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SUPPLEMENT ARTICLE

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Cell therapy for orofacial bone regeneration: A systematic review and meta-analysis

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Abstract

Aim: The objective of the present review was to answer the focused question: what is the effect of cell therapy in terms of orofacial bone regeneration compared to grafting with only biomaterial scaffolds and/or autogenous bone?

Methods: Electronic databases were searched for relevant controlled clinical and pre-clinical (large-animal) studies. Separate meta-analyses of quantitative data regarding histological or radiographic new bone formation were performed.

Results: Forty-seven eligible clinical and 57 pre-clinical studies were included. Clinical studies were categorized based on the use of "minimally manipulated" whole tissues (e.g., bone marrow) or ex vivo expanded cells from "uncommitted" (bone marrow, adipose tissue) or "committed" sources (periosteum, bone). Based on limited and heterogeneous clinical evidence, implantation of cells (mostly whole bone marrow), in combination with biomaterial scaffolds results in bone regeneration which is (a) superior compared to implantation of scaffolds alone in sinus and horizontal ridge augmentation, and (b) comparable to autogenous bone in alveolar cleft repair.

Conclusions: Although current evidence points to the benefits of cell therapy in certain clinical indications, it is unclear whether the use of ex vivo expanded cells, either uncommitted or committed, is superior to whole tissue fractions in terms of bone regeneration. The relatively larger effect sizes in favour of cell therapy observed in pre-clinical studies are diminished in clinical trials. Future controlled studies should include cost-effectiveness analyses to guide clinical decision-making.

KEYWORDS

bone grafting, bone tissue engineering, cell therapy, mesenchymal stem cells, meta-analysis, systematic review

1 | INTRODUCTION

Reconstruction of oral and maxillofacial bone deficiencies is often a clinical challenge. Ridge remodelling following tooth loss is the most common cause for alveolar bone deficiencies in the horizontal and/or vertical dimensions (Chiapasco & Casentini, 2018; Rocchietta, Ferrantino, & Simion, 2018), and in the posterior edentulous maxilla, this is further complicated by pneumatization of the maxillary sinus(es) (Corbella, Weinstein, Francetti, Taschieri, & Del Fabbro, 2017; Danesh-Sani, Engebretson, & Janal, 2017). More challenging segmental defects, which include the inferior mandibular border, often result from trauma, tumour resection, or radiation-related osteonecrosis (Chanchareonsook, Junker, Jongpaiboonkit, & Jansen, 2014). Further, congenital anomalies are frequently associated with alveolar defects such as orofacial clefts involving the maxilla (Janssen, Weijs, Koole, Rosenberg, & Meijer, 2014).

Several regenerative surgical approaches have been proposed to prevent and/or reconstruct alveolar defects, most commonly,

alveolar ridge/socket preservation (SP) following dental extraction (Avila-Ortiz et al., 2016), vertical and horizontal ridge augmentation (RA) (Daugela, Cicciu, & Saulacic, 2016; Elnayef et al., 2017, 2018), maxillary sinus-floor augmentation (SA) (Danesh-Sani et al., 2017), and alveolar cleft (AC) repair in the palatal aspect of the maxilla (Wu et al., 2017). All of these techniques mainly involve the use of autogenous bone (AB) grafts and/or bone substitute materials, and often in combination with barrier membranes, that is the guided bone regeneration (GBR) principle (Elgali, Omar, Dahlin, & Thomsen, 2017); in the case of more advanced (e.g., segmental) defects, vascularized tissue flaps are used (Hayden, Mullin, & Patel, 2012). Although AB transplantation is still considered the gold standard, larger defects may require volumes of bone locally unavailable, leading to the need for harvesting from a second surgical site, usually involving general anaesthesia, hospitalization and significantly increased costs (Dahlin & Johansson, 2011). Thus, the morbidity associated with invasive AB harvesting and flap transfer, especially from a remote donor site, along with its unpredictable resorption rate, are major limiting factors (Nkenke & Neukam, 2014; Shanbhag, Shanbhag, & Stavropoulos, 2014). Alternatives have included a range of allogeneic, xenogeneic and alloplastic AB substitutes, but no consensus currently exists on the effectiveness of one material over the other, in comparison with AB, or for specific clinical indications (Al-Nawas & Schiegnitz, 2014; Milinkovic & Cordaro, 2014; Sanz-Sánchez, Ortiz-Vigón, Sanz-Martín, Figuero, & Sanz, 2015).

Adult or postnatal stem cells represent promising candidates for regenerative therapy, since they have the potential to replicate in an undifferentiated state as well as to differentiate along committed lineages. Although adult stem cells are utilised in the clinic since many decades as haematopoietic stem cell (HSC) therapy through bone marrow transplantation (Mohty, Richardson, McCarthy, & Attal, 2015), more recently, a multipotent population of mesenchymal stromal or "stem" cells (MSCs) was identified in the non-haematopoietic fraction of bone marrow (Friedenstein, Chailakhjan, & Lalykina, 1970). These MSCs have been defined by various characteristics, such as plastic adherence, self-renewal or colony forming unit (CFU)-potential, stromal phenotype and surface marker expression ($CD73^+CD90^+CD105^+CD34^-CD45^-HLA\text{-}DR^-$), and the ability to differentiate into at least three stromal lineages, that is bone, fat and cartilage (Dominici et al., 2006). In addition to their differentiation capacity, MSCs also exert paracrine or trophic effects, via secretion of soluble bioactive molecules, which "empower" host progenitor cells and modulate immune cells (and thereby the immune response), to promote regeneration (Wang, Chen, Cao, & Shi, 2014). In fact, recent observations point to trophic activity as the primary mechanism of MSC-mediated regeneration, rather than direct differentiation (Caplan, 2017; Haumer et al., 2018).

In this context, tissue engineering aims to combine and deliver the cellular (progenitor cells), extracellular (scaffolds) and/or molecular elements (growth factors) involved in physiological regenerative processes, for therapeutic applications. Specifically, regarding bone tissue engineering (BTE), this usually involves harvesting osteogenic cells from an autologous source (e.g., bone marrow, adipose tissue), their "chair-side" manipulation or ex vivo amplification, and combination with an appropriate biomaterial scaffold for in vivo implantation (Evans et al., 2007; Oryan, Kamali, Moshiri, & Baghaban Eslaminejad, 2017). Thus, the "triad" of *osteogenic* cells, *osteoinductive* signals (growth factors released by cells), and *osteoconductive* scaffolds, aims to replicate the properties of AB, and alleviate the need for invasive harvesting (Oppenheimer, Mesa, & Buchman, 2012). The cells can be harvested by minimally, and relatively less, invasive techniques (compared to AB harvesting) from various tissues, most commonly bone marrow and adipose tissues, under local anaesthesia, and without the need for hospitalization. Thus, BTE strategies are indeed emerging as promising alternatives to AB and/or biomaterial-based grafting, as demonstrated by several pre-clinical and some clinical studies (for reviews, see Janssen et al., 2014; Padial-Molina et al., 2015; Shanbhag et al., 2015; Shanbhag, Pandis, Mustafa, Nyengaard, & Stavropoulos, 2016, 2018; Miguita, Mantesso, Pannuti, & Deboni, 2017). Among these BTE strategies, three main interventions using cell therapies have been tested: (a) use of "minimally manipulated" whole tissue fractions; (b) use of more-than-minimally manipulated or ex vivo expanded *uncommitted* stem/progenitor cells; and (c) use of ex vivo expanded *committed* bone-derived cells.

Minimally manipulated whole tissue fractions have mainly included bone marrow aspirates—either whole (BMA) or concentrated (BMAC), adipose stromal vascular fraction (A-SVF), and tissue "micrografts." The rationale for using whole tissue fractions are (a) feasibility of a chair-side protocol, (b) minimum cell manipulation, (c) cost-effectiveness, and (d) delivery of a heterogeneous cell population. In addition to minimizing the time and costs associated with clinical-grade cell culture—which requires expensive Good Manufacturing Practice (GMP)–grade facilities, this approach generates a population of cells that is not comprised solely of MSCs, but also includes a number of other cell types with therapeutic potential, including HSCs, endothelial cells (ECs), and immune cells (monocytes, macrophages, etc.) (Fraser et al., 2014). This preserves the physiological microenvironment or "niche," with all cells in their natural ratios, including those which produce paracrine signals to induce host osteoprogenitors and MSCs (Jager et al., 2011).

Clinical relevance

Scientific rationale for study: Although cell therapy has shown the potential to enhance bone regeneration, there are several aspects regarding the source(s) of cells, their manipulation, mode of application, as well as the cost-benefit that need further elaboration.*Principal findings:* Cell therapy may enhance alveolar bone regeneration in specific clinical indications.*Practical implications:* Further clinical trials are needed before cell therapy can become a routine clinical procedure.

Bone marrow is known to contain a heterogeneous population of progenitor cells (including MSCs, HSCs, and endothelial progenitor cells), and supporting growth factors and cytokines (Chahla et al., 2016; Patterson et al., 2017). Concentration of the mononuclear cell fraction (MNC) of bone marrow (which includes MSCs) via density gradient centrifugation steps to remove red blood cells, granulocytes, immature myeloid precursors, and platelets, represents an attractive clinical strategy, since it is currently FDA-approved and shown to be efficacious as a point-of-care method of autologous cell delivery (Chahla et al., 2017; Jager et al., 2011). Moreover, since self-renewing, plastic-adherent MSCs represent only a small fraction (0.001%–0.01%) of MNC within the bone marrow, it may be hypothesized that a concentrate (BMAC) could increase the likelihood of attachment of these cells when loaded onto biomaterial scaffolds, and thereby ensure successful delivery to the defect site (El-Jawhari, Sanjurjo-Rodriguez, Jones, & Giannoudis, 2016).

