QUESTION

Should bisphosphonate therapy vs. watchful waiting be used for children who may not yet meet osteoporosis criteria but have at least one fragility fracture with Friedreich ataxia?	
POPULATION:	children who may not yet meet osteoporosis criteria but have at least one fragility fracture with Friedreich ataxia
INTERVENTION:	bisphosphonate therapy
COMPARISON:	watchful waiting
MAIN OUTCOMES:	Bone mineral density; Fractures; Acute care utilization; Health-related quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Data from the FA Clinical Outcome Measures (FA-COMS) registry found 2.1% (23/1104) people with FRDA reported osteoporosis or osteopenia, while 9.7% (107/1104) reported a fracture. None of these were vertebral/spinal or femoral fractures. https://clinicaltrials.gov/ct2/show/NCT03090789	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of osteoporosis. 4/7 indicated that the problem was serious, 1/7 indicated probably serious, 2/7 indicated they didn't know if serious. 2/7 indicated that the problem was urgent, 3/7 indicated probably not urgent, 2/7 indicated they didn't know if urgent. 2/7 indicated that the problem was a priority, 1/7 indicated probably a priority, 2/7 indicated probably not a priority, 2/7 indicated they didn't know if priority. (Aug 2020)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 16 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014. Although there is no FRDA-specific evidence with respect to the benefit of anti-resorptive therapy, the pathophysiology and clinical course of FRDA-related bone disease is likely similar to what has been described in other forms of secondary osteoporosis arising from neuromuscular weakness and immobility. Data supporting the probable benefits of bisphosphonate therapy on BMD and possible benefit on fracture prevention are available for several of these conditions including cerebral palsy (Ozel et al., PMID: 27435427), Rett syndrome (Lambert et al., PMID: 29073271), and spinal muscular atrophy	

	(Nasomyont, et al., PMID: 31788718) Recent consensus statements regarding bisphosphonate use in children (e.g., Simm et al., 2018; PMID: 29504223; Galindo-Zavala et al., 2020; PMID: 32093703) emphasize the need for larger and longer-term studies, but also do recommend consideration of bisphosphonates for 2 or more long bone fractures and/or 1 vertebral fracture. Additional recommendations are offered stratified by bone DXA Z-score. This recommendation is based on the capacity of bisphosphonates to increase aBMD in other conditions. Effects on fracture rate may be present but are difficult to demonstrate.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort or case studies published from 2014 through to 16 July 2020 describing undesirable effects of bisphosphonates in children with FRDA. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines that was specific to Friedreich's ataxia, 2014. As reported in children without Friedreich's ataxia, the short-term risks of bisphosphonate therapy (especially IV formulations) include acute phase reaction (fever, myalgia, gastrointestinal upset), hypocalcemia, hypophosphatemia, and acute kidney injury. These risks are greatest with first infusion and can be mitigated with appropriate patient selection, pre-infusion laboratory screening, and provision of calcium and vitamin D supplements, and anti-pyretics (Simm et al., PMID: 29504223; George et al PMID: 26308295). Bisphosphonates may also have adverse effects whose long-term effect in pediatric cohorts is incompletely understood.	Bisphosphonate use in pediatric cohorts is typically off-label, thus we recommend that the decision to treat and treatment itself be carried out by a clinical team with appropriate expertise.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Although there is no FRDA-specific evidence, there is reasonable supporting evidence of a probable effect of bisphosphonates to increase aBMD and a possible effect to reduce fracture frequency in similar forms of secondary osteoporosis.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability		

○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Bone mineral density - not measured	IMPORTANT[a]	-
Fractures - not measured	CRITICAL[b]	-
Acute care utilization - not measured	CRITICAL[c]	-
Health-related quality of life - not measured	IMPORTANT[d]	-

a. Identified as critical (1/6), important (3/6) and low importance (2/6) by people with FA and important by expert authors on this topic.
b. Identified as critical (4/6) and important (2/6) by people with FA and important by expert authors on this topic.
c. Identified as critical (4/6) and low importance (2/6) by people with FA and critical by expert authors on this topic.
d. Identified as critical (2/6) and important (4/6) by people with FA and important by expert authors on this topic.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Although there is no FRDA-specific evidence, and the balance of effects should be evaluated on a case-by-case basis, in general there is reasonable supporting evidence from similar forms of secondary osteoporosis that bisphosphonates can be safely administered to children with probable efficacy to increase aBMD and possible efficacy to reduce fracture frequency.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if medication to increase bone strength in children with suspected reduced bone strength was acceptable (weighing up the balance between benefits, harms and costs). 1/3 indicated the intervention was acceptable, 1/3 indicated probably acceptable, 1/3 indicated they didn't know if acceptable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We conditionally recommend anti-resorptive (bisphosphonate) therapy for children with Friedreich ataxia who may not yet have an aBMD Z-score of -2.0 or lower, but have at least one clinically significant fragility fracture.

We recommend that treatment be undertaken by a clinical team with relevant expertise, such as a pediatric endocrinologist.

Justification

Although there is no FRDA-specific evidence with respect to the benefit of anti-resorptive therapy, FRDA-related bone disease likely shares features of other forms of secondary osteoporosis for which there is some available evidence, including from cerebral palsy, Duchenne's muscular dystrophy, and other disorders, particularly inflammatory and/or nutritional. Recent consensus statements (Galindo-Zavala, 2020; Simm et al, 2018) emphasize the need for larger and longer-term studies, but recommend consideration of bisphosphonates for two or more long bone fractures and/or one vertebral fracture, the latter being the prototype of a fragility fracture. Additional recommendations are offered stratified by bone DXA Z-score.

This recommendation is based on the capacity of bisphosphonates to increase aBMD and improve vertebral morphology in other conditions (Nasomyont et al, 2020). Effects on fracture rate may be present but are difficult to demonstrate. Since bisphosphonate therapy is off-label in pediatrics and has associated risks, both known and unknown, referral to an experienced center is appropriate.

Subgroup considerations

This recommendation is for children with Friedreich ataxia who may not yet have aBMD Z-score of -2.0 or lower, but have at least one clinically significant fragility fracture, where "clinically significant" is defined as a low trauma (fall from standing height or less, at no more than walking speed) fracture of vertebral body, lower extremity long bone, or humerus. The most appropriate treatment recommendations may depend on the age and pubertal status of the child; the longitudinal trajectory of aBMD Z-score and/or absolute aBMD or BMC, DXA and/or related imaging results; an integrated assessment of fall risk; risk of complications from bisphosphonate-related adverse events; as well as priorities of patients and families.

Research priorities

Studies assessing the most appropriate clinical use of bisphosphonate therapy in children with FRDA are needed.

References

Galindo-Zavala R, Bou-Torrent R, Magallares-Lopez B, Mir-Perello C, Palmou-Fontana N, Sevilla-Perez B, et al. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. Pediatr Rheumatol Online J. 2020;18(1):20.

Lynch D. FA Clinical Outcome Measures (FA-COMS) Registry (unpublished data): clinicaltrials.gov; 2017 [Available from: https://clinicaltrials.gov/ct2/show/NCT03090789

Nasomyont N, Hornung LN, Wasserman H. Intravenous bisphosphonate therapy in children with spinal muscular atrophy. Osteoporos Int. 2020;31(5):995-1000.

Simm PJ, Biggin A, Zacharin MR, Rodda CP, Tham E, Siafarikas A, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health. 2018;54(3):223-33.