Alveolar Ridge and Maxillary Sinus Augmentation Using rhBMP-2: A Systematic Review

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ABSTRACT

Purpose: The aim of this systematic review was to evaluate clinical and safety data for recombinant human bone morphogenetic protein-2 (rhBMP-2) in an absorbable collagen sponge (ACS) carrier when used for alveolar ridge/maxillary sinus augmentation in humans.

Materials and Methods: Clinical studies/case series published 1980 through June 2012 using rhBMP-2/ACS were searched. Studies meeting the following criteria were considered eligible for inclusion: >10 subjects at baseline and maxillary sinus or alveolar ridge augmentation not concomitant with implant placement.

Results: Seven of 69 publications were eligible for review. rhBMP-2/ACS yielded clinically meaningful bone formation for maxillary sinus augmentation that would allow placement of regular dental implants without consistent differences between rhBMP-2 concentrations. Nevertheless, the statistical analysis showed that sinus augmentation following autogenous bone graft was significantly greater (mean bone height: 1.6 mm, 95% CI: 0.5–2.7 mm) than for rhBMP-2/ACS (rhBMP-2 at 1.5 mg/mL). In extraction sockets, rhBMP-2/ACS maintained alveolar ridge height while enhancing alveolar ridge width. Safety reports did not represent concerns for the proposed indications.

Conclusions: rhBMP-2/ACS appears a promising alternative to autogenous bone grafts for alveolar ridge/maxillary sinus augmentation; dose and carrier optimization may expand its efficacy, use, and clinical application.

KEY WORDS: alveolar ridge augmentation, BMP, bone morphogenetic proteins, bone regeneration, maxillary sinus augmentation

INTRODUCTION

Inadequate alveolar ridge height and width due to resorption/remodeling following tooth loss, periodontal disease, or trauma pose a considerable challenge for prosthetic reconstruction. Several surgical techniques alone or in combination with autogenous bone preparations, cadaver-sourced, and synthetic bone biomaterials have, with mixed results, been proposed to overcome such alveolar ridge aberrations.[1] More recently, protein and cell-based technologies have been introduced in an effort to improve the native regenerative potential of patients in need of bone augmentation for dental implant-anchored prosthetic reconstructions.[1,2]

Bone morphogenetic proteins (BMPs), members of the transforming growth factor-β superfamily, were identified following the seminal work by Dr. Marshall Urist demonstrating ectopic and orthotopic bone formation following implantation of demineralized bone matrices using a variety of animal platforms.[3] Since then, several BMPs have been purified, cloned,

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and characterized as having important roles in cartilage and bone formation.[4,5] Recombinant technology has been employed to produce BMPs in pharmacological-relevant quantities to support bone formation for orthopedic indications.[6] Recombinant human BMP-2 (rhBMP-2) in an absorbable collagen sponge (ACS) carrier was approved in 2002 by the FDA for orthopedic indications including spine fusion and long bone fracture repair.[7] rhBMP-2/ACS was approved for oral/maxillofacial indications including alveolar ridge and maxillary sinus augmentation in 2007. rhBMP-2/ACS has since reached increasing acceptance in dentistry. Anecdotal information shows evidence of an increasing off-label use also including intraoral indications as well as combining rhBMP-2 with alternative carriers or bulking agents.[8–11] The aim of this systematic review was to evaluate clinical and safety data for rhBMP-2/ACS when used for alveolar ridge and maxillary sinus augmentation in humans.

MATERIAL AND METHODS

Search Strategy

The MEDLINE (PubMed) database was searched from 1980 through June 2012 for clinical studies evaluating the use of rhBMP-2 for alveolar ridge and maxillary sinus augmentation. The search strategy included a combination of the following MeSH terms: "bone morphogenetic proteins," "BMP," "alveolar ridge augmentation," "bone regeneration," and "maxillary sinus augmentation." Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, EMBASE, SciELO, and LILACS were also searched using similar strategy. The search was limited to human studies and the following study types: clinical trials, controlled clinical trials, randomized controlled trial (RCT), case reports, clinical trial phase I, II, III, and IV. Only studies published in the English, German, Spanish, or Portuguese languages were considered.

