New drugs

Burosumab

Approved indication: X-linked hypophosphataemia

Crysvita (Kyowa Kirin)
vials containing 10 mg/mL, 20 mg/mL, 30 mg/mL

X-linked hypophosphataemia is a rare cause of defective mineralisation of bone. The genetic mutation results in increased concentrations of fibroblast growth factor 23. This suppresses renal reabsorption of phosphate and inhibits the renal synthesis of 1,25-dihydroxyvitamin D. X-linked hypophosphataemia is a cause of rickets in children and osteomalacia in adults. Current management includes supplements of phosphate and vitamin D.

Burosumab is a monoclonal antibody that has been engineered to bind to fibroblast growth factor 23. By inhibiting the growth factor, burosumab increases concentrations of phosphate and 1,25-dihydroxyvitamin D.

The dose of burosumab is determined by the weight of the patient and fasting serum phosphate concentrations. It is given by subcutaneous injection every two weeks in children and every four weeks in adults. After the injection, it takes 7–13 days to reach the maximum concentration of burosumab. It is probably cleared like other antibodies and has a half-life of about 18 days. Burosumab should not be used in patients with severe renal impairment. Another contraindication is co-administration with phosphate and vitamin D. These supplements should be stopped one week before starting burosumab.

Phase II trials in children showed that burosumab increased serum phosphorous and reduced the severity of rickets.[1,2] An open-label phase III trial randomised 29 children to receive burosumab and 32 to continue conventional treatment. The average age of the children was approximately six years and they had a mean score of 3.2 on a 0–10 scale of rickets severity. After 40 weeks there was radiographic evidence of greater improvement in the children given burosumab. Their rickets severity score declined by 2.0 compared with a reduction of 0.7 in the control group. The difference between treatments was still present after 64 weeks.[3]

A double-blind phase III trial in adults randomised 68 patients to injections of burosumab and 66 to injections of placebo. These patients with X-linked hypophosphataemia were experiencing skeletal pain with most requiring analgesics. X-rays revealed nearly all patients had enthesopathy and 85 had a history of osteoarthritis. Fractures were present in 70 patients at the start of the study. A primary analysis after 24 weeks found a serum phosphate concentration above the lower limit of normal had been achieved by 94.1% of the burosumab group versus 7.6% of the placebo group. Concentrations of 1,25-dihydroxyvitamin D also increased. Stiffness was reduced with burosumab and more fractures had healed (43.1% vs 7.7%) during treatment. However, there was no clear benefit over placebo for pain or physical function.[4] An open-label extension of this trial treated all (119) patients with burosumab. Compared to baseline, patients reported improvements in pain, stiffness and physical function at 96 weeks.[5]

Injecting burosumab caused an injection-site reaction in 56% of the children and 12% of the adults. The site of injection should be rotated and no more than 1.5 mL should be injected into one site. In the paediatric phase III trial 38% of the children given burosumab had a hypersensitivity reaction, but these were not severe and treatment continued. Compared to conventional therapy, they also experienced more fever, headache, cough, arthralgia, diarrhoea and vomiting.[3] Dental infections were very common in children[3] and adults.[4] If hyperphosphataemia develops, the next dose should be withheld and a lower dose will be required when treatment resumes.

In animal studies burosumab had adverse effects during pregnancy. There are no data from pregnant women.

In children burosumab had favourable effects, but it is unclear which statistical differences from conventional treatment will be clinically significant. Longer term follow-up will be needed to see the effects on growth and deformity. In adults it is uncertain how burosumab compares with conventional treatment. Before the double-blind phase III trial, phosphate and vitamin D supplements had to be stopped.[4] Again, long-term monitoring of long-term treatment will be required.

T manufacturer provided the product information

REFERENCES

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Aust Prescr 2022;45:25–6
https://doi.org/10.18773/austprescr.2021.063
First published 10 December 2021

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.