An emerging and relatively less invasive alternative tissue source for minimally manipulated cell fractions is A-SVF, which, like bone marrow, contains a sub-population of adipose stem/stromal cells (ASCs) in addition to hematopoietic and ECs. Since the frequency of ASCs in A-SVF is reportedly much higher than that of BMSCs in BMA(C), the direct use of A-SVF, without culture-expansion, has been advocated (Fraser et al., 2014). However, although the use of minimally manipulated whole tissue fractions may be time- and cost-effective, the yield of progenitor cells obtained is relatively low. MSCs represent <1% of the MNC in BMA, and approximately 1.4% in A-SVF, based on CFU potential (Prins, Schulten, Ten Bruggenkate, Klein-Nulend, & Helder, 2016). This has encouraged ex vivo expansion strategies, which aim to exponentially increase the number of cells of a specific phenotype, that is *committed* or *uncommitted*, available for implantation, and thereby improve clinical outcomes (Petite et al., 2000).

The use of expanded *uncommitted* cells is based on the fact that MSCs, originally identified in bone marrow (BMSCs), are the most commonly reported cells in autologous regenerative therapies. MSCs have also been isolated from less invasive sources such as adipose tissue (ASCs), dental tissues and a range of adnexal gestational tissues, among others (Nancarrow-Lei, Mafi, Mafi, & Khan, 2017). Although MSCs from different tissue sources share biological characteristics, they have been reported to show functional differences in their properties, such as surface phenotype and differentiation potential (Al-Nbaheen et al., 2013). However, whether or not the tissue of origin regulates the epigenetics of MSCs and affects their subsequent in vivo differentiation potential remains to be determined in a comparative clinical study.

The use of expanded *committed* cells is based on obtaining as tissue source the alveolar bone itself—specifically, the periosteum and cancellous bone/marrow. The periosteum has been described as an osteoprogenitor cell-containing bone envelope with high regenerative potential (Hutmacher & Sittinger, 2003), while marrow-resident osteoblasts (OBs) are the fundamental cells of bone tissue involved in its formation, function, repair, and maintenance (Jayakumar & Di Silvio, 2010). Although multipotent MSC-like cells have been identified in both periosteum (Olbrich, Rieger, Reinert, & Alexander, 2012) and alveolar bone (Mason, Tarle, Osibin, Kinfu, & Kaigler, 2014), for the purpose of this review, cells obtained from these tissues were considered to be more osteogenically "committed" than those from other tissues (Akintoye et al., 2006; Pettersson, Kingham, Wiberg, & Kelk, 2017).

It was therefore the primary objective of the present review to systematically assess the literature to answer the focused question: in clinical studies, what is the effect of cell therapy in terms of orofacial bone regeneration compared to grafting with only biomaterial scaffolds and/or AB? Secondary objectives were (a) to assess the preclinical to clinical translation of cell therapy by comparing preclinical and clinical data, and (b) to determine which is the most suitable cell therapy approach for regenerating bone deficiencies.

2 | MATERIALS AND METHODS

Following Cochrane (Higgins & Green, 2011) and Preferred Reporting Items for Systematic Reviews guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009), an electronic literature search based on pre-defined inclusion criteria was performed in 3 repositories (PubMed, Embase and Cochrane library) up to May 2018 (Figure 1). Sampling of the clinical evidence was focused on controlled trials—either randomized (RCT) or non-randomized (CT). Uncontrolled studies (UT) and cases reports (with ≥3 patients) of cell-based BTE were also identified to capture possible relevant information regarding cell sources, delivery strategies, and adverse events, although data regarding bone regeneration from these studies were not considered for the meta-analyses. Sampling of pre-clinical data was limited to large-animal models and regards mainly an update of our previously published reviews (Shanbhag et al., 2016, 2018). These data were only included to compare with the clinical data, which is the focus of the present review. Quantitative data regarding histomorphometric or radiographic bone regeneration was included in meta-analyses. Separate analyses were performed for clinical (grouped by indication/defect-type and method of outcome evaluation) and pre-clinical studies (grouped by species and defect-type). Details of the review methodology are reported in the Appendix.

3 | RESULTS

3.1 | Summary of included studies

After screening, 47 controlled clinical studies were included, of which 22 were RCTs, mostly with a low to unclear risk of bias (Supporting Information Figure S8). Additionally, 30 UT and case series were identified (Supporting Information Tables S1–S3). A majority of the evidence was derived from studies of SA and horizontal RA (30 controlled studies). Additionally, studies of SP, AC and cranial defect (CD) repair, and reconstruction following fracture, cystectomy or tumour resection, were identified (Table 1). Most studies included a "split-mouth" design, utilized a

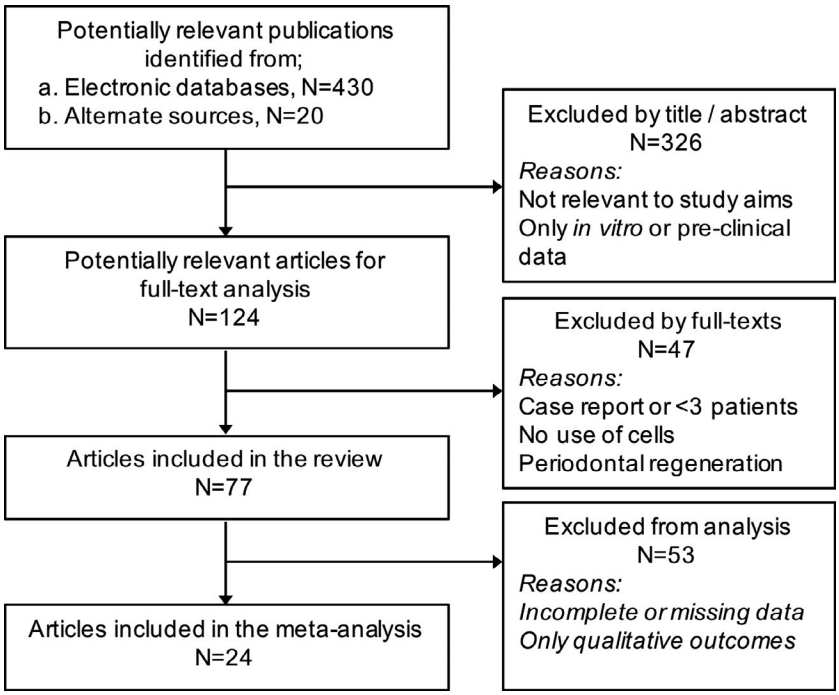

FIGURE 1 Flow chart for study inclusion (n = number of articles)

TABLE 1 Distribution of included clinical studies according to indications

Indication	Uncontrolled	Controlled
SA	7	25
RA	4	6
SA and/or RA (in the same patients or in different patients in the same study)	10	–
Ridge/SP	–	5
AC	3	7
CD	3	–
Other (fracture, cyst, tumour resection)	3	4
Total	30	47

SA: sinus augmentation; RA: ridge augmentation; SP: socket preservation; AC: alveolar cleft; CD: cranial defect.

GBR approach for augmentation, that is a membrane to cover the cell-scaffold construct, and reported the placement of implants in regenerated sites. Outcomes were assessed via in situ clinical examination and/or radiography [computed tomography (CT) or cone-beam CT (CBCT)], or via histological and/or micro-CT (μ-CT) assessments of biopsy specimens. The primary outcome measure was quantitative assessments of new bone formation (NBF) via histomorphometry or μ-CT of biopsies, or in situ CT-based assessments of "bone fill" (BF) within the treated defects.

Scaffolds used (xenogeneic and alloplastic) to deliver cells to the regeneration sites were: (a) *ceramic* scaffolds, such as deproteinized bovine bone mineral (DBBM), hydroxyl-apatite (HA), beta-tricalcium phosphate (β-TCP), biphasic HA/β-TCP (BCP) and freeze-dried bone allograft (FDBA); (b) *polymeric* scaffolds, such as collagen (COL) or gelatin sponges, platelet-rich/poor plasma (PRP/PPP) or fibrin (PRF), and polylactic–polyglycolic acid copolymer (PLGA); or (c) *composite* scaffolds, including various combinations of the above (Lee, Cuddihy, & Kotov, 2008).

Cell therapy approaches were categorized according to US Food and Drug Administration (FDA) guidelines on the use of Human Cells, Tissues, and cellular and tissue-based Products (HCT/P; Code of Federal Regulation Title 21-CFR-1271) and the European Medicines Agency (EMA) guidelines on the use Advanced Therapy Medicinal Products (ATMP; European Regulation 1394/2007), as: (1) "minimally manipulated" whole tissue fractions, usually involving a point-of-care or chair-side procedure, or (2) "more-than-minimally manipulated", that is ex vivo culture-expanded cells, further categorized (for the purpose of this review) as (a) uncommitted stem/progenitor cells, and (b) committed bone-derived cells (Supporting Information Figure S1). Summaries of the included clinical studies in each category are presented in Tables 2–4.

