GUIDELINES FOR REFERRERS: DENOSUMAB AND INTRAVENOUS IRON INFUSIONS

BACKGROUND

- Denosumab can cause hypocalcaemia and hypophosphataemia. Hypocalcaemia, is more severe in patients with chronic kidney disease and results from denosumab's inhibition of osteoclast-mediated bone resorption, which reduces calcium release from bone into the bloodstream, especially in the presence of vitamin D deficiency or low dietary calcium intake.
- Intravenous iron infusions (notably ferric carboxymaltose) can cause hypophosphataemia by increasing renal phosphate loss and impairing vitamin D activation.
- Comparative risk of hypophosphataemia with available iron formulations:
  - Ferric carboxymaltose: Associated with hypophosphataemia in up to 47% of patients, depending on population and comorbidities.
  - Ferric derisomaltose: Associated with a significantly lower incidence, around 4%
- Concurrent or closely sequenced administration of denosumab and IV iron can result in severe, potentially life-threatening hypocalcaemia, hypophosphataemia, and secondary hyperparathyroidism, even in patients with normal renal function and vitamin D levels.
- NOTE: Whilst the majority of published case reports on the exacerbation of hypophosphataemia with antiresorptive therapy involve denosumab and intravenous iron, a small number of case reports have also linked this complication with zoledronic acid. Therefore, it would be prudent to consider these guidelines applicable to all antiresorptive therapies, not just denosumab.

RECOMMENDATIONS FOR SAFE ADMINISTRATION

1. SCHEDULING OF THERAPIES

- Avoid co-administration: Do not administer denosumab and intravenous iron within a close timeframe.
- Recommended interval: Maintain at least a 3-month interval between denosumab and IV iron infusions whenever possible to minimise risk of severe electrolyte disturbances.
- If urgent treatment is required for both, consult with a specialist (endocrinology, nephrology, or clinical pharmacist) for individualised risk assessment and monitoring.
- If urgent treatment is required, consider using ferric derisomaltose formulation due to its lower risk of inducing hypophosphataemia.

2. PRE-TREATMENT ASSESSMENT

- Baseline blood tests: Check serum calcium, phosphate, magnesium, vitamin D, and renal function prior to either therapy.
- Correct deficiencies: Address and correct any hypocalcaemia, hypophosphataemia, hypomagnesaemia, or vitamin D deficiency before starting treatment.

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3. PATIENT SELECTION AND RISK FACTORS

- High-risk patients: Extra caution in those with chronic kidney disease, malnutrition, malabsorption, or previous electrolyte disturbances.
- Elderly and comorbid patients: These groups may be at higher risk and require closer monitoring.

4. MONITORING

- Frequent monitoring: Repeat serum calcium, phosphate, and magnesium 1–2 weeks after each infusion, and again at 4–6 weeks, as the lowest phosphate level may occur 1–2 weeks post-infusion and persist for up to 12 weeks.
- Monitor for symptoms: Be vigilant for symptoms of hypocalcaemia (muscle cramps, paraesthesia, confusion, cardiac arrhythmias) and hypophosphataemia (muscle weakness, respiratory distress, neurological symptoms).

5. MANAGEMENT OF ELECTROLYTE DISTURBANCES

- Prompt intervention: If severe hypocalcaemia or hypophosphataemia occurs, urgent intravenous replacement and specialist input are required.
- Withhold further doses: Delay subsequent denosumab or iron infusions until electrolyte abnormalities are corrected and stabilised.

6. COMMUNICATION

- Inform all treating clinicians: Ensure all members of the patient's care team are aware of the timing and risks associated with these therapies.
- Patient education: Advise patients to report any symptoms suggestive of electrolyte disturbances promptly.

SUMMARY

3-month interval between denosumab and IV iron

Calcium, phosphate, magnesium, vitamin D, renal function

Repeat labs at 1–2 and 4–6 weeks post-infusion

Extra caution and closer monitoring

Urgent replacement and specialist referral if severe disturbance occur

Inform care team and educate patient

Further reading

- Stokes G, Sheu A, Girgis CM, White CP. "Double Trouble" – the impact of iron infusion and antiresorptive therapy on calcium-phosphate homeostasis. JBMR Plus. 2025 Jan 5; ziae177. https://doi.org/10.1093/jbmrpl/ziae177
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