Denosumab as a Pharmacological Countermeasure Against Osteopenia in Long Duration Spaceflight

Anthony Rengel; Vienna Tran; Li Shean Toh

INTRODUCTION: Prolonged exposure to microgravity is associated with a significant reduction in bone density, exposing astronauts to renal calculi in flight and osteoporotic fractures on return to Earth. While physical countermeasures and bisphosphonates may reduce demineralization, additional therapies are needed for future interplanetary missions. This literature review aims to understand the current background pertaining to denosumab (a monoclonal antibody therapy used in osteoporosis) and its potential use for long duration spaceflight.

METHOD: A literature review was conducted using the following keywords: "osteoporosis"; "osteopaenia"; "microgravity"; "space flight"; "bed rest"; "denosumab"; "alendronate"; "bisphosphonates"; and "countermeasures". Additional articles were identified through references. Included for discussion were 48 articles, including systemic reviews, clinical trials, practice guidelines, and textbooks.

RESULTS: No previous bed rest or in-flight studies regarding denosumab were identified. In osteoporosis, denosumab is superior to alendronate in maintaining bone density with a lower rate of side-effects. Emerging evidence in reduced biomechanical loading state suggests denosumab improves bone density and decreases fracture risk. Concerns exists over vertebral fracture risk following discontinuation. The dosing regimen of denosumab offers practical advantages over bisphosphonates. Existing spaceflight studies with alendronate serve as a template for a study with denosumab and allow for a direct comparison of efficacy and safety.

DISCUSSION: Denosumab has numerous potential advantages as a countermeasure to microgravity-induced osteopenia when compared to alendronate, including: improved efficacy; fewer side-effects: better tolerability; and a convenient dosing regimen. Two further studies are proposed to determine in-flight efficacy and the suitability of monoclonal antibody therapy in the spaceflight environment.

KEYWORDS: denosumab, osteopenia, osteoporosis, microgravity, spaceflight, bone density, alendronate, bisphosphonate.

Rengel A, Tran V, Toh LS. *Denosumab as a pharmacological countermeasure against osteopenia in long duration spaceflight*. Aerosp Med Hum Perform. 2023; 94(5):389–395.

With humanity entering the next generation of space exploration, astronauts will be exposed to prolonged periods of microgravity and confinement beyond that of current missions in low Earth orbit. On the International Space Station (ISS), astronauts experience a decrease in bone mineral density (BMD) at a rate of 1–2%/mo, with the greatest loss occurring in the lower limbs.[10,38,45] This exposes astronauts to a significant increase in the risk of fractures on return to Earth, as well as renal calculi and cardiovascular events in-flight.[12,32,47] The National Space & Aeronautics Administration (NASA) has identified in the Human Research Roadmap that bone demineralization is a serious threat to astronaut health and, therefore, has prioritized research into the development of countermeasures.[33]

Specific exercise countermeasures including the Advanced Resistive Exercise Device (ARED),[39] combined with load bearing garments and nutritional regimes,[40] have been extensively assessed on the ISS. Despite showing a maintenance of BMD in the upper body, significant loss still occurs in the lumbar spine

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This manuscript was received for review in January 2022. It was accepted for publication in January 2023.

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DOI: https://doi.org/10.3357/AMHP.6053.2023

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and femur.[38–40] Although exercise may be considered sufficient for short duration spaceflights, pharmacological countermeasures should be considered for longer spaceflights. To date, only alendronate has been assessed with a bed rest study[26] and clinical trial during spaceflight.[25] While demonstrating maintenance of bone density, the method of administration and common side-effects are an issue, with 2 out of 11 astronauts participating in the in-flight study withdrawing due to gastrointestinal side-effects.[25]