The electronic search was supplemented using a "hand" search including *Journal of Periodontology*, *Clinical Oral Implants Research*, *The International Journal of Oral and Maxillofacial Implants*, *The Journal of Oral Implantology*, *Journal of Oral & Maxillofacial Surgery*, *Journal of Clinical Periodontology*, *Clinical Implant Dentistry and Related Research*, and *The International Journal of Periodontics & Restorative Dentistry*. Additionally, references of the articles identified during the electronic and review articles on the subject were also reviewed.

Selection Criteria

Study eligibility was assessed independently by three reviewers (R.M.F., R.S.N., and C.S.) based on the publication title and abstract. All eligible publications and studies which eligibility could not be determined were reviewed. Publications were selected by consensus if all the following criteria were met: >10 subjects at baseline, maxillary sinus/alveolar ridge augmentation not concomitant with implant placement, estimates of new bone formation.

Data Collection and Analysis

Data were independently extracted by three reviewers (R.M.F., R.S.N., and C.S.), and the findings were compiled in descriptive tables. A statistical analysis combining results from two randomized clinical trials[12,13] was conducted using a fixed effect model and Cohen's method for the standardized mean difference and 95% confidence intervals. Mean differences, standard deviations, and p values were calculated for the study by Fiorellini and colleagues[14] using the no treatment group as a reference.

RESULTS

Search Results

Fifty-eight publications were identified using MEDLINE and eleven additional references using alternate search strategies (Figure 1). Upon screening, eight of 26 publications were selected for further review. One article[15] was excluded for being a subanalysis of another study[14] already included in the review. After consensus among reviewers (R.M.F., U.M.E.W., and C.S.), six studies in seven publications were identified and summarized in Tables 1 and 2. One publication[16] represented a 36-month follow-up of a previous study.[17] Two studies (in three publications)[16–18] were classified as case series and four studies[12–14,19] as RCTs. Both case series included 12 subjects, and the RCT sample size ranged from 22[19] to 160[13] subjects. Three studies[14,16,19] had less than a 1-year follow-up, and three studies[12,13,16,17] had 36-month follow-ups. Dose range varied considerably within and between studies and treatment indications.

