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Review

Monoclonal Antibody Therapies in Chronic Inflammatory Diseases: Periodontal Outcomes, Oral Safety, and Clinical Implications—A Scoping Review

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Abstract

Monoclonal antibody-based therapies are widely used in chronic immune-mediated diseases, but their periodontal effects, dentoalveolar safety signals, and exposure characteristics remain incompletely characterized. This scoping review mapped periodontal clinical outcomes, biomarkers, microbiological and imaging findings, dentoalveolar safety, administration, treatment exposure, and pharmaceutical-context reporting. PubMed, Scopus, and Web of Science were searched in July 2026 without publication-year or language restrictions. Twenty-one reports representing 20 studies or cohort families were included. Evidence mainly concerned rheumatoid arthritis and therapies targeting tumor necrosis factor, interleukin-6 receptor, and cluster of differentiation 20. Evidence for interleukin-17A inhibition was insufficient and derived from one confounded five-patient case series. Tocilizumab showed the most consistent reductions in gingival inflammation and bleeding on probing, while structural changes were smaller and inconsistent. Tumor necrosis factor-directed findings were heterogeneous. Small rituximab studies showed favorable clinical or biomarker signals, whereas pharmacovigilance identified infectious and destructive dentoalveolar signals. Exposure reporting was incomplete, and no included periodontal study evaluated formulation stability, storage, cold-chain integrity, or handling deviations. This review integrates treatment-effect evidence, safety signals, and exposure variables across antibody targets and identifies a pharmaceutical–periodontal reporting gap requiring prospective investigation.

Keywords: monoclonal antibodies; antibody-based therapies; periodontal outcomes; administration route; treatment exposure; pharmaceutical stability; drug storage; dentoalveolar safety; scoping review

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1. Introduction

Periodontitis is a chronic inflammatory disease initiated by a dysbiotic dental biofilm and sustained by a dysregulated host response. The current classification uses staging to describe severity and treatment complexity and grading to estimate progression, incorporating modifiers such as smoking and glycemic status [1,2].

Tissue destruction reflects coordinated cytokine, protease, and osteoclastogenic pathways, including tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), receptor activator of nuclear factor kappa-B ligand, and matrix metalloproteinases [3,4].

Periodontitis frequently coexists with chronic immune-mediated inflammatory diseases. Rheumatoid arthritis has received the greatest attention because both conditions involve persistent inflammation, altered innate and adaptive immunity, tissue-destructive cytokines, and pathways related to protein citrullination. Clinical syntheses report a greater periodontal burden among patients with rheumatoid arthritis than among controls [5,6].

Monoclonal antibodies have transformed treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, hidradenitis suppurativa, multiple sclerosis, and other chronic disorders.

Their periodontal relevance differs by therapeutic target: TNF neutralization suppresses leukocyte recruitment and osteoclastogenic signaling; interleukin-6 receptor (IL-6R) blockade modifies acute-phase responses, B-cell activation, and matrix-degrading pathways; cluster of differentiation 20 (CD20)-directed therapy depletes B lymphocytes; and interleukin-17A (IL-17A) inhibition affects neutrophil recruitment and mucosal host defense [7].

As large protein therapeutics, monoclonal antibodies also differ from conventional small molecules in disposition, route, formulation, and handling. Pharmacokinetics are influenced by target-mediated disposition, neonatal Fc receptor recycling, body size, immunogenicity, disease burden, and repeated exposure [8].

Administration route also determines the product-handling pathway. Intravenous products may require reconstitution or dilution, transfer to an infusion container, visual inspection, and a defined preparation-to-administration interval, whereas subcutaneous products are commonly supplied in pre-filled syringes or pens and may be transported, stored, and administered outside an infusion unit [9].

Therapeutic antibodies are conformationally sensitive proteins. Temperature excursions, freezing and thawing, light exposure, agitation, and interfacial stress can promote partial unfolding, aggregation, or particle formation, while oxidation, deamidation, and hydrolytic pathways may alter charge, promote fragmentation, or reduce biological activity [10–12].

Elevated-temperature stress has been shown to alter mAb dimer structure and aggregation propensity, light exposure can cause photo-oxidation, aggregation, and loss of Fc-related or biological function, and spontaneously occurring aggregates can activate innate immune responses in vitro [11–13]. The magnitude and clinical relevance of these changes depend on the individual molecule, formulation, concentration, container-closure system, and duration of exposure. Stability liabilities should therefore be treated as product- and presentation-specific rather than as properties determined by the therapeutic target.

Previous reviews have addressed related components of this field, but their scopes and analytical purposes differ. Balta et al. reviewed host-modulation strategies for periodontal disease, González-Febles and Sanz examined the broader rheumatoid arthritis–periodontitis relationship, and Zamri and de Vries focused on TNF inhibitors in rheumatoid arthritis [4,5,7]. Subsequent systematic reviews evaluated bidirectional periodontal treatment and antirheumatic-drug effects or the broader impact of rheumatoid arthritis therapies on periodontal disease [14,15]. A 2024 scoping review addressed anti-TNF therapy specifi-

cally in rheumatoid arthritis and chronic periodontitis and included seven studies within that restricted clinical framework [16].

These syntheses overlap with individual components of the present evidence base, particularly TNF inhibition, rheumatoid arthritis treatment, and host modulation. They did not primarily map antibody-specific clinical, biological, microbiological, imaging, dentoalveolar safety, administration, exposure, and pharmaceutical-context variables across multiple therapeutic targets and chronic inflammatory indications. The present scoping review therefore complements earlier work by integrating these domains within one evidence map and by separating therapeutic-effect studies from case-based and pharmacovigilance evidence.

Periodontal tissues provide an accessible site in which anti-inflammatory effects, persistent structural disease, and treatment-related infection signals can be observed during chronic therapy, but findings with one molecule should not be extrapolated automatically to another.

The primary objective was to map periodontal inflammatory, structural, biological, microbiological, imaging, and periodontal or dentoalveolar safety outcomes associated with systemic antibody-based therapy.

The secondary objectives were to compare evidence across TNF, IL-6R, and CD20 targets while separately characterizing the insufficient IL-17A evidence; characterize reported routes, doses, dosing intervals, treatment duration, and concomitant therapies; assess how pharmaceutical stability, storage, or handling variables were reported; position the mapped evidence relative to previous reviews; and identify implications for risk-based periodontal surveillance and future research.

2. Materials and Methods

2.1. Review Design

This scoping review was designed to map and critically characterize the available clinical evidence on periodontal outcomes associated with systemic antibody-based therapies in adults with chronic systemic diseases. The review followed Joanna Briggs Institute (JBI) methodological guidance and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [17,18]. The review was not prospectively registered, and no separate publicly accessible protocol was prepared. Although the methodological framework, eligibility criteria, and Population, Concept, and Context criteria were defined before source selection, the absence of prospective registration and a public protocol limits external reproducibility and methodological transparency and may increase the potential for selection bias. This was an oversight during review initiation. Predefined eligibility criteria, a structured screening register, explicit full-text exclusion categories, documented source-selection decisions, and a structured data-charting form were used to maintain internal consistency.

The review aimed to describe the extent, characteristics, pharmacological targets, periodontal outcomes, methodological features, and evidence gaps within the available literature. A structured descriptive and thematic synthesis was undertaken because the purpose was evidence mapping rather than estimation of a pooled treatment effect.

2.2. Eligibility Criteria

Eligibility criteria were structured according to the Population, Concept, and Context (PCC) framework recommended for scoping reviews [18]. Studies involving adults aged 18 years or older who received systemic monoclonal antibody therapy for a chronic systemic disease were eligible. Eligible conditions included immune-mediated inflammatory, autoimmune, rheumatological, dermatological, neurological, gastrointestinal, and hema-

tological diseases. Studies conducted exclusively in pediatric populations were excluded. Mixed-age studies were eligible only when adult data could be identified separately.

The central concept was the occurrence, direction, and characteristics of periodontal outcomes associated with systemic antibody-based therapy. Eligible exposures comprised full-length therapeutic monoclonal antibodies and antigen-binding fragments directly derived from monoclonal antibodies, provided that the administered agent had an identifiable molecular target.

Certolizumab pegol was eligible as a PEGylated humanized anti-TNF Fab′ fragment; for reporting consistency, the umbrella term antibody-based therapy is used throughout for this exposure category. Fusion proteins such as etanercept, conventional disease-modifying antirheumatic drugs (DMARDs), small-molecule inhibitors, and other non-monoclonal biological therapies were not eligible as exposures of interest. Mixed biological regimens were included only when eligible data could be separated from etanercept or other ineligible therapies. Eligible evidence domains included clinical periodontal outcomes, local or systemic biomarkers relevant to periodontal inflammation, subgingival microbiological findings, periodontal or dentoalveolar imaging findings, and periodontal or dentoalveolar adverse events or pharmacovigilance signals.