Numerous advancements in osteoporosis pharmacotherapy have occurred in the last decade, including the introduction of the monoclonal antibody denosumab. Acting as an inhibitor of the receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL), denosumab selectively inhibits osteoclast activity via the RANKL-Osteoprotegerin (OPG) axis without impeding osteoblast activity to maintain bone density.[1] Unlike other antiresorptive therapies, it is available in a convenient 60-mg subcutaneous injection delivered every 6 mo.[1,27] Furthermore, systematic reviews comparing denosumab to bisphosphonates in osteoporosis demonstrated better rates of compliance, as well as improved long-term outcomes in maintenance of bone density.[2,4,9] Despite its real-world efficacy, it is not mentioned in the Human Research Roadmap as a potential pharmacological countermeasure for long-duration spaceflight. However, the recent European Space Agency SciSpace white papers on pharmacological countermeasures highlighted the need for a strategy to review new terrestrial therapies for space application.[8]

The aim of this literature review is to understand the current literature pertaining to denosumab use and its potential in long-duration spaceflight. This paper summarizes current knowledge of pharmacological countermeasures pertaining to bone health in spaceflights, discussing the potential benefits and disadvantages of both denosumab and alendronate. It then proposes further studies to assess the stability of monoclonal antibody therapies in spaceflight and the efficacy of denosumab as a countermeasure against microgravity-induced osteopenia.

METHODS

To assess the current knowledge of osteopenia in microgravity and its management, as well as the current evidence regarding the use of alendronate and denosumab, a literature review was undertaken. A search was conducted through the University of Otago library (which includes Medline, EMBASE, Scopus and PubMed databases), using the following terms: "osteopaenia"; "osteoporosis"; "bone"; "skeletal"; "bed rest"; "microgravity"; "countermeasures"; "space"; "alendronate"; "bisphosphonate"; or "denosumab". These terms were selected to broadly identify papers of interest, with additional articles identified through references of found literature, clinical practice guidelines, textbooks, and material provided by drug manufacturers.

Though no strict inclusion or exclusion criteria were used, clinical studies from prior to 1990 were excluded due to lacking relevance for both contemporary practice in osteoporosis and current space research. In addition, studies investigating antiresorptive therapies in malignancy were generally excluded. As the focus of the review primarily concerns denosumab and alendronate, articles detailing other antiresorptive agents and/or nutritional supplementation were excluded. However, one new monoclonal antibody therapy, romosozumab, which has been trialed with denosumab, was identified and thus included for discussion. While no form of meta-analysis was undertaken, relevant statistics derived from clinical research are quoted in this paper.

Therefore, this literature review draws from a total of 48 articles, including: systematic reviews; meta-analyses; randomized control trials; case studies; product information; textbooks; and clinical guidelines. A summary of the selection process is seen in **Fig. 1**.

RESULTS

Changes During Spaceflight

Cumulative data from across the Apollo, Space Shuttle, Mir, and ISS missions shows that a prolonged exposure to microgravity results in bone resorption and a total BMD loss rate of 1–2%/mo.[10,38,45] However, the greatest loss is seen in the high load-bearing bones, with up to 20% loss in the femur, pelvis, and lumbar spine.[45,47] The loss in BMD is persistent after spaceflight, with preflight BMD in the trochanter only 50% recovered by 9 mo and returned to baseline by 3 yr.[38]

In addition to the fivefold increased risk of fractures, the rapid resorption of bone during early spaceflight may result in hypercalcemia and hypercalciuria, contributing to the formation of renal calculi and atherosclerotic disease.[12,41,47] In comparison, terrestrial bone loss in older populations at the femoral neck is estimated at 0.82–0.96% per yr.[24] It is postulated that in antigravity, a lack of activity in the extensor muscles of the lower limbs and trunk reduces tension on the surrounding bones, which, when combined with the lack of mechanical

