OPEN

An update on Becker muscular dystrophy

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Purpose of review
The purpose of this review is to summarise the recent developments in trial readiness, natural history studies, and interventional clinical trials for Becker muscular dystrophy (BMD).

Recent findings
As several treatment concepts have claimed to convert patients with Duchenne muscular dystrophy (DMD) into a BMD phenotype, BMD itself has moved into the focus of clinical research. Natural history studies have helped to better characterize patients with BMD and the disease is now a target for interventional trials. In parallel, there have been advances in diagnostics and in the development of preclinical models.

Summary
Despite increased collaborative efforts to improve trial readiness amongst patients with BMD, there is still a lack of long-term natural history data, and the broad spectrum of disease severity remains a challenge for well designed clinical trials.

Keywords
Becker muscular dystrophy, Duchenne muscular dystrophy, interventional trials, natural history data, trial readiness

INTRODUCTION

Since the discovery that Becker muscular dystrophy (BMD) is a milder allelic form of Duchenne muscular dystrophy (DMD), with both diseases being caused by mutations in the *DMD* gene [1], BMD has very much been in the shadow of DMD. It is unfortunate that for historic reasons the diseases have rather been seen as distinct entities and not as a single condition with a broad clinical spectrum of severity, like several of the limb girdle muscular dystrophies (LGMD). This has excluded patients with BMD even from clinical trials that did not require a specific *DMD* mutation, from the development of outcome measures, biomarkers, and from initiatives to develop care standards, which are well established for DMD [2–4] but do not exist for BMD. BMD is also less trial ready because solutions for patients affected by rare diseases can only succeed with the support of a strong patient voice. Whilst there are many excellent and vocal advocacy groups for patients with DMD, there are very few BMD-specific patient foundations.

DMD and BMD have also been distinguished from each other by the type of mutation, with DMD mainly being caused by out-of-frame and BMD by in-frame mutations [5]. There are exceptions to this rule, but this is still the most appropriate explanation for the relatively homogenous phenotypic spectrum of DMD, caused by a loss of dystrophin expression, compared to the broader phenotypic spectrum of BMD, depending on the size of residual dystrophin and the level of its expression.

Over recent years, the field has focussed more on the mild end of BMD, as it is the desired phenotypic outcome for many of the most exciting interventional trials in DMD including exon skipping, gene transfer, and gene-editing trials. The focus has mainly been on skeletal muscle strength and function, but not as much on the heart, central nervous system, or other organ functions.

Only recently, BMD has been fully recognised as a disease in need of interventional trials, because of its progressive nature and high disease burden for most patients and carers.

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KEY POINTS

- The recent development of Becker muscular dystrophy specific animal models will support drug development programs for the progressive X-linked disease.
- Natural history studies in well defined cohorts of Becker muscular dystrophy have helped to define clinically meaningful outcome measures.
- First interventional clinical drug trials are underway to improve disease progression in Becker muscular dystrophy.

IMPROVED DIAGNOSTICS FOR BECKER MUSCULAR DYSTROPHY

As a result of improved sequencing technologies for all genetic diseases and more routine sequencing of the *DMD* gene due to approved therapies for patients with DMD, patients with BMD and female carriers with BMD mutations [6,7] are now more frequently diagnosed. BMD has a lower incidence rate than DMD, but due to longer life expectancy, is not much less prevalent. Better access to massive parallel sequencing has increased the diagnosis of BMD in ethnic groups beyond high-income countries [8–12] and has also improved the diagnosis of BMD through prenatal [13] and neonatal screening programs [14,15].

Sequencing studies for LGMD have nevertheless shown that BMD is often underdiagnosed and that patients are falsely labelled as having LGMD. This includes manifesting female carriers for BMD, who are more frequent than some rare forms of LGMD [16,17].

