Cumhuriyet Dental Journal, 25(4): 341-349, 2022
DOI: https://doi.org/10.7126/cumudj.1110413

Cumhuriyet Dental Journal

| cdj.cumhuriyet.edu.tr | Founded: 1998 | Available online, ISSN: 1302-5805 e-ISSN: 2146-2852 | Publisher: Sivas Cumhuriyet Üniversitesi

Is Sclerostin Antibody an Effective Agent for Alveolar Bone Regeneration in Animal Models? A Scoping Review

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Review

History

Received: 10/05/2022
Accepted: 22/12/2022

ABSTRACT

Objectives: *The use of Sclerostin Antibody(Scl-Ab) as a bone anabolic agent has shown significant benefit in bone disorders in preclinical animal models and human clinical trials. The objectives of this scoping review is to determine whether sclerostin antibody is an effective agent for alveolar bone regeneration in animal models and if sclerostin antibody is effective in syndrome/endocrine related diseases which may result in the reduction of alveolar bone quality.*

Materials and Methods: *An online search was conducted to locate published animal studies in the databases such as Medline/PubMed, Scopus, Web of Science, Google scholar. The articles published in the international peer-reviewed literature in the English language, from January 2010 up to and including February 2021 are included in this review. The initial search from the mentioned database resulted in 555 articles for review. Further, a search in the references led to additional 4 articles. After title and abstract screening and removing the duplicates, 9 articles were subjected to full text screening to determine their eligibility. Three articles were excluded and the remaining 6 articles were included in the review. The parameters describing bone quality and quantitiy such as, Bone Mineral Density (g/cm2), bone volume fraction (BVF), trabecular thickness in alveolar bone, Percentage of bone volume/tissue volume (BV/TV), were determined to ascertain the effects of Scl-Ab on alveolar bone regeneration.*

Results: *Scl-Ab was found to be effective in improving the bone quality and quantity. Scl-Ab has the potential to improve Bone Mineral Density (g/cm2), bone volume fraction (BVF), trabecular thickness in alveolar bone, Percentage of bone volume/tissue volume (BV/TV) and other parameters. Scl-Ab can improve the quality of bone in conditions that impairs the quality and density of bone such as osteoporosis, Down syndrome.*

Conclusions: *It was observed that Scl-Ab was useful in improving the quality and quantitiy of bone lost due to local infections such as periodontal diseases as well as reduced bone density associated with diseases and conditions affecting osteoblast activity. The review concluded that Scl-Ab promotes alveolar bone augmentation and improves bone quality without surgical interventions.*

Keywords: *Alveolar bone, Animal models, Preclinical models, Regeneration, Sclerostin, Sclerostin antibody.*

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How to Cite: Sunaina Banu S, Puzhankara L, Kedlaya MN, Varghese JM, Ramanarayanan V. (2022) Is Sclerostin Antibody an Effective Agent for Alveolar Bone Regeneration in Animal Models? A Scoping Review, Cumhuriyet Dental Journal, 25(4): 341-349.

Introduction

Periodontitis is a chronic inflammatory disease that affects the supporting structures of the tooth, which often presents with bleeding on gentle probing, loss of attachment and increased gingival crevicular fluid. This non-communicable disease is triggered by bacteria and their endotoxins, resulting in immunological and humoral response[1,2] with the production of proinflammatory cytokines and other biomolecules.[2] These signaling markers participate in upregulating the inflammatory cascade causing further destruction of the periodontal structures including the alveolar bone defects in the advanced stages of periodontal disease. Hence, various therapeutic modalities are being attempted to regenerate/ restore the lost periodontal structures. To achieve regeneration of alveolar bone, various anabolic agents or bone antiresorptive agents have been experimented with. Due to the various biological, biomechanical factors, achieving periodontal tissue regeneration remains a major clinical challenge.

In the quest to understand the human body, researchers have come across the interesting working of the beta-catenin pathway and sclerostin molecule in the functioning of osteocytes which have been shown to accomplish several functions that are crucial for bone formation and turnover.[3] Sclerostin, a 213-amino-acid glycoprotein expressed mainly by osteocytes, is a vital messenger in the communications between osteocytes and osteoblasts that impedes osteoblast differentiation and regulates bone resorption [Figure 1].[4,5] According to the genetic studies, mutations in the SOST(Sclerostin) gene encoding sclerostin, are responsible for higher bone mass

and density in the skull, mandible, ribs, clavicles and all the long bones[6-8] and similar results have been observed in animal studies. However, overexpression of the SOST gene leads to the development of osteopenia in mice.[9] Thus, recognizing the inhibitory effect of sclerostin on bone formation, research has led to the development of sclerostin-neutralizing antibody (Scl-Ab). Sclerostin and its inhibitors exhibit a potential role in prosthetic, regenerative and preventive therapy in dentistry. The sclerostin neutralizing antibody has been investigated for bone disorders in preclinical animal models and human clinical trials. Systemic administration of Scl-Ab to female rats with osteopenia due to ovariectomy-induced estrogen deficiency, or to aged (sixteen-month-old) male rats, was shown to increase the bone formation at various bone sites and improve bone mass, mineral apposition rate, and bone strength.[10-12] The systemic delivery of Scl-Ab has demonstrated its efficacy in treating generalized bone loss across various studies.[13,14]

Figure 1. Schematic representation of the effect of Sclerostin and Sclerostin-Antibody on Bone

Based on the literature above, the use of Scl-Ab as a bone anabolic agent may have potential benefits in the treatment of alveolar bony defects. However, no human trials have been conducted in which Scl-Ab has been used for alveolar bone regeneration and hence treatment of alveolar bony defects in animal models using Scl-Ab has drawn considerable attention. The study of regeneration of bones in animal models using Scl-Ab has analysed the effect over a varied range of experimental conditions including the effectiveness of the agent in experimental periodontitis, surgical bone defects and around implants. The dosage of drug administered and the route of administration that has been used is also different in the studies that have been done. An understanding of the best mode of drug administration, the effectiveness of each dosage, the complications associated with the use of the drug is essential for the translation of animal research into human clinical trials.

