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Complications of invasive oral procedures in patients with immune-mediated inflammatory disorders treated with biological and conventional disease-modifying antirheumatic drugs or glucocorticoids: a scoping review of the literature

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Abstract

Objectives By a scoping review, to evaluate whether patients with immune-mediated inflammatory disorders (IMIDs) treated with biological and conventional disease-modifying antirheumatic drugs (b/cDMARDs) and/or glucocorticoids (GCs) experience complications after invasive oral procedures.

Materials and methods Primary search was conducted on PubMed/MEDLINE database, Google Scholar, Embase and Web of Science up to December 31, 2023. The PICO question was "Does a patient with IMIDs and treated with b/cDMARDs in mono/bi or combination therapies have delayed oral wound healing or infectious complications after an invasive oral procedure?". To be included, references had to be primary studies written in English or French. Qualitative assessment was performed.

Results From 1,494 initial articles, 59 full-text articles were selected, including 47 case reports and case series, 7 comparative non-randomized studies, 1 randomized clinical trial, 2 case-case studies, 1 case–control study, and 1 prospective cohort study. Most reports involved patients with rheumatoid arthritis on methotrexate and/or anti-TNF. Complications (medication-related osteonecrosis of the jaw, delayed healing, local infection) occurred predominantly after tooth extractions, particularly affecting women, patients over 50 with bisphosphonate use, unhealthy lifestyle habits, or diabetes. They were generally managed with prolonged antibiotic and antiseptic courses, and surgical interventions.

Conclusions Local infectious complication or jaw osteonecrosis could occur post-invasive procedures, especially tooth extractions, in IMIDs patients on b/cDMARDs and/or GCs, often in patients with comorbidities and/or concurrent medications such as bone-modifying drugs.

Clinical relevance It is essential for dentists to be alert to the existence of local or focal infectious complications after tooth extraction in patients with IMIDs on immunosuppressive therapy.

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Keywords Immune-mediated inflammatory disorders (IMIDs), Disease-modifying antirheumatic drugs (DMARDs), Immunosuppressants, Invasive Oral procedure

Introduction

Immune-mediated inflammatory diseases (IMIDs) are a diverse group of complex inflammatory diseases that result from dysregulated immune pathways and can involve any system of the human body [1]. IMIDs include rheumatoid arthritis, the spondyloarthritis disease spectrum, connective tissue disorders, cutaneous inflammatory conditions (including psoriasis and atopic dermatitis), inflammatory bowel disease (IBD), and autoimmune neurological diseases such as multiple sclerosis [2]. The prevalence of IMIDs is estimated to 5–7% in the western population [3]. From a medical point of view, treatment goals are to gain rapid control of inflammation, prevent tissue damage, improve quality of life and, if possible, achieve long-term disease remission [4]. In last twenty years, medical treatment has changed from the extensive use of broad-spectrum immune modulators to the regular utilization of agents characterized by their precise specificity, an evolution driven by monoclonal and molecular biotechnology, and more recently, by highly targeted medicinal chemistry [2]. Therefore, contemporary treatment approaches encompass the use of biological disease-modifying antirheumatic drugs (bDMARDs), i.e. monoclonal antibodies and small molecules designed to target specific inflammatory pathways (e.g., TNF-α inhibitor, T-cell costimulatory blocking agents, B-cell depleting agents and IL-1 receptor antagonist therapy) [5], in conjunction with conventional disease-modifying antirheumatic drugs (cDMARDs) (e.g. cyclophosphamide, methotrexate, ciclosporin, azathioprine, leflunomide, hydroxycholoroquine, mycophenolate mofetil, sulfasalazine) and/or short-term glucocorticoids (GCs), especially the synthetic GCs (e.g. hydrocortisone, prednisolone/prednisone) [6].

The long-term use of bDMARDs and/or GCs impairs the patient's ability to defend against microorganisms, thereby increasing the infectious risk. Thus, serious infections have been reported when these drugs are associated with cDMARDs, with a strong dose–response relationship [7, 8]. Such a risk may exist after invasive oral procedures, which are currently defined as any act involving manipulation of the gingival or periapical region of the tooth, or perforation of the oral mucosa (including scaling and root canal procedures, but excluding the injection of a local anesthetic [9, 10]). The occurrence of oral complications (e.g. infections, delayed wound healing or jaw osteonecrosis) following invasive procedures depends also on the nature of the procedure and tissues concerned by the healing process, the severity of gingiva inflammation at the time the procedure is performed, its duration, extent and invasiveness, as well as the age of the patient, the presence of comorbidities (e.g., uncontrolled diabetes mellitus, cancer, immunodeficiency), specific medications (e.g. chemotherapy, bone-modifying agents (BMA), notably bisphosphates and denosumab) or harmful lifestyle habits (e.g. ethanol abuse, heavy smoking) [11].

Thus, depending on the procedure and the patient's state of health, the use of antibiotic prophylaxis until the mucosal wound has healed, or the temporary discontinuation of drugs for a therapeutic window, may be considered. Consequently, scientific medical associations have proposed recommendations for the perioperative care management of IMID patients under c/bDMARDS and/or GC. However, they are not specific to oral care (for example: ACR guidelines [12]), or provide no details by type of dental procedure and have not been updated for more than 10 years (for example: French guidelines [13]). Moreover, they are not based on the literature in the field of dentistry, and majorly are relying on studies with a low level of evidence.

So, the existing body of research regarding invasive oral care in patients with IMIDs and the potential associated complications is quite limited. The scarcity of data underscores the importance of conducting a comprehensive review of the existing literature to address this knowledge gap. Consequently, the aim of this work was to perform a scoping review focused on this particular subject matter.

Methods

Protocol development

The following focused question was put forth: "Does a patient with immune-mediated inflammatory diseases (IMIDs) and treated with biological or conventional disease-modifying antirheumatic drugs in mono/bi or combination therapies have infectious complications, delayed oral wound healing or jaw osteonecrosis after an invasive oral procedure?".

Articles to be included had to meet the following PICO (Patient, Intervention, Comparison, Outcome Glossary of Evidence-Based Terms 2007) criteria:

P: Type of participants: patients treated with bDMARDs and/or cDMARDs and/or GCs in mono/bi or multi-therapy for the treatment of IMIDs (with or without comorbidities and/or specific medications (e.g.,

BMA) exposing them to an infectious risk, delayed oral wound healing or jaws osteonecrosis).

I: Type of interventions: invasive oral care.

C: Comparison between interventions: patients with no treatment or another treatment than bDMARDs and/or cDMARDs and/or GCs.

O: Type of outcome measures: infectious complications, delayed oral wound healing or jaw osteonecrosis.

We performed the scoping review according to Levac and colleagues methodology [14] with a quality assessment of selected articles.

Information sources and search

Electronic research strategy

A systematic electronic search was performed using four electronic databases (Medline, Embase, Web of Science and Google Scholar) up to December 2023. For Pubmed, the strategy used was a combination of MeSH terms and free world text, listed below. The research equations were built for each database and can be consulted in the Annex 1.

Patients

Diseases

MeSH: Inflammatory Bowel Diseases; Pediatric Crohn's disease; Crohn's disease; Rheumatoid Arthritis; Spondylitis; Ankylosing; Psoriasis; (Lupus Erythematosus; Systemic); Giant Cell Arteritis; (Arthritis; Juvenile); (Arthritis; Psoriatic); (Polymyalgia Rheumatica); Behcet Syndrome; Sjögren's Syndrome; autoimmune diseases.

Immunomodulatory biotherapies

MeSH: Infliximab; Adalimumab; Golimumab; Certolizumab; Anakinra; Sarilumab; Ustekinumab; Rituximab; Belimumab; Abatacept; Secukinumab; Vedolizumab; Tofacitinib; Baricitinib.

Immunosupressive drugs

MeSH: Adrenal Cortex Hormones/drug therapy; Azathioprine; Methotrexate; Cyclophosphamide; Leflunomide; Mycophenolate mofetil; Sulfasalazine; Tacrolimus; Ciclosporine; Apremilast; Dapsone.

Interventions

Invasive oral care

In endodontics: MeSH: Root Canal Therapy; Pulpotomy; Pulpectomy; Apicoectomy; Dental Pulp Capping.

In periodontology: MeSH: Periodontal debridement; Root Planning; Dental Scaling; Subgingival Curettage; Gingivectomy; Gingivoplasty; Crown Lengthening; Guided Tissue Regeneration; Periodontal; Furcation defects/Surgery; Periodontal Pocket/Surgery; Aggressive Periodontitis/Surgery; Chronic Periodontitis/Surgery; Gingival Recession/Surgery; Vestibuloplasty; Mouth Mucosa; surgery; Surgical Flaps AND Periodontics.