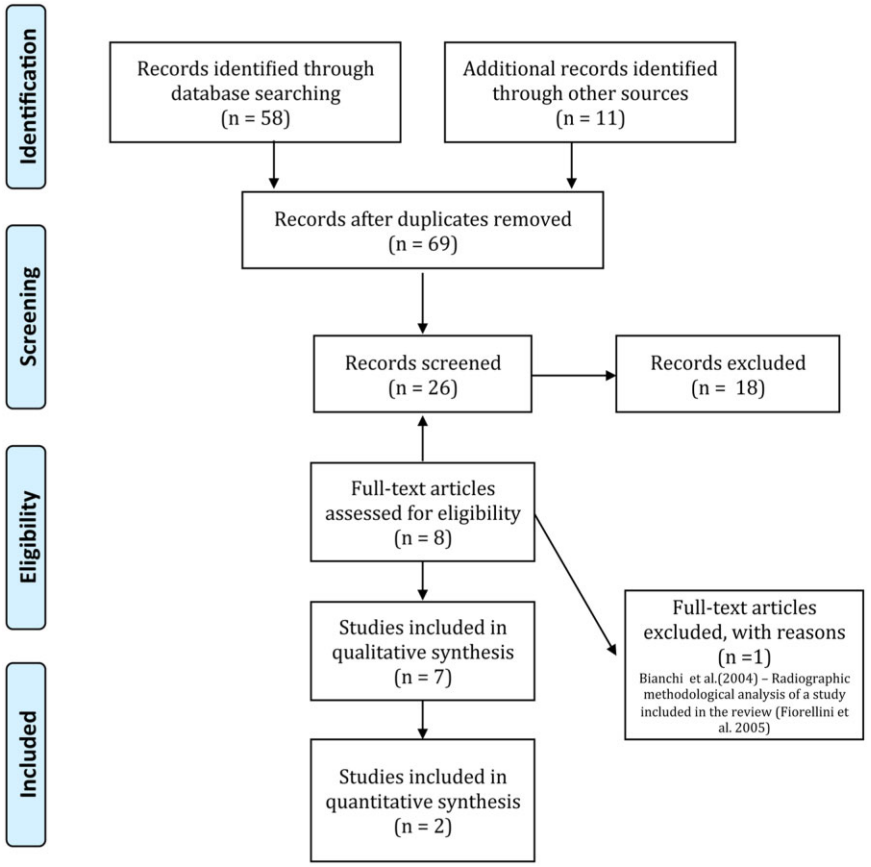

Figure 1 Flowchart of the search strategy.

Maxillary Sinus Augmentation

Maxillary sinus augmentation using rhBMP-2/ACS inlays was evaluated in four studies.[12,13,18,19] Three rhBMP-2 concentrations (0.43, 0.75, and 1.5 mg/mL) were used. The mean rhBMP-2 dose ranged between 2.9 and 20.8 mg per site.

rhBMP-2/ACS yielded clinically meaningful new bone formation for maxillary sinus augmentation – new bone height ranging between 7.8 and 10.2 mm (Table 1). No consistent differences in bone formation could be observed among rhBMP-2 concentrations. The statistical analysis showed that new bone height following autogenous bone grafting was 1.6 mm greater than for rhBMP-2/ACS (Table 2). Autogenous bone grafts yielded comparatively enhanced bone formation over rhBMP-2/ACS in sites with initial bone height ≤4 mm (mean difference: 2.3 mm; 95% CI: 0.6–4.0 mm, $p = .008$) and in sites with initial bone height ≤6 mm (mean difference: 2.4 mm; 95% CI: 0.7–4.0 mm, $p = .005$); however, no differences were observed for sites with an initial bone height ≥6 mm (mean difference: 1.3 mm; 95% CI: –0.02–2.6, $p = .05$).[13] Bone density at 4 to 6 months was significantly greater for the autogenous bone graft, whereas bone density was greater for rhBMP-2/ACS following functional loading (Table 2).

No major histological differences were observed among core biopsies from the experimental groups (Table 1). Residual ACS was not observed. rhBMP-2/ACS induced woven and lamellar bone with cell-rich fibrovascular marrow. A limited number of osteoblasts and osteoclasts were observed. No or minor inflammatory infiltrates were seen.

Alveolar Ridge Augmentation

Alveolar ridge augmentation using rhBMP-2/ACS as alveolar ridge onlays and extraction socket inlays was evaluated in two case series summarized in Table 3.[14,16,17] Three rhBMP-2 concentrations – 0.43, 0.75, and 1.5 mg/mL – were used. Mean rhBMP-2 dose ranged from 0.3 to 1.9 mg.

In one case series, two groups of six subjects each receiving rhBMP-2 at a wide dose range for alveolar

TABLE 1 Summary Data of Studies Evaluating rhBMP-2/ACS for Maxillary Sinus Augmentation (Means ± SD)