A predefined comparator was not required. The database search was designed to identify periodontal evidence associated with eligible antibody-based therapies. Periodontal and dentoalveolar adverse events were charted when reported within eligible records; the review was not designed as a comprehensive search of all oral adverse events associated with these agents. Studies conducted in any country and relevant clinical setting were eligible. Original clinical evidence included analytical cross-sectional studies, case-control studies, prospective and retrospective cohorts, longitudinal observational studies, quasi-experimental investigations, case series, case reports, and pharmacovigilance analyses. Reviews, editorials, conference abstracts without sufficient extractable information, animal studies, in vitro studies, and studies without relevant periodontal outcomes were excluded. No lower publication-year limit was applied.

2.3. Information Sources and Search Strategy

A structured electronic search was conducted in July 2026 in PubMed, Scopus, and Web of Science.

The reconstructed search strategies used free-text terms related to periodontal diseases, periodontal clinical and biological outcomes, monoclonal antibodies, biological therapies, and individual therapeutic agents. PubMed automatic term mapping was allowed and syntax was adapted to each database. No restrictions based on language, document access status, or geographic region were introduced during the database searches.

The searches retrieved 176 records from PubMed, 742 from Scopus, and 236 from Web of Science, resulting in 1154 records before duplicate removal. Platform settings, term blocks and the reconstructed database-specific strategies are provided in Supplementary Tables S1–S3. Reconstruction was based on saved exports, documented search fields, and retained search records. Complete verbatim search histories and the exact calendar day of execution were not retained; accordingly, the supplementary strategies are presented as faithful reconstructions rather than direct database exports.

2.4. Selection of Sources of Evidence

All records were consolidated into a single screening register. Duplicate records were removed through exact matching of the PubMed identifier (PMID), normalized digital object identifier (DOI), and normalized title. Potentially similar records remaining after exact matching were reviewed to identify additional duplicates. The screening register,

duplicate-detection fields, source-selection decisions, data-charting form, and critical-appraisal matrices were maintained in Microsoft® Excel® for Microsoft 365 MSO (Version 2605 Build 16.0.20026.20166), 64-bit.

Source selection proceeded in two sequential stages. Titles and abstracts were assessed against the predefined PCC criteria. Full texts of potentially eligible reports were then assessed for systemic indication, identity, and pharmacological class of the administered agent, separability of monoclonal antibody data from etanercept or other ineligible therapies, periodontal relevance of the reported outcomes, study design, and availability of original clinical data. Reasons for exclusion were recorded at the full-text stage. Reports that could not be obtained through available open-access or institutional routes were classified as reports not retrieved and were not counted as eligibility exclusions.

Study investigators or corresponding authors were not contacted to obtain the eight unavailable reports. The included-report register and the mapping of related reports to individual studies or cohort families are provided in Supplementary Tables S4 and S5. The report-level reasons for exclusion following full-text assessment are listed in Supplementary Table S6. Potentially related publications were compared according to authorship, center, recruitment period, sample size, participant characteristics, therapeutic exposure, and outcome assessment. Reports judged to originate from the same or substantially overlapping cohort were grouped as one study or cohort family, and participant numbers were not summed.

The selection process was conducted through a single documented assessment stream using predefined PCC criteria, explicit full-text exclusion categories and a structured decision register. Quality control included reconciliation of stage totals with the PRISMA flow and cross-checking report-level decisions against the inclusion and exclusion registers. Independent duplicate screening and formal inter-reviewer agreement assessment were not performed. The complete numerical flow is presented in Figure 1.

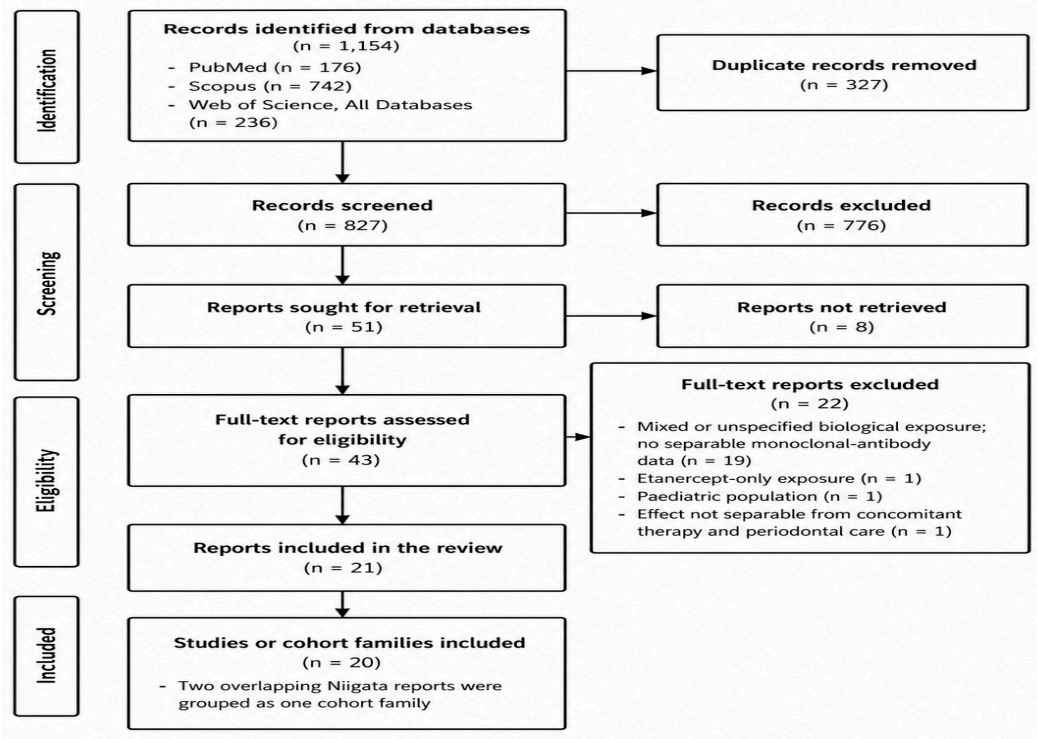

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) flow diagram of source selection. The 21 included reports represented 20 studies or cohort families because two overlapping Niigata reports were grouped to avoid participant double counting.

2.5. Data Charting Process and Data Items

Data were charted through one documented stream using a structured form developed for this scoping review. Variables included bibliographic information, country, clinical setting, design, systemic disease, eligible antibody-based agent, pharmacological target, formulation when reported, route of administration, dose, dosing interval, treatment duration, cumulative or repeated exposure, treatment interruptions, storage or handling deviations when reported, comparator, concomitant medication, periodontal diagnostic criteria, plaque indices, gingival inflammation, bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment level (CAL), tooth loss, alveolar bone findings, imaging outcomes, gingival crevicular fluid (GCF) biomarkers, salivary biomarkers, serum biomarkers, subgingival microbiology, periodontal or dentoalveolar adverse events, funding, conflicts of interest, and principal findings.

The evidence chart for periodontal, biological, microbiological, imaging, and safety outcomes is provided in Supplementary Table S7. Post-charting quality control comprised cross-checks of agent identity and pharmacological target, report-to-study mapping, outcome-domain classification and numerical totals across the included-report register, cohort-family mapping, evidence tables, and narrative synthesis. Independent duplicate charting was not performed.

Data were recorded at the level of eligible antibody-based exposure. When a study included mixed biological treatments, only a separable eligible subgroup was charted. Related reports were mapped to one study or cohort family. Numerical results were charted as reported; missing values were not estimated. Information absent from the full text was recorded as Not Reported. No investigators of included studies were contacted to obtain or confirm missing data. Case reports, case series, and pharmacovigilance data were charted separately from comparative and longitudinal studies and contributed to safety mapping rather than comparative treatment-effect interpretation.

2.6. Critical Appraisal of Included Evidence

Critical appraisal was undertaken to characterize methodological limitations and support interpretation of the evidence map. Appraisal results did not determine eligibility. Design-specific JBI critical appraisal tools were applied to analytical cross-sectional studies, cohort studies, quasi-experimental studies, case reports, and case series [18]. Pharmacovigilance evidence was appraised with attention to case definition, exposure description, reporting completeness, denominator availability, alternative explanations, and limitations in spontaneous reporting. The design-specific critical appraisal results are presented in Supplementary Tables S8–S11.

