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Atorvastatin May Have No Effect on Acute Phase Reaction in Children After Intravenous Bisphosphonate Infusion

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ABSTRACT: Intravenous bisphosphonate therapy is associated with acute phase reaction characterized by fever and musculoskeletal pain. Bisphosphonates have been shown in vitro to activate γδT-cells to proliferate and produce cytokines, suggesting a role in acute phase reaction, which can be effectively blocked by statins. We conducted a double-blind randomized crossover placebo controlled study in 12 children (12.1 ± 4.2 yr; 10 girls and 2 boys) receiving intravenous bisphosphonates to evaluate whether statins can be used to prevent acute phase reaction associated with therapy. Children received two cycles given 3–4 mo apart of intravenous bisphosphonate given on 2 consecutive days in each cycle. Atorvastatin 10 mg or placebo was given orally once a day for 3 days, starting the day before intravenous bisphosphonate therapy and on the 2 infusion days. We measured pain using a visual analog pain scale at five time points in 0–48 h, oxycodone use for pain, acetaminophen for fever, C-reactive protein (CRP), and total and percent γδT-cells. There was a nonsignificant decrease in pain, oxycodone use, and acetaminophen use with Atorvastatin compared with placebo. There was no difference in CRP and total or percent γδT-cells between the two groups. The results remained unchanged after adjustment for Atorvastatin versus placebo given with the first cycle. We conclude that in vivo Atorvastatin may not be as effective in modulating the acute phase reaction associated with intravenous bisphosphonate as would have been anticipated from in vitro studies.
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Key words: acute phase reaction, Atorvastatin, bisphosphonate, musculoskeletal pain

INTRODUCTION

Children with osteoporosis and various metabolic bone diseases are now being treated with both oral and intravenous bisphosphonate therapy.[1] Children will often complain of severe musculoskeletal pain and will develop fever with intravenous bisphosphonates, which at times cannot be alleviated with acetaminophen and/or nonsteroidal anti-inflammatory drugs. The adverse effects can be severe enough for the child to refuse further therapy. This acute phase reaction is observed in about one third of patients that receive the treatment for the first time.[2–6] The mechanism underlying this acute phase reaction is not known. Two recent in vitro studies have suggested that the acute phase reaction observed with bisphosphonates administration is mediated by increased cytokine production by γδT-cells, which can be effectively blocked by statins.[7,8] In this study, we investigated the ability of Atorvastatin (a statin approved by FDA in children) to protect from musculoskeletal pain and fever associated with intravenous bisphosphonate infusions. Concomitantly, we studied the mechanism that was proposed in these in vitro studies.

The authors state that they have no conflicts of interest.

MATERIALS AND METHODS

Twelve children with various metabolic bone diseases causing osteoporosis were studied in a double-blind randomized crossover placebo-controlled study. The inclusion criteria were age >6 yr and the ability to understand the study, swallow pills, and be competent to complete the visual analog pain scale. We excluded children who had received previous oral or intravenous bisphosphonate treatment, children with a seizure disorder associated or triggered by fever, sensitivity to statins, active liver disease, or elevated serum transaminases or creatinine phosphokinase (CPK). Children on erythromycin, cyclosporine, fibric acid, azole antifungals, cimetidine, and spironolactone were also excluded, given the drug interaction with Atorvastatin, as well as children on steroids, pain medications, or nonsteroidal anti-inflammatory drugs.

In our Bone and Mineral Disorder Clinic, intravenous infusion of pamidronate or zoledronic acid is given on 2 consecutive days referred to as ''cycles,'' which are given 3–4 mo apart. The dose of pamidronate, given over 4 h, is 0.5 mg/kg/dose on day 1 and 1 mg/kg/dose on day 2, and of zoledronic acid, given over 30 min, 0.0125 mg/kg/dose on day 1 and 0.025 mg/kg/dose on day 2. Subjects received Atorvastatin 10 mg or placebo, similar in appearance, in a crossover design. Both were given once daily for 3 days

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TABLE 1. EFFECT OF ATORVASTATIN VS. PLACEBO ON PAIN SCALE AND USE OF OXYCODONE AND ACETAMINOPHEN IN 12 CHILDREN RECEIVING INTRAVENOUS BISPHOSPHONATES FOR THE FIRST TIME

	Placebo	*Atorvastatin*	*Unadjusted (p value)*	*Adjusted (p value)*
Pain Scale 1	7.7 ± 23.8	6.3 ± 17.9	0.44	0.43
Pain Scale 2	14.1 ± 26.3	12.5 ± 25.0	0.89	0.88
Pain Scale 3	17.2 ± 28.1	10.2 ± 21.3	0.52	0.44
Pain Scale 4	24.3 ± 34.6	19.8 ± 27.9	0.70	0.64
Pain Scale 5	29.5 ± 37.5	18.3 ± 35.4	0.51	0.42
Cumulative pain score	92.7 ± 111.9	67.0 ± 87.9	0.53	0.38
Oxycodone use	1.0 ± 1.0	0.8 ± 1.4	0.62	0.54
Acetaminophen use	0.8 ± 1.1	0.3 ± 0.9	0.28	0.16

Pain scale score on visual analog scale at baseline (Pain Scale 1), postbisphosphonate therapy day 1 (Pain Scales 2 and 3), and postbisphosphonate therapy day 2 (Pain Scales 4 and 5) and number of doses of oxycodone for pain relief and acetaminophen for fever with bisphosphonate infusion. The statistical analysis was repeated after adjustment for receiving Atorvastatin vs. placebo with the first cycle of bisphosphonate infusion. Data are presented as mean ± SD.