With widely applied genetic panel testing, variants of unknown clinical significance in the *DMD* gene are regularly detected. These can be very difficult to interpret if dystrophin expression appears to be normal in a muscle biopsy in patients with elevated serum creatine kinase (CK) levels [18▪]. Furthermore, some deletions in the *DMD* gene do not actually cause elevated CK levels and patients may have been included in microarray-based comparative genomic hybridisation (array CGH) assays because of mild intellectual disability or behavioural problems. These patients are now more frequently referred to neuromuscular services without clear follow up plans. Should patients with deletions and other genetic variants in the *DMD* gene who may never develop skeletal muscle symptoms, but who do show hyperCKaemia and maybe CNS symptoms still be classified as BMD? It is not entirely clear where the mild range of the BMD clinical spectrum ends.

TRIAL READINESS IN BECKER MUSCULAR DYSTROPHY

Improved diagnostics are one of the requirements for trial readiness, but several other tools and developments are still missing for BMD to be fully trial ready.

Beside the well characterised *mdx* mouse model for DMD, there are several other DMD mouse models for which standardized operating procedures for their assessment have been agreed. For DMD, a rat model and other, larger animal models have been used to advance our understanding of dystrophin-deficiency and drug development programs. For BMD on the other hand, animal models for preclinical research have only very recently been generated [19,20▪▪] and there is still a lack of natural history data for them. Nevertheless, having a BMD rat and mouse model [20▪▪] is an important milestone for trial readiness.

For clinical trials in BMD, validated outcome measures are sparse and the North Star Ambulatory Assessment (NSAA), a 17-item rating scale and accepted primary endpoint used to measure functional motor abilities in ambulant patients with DMD, is not an appropriate endpoint for ambulant patients with BMD. Patient registries, used for feasibility studies, trial recruitment, and the collection of longitudinal clinical and patient reported data, now exist for more and more genetic neuromuscular diseases, but, with a few exceptions [21], are lacking in many countries for patients diagnosed with BMD. Most DMD-registries are restricted to patients with DMD and do not collect data for the wider spectrum of dystrophinopathies.

One incentive for industry to do trials in a specific disease is the availability of health economics data. Although this has now been addressed for DMD (https://hercules.duchenneuk.org/), there is hardly any published information on health economics in BMD. The same is true for standard of care guidelines, which again have been established for patients with DMD but are lacking for BMD.

The most important prerequisite for the launch of interventional trials in a rare genetic muscle disease, however, is the availability of robust natural history data, ideally including data on muscle function and strength, biomarker data, and data on surrogate markers like muscle magnetic resonance imaging (MRI).

NATURAL HISTORY STUDIES: LESSONS LEARNED

There is limited data on the natural history of BMD, mainly coming from single centre observational

studies [22] that also include muscle MRI [23]. These studies highlight the clinical variability of BMD and suggest that long-term follow up (>12 months) might be required to observe clinically meaningful changes in common functional outcome measures including the NSAA, the 6-min walking distance (6MWD), and timed function tests, especially in milder patients.

The past few years have seen an increased interest in understanding the natural history of BMD and in the development of robust, clinically meaningful, and sensitive functional outcomes for the condition. New therapies have moved from preclinical studies to clinical trials and BMD is now seen as a condition to potentially evaluate new, nonmutation specific therapeutic approaches for dystrophinopathies including the synthetic steroid vamorolone, the histone deacetylase (HDAC) inhibitor givinostat, and the small molecule EDG-5506, a selective fast myosin inhibitor.

Moreover, the most promising therapeutic approaches currently in development for DMD, including gene transfer therapy using micro/mini-dystrophin and exon skipping strategies, aim to restore the expression of a partially functional dystrophin, similar to that observed in patients with BMD. Therefore, a better understanding of the natural history of BMD is seen as a key step to inform not only drug development but also to understand the possible clinical, long-term implications of these therapies in DMD.

The first multicentre, international natural history study in BMD was completed in 2019 at 16 sites across four countries (US, Canada, UK and Italy), led by the Cooperative International Neuromuscular Research Group (CINRG) [24]. The study enrolled 83 patients with a broad age range (5.6–75.4 years) and a genetically confirmed diagnosis of BMD and followed them up for three years with annual assessments.