TABLE 2 Summary of controlled studies using whole tissue fractions

Study (design)	Site	Patients (sex, age)	Cell therapy group		Control group	Follow-up	Method	Outcome
			Cell source (culture)	Scaffold				
BMA or BMAC (n = 19)								
Wojtowicz et al., 2003; Wojtowicz, Chaberek, Urbanowska, & Ostrowski, 2007 (CC)	Cyst—max or man (15–21 mm)	17 (17M, 27–44 y)	Iliac BMA (*whole*, 1.4 ± 0.1 x10^8 MNC + 0.9 ± 0.1 × 10^6 CD34 + cells/transplant) *or* BMA (*Ficoll*, 0.6 ± 0.1 × 10^8 MNC + 1.9 ± 0.2 × 10^6 CD34 + cells/transplant)	DBBM (Bio-Oss®) + PRF/Col mem	PRP + DBBM + PRF/Col mem	3 m	Radio	PRP > BMA
Gimbel et al., 2007 (CC)	AC—uni	69 (6–12 y)	Iliac BMA (40 ml, passed through heparinized column)	Col sponge (Healos®)	Iliac AB (conventional *or* minimal invasive)	6w, 6 m, 2y	Clinical Patient-reported	+ (pain, cost T<C)
Sauerbier et al., 2010 (CT); *Duttenhoefer* et al., *2014*	SA (<3 mm) —uni/bi	11 (47–69 y)	Iliac BMAC (Harvest®, 3 ml)	DBBM (Bio-Oss®)	*BMA (Ficoll)* + DBBM	3 m 2.5 y	Histo IS	NS NS
Sauerbier et al., 2011 (RCT)	SA (<3 mm) —uni/bi	26 (38–68 y)	Iliac BMAC (Harvest®, 3 ml)	DBBM (Bio-Oss®)	DBBM + Man AB (70:30)	3–4 m	Histo	NS
Rickert et al., 2011 (RCT); *Rickert* et al., *2014*	SA (<4 mm) —bi	12 (48–69 y)	Iliac BMAC (Harvest®, 3 ml)	DBBM (Bio-Oss®)	DBBM + Man AB (70:30)	13–16 w 12 m	Histo IS	*S* C>T
Wildburger et al., 2014 (RCT), *Kuhl* et al., *2014*	SA (<3 mm) —bi	7 (47–72 y)	Iliac BMAC (Harvest®, 3 ml)	DBBM (Bio-Oss®)	DBBM only	3, 6 m 0.5, 6 m	Histo CT (V)	NS NS
Payer et al., 2014 (RCT), *Kuhl* et al., *2014*	SA (<3 mm) —bi	6 (3M, 43–70 y)	Tibial BMA (8 ml)	DBBM (Bio-Oss®)	DBBM only	3, 6 m 0.5, 6 m	Histo CT (V)	NS NS
Sununliganon (2013) (RCT)	SA (<5 mm) —uni/bi ± impl	4 (bi, 2F, 30–71 y); 9 (uni, 6M, 23–72 y)	Iliac BMAC (MarrowStim®, 3 ml)	BBM (Endobon®)	BBM only *or* Iliac AB	7 m 3, 6 m, 1, 2y	Histo (qual) μCT (BV/TV%)	NS NS
Bertolai et al., 2015 (RCT)	SA (<5 mm) —bi	20 (10M, 55.2 y)	Iliac BMAC (Regen®, 14–15 ml)	FDBA + PRP	FDBA only	3 m	Histo (qual)	T>C
Pasquali et al., 2015 (RCT)	SA (<4 mm) —bi	8 (~55y)	Iliac BMAC (Harvest®, 4 ml)	DBBM (Bio-Oss®)	DBBM only	6 m	Histo	*S*
De Oliveira et al., 2016 (RCT)	SA (<4 mm) —uni/bi	15 (12F, ~55y)	Iliac BMA—single *or* double centrifugation	DBBM (Bio-Oss®)	DBBM only	6 m	Histo	NS
Pelegrine, da Costa, Correa, & Marques, 2010 (RCT)	SP	13 (7M, 28–70 y)	Iliac BMA (4–5 ml)	None	Empty (clot)	6 m	Histo	NS
Da Costa, Pelegrine, Fagundes, Simoes Mde, & Taha, 2011 (RCT)	RA—ant max (hor; <5 mm)	10 (8F, 40–55 y)	Iliac BMAC (Harvest® 4 ml)	Allograft block	Allograft only	6 m	Histo	*S*
Pelegrine et al., 2016 (RCT)	RA—ant max (hor; <3 mm)	8 (~52y)	Iliac BMAC (Harvest® 4 ml)	EBM (Bio-Gen®)	EBM only	4 m 4, 8 m	Histo CBCT (BG)	NS

(Continues)

TABLE 2 (Continued)

Study (design)	Site	Patients (sex, age)	Cell therapy group		Control group	Follow-up	Method	Outcome
			Cell source (culture)	Scaffold				
Lavareda Correa et al., 2017 (RCT)	RA—ant max (hor; 2–4 mm)	10 (8F, 36–52 y)	Iliac BMAC (Harvest® 4 ml)	Allograft block + granules	Allograft only	6 m	Histo CBCT (BV, BD)	NS NS
Marx & Harrell, 2014 (RCT)	RA—man SD (6–8 cm)	40 (22M, 19–78 y)	Iliac BMA (10 ml; 15.5 × 10^6/ml TNC + 54 ± 38/ml CD34 +) *or* BMAC (Harvest® 10 ml; 98 × 10^6/ml TNC + 1000 ± 750/mL CD34 + cells)	Allograft + rhBMP-2/Col sponge	*BMA* + scaffold	6 m	Histo CT	*S* *S*
Talaat, Ghoneim, Salah, & Adly, 2018 (RCT)	Cyst—mand	20 (13M, 18–50 y)	Iliac BMAC (Harvest® 6–9 ml)	PRP + Col sponge	Empty defects	3, 6, 12 m	Panoramic	*S*
Du et al., 2017 (CT)	AC—uni	20 (12F, 8–28 y)	Iliac BMAC (TBD® 1 ml)	β-TCP (Bio-lu®)	Iliac AB	6, 12 m	CT (BV/TV%)	NS
Al-Ahmady et al., 2018 (RCT)	AC—uni	20 (12F, 8–18 y)	Iliac BMA (*Ficoll* 2 ml)	Col sponge-nHA + PRF	Iliac AB	6, 12 m	CBCT (grade)	T>C
Adipose SVF (n = 1)								
Prins et al., 2016 (CT); *Farre-Guasch* et al., *2018*	SA (4–8 mm) —uni/bi	10 (6F, 46–69 y)	Abdominal SVF (Celution®, 5 ml cell susp., mixed pop., 83% CD90 + , 67% CD34 +), 2 × 10^7 cells/2 g scaffold/SA (1.4 × 10^5 CFU-F/g)	β-TCP (Ceros®) or BCP (Bone Ceramic®)	β-TCP *or* BCP only	6 m 6 m 2.5y	Histo μCT IHC (CD34, SMA) IS	NS *S* NS 100%
Micrografts (n = 4)								
d'Aquino et al., 2009 (CT); *Giuliani* et al., *2013*	SP—bi	7	Dental pulp-derived (Rigenera®)	Col sponge (Gingistat®)	Col sponge only	3 m 36 m	Histo (qual) Histo	T>C *S*
Monti et al., (2016) (CT)	SP—bi	6 (4F, 22–60 y)	Dental pulp-derived (Rigenera®)		Col sponge only	45–70 days	Histo (qual)	T>C
D'Aquino et al. (2016) (CT)	SP (multi-rooted) —bi	35 (21F, 25–64 y)	Max periosteum-derived (Rigenera®)	Col sponge (Gingistat®)	Col sponge only	45–90 days	Clinical Histo (qual)	*S* T>C
Rodriguez et al. (2017) (CT)	SA—uni	24 (12F, 45–64 y)	Max periosteum-derived (Rigenera®)	PLGA/HA	PLGA/HA *or* DBBM (Bio-Oss®)	4 m	Histo	*S*

CT: controlled trial; RCT: randomized CT; CC: case–control; SA: sinus augmentation; RA: ridge augmentation/GBR; SP: socket preservation; AC: alveolar cleft; SD: segmental or continuity defects; CD: cranial defect; ORN: osteoradionecrosis; uni: unilateral; bi: bilateral; imp: simultaneous implant placement; man: mandible; max: maxilla; hor: horizontal; M: male; F: female; y: years; m: months; w: weeks; Histo: histomorphometry; Histo (qual): qualitative histology; IHC: immunohistochemistry; Radio: radiographic; CT: computed tomography; V: volume; μCT; micro-CT; BV/TV: bone volume/total volume; BG: bone gain; T: test group; C: control group; Comp: complications; IS: implant survival; +: favourable bone regeneration outcomes; BMA: bone marrow aspirate; BMAC: bone marrow aspirate concentrate; AB: autogenous bone; HA: hydroxyl-apatite; β-TCP: beta-tricalcium phosphate; BCP: biphasic calcium phosphate; BAG: bioactive glass; GAG: glycosaminoglycans; Col: collagen; DBBM: demineralized bovine bone mineral; ABB: anorganic bovine bone; Pep: PepGen; PRP: platelet-rich plasma; PRF: platelet-rich fibrin; rhBMP-2: recombinant human bone morphogenetic protein-2; FD: freeze-dried; PLA: polylactide; PLGA: polylactic-co-glycolic acid; *study/year in italics*: follow-up study reporting on the same patient sample; *S*: statistically significant differences between T and C groups; NS: no statistically significant differences between T and C groups.