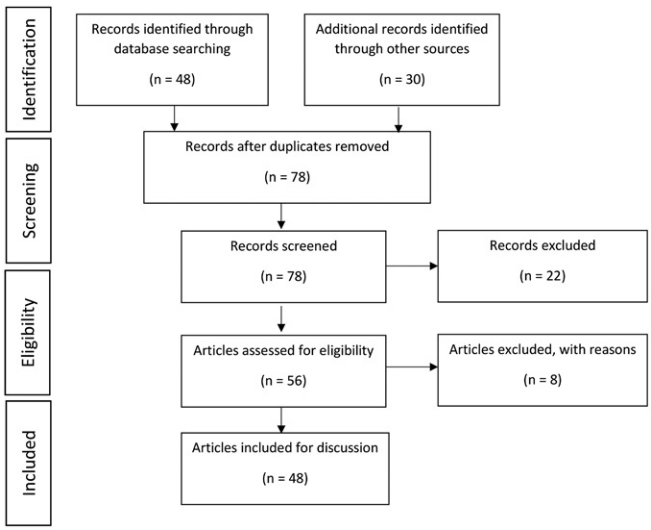

Fig. 1. Article selection flowchart.

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force normally induced by gravity, results in rapid reductions in bone density.[12,32,47]

Currently, astronauts on the ISS perform aerobic and resistive exercise for up to 2.5 h daily, inclusive of setup time.[12] When combined with strict adherence to the assigned diet with sufficient calorie, calcium, and vitamin D intake, overall BMD is maintained in the upper body.[40] However, significant loss is still seen in the lumbar spine, femur, and pelvis; this is associated with elevation of resorption markers C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX).[39,40] Whether the BMD decrease observed was associated with clinically significant bone geometry changes, including cortical thinning at the femoral neck, is not known due to CT imaging not being performed in either study.

Regardless of physical activity in-flight, increased levels of CTX and NTX are observed compared to preflight measurements,[42,43] indicating increased osteoclast activity. Due to bone resorption, there is an increased risk of renal stone formations from an increase in urinary calcium and oxalate excretion.[40,42,43] While baseline differences in bone biochemistry may exist between sexes prior to spaceflight, there is no difference in response to microgravity in the maintenance of bone density.[43]

Therefore, even with current countermeasures, astronauts on prolonged spaceflights are at risk of osteoporotic fractures in load-bearing bones upon return to a normal gravitational environment, as well as at elevated risk of renal calculus formation. However, numerous biochemical mechanisms exist through which bone density can be altered or maintained in microgravity; this is achieved through altering calcium homeostasis, enhancing bone deposition, or selectively targeting the RANKL-OPG axis.

Alendronate

Bisphosphonates are structurally similar moieties to pyrophosphate, with a high affinity for calcium that causes them to accumulate within skeletal tissue. Nitrogenous bisphosphonates, including alendronate and zoledronate, are antagonists of farnesyl diphosphate synthase, which interrupts subsurface protein trafficking in osteoclasts. This alters the cytoskeletal structure required for bone contact and, hence, inhibits osteoclastogenesis and bone resorption.[27]

Alendronate is taken as an oral tablet either daily, weekly, or monthly.[35] It can be stored for prolonged periods in a well-sealed container between 15–30 °C.[35] As dietary calcium, magnesium, and aluminum interact with bisphosphonates, alendronate must be taken after fasting and at least 30 min prior to food. It must be taken sitting upright to minimize gastroesophageal reflux—a common side-effect that often contributes to reduced compliance and discontinuation. This may be troublesome in microgravity, as astronauts are unable to sit upright and gastric emptying is often delayed during early spaceflight due to space motion sickness.[23] An alternative, zoledronate, is given as a yearly IV infusion to avoid most gastrointestinal side-effects, although post-infusion arthralgias are very common.[34]

Bisphosphonates are also associated with two rare phenomena. Osteonecrosis of the jaw can occur spontaneously; however, it is associated with dental trauma, poor oral health, and as a function of dose and number of years on therapy.[36] Atypical femur fractures are atraumatic, occurring along the diaphysis (shaft or subtrochanteric) and, like stress fractures, are transverse.[16,27] Counterintuitively, the atypical fracture risk increases with long-term therapy, with annual incidence of 1.78 per 100,000 with <1.9 yr of use increasing to 113.1 per 100,000 for >8 yr of use.[16] Both conditions are considered unlikely to occur in the astronaut population, due to their high baseline of health and therapy duration being unlikely to extend much beyond the 3 yr of an expected return Mars mission.