Overall judgments were assigned using review-specific qualitative categories and were not treated as numerical JBI scores. Low concern indicated adequate reporting across all or nearly all applicable domains without a major threat to interpretation. Moderate concern indicated limited unclear or negative responses that did not invalidate the principal interpretation. High concern indicated multiple limitations in important domains that materially reduced interpretability. Critical concern indicated a major internal inconsistency or absence of core methodological information that precluded reliable effect interpretation. Unclear was retained at the domain level when reporting was insufficient. Studies with major reporting problems remained in the evidence map for transparent narrative reporting but were separated from the principal interpretation. The overall judgments were used to contextualize the interpretability of findings during narrative synthesis rather than to assign formal comparative weights to individual studies. These judgments characterized methodological limitations within the evidence map and should not be interpreted as GRADE assessments of certainty.

2.7. Synthesis and Presentation of Results

The charted evidence was synthesized descriptively and thematically to map its extent, characteristics, direction, and methodological quality. Reported route, dose or dosing interval, treatment duration, repeated exposure, and stability or handling information were mapped before the outcome synthesis by therapeutic target. Stability, storage, cold-chain integrity, and handling were treated as pharmaceutical-context charting variables within the eligible periodontal literature rather than as independent search concepts. Their absence was interpreted as a reporting gap at the periodontal–pharmaceutical interface, not as an absence of stability research on therapeutic antibodies in general. Studies were then grouped by pharmacological target: TNF, IL-6R, CD20, and IL-17A. Within each target, evidence was organized by clinical periodontal outcomes, local and systemic biomarkers, microbiological findings, imaging outcomes, and periodontal or dentoalveolar safety signals. Detailed periodontal and dentoalveolar safety signals and administration/exposure mappings are provided in Supplementary Tables S12 and S13.

Previous reviews were consulted to position the evidence map relative to existing syntheses. Selected experimental pharmaceutical studies, two observational studies of real-world biologic storage, and current European regulatory product information were used solely to contextualize stability, storage, and handling mechanisms and to develop the preliminary hypothesis-generating framework. These contextual sources were not treated as eligible periodontal evidence, did not enter the PRISMA flow or the 21-report evidence map, and were not used to infer that documented periodontal outcomes resulted from product instability.

Therapeutic-effect studies were presented separately from case reports, case series, and pharmacovigilance evidence. Imaging outcomes were analyzed separately from conventional periodontal measurements. Findings were categorized as favorable, neutral, mixed, unfavorable, or indeterminate. These categories did not represent pooled estimates. A quantitative meta-analysis was not undertaken because sources differed substantially in systemic disease, monoclonal antibody, comparator, periodontal case definition, outcome measurement, follow-up, and statistical reporting.

3. Results

3.1. Selection of Sources of Evidence

The searches identified 1154 records: 176 from PubMed, 742 from Scopus, and 236 from Web of Science. After removal of 327 duplicates, 827 unique records underwent title and abstract screening, and 776 were excluded.

Fifty-one reports were sought for full-text assessment. Eight could not be obtained and were classified as reports not retrieved. Forty-three full-text reports were assessed, and 22 were excluded. Principal reasons included non-separable monoclonal antibody exposure, inclusion of etanercept or another ineligible therapy in an aggregated group, absence of relevant periodontal outcomes, ineligible populations, and inability to isolate the monoclonal antibody from concomitant interventions.

Twenty-one reports met the eligibility criteria. Two Niigata publications were grouped as one cohort family to prevent double counting. The final evidence map comprised 20 studies or cohort families. The selection process is shown in Figure 1.

As illustrated in Figure 1, the largest reduction occurred during title and abstract screening, while full-text assessment excluded reports primarily because the monoclonal antibody exposure or periodontal outcome could not be isolated. The separation of eight reports that could not be retrieved from the twenty-two full-text exclusions preserves the distinction between unavailable evidence and evidence assessed as ineligible.

Grouping the two overlapping Niigata reports as one cohort family prevented duplicate participant counting.

3.2. Characteristics of the Included Evidence

The included reports were published between 2008 and 2024. Most evaluated rheumatoid arthritis. Additional indications included psoriasis, hidradenitis suppurativa, neurological disorders, hematological conditions, and other chronic immune-mediated diseases. The principal characteristics of the included studies and cohort families are presented in Table 1.

Table 1 shows that rheumatoid arthritis dominated the evidence base and that most molecule-specific groups were small. Designs ranged from prospective follow-up to single-case and pharmacovigilance evidence, while periodontal assessment varied from full-mouth probing and formal case definitions to screening indices, imaging, or non-standardized clinical descriptions.

Table 1. Core characteristics and principal periodontal findings of the included studies. Detailed biological and microbiological charting is provided in Supplementary Table S7.

Study	Country, Design, and Systemic Context	Target or Exposure	Eligible Sample and Follow-Up	Principal Periodontal Finding	Interpretive Status
Samborska-Mazur et al., 2024 [19]	Poland; Cross-sectional; Rheumatoid arthritis	Anti-TNF antibodies vs tocilizumab	50; Single assessment	No between-group differences in API, PBI, or PSI	Neutral
Bartak et al., 2024 [20]	France/global; Case series + pharmacovigilance; Anti-CD20-treated disorders	Ocrelizumab, rituximab, ofatumumab	6 cases + VigiBase; Variable	Recession, periodontitis, abscesses, bone/tooth loss signals	Safety signal
Yao et al., 2023 [21]	Denmark; Case report; Hidradenitis suppurativa	Adalimumab	1; 3 months	Clinical improvement in pain, bleeding, inflammation, and plaque	Exploratory favorable
Hatipoğlu et al., 2022 [22]	Türkiye; Cross-sectional case-control; Rheumatoid arthritis	Rituximab	20 exposed; 70 total; Single assessment	No clinical differences; markedly lower GCF IL-1β under rituximab	Biomarker favorable
Wu et al., 2021 [23]	China; Cross-sectional; Rheumatoid arthritis	MTX + rituximab subgroup	122 eligible; 862 reported; Single assessment	Lower BOP and selected pathogen frequencies in rituximab subgroup	Critical reporting concerns; retained for mapping but not used for target-specific conclusions
Ancuța et al., 2021 [24]	Romania; Prospective pre-post; Rheumatoid arthritis	Tocilizumab	51; 3 and 6 months	GI/BOP improved at 3 months; PPD at 6 months; CAL unchanged	Favorable
Tachibana et al., 2020 [25]	Japan; Prospective imaging cohort; Rheumatoid arthritis	Tocilizumab subgroup	13 eligible; 60 total; 6 months	No significant change in periodontal SUVmax	Neutral periodontal

Table 1. *Cont.*

Study	Country, Design, and Systemic Context	Target or Exposure	Eligible Sample and Follow-Up	Principal Periodontal Finding	Interpretive Status
Brianti et al., 2020 [26]	Italy; Case series; Psoriasis	Adalimumab then secukinumab	5; 14 months after switch	Acute periodontitis during adalimumab; no recurrence after switch plus dental treatment	Insufficient IL-17A evidence; one confounded five-patient case series
Rinaudo-Gaujous et al., 2019 [27]	France; Longitudinal; Rheumatoid arthritis	Infliximab	79; 6 months	MMP-3 and RA activity improved; anti-P. gingivalis did not decrease	Dissociated
Äyräväinen et al., 2018 [28]	Finland; Prospective cohort; Rheumatoid arthritis	Multiple antibodies including rituximab/ anti-TNF	28 biologic RA subgroup; Mean 15.9 months	No consistent drug-specific change in salivary MMP-8	Neutral
Ziebolz et al., 2018 [29]	Germany; Cross-sectional; Rheumatoid arthritis	MTX + rituximab subgroup	19 eligible; 168 total; Single assessment	Lower BOP in MTX + rituximab; PPD/AL similar	Limited favorable
Martu et al., 2018 [30]	Romania; Cross-sectional; Rheumatoid arthritis	Rituximab, adalimumab, tocilizumab combinations	Not reported; Single assessment	Authors reported lower oral indices in some biological combinations	Critical reporting concerns; retained for mapping but not used for principal interpretation
Coat et al., 2015 [31]	France; Cross-sectional + longitudinal; Rheumatoid arthritis	Rituximab	21; 6 months; subgroup to 48 months	Lower MGI, PPD, and AL in repeatedly treated rituximab group	Exploratory favorable
Kobayashi et al., 2014–2015 [32,33]	Japan; Overlapping longitudinal cohort reports; Rheumatoid arthritis	Tocilizumab and adalimumab/ TNFi	60 broad cohort; overlapping adalimumab report; 3 and 6 months	GI, BOP, PPD, and CAL improved under TCZ and TNFi	Favorable
Kobayashi et al., 2014 [34]	Japan; Comparative longitudinal; Rheumatoid arthritis	Tocilizumab	28 exposed; 55 total; 8 weeks	Greater 8-week reductions in GI, BOP, PPD, CAL, MMP-3, and IL-6	Favorable
Üstün et al., 2013 [35]	Türkiye; Pre-post; Rheumatoid arthritis	Adalimumab or infliximab	16; 30 days	Early reductions in clinical inflammation and GCF/salivary mediators	Early favorable
Mayer et al., 2013 [36]	Israel; Cross-sectional; Autoimmune diseases; exposed RA subgroup	Infliximab	10 exposed; 58 total; Single assessment	More favorable periodontal parameters and lower GCF TNF-α	Cross-sectional favorable
Mirrielees et al., 2010 [37]	USA; Case-control cross-sectional; Rheumatoid arthritis	Monoclonal anti-TNF antibodies	18 exposed; 105 total; Single assessment	Altered salivary IL-1β, MMP-8, and TNF-α profiles	Mixed