Fifty-seven eligible pre-clinical in vivo studies in large-animal models [dogs, minipigs and small-ruminants (sheep and goats)] were also identified (Supporting Information Tables S4–S6). These studies represented SA, RA [in the form of critical size defects (CSD)], and AC models. The following section is focused on results of the meta-analyses. Details of the included clinical studies, along with relevant supporting literature, are presented in the discussion.

3.2 | Meta-analyses: Effect sizes of cell therapy

The clinical evidence is mostly based on randomized (SA, RA) and non-randomized controlled trials (AC repair). Twenty-six studies reporting quantitative outcomes of bone regeneration based on histomorphometry (NBF), μ-CT [regenerated bone volume/total volume (BV/TV)] or CT (BF) were included in separate meta-analyses. Pooled estimates of treatment effect [effect sizes (ES)] were calculated for the outcomes NBF, BV/TV and BF in SA/RA, SA and AC repair, respectively. For SA studies, sub-group analyses were performed according to the time of biopsy, that is at 3–4 months or 6 months after augmentation. Additionally, regression analyses were performed to evaluate the effect of time (</≥6 months) and types of cells used (whole tissue, uncommitted or committed) on bone regeneration. Overall, the clinical meta-analyses revealed:

a). in SA, significantly greater bone regeneration was observed after cell therapy in 1 meta-analysis of histomorphometric results (ES: 4.12% NBF, 6 studies, vs. scaffolds, 6 months) and in 1 meta-analysis of μ-CT results (ES: 4.76% BV/TV, 3 studies, vs. scaffolds, 4–7 months), while in 1 meta-analysis of histomorphometric results no benefit was observed (12 studies, vs. scaffolds, 3–4 months). Based on a meta-regression analysis of histomorphometric data from 15 studies, there were no differences between the various cell therapy strategies, that is whole tissues vs. expanded uncommitted cells vs. expanded committed cells, in terms of the amount of bone regeneration (Supporting Information Table S7).
b). in horizontal RA, significantly greater bone regeneration was observed after cell therapy in 1 meta-analysis of histomorphometric results (ES: 13.42% NBF, 3 studies, vs. scaffolds; 1 study, vs. scaffold + AB, 4–6 months).
c). in AC defects, 1 meta-analysis failed to show a benefit of cell therapy over AB, as evaluated with CT (3 studies, 6 months).

Overall, the clinical meta-analyses revealed moderate to high heterogeneity (I^2 70%–99%), and wide predictive intervals, often crossing the line of no effect (Table 5, Supporting Information Figures S2–S4).

A meta-analysis of 57 eligible preclinical studies was also performed to compare the preclinical and clinical evidence for cell therapy and thereby assess its translation. To allow comparison with clinical data, similar pooled estimates (ES) were calculated for histomorphometric NBF. Sub-group analyses according to species and observation times were performed; analysis according to cell types (whole tissue, uncommitted or committed) could not be performed due to insufficient numbers of studies/comparisons in each sub-group. Overall, the pre-clinical meta-analyses revealed:

a). in SA models, significantly greater bone regeneration was observed after cell therapy in dogs (ES: 10.21% NBF, 5 studies, vs. scaffolds, <6 months) and small-ruminants (ES: 11.11% NBF, 3 studies, vs. AB, 2–4 months).
b). in CSD models, significantly greater bone regeneration was observed after cell therapy in dogs (ES: 12.14/20.11% NBF, 12 studies, vs. scaffolds, 1–2/2–4 months and ES: 48.73%, 3 studies, vs. scaffolds, 12 months), pigs (ES: 14.84% NBF, 4 studies, vs. scaffolds, 2–3 months) and small-ruminants (25.78% NBF, 3 studies, vs. scaffolds, 3–5 months).
c). in AC defect models, no significant benefit of cell therapy over AB was observed in dogs (3 studies, 2–5 months).

Similar to clinical studies, the pre-clinical meta-analyses also revealed moderate to high heterogeneity (I^2 60%–99%) with wide predictive intervals (Table 5, Supporting Information Figures S5–S7). However, for all comparisons, larger ES were observed in the pre-clinical vs. clinical meta-analyses.

4 | DISCUSSION

The primary objective of the present review was to assess the current clinical evidence on the effectiveness of cell therapy for orofacial bone regeneration, compared to grafting with only biomaterial scaffolds and/or AB. Based on limited data from 26 (of 47 included) controlled studies, implantation of cells in combination with scaffolds seems to be (a) superior to implantation of scaffolds alone in SA (based on histological and μ-CT outcomes) and horizontal RA (based on histological outcomes), and (b) comparable to AB grafts in AC repair (based on CT outcomes). Although the meta-analyses revealed statistically significant outcomes for these comparisons, heterogeneity in the studies was high as evidenced by the wide prediction intervals (Table 5). While the current available evidence is insufficient to determine the best strategy in terms of cell–types and –sources (whole tissue, uncommitted or committed), a discussion around this topic seems to be clinically important and is presented herein.

4.1 | Use of minimally manipulated whole tissue fractions

A majority of included studies reported the use of minimally manipulated whole tissue fractions, particularly bone marrow—as either whole (BMA) or concentrated (BMAC) aspirates (Table 2, Supploring Information Table S1). In several studies, significantly greater NBF was observed when using autologous BMAC-loaded vs. cell-free scaffolds (most commonly DBBM) in SA and RA. While a majority of studies reported harvesting from the iliac crest, one study each reported harvesting from the femur (Ibanez, Agustina, Ibanez, & Ibanez, 2012) and tibia (Payer et al., 2014). Regarding the

TABLE 3 Summary of controlled studies using "uncommitted" culture-expanded cells

Study (design)	Site	Patients (sex, age)	Cell therapy group			Control group	Follow-up	Method	Outcome
			Cell source (culture)	Cell number	Scaffold				
BMSCs (n = 5)									
Hernandez Alfero et al. (2005) (RCT)	SA (3–13 mm) —bilat	5 (5F, 37–75 y)	Replicell® or Ixymyelocel-t® Iliac "TRCs" (IMDM + 10% FBS + 10% HS, 12–14 days)	7–20 × 10^7 cells/SA	DBBM (Bio-Oss®) + PPF	DBBM+ PPF	4 m	Histo CT	NS
Kaigler et al. (2015) (RCT)	SA (2–6.2 mm) —unilat	26 (10F, 26–66 y)	Replicell® or Ixymyelocel-t® Iliac "TRCs"	1.6–15 × 10^7 cells/SA	β-TCP (Cerasorb®)	β-TCP only	4 m	Histo µCT	*Unclear* NS overall
Kaigler et al. (2013) (RCT)	SP—unilat	24 (13F, 31–63 y)	Replicell® or Ixymyelocel-t® Iliac "TRCs"	1.5 × 10^7 cells/SP	Gelatin sponge (Gelfoam®)	Gelatin sponge only	6, 12 w	Histo µCT	NS *S 6w*, NS 12w
Bajestan et al. (2017) (RCT)	RA (hor; 2° to AC or trauma)	17 (12M, 18–54 y)	Replicell® or Ixymyelocel-t® Iliac "TRCs"	1.5–4.4 × 10^7 cells/cc (2–5 cc/pt)	β-TCP (Cerasorb®)	Man AB	4 m	Re-entry	NS Comp
Khalifa and Gomaa (2017) (CT)	AC	16 (7–12 y)	Iliac BMSCs (DMEM + 20% AS, pass. 3)	5 × 10^5 cells/scaffold	HA-Si (Nanobone®)	Man AB	3, 6 m	CT	*S*
ASCs (n = 5)									
Alekseeva, Kulakov et al. (2012) (CT)	SA (<5 mm) —uni/bilat	25 (29–60 y)	Abdominal ASCs (DMEM/F12 + 10% AS, osteo+ 7d)	5–7 × 10^6 cells/cm^3 scaffold	HA-Col/GAG + PRP	DBBM (Bio-Oss®) + PRP	4–6 m	Histo CBCT	T>C
Khojasteh and Sadeghi (2016) (CC)	RA—max/man (hor)	8 (5M, 25–60 y)	Buccal fat pad ASCs (DMEM + 10% AS, pass. 3–4)	10^6 cells/scaffold	Iliac AB + FDBA granules	Iliac AB + FDBA only	5 m	Histo CBCT	T>C NS
Khojasteh et al. (2017) (CT)	AC—uni	10 (3F, 8–14 y + 4 adults)	Buccal fat pad ASCs (DMEM + 10% AS, pass. 3–4)	10^6 cells/scaffold	Man AB + BBM (Cerabone®) *or* Iliac AB + BBM, + Col mem	Iliac AB + Col mem	6 m	CBCT Histo (n=2)	NS
Soliman, Ismail, Shouman, Bahaaeldin, and El-Hadidy (2018) (CC)	AC—uni/bi	24 (15M, 7–27 y)	Abdominal ASCs (DMEM + 10%–13% FBS)	3 × 10^6 cells/ml	Allograft *or* iliac AB	Iliac AB only	6 m	Radio	NS
Castillo-Cardiel et al. (2017) (RCT)	Man condyle fractures	20 (~29–31 y)	Abdominal ASCs (DMEM + 10% FBS, 24 h)	NR	Open reduction	Open reduction	4, 12 w	CT (BD)	*S*

