

the MPa200Z group, seven [12%] in the HRZE group, and eight [31%] in the DRMPa200Z group); and 25 (13%) had vomiting (seven [12%] in the MPa100Z group, seven [11%] in the MPa200Z group, seven [12%] in the HRZE group, and four [15%] in the DRMPa200Z group). Importantly, no episodes of QT interval in excess of 500 ms were identified.

Dawson and colleagues' results¹³ are encouraging for several reasons. First, the investigators have shown the efficacy of a rifampicin-sparing regimen, which has the potential to improve the ease and safety of treatment of patients with HIV taking protease inhibitors. Second, the 8 week period needed to achieve sputum culture conversion might benefit the individual patient (ie, rapid recovery) and the community (ie, reduced *M tuberculosis* transmission). The potential exists to shorten treatment duration and thereby improve adherence. As the investigators note,¹³ the efficacy of the rifampicin-sparing regimen in patients with MDR tuberculosis needs further investigation, since the study was not powered to detect an effect in the small subgroup of patients with MDR disease. Furthermore, the positive protective effect on the emergence of phenotypic drug resistance identified in this study needs to be further assessed in the longer term, especially during the continuation phase of treatment.

Much work still needs to be done to improve the present approach to clinical trials of antituberculosis drugs. The surrogate markers adopted to measure efficacy are old and need complex statistical approaches. Furthermore, the time needed to assess the pharmacological profile of a new drug is still very long, and the difficulty of enrolling susceptible individuals into trials is a further barrier.⁹ The new WHO End TB Strategy aims to support these efforts needed for research on new antituberculosis drugs.

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We declare no competing interests.

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Efficacy of idebenone in Duchenne muscular dystrophy

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In *The Lancet*, Gunnar Buyse and colleagues¹ report the results of DELOS, a double-masked, randomised, placebo-controlled, multicentre, phase 3 trial investigating the efficacy of idebenone on respiratory outcomes in patients with Duchenne muscular dystrophy. The authors report for the first time the possible efficacy of a non-steroidal drug in a cohort of patients with Duchenne muscular dystrophy, most of whom were non-ambulant. The results are promising

because of the favourable safety profile of idebenone, but also show that challenges exist for studies in people with this disease, especially non-ambulant patients, and raise questions about the choice of outcome measures and inclusion criteria for this population.

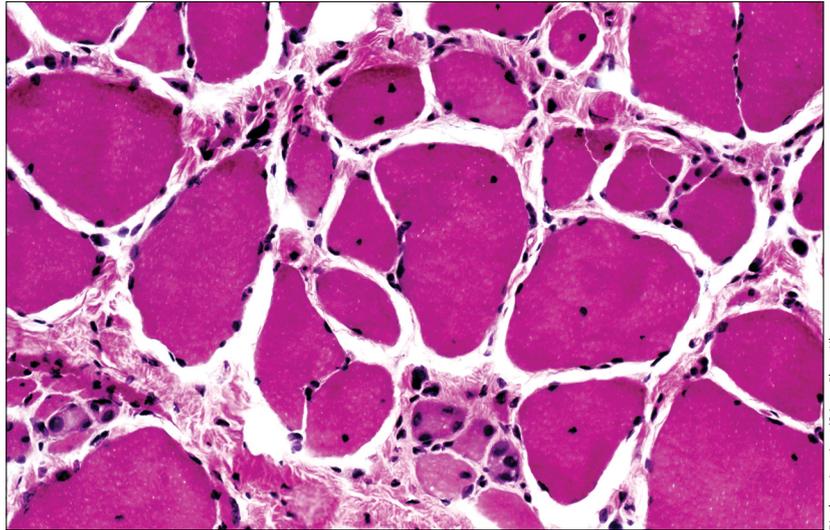
In the past few years, several experimental therapies have been studied in patients with Duchenne muscular dystrophy² and this research has strongly encouraged international collaboration to identify suitable outcome

measures for this population. Meetings with regulatory agencies have improved definitions of the criteria for identifying measures that should be statistically robust, validated, and suitable for multicentre studies, but also represent changes that are clinically meaningful for patients and their carers.³ The input from patients and advocacy groups has become as important as the clinical and statistical issues when outcome measures and their relevance are taken into consideration.

