Some 30 clinicians and scientists from all over the world met in a warm and friendly atmosphere on June 6 of this year in Monaco to review the subject of corticotherapy in Duchenne muscular dystrophy under the auspices of the Duchenne Parent Project France and the Association Monégasque contre les Myopathies.

In fact, treatment with glucocorticoids is controversial, especially in France, whereas physicians in the USA, Canada, Italy, and England now have some experience in management of boys who have taken either prednisone or deflazacort for several years. The purpose of this round table was to share experiences and discuss the best practices, and to establish a plan of action.

In the first presentation, Urs Ruegg of the University of Lausanne explained the principle of steroid action. The effect of steroids is to regulate gene expression, essentially resulting in an anti-inflammatory response and effects on cellular metabolism. More specifically in muscle, it has been shown that at low concentrations, steroids improve cell fusion and survival of cell cultures, notably on cells from the mdx mouse, which is a model for Duchenne muscular dystrophy.

Returning to the physiopathologic process, he reviewed the effect of the absence of dystrophin, which includes an increase in intracellular calcium concentration through still-unknown pathways, which is in turn responsible for muscle cell death. However, studies have shown that prednisone decreases the entry of calcium into cells. The mechanism for this remains to be discovered.

It is possible that steroids, and notably prednisone, have an effect on the over expression of utrophin, which, however, remains to be confirmed.

J. Andoni Urtizberea, from the Hôpital Raymond Poincare in Garches, presented the French experience in the field, though there is no official position on the subject. It is clear that steroids are not prescribed in France. In general, management of Duchenne muscular dystrophy in France places emphasis rather on rehabilitation, surgery, prevention of cardio-respiratory complications, etc., which has already led to a clear improvement in the life expectancy and quality of life for these patients. Moreover, the French medical
community as a whole is very cautious about the secondary effects of steroids. It is also true that the pharmaceutical industry has not been very active in this respect in France, where for example, deflazacort is not available, and research, notably supported by AFM, has prioritized curative treatments such as gene or cell therapy. Nevertheless, JA Urtizberea considers that there is no opposition in principle to the use of steroids in Duchenne muscular dystrophy in France, but rather a lack of information and knowledge that has been acquired by foreign groups.

Certain points need to be discussed, such as the risk of secondary scoliosis in adulthood and treatment modalities; also effects on the heart, etc.

Kate Bushby, of the University of Newcastle, presented an overview of findings on steroid effects on muscle strength. As with all experimental treatments, the evaluation of the effects of treatment comes up against the problem of measurement: how can strength be measured in a reproducible and stable manner; how can protocols and measurements be standardized, etc.

Intuitively, it is preservation or re-establishment of muscular function, rather than strength, that is important for the patient, and function is in general a good indicator of strength, even though the relation between the two is not so simple. According to the few published studies, steroids have a positive effect on muscular force for 3 to 6 months, followed by stabilization. It appears that the positive effects are greater if steroids are administered early, which brings up the question of the best age for the commencement of treatment. These questions will be central in the presentations and discussions to follow.

Adnan Manzur, of Hammersmith Hospital in London, is currently undertaking a complete review of published information on the subject. He looked at effects on four concrete aspects of the disease: walking, or more precisely, delay in loss of ability to walk, respiratory function, heart and life expectancy.

For respiration, the basic test is the measurement of vital capacity, FVC (Forced Vital Capacity). Short-term studies did not demonstrate any clear beneficial effects. On the other hand, publications with longer-term follow-up (3 to 5 years) suggest a stabilization of FVC, i.e. preservation of respiratory function over the long term.

Little data have been collected and published on the heart. However, the small amount of data available on long-term follow-up of patients taking steroids in comparison with boys not taking steroids, suggest that the level of cardiac complications is much lower in the steroid group (only 1 in 21 patients). According to Dr. Manzur, these data are still insufficient to draw statistically significant conclusions from a methodological point of view, but they reflect an interesting potential that should be explored more thoroughly.

Similarly, few comparative studies on the prolongation of walking ability which would enable demonstration of an effect are available. The small amount of information available does not suggest statistically significant delay in loss of the ability to walk, but here also, specific case reports should serve to encourage further study. A complete analysis will be published in three months within the framework of the systematic "Cochrane study."

The challenge for the future is to develop a consensus on treatment. To achieve this, within the framework of clinical networks, protocols need to be developed for collecting
and analyzing pertinent data, measuring the efficacy of various treatment regimes, the duration of long term effects, etc. Because a large number of Duchenne boys are undergoing treatment at this time, double-blind randomized studies are difficult to initiate. France could play an important role here, due to the absence of steroid treatment in this country. The problem of secondary effects remains, and it is clear that data collection procedures should include measurements of both beneficial and secondary effects.