In oral surgery (not cited before): MeSH: Tooth extraction; Tooth replantation; Alveolar ridge augmentation; Alveolectomy; Alveoloplasty; Alveolar bone grafting; Mouth mucosa; Jaw cysts/surgery; Jaw Diseases/surgery; Glossectomy; Salivary Glands; Minor/surgery; Sinus Floor Augmentation; Dental Implantation; Peri-Implantitis/surgery.

Intraligamentary local anaesthesia: MeSH: anesthesia; dental

In orthodontic and preprosthetic surgery: MeSH: Oral Surgical Procedures; Preprosthetic; Tooth; Impacted/surgery; Orthodontic Anchorage Procedures; Orthognathic Surgical Procedure.

Manual search

Hand searching was performed on the bibliography of the articles included for the scoping review and from a previous systematic review performed on this topic [15].

Articles selection and data collection

The assessment of the relevant publications was performed through the analysis of titles, abstracts, and full texts. Titles and abstracts were initially screened by two reviewers for possible inclusion in the review (MK and LR). The reviewers were calibrated for study screening against another reviewer (MG) with experience in conducting systematic reviews. Each round of calibration consisted of a duplicate, independent validity assessment of 20 titles and abstracts from the search. The reviewers had to achieve a consistent level of agreement (Kappa score > 0.9). Unclear abstracts were included in the full-text analysis not to exclude potentially relevant articles. The full text of all potentially relevant publications was then independently assessed by three reviewers (MK, LR, and MG) against the inclusion criteria listed below. Any disagreement was resolved by discussion among the reviewers. All quality assessments were conducted by LR and MG. Data were extracted from full-text articles directly into electronically extraction sheet independently by MK, and completed tables were further rechecked to validate accuracy of the data extraction by MG and LR. All data were available in the articles (no direct contact with the study investigators was necessary).

Inclusion criteria

Only articles, written in English and French, and carried out in humans, were included. Reviews of the literature were excluded.

We considered the following inclusion criteria and types of publications:

i. *articles where patients treated with bDMARDs and/or cDMARDs and/or GCs as monotherapy or combination therapies for an IMID (with or without comorbidities and/or specific medications (e.g., BMA) have received invasive oral care during the treatment.* During the follow-up of these patients, complications of the invasive procedures may have arisen and been reported.
ii. *other articles focused only on complications occurring spontaneously in the natural history of the IMIDs, or provoked by an invasive oral procedure previously carried out by another dentist/oral care physician,* requiring urgent consultation with another practitioner who reported only its management and the patient's follow-up. These articles were included only if the oral complication has been treated surgically and the patient was followed up.

Among the IMIDs, we considered: Inflammatory Bowel Diseases (Crohn Disease and Ulcerative Colitis); Rheumatoid Arthritis; Spondylitis, Ankylosing; Psoriasis; Lupus Erythematosus, Systemic; Giant Cell Arteritis; Arthritis, Juvenile; Arthritis, Psoriatic; Polymyalgia Rheumatic; Behcet Syndrome; and Sjogren's Syndrome.

With regard to drugs, we considered 3 classes of drugs: 1- cDMARDs (e.g. methotrexate, leflunomide, tacrolimus, mesalazine, sulfasalazine, mycophenolate mofetil, hydroxychloroquine); 2- bDMARDs (e.g. adalimumab; rituximab; infliximab; tocilizumab; etc.); and 3- GCs. Only systemic treatments were considered.

Invasive oral care was defined as all procedures involving manipulation of the gingiva, pulp or periapical region of the tooth or perforation of the oral mucosa (apart from local or locoregional anesthesia). They were classified into three categories: i- interventions involving mucosal healing (e.g. periodontal scaling; periodontal probing; oral biopsy; connective tissue graft; frenotomy) or connective tissue healing (e.g. pulp capping); ii- interventions involving bone healing (endodontic treatment with the presence of a periapical lesion) and iii- those involving mucosal and bone healing (e.g. tooth extraction, implant placement, dental implant removing, orthognathic surgery, bone graft, temporomandibular joint (TMJ) arthroplasty).

The exclusion criteria were as follows: patients who underwent a non-invasive oral procedure (ex: dental fillings); patients without bDMARDs and/or cDMARDs and/or GCs during the oral procedure under evaluation; patients who do not have an IMID. Studies for which the full text could not be obtained were also excluded.

Outcome measures

i. *In the articles reporting oral interventions in patients with an IMID on b/cDMARDS and/or GCs*, the primary outcome considered was the absence or the presence of a local complication at the site of the intervention. Local complications were defined as follows: delayed wound healing, infectious complication (periapical/periodontal abscess; dry socket; alveolar or jaw osteitis/osteomyelitis/periostitis; cellulitis), or others (e.g. medication-related osteonecrosis of the jaw as defined by the American Association of Oral and Maxillofacial Surgeons in 2022 [16]). We also considered reports of general/focal infectious complications arising from the oral site after an invasive procedure. The complications were reported by the practitioner who performed the procedure and followed up the patient. They were described by type of oral procedure, type of IMID and type of drug. The secondary outcome was, in the case of an oral complication, the management and the duration of the follow-up of cases until the complication has been solved (partial or total mucosa and bone healing).
ii. *In the articles reporting complications occurring spontaneously or after an oral invasive procedure performed previously in patients with an IMID on b/c DMARDs and/or GCs*, we analyzed the management of the complication (including mandatorily an invasive intervention), its outcome (healing or non-healing of the oral site) and the duration of follow-up.

Summary measures and synthesis of the results

Tables were created for the review question to provide an overview of the included studies and summarize their characteristics such as year of publication and journal; country of origin; study design; invasive oral procedure (nature, site); patient characteristics (gender, age, IMID (type, stage)), medical treatment (molecules, dosages, duration), concurrent medications (e.g. chemotherapy, BMA: bisphosphonates/denosumab) and cofactors known to impair mucosa and bone healing and to increase the infectious risk (e.g. smoking, alcohol or substance abuse, malnutrition, immunodeficiency, unbalanced diabetes, poor oral health); perioperative medication use (antibiotics and antiseptics: molecules, dosages, duration); existence of a triggering factor (spontaneous/post-traumatic/post-operative complication); outcome measures (type: local/focal/general complication, diagnosis, management); follow-up time; evolution of the oral

complication until the end of follow-up (recovery, non-recovery, in recovering).

Articles may have been counted multiple times in the analyses for type of disease, drug class, interventions, and complications, depending on the patients' characteristics.

Methodological quality assessment

Randomized clinical trials

Cochrane Risk of Bias (RoB 2), a tool for risk of bias assessment, was used. Bias is assessed in five distinct domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) [17]. Within each domain, users of RoB 2 answer one or more signaling questions. These answers lead to judgments of "low risk of bias," "some concerns," or "high risk of bias". The judgments within each domain lead to an overall risk-of-bias judgment: low risk of bias if the study is judged to be at low risk of bias for all domains; some concerns if the study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain; high risk of bias if the study is judged to be at high risk of bias in at least one domain, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Non-randomized comparative studies and cohort studies

Newcastle–Ottawa scale was used to conduct qualitative assessment of case–control studies/case-case studies/comparative studies dealing with two or more groups receiving different interventions, and cohort studies [18]. A maximum of 9 stars can be awarded to a study based on the following items: quality of selection (definition of the appropriate case, representativeness of the cases, selection and definition of controls) (4 stars); comparability of exposed and unexposed subjects (2 stars); determination of exposure, non-response rate, and duration of the study for a sufficient analysis (3 stars).

Case report and series of cases

Inspired by MINORS (methodological index for non-randomized studies) [19], we have established a qualitative analysis grid for the case reports and the series of cases. We defined 5 criteria:

1. The case report included at least 3 patients.
2. The medical record was complete (e.g. age, gender, type of IMID, concurrent medications, comorbidities, tobacco smoking).
3. The drug exposure was clearly defined (indication; start date of the treatment; dosage; name of the molecule).
4. The invasive procedure was clearly defined (nature of the procedure; location of the operating site; timing in relation to the start of the treatment).
5. The follow-up of cases was extended at least until mucosal and/or bone healing.

For each item, the scoring was binary (1 or 0); the global score for each article ranged from 0 to 5. Based on this score, the articles were divided into three categories: A- high quality (≥ 4), B- moderate quality (2–3); C- low quality (≤ 1). When we evaluated a series of cases, the evaluation of criteria 2 through 5 was performed for each case. The lowest score was retained for criterion scoring.