Table 1. *Cont.*

Study	Country, Design, and Systemic Context	Target or Exposure	Eligible Sample and Follow-Up	Principal Periodontal Finding	Interpretive Status
Mayer et al., 2009 [38]	Israel; Cross-sectional; Rheumatoid arthritis	Infliximab	10 exposed; 30 total; Single assessment	More favorable clinical parameters and lower GCF TNF-α	Exploratory favorable
Pers et al., 2008 [39]	France; Cross-sectional + longitudinal; Rheumatoid arthritis	Infliximab	40; longitudinal subgroup 9; Long-term; ≥9 infusions	Greater gingival inflammation without worsening attachment loss	Divergent

Abbreviations: AL, attachment loss; BOP, bleeding on probing; CAL, clinical attachment level; CD20, cluster of differentiation 20; CPITN, Community Periodontal Index of Treatment Needs; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; GCF, gingival crevicular fluid; GI, gingival index; IL-6R, interleukin-6 receptor; MGI, modified gingival index; MMP, matrix metalloproteinase; MTX, methotrexate; PPD, probing pocket depth; RA, rheumatoid arthritis; SUVmax, maximum standardized uptake value; TCZ, tocilizumab; TNF, tumor necrosis factor; TNFi, tumor necrosis factor inhibitor.

The evidence map included analytical cross-sectional studies, prospective and retrospective cohorts, longitudinal pre-post investigations, case-control studies, case reports, case series, and pharmacovigilance analyses. Investigated targets were TNF, IL-6R, CD20, and IL-17A. Eligible sample sizes ranged from one patient to 862 participants, although most molecule-specific groups contained fewer than 60 exposed participants and several contained fewer than 20.

Periodontal measures included plaque indices, the gingival index (GI), the papillary bleeding index (PBI), BOP, PPD, CAL, screening indices, tooth mobility, tooth loss, alveolar bone changes, and one fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) measure. Biological outcomes included cytokines, matrix metalloproteinases, acute-phase reactants, and antibody responses measured in GCF, saliva, or serum. Two studies assessed subgingival microorganisms through targeted polymerase chain reaction (PCR). Periodontal and dentoalveolar safety findings included gingival recession, acute periodontitis, abscesses, alveolar bone loss, tooth mobility, tooth loss, and dental infection.

3.3. Distribution of Evidence by Pharmacological Target

TNF-targeted agents represented the largest category. Five studies or cohort families contributed IL-6R evidence, principally for tocilizumab. CD20-targeted evidence included rituximab clinical studies and pharmacovigilance data for ocrelizumab, rituximab, and ofatumumab. IL-17A evidence was insufficient for periodontal conclusions and consisted of one confounded five-patient case series. The integrated study-level overview is presented in Table 1.

3.4. Administration and Exposure Characteristics of the Included Therapies

Administration reporting varied substantially. Intravenous regimens included infliximab at 3 mg/kg every 6–8 weeks or a fixed 200 mg every 8 weeks, tocilizumab at 8 mg/kg every 4 weeks, and rituximab at 1000 mg in two infusions separated by two weeks, with repeated courses at approximately 24-week or longer intervals [22,31,32,36,38,39]. Ocrelizumab was administered intravenously at six-month intervals in the anti-CD20 case series [20].

Subcutaneous exposure included weekly tocilizumab [24], tocilizumab 162 mg every two weeks [32], adalimumab 40 mg every two weeks in the Niigata cohort [33], a hidradeni-

tis suppurativa loading regimen followed by adalimumab 40 mg weekly [21], adalimumab 40 mg every 15 days and secukinumab 300 mg every 30 days in the psoriasis case series [26], and ofatumumab in the anti-CD20 pharmacovigilance analysis [20].

Table 2 summarizes reported administration patterns and limitations, with molecule-level details in Supplementary Table S13. No included periodontal study evaluated formulation stability, cold-chain integrity, storage, or handling.

Table 2. Descriptive summary of reported administration routes, doses, schedules, and exposure limitations.

Target	Eligible Agents	Reported Route	Reported Dose and Schedule	Principal Reporting Limitation
TNF	Infliximab; adalimumab; golimumab; certolizumab pegol	Infliximab, IV; adalimumab and other subcutaneous products, SC when specified	Infliximab 3 mg/kg every 6–8 weeks or 200 mg every 8 weeks; adalimumab 40 mg weekly or every 2 weeks in specific reports [19,21,26,27,33,35–39]	Molecule-specific route, dose, duration, cumulative exposure, and interruptions were frequently not reported
IL-6R	Tocilizumab	IV infusion or SC injection	IV 8 mg/kg every 4 weeks; SC 162 mg weekly or every 2 weeks in specific studies [19,24,25,32–34]	Cumulative exposure, formulation, and treatment interruptions were incompletely reported
CD20	Rituximab; ocrelizumab; ofatumumab	Rituximab and ocrelizumab, IV; ofatumumab, SC in pharmacovigilance data	Rituximab commonly involved two 1000 mg infusions 2 weeks apart, with repeated courses at approximately 24-week or longer intervals; ocrelizumab was reported at 6-month intervals [20,22,23,28,29,31]	Dose and cumulative exposure were unavailable for several cases and pharmacovigilance reports
IL-17A	Secukinumab	SC injection	300 mg every 30 days after adalimumab discontinuation in the only eligible case series [26]	One confounded five-patient case series; concurrent debridement and antibiotics; no standardized primary IL-17A evaluation

Abbreviations: CD20, cluster of differentiation 20; IL-6R, interleukin-6 receptor; IL-17A, interleukin-17A; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.

Table 2 shows that administration and exposure were sufficiently detailed in only a subset of studies. The table reports the available route, dose, and schedule data without attributing periodontal effects to a specific route or regimen. Clinical implications are addressed separately in the Discussion.

3.5. IL-6R-Targeted Evidence

Five studies or cohort families mapped periodontal outcomes associated with IL-6R inhibition [24,25,32–34]. The most consistent findings concerned gingival inflammation and BOP.

In a prospective study of 51 patients, GI and BOP decreased after three months of weekly subcutaneous tocilizumab, while PPD decreased after six months. CAL, plaque, and tooth number remained unchanged [24].

Kobayashi et al. compared 28 patients receiving tocilizumab with 27 rheumatoid arthritis controls. After eight weeks, the mean change in BOP was $-5.06 \pm 1.39\%$ versus $+2.61 \pm 1.49\%$; PPD changed by -0.12 ± 0.03 mm versus $+0.03 \pm 0.03$ mm; and CAL changed by -0.10 ± 0.03 mm versus $+0.03 \pm 0.03$ mm. Plaque remained stable.

Serum matrix metalloproteinase-3 (MMP-3) changed by −32.92 ± 15.91 ng/mL versus +17.86 ± 7.37 ng/mL [34].

Related Niigata reports described improvements in GI, BOP, PPD, and CAL after tocilizumab and were mapped as one cohort family [32,33]. A cross-sectional comparison found no significant differences between anti-TNF therapy and tocilizumab for plaque, PBI, or periodontal screening score [19]. A prospective FDG-PET/CT study reported no significant change in periodontal maximum standardized uptake value (SUVmax) after six months; higher baseline uptake correlated with a smaller improvement in rheumatoid arthritis activity [25].

3.6. TNF-Targeted Evidence

TNF-targeted evidence included infliximab, adalimumab, golimumab, and certolizumab pegol [19,21,26,27,33,35–39]. As defined in the eligibility criteria, certolizumab pegol was retained as an antigen-binding fragment rather than a full-length antibody. Several studies reported reductions in gingival inflammation, BOP, PPD, or local inflammatory mediators.

In a 16-patient pre–post study, adalimumab or infliximab was associated with reductions in periodontal inflammatory indices and GCF IL-1β, interleukin-8 (IL-8), and monocyte chemoattractant protein-1 after 30 days [35]. Two cross-sectional studies from one Israeli center, conducted during separate recruitment periods, reported more favorable periodontal parameters and lower GCF tumor necrosis factor alpha (TNF-α) in infliximab-treated patients than in rheumatoid arthritis comparators not receiving anti-TNF therapy [36,38].