CT: controlled trial; RCT: randomized CT; CC: case–control; SA: sinus augmentation; RA: ridge augmentation/GBR; SP: socket preservation; AC: alveolar cleft; SD: segmental or continuity defects; CD: cranial defect; ORN: osteoradionecrosis; uni: unilateral; bi: bilateral; imp: simultaneous implant placement; man: mandible; max: maxilla; hor: horizontal; M: male; F: female; y: years; m: months; w: weeks; Histo: histomorphometry; Histo (qual): qualitative histology; IHC: immunohistochemistry; Radio: radiographic; CT: computed tomography; µCT; micro-CT; V: volume; BV/TV: bone volume/total volume; BG: bone gain; T: test group; C: control group; Comp: complications; IS: implant survival; +: favourable bone regeneration outcomes; BMSC: bone marrow MSC; ASC: adipose tissue-derived MSC; TRCs: tissue repair cells; FBS: foetal bovine serum; HS: horse serum; AS: autologous serum; osteo+: osteogenic induction; pass.: passage; AB: autogenous bone; HA: hydroxyl-apatite; Si: silica; β-TCP: beta-tricalcium phosphate; BCP: biphasic calcium phosphate; BAG: bioactive glass; GAG: glycosaminoglycans; Col: collagen; DBBM: demineralized bovine bone mineral; ABB: anorganic bovine bone; Pep: PepGen; PRP: platelet-rich plasma; PRF: platelet-rich fibrin; *S*: statistically significant differences between T and C groups; NS: no statistically significant differences between T and C groups.

TABLE 4 Summary of controlled studies using "committed" culture-expanded cells

Study (design)	Site	Patients (sex, age)	Cell therapy group			Control group	Follow-up	Method	Outcome
			Cell source (culture)	Cell number	Scaffold				
POCs (n = 6)									
Springer et al. (2006) (CC)	SA—uni/bilat	8 (4F, 43–65 y)	Man POCs (aMEM + 20% AS, osteo+, 21d)	6×10^6 cells/scaffold + 1 w culture	Col fleece (Lyostypt®)	DBBM (Bio-Oss®)	6–8 m	Histo (qual) Radio	*S*
Zizelmann et al. (2007) (CT)	SA (<5 mm) —uni/bilat ± impl	20	Man POCs (Bioseed-Oralbone®, DMEM/F12 + 10% AS, pass. 3–4, osteo+, 6w, +fibrinogen)	1.5×10^6 cells/disc + 6–9 days culture	PLGA (Ethisorb®) discs	Iliac AB	3 m	CT (V-loss%)	T 90%, C 29%
Voss et al. (2010) (CC)	SA (class 4,5) —uni/bilat ± impl	35 (21F, 35–69 y) (41C pts 38–73 y)	Man POCs (Bioseed-Oralbone®)	1.5×10^6 cells/disc + 6–9 days culture	PLGA (Ethisorb®) discs	Iliac AB	15 w	Histo (qual)	Comp T > C
Mangano et al. (2009) (CT)	SA (2–10 mm) —bilat	5 (3F, 45–64 y)	Man POCs (Bioseed-Oralbone®)	1.5×10^6 cells/disc + 6–9 days culture	PLGA (Ethisorb®) discs	CaP (Coral)	6 m	Histo CT (BD)	C > T C > T
Nagata et al. (2012) (CC)	SA (<2 mm) —uni/bi (n = 15) or RA (hor + ver; n = 14)	25[a] (+15C pts) (13F, 18–76 y)	Man POC sheet (M199 + 10% FBS + AA, 6w)	NR	Man AB + PRP	Man AB + PRP	4 m 3, 12 m	IHC CT (V)	*S* NS
Ogawa et al. (2016) (CC)	SA (<2 mm) —uni/bilat	23[a] (+15C pts) (10M, 40–70 y)	Man POC sheet	NR	Man AB + PRP	Man AB + PRP	4, 12 m	CT (V%)	NS
OBs (n = 6)									
Pradel et al. (2006) (CC)	Man cysts	8 (7M, 8–16 y)	Max/man OBs (Exp, DMEM + 10% AS, osteo+, pass. 2, 8–12w)	5×10^5 cells/scaffold	DBBM (Osteovit®)	Iliac AB	3, 6, 12 m	Radio (BD)	NS
Pradel and Lauer (2012) (CC)	AC—uni/bi	20 (15M, 16–72 y)	Max/man OBs	5×10^5 cells/scaffold	DBBM (Osteovit®)	Iliac AB	6 m	CBCT (%fill)	T 40.9%, C 36.6%
Pradel, Mai, Manolo Hagedorn, Lauer, and Allegrini (2008) (CC)	SA (mod-sev) —uni/bi	6 (6F, 38–52 y)	Max/man OBs	5×10^5 cells/scaffold	DBBM (Osteovit®)	OBs + S-BBM (Tutobon®)	5 m	Histo (qual)	S-BBM>BBM
Gonshor et al. (2011) (RCT)	SA (<6 mm) —uni/bilat	18 (12F, 42–79 y)	Cellular allograft (Osteocel®)	$>5 \times 10^4$ cells/cm^3	Allograft	Allograft only	3–4 m	Histo	*S*
Springer et al. (2006) (CC)	SA—uni/bilat	5 (4F, 43–65 y)	Max tuberosity OBs (Exp, DMEM + 20% AS)	3.3×10^6 cells/cm^2 scaffold (+40 days cult)	DBBM (Bio-Oss®)	DBBM only	6–8 m	Histo (qual) Radio	*S*
Hermund, Stavropoulos, (2012), *Hermund et al., (2013)* (RCT)	SA (<3 mm)—uni	20 (11F, ~58–60 y)	Max tuberosity OBs (Exp, DMEM/F12 + 20% FBS + AA, 10% AS 1w, 1 m)	2×10^6 cells/ml	DBBM (Bio-Oss®) + Max AB (1:1)	DBBM + Max AB (1:1)	4 m	Histo *IS*	NS NS

CT: controlled trial; RCT: randomized CT; CC: case–control; SA: sinus augmentation; RA: ridge augmentation/GBR; SP: socket preservation; AC: alveolar cleft; SD: segmental or continuity defects; CD: cranial defect; ORN: osteoradionecrosis; uni: unilateral; bi: bilateral; imp: simultaneous implant placement; man: mandible; max: maxilla; hor: horizontal; ver: vertical; mod-sev: moderate-severe; M: male; F: female; y: years; m: months; w: weeks; Histo: histomorphometry; Histo (qual): qualitative histology; IHC: immunohistochemistry; Radio: radiographic; CT: computed tomography; V: volume; BD: bone density; T: test group; C: control group; Comp: complications; IS: implant survival; +: favourable bone regeneration outcomes; POCs: periosteal cells; OBs: osteoblasts; Exp: explant culture; FBS: foetal bovine serum; HS: horse serum; AS: autologous serum; osteo+: osteogenic induction; pass.: passage; AB: autogenous bone; HA: hydroxyl-apatite; Si: silica; β-TCP: beta-tricalcium phosphate; BCP: biphasic calcium phosphate; BAG: bioactive glass; GAG: glycosaminoglycans; Col: collagen; DBBM: demineralized bovine bone mineral; ABB: anorganic bovine bone; Pep: PepGen; PRP: platelet-rich plasma; PRF: platelet-rich fibrin; *S*: statistically significant differences between T and C groups; NS: no statistically significant differences between T and C groups; a: overlapping patient samples.

TABLE 5 Comparison of cell therapy effect sizes in preclinical and clinical meta-analyses

	Preclinical					Clinical				
	Category	*n*	ES	95% CI	PI	Category	*n*	ES	95% CI	PI
Sinus augmentation										
Dogs	vs. Scaffolds (<6 m)	5	10.21	4.00, 16.42	−12.17, 32.59	vs. Scaffolds (6 m)	6	4.12	0.25, 7.98	−7.42, 15.65
Sheep/goats	vs. AB (2–4 m)	3	11.11	5.33, 16.90	−13.37, 35.60	vs. Scaffolds[b] (4–7 m)	3	4.76	2.80, 6.71	0.47, 9.04
Pigs, sheep/goats	vs. Scaffolds (2–4 m)	2, 5	NS	–	–	vs. Scaffolds (3–4 m)	12	NS	–	–
Ridge augmentation (CSD[a])										
Dogs	vs. Scaffolds (1–2 m)	5	12.14	6.16, 18.11	−8.73, 33	vs. Scaffolds (4–6 m)	4	13.42	7.75, 19.09	−2.09, 28.93
Dogs	vs. Scaffolds (2–4 m)	9	20.11	11.65, 28.56	−15.17, 55.39					
Dogs	vs. Scaffolds (12 m)	3	48.73	43.87, 53.60	17.20, 80.26					
Pigs	vs. Scaffolds (2–3 m)	4	14.84	9.66, 20.01	−2.50, 32.19					
Sheep	vs. Scaffolds (3–5 m)	3	25.78	18.55, 33.01	−52.77, 104.32					
Dogs	vs. AB (12 m)	3	NS	–	–					
Alveolar cleft repair										
Dogs	vs. AB (2–5 m)	3	NS	–	–	vs. AB (6 m)	3	NS	–	–