To date, alendronate is the only pharmacological agent to be assessed as a countermeasure against microgravity-induced osteopenia.[25] A 17-wk bed rest study demonstrated that, compared to controls, administration of alendronate not only maintained bone density in all bones examined (with exception of the calcaneus), but also suppressed markers of bone turnover and loss of calcium.[26] A follow-up in-flight study examined 10 astronauts who were prescribed 70 mg of alendronate weekly, commencing 3 wk prior to a 5.5-mo ISS expedition and continuing throughout.[25] Astronauts were required to undertake the normal 2.5-h daily exercise regime during the study.

BMD at the femoral neck, trochanter, total hip, pelvis, and lumbar spine was assessed pre- and postflight using dual-energy X-ray absorption (DXA) and quantitative computed tomography (QCT). Markers of bone turnover, including urinary and serum calcium, NTX, CTX, Vitamin D, and PTH, were recorded at specified intervals pre-, during, and post-flight. The data was compared to historical ISS data of 18 astronauts who undertook ISS missions prior to 2008 using the interim resistive exercise device, as well as to data from missions post-2008 with 11 astronauts who used the ARED. Of note, no QCT was available for the ARED group for comparison to the alendronate group. All astronauts continued to take standard vitamin D and calcium supplementation with a normal expedition diet. During the study, three astronauts withdrew from the alendronate group – one for personal reasons, one from gastrointestinal discomfort following a test dose, and one from developing dyspepsia in flight.[25]

Compared to the exercise-only groups, the alendronate group showed a clinically significant maintenance of preflight bone density scores on DXA, with relative suppression of markers of bone turnover.[25] There was also a significant difference in BMD and bone mineral content (BMC) on QCT across all sites between pre-ARED and the alendronate group.[25] As it was unclear whether the use of ARED in the alendronate group accounted for the significant difference in QCT BMD/BMC, a follow-up study recruiting an additional 10 astronauts using the same protocol and investigations was undertaken.[39] Although this demonstrated that ARED did ameliorate overall bone loss, it did not significantly reduce trabecular BMD and BMC loss in the hip, nor did it suppress markers of bone turnover.[39] Therefore, it can be concluded that the effects in BMD maintenance seen are due to the antiresorptive effect of alendronate.[25,39]

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Denosumab

Denosumab is a novel human monoclonal antibody approved by the FDA in 2010 for treatment of osteoporosis and fracture prevention in bone metastasis, which acts as a specific inhibitor of RANKL.[1,27] RANK is expressed on the surface of preosteoclasts, and by binding to RANKL, it triggers maturation into osteoclasts. The maturation of osteoclasts is controlled by OPG, which is expressed by osteoblasts and regulated by exposure to estradiol. It is thought that in osteoporosis, decreased estradiol exposure leads to decreased OPG expression and, hence, unchecked osteoclast maturity.[27] This imbalance in osteoclast activity progressively leads to decreased bone density. Denosumab therefore inhibits RANKL to prevent osteoclast maturity in a manner akin to OPG but independent of estradiol.

Denosumab is packaged in pre-drawn syringes, which must be protected from light, freezing, and excessive vibration; they must be stored at 2–8 °C until use.[1] Once removed from refrigeration, a syringe may be kept at room temperature <25 °C for up to 30 d.[1] For osteoporosis, it is administered as a 60-mg subcutaneous injection every 6 mo. Following administration, CTX falls rapidly and stabilizes after 3 d.[1] While the peak serum concentration is reached in 10 d and the half-life is 26 d, denosumab has been shown to control bone resorption for up to 6 mo, corresponding with suppressed CTX and maintenance of BMD during this period.[1]