So far, most of the published trials in Duchenne muscular dystrophy have focused on young cohorts, mainly including ambulant boys, with measures of motor function such as the 6 min walk test.⁴⁻⁶ Over the past few years, national and international networks have produced an impressive amount of work on these measures, providing natural history data, trajectories of changes according to specific characteristics such as age and baseline values, and the effect of corticosteroids, trying to establish statistical robustness and clinical meaningfulness by relating the measures to life-changing events and quality of life measures.^{7,8} This collaborative work has provided reference data that have been used both to power studies and to allow regulators to define the efficacy of recent trials in ambulant patients with Duchenne muscular dystrophy.⁹

In DELOS, the placebo and idebenone groups comprised 33 patients and 31 patients respectively, with patients aged 10–18 years eligible for inclusion. The trial's primary endpoint was change in peak expiratory flow as percentage predicted (PEF%p), with secondary outcome measures of respiratory function including forced vital capacity (FVC) and peak cough flow. In the intention-to-treat analysis, the fall in PEF%p up to 52 weeks was significantly smaller in the idebenone group (-8.84% in the placebo group [95% CI -12.73 to -4.95] vs -2.57% [-6.68 to 1.54] in the idebenone group, difference 6.27% [0.61 to 11.93]).

The choice of respiratory measures in the age range of the patients with Duchenne muscular dystrophy recruited by Buyse and colleagues¹ is justified by evidence that respiratory function progressively declines in the second decade, especially after loss of ambulation. The rationale for the choice of peak expiratory flow as primary efficacy measure is that it is a measure of expiratory muscle strength, and enables assessment of the weakness of chest wall muscles that are involved before the diaphragm in the early phases of the disorder.¹⁰ More information



Muscle tissue affected by Duchenne muscular dystrophy

is now available about the validity of other measures of respiratory function such as FVC, maximum inspiratory and expiratory pressures, and nasal inspiratory pressure for the monitoring of disease progression than about the validity of the DELOS primary outcome measure PEF%p,¹¹ reducing the impact of the study. However, information about other outcome measures was not available at the time Buyse and colleagues' study was designed.

Although no positive effects were noted by Buyse and colleagues¹ in peak cough flow, maximum inspiratory pressure, or maximum expiratory pressure, nor in arm strength and function, the congruent positive results for both PEF%p and the secondary outcome measure FVC are promising and suggest efficacy of the investigational drug in a population that is largely composed of non-ambulant patients for whom no other experimental therapy is being studied. A great effort was made by the investigators to ensure that the respiratory function at baseline was similar between the two groups; however, the patients who received idebenone had a shorter mean time since last glucocorticoid use than did those in the placebo group. Although there is little information about the long-term effect of corticosteroids after their discontinuation, the possibility of a contribution to the favourable trajectory for treated patients cannot be ruled out.

It is now important to investigate further the relation between some of the outcome measures used in DELOS,¹ particularly the primary outcome measure (PEF%p), and their value in predicting subsequent milestones such as time to ventilation or survival that

are clinically meaningful to patients and their families. Further studies should also be done to assess the relation of peak expiratory flow with other measures, such as those for assessment of motor function in the upper limbs. Some measures^{12,13} have recently been proposed, but were not available at the time Buyse and colleagues' study was designed and might be even more relevant in young patients on the verge of losing, or who have recently lost, ambulation.

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Community management of neonatal infections

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The substantial reduction of mortality in children younger than 5 years during the past decade is one of the most notable recent achievements in global health. The total number of deaths among children in this age group decreased from 9.88 million in 2000 to 6.28 million in 2013.¹ However, the reduction in neonatal mortality during the same period has been less impressive. Neonatal mortality decreased at an annual rate of 2.9% compared with 4.9% in children aged 1–59 months.¹ This comparatively small decrease has contributed to the global failure to achieve Millennium Development Goal 4.

Severe bacterial infection (ie, sepsis, pneumonia, and meningitis) in neonates is an important cause of child morbidity and mortality. Estimates suggest that, in 2012, 6.9 million such cases occurred and 557 000 neonates died as a result.^{1,2} Furthermore, the risk of impairment in survivors is high.³ Presentation is typically

with non-specific symptoms and signs that suggest severe disease, and clinical distinction between sepsis, pneumonia, and meningitis is very difficult. In resource-poor settings, many cases never reach a health facility. Thus, treatment of young infants with suspected severe bacterial infection in developing countries has been based on clinical signs. Clinical approaches to identify and manage these young infants, such as WHO's Integrated Management of Childhood Illnesses (IMCI), have deemed these children to have possible severe bacterial infection, and traditionally targeted the first point of contact with the health system—ie, first-level trained health workers.⁴

Challenges exist in the diagnosis of young infants with severe bacterial infections. Bacteriological tests have poor sensitivity and most studies of causation are from tertiary care settings, which are not truly representative of cases in the general population. Thus, data for