A Scoping review will provide an overview of the available research evidence of the effectiveness of Scl-Ab on alveolar bone regeneration. It is used to identify the number, nature, and characteristics of the primary research in terms of effectiveness of Scl-Ab on alveolar bone regeneration as the topic has not yet been extensively reviewed and the existing research is heterogeneous in nature. It also helps to summarize and disseminate research findings as well as determine the research gaps in the literature on the topic. Studies on pre-clinical animal models constitute the currently available evidence on the topic and hence this scoping review encompasses the animal studies conducted to ascertain the effectiveness of Scl-Ab on alveolar bone regeneration. Literature search and protocol databases did not identify any systematic or scoping review on the topic. The aim of the present scoping review of animal studies is to determine the effectiveness of Scl-Ab in alveolar bone regeneration. The articles published in the international peer-reviewed literature in the English language, from January 2010 up to and including February 2021 have been included in this review. This would help identify areas for future research, and also help develop strategies for research implementation.

Review question

The review has been registered in the Open Science frame registries (Registration DOI:10.17605/OSF.IO/DQY5F). In preparing the scoping review with the objective to determine the effectiveness of Scl-Ab in alveolar bone regeneration, we examined the following review questions: Is sclerostin antibody an effective agent for alveolar bone regeneration in animal models? Is sclerostin antibody effective in syndrome/endocrine related diseases which may result in the reduction of alveolar bone quality?

Inclusion and exclusion criteria

Studies Included

Animal studies in which the treatment arm includes Scl-Ab administration for alveolar bone preservation or regeneration were included. Rodents models and canine models which are most commonly used for periodontal research were the animal models included in the study. There were no restrictions regarding the route and the dosage of application. Clinical trials and ex-vivo studies were excluded.

Concept

The use of Scl-Ab for bone disorders has been studied in preclinical animal models and human clinical trials. However, its use in alveolar bone regeneration has seen limited research exposure with studies confined to animal research. This review studied the concept of the role of Scl-Ab on alveolar bone preservation and regeneration in animal models. Studies in which there is the use of Scl-Ab for purposes other than healing and regeneration of alveolar bone defects were excluded.

Context

Alveolar bone regeneration in patients with periodontal disease and bone defects has been an avenue that has been studied extensively. Studies have shown that osteocytes have a mechanosensory function via sclerostin which helps in bone preservation. Alveolar bone regeneration using Scl-Ab is a less explored territory with research on pre-clinical

models being the currently available evidence. This review included animal studies on the effectiveness of Scl-Ab on alveolar bone regeneration. There were no restrictions regarding the gender or age of the animal model being used. However, Studies utilizing bisphosphonates and other agents that facilitate bone formation were excluded.

Types of Sources

This scoping review considered experimental animal studies for inclusion. Animal studies exploring qualitative and quantitative data pertaining to the topic were included. The databases, Medline/PubMed, SCOPUS and Web of Science were used as sources of evidence.

Methods

Information sources and search strategy

Articles on the topic were identified through an initial limited search of Medline/PubMed. A full search strategy for SCOPUS and Web of Science was developed using the text words in the titles and abstracts of relevant articles as well as the index terms used in the description of the article. The reference list of all included sources of evidence was screened for additional studies. All articles from January 2010 to February 2021 about animal studies regarding the efficacy of Scl-Ab in the treatment of alveolar defects were included in the review. The articles published in the international peer-reviewed literature in the English language were included.

The search terms used were (((Animal model) OR Rodent) AND Alveolar bone defect) AND Anti sclerostin antibody) OR Sclerostin antibody) AND Alveolar bone regeneration) OR Bone regeneration) AND Bone fill. The search details in PubMed was ((("models, animal"[MeSH Terms] OR ("models"[All Fields] AND "animal"[All Fields]) OR "animal models"[All Fields] OR ("animal"[All Fields] AND "model"[All Fields]) OR "animal model"[All Fields]) OR ("rodentia"[MeSH Terms] OR "rodentia"[All Fields] OR "rodent"[All Fields])) AND (Alveolar[All Fields] AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND defect [All Fields])) AND (Anti[All Fields] AND sclerostin[All Fields] AND ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields])) OR (Sclerostin[All Fields] AND ("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "antibody"[All Fields] OR "antibodies"[MeSH Terms] OR "antibodies"[All Fields])) AND (Alveolar[All Fields] AND ("bone regeneration"[MeSH Terms] OR ("bone"[All Fields] AND "regeneration"[All Fields]) OR "bone regeneration"[All Fields])) OR ("bone regeneration"[MeSH Terms] OR ("bone"[All Fields] AND "regeneration"[All Fields]) OR "bone regeneration"[All Fields]) AND (("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND fill[All Fields]) AND ("2011/02/05"[PDat] : "2021/02/01"[PDat]).

Following the search, all relevant citations were collected and uploaded into Mendeley reference manager (version 1.19.4) and duplicates were removed. Titles and abstracts were screened by two independent reviewers (LP, SB) for assessment against the inclusion criteria for the review. Potentially relevant articles were identified and retrieved in full and were assessed in detail by the reviewers (LP, SB) and the reasons for the exclusion of articles were recorded. Any disagreements between the reviewers regarding the inclusion of the articles during the selection process were resolved through discussion or consultation with additional reviewers. The results of the search and the study inclusion process have been presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR)[15] flow diagram [Figure 2].