During the literature search, no previous bed rest or in-flight studies involving denosumab were identified. However, denosumab is currently recommended as an alternative first-line option to bisphosphonates for fracture prevention in osteoporosis due to its efficacy.[1,27,46] The FREEDOM blind randomized control trial demonstrated significant reductions in relative risk of vertebral (68%), hip (40%), and nonvertebral (20%) fractures compared to placebo over 3 yr of treatment.[15] In addition, this was accompanied by a 9.2% and 6.0% relative increase in total vertebral and hip BMD compared to placebo.[15] In the phase III DECIDE double-blind randomized noninferiority trial, the denosumab group showed a further 0.9% and 1.1% absolute increase in BMD measured via DXA compared to treatment alendronate at the hip and lumbar spine, respectively.[9] The FREEDOM trial extension demonstrated that BMD continued to improve up to 10 yr, with up to a 21.7% increase in lumbar spine and 9.2% in total hip from study baseline.[7]

Furthermore, the efficacy of denosumab over alendronate has been confirmed in additional independent studies. A 2017 retrospective analysis assessed both agents over a 12-mo period, with the denosumab group showing superior improvement in femoral neck density on DXA.[4] Though not seen in the alendronate group, denosumab showed significant increase in lumbar BMD.[4] A 2015 meta-analysis looking at multiple antiresorptive therapies showed that denosumab was as efficacious as bisphosphonates at preventing hip fractures (denosumab OR 0.60, alendronate OR 0.61); additionally, it demonstrated a significant decrease in the risk of vertebral fractures (OR 1.67), echoing denosumab's real-world superiority and efficacy.[48]

Pooled data from phase III trials[15] showed that the most commonly reported side-effects in denosumab and placebo groups were: back pain (34.1% vs. 34.0%); arthralgia (20.4% in both); hypertension (15.3% vs. 16.1%); nasopharyngitis (14.8% vs. 15.6%); pain in the extremities (11.8% vs. 11.2%); osteoarthritis (10.9% vs. 11.1%); eczema (3.0% vs. 1.7%); and skin infections (0.4% vs. 0.1%).[1] Pancreatitis was reported in 0.1% of cases in the denosumab group vs. 0.2% in the placebo group; however, most of these cases were due to pre-existing pathology, such as gallstones.[1] Of note, there was no significant statistical difference in the occurrence rate of any serious side-effects between treatment and placebo groups in the FREEDOM trial ($P = 0.91$ & 0.61).[15] Anaphylaxis is rare with denosumab administration, with five reported cases in post-marketing surveillance and no fatal outcomes.[21] No evidence of neutralizing antibodies to denosumab have been reported.[7,15]

Hypocalcemia is a potential concern with a dose-dependent effect. A head-to-head trial of 5677 patients with bone metastases, in which denosumab was administered at a higher 120 mg dose monthly, showed that hypocalcemia occurred in 9.6% of denosumab patients compared to 5.0% of those treated with zoledronic acid.[29] Severe symptomatic hypocalcemia (requiring treatment with IV calcium) occurred in 3.7% and 1.7% of cases in each respective treatment group.[29] No cases were seen within the denosumab group in the initial FREEDOM trial,[15] with overall annual incidence remaining ≤0.1 per 100,000 in the 10 yr extension trial.[7] In 2013, post-marketing surveillance of denosumab use in osteoporosis patients only identified eight cases of severe symptomatic hypocalcemia, of which seven cases were associated with chronic kidney disease.[21] Though the risk of hypocalcemia is low in the dose used for osteoporosis, it is recommended that serum calcium be checked prior to commencement of denosumab, and adequate dietary intake or supplementation with calcium and vitamin D should be maintained during denosumab treatment.[1,18,27]

While there were no reported incidences of osteonecrosis of the jaw or atypical femur fractures in the DECIDE trial,[9] the FREEDOM extension trial recorded 14 cases of jaw osteonecrosis and 2 of confirmed atypical femur fractures, with an overall annual incidence of ≤0.1 per 100,000 for both conditions, respectively.[7]

Discontinuation of denosumab in osteoporosis cases shows an elevation of resorption markers at 6 mo, exceeding pretreatment levels at 12 mo, accompanied by a decline toward or below baseline BMD.[30,31] While these studies did not show an increased fracture risk in the groups that discontinued treatment,[30,31] a post hoc analysis of the 10-yr FREEDOM trial extension showed that there was a significant increase in single and multiple vertical fractures in the individuals who ceased denosumab,[14] confirming the findings in a series of case reports.[44] However, it is noted that the rate does not exceed that of the placebo group and this was strongly associated with individuals who had a prior history of vertebral fractures.[14] While recommencing denosumab results in clinically significant improvements in BMD after a period of discontinuation,[7] treatment guidelines for osteoporosis warn against drug holidays