Numbers indicate Effect Sizes (ES), 95% Confidence Intervals (CI) and estimated Prediction Intervals (PI); n: number of studies; NS: non-significant effects; AB: autogenous bone; m: months; CSD: critical size defects

[a]In preclinical studies; all comparisons are based on histomorphometric outcomes, except [b]Based on micro-CT.

morbidity associated with BMA harvesting, lower donor site morbidity and donor site pain-intensity and -frequency were reported in patients treated with BMA/scaffolds vs. iliac AB grafting for AC repair (Gimbel et al., 2007). In one RCT of mandibular segmental defect-repair (Marx & Harrell, 2014), significantly greater NBF was observed when using BMAC—containing a higher fraction of $CD34^+$ cells (1012 ± 752 cells/ml) compared to un-concentrated BMA (54 ± 38 cells/ml), although both groups had similar concentrations of $CD90^+CD105^+$ MSCs (15×10^6 cells/ml) and were delivered in combination with rhBMP-2-loaded COL and allograft scaffolds. Interestingly, the NBF was higher when BMAC (67% ± 13%), but not BMA (36% ± 10%), was added to the constructs compared to only rhBMP-2 (+PRP; 59% ± 12%) or AB (54% ± 10%), as reported by the group in a previous study (Marx, Armentano, Olavarria, & Samaniego, 2013). The authors highlighted an important complimentary role of $CD34^+$ HSCs in MSC-mediated bone regeneration, and the benefits of implanting heterogeneous cell populations at regeneration sites (Marx & Harrell, 2014).

One controlled trial (Prins et al., 2016) reported the application of autologous A-SVF for SA via enzymatic digestion of abdominal adipose tissues using a chair-side isolation system (Celution®, Cytori Therapeutics, San Diego, CA, USA). Significantly greater NBF was observed in six patients treated with A-SVF-loaded vs. cell-free β-TCP or BCP scaffolds after 6 months—most markedly in the "cranial" portion of the augmentation sites distant from the native residual ridge (Prins et al., 2016). Interestingly, subsequent immunohistochemical analyses of biopsy specimens also revealed a higher quantity and quality/maturity of blood vessels in the areas of active bone formation (Farre-Guasch et al., 2018). Similar results were observed in a phase I clinical study of orthopaedic fracture treatment with A-SVF (Saxer et al., 2016). Indeed, previous studies have demonstrated the angiogenic and vasculogenic potential of A-SVF, attributed to the

presence of ECs and perivascular cells (Jin, Chae, Son, & Kim, 2017; Zakhari, Zabonick, Gettler, & Williams, 2018). However, whether the in vivo bone-forming potential of A-SVF may be enhanced by prior osteogenic stimulation, remains to be clinically determined (Scherberich, Muller, Schafer, Banfi, & Martin, 2010). Nevertheless, the expected surge in clinical use of A-SVF may be hampered by recent US and European guidelines, which seek to classify A-SVF as "more-than-minimally manipulated" cells (Raposio & Ciliberti, 2017).

One research group has reported the use of a proprietary chairside mechanical tissue disaggregation system (Rigenera®, Human Brain Wave srl, Turin, Italy) to isolate cell fractions termed "autologous micrografts" from dental pulp (d'Aquino et al., 2009; Monti et al. 2016) and periosteal tissues (D'Aquino et al., 2016; Rodriguez et al., 2017). Significantly greater histological and/or radiographic bone regeneration was observed with dental pulp or periosteum micrograft-loaded versus cell-free scaffolds in SP and SA. The protocol involves simultaneous mechanical disaggregation (using a micro-blade grid) of a small tissue sample and filtering of the solution through a 50-μm strain, to yield a suspension of "side population" progenitor cells, which is then loaded onto a biomaterial prior to implantation. Characterization of this "side population" following in vitro culture revealed a heterogeneous population including MSC-like cells ($CD73^+CD90^+CD105^+CD45^-CD14^-$) with multi-lineage differentiation potential (Trovato et al., 2015).

Although the use of minimally manipulated whole tissue fractions is time- and cost-effective, the yield of progenitor cells obtained is relatively low. MSCs represent <1% of the MNC in BMA, and approximately 1.4% in A-SVF, based on CFU potential (Prins et al., 2016). This has encouraged ex vivo expansion strategies, which aim to exponentially increase the number of cells of a specific phenotype, that is *committed* or *uncommitted*, available for implantation, and thereby improve clinical outcomes.

4.2 | Use of expanded uncommitted cells

Ten controlled (and 18 uncontrolled) studies reported the implantation of autologous MSCs from bone marrow or adipose tissues (Table 3, Supporting Information Table S2). Culture-expanded BMSCs were used in SA (Hernandez Alfero et al., 2005; Kaigler et al., 2013, 2015), RA (Bajestan et al., 2017) or AC repair (Khalifa & Gomaa, 2017). Of these, the former four studies reported the use of a commercial automated bioreactor system (Replicell® or Ixymyelocel-t®, Aastrom Biosciences Inc., Ann Arbor, MI, USA) for isolation of a mixed population of $CD90^+$ MSCs, HSCs, endothelial and inflammatory cells, termed "tissue repair cells" (TRCs), from the MNC-fraction of bone marrow (Bartel et al., 2012). TRCs were obtained via a single-step process following a 12–14 day-expansion period in a "single-pass perfusion" bioreactor, in which, unlike typical MSC cultures, the non-adherent (i.e., hematopoietic, endothelial and inflammatory) cell fractions were retained and the adherent cells were not passaged. The authors hypothesize that these accessory cells may serve to enhance tissue regeneration by promoting vascularization and modulating the inflammatory response in the regenerating tissues (Dennis et al., 2007). However, no significant differences in NBF were observed when comparing TRC-scaffold constructs with scaffolds alone (Hernandez Alfero et al., 2005; Kaigler et al., 2013, 2015) or AB (Bajestan et al., 2017).

One strategy to enhance the regenerative efficacy of MSCs is via osteogenic induction and pre-differentiation (Oryan et al., 2017). In the present review, the evidence for osteogenic pre-differentiation of BMSCs prior to clinical application was conflicting. Among the UT, one group reported the application of osteogenically pre-induced MSCs seeded on HA scaffolds for RA/SA. The authors reported successful bone regeneration, suggestive of "osteogenesis" by the implanted cells, in only one of six patients (Meijer, de Bruijn, Koole, & van Blitterswijk, 2008). Two other groups reported favourable bone regeneration in RA (Wojtowicz, Jodko, Perek, & Popowski, 2014; Wojtowicz et al., 2013), AC (Chai et al., 2006) and CD repair (Chai, Zhang, Liu, Cui, & Cao, 2003) when using osteogenically pre-differentiated cells. Conversely, another group has reported extensively on the application of autologous non-induced BMSCs mixed with PRP, termed "injectable tissue engineered bone" for successful SA and RA (Ueda, Yamada, Kagami, & Hibi, 2008; Ueda, Yamada, Ozawa, & Okazaki, 2005; Yamada et al., 2008; Yamada, Nakamura, Ito, et al., 2013; Yamada, Nakamura, Ueda, & Ito, 2013). Other studies also reported favourable outcomes when using non-induced BMSCs seeded on BCP scaffolds for SA (Shayesteh et al., 2008) and AC repair (Behnia, Khojasteh, Soleimani, Tehranchi, & Atashi, 2012). Moreover, one recent controlled study reported superior bone regeneration following AC repair with non-induced BMSC-loaded HA scaffolds, compared to the gold standard, that is AB grafts (Khalifa & Nowair, 2017). Nevertheless, since the current pre-clinical evidence from large-animal models is also conflicting (Adamzyk et al., 2016; Corbella et al., 2017), no clear conclusions can be drawn regarding the benefits of osteogenic pre-differentiation of MSCs.

A majority of the included studies (and all studies in the meta-analysis) of cell therapy for RA reported augmentation in the horizontal dimension, as a treatment for "narrow ridges." It is well accepted that different types of ridge deficiencies, that is horizontal, vertical and segmental (in ascending order of complexity), have different regenerative potentials, and thus, may require different treatment strategies (Esposito et al., 2009). In context, a recent phase I feasibility study reported the use of autologous BMSCs to regenerate deficient ridges in the posterior mandible (Gjerde et al., 2018). Regeneration in the atrophic posterior mandible is reported to be especially challenging due to difficulties in achieving optimal flap closure and graft stabilization, and the local microarchitecture of dense cortical bone with limited vascularity (Elnayef et al., 2017). Nevertheless, successful regeneration in both horizontal and vertical dimensions was reported in 11 patients treated with BMSC-loaded BCP scaffolds contained by a titanium-reinforced membrane (Gjerde et al., 2018). A similar strategy was successfully applied in the treatment of orthopaedic non-unions in a recent multicenter trial (Gómez-Barrena et al., 2018). Both studies included a highly standardized laboratory protocol for cell manufacturing and provide examples of successful regeneration in challenging bone deficiencies.