Corrado Angelini, of the University of Padua in Italy, presented his data on walking and several other motor functions. He initially established a base line for comparison of potential beneficial effects by follow-up of 112 boys who were not treated with steroids. His measures included walking 10 meters, getting up from a sitting position on the floor (Gower’s sign*), getting up from a chair, climbing four steps, and manual testing of specific muscle groups using the MRC* scale. Several results were presented, including both comparison between prednisone and deflazacort, and comparison with the natural progression of the disease. Firstly, treatment with deflazacort stabilized the manual testing measurements, which confirmed the trials with prednisone. Comparison of the two products did not demonstrate any notable differences after 1 year of treatment, and both treatment groups demonstrated stabilization of motor function in comparison with the natural progression of the disorder. Concerning secondary effects, weight gain was greater in the prednisone group than in the deflazacort group.

Other secondary effects were reported, but they were not considered important.

In a more fundamental domain, Corrado Angelini studied the steroid receptor, and performed polymorphism* analysis in order to explain the differences in individual responses to steroids, and notably why some children walk for a much longer period. In fact, the average age of loss of ability to walk in the treated groups appears to be older than in the control group, but some treated boys still walk at very advanced ages (16 years, for example), and we need to know why.

In conclusion, Corrado Angelini notes that:
--Deflazacort and prednisone are equivalent in slowing the progression of the disease.
--After 6 months of treatment, there is a clear improvement in muscle function.
--Secondary effects are similar for both substances, except for weight gain, which is more to be feared with prednisone.
--As regards polymorphisms, some boys may respond especially favourably to steroid treatment.

In a second presentation, Corrado Angelini stressed more long-term effects. In a trial including 48 boys, he measured efficacy of treatment after one year. The effect was globally positive, but with very large variations, +/- 50%. However, he was able to establish a significant correlation between the age of initiation of treatment and improvement: the youngest patients have a tendency to respond much better to treatment.

Concerning secondary effects, this correlation is also applicable; it should be noted that the children who began treatment very early (age about 3=4 years) do not display weight gain, nor Cushingoid* appearance. The treatment regimens also have an influence on secondary effects, and treatment schemes on alternate days (deflazacort taken every other day) induce far fewer secondary effects on behaviour or bone mineralization. Moreover, with the on/off scheme, no weight gain was observed (except of course, that linked to growth).
Imelda de Groot, from the Trappenberg center at Huizen (the Netherlands), attempted to reply to the question of contractures. An analysis of the literature, which has little to report on the question of contractures, revealed that prednisone had no influence on contractures. This finding, however, is tentative, because questions on the functional state of the muscle and joint at the moment of measurement and on the precision of measurements, etc., remain open. It seems, in fact, that the physiopathology of the myotendinous junction, and notably the role of dystrophin is distinctive, and that steroids have no action on this process. However, since the evolution of contractures depends on movement, and notably walking, the delay in loss of ability to walk induced by the treatment may indirectly have a positive effect on contractures.

Doug Biggar, of the Neuromuscular Center of the University of Toronto (Canada), presented results on ocular complications. He noted that there are several forms of cataracts, and that the form induced by steroids is benign and, in general, does not alter vision. Therefore, in the absence of symptoms, treatment is not necessary. Nevertheless, all patients should be regularly checked if steroids are administered. Analysis of the literature shows an incidence of the order of 30% in patients followed on a long-term basis for treatment with steroids at high doses for diseases other than Duchenne muscular dystrophy. In these cases, detection of cataracts may occur between 6 months and 30 years after initiation of treatment.

In Duchenne muscular dystrophy, deflazacort once a day leads to a similar incidence, but in these cases also, years may go by before a cataract is detected. It should be noted that when an alternate day treatment is followed (ever other day), or an on/off regime (10 days/20 days) for deflazacort, the incidence falls to 0%.

Maria Kinali, of Hammersmith Hospital in London, presented skeletal and bone effects. Bone density is normally maximal for a person in good health at 30 years of age, and is increased with calcium and exercise. Osteoporosis is a modification in the micro-architecture of bone structure, which fragilizes the bone and thus increases the probability of fracture. It has been known for a long time that steroids have a cumulative toxicity in bone and, in the general population, induce a form of osteoporosis. There are few studies on this subject in Duchenne patients. However, some case reports show that there is no significant difference in bone density between treated and untreated boys.

Dr. Kinali therefore undertook a more detailed study and followed 32 untreated boys and 18 boys who had been treated for 12 months or more using an on/off regimen (10 days/20 days). 12 boys out of 50 had fractures, 9 in the non-treated group and 3 in the treatment group. Duchenne boys have a bone density which is lower than normal independent of any treatment. According to the results of this study, the bone density of the treatment group is even better than that of the untreated group.