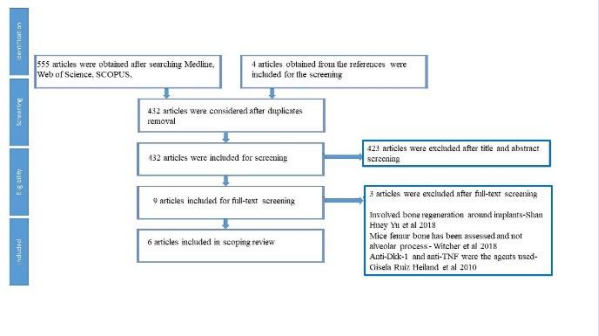

Figure 2. PRISMA Flow diagram for the scoping review

Data Extraction

Data were extracted from papers included in the scoping review by two independent reviewers (LP, SB). Disagreements, if any, that arose between the reviewers were resolved through discussion or consultation with additional reviewers (JV, MK). The data extracted included details like the author, year, country, Animal used, genetic modifications/mutations of the animal used, ethical clearance, type of disease model, the grouping of the animal models based on drug used, the dosage of the drug used, route of administration, type of disease model (Supplementary file 1), parameters assessed (Table 1) such as Bone Mineral Density (BMD) (g/cm2), bone volume fraction (BVF), Serum Osteocalcin (ng/ml), N-terminal propeptide of procollagen type I, tartrate-resistant acid phosphatase 5b, Trabecular thickness (Tb.Th) in alveolar bone, Percentage of bone volume/tissue volume (BV/TV), Mean tooth to alveolar crest length, mm (SD), Trabecular separation(mm), Trabecular Number (Tb.N), BFR/BS (bone formation rate/bone surface) for alveolar and basal bone,Osteocyte (Ocy) surface area(µm2), Ocy dendrite length(µm), Ocy total cell Volume (μm^3) presented either in qualitative or quantitative form and other parameters assessing changes in bone structure and regeneration of periodontal supporting tissues. The six articles included in this review were analysed and the data obtained have been described in a narrative summary.

Results

The initial search from the mentioned database resulted in 555 articles for review. Further, a search in the references led to additional 4 articles. After removing the duplicates, 9 articles were subjected to full text screening to determine their eligibility. Three articles [Shan Huey Yu *et al.* 2018, Witcher *et al.* 2018, Ruiz Heiland *et al.* 2010][16-18] were excluded and the remaining 6 articles [Yao Yao etal2020, M Liu *et al.* 2018, Chen *et al.* 2015, Taut *et al.* 2013, Ren *et al.* 2015, Tamplen *et al.* 2018] [19-24] were included in the review.

Characteristics of sources of evidence

The animal models used in the study ranged from Sprague Dawley rats[19-22], Periostin Knock-out mice(PKO), Double Knockout mice(DKO),mice with the C57BL/6 background[23], Ts65 male mice and wild type euploid littermate.[24] The characteristics of the articles included are given in Supplementary file 1 and the parameters assessed in the included studies are given in Table 1.

Table 1: Parameters assessed

S No	Parameter Assessed	Yao Yao et al 2020	Taut AD et al. 2013	Liu et al 2018	Tamplen M et al 2018	Ren Y et al 2015	Chen et al 2015
1	Length of new bone (mm)	✓					
2	Linear bridging bone (%)	✓					
3	Area of new bone (mm2)	✓					
4	Bone fill %	✓					
5	New cementum	✓					
6	New cementum length (mm)	✓					
7	New cementum length (%)	✓					
8	Root resorption	✓					
9	Bone volume	✓					
10	Bone fill	✓					
11	Bone mineral density/bone mineral content	✓	✓	✓			✓
12	Bone volume fraction (BVF)		✓	✓			✓
13	Linear alveolar bone loss (ABL) in millimeters		✓				
14	Osteoprotegerin(pg/ml)						✓
15	Serum P1NP(ng/ml)		✓	✓			
16	Serum Osteocalcin (ng/ml)		✓	✓			✓
17	Trap5b		✓	✓			✓
18	Trabecular thickness (Tb.Th) in alveolar bone			✓	✓		✓
19	BFR/BS (bone formation rate/bone surface) for alveolar and basal bone/ Mineral Apposition Rate(MAR)			✓			✓
20	ES/BS (eroded surface/bone surface) for alveolar and basal bone			✓			
21	mRNA expression for the genes encoding sclerostin (Sost)			✓			
22	mRNA expression for the genes encoding Dkk1			✓			
23	Maxillary alveolar ridge volume			✓			
24	Maxillary height loss			✓			
25	Percentage of bone volume/tissue volume (BV/TV)				✓	✓	
26	Mean tooth to alveolar crest length, mm (SD)/ CEJ-Alveolar bone crest(mm)				✓		✓
27	Trabecular spacing, mm (SD)				✓		✓
28	Ratio of SOST positive cells/total cells					✓	
29	Ocy surface area(µm2)					✓	
30	Ocy dendrite length(µm)					✓	
31	Ocy total cell Volume (µm3)					✓	
32	Dendrite numbers					✓	
33	Cementum-enamel junction (cm2)					✓	
34	Qualitative assessment: TRAP, DMP1, OSX, Biglycan, Decorin, Collagen					✓	
35	Trabecular Number (Tb. N) (I/mm)						✓
36	CTx-1(ng/mL)						✓
37	Mineral Apposition Rate(MARµm/d)						✓

Critical appraisal of an individual source of evidence

Length of new bone (mm), Linear bridging bone (%), Area of new bone (mm2), Bone fill %, New cementum, New cementum length (mm), New cementum length (%), Root resorption, Bone volume (BV), Bone fill (BF) have been assessed in the study by Yao Yao *et al.* 2020.[19] In this study it was shown that local application of Scl-Ab microspheres (MS) did not have an improved effect on length of new bone formation (2.43±0.14mm), Linear bridging bone (%) (89.9±4.8) , Area of new bone (mm^2) (0.83±0.09), Bone fill % (45.3±4.1), New cementum length (mm) (0.38±0.10), New cementum length (%) (32.4±8.5) ,Root resorption (6/12) as compared to systemic administration of Sclerostin antibody (Sys Scl-*Ab*), Empty microspheres(Emp), Controls (c) [length of new bone formation (Sys Scl-Ab-2.69±0.09, Emp- 2.60±0.12, C- 2.52±0.07), Linear bridging bone (%) (Sys Scl-Ab-97.3±1.8, Emp- 93.8±3.4, C- 96.4±2.0) , Area of new bone (mm2) (Sys Scl-Ab-1.03±0.05, Emp- 0.89±0.06, C- 0.92±0.07), Bone fill % (Sys Scl-Ab-61.2±3.0, Emp- 46.0±2.8, C- 53.9±3.5), New cementum length (mm) (Sys Scl-Ab- 0.58±0.12, Emp- 0.40±0.09, C- 0.39±0.08), New cementum length (%) (Sys Scl-Ab-52.5±9.8, C- 32.8±7.1) and Root resorption (Sys Scl-Ab-1/9, C-3/12)]. In terms of new cementum length percentage (%) and the number of roots having root resorption, the locally administered Scl-Ab microspheres gave better results as compared to empty microspheres (new cementum length %-31.9±7.5, root resorption-7/12). The number of teeth with new cementum formation was similar for local and systemic administration of Scl-Ab but reduced for Empty microspheres and control group [New cementum for local Scl-Ab- (7/12), New cementum (Sys Scl-Ab-4/9, Emp- 6/12, C- 6/12)]. BV, BF and BMD showed a significant difference in the systemic Scl-Ab group as compared to the microsphere groups.