In the case of mandibular defects (Gjerde et al., 2018), the authors also reported an unexpected additional benefit on soft tissue healing, that is increased keratinized mucosa, at the augmented sites, attributed to the well-documented paracrine effects of MSCs (Vizoso, Eiro, Cid, Schneider, & Perez-Fernandez, 2017). Interestingly, this was the only study in which ex vivo MSC-expansion was performed using human platelet lysate (HPL)—an emerging alternative to animal- and human-derived serum supplements for cell culture (Shanbhag, Stavropoulos, Suliman, Hervig, & Mustafa, 2017). A majority of the included studies reported the use of autologous or animal-derived serum [foetal bovine serum (FBS)] for cell expansion. Several advantages of HPL over FBS and human serum have been documented, owing largely to the wide range of growth factors released by platelets, which can enhance the osteogenic potential and paracrine efficacy of MSCs (Shanbhag et al., 2017). Indeed, the authors of the present study acknowledged that expansion in HPL may have resulted in osteogenic "pre-conditioning" of the BMSCs, leading to bone formation, and the observed paracrine effects on soft tissues (Gjerde et al., 2018).

In the context of MSCs paracrine effects, it is relevant to mention the emerging "cell-free" strategies, which exploit the secretome or "conditioned media" from MSCs, that is the secreted bioactive molecules including extracellular vesicles, to promote regeneration (Vizoso et al., 2017). This concept is based on observations that a very small fraction of implanted MSCs survives long enough in vivo to differentiate, suggesting that MSCs mainly exert their regenerative effects via paracrine mechanisms (Haumer et al., 2018). Following promising pre-clinical results, one group has recently reported the clinical application of allogeneic MSCs conditioned medium, in combination with β-TCP or COL sponge scaffolds, for bone regeneration in SA, RA and SP, in nine patients with favourable outcomes and no adverse events (Katagiri, Osugi, Kawai, & Hibi, 2016; Katagiri et al., 2017). The safety and efficacy of allogeneic MSCs secretome (lyophilised) as an "off-the-shelf" therapy for bone regeneration should be investigated in future clinical trials.

As previously discussed, abdominal adipose tissue represents a promising alternative to iliac bone marrow, since; (a) it is relatively less invasive to harvest, and (b) the average yield of MSC-like cells are reportedly greater compared to bone marrow (Bajek et al., 2016; Qadan et al., 2018). However, previous studies have suggested a lower intrinsic osteogenic potential of ASCs versus BMSCs in vitro and in vivo (Brennan et al., 2017; Liao & Chen, 2014). Moreover, the in vivo bone-forming potential of ASCs has been demonstrated only when pre-cultured in the presence of additional osteogenic stimulating factors (Scherberich et al., 2010). In this context, one research group reported the use of osteogenically pre-induced ASCs together with HA-COL scaffolds and PRP for treatment of various alveolar defects (Alekseeva, Kulakov, Gol'dshteĭn, & Kulakov, 2012; Alekseeva, Rachinskaia, Volkov, Kulakov, & Gol'dshteĭn, 2012; Alekseeva, Volkov, Kulakov, & Gol'dshteĭn, 2012; Kulakov et al., 2008) . In one controlled study of SA, the authors reported greater histological NBF with the ASC-constructs compared to DBBM alone (Alexeeva et al., 2012). Another research group reported the use of non-induced autologous ASCs and ceramic scaffolds, with or without additional recombinant human bone morphogenetic protein-2 (rhBMP-2) to treat challenging segmental mandibular (Sandor et al., 2014; Wolff et al., 2013) or CDs (Thesleff et al., 2011, 2017), respectively. While uneventful healing and successful reconstruction ("bridging") of segmental defects was reported in three patients treated with ASCs *with* rhBMP-2 (average follow-up of 35 months), late complications (6–7 years post-operative) such as infection and partial or total graft resorption were observed in the cranial reconstructions of 4/5 patients receiving ASCs *without* rhBMP-2. The authors attributed the compromised results to large defect sizes, rapid resorption of the ceramic scaffolds, and possibly the lack of osteoinductive signals in the form of rhBMP-2. In context, a recent study demonstrated enhanced osteogenic differentiation of cells from "whole adipose tissue" stimulated by rhBMP-2 compared to stimulation by osteogenic medium alone (Bondarava et al., 2017).

An alternative source of ASCs identified in the present review was the intra-oral buccal fat pad (BFP). Similar to abdominal adipose tissue, BFP is reported to harbour a SVF with a sub-population of ASCs with osteogenic differentiation potential (Farre-Guasch et al., 2018), which can be enhanced by additional stimulation with rhBMP-2 (Shiraishi, Sumita, Wakamastu, Nagai, & Asahina, 2012). Moreover, BFP shows limited donor-variation in size and is independent of body weight and fat distribution, thereby making it an attractive source of ASCs for orofacial BTE (Salehi-Nik & Rezai Rad, 2017). In the present review, one research group reported RA (Khojasteh & Sadeghi, 2016) and AC repair (Khojasteh et al., 2017) using autologous BFP-ASCs compared to AB. Superior NBF was observed in both studies when AB scaffolds were supplemented with BFP-ASCs compared the gold standard of AB grafts alone (Khojasteh & Sadeghi, 2016; Khojasteh et al., 2017).

One completed single-arm trial has reported the use of autologous dental pulp stem cells (DPSCs) to treat unilateral AC defects in five 7–12-year-old patients (Bueno, 2015). A sub-population of multipotent progenitor cells has been identified in the dental pulp of both permanent (DPSCs) and deciduous teeth [stem cells from human exfoliated deciduous teeth (SHED)] (Ducret et al., 2015). The proposed benefits of DPSCs and SHED include the ease of accessibility from unerupted third molars or exfoliated deciduous teeth, respectively, and their high proliferation and osteogenic differentiation potential, both in vitro and in vivo (Leyendecker Junior, Gomes Pinheiro, Lazzaretti Fernandes, & Franco Bueno, 2018; Nakajima et al., 2018). In particular, SHED might represent a promising strategy for AC repair, since patients are usually treated with secondary bone grafts, most frequently iliac AB, between 6 and 11 years of age (Kang, 2017; Pinheiro, de Pinho, Aranha, Fregnani, & Bueno, 2018). In the included study, a substantial amount of regeneration (89% BF) was observed in AC defects, 6 months after treatment with autologous SHED-loaded DBBM scaffolds (Bueno, 2015). However, whether DPSCs and SHED represent a feasible alternative to the gold standard (AB grafts) in AC repair remains to be determined.

4.3 | Use of expanded committed cells

The rationale for using committed cells is to circumvent the possible limitation of differences in degrees of osteogenic potential found in heterogeneous cell populations, for example bone marrow and adipose tissues. However, these cells may not possess self-renewal capacity and multipotency to the same extent as MSCs (Akintoye et al., 2006; Pettersson et al., 2017). Nine studies (six controlled) reported the use of ex vivo expanded periosteal cells (POCs) for SA (Table 4, Supporitng Information Table S3). Six studies reported the use of a commercial POC-seeded bone graft (BioSeed–Oralbone®, Biotissue Technologies, Freiburg, Germany) with conflicting results. The graft consists of autologous ex vivo expanded POCs seeded on PLGA scaffolds and osteogenically induced for 1 week. While promising results were observed in preliminary reports (Beaumont, Schmidt, Tatakis, & Zafiropoulos, 2008; Trautvetter, Kaps, Schmelzeisen, Sauerbier, & Sittinger, 2011), other studies frequently reported complications and/or graft failure, especially when extensive sinus grafting was performed, that is in patients with the most compromised residual ridges (Mangano et al., 2009; Schimming & Schmelzeisen, 2004; Voss et al., 2010; Zizelmann et al., 2007). In three controlled studies, inferior outcomes of the POC-autograft were observed in comparison to ceramic scaffolds (Mangano et al., 2009) or AB (Voss et al., 2010; Zizelmann et al., 2007). The authors attributed the compromised outcomes to (a) poor vascularization of the constructs upon implantation in vivo, and (b) the degradation profile of the PLGA scaffolds, which creates an acidic local microenvironment unconducive to cell survival and function (Liu, Slamovich, & Webster, 2006). In contrast, when a similar strategy for ex vivo expansion and pre-differentiation of POCs was used in combination with collagen scaffolds, based on preliminary in vitro screening (Petrovic, Schlegel, Schultze-Mosgau, & Wiltfang, 2006), superior bone regeneration was observed after SA in comparison to cell-free NBBM scaffolds (Springer et al., 2006).

One group reported the use periosteal "cell-sheets" formed by ex vivo expanded POCs, in combination with AB and PRP for SA and RA (Nagata et al., 2012; Ogawa et al., 2016). The cell sheet technique is based on implantation of cells grown as single or multiple layers together with their secreted extracellular matrix (ECM), as opposed to conventional single-cell suspensions. Proposed advantages of this technique include preservation of the cell-to-cell connections and ECM components along with a high cell-seeding efficacy (Yorukoglu, Kiter, Akkaya, Satiroglu-Tufan, & Tufan, 2017). Superior NBF after 4 months and comparable volumetric stability of augmented sites after 6–12 months were observed in the POC-seeded AB (+PRP) grafts compared to conventional AB (+PRP) grafts (Nagata et al., 2012; Ogawa et al., 2016). The authors suggested that inclusion of POCs in tissue-engineered constructs could reduce the volume of AB needed by up to 40%, thereby reducing donor site morbidity (Nagata et al., 2012). However, whether POC sheets used in combination with a biomaterial could entirely eliminate the need for AB harvesting remains to be determined.

