophagy and increased erythropoiesis in a DBA model.[41] These cells may serve as a tool to identify novel actionable target pathways leading to new therapies. Hematopoietic stem and progenitor cells can now be produced from iPS cells.[41] The combination of patient-specific iPS cells, new genome editing strategies, and gene therapy may have a major impact on the treatment of patients with inherited bone marrow failure syndromes in the future.

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