Bone mineral density/bone mineral content has been assessed in four of the included studies (Yao Yao etal2020, M Liu *et al.* 2018, Chen *et al.* 2015, Taut *et al.* 2013).[19-22] The group which received systemic Scl-Ab showed significantly higher BMD compared to locally delivered Scl-Ab MS (Yao Yao *et al.* 2020).[19] In the study by Taut *et al.* 2013[22], it was shown that twice-weekly subcutaneous administration of 25 mg/kg Scl-Ab for 3 weeks, increased the serum concentration of osteocalcin and P1NP which are bone formation markers and increased the mineral apposition rate(MAR) in the alveolar bone. Twice weekly subcutaneous administration of 25 mg/kg Scl-Ab for 6 weeks showed significantly greater BMD and BVF in ovariectomized(OVX) rats with ligature induced periodontitis as compared with vehicle treated controls[21]. Assessment of percentage change in bone mineral content (BMC) by Liu *et al.* 2018[20] showed that DKK1 antibody (DAB) in combination with Scl-Ab had a significantly more increase in BMC as compared to Scl-Ab alone.

M Liu *et al.* 2018[20], Chen *et al.* 2015[21], Taut *et al.* 2013[22] have assessed the bone volume fraction(BVF) post Scl-Ab administration. Scl-Ab group had higher BVF as compared to the control group in the studies by Chen *et al.* 2015[21] (P< 0.001) and Taut *et al.*[22] (P<0.05). The study by Taut *et al.*[22] also showed that a 6 week treatment with systemic Scl-Ab resulted in the reversal of ligature-induced bone loss. M Liu *et al.* 2018[20] have shown that five weeks of Scl-Ab or Scl-Ab+DAB therapy initiated 9 weeks post-surgery, restores BVF to levels greater than that with vehicles and controls. Assessment of linear Alveolar Bone Loss (ABL) in the study by Taut *et al.*[22] showed that 6 weeks of systemic Scl-Ab administration resulted in statistically significant improvement in linear ABL (p<0.05) as compared to vehicle treatment.

Serum osteocalcin levels and serum Tartrate-resistant acid phosphatase (TRAP) 5b are markers of bone metabolism and their levels have been assessed in studies by M Liu *et al.* 2018[20], Chen *et al.* 2015[21], Taut *et al.* 2013[22], while Serum Procollagen 1 Intact N-Terminal Propeptide (P1NP) levels, another marker of bone metabolism has been assessed in studies by M Liu *et al.* 2018[20] and Taut *et al.* 2013.[22] In the study by Chen *et al.*[21], a significant elevation in the serum osteocalcin and osteoprotegerin and a decrease in serum TRAP5b were noted after 6 weeks of treatment with Scl-Ab. Type I Collagen Cross-Linked C-Telopeptide (CTX-1) which is a bone resorption marker, was found to be increased in ovariectomized (OVX) rats when compared to sham and control groups even if Scl-Ab was administered, however, the levels were significantly lower than that in the ovariectomized (OVX) rats receiving vehicle instead of Scl-Ab (P=0.001). Liu *et al.*[20] have found a significant increase in serum P1NP in the SAB group (P<0.05 versus Veh), and a significant reduction in serum TRACP-5b in the Scl-Ab +DAB group (P<0.05). There was no mention regarding the serum osteocalcin levels in the result section of the study. Taut *et al.*[22] have shown an increase with respect to serum osteocalcin levels in comparison to intact (p=0.0019) and vehicle (p=0.0001) groups after 3 weeks of treatment and at 6 weeks after the treatment commenced (p=0.034). However, Scl-Ab did not demonstrate any statistical difference between the intact (p=0.10) and vehicle-treated Experimental Periodontitis (EP) (p = 0.058) groups at 6 weeks in serum P1NP levels although the difference was significant at 3 weeks. Scl-Ab treatment after ligature-induced EP did not produce any change in serum TRAP 5b levels during the therapeutic phase.

M Liu *et al.* 2018, Chen *et al.* 2015, Tamplen *et al.* 2018[20,21,24] have assessed the effect of Scl-Ab on trabecular thickness (Tb.Th) in the alveolar bone. Tamplen *et al.* have found that the trabecular thickness in alveolar bone was higher for Scl-Ab [0.177 (0.01) in wild type mice and 0.167 (0.02) in Ts65 mice] as compared to the vehicle [0.154 (0.01)]. A similar result was seen in the study by M Liu *et al.*[20], where an increased Tb.Th was found in Scl-Ab and Scl-Ab+DAB groups as compared to controls. The microarchitecture parameters, Tb.Th and Tb.N was higher in the OVX + Ligature + Scl-Ab group as compared with the OVX + Ligature + Vehicle group (P = 0.001) in the study by Chen *et al.*[21]

Bone formation rate/bone surface (BFR/BS) and Mineral apposition rate (MAR) for alveolar and basal bone assessed in studies by Liu *et al.*[20] and Chen *et al.*[21] shows that a significantly greater BFR/BS (bone formation rate/bone surface) in alveolar and basal bone was noted in

the Scl-Ab and Scl-Ab+DAB groups versus Veh, with Scl-Ab+DAB demonstrating a higher BFR/BS in basal bone compared to Scl-Ab[20]. In the study by Chen *et al.*[21] Scl-Ab and Scl-Ab+DAB groups had significantly lower eroded surface/bone surface (ES/BS) values in comparison with OVX-Veh rats. MAR was significantly increased in the OVX + Ligature + Scl-Ab group compared with the Sham +Ligature + Vehicle (P = 0.003) and OVX + Ligature + Vehicle groups (P = 0.001).

mRNA expression for the genes encoding sclerostin (Sost), mRNA expression for the genes encoding Dkk1, Maxillary alveolar ridge volume, Maxillary height loss has been assessed in a study by Liu *et al.*[20] The alveolar osteocytes in the non-extracted and extracted maxilla expressed high levels of Sost mRNA while Dkk1 was moderately expressed by osteocytes in the non-extracted maxillae. Molar extraction resulted in an increase in Dkk1 levels within 1 week and the Dkk1 mRNA expression remained high even after 2 weeks of extraction. The Dkk1 levels returned to non-extracted levels 3 to 5 weeks post-extraction.