Author Study Type Sample Size Follow-Up	Intervention/Dose (Sample Size per Group)	Results
Boyne et al. (1997) Case series 12 subjects 16 weeks	rhBMP-2/ACS 0.43 mg/mL Mean dose: 2.9 mg (range 1.8–3.4 mg)	Radiographic findings: Bone height gain: 8.5 ± 4.1 mm (95% CI: 6.1–11.0). Eight of 11 subjects (73%) presented adequate bone height for dental implant placement Histologic findings: osteoblastic cells and capillaries in the newly induced bone marrow. No residual ACS.
Boyne et al. (2005) RCT 48 subjects 36 months	rhBMP-2/ACS rhBMP-2 at 0.75 mg/mL ($n = 18$) rhBMP-2 at 1.5 mg/mL ($n = 17$) Autogenous bone alone or combined with allogeneic bone biomaterial ($n = 13$) Mean dose: 8.9 mg (range 5.2–12 mg) for the 0.75 mg/mL group 20.8 mg (range 10.8–24.0 mg) for the 1.5 mg/mL group	Radiographic findings: Bone graft / rhBMP-2/ACS 0.75 mg/mL / rhBMP-2/ACS 1.5 mg/mL New bone height (mm): 11.3 ± 4.2 / 9.5 ± 5.7 / 10.2 ± 4.7 New bone width at subcrestal level (mm)*: 4.7 ± 2.8 / 2.2 ± 2.7 / 2.0 ± 2.4 New bone width at midcrestal level (mm): 10.2 ± 3.0 / 8.5 ± 5.5 / 7.8 ± 3.9 New bone width at apical crestal level (mm): 10.6 ± 3.2 / 11.7 ± 5.2 / 10.8 ± 4.6 Bone density at 4 months (mg/cc)*: 350 ± 243 / 84 ± 50 / 137 ± 77 Bone density at 6 months postloading (mg/cc): 448 ± 213 / 456 ± 131 / 508 ± 126 Histologic findings: woven and lamellar bone, limited number of osteoblasts and osteoclasts, moderately vascular bone marrow with small amount of fibrotic material, and limited inflammatory infiltrate. No residual ACS. No noteworthy differences among experimental groups. Acellular remnants found in the bone graft group.
Triplett et al. (2009) RCT 160 subjects 36 months	rhBMP-2/ACS 1.5 mg/mL ($n = 78$) Autogenous bone alone or in combination with allogeneic bone biomaterial ($n = 82$) Mean dose: 19.4 mg (range 1.6–24.0 mg)	Radiographic findings: Bone graft / rhBMP-2/ACS 1.5 mg/mL Bone height gain at 6 months postsurgery Sites with ≤4 mm at baseline (mm)*: 12.7 ± 6.0 / 10.4 ± 5.0 Sites with ≤6 mm at baseline (mm)*: 12.1 ± 5.8 / 9.7 ± 4.7 Sites with ≥6 mm at baseline (mm)*: 6.6 ± 4.9 / 5.3 ± 4.2 Overall new bone height (mm)*: 9.5 ± 4.1 / 7.8 ± 3.5 Bone density at 6 months postsurgery (mg/cc)*: 283 ± 140 / 200 ± 80 Bone density at 6 months postloading (mg/cc)*: 298 ± 133 / 358 ± 120 Histologic findings: rhBMP-2/ACS group showed cell-rich, vascular marrow space without residual ACS. Bone graft group presented nonviable, fibrous encapsulated graft material in some samples, large volume of trabecular bone, the new bone comparable in density to the native bone, moderate amounts of osteoblasts, small number of samples containing few osteoclasts, inflammatory cell infiltration.
Kao et al. (2012) RCT 22 subjects 24 to 36 weeks	rhBMP-2/ACS 1.5 mg/mL + xenogeneic bone substitute + absorbable collagen membrane ($n = 11$) Xenogeneic bone substitute + absorbable collagen membrane ($n = 11$) Mean dose: not reported	Bone height gain (mm) / Xenogeneic biomaterial / rhBMP-2/ACS Xenogeneic biomaterial New bone (%)*: 24.9 ± 5.8 / 16.0 ± 7.5 Residual xenogeneic biomaterial (%)*: 39.7 ± 7.3 / 15.7 ± 5.0 Sites with ≥6 mm at baseline*: 35.5 ± 4.9 / 68.3 ± 7.5 Histologic findings: newly formed bone consisting of woven and mature bone observed in both groups. Bone apposition could be observed over the biomaterial particles. Larger proportions of bone marrow were observed in sites that received rhBMP-2 in combination with the biomaterial. No sign of inflammation in any sites.