Results

Articles selection

The electronic search identified 1,494 articles. Hand searching produced 19 additional articles for the full-text analysis. After duplicates removal, in total 1,438 potentially relevant articles were identified (Fig. 1). Among them, 1,323 articles were excluded after the screening of titles and abstracts, leaving 115 papers for full-text analysis. Fifty-six articles were excluded after full-text screen because the medical history/treatment and/or the oral invasive procedure were not sufficiently defined to be included. Fifty-nine articles were finally included in the qualitative synthesis of this scoping review (Fig. 1).

Articles characteristics

Design and origin of the articles

The repartition of the 59 articles included was as follows: 47 (79.7%) case reports or series of cases [20–66]; 7 (11.9%) comparative non-randomized studies [67–73]; 1 (1.7%) randomized controlled trial (RCT) [74]; 2 (3.4%) case-case studies [68, 75]; 1 (1.7%) case–control study [76]; and 1 (1.7%) prospective cohort study [77] (Tables 1, 2, 3, 4, 5 and 6). All articles were published between January 2001 and July 2023, and 28 (47.5%) of them dated back 10 years or less. There were primarily European articles ($n=25$, 42.4%) and then Asian ones ($n=18$, 30.5%). Regarding the first authors of the publications, 16 (27.1%) were non-specialists of the oro-facial region (e.g. rheumatologists, internists, neurologists…) and 43 (72.9%) were practitioners of the oro-facial region (e.g. general dentists, oral and maxillo-facial surgeons, periodontists, endodontists…).

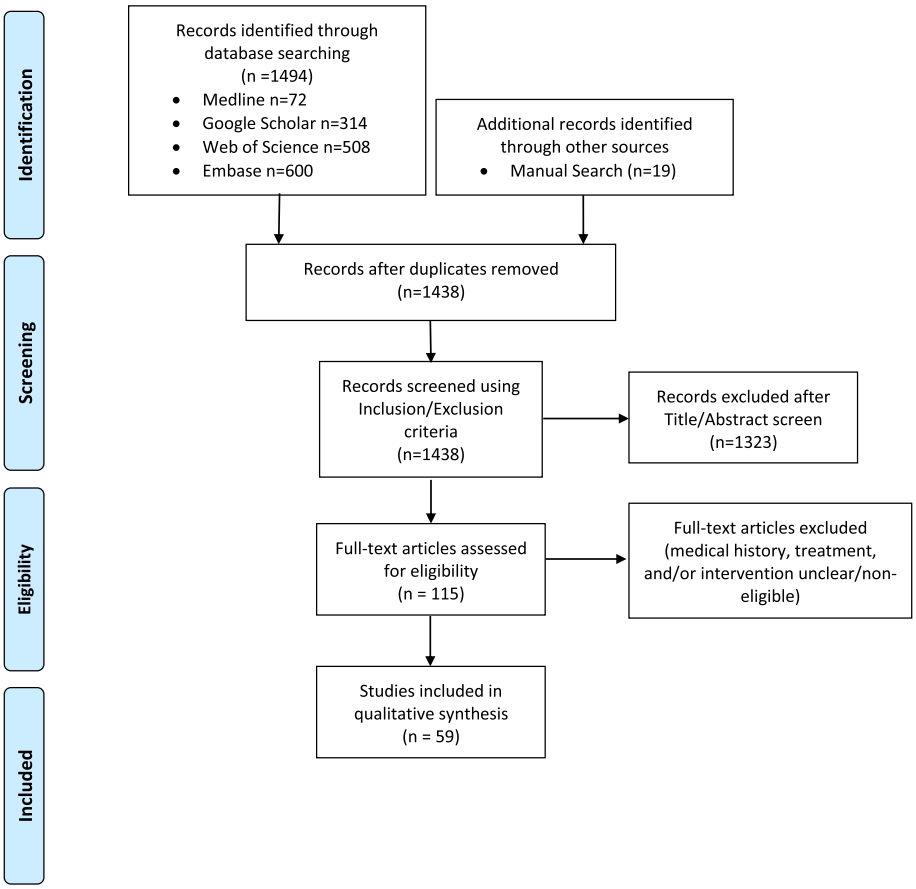

Fig. 1 PRISMA-ScR flow diagram. The figure shows the inclusion/exclusion process. PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; PRISMA-ScR = PRISMA extension for Scoping Reviews

Assessment of the quality of the included articles

Among the 47 case reports and series of cases, there were 10 articles in category A (high quality) (21.3%), 32 articles in category B (average quality) (68.1%) and 5 articles in category C (low quality) (10.6%) (Table 7). The number of YES attributed by criterion was as following: the case report included at least 3 patients (7/47- 14.9%); the medical record was complete (21/47 – 44.7%); the drug exposure was clearly defined (27/47 – 57.4%); the invasive oral procedure was clearly defined (42/47 – 89.4%); the follow-up of cases was extended at least until mucosal and/or bone healing (33/47 – 70.2%).

The assessment of the risk of biases of the single RCT included in the review, using the Cochrane RoB 2 tool (Table 8), showed that it was at high risk of bias. The qualitative analysis of the 11 other studies (comparative non-randomized, cohort, case-case, and case–control studies), assessed using the Newcastle–Ottawa scale, revealed an average rating of 4 out of 9 stars (range 1 to 6). There were 5 studies (5/11—45.5%) with a rating of less than 5 stars, indicating poor or average quality (Tables 9 and 10).

Patients' characteristics

Number of patients

The total number of patients with IMIDs, treated by b/cDMARDs and/or GCs and undergoing invasive dental procedures was 455, mostly patients with rheumatoid arthritis (306/455 – 67.3%), followed by patients with systemic lupus erythematosus (53/455 – 11.6%), inflammatory bowel diseases (27/455 – 5.9%), or vasculitis (majorly Behçet's disease) (26/455 – 5.7%). Some publications included patients with 2 IMIDs (13/455 – 2.9%). Finally, some articles included patients with IMIDs on other therapies than those of interest (e.g. non-steroidal anti-inflammatory drugs, analgesics, or colchicine); therefore these subjects were excluded from the analyses.

Type of IMIDs

The articles concerned patients with rheumatoid arthritis (31/59 – 52.5%); inflammatory bowel diseases (Crohn's

Table 1 Description of case reports and series of cases included in the review

Authors	Year	Country	Number of patients	Age (years) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration	Other medications *	Diseases, conditions or lifestyle risk factors **	Invasive procedure	Type of complication	Treatment of the complication	Follow-up time	Evolution
Aghaloo T et al.	2017	US	3	83 W	Rheumatoid Arthritis	/	Methotrexate	None	5 years	NI	None	Placement of 2 maxillary crowns, scaling and root planning	Osteonecrosis of the jaw	Prolonged course of antibiotic and sequestrectomy and endodontic treatment	> 2 years	Complete resolution
				42 W	Rheumatoid Arthritis	Prednisone	/	Etanercept	2 years	NSAID	NI	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic, sequestrectomy	18 months	Complete resolution
				66 W	Rheumatoid Arthritis	Prednisone	Hydroxycholoroquine	/	NI	BP, Adalimumab, Etanercept (in the past)	NI	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic	NI	Minimal improvement
Andersen K-M et al.	2003	Norway	1	28 M	Crohn's disease	Prednisone	Azatioprine, Mesalazine	/	UC	None	None	3 periodontal plastic surgeries (under 6 days antibiotic coverage); surgeries 2 and 3 were performed under Emdogain®	Delayed healing for the first surgery	Longstanding antiseptic	> 4 months	Complete resolution
Bakal O et al.	2015	Turkey	1	71 W	Rheumatoid Arthritis	Prednisone	Methotrexate Leflunomide	/	20 years (methotrexate and leflunomide), 10 years (prednisone)	BP	NI	Tooth extraction	Osteonecrosis of the jaw	NI	NI	NI
Barrier A, et al.	2010	France	3	36 M	Juvenile polyarthritis	Corticosteroids	Methotrexate	Anakinra	NI	BP	Never smoker	Tooth extraction	Osteonecrosis of the jaw	Antibiotic and antiseptic; Sequestrectomy, curetage and tooth extraction	6 months	Complete resolution according to the physician
				50 W	Rheumatoid arthritis	Corticosteroids	Methotrexate	/	NI	BP	Tobacco smoker	Tooth extraction	Osteonecrosis of the jaw	Antibiotic and antiseptic	NI	NI
				82 W	Vasculitis	Corticosteroids	Methotrexate	Infliximab	NI	BP	Never smoker	Tooth extraction	Osteonecrosis of the jaw	Antibiotic and antiseptic; Sequestrectomy, curettage, bucco-sinusal communication closure	3 months	Minimal improvement
Bencharit S et al.	2010	US	1	74 W	Polymyalgia rheumatica	Prednisone	/	/	> 1 year	None	NI	Tooth extraction and dental implant placement	None	/	/	/
Brijs K et al. #	2020	Belgium	2	57 W	Inflammatory bowel disease	/	Mesalazine	Infliximab	UC	Corticosteroids, other bDMARDs (in the past)	Poor oral health	Tooth extraction	Osteonecrosis of the jaw	Antibiotics, Antiseptics, Sequestrectomy	4 months	Complete resolution
				46 M	Inflammatory bowel disease	Corticosteroids	/	Infliximab	UC	Adalimumab, other bDMARDs (in the past)	Poor oral health, smoking	Tooth extraction	Osteonecrosis of the jaw	Antibiotics, Antiseptics	15 months	Complete resolution
Cafone J et al.	2018	US	1	57 W	Multiple sclerosis, rheumatoid arthritis	/	/	Rituximab	NI	NI	NI	"Dental work" and tooth extractions	Infective endocarditis; multiple organ failure	Aggressive antibiotic treatment	1 week	Death
Cassoni A et al.	2016	Italy	1	63 W	Idiopathic arthritis	/	Sulfalazine	Adalimumab	4 years	None	Never smoker, No alcohol abuse	Tooth extractions and dental implants placement	Osteonecrosis of the jaw	Sytemic antibiotic, Curettage, Tooth extraction, Sequestrectomy	> 6 years	Minimal improvement
Ciantar M et al.	2007	UK	1	25 W	Idiopathic juvenile arthritis, autoimmune thyroid disease	Prednisolone	/	Infliximab	NI	NSAID	NI	Tooth extraction	Osteomyelitis	Prolonged course of antibiotic and antiseptic	> 5 months	Complete resolution