(starting the day before infusion and continuing through the 2 infusion days). The randomization was done by a pharmacist using random blocks of two using a standard statistical program (CLINSTAT). The investigators and subjects were blinded to therapy. In each cycle, before infusion on day 1 and again after completion of infusion on day 2, blood was collected for blood count, γδT-cell count, and C-reactive protein (CRP). To monitor possible effect of Atorvastatin on muscle, we also checked for serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), and CPK. Serum samples were stored at −80°C for later batch analysis. The γδT-cell enumeration was performed by flow cytometry on a Becton Dickinson FACS Calibur cytometer with antibodies TCR-αβ tagged to FITC, TCR-γδ tagged to PE, CD3 tagged to APC, and CD45 tagged to PerCP (BD Biosciences).

Children completed the visual analog pain scale (0–100 mm) at baseline before the infusion (Pain Scale 1). Pain Scale 2 was completed on day 1 late evening/ night and Pain Scale 3 on day 2 late morning/noon before infusion. Pain Scale 4 was completed on day 2 late evening/ night and Pain Scale 5 late morning/noon the day after infusion. For each subject, the five time points were identical in the two cycles. The children's families also noted if they needed medications to alleviate their pain or fever, as either Yes or No. For musculoskeletal pain, children were given oxycodone, considered not to interfere with the inflammatory markers being evaluated. For fever (≥39°C), if tepid sponging did not bring down the temperature, they were instructed to take acetaminophen. A power analysis for the study to detect a minimum detectable difference of 5-, 10-, 15-, 20-, and 25-mm units on a 0- to 100-mm pain scale measurement with the assumption of a two-sided α level of 0.05 and SD observed in this study at 80% power, would require a sample size of 235, 61, 28, 17, and 12 children.

The primary study outcome was prevention of musculoskeletal pain and fever by Atorvastatin compared with placebo by visual analog pain scale and need for oxycodone and acetaminophen; the secondary outcomes were changes in blood count, γδT-cell count, and CRP. A pain scale score of >50 mm was defined as severe pain.[9] The statistical analysis was performed by two-tailed Student's paired *t*-test for group comparison using SPSS 15.0. The musculoskeletal pain is reported to be more common with the initial dose of bisphosphonate therapy in the reported literature.[6] Therefore, to adjust for possible order effect in a crossover placebo-controlled clinical study, we also used the repeated-measures ANOVA model with treatment and order as between-subject factors.[10] $p < 0.05$ was considered as significant.

RESULTS

Twelve children (10 girls and 2 boys) participated in the study. The mean age was 12.1 ± 4.2 yr. These included six children with secondary osteoporosis (four with inflammatory bowel disease, one with cystic fibrosis, and one with Ehlers-Danlos syndrome), four with idiopathic osteoporosis, one with osteogenesis imperfecta, and one with Ollier's disease. Eleven children received zoledronic acid and one received pamidronate. Six children received Atorvastatin in the first cycle, whereas the other six received it in the second cycle. All completed the visual analog pain scale evaluation and medication report as shown in Table 1. The mean pain scores across the five study points were lower in the Atorvastatin group compared with the placebo group but did not reach statistical significance, which was not influenced by analysis of the data after its adjustment for Atorvastatin given in the first cycle (Table 1). With placebo therapy, six children (50%) rated their pain >50 mm on the pain scale and required oxycodone therapy, and four children (33%) required acetaminophen for fever. With Atorvastatin, four children (33%) rated their pain >50 mm on the pain scale and required oxycodone therapy, and one child (8%) required acetaminophen for fever. Although the use of oxycodone and acetaminophen was lower in the Atorvastatin group compared with placebo, it did not reach statistical significance.

As shown in Table 2, there was no difference in total and percent lymphocytes on blood count nor in CD3+ lymphocytes and γδT-cells in blood by flow cytometry. There was also no difference in CRPs. There were no changes observed in serum LDH, SGOT, or CPK with Atorvastatin therapy (data not shown).

