Zoledronic acid: future potential use in rheumatology

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Zoledronic acid, a third-generation bisphosphonate, is the monohydrate of 1-hydrox-2 ([H-imidazole-1-yl] ethylidene) bisphosphonic acid. Zoledronic acid is registered in over 80 countries throughout the world for tumor-induced hypercalcemia and for the prevention of skeletal-related events in patients with solid tumor metastases or multiple myeloma with bone lesions. Zoledronic acid currently has investigational status for the treatment of Paget's disease of bone, osteoporosis and a number of other bone disorders. This review will focus on the potential future use of zoledronic acid, a potent and easily administered intravenous bisphosphonate, in Paget's disease of bone and osteoporosis – two disorders likely to be commonly treated by rheumatologists. Another potential utility, the suppression of osteoclast-mediated bone erosions in inflammatory arthritis, will be briefly mentioned.

Paget's disease of bone

Paget's disease of bone (PD) is a common skeletal disorder of the elderly that often results in significant morbidity and disability. PD is the second most common bone disorder after osteoporosis [1]. PD is rare in those under 50 years of age, and increases in incidence with age.

Up to 20% of patients affected with PD have a first-degree relative with the disease [2]. Mutations in the sequestosome 1/*p62* gene (*SQSTM1*) have been identified in up to 30% of kindreds with PD [3]. *SQSTM1* encodes sequestosome, an ubiquitin-binding protein involved in interleukin (IL)-1, tumor necrosis factor (TNF) and RANKL-induced stimulation of osteoclastogenesis [4].

PD is characterized histologically by focal increases in bone resorption, followed by corresponding marked increases in bone formation. PD is primarily a disorder of the osteoclasts, which are increased in number, size and activity and demonstrate increased sensitivity to stimulators of osteoclastogenesis, including RANKL and 1,25-dihydroxy vitamin D. The increased osteoblastic activity in PD occurs in a chaotic fashion, leading to immature woven bone of poor quality. These histological features contribute to the skeletal complications of PD, including bone pain, skeletal deformity, pathological fractures, premature arthritis and neurological complications, such as cord or root compression and deafness [5–7].

Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [8]. The most common etiologies of osteoporosis in a rheumatology practice are estrogen deficiency and glucocorticoid-induced osteoporosis (GIOP). Estrogen deficiency leads to an increase in osteoclastogenesis and the number of active bone-remodeling units. This process is mediated by an increase in the expression of RANKL, which is secreted by osteoblasts [9]. RANKL binds and activates its receptor RANK on the surface of osteoclast precursors, and induces osteoclast differentiation and subsequent activation. Osteoprotegerin (OPG) is a natural inhibitor of RANKL, which prevents RANKL from binding to its osteoclast receptor. GIOP results from an increase in the expression of RANKL and decreased OPG expression by osteoblasts and stromal cells. Glucocorticoids also induce osteoblast apoptosis, which leads to a marked decrease in bone formation and a decrease in bone remodeling and osteocyte apoptosis (cells thought to participate in the detection and healing of bone microdamage) [10].

Treatment of PD

The aims of the treatment of PD are relief of symptoms and prevention of complications. Current generally accepted indications for the initiation of medical treatment for PD include [5–7]:

- Serum alkaline phosphatase level twice the upper limit of normal;
- Bone pain;
- Pathological fracture or insufficiency fracture in a bone involved with PD, prevention of hearing loss in a patient with PD, involving the petrous bone and the cochlea, nerve or cord compression;
- Paget's near a weight-bearing joint (to prevent accelerated osteoarthritis);
- In preparation for elective surgery to decrease the vascularity of Pagetic bone and avoid blood loss.

Keywords: osteoporosis, Paget's disease of bone, rheumatoid arthritis, zoledronic acid

future medicine

The indications for initiation of treatment in PD are not universally agreed. The lack of consensus is predominantly due to the absence of evidence from controlled trials demonstrating that medical treatments will not only suppress markers of bone turnover, but actually result in decreasing the aforementioned complications of Paget's.

The Paget's disease: a Randomised Trial of Intensive versus Symptomatic Management (PRISM) trial is an ongoing study of 1700 patients with PD, which is being conducted over 3 years in the UK to determine whether medical treatment will decrease complications and lead to an increase in quality of life for PD patients.