Table 1 (continued)

Cillo JE & Barbosa N	2019	US	1	55 W	Ulcerative colitis	/	/	Adalimumab	5 years	None	NI	Tooth extraction and dental implants placement	Cellulitis	Drainage, Prolonged course of antibiotic, Implants removal	> 5 months	Complete resolution
Darley MD et al.	2015	US	1	64 M	Rheumatoid Arthritis	Prednisone	Methotrexate	Adalimumab	NI	NI	Well controlled type II diabete; Tobacco smoker	UC (minimally invasive dental examination)	Spinal epidural abscess	Prolonged course of antibiotic	12 weeks	Minimal improvement
Diniz-Freitas M et al.	2012	Spain	2	62 W	Rheumatoid Arthritis	Corticosteroids	Methotrexate	/	NI	BP	Ex-tobacco smoker	Tooth extraction	Osteonecrosis of the jaw	/	/	/
				66 W	Rheumatoid Arthritis	Corticosteroids	Methotrexate	/	NI	BP	None	Tooth extraction	Osteonecrosis of the jaw	/	/	/
Ebker T et al.	2013	Germany	1	74 W	Rheumatoid Arthritis	Prednisolone	Methotrexate	Infliximab	> 3 years	BP, NSAID	NI	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic, drainage, sequestrectomy	18 months	Complete resolution
												Dental cleaning	Osteonecrosis of the jaw	Prolonged course of antibiotic, mandibular resection and reconstruction with titanium plate	> 4 months	Minimal improvement
Ella B et al.	2011	France	1	56 W	Rheumatoid Arthritis	Prednisone	Mycophenolate mofetil	/	UC	None	None	Dental implants placement	None	/	/	/
Favero M et al.	2009	Italy	1	46 W	Rheumatoid Arthritis	/	/	Etanercept	2 years	NSAID	Poor oral hygiene	Endodontic treatment	Knee septic arthritis	Prolonged course of antibiotics	NI	Complete resolution
Favia G et al.	2017	Italy	1	49 W	Crohn's disease	/	Sulfasalazine, Mesalazine	Infliximab	> 12 years	None	Periodontal disease	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic, mandibular resection	16 months	Complete resolution
Fukumoto K et al.	2018	Japan	1	80 W	Rheumatoid Arthritis	Prednisolone	Tacrolimus, Methotrexate	/	11 years	None	Well controlled type II diabete	Dental implant removal	Meningitis	Prolonged course of antibiotic	1 month	Complete resolution
Goel RM & Hullah E	2015	UK	1	28 M	Crohn's disease	UC (immunosuppressant and biologic therapies)	UC (immunosuppressant and biologic therapies)	UC (immunosuppressant and biologic therapies)	UC	NI	NI	/	Spontaneous oro-facial fistulae as results of the natural history of the disease	Tooth extraction and curettage of the sinus tract for granulomatous fistulae, antibiotics	1 year	Compete resolution
Goldberg DA et al.	2018	US	1	41 W	Linear scleroderma	/	Methotrexate	/	7 weeks	NI	NI	Tooth extractions ; Bone and connective tissue graft	None	/	/	/
Goto M et al.	2014	Brazil	1	42 M	Behcet's disease	Prednisolone	/	/	2 months	NI	NI	Tooth extraction	Relapse of Behcet's disease - no complication at the site of tooth extraction	/	/	/
Grimaldo-Carjevschi M et al.	2011	Venezuela	1	38 W	Systemic Lupus Erythematosus	Methylprednisolone	Cyclophosphamide Hydroxychloroquine	/	6 bolus of cyclophosphamide over 10 months	BP	Tobacco smoker	Mucosal biopsy and Palatectomy fo oral cancer	None	/	/	/
Gutierrez GM et al.	2018	Brazil	1	12 W	Juvenile Idiopathic Arthritis	/	Methotrexate,	Etanercept	NI	None	None	Frenectomy and tooth extraction	None	/	/	/
Hayashi M et al. #	2018	Japan	3	68 W	Vasculitis	Prednisolone	/	/	NI	No bisphosphonate	Diabete Mellitus	Multiple tooth extraction	Delayed Wound Healing	/	/	/
				59 W	Systemic Lupus Erythematosous	Prednisolone	Tacrolimus, Mizoribine	/	NI	No bisphosphonate	None	Tooth extraction	Delayed Wound Healing	/	/	/

Table 1 (continued)

				63 M	Rheumatoid Arthritis	Prednisolone	Methotreaxate	/	NI	No bisphosphonate	None	Multiple tooth extraction; Tooth extraction (second intervention)	Osteonecrosis of the jaw; Delayed Wound Healing (second intervention)	/	/	/
Henien M et al.	2017	UK	2	66 W	Rheumatoid Arthritis	/	Methotrexate, Leflunomide	/	20 years	None	Periodontal disease; Ex-tobacco smoker, Alcohol consumption	Tooth extraction	Osteonecrosis of the jaw	Sequestrectomy	6 months	Complete resolution
				54 M	Psoriatic arthritis	/	Methotrexate, Leflunomide	/	20 years	None	None	Spontaneous complication	Osteonecrosis of the jaw	Tooth extraction, Sequestrectomy, Prolonged course of antibiotics	/	/
Irshied J., et Bimstein E.	2001	Israel	1	11 W	Behcet's disease	Prednisone	Cyclosporine	/	> 3 months (Cyclosporine)	None	None	Tooth extraction	None	/	/	/
Işleten B et al.	2011	Turkey	1	58 W	Ankylosing Spondylitis	/	/	Etanercept	> 4 years	BP	NI	Tooth extraction	Osteonecrosis of the jaw	/	1 year	Complete resolution
Junquera L et al.	2009	Spain	1	73 M	Rheumatoid Arthritis	Prednisone	Methotrexate	/	5 years	BP	NI	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotics and antiseptics, sequestrectomy, tooth extraction	1 year	Complete resolution
Kam AY et al.	2006	Hong Kong	1	28 W	Systemic Lupus Erythematosus, Scleroderma	Prednisolo	Azathioprine	/	NI	None	NI	Tooth extractions	None	/	/	/
Kasfikis G et al.	2009	Greece	1	18 W	Juvenile Idiopathic Arthritis + Crohn's disease	/	Mesalazine	/	9 years	None	None	Orthognathic surgery	None	/	/	/
Kim UG et al.	2017	Korea	1	51 W	Rheumatoid Arthritis	/	Leflunomide, Methotrexate	/	2 years	NI	Diabete Mellitus	Infected nodule excision	None	/	/	/
Kudo C et al.	2014	Japan	1	32 M	Behcet's disease	Prednisolone	Cyclosporine	/	9 years	Colchicine	Poor oral hygiene	Scaling and root planing, tooth extraction, endodontic treatment	None	/	/	/
de Kruif MD et al.	2012	Netherlands	1	63 W	Vasculitis	Prednisone	Azathioprine	Tocilizumab	> 6 months	NI	NI	Endodontic treatment	None	/	/	/
Lescaille G et al. #	2013	France	7	51 W	Rheumatoid Arthritis, Sjögren syndrome	/	Methotrexate	/	NI	BP	Hyposialia; No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic	/	/
				59 W	Rheumatoid Arthritis	Prednisone	Leflunomide	/	NI	BP	None	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic, sequestrectomy +/- resection	24 months	Complete resolution
				56 M	Rheumatoid Arthritis	Prednisone	/	/	NI	BP	No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic	6 months	Complete resolution
				39 M	Rheumatoid Arthritis	Prednisone	Hydroxycholoquine, Methotrexate	/	NI	BP	Renal failure, No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic	/	/
				82 W	Rheumatoid Arthritis	Prednisone	/	/	NI	BP	No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic, sequestrectomy +/- resection	13 months	Complete resolution
				84 W	Rheumatoid Arthritis	Prednisone	Methotrexate	/	NI	BP	No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic, sequestrectomy +/- resection	24 months	Complete resolution
				89 W	Rheumatoid Arthritis	Prednisone	/	/	NI	BP	No smoker	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic	5 months	Complete resolution