*Statistically significant differences were observed between/among groups ($p < 0.05$).
ACS, absorbable collagen sponge; CI, confidence interval; RCT, randomized controlled trial; rhBMP-2, recombinant human bone morphogenetic protein-2.

TABLE 2 Statistical Analysis of Radiographic Observations Comparing Autogenous Bone Graft with rhBMP-2/ACS (rhBMP-2 at 1.5 mg/mL) for Maxillary Sinus Augmentation

		Weighted Mean Difference*	95% Confidence Interval		% Weight	*p* Value
New bone height (mm)	Boyne et al. 2005 ($n = 30$)	1.1	−2.0	4.3	12.4	
	Triplett et al. 2009 ($n = 160$)	1.6	0.4	2.8	87.6	
	Overall ($n = 190$)	1.6	0.5	2.7	100.0	0.006
New bone density (mg/cc)	Boyne et al. 2005 ($n = 30$)	213.0	75.9	350.1	6.3	
	Triplett et al. 2009 ($n = 160$)	83.0	47.4	118.6	94.0	
	Overall ($n = 190$)	91.2	56.8	125.6	100.0	0.0001
New bone density post-functional loading (mg/cc)	Boyne et al. 2005 ($n = 30$)	−60.0	−190.4	70.4	8.3	
	Triplett et al. 2009 ($n = 160$)	−60.0	−99.3	−20.7	91.7	
	Overall ($n = 190$)	−60.0	−97.6	−22.4	100.0	0.002

*Positive estimates favor autogenous bone graft; negative estimates favor rhBMP-2/ACS.

ridge or extraction socket augmentation were followed for up to 36 months.[16,17] The lack of controls complicates the interpretation of the results; nevertheless, only limited new bone formation was observed.

Fiorellini and colleagues in a large study demonstrated that rhBMP-2/ACS inlays (rhBMP-2 at 1.5 mg/mL) maintained the alveolar ridge height at extraction socket sites, whereas sites that did not receive treatment lost 1.2 ± 1.2 mm.[14] Compared with no treatment, new bone width at the subcrestal (2.0 ± 2.9 mm) and midcrestal (2.8 ± 2.7 mm) levels was significantly greater following application of rhBMP-2/ACS (rhBMP-2 at 1.5 mg/mL; $p < .05$). ACS alone and rhBMP-2/ACS (rhBMP-2 at 0.75 mg/mL) displayed intermediate performances compared with no treatment and rhBMP-2/ACS (rhBMP-2 at 1.5 mg/mL).

Safety

Safety data were reported in five of six studies (Table 4).[12–14,16–18] Four of 176 (2.3%) subjects receiving rhBMP-2/ACS displayed rhBMP-2 antibodies.[12–14,17,18] Thirty-one of 136 (22.8%) subjects receiving ACS alone or in combination with rhBMP-2 displayed bovine type I collagen antibodies.[12,13,17,18] Twenty-eight of 96 (29.2%) subjects receiving autogenous bone graft alone or in combination with biomaterials also showed bovine type I collagen antibodies.[12,13] One study reported antibody for bovine type I collagen in 11 subjects; however, the authors did not distinguish between experimental groups.[14] Clinical adverse events included, but were not limited to, reversible edema, pain, sensory loss, and erythema. In all cases, safety concerns were considered transient to not affect the treatment outcomes.

DISCUSSION

This systematic review assessed the available clinical evidence on the use of rhBMP-2/ACS for alveolar ridge/maxillary sinus augmentation. Of 69 identified publications, seven reports meeting inclusion criteria were reviewed. Although three rhBMP-2 concentrations (0.43, 0.75, and 1.5 mg/mL) were used, the absolute dose received at different sites for the same indication varied considerably. rhBMP-2/ACS yielded less vertical bone formation than autogenous bone for maxillary sinus augmentation; nevertheless and importantly, clinically relevant bone formation allowing implant placement was achieved for both treatments. In extraction sockets, rhBMP-2/ACS maintained alveolar ridge height while enhancing alveolar ridge width in a dose-dependent order. Induced new bone was histologically compatible with the resident alveolar bone as did bone formed following autogenous bone grafting. No major adverse events were reported; nevertheless, treatment with rhBMP-2/ACS was associated with transient signs of local inflammation.