The adalimumab-specific Niigata report described reductions in periodontal inflammatory indices and changes in serum inflammatory profiles after three months and was mapped within the broader cohort family [33]. Infliximab reduced serum MMP-3 from 119 ± 103 ng/mL to 62.44 ± 52 ng/mL after six months, whereas antibodies against Porphyromonas gingivalis did not decrease [27].

Salivary IL-1β, matrix metalloproteinase-8 (MMP-8), and TNF-α profiles differed among anti-TNF users, non-users, periodontitis patients, and controls in a cross-sectional study [37].

Findings were not uniformly favorable. Long-term infliximab was associated with greater gingival inflammatory expression without worsening CAL [39]. One case report described clinical improvement after adalimumab [21], while a five-patient case series reported acute periodontitis after 8–14 months of adalimumab, with PPD of 4–6 mm, BOP, recession, alveolar bone resorption, and periodontal ligament destruction [26].

The TNF-targeted map therefore included favorable, neutral, divergent, and adverse findings across clinical, biological, and safety domains.

3.7. CD20-Targeted Evidence

CD20-targeted evidence was derived mainly from rituximab studies, while ocrelizumab and ofatumumab appeared primarily in pharmacovigilance data [20,22,23,28,29,31].

Rituximab-treated patients had GCF IL-1β concentrations of 1.85 ± 1.67 pg, compared with 10.50 ± 13.16 pg in patients receiving other DMARDs and 34.12 ± 29.45 pg in controls. Clinical periodontal parameters did not differ significantly [22].

A German cross-sectional study reported BOP of 25.75 ± 19.96% in the methotrexate plus rituximab subgroup and 43.74 ± 19.72% in the methotrexate plus TNF-antagonist subgroup, without significant differences in PPD, attachment loss, or periodontal severity [29].

Coat et al. reported lower modified GI, PPD, and attachment loss among patients receiving repeated rituximab courses. Mean PPD was 2.06 ± 0.37 mm versus 2.63 ± 0.73 mm, and attachment loss was 2.59 ± 0.80 mm versus 2.90 ± 0.97 mm [31].

Two reports evaluated subgingival microbial patterns in methotrexate plus rituximab groups. The German study identified treatment-related differences in selected microorganisms [29].

A larger Chinese study reported lower frequencies of selected pathogens but contained major inconsistencies in sample-size calculation, age criteria, and numerical reporting and was mapped separately [23]. A Finnish cohort did not identify a consistent drug-specific reduction in salivary MMP-8 [28].

Pharmacovigilance data involving ocrelizumab, rituximab, and ofatumumab included gingival recession, gingivitis, periodontitis, abscesses, alveolar bone loss, tooth mobility, and tooth loss. Gingival recession generated a disproportionality signal for ocrelizumab [20].

3.8. IL-17A-Targeted Evidence

The available evidence for IL-17A inhibition was insufficient for periodontal conclusions and consisted of one case series of five patients. Acute periodontitis developed during adalimumab treatment, after which secukinumab was introduced together with periodontal debridement and systemic antibiotics. No recurrence was reported during 14 months, but secukinumab was not evaluated as an isolated primary exposure and standardized periodontal outcomes were not assessed prospectively. The report therefore does not permit attribution of periodontal changes to IL-17A inhibition [26].

3.9. Periodontal and Dentoalveolar Safety Evidence

Three reports contributed direct periodontal or dentoalveolar safety evidence, and one additional study described a divergent gingival response [20,21,26,39]. The individual observations and their principal interpretive limitations are summarized in Table 3. Complete charting is provided in Supplementary Table S12.

Table 3 separates direct adverse-event observations from therapeutic-effect evidence. Its entries should be interpreted as signals requiring clinical attention, not as incidence estimates or proof of causation, because the reports lacked controlled denominators and were affected by co-treatment, baseline periodontal disease, and spontaneous-reporting limitations.

The anti-CD20 pharmacovigilance study combined six clinical cases with a VigiBase disproportionality analysis. Reported complications included recession, gingivitis, periodontitis, infection, abscess formation, bone loss, tooth mobility, and tooth loss.

Time to onset ranged from 10 days to 2 years for ocrelizumab and 6 to 12 years for rituximab in the clinical cases [20].

The adalimumab case series documented acute periodontitis after a mean exposure of approximately 11 months.

All patients received periodontal instrumentation and antibiotics, and one underwent guided bone regeneration [26].

The hidradenitis suppurativa case documented improvement rather than deterioration after adalimumab but lacked standardized measurements and a comparator [21].

No controlled study reported a reliable incidence of periodontal adverse events. These findings therefore represent safety signals and clinical observations rather than quantified treatment-related risks.

Table 3. Concise mapping of periodontal and dentoalveolar safety signals reported with eligible antibody-based therapies. Complete charting is provided in Supplementary Table S12.

Study	Therapy/Target	Reported Periodontal or Dentoalveolar Finding	Clinical Course/Management	Interpretive Limitation
Bartak et al., 2024 [20]	Ocrelizumab, rituximab, ofatumumab (CD20); neurological/hematological indications	Recession, gingivitis, periodontitis, bone loss, abscess, infection, mobility, and tooth loss	Onset ranged from 10 days to 2 years for ocrelizumab and 6–12 years for rituximab. Management and outcomes varied and included scaling, antibiotics, restorative/prosthetic care, implants, and proposed grafting.	Spontaneous reporting, no denominator, and confounding by disease, smoking, xerostomic drugs, and previous therapies
Yao et al., 2023 [21]	Adalimumab (TNF); hidradenitis suppurativa	No adverse events; improvement in pain, bleeding, and gingival inflammation after 3 months	No specific periodontal treatment was initiated; clinical and photographic improvement was reported.	Single uncontrolled case without standardized periodontal measurements
Brianti et al., 2020 [26]	Adalimumab then secukinumab (TNF/IL-17A); psoriasis	Acute periodontitis after 8–14 months of adalimumab, with PPD 4–6 mm, BOP, recession, and bone/ligament destruction	Debridement and antibiotics accompanied switching; no recurrence was reported during 14 months. One patient underwent guided bone regeneration.	Concurrent dental treatment and antibiotics prevent attribution of non-recurrence to secukinumab
Pers et al., 2008 [39]	Infliximab (TNF); rheumatoid arthritis	Higher gingival inflammation without worsening clinical attachment loss during long-term therapy	No periodontal intervention was delivered within the study; the longitudinal subgroup had received at least 9 infusions.	Small longitudinal subgroup and non-randomized design

Abbreviations: BOP, bleeding on probing; CD20, cluster of differentiation 20; IL-17A, interleukin-17A; PPD, probing pocket depth; TNF, tumor necrosis factor.

3.10. Critical Appraisal of the Included Evidence

Critical appraisal identified moderate methodological concerns in twelve studies, high concerns in six studies, and critical concerns in two studies. No source was classified as having low concern.

Recurrent limitations included inadequate management of confounding, small molecule-specific groups, incomplete reporting of exposure and concomitant treatment, heterogeneous periodontal assessment, lack of examiner calibration, and uncontrolled pre–post designs.

The two studies with critical concerns presented substantial deficiencies in sample description, eligibility criteria, group allocation, numerical results, or statistical reporting [23,30]. Their findings were retained for transparency but separated from the principal interpretation. Case-based and pharmacovigilance evidence was analyzed independently from comparative clinical studies.

4. Discussion

This scoping review mapped 21 reports representing 20 studies or cohort families and identified a heterogeneous evidence base dominated by observational designs, small molecule-specific groups, variable periodontal definitions, incomplete exposure reporting, and limited control of confounding.

The principal pattern was a more frequent change in periodontal inflammation than in structural periodontal support.

The included evidence also showed that administration route and dosing schedule were reported inconsistently and that stability, storage, cold-chain integrity, and handling were not evaluated within the included periodontal studies.

4.1. Pharmacological Interpretation by Therapeutic Target

IL-6R inhibition with tocilizumab showed the most coherent pattern. Longitudinal studies reported reductions in GI and BOP, while changes in PPD and CAL were smaller or absent [24,32–34].

A cross-sectional comparison and an FDG-PET/CT study provided neutral findings for screening and imaging outcomes [19,25].

IL-6R blockade interrupts membrane-bound and soluble receptor signaling, attenuates acute-phase responses, and may reduce downstream matrix-degrading and osteoclastogenic activity.

This pharmacodynamic profile provides biological plausibility for relatively rapid reduction of gingival inflammation without predictable restoration of attachment [3,4].

TNF-targeted evidence was broader but less consistent. Several studies reported lower clinical inflammatory indices or local mediators [35,36,38], while others identified stable periodontal serology, unchanged salivary biomarkers, or greater gingival inflammation without additional attachment loss [27,37,39].

A single adalimumab case improved, whereas five patients developed acute periodontitis during adalimumab exposure [21,26].