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and state that if a drug is being discontinued, bridging therapy such as a bisphosphonate should be considered.[18,27,46]

This may be a potential concern for astronauts returning after a long-duration spaceflight, who may need to take an antiresorptive agent for a period following a return to Earth. However, further data is needed in younger and healthier populations to confirm whether the discontinuation effect occurs outside of the elderly populations previously studied. A summary of denosumab compared to alendronate is presented in **Table I**.

Future Applications

Cirnigliaro et al. 2020 investigated the use of denosumab in maintaining lower limb BMD in total motor spinal cord injury patients.[11] Even without exercise countermeasures, significant maintenance of bone density occurs when administered shortly after injury, with control groups showing >10% density loss and up to 43% increased absolute risk of lower limb fractures compared to the denosumab treatment group.[11] While no bed rest studies have been performed on healthy neurologically intact individuals, this is the first study to show the role of denosumab in maintaining density in a low mechanical loading setting, which could be considered analogous to the unloading seen in microgravity. Further bed rest studies could be used to confirm this finding in healthy individuals.

Other Potential Therapies

During the literature review, an additional agent that has been trialed with denosumab was identified. Romosozumab is a novel monoclonal antibody that targets sclerostin and has recently been approved for treatment in postmenopausal osteoporosis.[5] Sclerostin is secreted by osteocytes and acts as an antianabolic agent via the Wnt signaling pathway, inhibiting osteoblast activity.[27] Its secretion is regulated by mechanical loading as well as PTH and estrogen.[27]

A large international study assessing vertebral fracture risk randomized postmenopausal women to receive either 210 mg of romosozumab or a placebo monthly for 12 mo, followed by doses of denosumab every 6 mo for an additional year.[13] In the romosozumab group, vertebral fractures occurred in 0.6% of participants at 24 mo compared to 2.5% placebo group.[13]

However, there are no published trials comparing it as a single agent head-to-head with other antiresorptive therapies. Also, unlike denosumab, it is administered by subcutaneous injection every 1 mo instead of every 6 mo. It is only effective for up to 12 mo, with 18% of patients being shown to develop neutralizing antibodies, which requires switching to a different antiresorptive agent.[5] Of concern is the reported increase in cardiovascular events with romosozumab, with a 2.5–4.9% incidence in treatment groups.[3,28,37] Thus, it is contraindicated in individuals with previous ischemic heart and cerebrovascular disease.[3] The elevated cardiovascular risk associated with romosozumab may preclude its utility in long-duration spaceflight.

DISCUSSION

This literature review is the first to discuss the use of denosumab for human spaceflight and has attempted to compare it to alendronate, a previously trialed agent on the ISS. It has shown that denosumab has real-world advantages over alendronate in the management of osteoporosis and could be an ideal candidate for long-duration spaceflight. It demonstrates no increase in common side-effects versus placebo or alendronate, with a lower rate of rare side-effects. Importantly, it does not cause the gastrointestinal side-effects seen in alendronate. The initial dose can be administered a fortnight prior to flight and have full effect once in microgravity. Additional doses would need to be carried for every 6 mo of mission length and can be easily administered via a subcutaneous injection without the complications of PO or IV administration of bisphosphonates.

A limitation of this review is that there are no published trials regarding denosumab in bed rest or spaceflight and, hence, all potential benefits are inferred from terrestrial studies. In addition, as there is a paucity of research in pharmacological countermeasures in space, it was not possible to undertake a systematic review or meta-analysis. Therefore, further research is required to validate the use of denosumab in space with bed rest analog studies and in actual spaceflight. Though it is anticipated that the spaceflight environment alters the pharmacokinetics, pharmacodynamics, and active pharmaceutical content in medication,[17,19,22] no monoclonal antibody therapies have been assessed to date. Denosumab and monoclonal antibodies also have more stringent storage requirements compared to alendronate which may impact suitability for spaceflight. The authors would encourage future

Table I. Comparison of Alendronate and Denosumab in Spaceflight.