The full results of longitudinal outcome measures, including skeletal muscle, respiratory and cardiac function data, are pending publication. The cross-sectional baseline data and preliminary longitudinal data confirm previously reported challenges for BMD related to the broad phenotypic variability and age of symptom onset [25]. Patients showed very heterogeneous skeletal muscle, cardiac and respiratory manifestations. Moreover, a negative correlation between age and functional measures (timed function tests, the NSAA and the 6MWD) was suggested for adults but not for patients <18 years old. Baseline data failed to demonstrate a correlation between age and upper limb function as measured by the 9-Hole Peg Test, suggesting that these outcome measures might not be sensitive to change in patients with BMD unless an intervention is expected to result in clear functional improvement, rather than slowing down disease progression.

The ongoing 24-month observational study in BMD led by the Genetic Resolution and Assessments Solving Phenotypes (GRASP) consortium aims to recruit up to 150 patients. It will collect motor, respiratory, and cardiac function measures and includes muscle MRI (https://clinicaltrials.gov/ct2/show/NCT05257473). The higher recruitment target and the inclusion of a more comprehensive battery of functional outcome measures aiming to cover a broader range of clinical features, will hopefully support the identification of sensitive and clinically meaningful outcomes to inform clinical practice and clinical trial design and identify predictive factors of functional trajectories.

Until robust natural history data is available, designing clinical trials for BMD will be challenging in terms of power calculations, patient selection, choice of clinical endpoints, and study duration. The publication and sharing of natural history data will be one requirement to accelerate the elaboration of clinical trials in BMD.

INTERVENTIONAL TRIALS IN BECKER MUSCULAR DYSTROPHY: WHERE DO WE STAND?

To date, no treatments are approved for BMD; however, the past few years have seen an increased number of interventional clinical trials in BMD with treatments targeting different molecular pathways downstream of the lack of functional dystrophin.

Small pilot studies with different molecules including metformin [26] (as a single and combined treatment with L-citrulline) and tadalafil [27] have been conducted over the past years without showing convincing results. A recent single centre open label study was conducted to evaluate the efficacy of once-weekly prednisone (0.75–1 mg/kg) administered over 24 weeks to patients with LGMD or BMD [28]. The study, however, only recruited one patient with BMD and therefore no safety or efficacy conclusions could be reached. The study illustrated what had been experienced in other research studies, that recruiting patients with BMD can be challenging, despite the relatively high prevalence of the disease.

In 2021, Italfarmaco completed a phase II clinical trial evaluating the safety and efficacy of givinostat as a potential therapeutic approach for BMD. The HDAC inhibitor is administered as an oral suspension that is taken twice per day at home.

HDACs are enzymes that regulate the deacetylation of numerous proteins, and therefore affect a

wide range of cellular processes. In skeletal muscles, HDCAs involvement has been described to be involved in tissue remodelling both in physiological and pathological conditions [29▪]. The role of HDACs in muscular dystrophies is not fully understood, however, their activity has been reported to be aberrantly upregulated in dystrophinopathies, because of the reduction in nNOS (NOS-1) expression [30].

The phase II, double-blind, placebo-controlled study enrolled 51 ambulatory patients with a genetically confirmed diagnosis of BMD, aged 18–65 years, who received either givinostat or placebo (randomization ratio 2 : 1) over 12 months [31▪]. This aimed to demonstrate the effect of givinostat on muscle pathology (by histology and MRI) and function (timed function tests, 6MWD, motor function measures and hand-held myometry). The study failed to achieve its primary (changes in quantitative muscle MRI) and secondary endpoints (histology parameters, MR spectroscopy, and functional evaluations) except for a positive trend in muscle MRI fat fraction in the thigh, which remained stable in the givinostat group but increased in the placebo group [31▪]. However, the study also showed that mean total fibrosis, as well as muscle histology and functional outcomes did not change over time in either group.