The PRISM trial will compare two different regimens of treating Paget's disease. One arm will involve 'symptomatic treatment' and the other 'intensive treatment'. Patients allocated to 'symptomatic treatment' will be given medication only if the Paget's disease is causing pain.

Theoretically, intensive treatment might be expected to prevent complications of the disease. However, intensive treatment could be associated with more side effects or make some aspects of the disease worse. The PRISM trial should clarify the benefits of each treatment strategy, and provide firm clinicial evidence of complication reduction for the first time.

Current medical treatments for PD

Currently available treatments for PD include:

- Injectable calcitonin (100 Medical MRC Units or 0.5 mg subcutaneous);
- disodium etidronate (5 mg/kg/day for 6 months, followed by a drug-free interval of at least 3 months to prevent impaired mineralization of bone);
- risedronate (30 mg/day for 2 months) [11];
- alendronate (40 mg/day for 6 months) [12];
- tiludronate (400 mg/day for 3 months);
- intravenous pamidronate.

A variety of treatment regimens with pamidronate have been utilized [13]. A single 60 mg dose may be effective for some patients with mild disease, but higher doses of 60–90 mg daily infusions for three to five doses (and occasionally higher) with monthly re-evaluation have been utilized. The most common adverse reactions to pamidronate are transient fever and myalgia (a flu-like syndrome), noted most commonly only after the first dose. Other rare adverse reactions include uveitis and acute renal failure.

Current medical treatments for osteoporosis

Current approved therapies for the prevention and/or treatment of osteoporosis include the selective receptor modulator raloxifene, and the bisphosphonates alendronate, risedronate, ibandronate and etidronate (the latter is registered in most countries except for the USA). In the USA, calcitonin nasal spray and teriparatide are approved for treatment, and estrogen therapy is approved for the management of postmenopausal symptoms, but is no longer approved for treatment. The bisphosphonates are considered to be the drugs of choice based upon their demonstrated efficacy in reducing vertebral and nonvertebral fracture risk.

Zoledronic acid

Zoledronic acid, a third-generation bisphosphonate, is the monohydrate of 1-hydrox-2 ([H-imidazole-1-yl] ethylidene) bisphosphonic acid [14]. In contrast to other nitrogen-containing bisphosphonates, zoledronic acid has two nitrogen atoms contained in a heterocyclic imidazole ring.

Mechanism of action

Nitrogen-containing bisphosphonates exert their cellular effects by specifically inhibiting farnesyl pyrophosphate synthase (FPP) [15]. Zoledronic acid has been shown to be the most potent inhibitor of FPP demonstrated to date [1], and inhibition of the mevalonate pathway in intact osteoclasts treated with zoledronic acid has been demonstrated. Zoledronic acid inhibits osteoclastogenesis in fetal rat calvaria and in cultures of murine monocytes/macrophages treated with monocytes/macrophage colony-stimulating factor (M-CSF) and RANKL. Zoledronic acid stimulates osteoprotegerin production by primary human osteoblasts, which also contributes to the decrease in bone resorption [16]. In cultures of human and rat osteoclasts, zoledronic acid induces apoptosis of these cells [17] and also affects the regulation of proliferation and differentiation of human osteoblasts [18].

Administration

In studies of osteoporosis and PD, zoledronic acid (5 mg/5 ml concentrate for solution diluted with 100 cc of 0.9% sodium chloride) has been administered as a short intravenous infusion of no less than 15 min. Similar to other bisphosphonates, zoledronic acid displays a rapid elimination from the circulation and most soft tissues with no evidence of biotransformation and a high affinity for bone tissue [18].

The pharmacokinetics of zoledronic acid, determined by specific radioimmunoassay, demonstrate a pattern similar to that of other bisphosphonates. Plasma concentrations achieve peak levels at the end of infusion, followed by a rapid decline to less than 1% of peak after 24 h. The mean urinary excretion of zoledronic acid over the first 24 h is approximately 50%, which indicates that 50% of the administered dose of zoledronic acid may be taken up by bone.