Six studies reported the use of autologous OBs for SA, RA or AC repair (Table 4). As previously stated, OBs are the fundamental cells involved in the function, repair, and maintenance of bone (Jayakumar & Di Silvio, 2010). In the present review, OBs were isolated via enzymatic digestion or explant culture of intra-oral bone biopsies and usually cultured in osteogenic induction medium. The observed pre-clinical benefits of autologous OB-seeded DBBM scaffolds were favourably translated in an early patient case series (Fuerst et al., 2009). In three controlled studies, comparable bone regeneration in SA and RA was observed with autologous ex vivo expanded OB-seeded DBBM scaffolds versus cell-free DBBM scaffolds (Springer et al., 2006), AB (Pradel, Eckelt, & Lauer, 2006), or their 50–50 combination (Hermund, Donatsky, Nielsen, Clausen, and Holmstrup, 2012). Interestingly, one study reported comparable bone regeneration in SA using POC-seeded collagen and OB-seeded DBBM scaffolds (both superior to cell-free scaffolds), suggesting a comparable degree of osteogenic commitment in the two cell types (Springer et al., 2006). In one study, superior BF was observed when using autologous OB-seeded DBBM scaffolds versus the gold standard, iliac AB, for AC repair (Pradel & Lauer, 2012). Since the OBs were isolated from a small (3–4 mm) biopsy of maxillary bone, the authors proposed the cell-based strategy as a feasible alternative to more invasive AB grafting (Pradel & Lauer, 2012).

While all of the above studies reported the use of autologous cells, two SA studies (one controlled) reported the use of a commercial "allogeneic cellular bone matrix" (Osteocel®, NuVasive Biologics, CA, USA) containing viable osteoprogenitor cells (Gonshor, McAllister, Wallace, & Prasad, 2011; McAllister, Haghighat, & Gonshor, 2009). Although, the clinical use of allografts has been limited by safety concerns with regards to disease transmission and lack of osteogenic properties comparable to autologous bone, recent advances in donor screening and viral testing have greatly improved allograft safety. Moreover, novel tissue processing methods which selectively remove immune cells and preserve osteogenic cells, have been applied to allografts. Osteocel® is obtained from cadaveric cancellous bone of screened donors following selective cell preservation. Previous studies have identified MSC-like cells in Osteocel® at a higher frequency than those found in freshly isolated iliac bone or BMA (Baboolal et al., 2014; Skovrlj et al., 2014). In one RCT, significantly greater NBF was observed following SA with Osteocel® compared to cell-free allograft (Gonshor et al., 2011). Nevertheless, the need for further studies to investigate the mechanism of action of osteoprogenitors in cellular allografts, that is whether these cells participate directly in NBF via differentiation or whether they act as immunoregulators of host MSCs, has been highlighted (Baboolal et al., 2014).

4.4 | Clinical relevance of findings

While significant overall benefit of cell therapy (BTE) was observed in most pre-clinical in vivo studies and for most indications, in general, this benefit was not translated in the clinical studies included herein, that is the ES were much smaller in patients than large-animals and

did not extent to all indications, but only to SA and horizontal RA (no studies of vertical RA were eligible for the meta-analysis). In this context, the model used is critical when interpreting the results regarding the potential of a therapeutic intervention to enhance bone regeneration. In particular, the maxillary sinus represents a *spontaneously healing defect*, in the sense that space provided, that is the Schneiderian membrane is elevated and kept at a distance to the sinus bone wall, and in the absence of infection, bone regeneration occurs in the sinus cavity in a predicable fashion—even without the need for any grafting (Duan et al., 2017; Lundgren, Andersson, Gualini, & Sennerby, 2004; Riben & Thor, 2016). The major bulk of bone regeneration in an augmented sinus forms within the first 4–5 months post-operatively, and thereafter only relatively smaller increases in bone formation may be observed (Handschel et al., 2009; Klijn, Meijer, Bronkhorst, & Jansen, 2010). Thus, it appears that the regenerative potential of the sinus is "exhausted" after a certain amount of bone formation is achieved and no intervention can produce larger amounts of bone regeneration within the sinus. This view appears supported by the circumstantial evidence indicating that even application of growth factors, including BMPs—highly potent growth factors for bone regeneration, does not result in considerably different bone densities compared with any other type of augmentation material (Schliephake, 2015). Even in the present analysis, the significant effect of BTE in SA (after 6 months) was largely due to a single study (Pasquali et al., 2015), showing a large positive effect over the control intervention. Thus, in retrospect, it may come as no surprise that BTE failed to show similarly remarkable potential in enhancing bone formation in human sinuses, comparing with animals. A similar concern regards the use of the extraction socket model, representing also a largely spontaneously healing defect; remarkable differences in terms of histological outcome of healing within the socket may not be expected among various types of treatments with similar mechanical stability and space provision capacities, in the absence of infection (MacBeth, Trullenque-Eriksson, Donos, & Mardas, 2017).

The lack of similarly remarkable effects of BTE in the clinic compared with those observed in pre-clinical in vivo models, may also be related to dimensional (size) differences in human and animal defects. In particular, "diffusion distances," important aspects for characterization of mass transport limitations (e.g., diffusion of oxygen and removal of metabolic waste) relevant to the survival of transplanted cells, are usually smaller in animals compared with humans (Muschler, Raut, Patterson, Wenke, & Hollinger, 2010); this in turn may have allowed a better performance of the transplanted cells in animals compared with humans. In this context, it is also worth discussing the different outcome measures employed in the studies. Histomorphometry of biopsy specimens is considered the "gold standard" method for quantitative evaluation of bone structure (Vidal et al., 2012), and was therefore considered as the primary outcome measure in the meta-analyses. More recently, micro-CT has been proposed as a less-destructive and –time/-labour intensive method for assessing 3-D bone microarchitecture (Hedberg et al., 2005). In the present review, histological and radiographic data were analysed separately. However, it must be acknowledged that obtaining biopsy specimens of regenerated tissues is considerably easier in animals (usually following euthanasia) than in clinical situations. Loss or damage to clinical specimens during harvesting and/or processing cannot be excluded and may be a further contributing factor to the differences in outcomes. Moreover, variation between the studies regarding processing methods, difficulty in differentiating between mineralized scaffolds and regenerated mineralized bone and investigator-related factors (inter-observer variation, lack of blinding, etc.), may have contributed to heterogeneity in the observed results (Shanbhag et al., 2017).

It is relevant to discuss the results herein, in the context of future studies. Although statistically significant benefits of BTE were observed in certain indications, the prediction intervals in both the clinical and pre-clinical meta-analyses were generally quite large and often crossing the line of no effect, that is the "zero line." Prediction intervals reflect the heterogeneity in the current studies and provide a range for the expected effect of the intervention in a future study under a different setting. Thus, although statistically significant effects of BTE were observed in certain indications in the current analysis, the wide prediction intervals suggest that future studies in different settings may show no, or even opposite, effects, that is in the favour of scaffolds alone (IntHout, Ioannidis, Rovers, & Goeman, 2016). Only in the case of clinical SA (vs. scaffolds, 4–7 months) evaluated by μ-CT, did BTE show a significant effect with a narrow prediction interval.

Finally, the cost of BTE, in comparison to current alternatives, is an important factor in clinical decision-making. One included study, reporting the use of autologous ASCs to treat extensive mandibular defects, estimated the cost of GMP-grade cell expansion alone to be 12,000 USD (Wolff et al., 2013). In this context, the use of whole tissue [BMA(C) or SVF] would considerably reduce costs in comparison to expanded cells. However, the per-patient costs associated with the "gold standard" treatment, that is iliac crest-derived AB grafting, are also reported to be considerably high, primarily due to the need for hospitalization and general anaesthesia (Dahlin & Johansson, 2011; Francis et al., 2013; Mehta et al., 2018). Indeed, one included study reported significantly greater costs (in addition to higher complications and morbidity) associated with AB grafting versus BTE (BMA + scaffolds) for AC repair (Gimbel et al., 2007). Thus, in addition to clinical efficacy, future controlled studies should evaluate the cost-effectiveness of cell therapy for bone regeneration to guide clinical decision-making.

5 | CONCLUSIONS

Based on the reviewed evidence, the following conclusions may be drawn:

1. Based on limited and heterogeneous evidence from clinical studies, transplantation of cells, most commonly whole BMA or BMAC, in combination with biomaterial scaffolds results in superior bone regeneration compared to implantation of

scaffolds alone in SA and horizontal RA, and comparable bone regeneration to the gold standard (AB grafts) in AC repair.
2. It is unclear whether implantation of ex vivo expanded cells is superior to minimally manipulated whole tissue fractions (BMA/C or A-SVF). In the case of ex vivo expanded cells, it is unclear whether implantation of committed cells (POCs or OBs) is superior to uncommitted cells (BMSCs or ASCs) in terms of bone regeneration.
3. In the case of BMSCs, it is unclear whether osteogenic pre-differentiation is beneficial. In the case of ASCs, additional osteogenic stimulation, via osteogenic pre-differentiation or addition of osteoinductive factors, for example BMP-2, may be beneficial.
4. The relatively larger ES in favour of cell therapy observed in pre-clinical studies are diminished in clinical trials, suggesting a gap in translation.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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