The percentage of bone volume/tissue volume (BV/TV) has been assessed by Tamplen *et al.*[24] and Ren *et al.*[23] Volumetric analysis in the study by Tamplen *et al.*[24] has shown that the average mandibular bone volume (bone volume per total volume) was higher in wild-type mice treated with Scl-Ab as compared with vehicle-treated mice. Ren *et al.*[23], have shown through microCT data, the restoration of Bone Volume (BV) in the PKO mice qualitatively and quantitatively as a result of Scl-Ab treatment.

Mean tooth to alveolar crest length, (mm)/ CEJ-Alveolar bone crest(mm), Trabecular spacing, mm (SD) were assessed in studies by Tamplen *et al.*[24] and Chen *et al.*[21] A significant decrease in the average CEJ-ABC distance was noted in both the studies as a result of Scl-Ab treatment. Tamplen *et al.*[24] have found that trabecular spacing was least for Scl-Ab treated wild type mice [0.073, (0.005)] as compared to vehicle treated and Scl-Ab treated Ts65 mice [0.079, (0.004)] while it was highest for Ts65 mice [0.085, (0.007)] and a similar result has been suggested in the study by Chen *et al.*[21]

Quantitative assessment of Ocy surface area(μm^2), Ocy dendrite length(μm), Ocy total cell Volume (μm^3), Dendrite numbers and qualitative assessment of TRAP, DMP1, OSX, Biglycan, Decorin, Collagen was done by Ren Y *et al.*[23] The statistical analysis revealed that there were significant differences in the quantitative parameters assessed among WT, PKO mice treated with Scl-Ab for 8 weeks (P< 0.01) with a higher value evident in specimens treated with Scl-Ab. The molecular markers and collagen were shown to be restored in the DKO mice and the PKO mice treated with Scl-Ab for 8 weeks.

The effect of Scl-Ab on surgical defect has been evaluated in the study by Yao Yao *et al.*[19] Quantitative μCT measurements showed a 40% greater bone mineral density, bone volume, bone fill in the systemic Scl-Ab group than the control, empty MS, Scl-Ab MS groups. It was observed that there was increased bone bridging and osteogenesis in the systemic Scl-Ab group.

The effect of Scl-Ab on experimental periodontitis has been studied by Taut *et al.*[22] and Chen *et al.*[21] Six weeks of Scl-Ab restored the bone quality and quantity to levels comparable to intact control and brought about an increased bone apposition rate.[22] Similar results have been observed in the study by Chen *et al.*[21] Taut *et al.*[22] have also shown that systemic Scl-Ab can be effective in the prevention of the progression of periodontal disease

Tamplen *et al.*[24] and Chen *et al.*[21] have assessed the effect of Scl-Ab on alveolar bone quality in models with metabolic diseases/disorders that affect the bone quantity and quantity. Tamplen *et al.* [24]have found that the low bone mass phenotype of Down syndrome mandibular bone in the Ts65 mice can be completely normalized using Scl-Ab treatment. An increase in serum osteocalcin and osteoprotegerin has been shown in the study by Chen *et al.*[21] while levels of serum tartrate-resistant acid phosphatase and CTx-1 decreased with the administration of Scl-Ab resulting in increased alveolar bone mass in OVX rats with estrogen deficiency osteopenia plus periodontitis.

Effect on underloaded alveolar bone following extraction of teeth was studied by Liu *et al.*[20] The study demonstrated that systemic Scl-Ab administration improved the volume and height of atrophic alveolar ridges and DAB had a synergistic effect when used in combination with Scl-Ab. Complete reversal of bone loss in the opposing mandible as a result of hypo-occlusion was achieved with the use of Scl-Ab and Scl-Ab +DAB.

It has been shown in the study by Taut *et al.*[22] that after 6 weeks of treatment, BVF and TMD values in the experimental periodontitis group with Scl-Ab administration were similar to those of healthy controls. In the study by Liu *et al.*, it was observed that by treatment week 15, the Scl-Ab group had 42% and the Scl-Ab+DAB group had 81% greater alveolar ridge volume when compared to extracted Veh controls (both P<0.05) and a significant gain in ridge height was also observed within 2 and 4 weeks of treatment initiation. The Scl-Ab+DAB group achieved complete height recovery by week 9 while the Scl-Ab group had only about two-thirds of alveolar bone height recovery in 15 weeks. Summarization of the findings is given in Supplementary file 2.

Summarization of response to the review questions

Scl-Ab has the potential to improve the quantity and quality of alveolar bone by improving Bone Mineral Density (g/cm2), bone volume fraction (BVF), trabecular thickness in alveolar bone, Percentage of bone volume/tissue volume (BV/TV) and other parameters.

Scl-Ab can improve the quality of bone in conditions that impairs the quality and density of bone such as osteoporosis, Down syndrome.