Only a few industry-sponsored RCTs linked to the FDA approval process for rhBMP-2/ACS for craniofacial indications including maxillary sinus and alveolar ridge augmentation have been reported.[14,16,17] Also, a few case series have been reported using the rhBMP-2/ACS as a treatment option beyond indications approved by the FDA.[8–11] Most of the subjects treated

TABLE 3 Summary Data of Studies Evaluating rhBMP-2/ACS for Alveolar Ridge Augmentation (Means ± SD)

Author Study Type Sample Size Follow-up Indication	Intervention/Dose (Sample Size per Group)	Results
Howell et al. (1997) & Cochran et al. (2000) Case series 12 subjects 16 weeks and 36 months Alveolar ridge (6 subjects) and extraction socket (six subjects) augmentation	rhBMP-2/ACS 0.43 mg/mL Mean dose: Alveolar ridges: 0.8 mg (range 0.2–1.8 mg) Extraction sockets: 0.3 mg (range 0.2–0.9 mg)	Clinical assessment at 16 weeks: Alveolar ridges: socket width fill 4.9 ± 2.4 mm, socket length fill 3.7 ± 2.1 mm, and socket depth fill 10.4 ± 6.6 mm Extraction sockets: bone height gain −0.8 ± 2.5 mm, bone width 0.4 ± 0.9 mm, and bone length 1.2 ± 1.3 mm Radiographic findings at 16 weeks (CT scan): Alveolar ridges: bone height gain 0.3 mm (95% CI: 0.9–1.6 mm); bone density increase 248.3 mg/cc (95% CI: 86.9–410.4 mg/cc). Statistically significant linear dose-response relationship between rhBMP-2 dose and bone height Extraction sockets: bone height gain 0.2 mm (95% CI: 2.0–2.3 mm); bone width gain 0.2 mm (95% CI: 0.2–0.7 mm); bone density increase 21.6 mg/mL (95% CI: 21.3–64.5 mg/mL). No dose-response relationship between rhBMP-2 dose and radiographic parameters observed. Radiographic findings at 8 to 12 months post-loading (periapical x-ray): Alveolar ridges: mean crestal bone loss amounting to 1.4 and 1.8 mm for mesial and distal sites, respectively. Extraction sockets: crestal bone loss >2 mm Histological analysis at 16 to 30 weeks: Alveolar ridges ($n = 5$): no residual ACS, variable amount of woven bone, limited number of osteoblasts and osteoclasts, moderate numbers of capillaries, limited inflammation Extraction sockets ($n = 2$): no residual ACS, variable amount of woven bone, frequent bone remodeling, variable number of osteoblasts and osteoclasts, moderate number of capillaries, limited inflammation
Fiorellini et al. (2005) Randomized clinical trial 80 subjects 16 weeks Alveolar ridge augmentation following tooth extraction	rhBMP-2/ACS 0.75 mg/mL ($n = 20$) rhBMP-2/ACS 1.5 mg/mL ($n = 20$) ACS alone ($n = 20$) No treatment ($n = 20$) mean dose: 0.9 and 1.9 mg/site for rhBMP-2 at 0.75 and 1.5 mg/mL, respectively	