Diana Escolar, of the Children’s National Medical Center in Washington (USA) posed the question of benefit after the loss of ability to walk. This question has two parts in fact: should treatment initiated before the loss of ability to walk be continued and can treatment be initiated, or resumed after loss of ability to walk?
A few studies have followed Duchenne boys for long periods of steroid treatment, up to 9 years, and it seems that the FVC is increased at all age levels. This delays the time at which respiratory assistance is necessary. Therefore, the response to the first question is clearly that it is better to avoid interruption of treatment which has been started before walking ability is lost.

To answer the second question, a protocol has been launched in the US within the framework of the CINRG Consortium comparing non-pharmacologic respiratory management with groups of patients treated with prednisone, coenzyme Q or both substances simultaneously. Effects on respiratory and cardiac function will be studied; results are expected in two years.

Bernd Reitter, of the CHU of Mayence in Germany, performed a comparative study from 1992 to 1997 between two groups of boys, one group treated with prednisone and the other with deflazacort. Definitive results are in the process of being published. Of the 100 initial participants in the study, 14 children on prednisone and 6 on deflazacort had to withdraw from the trial, one because of a fracture and the others because of excessive weight gain.

Secondary effects reported for the patients remaining in the study included weight gain in 40 boys (26 on prednisone and 14 on deflazacort), and 17 cataracts (1 on prednisone and 16 on deflazacort). Except for these findings, no other differences between the two products were noted.

Concerning mobility, which represented a sum of several functional tests, he found similar results in both groups. It was the same for manual testing of muscular force after 24 months of treatment; there was no significant difference between the two groups, which leads to the conclusion of an equivalence of the two substances in terms of beneficial effects.

After the trial, he continued to administer steroids to a total of 125 boys over time spans which were variable. These boys were seen every 3 months, and more detailed specific examinations were performed yearly. The results are as follows:

--Regarding the heart: there is no acceleration of cardiomyopathy with steroids, and when treatment is halted, this complication seems to progress more rapidly.

--Increased susceptibility to infections was not observed (there were in fact fewer infections in the treated boys). None of the treated boys had to be hospitalized for infection.

--All the treated boys had a tendency to grow more slowly.

--Regarding weight gain, a nutritional expert can help with this problem.

--A total of 15 fractures were reported, all of them in children who were still able to walk. A complementary treatment with calcium and vitamin D is given to the children.

Although he was not able to demonstrate a statistically significant difference in age at which the ability to walk occurs, he nevertheless gave an example of one of his patients who was still walking at 15 years of age.

In a second presentation, Doug Biggar (Toronto, Canada) shared his experience with deflazacort which he has been using for several years now. Concerning weight gain, he first noted that in the natural progression of the disease, there is a loss of weight after 15 years, probably due to loss of muscle mass. Consequently, if the boys treated with deflazacort do not lose weight, this could be an argument in favour of preservation of muscle mass by the drug. As for management of scoliosis, only 4 of 24 boys under treatment required this operation; in two of them the initiation of treatment was
late (14 and 17 years of age) and there was some doubt about treatment compliance in the other two boys.

His conclusions are the following:
-- Loss of ability to walk is delayed.
-- Respiratory function is improved.
-- Muscle function is improved (better use of arms, for example).
-- Surgical intervention on the spine is delayed.
-- Cardiac function is preserved.

The secondary effects observed are weight gain and delayed growth, and a form of cataract which is not clinically visible. No effects on the kidneys, the liver, or diabetes, etc. were reported.

Following the presentations, a round table was held, in which there was a general discussion on several of the themes presented above.

At what age should treatment commence?

This question concerns the effects of these drugs when they are administered early and over a long period of time, and what are the later effects on disease progression.

Although it is quite difficult to obtain reliable data on very young children, a large number of cases have been analyzed and published. For example, Duchenne children who also suffer from asthma, or the personal experiences of clinicians who state that there is a clear advantage in early commencement of treatment. Young children respond better to treatment, and specific cases with spectacular results have been reported.

The CINRG in the US even plans to launch a trial which will include 4-year-old children and will produce more precise data. This would constitute an argument in favor of more systematic and early detection of Duchenne muscular dystrophy.

The problem of growth, which has already been noted, still exists, and both parents and the patients themselves are asked whether it would be acceptable to be "smaller than the others"—in order to balance this against benefits in terms of prolongation of the ability to walk, etc.

There has not, unfortunately, been enough time to evaluate this treatment over a long period of time, and only a follow-up of patients who are currently under treatment will produce the answers to the question of long-term treatment.

What is the optimum dosage and administration scheme?

