New Zealand Paediatric Neurology Clinical Network

# Duchenne Muscular Dystrophy and steroid use

## Clinician resource

### Key points

- DMD is a complex disorder with the gold standard of care being management by an MDT and steroid therapy
- Steroids should be commenced during the plateau phase, prior to motor skills being lost.
- Completion of immunisations, especially Varicella, should be considered prior to commencement.
- We recommend treatment with prednisolone 0.75mg/kg once daily, given in the morning.
- Long term steroid use is associated with multiple potential side effects for which careful surveillance is required.
- Ongoing use of steroids in non-ambulant patients is potentially beneficial. The best time to stop steroids is unclear and needs to take the burden of side effects into consideration.
- **Steroids should never be stopped suddenly:** a weaning schedule is required prior to discontinuation of steroid therapy.

### Background

Duchenne muscular dystrophy (DMD) is one of the most common muscle diseases in males, affecting around 1 in 5000 boys[1]. The gold standard of care for these children includes management by a multidisciplinary team (MDT) and the use of corticosteroids in ambulant boys with DMD [2, 3]. In New Zealand, most boys with DMD are treated with steroids, but knowing which steroids to use, what benefits to expect, when to start steroids, how to management their side-effects, and when to stop steroid therapy can pose significant challenges to the prescribing physician.

### Steroids

Corticosteroids are hormones produced in the adrenal cortex. Synthetic corticosteroids are used to mimic natural steroid effects. In DMD, steroid medications with primarily glucocorticoid effects are used: these include prednisone, prednisolone and deflazacort. Their effectiveness in DMD is poorly understood, but is postulated to result at least partly from suppression of the inflammatory response, reducing the degeneration of muscle caused by the lack of dystrophin [4].

Prednisone and prednisolone, the active metabolite of prednisone, are equivalent medications and can be used interchangeably. Previously it was felt that prednisolone should be used preferentially in patients with liver dysfunction due to the need for prednisone to be converted into prednisolone in the liver, but this was not borne out by *in vivo* studies [5]. Clinical trials have identified a daily prednisolone dose of 0.75mg/kg/day as being optimally effective and generally well tolerated [6]. This is usually given in the early morning, to minimise adrenal suppression.

Deflazacort is a synthetic derivative of prednisolone and has a slightly different side-effect profile, causing less weight gain, improved lipid profiles [7] and less glucose intolerance [8], but a greater risk of cataract formation and fractures [9] and short stature. When compared directly to prednisolone in patients with DMD, motor outcomes were equivalent and there was less weight gain in the group treated with deflazacort. Deflazacort is not widely available, and is currently not funded in Australia or New Zealand. Use of deflazacort is usually restricted to patients with severe behavioural side-effects or excessive weight gain from prednisolone. A dose of 0.9mg/kg in daily dosing is recommended [10].

## Benefits of steroids

Steroids slow the decline in muscle strength and function in DMD, reducing the risk of scoliosis, stabilising pulmonary function [2], prolonging ambulation [11], delaying the onset of cardiomyopathy [12] and prolonging life [13]. The benefits of steroid use vary from patient to patient but the use of steroids is strongly recommended in children with this condition.

## Starting steroids

Commencement of steroids is recommended during the plateau phase of DMD, generally between the ages of 4-6 years, when the patient is no longer making progress in his motor skills but has not yet lost any skills. The plateau phase can be identified on the basis of clinical history and/or timed testing, such a serial use of timed 10 metre or 6 minute walk tests. The plateau phase may only last a few months so close follow-up during this period is required to ensure treatment initiation at an optimal time [2].

High dose steroid therapy is associated with a risk of immune suppression. It is important to ensure the child has received the varicella vaccination, or check for varicella IgG prior to commencement. If non-immune, immunisation is recommended, and commencement of steroid therapy should be deferred one month. If there is a risk of TB exposure, testing should be considered and further advice sought.

The recommended dose is prednisone 0.75mg/kg or deflazacort 0.9mg/kg. Doses should be based on *lean body weight,* and should not be increased above 30mg/day prednisone, or 36mg/day deflazacort [2].

