BSPED Recommendations for Recombinant IGF-I Therapy in Children with Severe Insulin Resistance Syndromes

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Scope: To guide UK paediatric endocrinologists who are considering the use of rhIGF-I for severe insulin resistance syndromes (SIR) secondary to insulin receptoropathies.

A. Background

Severe insulin resistance syndromes (SIR) are a heterogeneous group of rare disorders characterised by insulin resistance and metabolic abnormalities, associated with a range of clinical manifestations and complications. These syndromes can be hereditary or acquired, due to defects in insulin potency and action, cellular responsiveness to insulin, and/or aberrations in adipose tissue function/development. This guidance is focussed on insulin receptoropathies.

The most severe forms of SIR are associated with genetic defects in the insulin receptor gene (*INSR*) e.g. Rabson-Mendenhall and Donohue syndromes. These patients rarely survive beyond 2 years. Large doses of insulin and insulin sensitisers do not effectively control the associated diabetes and patient outcomes are poor[1-3]. However, SIR may be amenable to treatment with recombinant IGF-1 (rhIGF-1).

B. Treatment of SIR with Recombinant human Insulin-like Growth Factor I (rhIGF-I)

Since insulin and IGF-1 mediate their effects through similar tyrosine kinase receptors and can interchangeably activate the alternate receptor with reduced affinity, rhIGF-1 provides a therapeutic strategy for SIR[4]. rhIGF-1 therapy can improve metabolic control i.e. increasing glucose uptake from peripheral tissues and reducing hepatic gluconeogenesis. Data suggest rhIGF-1 can also increase the life span of patients with Donohue syndrome.

rhIGF-I is licensed for use in Severe Primary IGF-1 Deficiency (SPIGFD) and can be available for cases of SIR unresponsive to conventional diabetes therapies. Although early rhIGF-1 therapy may improve outcomes in SIR, side effects have prevented its approval and wide use for this indication, so it is currently unlicensed for this indication. Few publications exist and are either single case reports or include few patients, rendering a direct comparison of treatment efficacy inconclusive[5-18].

C. Dose of rhIGF-1 for SIR

The dose of rhIGF-1 used in SIR is higher than SPIGFD. The maximum recommended dose is 0.2mg/kg/dose SC twice a day[19].

rhIGF-I should be supervised locally by a physician experienced in the management of complex forms of diabetes with support available from quaternary centres as needed (see below).

D. Management of rh-IGF-1 for SIR

There are separate **BSPED Recommendations for Recombinant IGF-I Therapy in Children with Severe Primary IGF-I Deficiency (SPIGFD)** (link below). These should be used for guidance on contraindications, initiation, monitoring, maintenance, and discontinuation of rhIGF-1 therapy in SIR.

E. Adverse Reactions

Adverse reactions associated with rhIGF-1 e.g. hypoglycaemia, lymphoid tissue hyperplasia, intracranial hypertension, slipped capital femoral epiphysis, coarsening of facial features, allergic reactions, antibodies, lipohypertrophy, benign and malignant neoplasms are listed in section F of the **BSPED Recommendations for Recombinant IGF-I Therapy in Children with Severe Primary IGF-I Deficiency (SPIGFD)** which can be found on the Guidelines page of our website here: https://www.bsped.org.uk/clinical-resources/guidelines/

F. Information

For more information contact the **National Severe Insulin Resistance (SIR) Service** in Cambridge:

https://www.cuh.nhs.uk/our-services/diabetes/national-severe-insulin-resistance-service/

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