Similar to other bisphosphonates, zoledronic acid does not appear to be metabolized and does not inhibit the major cytochrome P450 enzymes in human liver microsomes. Plasma protein binding in humans is low (~22%), and thus zoledronic acid is unlikely to lead to significant displacement of other drugs highly bound to plasma proteins.

Preliminary studies of zoledronic acid in PD

An international multicenter, placebo-controlled, dose-ranging study of 176 Paget's patients with a serum alkaline phosphatase of at least twice normal has been published [19]. Patients were randomized to receive a single 1 h intravenous infusion of 50, 100, 200 or 400 µg of zoledronic acid or placebo. The primary objective of the study was to determine the effect of these doses of zoledronic acid compared with placebo on the maximum percentage reduction in serum alkaline phosphatase (SAP) and urinary hydroxyproline (UOHP/CR) over 3 months.

A rapid and significant reduction in UOHP/CR excretion was observed in all four treatment groups compared with placebo, and reached a nadir by day 10. The reduction was significantly greater for 200 and 400 µg compared with placebo, and for 400 µg compared with the other treatment groups at all post-treatment visits. The SAP reached a nadir by day 60 for the 50, 100 and 200 µg groups, but continued to decrease at post-treatment day 90 for the 400 µg group. The proportion of therapeutic responders (defined as a 50% decrease from baseline or normalization) for SAP demonstrated a dose–response relationship. With 400 µg, 46% of patients had at least a 50% decrease from pretreatment values of SAP, and 20% normalized their SAP.

Overall, drug-related adverse events (AEs) were reported with the same frequency as placebo. The most common drug-related AEs were fever, back pain and skeletal pain that revealed a dose-related trend. Three patients treated with 400 µg developed mild hypocalcemia that resolved without treatment.

Comparison of zoledronic acid with risedronate for PD

Two randomized, controlled, double-blind trials following identical protocols and involving a total of 357 men and women with active PD (defined as a SAP at least twice normal) were performed between 2002 and 2004 in ten countries [20]. Patients were randomized to receive either a 5-mg infusion of zoledronic acid over 15 min followed by placebo tablets for 60 days, or a saline infusion followed by 30 mg of risedronate per day for 60 days. The primary end point of the trial was the proportion of patients who had a therapeutic response (defined as normalization of the alkaline phosphatase or reduction of at least 75% in the alkaline phosphatase excess [the difference from the midpoint of the reference range] at 6 months. Secondary efficacy variables included biochemical markers of bone resorption (serum βC-telopeptide of Type I collagen, urinary αC-telopeptide of Type I collagen–creatinine ratio) and biochemical markers of bone formation (N-terminal propeptide of Type I collagen). Quality of life was measured with the Medical Outcomes Study-36 Short Form General Health Survey SF-36.

Serum alkaline phosphatase levels demonstrated a more rapid, marked and persistent reduction in the zoledronic acid group than in the group given risedronate. At 6 months, 96.0% had a therapeutic response compared with 75.3% in the risedronate group. The median time to a first therapeutic response was 64 days in the zoledronic acid group compared with 89 days in the risedronate group. The response rates were independent of age, sex, baseline alkaline phosphatase and the presence of previous treatment for PD.

This was the first study to examine the comparative effects of treatment on quality-of-life measurements. Mean scores for each of the eight components of the SF-36 trended upward at both 3 and 6 months in the zoledronic acid group, while the results in the risedronate group were mixed. Multivariate testing of all components of the SF-36 suggested superiority of zoledronic acid.

With regard to safety, bone biopsies were taken in 12 patients taking zoledronic acid and 10 taking risedronate. Neither evidence of adynamic bone nor other qualitative abnormalities were noted.

Other AEs of concern that were observed were flu-like symptoms, renal impairment and hypocalcemia. Flu-like symptoms, common to

the use of other intravenous nitrogen-containing bisphosphonates, were more common in the zoledronic acid group than in the risedronate group, and tended to occur during the first 3 days post-administration. The mean serum creatinine decreased slightly in the zoledronic acid group compared with the risedronate group (-0.05 ± 0.10 mg/dl vs 0.00 ± 01. mg/dl; $p < 0.001$) by day 10; however, at subsequent time points there was no significant difference between the two groups. No patient developed persistent, significant deterioration of their renal function.