Table 1 (continued)

Leshem D et al.	2006	Canada	4	UC	Juvenile Idiopathic Arthritis	+/- Corticosteroids	+/- Methotrexate	/	NI	+/- NSAIDs	NI	Orthognathic surgery	None	/	/	/
Liao L et al.	2004	Germany	1	50 W	Systemic Lupus Erythematosus	Corticosteroids	/	/	Several years	None	NI	Mandibular reconstruction by micro-anastomosed free fibula flap and dental implants placement	None	/	/	/
Manzon L et al.	2014	Italy	1	68 W	Rheumatoid Arthritis	Prednisone	Leflunomide, Methotrexate,	/	21 years	BP, gold salts	NI	Tooth extraction	Osteonecrosis of the jaw and temporal abscess	Prolonged course of antibiotic, tooth extraction, drainage	3 months	Complete resolution
Mathai PC et al.	2018	India	3	70 W	Rheumatoid Arthritis	/	Methotrexate	/	4 to 10 years	BP	Leucopenia	Tooth extractions	Osteonecrosis of the jaw	Prolonged course of antibiotic,surgical debridement, sequestrectomy	3-6 months	Ongoing healing
				60 W	Rheumatoid Arthritis	/	Methotrexate	/	4 to 10 years	BP	Leucopenia	Tooth extractions	Osteonecrosis of the jaw	Prolonged course of antibiotic,surgical debridement, sequestrectomy	3-6 months	Ongoing healing
				50 W	Rheumatoid Arthritis	/	Methotrexate	/	4 to 10 years	BP	Leucopenia; Periodontitis	Deep scaling	Osteonecrosis of the jaw	Prolonged course of antibiotic, surgical debridement, sequestrectomy	3-6 months	Ongoing healing
Nomura T et al.	2013	Japan	2	72 W	Rheumatoid Arthritis	Prednisolone	/	/	NI	BP	NI	Tooth extractions	Osteonecrosis of the jaw	Prolonged course of antibiotic, sequestrectomy	11 months	Complete resolution
				81 W	Rheumatoid Arthritis	Prednisolone	/	/	NI	BP	Diabete mellitus	Dental implant placement	Osteonecrosis of the jaw	Prolonged course of antibiotic, curettage	24 months	Progression of the osteonecrosis
Oh W-M et al.	2008	Korea	1	63 M	Rheumatoid Arthritis	Corticosteroid	Azathioprine	/	NI	None	None	Endodontic treatment	Apical abscess with rapid and severe bone destruction	Prolonged course of antibiotic, endodontic treatment	3 months	Complete resolution
Pessoa L et al.	2011	Brazil	1	22 W	Adult-onset Still's disease (inflammatory arthritis)	Prednisone	Methotrexate	/	>1 year	NI	Poor oral hygiene, Periodontitis	Scaling and root planing; Tooth extractions	None	/	/	/
Preidl RHM et al.	2014	Brazil	1	36 W	Crohn's disease	/	/	Adalimumab	5 years	BP	NI	Tooth extraction	Osteonecrosis of the jaw	Prolonged course of antibiotic and antiseptic, bone resection, tooth extraction	6 months	Complete resolution
Rahman N et al.	2010	Ireland	2	55 W	Rheumatoid Arthritis	/	Methotrexate, Leflunomide	Etanercept	12 years (methotrexate) 1 month (leflunomide) 3 years (etanercept)	None	None	Partial glossectomy (for a carcinoma treatment)	None	/	/	/
				61 M	Rheumatoid Arthritis	/	Methotrexate	Adalimumab	> 10 years (methotrexate) 15 months (adalimumab)	Celecoxib, Gold salts	Ex-tobacco smoker, Alcohol consumption	Excisional biopsy	None	/	/	/
Toledo Rojas R et al.	2010	Spain	1	56 W	Primitive Sjögren syndrome	Corticosteroids	Methotrexate	/	Few months (methotrexate) 13 years (corticosteroids)	NSAID	NI	Dental implants placement	**Local :** peri-implant infection ; **Focal** : Cryoglobulinemic glomerulopathy and renal failure	**Local :** NI; **Focal:** Haemodialysis , plamapheresis, medical treatment	**Local**: NI; **Focal:** > 1 year	**Local :** NI; **Focal :** complete resolution
Tsuchiya S et al.	2016	Japan	1	29 M	Crohn's disease	/	/	Infliximab	12 years	None	NI	Endodontic treatment	Mandibular suppurative osteomyelitis	Antibiotic treatment, Tooth extraction	4 years	Complete resolution

Table 1 (continued)

Unsworth JD et al.	2013	UK	1	29 W	Systemic lupus erythematosus	Prednisolone	Azathioprine	/	5 years	None	Tobacco smoker	Glossectomy, Mandibulotomy, Tracheostomy, Lymph Node Dissection, Mandibular reconstruction by micro-anastomosed free radial flap and skin graft	None	/	/	/
Weinländer M et al.	2010	Austria	6	UC, W	Scleroderma	Corticosteroids	/	/	NI	No bisphosphonate	NI	Multiple dental implant placement	None	/	/	/
				UC, W	Rheumatoid Arthritis	/	Methotrexate	/								
				UC, W	Rheumatoid Arthritis, Sjögren syndrome	/	Methotrexate	/								
				UC, W	Rheumatoid Arthritis	Corticosteroids	/	/								
				UC, W	Rheumatoid Arthritis	/	Methotrexate	/								
				UC, W	Rheumatoid Arthritis	Corticosteroids	/	/								
Zigdon H et al.	2011	Israel	1	45 W	Scleroderma	Corticosteroids	Methotrexate	/	NI	NI	Poor oral hygiene, Periodontitis	Tooth extraction, bone augmentation and dental implants placement	None	/	/	/

All articles report on the follow up after an invasive oral procedure excepting the articles highlighted in yellow which report the management and the follow up of complications after invasive oral procedures performed previously by general practitioner, or highlighted in orange which report the management of a spontaneous oral complication of an IMID

NI No Information, *UC* UnClear, *BP* bisphosphonate

* Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing

** Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing

Only patients of interest were extracted from the sample of patients included in the study

disease or ulcerative colitis) (9/59 – 15.3%); systemic lupus erythematosus (6/59 – 10.2%); idiopathic juvenile arthritis (6/59 – 10.2%); vasculitis (mainly Behçet's disease) (6/59 – 10.2%), scleroderma (4/59 – 6.8%) and other diseases (primary or secondary Sjögren's disease 3/59 – 5.1%, ankylosing spondylarthritis 2/59 – 3.4%; polymyalgia rheumatica 1/59 – 1.7%; and psoriatic arthritis 1/59 – 1.7%. It should be noted that some articles (7/59 – 11.9%) included patients suffering from two different IMIDs (e.g. rheumatoid arthritis and multiple sclerosis or Sjögren's disease or scleroderma; idiopathic juvenile arthritis and Crohn's disease; systemic lupus erythematosus and scleroderma…), while other articles included several patients/groups of patients, each with a specific IMID. Therefore, these publications were counted several times.

Drug classes and treatment regimen

Patients were on monotherapy in 34 articles: GCs (14/59 – 23.7%); cDMARDs (12/59 – 20.3%); or bDMARDs (8/59 – 13.6%). In 35 articles, patients were on bi-therapy: mostly on GCs and cDMARDs (21/59 – 35.6%); cDMARDs and bDMARDs (7/59 – 11.9%); GCs and bDMARDs (4/59 – 6.8%); or 2 cDMARDs (3/59 – 5.1%). Tri-therapy was reported in 17 articles: GCs and 2 cDMARDs in 8 articles (8/59 – 13.6%); GCs, cDMARDs and bDMARDs in 6 articles (6/59 – 10.2%); associations of 3 cDMARDs/2 cDMARDs and 1 bDMARD in 3 articles (3/59 – 5.1%).