Concerning the dose, there seems to be a consensus about the fact that there is a minimum dose necessary, and that doses which are too low do not seem to produce positive results. The usual doses administered by the participants at the moment are 0.75 mg/kg/day for prednisone and 0.9 mg/kg/day for deflazacort. In order to avoid secondary effects, various administration schemes have been devised: administration on alternate days, on/off scheme of 10 days/10 days or 10 days/20 days, a high dose at the end of the week, etc.

Here also, the only way to respond scientifically to this question would be to propose a protocol for a trial comparing several protocols with each other. However, this seems rather difficult today: for one thing, many children already take steroids, and another, when the available results are taken into account, there are already arguments which show potentially beneficial effects with all forms of administration. For many, it is better to administer steroids with any protocol rather than to do nothing.
These trials could easily be carried out in France, because in general, Duchenne boys in this country do not take steroids.

For older boys, it is advisable to reduce the dosage, because the loss of muscle mass means that the mg/kg ratios are not directly applicable.

**How can the medical community be convinced?**

Despite these tangible results, many myologists, especially but not exclusively in France, do not prescribe steroids. There is a very marked caution related to secondary effects. Furthermore, uncertainty about the effects (some patients respond better to treatment than others) and different possible administration schemes does not calm the disquiet that the physicians have about this treatment.

In England, a collaborative group of 14 reference centers has created a written document which can serve as a basis for physicians and families: it lists all the information for the families about beneficial and secondary effects, both that which is certain and that which has not yet been scientifically tested but is based on experience. It leaves the question of the administration scheme open, and the family can thus choose between daily administration and an on/off 10 days/10 days protocol. This same group of centers has also created a standardized protocol for follow-up of these patients, and collection of data on strength measures and secondary effects in a homogeneous manner.

**Beneficial and secondary effects?**

Going back over the diverse presentations as a conclusion, it is possible to say today that steroids have a beneficial effect on muscular strength and function in general, on prolongation of the ability to walk and probably on respiratory function. Despite some positive results in this direction, the effect on the heart remains to be studied. Secondary effects are not masked, and it is important to follow these children, notably for weight, and eye and bone problems. Since there is some variability in response, the decision to initiate and/or continue corticotherapy must be made on an individual basis.

The panel of experts and representatives of associations left the discussion with a positive conclusion to the day’s proceedings. Although the participants were in agreement that there are still many unknowns, and about the need for further studies at the level of fundamental research as well as clinical aspects as a whole, there is a convergence of data supporting the idea that steroids may produce stabilization or at least a decrease in aggravation for the patients. This does not constitute a cure, but makes it possible to maintain the patients in better physical condition for a longer time period while awaiting curative treatments.

Concerning more specifically the French position, the physicians who were present agreed to meet to study the question in detail in a debate which will include the enlarged network of French clinicians who practice in specialized consultations.
Glossary

Utrophin: Protein which is structurally similar to dystrophin. It replaces dystrophin during embryonic development, and is present in adult muscle at the neuromuscular junction and the musculo-tendinous junction. Some scientists, including T. Khurana (USA) and Kay Davies (UK) who discovered it, believe that utrophin could compensate for the absence of dystrophin if it could be overexpressed in muscle.

Cochrane Group: Network of scientists and clinicians for which the objective is to perform transversal analyses of published studies on a given subject. In this case, the Cochrane group’s aim is to review the ensemble of literature on the effects of steroids in Duchenne muscular dystrophy, and to prepare a scientifically acceptable synthesis.

FVC or Forced Vital Capacity (or vital capacity): the pulmonary volume mobilized during forced inspiration and expiration. It is expressed in liters, and measures the respiratory capacity of an individual. For patients with Duchenne muscular dystrophy, this measure is fundamental for determining the functional respiratory state of the patient, and for the determination of a requirement for ventilatory assistance, tracheotomy, etc.

Double blind randomized trials: In order to compare the effects of drugs, simply to verify the effect of a substance in relation to the progression of a disease and thus ensure the validity and efficacy of the substance, treatment groups are chosen at random: the study is said to be "randomized." In order to preserve objectivity of the measures of efficacy, neither the physician nor the patient know whether they are receiving the drug to be tested or a placebo; such trials are said to be "double blind."

Gower's sign: The very characteristic manner in which young children with Duchenne muscular dystrophy get up from the floor by placing their arms on their knees and thighs. Consequently, an absence of Gower’s sign demonstrates a functional improvement in this function.

MRC Scale: A scale for measuring muscle force. Patients are asked to push against the evaluator, who then estimates the resistant force on a scale of 1 to 5, with 5 corresponding to normal force and 1 the minimum.

Polymorphism: Although we all share the same genes, there are minor differences which make each of us unique. These minor differences in the same gene are called polymorphisms.

Cushingoid: Cushing’s syndrome is a disease which is usually due to excessive and prolonged use of corticosteroids. In addition to other symptoms, the most obvious characteristic is an enlargement of the face in these persons.

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