Hypocalcemia developed in eight patients in the zoledronic acid group (asymptomatic in six and mildly symptomatic in two patients) and in one patient in the risedronate group who required hospitalization and intravenous calcium. At day 10, mean decreases in serum calcium levels were significantly greater in the zoledronic acid group (-0.80 ± 0.50mg/dl) compared with the risedronate group (-0.32 ± 0.50 mg/dl). Calcium levels returned to baseline in both groups by month 6.

Patients who met the definition of a therapeutic response were eligible to enter an observational trial extension [21]. Alkaline phosphatase was then measured every 6 months in the 143 patients in the zoledronic acid group and 107 patients in the risedronate group that entered the extension. At a median of 18 months after the initiation of therapy, only two of 143 of the zoledronic acid patients versus 36 of 107 of risedronate patients lost their therapeutic response ($p < 0.001$).

Preliminary studies of zoledronic acid in osteoporosis

A Phase II study to examine the effect of intravenous zoledronic acid in postmenopausal women on bone density and bone turnover, and to assess the effects of varying the total administered dose and dosing interval has been published [22]. In this study, 351 postmenopausal women aged 45–80 years with a lumbar spine T-score that was at least -2.0 standard deviation (SD) were entered into a 1-year randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25, 0.5 or 1 mg at 3-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, 6 months apart. Lumbar spine bone mineral density (BMD) was the primary end point.

Throughout the study, lumbar-spine BMD increases achieved with all zoledronic acid regimens were significantly higher than those in the placebo group ($p < 0.001$), and there were no significant differences among the zoledronic acid groups. BMD gains for the spine were 4.3–5.1% higher than those in the placebo group ($p < 0.001$), and values for the femoral neck were 3.1–3.5% higher than those in the placebo group ($p < 0.001$).

All zoledronic acid regimens, except the four doses of 0.25 mg, each resulted in distal radial BMD that was significantly greater than that in the placebo group ($p < 0.05$ for all comparisons). The results for total body BMD were similar and were significant ($p < 0.03$ for all comparisons) for all regimens, except the four doses of 0.5 mg each. Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Markers of bone resorption reached a nadir at one month (median decreases of 65–83% in serum C-telopeptide and 50–69% in the urinary N-telopeptide:creatinine ratio), whereas there were no significant changes in the placebo group. The decrease in markers of resorption tended to be dose-dependent, particularly at 3 months. Significant suppression of bone turnover was maintained at 12 months. At 12 months, the zoledronic acid regimens were associated with decreases of 49–52% in serum C-telopeptide and decreases of 54–65% in the ratio of urinary N-telopeptide:creatinine. Since patients were not followed beyond the originally planned 12 months of the study, it is not known how long the bone turnover markers remained suppressed.

Zoledronic acid is not currently approved for the treatment of osteoporosis. Studies are now being conducted using zoledronic acid in postmenopausal osteoporosis, glucocorticoid-induced osteoporosis and osteoporosis in men.

Zoledronic acid in the prevention of erosions in inflammatory arthritis

There is now firm scientific support that the cellular mechanisms involved in the pathogenesis of focal articular bone erosions are dependent on osteoclasts [23]. Furthermore, selective targeting of the osteoclast with zoledronic acid in animal models of arthritis, such as the collagen-induced arthritis (CIA) model in rats [24] and the spontaneous arthritis in tumor necrosis factor (TNF)-transgenic mice [25], has been demonstrated to prevent the progression of focal articular bone erosions. The success of zoledronic acid observed in

these studies compared with prior unsuccessful studies with earlier bisphosphonates could be related to the high potency of zoledronic acid and its ability to achieve high concentrations achievable in the joint.

In a 6-month proof-of-concept study in humans with rheumatoid arthritis, Jarrett and colleagues studied 39 patients with early RA [26]. Both arms of the study received methotrexate (MTX) 7.5–20 mg/week with no other disease-modifying anti-rheumatic drugs (DMARDS) allowed. Patients were then given either zoledronic acid 5 mg intravenous at baseline and 13 weeks or placebo intravenous at baseline and 13 weeks. The primary objective was to demonstrate a 50% reduction in progression of erosions with zoledronic acid compared with placebo, as measured by magnetic resonance imaging (MRI). Secondary outcomes included the number of bone erosions measured by x-ray and bone edema evaluation by MRI.