	No treatment	ACS	rhBMP-2/ACS 0.75 mg/mL	rhBMP-2/ACS 1.5 mg/mL
New bone height (mm)*	-1.2 ± 1.2^{A}	-1.0 ± 1.4^{AB}	-0.6 ± 1.4^{AB}	-0.02 ± 1.2^{BC}
New bone width at subcrestal level (mm)*	0.6 ± 2.6^{A}	0.8 ± 1.4^{AB}	1.8 ± 1.7^{AB}	3.3 ± 2.5^{C}
New bone width at midcrestal level (mm)*	1.6 ± 2.5^{A}	1.8 ± 1.7^{AB}	2.5 ± 1.4^{AB}	3.97 ± 2.5^{C}
New bone width at apical crestal level (mm)*	1.7 ± 2.1^{A}	1.8 ± 1.5^{A}	2.3 ± 1.1^{A}	2.7 ± 1.4^{A}

Histological findings: trabecular bone (remodeling from woven to lamellar was most common), active osteoblasts (small to moderate quantity), few or no osteoclasts, vascular unremarkable, no ACS, and no inflammation sign

*Estimates followed by the same capital letter were not statistically different ($p < 0.05$).
CT, computed tomography; CI, confidence interval; rhBMP-2, recombinant human bone morphogenetic protein-2; ACS, absorbable collagen sponge.

TABLE 4 Safety Data of Studies Evaluating rhBMP-2/ACS

Author	Immunological Findings	Clinical Adverse Events
Howell et al. (1997)	Antibodies for rhBMP-2, bovine type I collagen and human type I collagen were not detected	Erythema (some subjects, mostly between 2 and 5 days postsurgery, but two cases at 4 and 12 weeks), edema (nine subjects at 2 and 5 days postsurgery), and sensory loss (one subject at 2 and 5 days postsurgery) Undesirable outcome: augmented site hard to palpation at 4 weeks (all subjects), but for two subjects, surgical site became soft to palpation at 16 weeks
Boyne et al. (1997)	Antibodies for rhBMP-2 and human type I collagen were not detected. One subject was positive for anti-bovine type I collagen antibody.	Oral pain (eight subjects), facial edema (six subjects), rhinitis (four subjects), sinusitis (two subjects), and ecchymosis (two subjects)
Cochran et al. (2000)	Not reported	Oral pain (10 subjects), oral erythema (three subjects), colitis (one subject), and infection (two subjects)
Boyne et al. (2005)	Bone graft / rhBMP-2/ACS 0.75 mg/mL / rhBMP-2/ACS 1.5 mg/mL rhBMP-2: — / — / 2 Bovine collagen: 3 / 2 / 4	Bone graft / rhBMP-2/ACS 0.75 mg/mL / rhBMP-2/ACS 1.5 mg/mL Edema: 6 / — / — Facial edema: 5 / 7 / 14 Rash: 6 / 2 / 1
Fiorellini et al. (2005)	Antibody to rhBMP-2 and human type 1 collagen was not detected. Anti-bovine type I collagen antibodies present in 11 subjects – occurrence was not specified to experimental groups	Adverse event*: oral edema (75% subjects), mouth pain (68% subjects), and oral erythema (46% subjects) – occurrences were not specified by experimental groups.
Triplett et al. (2009)	Bone graft / rhBMP-2/ACS 1.5 mg/mL rhBMP-2: — / 2 Bovine collagen: 25 / 24	Undisclosed number of subjects receiving autogenous bone graft experienced pain, sensory loss, and gait disturbance. Sensory loss* was still present in 17% of subjects at 6 months postsurgery. Incidence of facial edema was higher among subjects receiving rhBMP-2/ACS than autogenous bone graft ($p = .048$)
Kao et al. (2012)	Not reported	No postsurgery complications

*Only percent of subjects with adverse events was provided.
rhBMP-2, recombinant human bone morphogenetic protein-2; ACS, absorbable collagen sponge.

