Position Statement on the use of genistein to treat Sanfilippo disease (Mucopolysaccharidosis type IIIA-D).

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The Manchester team have recently published preclinical data in the mouse model of Sanfilippo disease IIIB (MPSIIIB) showing significant delay in neurodegeneration and behavioural correction following high daily doses of the drug genistein aglycone delivered over a 9 month period.

The mouse model of MPSIIIB is affected by increasing pathological heparan sulphate storage in the brain and other organs, neuroinflammation, progressive neurodegenerative decline, abnormal behaviour and hyperactivity with a shortened lifespan and as such shows many similarities with patients with the disease.

Following 9 months of high daily doses (160 mg/kg/day) of genistein aglycone we have shown a 31-34% reduction in lysosomal compartment size in the brain and 37% reduction in brain levels of pathological heparan sulphate in the mouse model of MPSIIIB.

Neuroinflammation was reduced by 12-19% whilst most behavioural abnormalities observed at 8 months including the lack of a sense of danger and hyperactivity were corrected by drug treatment.

We are aware that many parents already give their affected children different forms of genistein and other supplements and thus feel that it is important to offer interim advice prior to a clinical trial due to the widespread availability of genistein as a dietary supplement.

Genistein may have several modes of action including blocking protein tyrosine kinase receptor function and is also a mild oestrogen analogue. It has undergone significant safety testing in rodents and dogs but has only been tested in humans at low doses for its use as a food supplement or for treatment of osteopenia and menopausal flushes in the USA.

Genistein used in the preclinical study was synthetically produced and is the pure aglycone form of the drug. Genistein can also be purified from soy extract but this is not necessarily the same product and we would advise against its use since the naturally occurring form of genistein may not be absorbed as effectively by the digestive system.

Whilst genistein is available as a dietary supplement at lower doses, there is not yet any clear clinical data to suggest that it is effective at these doses in Sanfilippo.

Synthetic genistein aglycone is not widely available and has not been tested in a clinically controlled manner in humans at the effective and very high doses used in mice. The use of genistein in this disease at high doses is considered to be an Investigational Medicinal Product by European regulatory agencies, thus we would caution against its use by families with affected children.

We intend to run a placebo controlled clinical trial using high doses of pharmaceutical grade genistein aglycone in patients with MPSIIIA, B and C in the near future in Manchester subject to appropriate regulatory approval.

It is important that we are able to run a clinical trial comparing genistein at high doses to a placebo control as this is the only way that we can be sure if it really has an effect or not. We are currently evaluating the appropriate dose for human use as this is often relatively lower than those used in mice and again would advise against the use of high doses of genistein until we have concluded this work.

We will update this bulletin and make a formal trial announcement when we have further information in due course.

The preclinical genistein publication is available for free from PLoSONE at the following link
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014192

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