TNF blockade may reduce cytokine amplification and vascular inflammatory activity, but it does not remove dysbiotic biofilm or reverse established connective-tissue and bone damage.

Differences in molecular structure, Fc-related properties, route, interval, tissue exposure, systemic indication, and concomitant therapy probably contributed to the heterogeneous map. Accordingly, the evidence does not support a class effect for TNF-directed agents or extrapolation from one molecule to another.

CD20-targeted findings were also mixed. Rituximab was associated with lower GCF IL-1β and favorable clinical findings in several small studies [22,29,31]. B-cell depletion may reduce antigen presentation, autoantibody-related immune activation, and selected cytokine pathways, but may also alter humoral defense and infection susceptibility.

The better-documented German study identified selected microbiological differences without demonstrating restoration of a health-associated microbiome [29]. The larger Chinese report was classified as having critical reporting concerns and was retained for mapping only; it did not support target-specific microbiological conclusions [23]. The second report with critical concern was likewise excluded from the principal interpretation because its group definitions and numerical reporting were insufficient [30].

Pharmacovigilance evidence contained reports of infectious and destructive dentoalveolar events during rituximab, ocrelizumab, and ofatumumab exposure [20]. These signals cannot estimate incidence or establish causality and should not be merged with clinical effect studies.

Evidence concerning IL-17A inhibition was insufficient for periodontal conclusions. The only eligible report was a five-patient case series in which secukinumab followed adalimumab-associated acute periodontitis and was introduced alongside periodontal debridement and antibiotics. The report did not assess secukinumab as an isolated primary exposure and cannot establish a periodontal effect of IL-17A inhibition [26].

IL-17A participates in neutrophil recruitment and mucosal antimicrobial defense, so both anti-inflammatory benefit and infection-related harm are biologically plausible, but neither could be established clinically.

4.2. Positioning of the Present Review Relative to Previous Reviews

The present review overlaps with earlier syntheses and should be interpreted as complementary to them. Previous reviews addressed host modulation, the rheumatoid arthritis–periodontitis relationship, TNF inhibition, or the effects of broader antirheumatic treatment [4,5,7,14–16]. The current review does not claim that the individual tocilizumab, TNF-directed, or rituximab findings are newly reported. Its incremental contribution is the integration of these evidence streams within an antibody-specific scoping framework.

Differences in eligibility and search coverage also affected the evidence base. The 2024 anti-TNF scoping review included seven studies in rheumatoid arthritis and chronic periodontitis and considered etanercept within the TNF inhibitor category [16]. The present review excluded fusion proteins and mixed biological cohorts when antibody-specific results could not be separated. Relative to reviews searched through January or September 2023, the present map also includes later or differently scoped evidence, including the Yao, Bartak, and Samborska-Mazur reports [19–21].

The analytical distinction lies in mapping clinical periodontal measures, biomarkers, microbiology, imaging, dentoalveolar safety, administration, and treatment exposure together while separating comparative treatment evidence from case-based and pharmacovigilance signals. This structure shows that inflammatory measures changed more often than structural support, that safety signals cannot estimate incidence, and that exposure reporting remained incomplete. Table 4 summarizes the relationship between the present review and the principal prior sources.

Table 4. Positioning of the present scoping review relative to previous reviews and focused evidence sources.

Source	Design	Scope	Primary Analytical Focus	Complementary Contribution of the Present Review
Balta et al., 2021 [4]	Critical review	Host-modulation strategies for periodontal disease	Mechanisms and therapeutic approaches	Antibody-specific evidence mapping across clinical, exposure, and safety domains
Zamri and de Vries, 2020 [7]	Narrative review	TNF inhibitors in rheumatoid arthritis	Periodontal measures and treatment duration	Multiple antibody targets, non-RA indications, and pharmaceutical-context reporting
Inchingolo et al., 2023 [14]	Systematic review	Periodontal treatment and DMARD effects in rheumatoid arthritis	Bidirectional periodontal and rheumatological outcomes	Antibody-specific eligibility, exposure mapping, and distinct safety evidence
Petit et al., 2024 [15]	Systematic review; 35 studies	Rheumatoid arthritis treatments, including csDMARDs and bDMARDs	Treatment effects on periodontal disease	Cross-indication antibody–target mapping and pharmaceutical-context variables
Shyamkumar et al., 2024 [16]	Scoping review; 7 studies	Anti-TNF therapy in rheumatoid arthritis and chronic periodontitis	TNF-directed periodontal effects	Fusion-protein exclusion, multiple antibody targets, and exposure and safety domains
Bartak et al., 2024 [20]	Case series and VigiBase analysis	Anti-CD20 therapies	Dental adverse events and disproportionality signals	Integration with comparative periodontal evidence while retaining a separate safety interpretation

The pharmaceutical–periodontal component adds a reporting lens rather than a demonstrated clinical mechanism. No included periodontal study measured product

quality or connected a documented handling deviation with an oral outcome. The resulting framework therefore defines testable variables for future research and does not establish causal or comparative treatment effects.

4.3. Inflammatory Control and Structural Periodontal Recovery

A recurrent finding was the dissociation between inflammatory improvement and structural periodontal change. GI, BOP, and inflammatory biomarkers responded more frequently than CAL, tooth support, or alveolar bone outcomes. Cytokine inhibition can modify inflammatory signaling within weeks or months, whereas attachment gain and bone recovery require sustained biofilm control, mechanical periodontal therapy, favorable healing, and longer observation. Biomarker reductions should therefore not be interpreted as surrogates for periodontal stability [3,4]. Mechanistically, this pattern supports a distinction between modulation of periodontal inflammation and restoration of structural periodontal support. It does not establish a target-specific causal mechanism because the underlying studies differed in periodontal treatment, systemic disease activity, concomitant medication, follow-up, and confounding control.

Interpretation was also constrained by variation in periodontal treatment, antibiotic exposure, background DMARDs and corticosteroids, smoking, diabetes, plaque control, and systemic disease activity. These factors were incompletely reported or controlled and may independently alter periodontal inflammation and healing. Observed changes therefore cannot be attributed exclusively to monoclonal antibody exposure.

4.4. Administration, Exposure, and Pharmaceutical Context

The included therapies ranged from repeated intravenous infusions to weekly, fortnightly, or monthly subcutaneous injections. Route and interval influence the temporal profile of exposure, treatment burden, adherence, and tolerability. Intravenous dosing provides immediate systemic availability, whereas subcutaneous absorption is slower and may be influenced by injection volume, formulation, device, site, and local tissue transport [8,9]. The periodontal studies were not designed to compare routes, and their findings do not support an intravenous-versus-subcutaneous effectiveness conclusion.

Exposure reporting was often insufficient for interpreting cumulative pharmacodynamic effects. Exact dose, route, interval, prior biological exposure, treatment interruption, and concomitant corticosteroid or DMARD use should be documented consistently. These data are particularly important when oral events occur after months or years of therapy or shortly after repeated administration.

Monoclonal antibody formulations are sensitive to temperature excursions, freezing, light exposure, agitation, and interfacial stress. Depending on the individual molecule and formulation, these stressors can promote aggregation or particle formation, oxidation, fragmentation, or loss of biological activity [10–13]. Current regulatory product information for representative TNF-, IL-6R-, CD20-, and IL-17A-directed therapies therefore specifies product- and presentation-specific refrigeration, protection from light, restrictions on freezing or shaking, and controlled preparation or in-use conditions [40–46].

External rheumatology studies indicate that temperature deviations can occur during home storage of biologic medicines. In a multicenter Dutch study using validated temperature loggers, only 17 of 255 patients (6.7%) stored bDMARDs continuously within the recommended range; 24.3% recorded temperatures below 0 degrees C for more than 2 consecutive hours [47]. In a Brazilian prospective study, 67 of 81 participants (82.7%) had at least one temperature excursion, including 12.3% with a negative temperature measurement [48]. These findings establish the practical occurrence of storage deviations in selected

rheumatology settings, but they do not demonstrate degradation of the administered product or any periodontal consequence.

Periodontal studies may not capture these variables because product transport and storage usually occur outside the dental research setting, while study protocols prioritize therapeutic exposure and clinical outcomes. Retrospective verification requires temperature records, product and lot identification, presentation-specific thresholds, and documentation of preparation or device handling. Even when a deviation is recorded, attribution requires confirmation that product quality or delivered exposure changed.

None of the included periodontal studies documented a product-quality deviation or analytically assessed the material administered to patients. Accordingly, no observed change in GI, BOP, PPD, CAL, infection, bone support, mobility, or tooth loss can be attributed to pharmaceutical instability. The contribution of the present review is hypothesis-generating. A deviation that reduces delivered activity could theoretically weaken systemic inflammatory control, while aggregate or particle formation could theoretically modify immunogenicity, exposure, or tolerability. These mechanisms remain untested in periodontal populations and do not support a causal pathway to attachment loss, bone loss, or tooth loss.