Risk of bias

SYRCLE's (SYstematic Review Center for Laboratory animal Experimentation) tool was used for assessing the risk of bias.[25] Low risk of bias was recorded in terms of

attrition bias and other sources of bias for all included studies.[19,20,21,22,23,24] Reporting bias was unclear for the study by Liu *et al.* 2018[20] as there was no mention regarding the serum osteocalcin levels in the result section of the study. All other studies had a low reporting bias. Unclear risk of bias was noted for sequence generation and baseline characteristics in studies by Yao Yao *et al.*2020, Chen *et al.* 2015, Taut *et al.* 2013, Ren *et al.* 2015, Tamplen *et al.* 2018 [19,21,22,23,24] as well as in allocation concealment, random outcome assessment in studies by Yao Yao etal2020, M Liu *et al.* 2018, Chen *et al.* 2015, Taut *et al.* 2013, Ren *et al.* 2015, Tamplen *et al.* 2018[19,20,21,22,23,24], and in random housing of animals [M Liu *et al.* 2018, Taut *et al.* 2013, Ren *et al.* 2015, Tamplen *et al.* 2018].[20,22,23,24] Random housing of animals had a low risk of bias in studies by Yao Yao *et al.* 2020 [19] and Chen *et al.* 2015.[21] The study by Yao Yao *et al.*[19] had a low risk of bias in terms of blinding of caregivers/investigators as well as outcome assessors while the other included studies had a high risk of bias in terms of these two criteria. The risk of bias assessment across studies and within studies is given in Figure 3 and Figure 4.

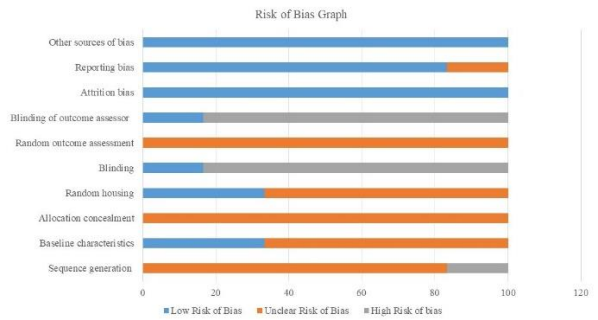

Figure 3. Risk of bias graph

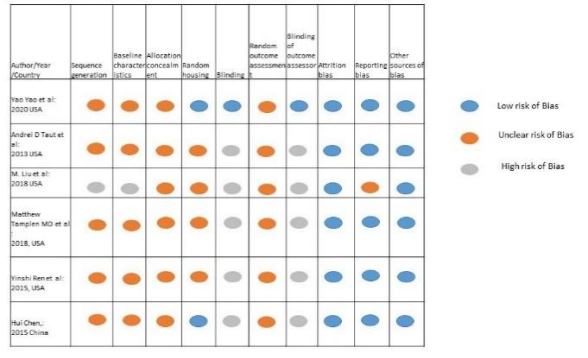

Figure 4. Risk of bias summary

Discussion

Sclerostin is an inhibitor of the canonical Wnt pathway which is involved in bone remodelling. It is produced by several cells and tissues such as mature osteocytes, cementocytes, kidney, liver, heart, or carotid arteries. Due to its effect on bone formation and resorption, its potential as a therapeutic agent for increasing bone formation has been explored.[26] Alveolar bone loss is a sign of periodontal disease which results in tooth loss. An agent that can modulate bone quality and quantity can have profound effects on treatment strategies for periodontal disease. The use of Scl-Ab in management of alveolar bone loss is a territory that requires further study. Hence this scoping has been performed to determine whether sclerostin antibody is an effective agent for alveolar bone regeneration. Scoping reviews facilitate a systematic identification and analysis of the existing data. It helps to chart out the literature on a particular topic and presents a descriptive overview of the research question[27] so that it would be possible to perform further studies to anwer the potential hypothesis that arise as a result of performing the scoping review.

All articles from January 2010 to February 2021 about animal studies regarding the efficacy of Scl-Ab in the treatment of alveolar defects were included because the research on sclerostin as a bone anabolic agent with a focus on alveolar bone regeneration has become robust only in the past 10 years.

Bone fill percentage, Bone volume, Bone fill, trabecular thickness, bone volume fraction, bone formation rate/bone surface, mineral apposition rate, percentage of bone volume/tissue volume, trabecular spacing are parameters indicative of bone quantity and quality.[28,29,30] An increase in these parameters are suggestive of increase in the amount of bone formed. The studies included in the review have attempted to identify the bone forming potential of Scl-Ab using these parameters and it was observed that the agent is capable for facilitating bone formation. The local and systemic administration of the drug were found to be equally effective in providing a positive effect on bone quantity[19] and osteogenesis is found to be increased with the use of Scl-Ab thereby enabling bone formation.[31]

High bone mineral density has been observed in patients with high serum sclerostin levels and an inverse relation was noticed between PTH and sclerostin[32]. In the studies included in this review, Scl-Ab has been shown to have the ability to increase the bone mineral density as well as increase the osteocyte length, number and volume which is indicative of an improvement in the bone quality.[23] The enhancement in bone mass parameters after Scl-Ab treatment can be ascribed to the increase in osteoblastic activity.[33]

Serum osteocalcin levels, TRAP 5b, P1NP levels, CTX-1 are markers of bone metabolism which have been assessed in the included studies. The increase in osteocalcin, P1NP levels are indicative of increase in bone formation whereas CTX-1and TRAP are associated with bone resorptive activities.[34,35,36] It has been observed from the studies included in the review that Scl-Ab favours an increase in the bone formative markers and a reduction in bone resorptive markers.

A detailed review of the Scl-Ab indicated its beneficial effect in restoring alveolar bone. Existing literature has shown that Scl-Ab can improve the quality of bone in conditions that predispose towards impaired trabecular

quality and density such as osteoporosis.[37,38] Clinical trials using Scl-Ab therapy have resulted in increased bone mineral density and reduced fracture risk.[39] In this review, a similar beneficial effect was observed in the alveolar bone of OVX rats. In the case of the Ts65 Down syndrome mice, the balance between the osteoblast and osteoclast activity results in bone resorption which may be reversed using Scl-Ab as it facilitates a pro-osteoclastogenic cell signaling between osteocytes and osteoclasts. [40] Thus Scl-Ab can be beneficial for the low alveolar bone mass seen in Down syndrome.