The findings highlighted the challenges of conducting interventional trials in BMD (already seen in natural history studies), due to the clinical heterogeneity and requirement for longer study durations and/or more sensitive clinical outcomes to show any drug effect, when the main aim is to slow down disease progression rather than improve the clinical phenotype.

Edgewise Therapeutics is currently recruiting both adolescents and adults with BMD in three countries into a multicentre, international phase II safety and efficacy clinical trial with EDG-5506. EDG-5506 is an orally administered small molecule designed to protect contraction-induced muscle damage in dystrophinopathies by selectively inhibiting type II fast skeletal muscle myosin in a concentration dependent manner.

A phase 1b safety, tolerability, and pharmacokinetic study in 12 adults with BMD over a 24-month treatment period is ongoing (ClinicalTrials.gov Identifier: NCT05160415) and the phase II randomized, double-blind, placebo-controlled study has recently started recruitment (ClinicalTrials.gov Identifier: NCT05291091). The phase II study, aiming to enrol 66 ambulant patients (approximately 48 adults and 18 adolescents) with genetically confirmed diagnoses of BMD, will evaluate safety, biomarkers, pharmacokinetics, and functional measures of three different doses of EDG-5506 over a 12-month-treatment period.

Following positive results of the phase IIb study with vamorolone [32,33], a glucocorticoid-like drug developed by ReveraGen BioPharma first tested in DMD, the company has initiated a six-month phase II pilot, randomized, double-blind, placebo-controlled study to assess safety, tolerability, pharmacokinetics and pharmacodynamic effects of a single dose of vamorolone in BMD (ClinicalTrials.gov Identifier: NCT05166109).

Vamorolone is a dissociative steroid optimised to retain a potent anti-inflammatory activity through nuclear factor (NF)-κB inhibition, improve muscle cell membrane stability and reduce glucocorticoid responsive element (GRE) mediated transcriptional activities associated with side effects. Moreover, vamorolone acts as a mineralocorticoid antagonist with a potential positive effect on DMD-associated cardiomyopathy.

The ongoing pilot study, enrolling ambulant adults with clinical signs of muscle weakness at screening, has been designed for a 6-month treatment period and is estimated to be completed by the end of 2024.

Finally, following a small single centre pilot study [34], a phase 1 clinical trial evaluating safety and pharmacokinetics of incremental doses of epicatechin, hypothesized as an antioxidant and natural myostatin inhibitor, in BMD was completed last year and results are awaited (ClinicalTrials.gov Identifier: NCT04386304).

CONCLUSION

Although first described by Peter Emil Becker in 1955, the natural history of BMD has only recently been studied more comprehensively and first interventional clinical trials have only now been concluded or are ongoing. To make sure that patients with BMD benefit from these encouraging developments, it is important to invest in translational research efforts and infrastructures for this progressive condition and also to strengthen the patient voice.

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Conflicts of interest

V.S. is or has been on advisory boards for Astellas Gene Therapies, Biogen, Edgewise Therapeutics, Ipsen, Kate Therapeutics, ML Bio Solutions, Novartis Gene Therapies, PepGen, Roche, Sanofi, Sarepta Therapeutics, Vertex Pharmaceuticals, and Wave Therapeutics. He received speaker fees/honoraria from Novartis Gene Therapies, Pfizer, Roche, Sanofi, and Sarepta Therapeutics. He has research collaborations with Sarepta Therapeutics and Sanofi. M.G. reported receiving clinical trial and grant support from ReveraGen; grants from the European Commission and the National Institutes of Health; speaker honoraria from Sarepta Therapeutics; serving as principal investigator of a clinical trial of Duchenne muscular dystrophy from Sarepta Therapeutics, Pfizer, Santhera, and Italfarmaco; serving on the advisory board for Pfizer (honoraria to Newcastle University), NS Pharma (honoraria to Newcastle University), and Dyne (honoraria to Newcastle University) outside the submitted work.

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