The potential relationships are summarized by therapeutic target in Table 5. Stability remains determined by the individual molecule, formulation, presentation, container-closure system, and handling history rather than by the therapeutic target.

Interpretive disclaimer. Table 5 is a preliminary mechanistic and hypothesis-generating framework constructed from selected, non-systematically identified external pharmaceutical literature and representative regulatory product information. It is not supported by direct clinical evidence from the 21 included reports and should not be interpreted as evidence that product instability caused or modified any periodontal outcome.

Table 5. Preliminary hypothesis-generating mapping of product- and presentation-specific stability and handling liabilities to periodontal and dentoalveolar outcome domains.

Therapeutic Target and Represented Agents	Pharmaceutical Stability and Handling Context	Hypothesized Relationship with Mapped Periodontal or Oral Outcomes
TNF: infliximab, adalimumab, golimumab, and certolizumab pegol	IV infliximab involves reconstitution, dilution, transfer, and a defined preparation-to-administration interval. SC products introduce cold-chain, pre-filled-device, and self-administration variables. Temperature excursions, freezing, light, agitation, and interfacial stress may produce product-specific degradation or particle formation [10–13,40,41].	Reduced delivered activity or altered immunogenicity risk could theoretically attenuate systemic and gingival inflammatory control, increasing variability in GI, BOP, or local biomarkers. Acute periodontitis and destructive findings reported in the evidence map remain unlinked to product quality.
IL-6R: tocilizumab	IV and SC presentations involve different dilution, in-use, storage, and device-handling pathways. Refrigeration, protection from light, and avoidance of freezing are presentation-specific requirements [10–13,42].	Variable active exposure could theoretically reduce the otherwise coherent improvements observed in GI and BOP or obscure relationships with PPD and CAL. No periodontal outcome was associated with a documented storage or handling deviation.

Table 5. *Cont.*

Therapeutic Target and Represented Agents	Pharmaceutical Stability and Handling Context	Hypothesized Relationship with Mapped Periodontal or Oral Outcomes
CD20: rituximab, ocrelizumab, and ofatumumab	IV preparations involve dilution, infusion–container compatibility, aseptic preparation, and defined in-use conditions; SC ofatumumab introduces pre-filled-device and home-storage variables. Temperature, light, freezing, agitation, and dose-delivery errors remain product-specific concerns [10–13,43–45].	Altered exposure could theoretically modify the depth or duration of B-cell depletion or immunogenicity and thereby confound inflammatory biomarkers and infectious or dentoalveolar signals. The pharmacovigilance events identified in the review do not demonstrate a product-quality mechanism.
IL-17A: secukinumab. Evidence was insufficient and derived from one confounded case series.	SC pre-filled syringes or pens require product-specific refrigeration, protection from light, avoidance of freezing or shaking, and correct device use [10–13,46].	Variable active exposure could theoretically modify anti-inflammatory control and the balance of mucosal host defense. The only eligible case series cannot separate the effects of secukinumab from periodontal treatment and antibiotics and provides no information on product handling.

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; CD20, cluster of differentiation 20; Fab′, antigen-binding fragment; GI, gingival index; IL-6R, interleukin-6 receptor; IL-17A, interleukin-17A; IV, intravenous; PPD, probing pocket depth; SC, subcutaneous; TNF, tumor necrosis factor.

Stability and handling requirements are formulation- and product-specific rather than intrinsic to therapies directed against TNF, IL-6R, CD20, or IL-17A. The periodontal and oral consequences presented in Table 5 are mechanistic hypotheses, not effects observed after documented product-quality deviations. None of the included periodontal studies documented cold-chain deviations or assessed pharmaceutical product quality. Certolizumab pegol is a PEGylated Fab′ fragment included within the review's antibody-based exposure category.

4.5. Periodontal Safety Surveillance and Clinical Implications

The following clinical considerations are pragmatic, risk-based implications of the mapped evidence; they are not validated monitoring protocols or formal guideline recommendations. The mapped evidence does not support selecting, discontinuing, or switching a monoclonal antibody solely to modify periodontal status. Biological therapy should remain guided by systemic indication, disease activity, previous response, contraindications, and medical safety.

Periodontal findings should inform interdisciplinary assessment rather than replace systemic treatment criteria.

In practice, baseline and follow-up dental assessment may document plaque, BOP, PPD, CAL, mobility, furcation involvement, and radiographic bone support when indicated. Reduced gingival bleeding during antibody-based therapy does not exclude persistent pockets or attachment loss. Conventional periodontal treatment, control of active infection, and supportive care remain necessary.

Prompt dental evaluation is warranted when recession, recurrent abscesses, tooth mobility, unexplained bone loss, or persistent infection develops, particularly during CD20-directed therapy or combined immunosuppression.

The evidence did not establish an optimal recall interval. Any individualized schedule should reflect periodontal history, plaque control, smoking, diabetes, systemic inflammatory burden, route and duration of biological therapy, and concomitant medication.

Figure 2 summarizes the relationship between administration, molecular target, periodontal response, and risk-based periodontal safety surveillance.

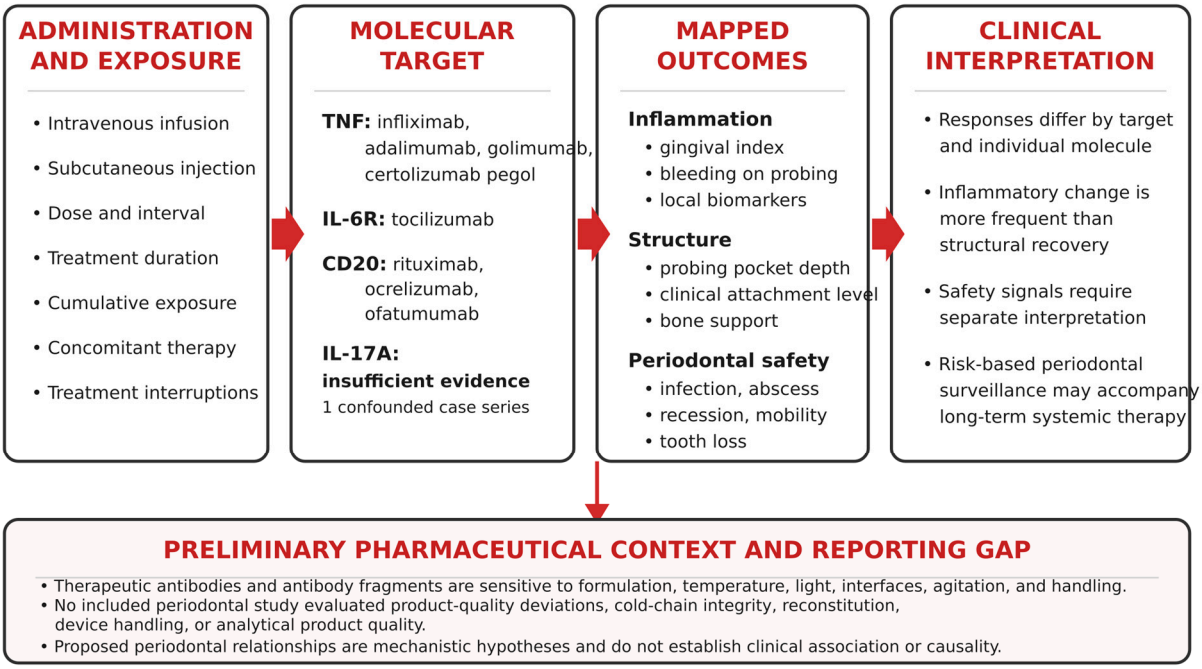

Figure 2. Pharmacological targets, administration and exposure characteristics, periodontal outcome domains, and clinical interpretation. The diagram distinguishes inflammatory responses, structural outcomes, and periodontal or dentoalveolar safety signals and identifies an interface-specific reporting gap concerning product stability, storage, and handling. IL-17A is shown separately as insufficient evidence from one confounded case series. The pharmaceutical-context panel represents a preliminary research framework, not an observed adverse effect or evidence of product instability. No included study associated a documented product-quality deviation with a periodontal outcome. Certolizumab pegol is a PEGylated antigen-binding fragment included within the review's antibody-based exposure category. BOP, bleeding on probing; CAL, clinical attachment level; CD20, cluster of differentiation 20; GI, gingival index; IL-6R, interleukin-6 receptor; IL-17A, interleukin-17A; IV, intravenous; PPD, probing pocket depth; SC, subcutaneous; TNF, tumor necrosis factor.