CATEGORY	ALENDRONATE	DENOSUMAB
Advantages	• Multiple formulations (daily, weekly or monthly) • No special storage requirements • Inexpensive • Proven in spaceflight	• Six monthly dosing via subcutaneous injection • Superior relative fracture risk reduction and BMD maintenance • No GIT side-effects • Lower risk of osteonecrosis and atypical femur fractures
Disadvantages	• GIT side-effects common • Administered upright (not possible in microgravity) • Interactions with dietary calcium and magnesium	• Expensive • Requires refrigeration • No spaceflight data • Increased vertebral fracture risk on discontinuation (rare) • Risk of hypocalcaemia (rare)

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spaceflights to have a dedicated storage area for medications needing cooler storage.

To assess denosumab's efficacy in long-duration spaceflight, the authors propose a study. Following on from LeBlanc et al. 2013[25] and Sibonga et al. 2019,[39] a minimum of 10 astronauts will be recruited prior to a 3–6-mo ISS expedition. We expect the study to show that the denosumab treatment group demonstrates significantly greater maintenance of BMD compared to exercise (with or without GLCS) groups in the previous studies.

While on the ISS, astronauts will continue to undertake a standard $2.5\,h \cdot d^{-1}$ exercise routine using the cycle ergometer and ARED.[12] Following the return to Earth, biochemistry and BMD will be reassessed. This data will then be compared to historical study data regarding mechanical countermeasures and alendronate.

Due to potential discontinuation effects following cessation of denosumab, astronauts will need to be studied at 6 and 12 mo postflight to determine whether there is a rebound loss of bone density and increased risk of fractures. Consideration could be given to also studying whether a bridging agent—such as alendronate—could be used to ameliorate such a discontinuation effect, in line with clinical guideline recommendations.[1,18,46] The authors consider that, in a healthy astronaut population, the rebound effect may not be seen, due to the absence of the hormonal deficits and advanced ageing in the osteoporotic patients previously studied.

A limitation of this study would be that the ISS is situated within Earth's magnetosphere and, therefore, cannot accurately reflect the radiation environment seen while traversing the interplanetary medium.[20] An additional study could be conducted on Earth using a cyclotron with exposure to an appropriate radiation source. This would not only determine denosumab's viability and stability as a medication for an interplanetary mission, but would serve as the first study examining pharmaceutical monoclonal antibodies in a spaceflight-like environment.

Finally, it is worthwhile to discuss the role of maintaining a space pharmacopeia based on the best current practice on Earth. Before use in spaceflight, medication undergoes extensive and expensive bed rest studies before consideration of in-flight trials.[6] Not only does the cost input make trialing new and emerging medication unattractive for budget-strapped government agencies and the private industry, but it also delays the introduction of potentially useful agents. Acknowledging the well-documented pharmacokinetic and pharmacodynamic changes in spaceflight, thought should be given to fast-tracking the use of newer agents once there is a demonstrated safety record and efficacy on Earth-bound applications.

This literature review has examined denosumab as a potential countermeasure for microgravity-induced osteopenia, showing that from its real-world performance, denosumab has numerous promising benefits that extend to long-duration spaceflight. Considering its superiority to alendronate, which has thus far been proven as a useful pharmacological countermeasure, denosumab should be considered for investigation of its utility in preventing microgravity-induced osteopenia. The proposed studies may address the current knowledge gap surrounding the use of denosumab and monoclonal antibodies in spaceflight. As per the NASA Human Research Roadmap, by developing more robust countermeasures to prevent fractures and renal calculi, this could ensure the success of future astronauts undertaking interplanetary exploration.

ACKNOWLEDGMENTS

We would like to acknowledge Mrs. Grace Mowtschan, BSc(Nursing), GradDipMid, for proofing and editing services.

Financial Disclosure Statement: The authors have no competing interests to declare.

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