## Side effects and management

Careful monitoring for side-effects of steroids and management of these effects is key once steroids are commenced in boys with DMD. Side effects to monitor include:

- **Increased appetite and weight gain**. Monitoring of weight gain, and regular review by a dietician is ideally instituted prior to steroid commencement. As noted previously, if weight gain is a particular problem from prednisolone therapy, and not controlled by dietary interventions, a change to deflazacort may be considered (unfunded)
    - Measure glucose and HbA1c annually
- **Gastrointestinal symptoms** such as dyspepsia and abdominal discomfort. These can be minimised by taking steroids with meals, avoidance of NSAIDs and prescription of anti-reflux medications where needed.
- **Behavioural problems** .This is particularly seen in the first six weeks of treatment, and often settles after that time. Identification and management of pre-steroid behavioural issues is important, and further support with referral to a mental health service may be helpful.
- **Bone demineralisation and the increased fracture risk**
    - DEXA scans should be performed at baseline (5-7 years) and every 24 - 36 months, using a DEXA machine running paediatric software. Results should include body mass composition (lean weight).
    - Bone health should be optimised with regular supplementation of Vitamin D (cholecalciferol 50 000 IU monthly).
    - Bisphosphonate therapy should be considered in children with pathologic fractures or bone pain secondary to steroid-related osteopenia.

- **Adrenal and immune suppression can be seen to a variable degree.**
    - Promptly address minor infections.
    - Influenza vaccine is recommended yearly.
    - Pneumococcal and pertussis booster vaccination should be considered.
    - Avoid live virus vaccines
    - In the event of major surgery or illness, IV dosing of steroids may be indicated – see DMD Steroid Management Plan
- **Growth retardation.** Patients with DMD have a reduced height regardless of steroid use [14]. Pubertal delay is common in boys with DMD.
    - Height, weight and BMI measurements and comparison against age appropriate centiles should be obtained at every clinic appointment.
    - If growth plateaus, reduction of steroid dose should be considered
    - An assessment of bone age should be considered every 2 years.
    - Referral to endocrinology service should be considered if there is a plateau in height or a significant pubertal delay (no signs of puberty by 13 years).
- **Cushingoid facies, hirsutism and acne**. Families should be informed of the risks of these symptoms prior to starting steroids.
- **Cataracts.** Refer for annual ophthalmology review
- **Hypertension.** *Measure BP at each visit.*
- **Annual bloods are recommended** including LFTs, calcium, Mg, phosphate, glucose and HbA1c. If regular Vitamin D supplementation is given, levels only need to be considered for those in high risk ethnic populations.

If side effects are considered intolerable and cannot be managed, then the steroid dose may be decreased to 0.3-0.5mg/kg/day or alternative dosing schedules may be trialled (alternate day, high-dose weekend or 10 day alternating regimes have been suggested [2]), in the knowledge that these treatment regimens are likely to reduce the effectiveness of the medication.

## Stopping steroids

Even once ambulation is lost, there are ongoing benefits of steroid medication in DMD. There is a reduced risk of progressive scoliosis, ongoing stabilisation of respiratory function, delay in development of cardiomyopathy, and prolonged independence in self-feeding and upper limb function [12, 15, 16] in steroid-treated non-ambulant patients with DMD. As such, there is good evidence for continuing steroids in the non-ambulant subject. However the risk of side effects is significant, and dose reduction should be considered (E.g. reduction by 5mg/month to 20mg/day).

There is no consensus as to when steroids should be discontinued. This decision needs to be made on an individual basis in consultation with the patient, his family and their clinician.

It's important to emphasize to the family that **steroids should not be stopped suddenly**. When steroids are to be stopped, careful weaning of medication is required to allow for gradual resolution of adrenal suppression.

- We recommend reducing the dose of steroids by 20% every two weeks until patients are at a dose of 5mg/day.
- After two weeks of 5mg/day, give 5mg every alternate day for 4 weeks. Then give 2.5mg every alternate day for 4 weeks, then stop.

It is important to consider the patient adrenally insufficient for up to 6 months after discontinuation of steroids.

- If the child becomes unwell during the weaning period, steroid doses need to be increased to at least equivalent to stress dose (15mg/$m^2$/day for mild illness and 25mg/$m^2$/day for serious illness).
- A synacthen test 6 months after stopping could be considered to demonstrate normalisation of adrenal function.

Live virus vaccinations should be avoided for 3 months after discontinuation of steroids.

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