Among the cDMARDs, the methotrexate was the most widely used molecule (37/59 – 62.7%), followed by mesalazine/sulfasalazine (10/59 – 16.9%), leflunomide (9/59 – 15.3%), azathioprine (6/59 – 10.2%), hydroxychloroquine (5/59 – 8.5%), cyclosphosphamide (2/59 – 3.4%), cyclosporine (2/67 – 3.4%), tacrolimus (2/59 – 3.4%) and mycophenolate mofetil (1/59 – 1.7%).

Regarding the bDMARDs, the anti-TNF alpha drugs were the mostly prescribed: infliximab (11/59 – 18.6%), adalimumab (9/59 – 15.3%), and etanercept (7/59 – 11.9%); other bDMARDs comprised tocilizumab (1/59 – 1.7%), rituximab (1/59 – 1.7%), and anakinra (1/59 – 1.7%).

In 5 articles (5/59 – 8.5%), the name of the c/bDMARD treatment was not clearly indicated. The duration of immunosuppressive treatments ranged from 1 month to 21 years. Nevertheless, information was missing or unclear for 29/46 (63%) of articles.

Table 2 Description of comparative non-randomized studies included in the review

Authors	Year	Country	Number of patients	Age (mean +/- SD) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration (years; mean +/- SD)	Other medications *	Diseases, conditions or lifestyle risk factors **	Invasive procedure	Type of complications
Cotti E et al.	2018	Italy	19	46 +/- 10.4 41% female	Crohn's disease or Ulcerative colitis	None	None	Infliximab (n = 8) Adalimumab (n=11)	Infliximab : 41.9 +/- 34.7 Adalimumab : 34.9 +/- 25.3	NI	NI	Endodontic treatment	None
Fabbri C et al.	2014	Brazil	Control group = 17	29.7 +/- 8.2 - 94.1% female	Systemic Lupus Erythematosus	Prednisone	Cyclophosphamide	None	11.0 +/- 6.6	None	Periodontal disease	Periodontal probing	None
			Treated group = 32	32.7 +/- 10.4 - 78.1% female					10.7 +/- 6.8			Periodontal probing, Non surgical periodontal treatment (scaling/root planing), Endodontic treatment, Tooth extraction	None
Jung GU et al.	2018	Republic of Korea	32	60.4 +/- 10.0 - 81% female	Rheumatoid Arthritis	None	Methotrexate, Hydroxychloroquine, Sulfasalazine	None	NI	none : n=8 + NSAIDs : n= 4 + steroids : n=7 + NSAIDs + steroids : n= 13	Well controlled type II diabete : n=1 Current tobacco smoker (< 10 cigarettes/day) : n=2	Periodontal probing, Nonsurgical periodontal treatment (scaling and root planing)	None
Karacayli U et al.	2009	Turkey	Control group = 10	Not Calculable	Behcet's disease	+/- Corticosteroids	+/- Azathioprine	None	NI	NI	NI	Periodontal probing	None
			Treated group = 10	Not Calculable								Periodontal probing, Nonsurgical periodontal treatment (scaling and root planing), Tooth extraction	
Pers JO et al.	2008	France	Control group = 20	53.2 +/- 8.2 - 80% female	Rheumatoid Arthritis	None	Methotrexate	Infliximab	UC	NI	5 current smokers	Periodontal probing	None
			Treated group = 11	53.45 +/- XXX - 63.63 female							1 current smoker	Periodontal probing, Non surgical periodontal treatment (scaling/root planing), Endodontic treatment, Tooth extraction	
Ribeiro J et al.	2005	Brazil	Control group = 16	47.7 +/- 9.5 - 93% female	Rheumatoid Arthritis	Corticosteroids,	Immunosuppressors, antineoplasic drugs, Sulfasalazine	None	NI	NSAIDs	None	Periodontal probing	None
			Treated group = 26	51.6 +/- 10.3 - 88.5% female								Periodontal probing, Non surgical periodontal treatment (scaling and root planing)	
Zhao X et al.	2018	China	Group A = 16	42.8 +/- 11.2 - 78% female	Rheumatoid Arthritis	Corticosteroids	None	+/- bDMARDs (Name not specified)	NI	NSAIDs	Periodontitis	Periodontal probing, Non surgical periodontal treatment (scaling and root planing)	None
			Group B = 16	43.6 +/- 12.8 - 83% female					NI		/	Periodontal probing	None

In the articles highlighted in blue, authors analyzed clinical results of an invasive procedure on a group of patients with IMIDs compared to a group of healthy patients. The table only report the data of the group of patients with IMIDs with ongoing treatment. The others compared a group of IMID patients with intervention and a group of IMID patients without intervention

NI No Information, *UC* UnClear

* Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing. The others compared a group of IMID patients with intervention and a group of IMID patients without intervention

** Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing. The others compared a group of IMID patients with intervention and a group of IMID patients without intervention

Interventions and outcome measures

i- Articles on invasive oral procedures performed in patients with IMIDs on immunosuppressive drugs (n = 46)

Invasive oral procedures

Among the 46 articles, twelve categories of interventions were identified and classified into 3 groups: (1) oral

Table 3 Description of the randomized clinical trial included in the review

Authors	Year	Country	Number of patients	Age (median; min - max) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration (years; mean +/- SD)	Other medications *	Diseases, conditions or lifestyle risk factors **	Invasive procedure	Type of complications
Ortiz P et al.	2009	US	Group A = 10	69 (46 - 83); 80% female	Rheumatoid Arthritis	None	methotrexate, hydroxychloroquine, leflunomide, sulfazalazine	None	NI	NI	No smoker, No diabete	Periodontal probing, Non-surgical periodontal treatment (scaling and root planing)	None
			Group B = 10	49 (42 - 68); 100% female		None	methotrexate, hydroxychloroquine, leflunomide, sulfazalazine	None				Periodontal probing	
			Group C = 10	54,5 (40 - 88); 80% female		None	methotrexate, hydroxychloroquine, leflunomide, sulfazalazine	None				Periodontal probing, Non-surgical periodontal treatment (scaling and root planing)	
			Group D = 10	63 (39 - 87); 90% female		None	methotrexate, hydroxychloroquine, leflunomide, sulfazalazine	None				Periodontal probing	

[a] Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing

[b] Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing. *NI* No Information

invasive procedures involving mucosal healing only (e.g. periodontal scaling; periodontal probing; oral biopsy; connective tissue graft; frenotomy, periodontal plastic surgery, glossectomy) (38/46 – 82.6%); (2) involving bone healing only (endodontic treatment in the presence of a periapical lesion) (8/46 – 17.4%); and (3) involving both bone and mucosal healing (e.g. tooth extraction, implant placement, dental implant removing, orthognathic surgery, bone graft, carcinologic maxillofacial resection and reconstruction) (45/46 – 97.8%). The intervention was not clearly defined in only one publication ("minimally invasive dental examination"). Multiple procedures have been carried out on the same patient, which explains the total number of categories exceeding 46.

The most reported procedures were dental extractions (28/46 – 60.9%), following by periodontal probing (16/46 – 34.8%), root planning/periodontal scaling (14/46 – 30.4%), implant placement (8/46 – 17.4%), and endodontic treatment (8/46 – 17.4%)).

Outcomes

Primary outcomes

In 65.2% of the articles (30/46), no complications were reported during patient follow-up after invasive oral procedures, whereas 25 complications were reported in 16 articles (16/46 – 34.8%): 20 local complications in 11 articles (11/46 – 23.9%); and 5 focal/general complications in 5 articles (5/46 – 10.9%). The same patient may have presented several complications related to different interventions. Patients with complications were mostly women (18/25 – 72%) and subjects aged 50 or more (17/25 – 68%).

Local complications

Among the 11 articles reporting local complications, 6 articles reported 12 cases of medication-related osteonecrosis of the jaw (6/11 – 54.5%). Among them, 4 articles (4/6 – 66.7%) reported this complication in patients undergoing a bisphosphonate in addition to bDMARDs alone or in association with cDMARD and/or GCs treatment. Medication-related osteonecrosis of the jaw was reported after tooth extractions, with no mention of the reason for tooth extraction (6/6 – 100%), dental scaling (2/6 – 3.3%), and dental implant placement (1/6 – 1.7%). Other risk factors for jaw osteonecrosis were present in some cases: current smoking in one case, and leucopenia in 3 patients. Two articles (2/6 – 33.3%) reported jaw osteonecrosis in patients under immunosuppressive drugs without mention of bisphosphonate use, comorbidities or unhealthy lifestyle habits, after tooth extraction (2/2 – 100%), and dental implant placement (1/2 – 50%). In the case report from Hayashi et al. [42], the patient was under prednisolone and methotrexate, and in the case report from Cassoni et al. [27], the patient was treated with adalimumab and sulfalazine (Table 1).