Figure 2 should be read from left to right. Administration and exposure provide the context for interpretation by molecular target. Inflammatory, structural, and safety domains remain separate because reductions in GI, BOP, or local biomarkers did not consistently coincide with improvements in PPD, CAL, or bone support. IL-17A is marked as insufficient evidence because the only report combined a treatment switch with debridement and antibiotics. The final panel translates the mapped findings into risk-based dental surveillance, while the lower panel defines a pharmaceutical-context reporting gap. Table 5 extends this gap into a preliminary hypothesis-generating framework based on selected external pharmaceutical literature and representative regulatory information.

4.6. Research Gaps and Future Directions

Most evidence involved rheumatoid arthritis, while other indications were represented by isolated sources. Future studies should recruit patients before antibody-based therapy initiation and use calibrated full-mouth examinations at six sites per tooth.

Protocols should report the exact molecule, brand or biosimilar status, formulation and concentration, route, administration device, dose, dosing interval, cumulative exposure, previous biological therapy, treatment interruptions, concomitant medication, smoking, diabetes, plaque control, and periodontal treatment.

Longitudinal studies should distinguish rapid inflammatory changes from long-term attachment and bone outcomes and should include follow-up sufficient to capture chronic administration. Route-specific analyses should be prespecified when both intravenous and subcutaneous formulations are used. Pharmaceutical-context reporting should document who transported, stored, prepared, and administered the product; the required and recorded temperature range; the minimum and maximum recorded temperature; the duration and number of excursions; freezing or thawing; light exposure; agitation, dropping, or other mishandling; time out of refrigeration; reconstitution or dilution method; preparation-to-administration time; visual inspection and visible particles; infusion duration; device malfunction or incomplete dose; batch or lot number; and any corrective action. Where feasible, trough concentrations, anti-drug antibodies, B-cell counts, serum immunoglobulins, or other target-relevant pharmacodynamic measures should be aligned temporally with periodontal assessments. Periodontal effects should not be attributed to product instability without a documented deviation and, ideally, analytical confirmation of altered product quality.

Microbiological studies should combine standardized clinical assessment with longitudinal sequencing-based sampling. Periodontal and dentoalveolar safety studies require denominators, exposure duration, baseline periodontal history, time to event, dental management, and outcomes after continuation, withdrawal, or switching. Pharmacovigilance signals should be complemented by prospective registries and active dental surveillance. Dedicated systematic reviews should evaluate the broader pharmaceutical-quality literature independently from the periodontal evidence map. Prospective studies should then test prespecified pharmaceutical-context variables alongside standardized periodontal outcomes and should require documented deviations and, where feasible, analytical confirmation before attributing an oral event to product instability.

4.7. Strengths and Limitations

This scoping review searched PubMed, Scopus, and Web of Science without a lower publication-year limit, explicitly distinguished full-length antibodies and the eligible Fab′ fragment from fusion proteins, and excluded mixed biological cohorts when eligible exposure could not be isolated. The Web of Science search used the All Databases interface with 12 collections selected.

Therapeutic-effect studies were mapped separately from case-based and pharmacovigilance evidence. Potential cohort overlap was addressed by grouping related Niigata reports and avoiding participant summation.

Data charting covered clinical, biological, microbiological, imaging, administration, exposure, and periodontal or dentoalveolar safety domains. The addition of route, dose, interval, duration, and stability or handling fields made gaps in pharmaceutical reporting explicit. Missing information remained classified as Not reported, and two studies with critical reporting concerns were separated from the principal interpretation.

Limitations include observational designs, small exposed groups, heterogeneous periodontal definitions, incomplete administration and exposure reporting, insufficient confounding control, sparse evidence outside rheumatoid arthritis, and eight reports that could not be retrieved through available routes; authors were not contacted.

Complete verbatim search histories and the exact execution day were unavailable, so the database strategies were reconstructed from retained records. The review was not

prospectively registered and had no publicly accessible protocol. Although the methodological framework and eligibility criteria were defined before source selection, this oversight limited external transparency and reproducibility and may have increased the potential for selection bias. Source selection and data charting used one structured assessment stream rather than independent duplicate processes, and no formal inter-reviewer agreement was calculated. This approach may have increased the risk of selection, extraction, and recording errors despite predefined criteria, structured documentation, and quality-control checks.

The search strategy was designed for periodontal evidence and was not intended to identify all oral adverse events or the general therapeutic-antibody stability literature. Stability, storage, cold-chain integrity, and handling were secondary charting variables, so their absence defines a reporting gap at the periodontal–pharmaceutical interface. The selected reviews, experimental studies, real-world storage reports, and regulatory sources used to contextualize this gap and construct Table 5 were not identified through a systematic search of pharmaceutical stability literature. Table 5 is preliminary and hypothesis-generating and does not constitute a comprehensive comparative assessment of individual products. Clinical and methodological heterogeneity did not support a defensible meta-analysis.

5. Conclusions

This scoping review identified 21 reports representing 20 studies or cohort families and mapped clinical, biological, microbiological, imaging, administration, treatment-exposure, and dentoalveolar safety domains across distinct antibody-based therapeutic targets. Clinical treatment-effect evidence concentrated on rheumatoid arthritis. Tocilizumab produced the most consistent reductions in gingival inflammation and bleeding on probing, while changes in probing depth and clinical attachment level were smaller and less uniform. TNF-directed evidence remained heterogeneous. Small rituximab studies showed favorable clinical or biomarker signals, whereas anti-CD20 pharmacovigilance contained infectious and destructive dentoalveolar signals. Evidence for IL-17A inhibition was insufficient for periodontal conclusions and derived from one confounded five-patient case series.

The mapped effects were predominantly anti-inflammatory rather than structurally regenerative. Antibody-based therapy does not replace conventional periodontal treatment, and periodontal findings alone do not justify initiating, interrupting, or switching systemic therapy. Risk-based periodontal surveillance may accompany long-term care when active periodontal disease, diabetes, smoking, recurrent infection, or combined immunosuppression is present, but the evidence did not establish a validated monitoring protocol or recall interval.

A distinctive feature of this review was the integration of periodontal outcomes with administration, treatment exposure, safety, and pharmaceutical-context reporting. Dose, interval, duration, cumulative exposure, and treatment interruptions were often incompletely reported. No included periodontal study evaluated formulation stability, storage, cold-chain integrity, or handling deviations. The preliminary framework identifies testable variables for future research but does not establish a clinical relationship between product-quality deviations and periodontal outcomes. Future multicenter studies should combine standardized periodontal examinations, route-specific analyses, active dentoalveolar safety surveillance, and prospective product-specific exposure and handling documentation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/scipharm94030078/s1, Table S1. PubMed search documentation; Table S2. Scopus search documentation; Table S3. Web of Science search documentation; Table S4. Characteristics of the Included Studies or Cohort Families; Table S5. Mapping of Included Reports to Studies or Cohort Families and Funding of Included Sources of Evidence; Table S6. Full-text reports excluded with reasons; Table S7. Evidence chart for periodontal, biological, microbiological, imaging,

and safety outcomes; Table S8. JBI appraisal of analytical cross-sectional studies; Table S9. JBI appraisal of cohort studies; Table S10. JBI appraisal of quasi-experimental studies; Table S11. Appraisal of Case Reports, Case Series, and Pharmacovigilance Evidence; Table S12. Periodontal and dentoalveolar safety signals reported with eligible antibody-based therapies; Table S13. Administration, exposure, and pharmaceutical-context mapping.

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Abbreviations

The following abbreviations are used in this manuscript:

AL	Attachment loss
API	Approximal Plaque Index
BOP	Bleeding on probing
CAL	Clinical attachment level
CD20	Cluster of differentiation 20
CPITN	Community Periodontal Index of Treatment Needs
CRP	C-reactive protein
CT	Computed tomography
DMARD	Disease-modifying antirheumatic drug
DMARDs	Disease-modifying antirheumatic drugs
FDG-PET/CT	Fluorodeoxyglucose positron emission tomography/computed tomography
GCF	Gingival crevicular fluid
GI	Gingival Index
IL	Interleukin
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
IL-8	Interleukin 8
IL-17A	Interleukin 17A
IV	Intravenous
JBI	Joanna Briggs Institute
MGI	Modified Gingival Index
MMP	Matrix metalloproteinase
MMP-3	Matrix metalloproteinase 3
MMP-8	Matrix metalloproteinase 8

MTX	Methotrexate
PBI	Papillary Bleeding Index
PCC	Population–Concept–Context
PCR	Polymerase chain reaction
PI	Plaque Index
PIBI	Periodontal inflammatory burden index
PPD	Probing pocket depth
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PSI	Periodontal Screening Index
RA	Rheumatoid arthritis
SC	Subcutaneous
SUVmax	Maximum standardized uptake value
TCZ	Tocilizumab
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
VPI	Visible Plaque Index

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