In addition to the above findings, this review also showed that a combination of DAB along with Scl-Ab had a better bone anabolic activity as compared to Scl-Ab alone. DKK1 acts as an endogenous factor that limits jaw bone volume and density[41]. Thus inhibition of both sclerostin and DKK1 resulted in better alveolar bone regeneration as compared to either one alone. Systemic administration of the drug had better bone regenerative potential than the local application of Scl-Ab microspheres. PLGA biodegradation in vivo in osseous defects might limit the efficacy of Scl-Ab MS[42] apart from the different dosing levels between local (125 µg per defect) and systemic groups (31.25 mg in total per animal). Application of a higher dose locally using the local drug delivery system has potential disadvantages such as insufficient loading capacity, unsatisfactory polymer biodegradation, and material-mediated inflammation. However, local application of the drug can reduce the potential systemic side effects.

Disadvantages of Scl-Ab may be the possibility that inhibition of sclerostin may be deleterious to cartilage and may facilitate acceleration of disease in a rheumatoid arthritis mouse model as shown in studies on Sclerostin-deficient mice.[43,44]

This review is limited by the diverse methodology utilized in each of the articles and the limited number of articles satisfying the inclusion criteria. A systematic review has not been made due to the wide clinical and methodological heterogeneity.

Conclusions

This scoping review highlights the potential benefits of Scl-Ab in improving Bone Mineral Density (g/cm^2), bone volume fraction (BVF). It can bring about favourable changes in bone biomarkers such as Serum Osteocalcin (ng/ml), N-terminal propeptide of procollagen type I, tartrate-resistant acid phosphatase 5b, and improve the quality of bone by improving trabecular thickness in alveolar bone, Percentage of bone volume/tissue volume (BV/TV). Another valuable observation was that systemic administration of Scl-Ab might be more beneficial than local administration. The osteoanabolic effects of Scl-Ab may also be beneficial in conditions like Down syndrome, osteoradionecrosis which is characterized by a reduction in osteoblast activity.

The research for alveolar bone regeneration has resulted in different non-bone and bone graft materials. Bone anti-resorptive agents like Scl-antibody are one of the components of the wide-arsenal available to preserve and regenerate bone which is still under research. Additionally, Scl-Ab promoted the vertical restoration of the atrophic edentulous maxillary ridge of rats without surgical interventions suggesting its possible use in vertical alveolar bone augmentation. The conclusions drawn from this review may be applied to design clinical trials to test the effectiveness of Scl-Ab in alveolar bone preservation as well as augmentation/ regeneration.

Data availability statement

As this is a scoping review, the data availability is not applicable.

Funding

This scoping review has not received any funding.

References

1. Könönen E, Gursoy M, Gursoy UK. Periodontitis: A Multifaceted Disease of Tooth-Supporting Tissues. J Clin Med. 2019;8(8):1135. doi:10.3390/JCM8081135
2. Cekici A, Kantarci A, Hasturk H, Dyke TE Van. Inflammatory and immune pathways in the pathogenesis of periodontal disease. Periodontol 2000. 2014;64(1):57. doi:10.1111/PRD.12002
3. Bansal P, Singh P, Bey A, Gupta ND. Sclerostin and occlusion: A brief review. J Indian Soc Periodontol. 2015;19(1):11. doi:10.4103/0972-124X.145785
4. Ten Dijke P, Krause C, de Gorter DJ, Löwik CW, van Bezooijen RL. Osteocyte-derived sclerostin inhibits bone formation: its role in bone morphogenetic protein and Wnt signaling. J Bone Joint Surg Am. 2008;90 Suppl 1(SUPPL. 1):31-35. doi:10.2106/JBJS.G.01183
5. van Bezooijen RL, Roelen BA, Visser A, et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. J Exp Med. 2004;199(6):805-814. doi:10.1084/JEM.20031454
6. Balemans W, Cleiren E, Siebers U, Horst J, Van Hul W. A generalized skeletal hyperostosis in two siblings caused by a novel mutation in the SOST gene. Bone. 2005;36(6):943-947. doi:10.1016/J.BONE.2005.02.019
7. Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet. 2001;10(5):537-543.
8. Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet. 2001;68(3):577-589. doi:10.1086/318811
9. Loots GG, Kneissel M, Keller H, et al. Genomic deletion of a long-range bone enhancer misregulates sclerostin in Van Buchem disease. Genome Res. 2005;15(7):928-935. doi:10.1101/GR.3437105
10. Li X, Warmington KS, Niu QT, et al. Inhibition of sclerostin by monoclonal antibody increases bone formation, bone mass, and bone strength in aged male rats. J Bone Miner Res. 2010;25(12):2647-2656. doi:10.1002/JBMR.182
11. Li X, Ominsky MS, Warmington KS, et al. Increased bone formation and bone mass induced by sclerostin antibody is not affected by pretreatment or cotreatment with alendronate in osteopenic, ovariectomized rats. Endocrinology. 2011;152(9):3312-3322. doi:10.1210/EN.2011-0252
12. Li X, Ominsky MS, Warmington KS, et al. Sclerostin antibody treatment increases bone formation, bone mass, and bone

strength in a rat model of postmenopausal osteoporosis. J Bone Miner Res. 2009;24(4):578-588. doi:10.1359/JBMR.081206