Four cases of delayed healing of the surgical site were reported in 2 articles (2/11 – 18.2%), after multiple extractions or periodontal plastic surgery, in patients on immunosuppressive drugs without bisphosphonate treatment, tobacco smoking or comorbidities, except for a single diabetic patient.

Table 4 Description of the case–control study included in the review

Authors	Year	Country	Number of patients	Age (mean ± SD) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration (years; mean ± SD)	Other medications[b]	Diseases, conditions or lifestyle risk factors[c]	Invasive procedure	Type of complications
Kaneko C et al	2018	Japan	40[a]	59.9 ± 13.3—85% female	Rheumatoid Arthritis	Corticosteroids	± cDMARDs	None	NI	± NSAIDs	35% former smoiker	Periodontal probing and non-surgical periodontal treatment ($n = 22$)	None

[a] controls: $n = 73$ (30 patients with periodontitis, and 43 systemically and periodontally healthy controls

[b] Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing.

[c] Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing. *NI* No Information, *UC* UnClear, *BP* bisphosphonate. *NSAID* non-steroidal anti-inflammatory drug

Table 5 Description of the case-case studies included in the review

Authors	Year	Country	Number of patients	Age (mean +/- SD) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration (years; mean +/- SD)	Other medications *	Diseases, conditions or lifestyle risk factors **	Invasive procedure	Type of complications
Fabri G et al.	2015	Brazil	15	39.9 +/- 12.9 26% female	Spondyloarthritis	Prednisone	Methotrexate Sulfalazine	TNFa antagonists (infliximab etanercept adalimumab)	UC	NSAIDs	No diabetes; No severe periodontitis	Periodontal probing	None
			15	48.6 +/- 11.6 93% female	Rheumatoid Arthritis	Prednisone	Methotrexate Leflunomide	TNFa antagonists (infliximab etanercept adalimumab)	UC				
Krennmair G et al.	2010	Austria	19	46.36 100% female	Rheumatoid Arthritis	Glucocorticoids	None	None	NI	NSAIDs	No periodontitis	Multiple implant placement; Peri-implant probing	None
			7	49.57 100% female	Rheumatoid Arthritis + Connective tissue disease (Sjögren, Scleroderma, Dematomyositis)	Glucocorticoids	None	None	NI				

In the articles highlighted in blue, only data of patients with IMIDs with ongoing treatment are reported

* Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing. The others compared a group of IMID patients with intervention and a group of IMID patients without intervention

** Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing. The others compared a group of IMID patients with intervention and a group of IMID patients without intervention

Four articles (4/11 – 36.4%) reported infectious complications in 4 patients: cervico-facial cellulitis after tooth extraction and dental implant placement (1/4 – 25%); mandibular osteomyelitis after endodontic treatment (1/4 – 25%) and tooth extraction (1/4 – 25%); and apical abscess with rapid and severe bone destruction after endodontic treatment (1/4 – 25%).

Focal or general complications

The focal or general complications reported in 5 articles were: infective endocarditis related to tooth extraction (1/5 – 20%), spinal epidural abscess after minimally invasive dental examination (1/5 – 20%), septic arthritis of the knee after endodontic treatment (1/5 – 20%), meningitis after dental implant explantation (1/5 – 20%), and relapse of Behçet's disease after tooth extraction (1/5 – 20%). Of the patients with focal complications, one patient cumulates local and general risk factors (periodontal disease, tobacco smoking and diabetes mellitus, well balanced at the time of the spinal abscess). The patient developing bacterial meningitis has a well-balanced diabetes, and the one developing a septic arthritis of the knee presented poor oral hygiene. For the others, comorbidities or lifestyle habits were not indicated.

Invasive procedures associated with complications

Among the 16 articles reporting complications (local or focal), tooth extractions were involved in 10 articles (10/16 – 62.5%); endodontic treatment in 3 articles (3/16 – 18.8%); implant placement in 2 articles (2/16 – 12.5%); periodontal procedures in 2 articles (2/11 – 12.5%); and implant removal in 1 article (1/16 – 6.3%).

Complications according to the type of medical treatment

Of the articles dealing with patients on monotherapies, 17 were case reports or case series, 1 was a case-case study, and 1 was a comparative study. Among these 17 case reports or case series, no complications were reported for 6 patients on GCs and 5 patients on cDMARDs. For the other case reports or case series, complications were reported as follows: 5 cases of jaw osteonecrosis and 1 local infectious complication in patients on GCs; 5 cases of jaw osteonecrosis in patients on cDMARDs; 2 focal complications, 2 local infectious complications and 2 jaw osteonecrosis in patients on bDMARDs. Finally, in the comparative study by Cotti et al., no complications were reported in patients treated exclusively with bDMARDs [67]. The same is true of the case-case study by Krennmair et al., in which patients were treated exclusively with GCs [75].

The other complications described in the section "primary outcomes" occurred in patients on associations of GCs and/or cDMARDs and/or bDMARDs.

Secondary outcomes

In the 11 articles describing local complications, their management consisted in antiseptic use (3/11 – 27.3%); prolonged course of antibiotic (8/11 – 72.7%); surgical

Table 6 Description of the prospective cohort study included in the review

Authors	Year	Country	Number of patients	Age (mean (SD or min/max)) and sex	IMIDs	GCs	cDMARDs	bDMARDs	Treatment duration (years; mean ± SD)	Other medications[a]	Diseases, conditions or lifestyle risk factors[b]	Invasive procedure	Type of complications
Kobayashi T et al	2014	Japan	20	51.7 ± 2.2 95% female	Rheumatoid arthritis	Corticosteroids,	Name not specified	Adalimumab,	UC	NSAIDs	No diabetes; Former smoker: *n* = 3	Periodontal probing	None

[a] Other medications: concurrent medications (e.g. anti-inflammatory drugs, anti-resorptive drugs, anti-neoplasic drugs) and past medications (i.e. bisphosphonates) which could impact bone or mucosal healing.

[b] Diseases, conditions or lifestyle risk factors which could impact bone or mucosal healing. *NI* No Information, *UC* UnClear, *BP* bisphosphonate, *NSAID* non-steroidal anti-inflammatory drug

Table 7 Qualitative analysis of the case reports and series of cases

Reference	The case report includes at least 3 patients	The medical record is complete	Drug exposure is clearly defined	The invasive procedure is clearly defined	Follow-up of cases extends at least until mucosal and bone healing	SCORE
Aghaloo T et al., 2017 [20]	YES	NO	NO	YES	NO	B
Andersen K-M et al., 2003 [21]	NO	YES	NO	YES	YES	B
Bakal O et al., 2015 [22]	NO	NO	YES	NO	NO	C
Barrier A et al., 2010 [23]	YES	YES	NO	YES	NO	B
Bencharit S et al., 2010 [24]	NO	NO	YES	YES	YES	B
Brijs K et al., 2020 [25]	NO	YES	NO	YES	YES	B
Cafone J et al., 2018 [26]	NO	NO	NO	NO	NO	C
Cassoni A et al., 2018	NO	YES	YES	YES	NO	B
Ciantar M et al., 2007 [28]	NO	NO	NO	YES	YES	B
Cillo JE & Barbosa N, 2019 [29]	NO	NO	YES	YES	YES	B
Darley M et al., 2015 [30]	NO	NO	NO	NO	NO	C
Diniz-Freitas M et al., 2012 [31]	NO	YES	NO	YES	NO	B
Ebker T et al., 2013 [32]	NO	NO	YES	NO	NO	C
Ella B et al., 2011 [33]	NO	YES	NO	YES	YES	B
Favero M et al., 2009 [34]	NO	YES	YES	YES	YES	A
Favia G et al., 2017 [35]	NO	YES	YES	YES	YES	A
Fukumoto K et al., 2018 [36]	NO	YES	YES	YES	YES	A
Georgios K et al., 2009	NO	YES	YES	YES	YES	A
Goel R et al., 2015 [37]	NO	NO	NO	YES	YES	B
Goldberg D et al., 2018 [38]	NO	NO	YES	YES	YES	B
Goto M et al., 2014 [39]	NO	NO	YES	YES	YES	B
Grimaldo-Carjevschi M et al., 2011 [30]	NO	YES	YES	YES	YES	A
Gutierrez G et al., 2018 [41]	NO	YES	NO	YES	YES	B
Hayashi M et al., 2018 [42]	YES	YES	NO	YES	NO	B
Henien M et al., 2017 [43]	NO	YES	YES	NO	NO	B
Irshied J & Bimstein E, 2001 [44]	NO	YES	YES	YES	YES	A
Işleten B et al., 2011 [45]	NO	NO	YES	YES	YES	B
Junquera L et al., 2009 [46]	NO	NO	YES	YES	YES	B
Kam A et al., 2006 [47]	NO	NO	NO	YES	YES	B
Kim U et al., 2017 [49]	NO	NO	NO	YES	YES	B
Kudo C et al., 2014 [50]	NO	YES	YES	YES	YES	A
Kruif M et al., 2012 [51]	NO	NO	YES	YES	YES	B
Lescaille G et al., 2013 [52]	YES	YES	NO	YES	NO	B
Leshem D et al., 2006 [53]	YES	NO	NO	YES	YES	B
Li L et al., 2004	NO	NO	YES	YES	YES	B
Manzon L et al., 2014 [55]	NO	NO	YES	YES	YES	B
Mathai P et al., 2018 [56]	YES	YES	YES	YES	NO	A
Nomura T et al., 2013 [57]	NO	NO	NO	YES	NO	C
Oh WM et al., 2008	NO	YES	NO	YES	YES	B
Pessoa L et al., 2011 [59]	NO	NO	YES	YES	YES	B
Preidl RHM et al., 2014 [60]	NO	NO	YES	YES	YES	B
Rahman N et al., 2010 [61]	NO	YES	YES	YES	YES	A