There was a 61% decrease in mean change in hand/wrist erosions by MRI in the zoledronic acid group compared with placebo, with most of the change attributable to reduction of erosion progression in the wrist. Similar results were observed on hand x-rays (mean change in erosions 0.1 ± 0.9 zoledronic acid vs 0.5 ± 2.1 placebo). Fewer patients developed new bone edema in the zoledronic acid group versus placebo (33.3 vs 57.9%, $p = 0.12$). The safety profile was similar in zoledronic acid and placebo.

This appears to be the first evidence of structural benefit with bisphosphonate in patients with rheumatoid arthritis and thus, warrants further investigation.

Special considerations in the use of zoledronic acid

Special considerations in using zoledronic acid, as opposed to other oral bisphosphonates, would include precautions to avoid hypocalcemia and renal insufficiency, and the issue of osteonecrosis of the jaw.

Renal insufficiency, renal failure and acute tubular necrosis have been reported following treatment with zoledronic acid [27]. This has occurred almost exclusively in patients treated with malignancies at high risk for renal-related AEs due to concurrent dehydration, concurrent use of nephrotoxic chemotherapeutic agents and myeloma kidney. As with other bisphosphonates, zoledronic acid should be used with caution (if at all) in patients with a creatinine clearance of less than 30 ml/min. Patients should be adequately hydrated prior to infusion and the infusion time should not be less than 15 min.

Hypocalcemia may occur and, in rare instances, be symptomatic. In patients considered as candidates for zoledronic acid, risk factors for hypocalcemia, including vitamin D deficiency, calcium or vitamin D malabsorption and parathyroid gland insufficiency (due to prior thyroid surgery or irradiation), should be evaluated. A normal serum calcium level should be obtained before infusion. Considering the high prevalence of vitamin D insufficiency and the risk of hypocalcemia following intravenous bisphosphonate administration, a strong argument could also be made for routine checking of a 25-hydroxy vitamin D level prior to infusion [28].

Osteonecrosis of the jaw (ONJ) is a disorder characterized by nonhealing of exposed bone (spontaneous or induced by oral surgery) despite good medical care, lasting for at least 3–6 weeks. ONJ may be, and often is, associated with infection of the soft tissue and/or bone. Most cases have been in cancer patients (breast cancer and multiple myeloma patients). Besides receiving intravenous bisphosphonates (usually in monthly doses), other risk factors of ONJ include malnutrition, local radiation, concurrent glucocorticoids and systemic chemotherapy. The exact incidence in cancer patients is unknown, but may be as high as 0.8% [29]. To date, ONJ has not been reported when zoledronic acid has been given for benign indications in trials of Paget's or osteoporosis patients.

Conclusion

Zoledronic acid is a potent intravenously administered bisphosphonate that appears to hold great promise for the treatment of PD, osteoporosis and other metabolic bone disorders associated with increased osteoclastic activity. More research is urgently needed to determine whether it is effective in the prevention of erosions in inflammatory arthritis, especially in combination with other biological agents.

The main potential advantages of zoledronic acid will be its rapid onset of action, enhanced compliance and its ability to bypass the gastrointestinal tract, thus avoiding the most common AE of oral bisphosphonates, which is esophagitis. The question of whether increased potency will translate into a superior reduction in complications of PD and osteoporosis remains to be demonstrated.

Executive summary

Mechanisms of action

- Zoledronic acid is a potent inhibitor of the enzyme farnesyl pyrosphosphate synthase, a key enzyme of the mevalonate pathway necessary for protein prenylation (a process necessary for cytoskeleton organization, vesicle transport, membrane ruffling and apoptosis of osteoclasts).
- In cultures of human and rat osteoclasts, zoledronic acid induces apoptosis of these cells and also affects the regulation of proliferation and differentiation of human osteoblasts.

Pharmacokinetic properties

- The pharmacokinetics of zoledronic acid, determined by specific radioimmunoassay, demonstrate a pattern similar to that of other bisphosphonates.
- Plasma concentrations achieve peak levels at the end of infusion, followed by a rapid decline to less than 1% of peak after 24 h.
- The mean urinary excretion of zoledronic acid over the first 24 h is approximately 50%, with the other 50% taken up by bone.