in these case series or case reports were successfully rehabilitated; however, additional bone augmentation was necessary in some studies.[9,16] These clinical results validate preceding preclinical work demonstrating rhBMP-2/ACS *de novo* bone formation in the axial and appendicular skeleton.[20,21] For craniofacial indications, the bone inductive functionality of rhBMP-2/ACS has been evaluated in calvarial critical-size defects in rodents,[22,23] segmental mandibular defects in dogs[24] and nonhuman primates,[25] supraalveolar onlay defects in dogs,[26–28] peri-implantitis defects in nonhuman primates,[29] as well as for maxillary sinus augmentation using nonhuman primate[30] and minipig platforms.[31] Long-term evaluation of rhBMP-2/ACS-induced bone revealed an increase in bone density after functional loading.[12,13] Similar results have been shown in preceding studies following 12 months of functional loading using a dog model.[32]

Different rhBMP-2 concentrations (0.43, 0.75, and 1.5 mg/mL) providing a wide dose range were used in the clinical studies. Side-by-side comparisons for rhBMP-2 at 0.75 versus 1.5 mg/mL were available in two studies.[12,14] However, different total doses were used independent of concentration relative to indication, defect characteristics, and clinician intuition or experience complexing interpretation of the results. Although no marked differences were observed between rhBMP-2 at 0.75 and 1.5 mg/mL for maxillary sinus augmentation,[12] a dose-effect relationship was reported for extraction socket alveolar ridge augmentation.[14] In perspective, preclinical studies conducted in our laboratory clearly demonstrate an inverse dose-effect relationship indicating that above a yet unknown optimal dose, rhBMP-2 negatively influences bone formation and delays bone maturation.[33,34] These findings strongly call for research on dose optimization for effective treatments in clinical settings.

rhBMP-2/ACS has been proposed as an alternative to autogenous bone grafts and surrogate bone biomaterials. Two studies reported that the use of autogenous bone alone or in combination with bone biomaterials yielded greater bone formation than rhBMP-2/ACS for maxillary sinus augmentation.[12,13] These clinical observations contrast histological observations from a highly standardized preclinical study in the minipig concluding that "rhBMP-2/ACS induces bone of superior quality compared with an iliac crest particulate autogenous cancellous bone graft when used for maxillary sinus augmentation, and should perhaps be considered the new standard for this indication."[31] Moreover, harvesting bone from extraoral sites incurs a secondary major surgical procedure with associated risks and costs, whereas intraoral sources of autogenous bone are limited. Regardless of source, bone harvesting is associated with postsurgery pain, edema, nerve, and soft tissue injury.[35–37] Although new bone formation for autogenous bone exceeded that following rhBMP-2/ACS by 1.6 mm (weighted average) for maxillary sinus augmentation, final bone height (combined residual alveolar ridge and new bone) was frequently greater than 10 to 12 mm irrespective of the initial ridge height and protocol allowing implant placement. From a clinical perspective, these results indicate that implants could be placed into the augmented maxilla without major restrictions. In perspective, bone biomaterials have also been used as a surrogate to autogenous bone graft with mixed results for maxillary sinus augmentation[38] and extraction socket preservation.[39]

Safety is a major concern regarding the clinical use of biologics also including the use of rhBMP-2/ACS. Adverse effects related to on- and off-label rhBMP-2/ACS use for spine surgery have gained considerable attention.[40–42] In comparison, rhBMP-2/AC safety data for craniofacial indications are limited to that reported in mostly industry-sponsored studies. Frequent postsurgery events include transient oral and facial erythema, edema, sensory loss, and pain, some subjects experiencing significant facial swelling. rhBMP-2 antibody formation appears a rare event with most individuals exhibiting antibodies to bovine type I collagen used in the carrier.[12–14,18] In perspective, studies are needed to better assess rhBMP-2/ACS safety and efficacy to control/manage/preclude adverse events following application in craniofacial settings including alveolar ridge and maxillary sinus augmentation procedures. Also, such studies will likely focus on dose and delivery/release kinetics as well as alternative carrier technologies.

CONCLUSION

rhBMP-2/ACS appears a promising alternative to autogenous bone grafts for alveolar ridge/maxillary sinus augmentation; dose and carrier optimization may expand its efficacy, use, and clinical application.

CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

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