DISCUSSION

A common adverse effect of intravenous administration of bisphosphonates such as pamidronate and zoledronic

TABLE 2. EFFECT OF ATORVASTATIN VS. PLACEBO IN 12 CHILDREN RECEIVING INTRAVENOUS BISPHOSPHONATE FOR THE FIRST TIME ON TOTAL AND PERCENT γδT-CELLS AND CRP

	Placebo	*Atorvastatin*	*Unadjusted (p value)*	*Adjusted (p value)*
Total γδT-cells (preinfusion)	87.2 ± 59.9	57.4 ± 47.3	0.14	0.06
Total γδT-cells (postinfusion)	29.0 ± 21.0	35.1 ± 21.6	0.56	0.62
Percent change in total γδT-cells	−52.2 ± 32.5	5.5 ± 152.9*	0.22	0.24
Percent γδT-cells (preinfusion)	7.9 ± 10.6	4.9 ± 4.8	0.15	0.10
Percent γδT-cells (postinfusion)	4.0 ± 3.7	4.4 ± 4.4	0.85	0.79
Percent change in γδT-cells	−29.6 ± 26.7	−13.7 ± 24.2	0.24	0.26
CRP (preinfusion)	0.5 ± 0.8	0.3 ± 0.2	0.50	0.46
CRP (postinfusion)	0.6 ± 0.7	0.2 ± 0.1	0.11	0.13
Percent change in CRP	131 ± 335	3.3 ± 75.3	0.25	0.27

The statistical analysis was repeated after adjustment for receiving Atorvastatin vs. placebo with the first cycle of bisphosphonate infusion. Data are presented as mean ± SD.

* The large SD is because of a one large outlier value.

acid, especially during the first and second rounds, is the development of an acute phase reaction seen in approximately one third of patients.[2–6] In children treated with intravenous zoledronic acid, an acute phase reaction can be seen in as many as 85%.[11] The acute phase reaction is characterized by transient pyrexia, musculoskeletal pain, and increased circulating levels of TNF-α, interleukin 1 (IL-1), and IL-6.[3–5] In an elegant in vitro study, Thompson and Rogers[7] showed that bisphosphonates cause γδT-cell activation and proliferation by an indirect mechanism through inhibition of farnesyl pyrophosphate synthase, an effect that can be overcome by inhibiting HMG-CoA reductase with a statin. They suggested that activation of γδT-cells could be the initiating event in the acute phase response to bisphosphonate therapy and that co-administration of a statin could be an effective approach to prevent this adverse effect. Their study was performed with human peripheral blood mononuclear cells and used concentrations of bisphosphonates and statins observed in human patients, thus making them clinically relevant.[7] Their data were supported by another in vitro study by Hewitt et al.[8] using a human T-cell clone. Thus, the in vitro data were convincing to suggest a role for statin use to abrogate the acute phase reaction associated with bisphosphonate therapy. Because of the high incidence of acute phase reactions in children, at times causing them to refuse further treatment, we studied whether concomitant administration of Atorvastatin would eliminate the acute phase reaction in children receiving intravenous bisphosphonate for the first time.

The children were studied for 48 h after the initial infusion, which captured all pain and febrile events because the acute phase response is maximal within 28–36 h of intravenous administration and disappears 2–3 days later, despite continuing treatment.[2] The doses of bisphosphonate therapy used in these children were similar to those reported in literature.[12] In an analysis of 2042 adult patients treated with zoledronic acid 4 mg, pamidronate 90 mg, or placebo in three controlled multicenter bone metastases trials, fever was observed in 31–32% and bone pain in 55–57%.[13] Similarly, in our study, one third of the children receiving placebo developed fever and one half had moderate to severe pain. The incidence of pain and fever was not significantly decreased with Atorvastatin (Table 1). We did not analyze for a difference between the two intravenous bisphosphonate preparations because all children except one received zoledronic acid. There was no change in SGOT, LDH, or CPK to suggest adverse effects of Atorvastatin on muscle as a contributory factor to musculoskeletal pain.

The two in vitro studies suggested a role for γδT-cell proliferation with increased production of TNF-α, interferon γ (IFNγ), and IL-6 as the underlying mechanism for the acute phase reaction to bisphosphonate administration.[7,8] As shown in Table 2, our subjects had no significant change in CRP and γδT-cells with or without Atorvastatin as might have been anticipated from the above studies.[7,8] Furthermore, as part of the original study design, we did collect and store serum samples for TNF-α, IFNγ, and IL-6, but because the analysis of data showed no beneficial effect on the primary outcome of musculoskeletal pain and fever or a significant change in serum CRP and γδT-cells, we elected not to analyze them. The reason for the discrepancy between the findings in the previous in vitro studies and our in vivo study is unclear. However, when it comes to a clinical study, one can anticipate additional confounders to be involved compared with results in the test tube. One can also argue that the sample size was small; however, the double-blind crossover study design allowed the achievement of meaningful results. Our study with 12 children would have been able to detect a change in pain scale of 25-mm units. A bigger sample size would have been able to detect a smaller difference in the pain scale; however, a smaller change on a VAS pain scale may be less relevant clinically.[14–16]

We conclude that Atorvastatin may not be effective in modulating the acute phase reaction associated with intravenous bisphosphonate in vivo. The changes in γδT-cells and CRP observed in previous in vitro studies were not observed in our clinical study. Further research is needed for means to eliminate the acute phase reaction associated with intravenous bisphosphonate therapy.

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