13. Ominsky MS, Boyce RW, Li X, Ke HZ. Effects of sclerostin antibodies in animal models of osteoporosis. Bone. 2017;96:63-75. doi:10.1016/J.BONE.2016.10.019
14. Axelrad TW, Kakar S, Einhorn TA. New technologies for the enhancement of skeletal repair. Injury. 2007;38 Suppl 1(SUPPL. 1). doi:10.1016/J.INJURY.2007.02.010
15. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-473. doi:10.7326/M18-0850
16. Yu SH, Hao J, Fretwurst T, et al. Sclerostin-Neutralizing Antibody Enhances Bone Regeneration Around Oral Implants. Tissue Eng - Part A. 2018;24(21-22):1672-1679. doi:10.1089/ten.tea.2018.0013
17. Witcher PC, Miner SE, Horan DJ, et al. Sclerostin neutralization unleashes the osteoanabolic effects of Dkk1 inhibition. JCI insight. 2018;3(11). doi:10.1172/jci.insight.98673
18. Heiland GR, Zwerina K, Baum W, et al. Neutralisation of Dkk-1 protects from systemic bone loss during inflammation and reduces sclerostin expression. Ann Rheum Dis. 2010;69(12):2152-2159. doi:10.1136/ard.2010.132852
19. Yao Y, Kauffmann F, Maekawa S, et al. Sclerostin antibody stimulates periodontal regeneration in large alveolar bone defects. Sci Rep. 2020;10(1):1-10. doi:10.1038/s41598-020-73026-y
20. Liu M, Kurimoto P, Zhang J, et al. Sclerostin and DKK1 Inhibition Preserves and Augments Alveolar Bone Volume and Architecture in Rats with Alveolar Bone Loss. J Dent Res. 2018;97(9):1031-1038. doi:10.1177/0022034518766874
21. Chen H, Xu X, Liu M, et al. Sclerostin antibody treatment causes greater alveolar crest height and bone mass in an ovariectomized rat model of localized periodontitis. Bone. 2015;76:141-148. doi:10.1016/j.bone.2015.04.002
22. Taut AD, Jin Q, Chung JH, et al. Sclerostin antibody stimulates bone regeneration after experimental periodontitis. J Bone Miner Res. 2013;28(11):2347-2356. doi:10.1002/jbmr.1984
23. Ren Y, Han X, Ho SP, et al. Removal of SOST or blocking its product sclerostin rescues defects in the periodontitis mouse model. FASEB J. 2015;29(7):2702-2711. doi:10.1096/fj.14-265496
24. Tamplen M, Fowler T, Markey J, Knott PD, Suva LJ, Alliston T. Treatment with anti-Sclerostin antibody to stimulate mandibular bone formation. Head Neck. 2018;40(7):1453-1460. doi:10.1002/hed.25128
25. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14(1). doi:10.1186/1471-2288-14-43
26. Fabre S, Funck-Brentano T, Cohen-Solal M. Anti-Sclerostin Antibodies in Osteoporosis and Other Bone Diseases. J Clin Med 2020, Vol 9, Page 3439. 2020;9(11):3439. doi:10.3390/JCM9113439
27. Pham MT, A R, JD G, JM S, A P, SA M. A scoping review of scoping reviews: advancing the approach and enhancing the consistency. Res Synth Methods. 2014;5(4):371-85.
28. Cunningham C, Scheuer L, Black S. Bone Development. Dev Juv Osteol. 2016:19-35. doi:10.1016/B978-0-12-382106-5.00003-7
29. Bellido T, Plotkin LI, Bruzzaniti A. Bone Cells. Basic Appl Bone Biol. August 2013:27-45. doi:10.1016/B978-0-12-416015-6.00002-2
30. Morgan EF, Unnikrisnan GU, Hussein AI. Bone Mechanical Properties in Healthy and Diseased States. https://doi.org/101146/annurev-bioeng-062117-121139. 2018;20:119-143. doi:10.1146/ANNUREV-BIOENG-062117-121139
31. Hong AR, Yang JY, Lee JY, et al. Reactivation of Bone Lining Cells are Attenuated Over Repeated Anti-sclerostin Antibody Administration. Calcif Tissue Int. November 2022. doi:10.1007/S00223-022-01013-8
32. Kuo T-H, Lin W-H, Chao J-Y, et al. Serum sclerostin levels are positively related to bone mineral density in peritoneal dialysis patients: a cross-sectional study. BMC Nephrol. 2019;20(1):266. doi:10.1186/s12882-019-1452-5
33. Cardinal M, Chretien A, Roels T, et al. Gender-Related Impact of Sclerostin Antibody on Bone in the Osteogenesis Imperfecta Mouse. Front Genet. 2021;12. https://www.frontiersin.org/articles/10.3389/fgene.2021.705505.
34. Greenblatt MB, Tsai JN, Wein MN. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. Clin Chem. 2017;63(2):464-474. doi:10.1373/clinchem.2016.259085
35. Saad MA, Aboelwafa RA, Elsayed EH. Could procollagen type I N-terminal propeptide (PINP) and bone alkaline phosphatase (B-ALP) be valid alternative diagnostic markers to dual X-ray absorptiometry (DEXA) in elderly females with osteoporosis? An Egyptian radiological and laboratory monocentric study. Egypt Rheumatol Rehabil 2021 481. 2021;48(1):1-10. doi:10.1186/S43166-021-00069-Y
36. Blumer MJF, Hausott B, Schwarzer C, Hayman AR, Stempel J, Fritsch H. Role of tartrate-resistant acid phosphatase (TRAP) in long bone development. Mech Dev. 2012;129(5-8):162-176. doi:10.1016/J.MOD.2012.04.003
37. Zhang D, Hu M, Chu T, et al. Sclerostin antibody prevented progressive bone loss in combined ovariectomized and concurrent functional disuse. Bone. 2016;87:161-168. doi:10.1016/j.bone.2016.02.005
38. Stolina M, Dwyer D, Niu QT, et al. Temporal changes in systemic and local expression of bone turnover markers during six months of sclerostin antibody administration to ovariectomized rats. Bone. 2014;67:305-313. doi:10.1016/j.bone.2014.07.031
39. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. 2014;370(5):412-420. https://europepmc.org/article/med/24382002. Accessed May 27, 2021.
40. Allison H, Holdsworth G, McNamara LM. Scl-Ab reverts pro-osteoclastogenic signalling and resorption in estrogen deficient osteocytes. BMC Mol Cell Biol. 2020;21(1). doi:10.1186/s12860-020-00322-w
41. Pinzone JJ, Hall BM, Thudi NK, et al. The role of Dickkopf-1 in bone development, homeostasis, and disease. Blood. 2009;113(3):517-525. doi:10.1182/blood-2008-03-145169
42. Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev. 1997;28(1):5-24. doi:10.1016/S0169-409X(97)00048-3
43. Bouaziz W, Funck-Brentano T, Lin H, et al. Loss of sclerostin promotes osteoarthritis in mice via β-catenin-dependent and -independent Wnt pathways. Arthritis Res Ther. 2015;17(1):24. doi:10.1186/s13075-015-0540-6
44. Wehmeyer C, Frank S, Beckmann D, et al. Sclerostin inhibition promotes TNF-dependent inflammatory joint destruction. Sci Transl Med. 2016;8(330). doi:10.1126/scitranslmed.aac4351