Clinical efficacy

- In the largest osteoporosis trial with zoledronic acid published to date, 351 postmenopausal women received placebo or intravenous zoledronic acid in doses of 0.25, 0.5 or 1 mg at 3-month intervals, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, 6 months apart. At 12 months, lumbar spine and femoral neck bone mineral density (BMD) increases achieved with all zoledronic acid regimens were significantly higher than those in the placebo group ($p < 0.001$), and there were no significant differences among the zoledronic acid groups. Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Significant suppression of bone turnover was maintained at 12 months.
- In two randomized, controlled, double-blind trials involving a total of 357 men and women with active Paget's disease (PD) comparing a 5-mg infusion of zoledronic acid over a 15-min infusion versus 30 mg of risedronate per day for 60 days, serum alkaline phosphatase levels demonstrated a more rapid, marked and persistent reduction in the zoledronic acid group than in the group given risedronate. At 6 months, 96.0% had a therapeutic response compared with 75.3% in the risedronate group. The median time to a first therapeutic response was 64 days in the zoledronic acid group compared with 89 days in the risedronate group. The response rates were independent of age, sex, baseline alkaline phosphatase and the presence of previous treatment for PD.

Safety & tolerability

- Adverse events of concern are flu-like symptoms, renal insufficiency, hypocalcemia and osteonecrosis of the jaw.
- Flu-like symptoms, common to the use of other intravenous nitrogen-containing bisphosphonates, occur in up to 15% of patients treated for osteoporosis during the first 3 days post-administration, and tend not to reoccur with subsequent readministration of the drug.
- Renal insufficiency is rare and tends to occur mainly in patients being treated for malignancy. As with other bisphosphonates, zoledronic acid should be used with caution (if at all) in patients with a creatinine clearance of less than 30 ml/min. Patients should be adequately hydrated prior to infusion and the infusion time should not be less than 15 min.
- Since zoledronic acid is a potent osteoclast inhibitor, hypocalcemia may occur. It will be important to ensure calcium and vitamin D sufficiency prior to administration of intravenous zoledronic acid.
- Most cases of ONJ have been in cancer patients (breast cancer and multiple myeloma patients). Besides receiving intravenous bisphosphonates (usually in monthly doses), other risk factors of ONJ include malnutrition, local radiation, concurrent glucocorticoids and systemic chemotherapy. To date no patients with ONJ have been reported receiving zoledronic acid for either Paget's disease or osteoporosis in clinical trials.

Drug interaction

- Similar to other bisphosphonates, zoledronic acid does not appear to be metabolized and does not inhibit the major cytochrome P450 enzymes in human liver microsomes.
- Plasma protein binding in humans is low (~22%), and thus zoledronic acid is unlikely to lead to significant displacement of other drugs highly bound to plasma proteins.

Dosage & administration

- For both osteoporosis and Paget's disease, zoledronic acid (5 mg/5 ml) concentrate for solution is diluted with 100 cc of 0.9% sodium chloride) and administered as a short intravenous infusion of no less than 15 min.

Potential disadvantages of zoledronic acid include an increased incidence of ONJ, and possibly an increased incidence of hypocalcemia compared with oral bisphosphonates. Costs and the requirement for an intravenous infusion are factors that could limit its use, particularly in the primary care setting.

Future perspective

The ability to deliver high-potency intravenous bisphosphonates is likely to add a very valuable therapeutic option for rheumatologists in the treatment of PD and osteoporosis, especially in patients with very high bone turnover, and in those patients who are not able to take oral

bisphosphonates. Refinements in dosing, speed of administration and utilization of short-term surrogate markers, such as biochemical markers of bone turnover, will add to our knowledge of how to administer these drugs as safely as possible in order to achieve the desired end points of reduction in the complications associated with PD and osteoporosis.

The observation that focal articular bone erosions are dependent on osteoclasts and that this process can be inhibited by zoledronic acid may provide the ability to further suppress bone erosions and joint damage, above that already possible with current disease-modifying and biological agents. Much more work in this area on dosing and frequency of administration is urgently needed.

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