Table 7 (continued)

Reference	The case report includes at least 3 patients	The medical record is complete	Drug exposure is clearly defined	The invasive procedure is clearly defined	Follow-up of cases extends at least until mucosal and bone healing	SCORE
Toledo Rojas R et al., 2010 [61]	NO	NO	YES	YES	NO	B
Tsuchiya S et al., 2016 [63]	NO	NO	YES	YES	YES	B
Unsworth JD et al., 2013 [64]	NO	YES	YES	YES	YES	A
Weinländer M et al., 2010	YES	NO	NO	YES	YES	B
Zigdon H et al., 2011 [66]	NO	NO	NO	YES	YES	B

debridement/curettage/sequestrectomy (5/11 – 45.5%); tooth extraction (3/11 – 27.3%); mandibular resection and reconstruction (1/11 – 9.1%); implant removal (1/11 – 9.1%); and endodontic treatment (1/11 – 9.1%). Patients were followed up 3 months to 6 years, depending on the complication severity.

In the 5 articles reporting focal/general complications, antibiotic treatment was prescribed in 4 cases (4/5 – 80%). Patients were followed up from 1 week (up to death) to 3 months.

At the end of the follow-up period, among the 25 patients with complications (local/focal), 11 recovered completely or partially (44%), 4 presented a minimal improvement (16%) and 1 patient had died (4%). No information was provided for the rest of patients (36%).

ii- Articles on complications in patients with IMIDs on immunosuppressive drugs (n = 13)

Those 13 articles reported complication occurred spontaneously or after an invasive procedure performed previously by another practitioner in 24 patients with IMIDs, on immunosuppressive drugs (18 women – 75%, 75% subjects aged 50 or more). Rheumatoid arthritis was the IMID the most frequent (17/24 patients – 70.8%), followed by IBD (4/24 – 16.7%), and Sjogren's syndrome (2/24 – 8.3%). Patients were mostly under associations of two or three immunosuppressive drugs (13/24 – 54.2%).

Previous oral invasive interventions

Patients have received oral surgeries before presentation with complications in 24 cases: tooth extraction (19/24 – 79.2%), dental implant placement (2/24 – 8.3%), and prosthetic and periodontal treatments (1/24 – 4.1%). Two patients had spontaneous complications (oro-facial fistula and respectively jaw osteonecrosis).

Type of complications

Complications were local, majorly medication-related osteonecrosis of the jaw (22/24 – 91.7%), followed by infections (1 peri-implantitis and 1 oro-facial fistula). Only one patient presented both complications, local (peri-implantitis) and focal/general (cryoglobulinemic glomerulopathy and renal failure).

Concerning comorbidities and concurrent medications altering bone metabolism: 15 patients on 24 (62.5%) had current or past history of bisphosphonate treatment; 2 patients (8.3%) had general conditions with potential oral impact (diabetes, renal failure); 2 patients (8.3%) were current smoker/drinker; and 4 patients (16.7%) had oral pathologies (poor oral health or periodontitis). Information on these parameters is lacking for 9 patients (37.5%).

Management of the complications and follow-up

Local complications were treated with prolonged course of antibiotic (19/24 – 79.2%), antiseptics (13/24 – 54.2%), sequestrectomy/bone resection (13/24 – 54.2%), tooth extraction (4/24 – 16.7%) and endodontic treatment (1/24 – 4.1%).

The duration of follow-up ranged from 3 to 24 months. At the end of follow-up, 18 complications (75%) were completely cured, 1 was partially resolved, 1 was in progress and no information was available for 5 patients (20.8%).

Discussion

We conducted a scoping review on the complications of invasive oral procedures in patients with IMIDs treated with bDMARDs and/or cDMARDs, and/or GCs. By potentially inhibiting key molecules in normal inflammatory pathways, the immunosuppressive drugs may pose at least a theoretical risk of perioperative infection and delayed wound healing. Prediction of infectious or healing complications in dentistry represent a challenge in these patients. Several confounding factors may affect post-operative complications, including disease severity and flare up, comorbidities and concurrent immunosuppressive or bone-modifying drugs, the type of invasive procedure and the surgical stress

Table 8 Quality assessment (RoB2 score) for the randomized clinical trial included in the review

Domain 1: Risk of bias arising from the randomization process	
Signalling questions	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
Risk-of-bias judgement	**Low**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
Signalling questions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	/
Risk-of-bias judgement	**Some concerns**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
Signalling questions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	/
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	/
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	/
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NI
Risk-of-bias judgement	
Domain 3: Missing outcome data	
Signalling questions	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	**Some concerns**
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	/
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	/
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	/
Risk-of-bias judgement	**Low**
Domain 4: Risk of bias in measurement of the outcome	
Signalling questions	
4.1 Was the method of measuring the outcome inappropriate?	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY
Risk-of-bias judgement	**High**
Domain 5: Risk of bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
5.3 ... multiple eligible analyses of the data?	PN
Risk-of-bias judgement	**Low**

Table 9 Newcastle–Ottawa quality assessement scale for case–control/case-case/comparative studies included in the review

Reference	Selection				Comparability of cases and control/exposed and non-exposed	Exposure			Total score/9
	Adequate cases definition	Representativeness of the cases	Selection of the controls	Definition of the controls/ non-exposed		Ascertainment of exposure	Same for cases and controls ?	Non-Response rate	
Cotti E et al., 2018	yes, eg record linkage or based on self reports	potential for selection biases or not stated	hospital controls	no history of disease (endpoint) *	study controls for the most important factor *	interview not blinded to case/control status	yes *	rate different and no designation	3
Fabbri C et al., 2014 [68]	yes, with independent validation *	consecutive or obviously representative series of cases *	hospital controls	no description of source or not concerned#	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	5
Fabri G et al., 2015	yes, with independent validation *	consecutive or obviously representative series of cases *	hospital controls	no description of source or not concerned#	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	5
Kaneko C et al., 2018 [76]	yes, with independent validation *	potential for selection biases or not stated	community controls *	no history of disease (endpoint) *	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	6
Krennmair G et al., 2010 [65]	yes, eg record linkage or based on self reports	potential for selection biases or not stated	no description	no description of source or not concerned#	study does not control for the factors	interview not blinded to case/control status	yes *	rate different and no designation	1
Jung GU et al., 2018 [69]	yes, with independent validation *	potential for selection biases or not stated	community controls *	no history of disease (endpoint) *	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	6
Karacayli U et al., 2009 [70]	yes, with independent validation *	potential for selection biases or not stated	hospital controls	no description of source or not concerned#	study controls for the most important factor + other factor **	interview not blinded to case/control status	no	rate different and no designation	3
Pers JO et al., 2008 [71]	yes, eg record linkage or based on self reports	potential for selection biases or not stated	hospital controls	no description of source or not concerned#	study controls for other factor *	interview not blinded to case/control status	yes *	rate different and no designation	2

Table 9 (continued)

Reference	Selection				Comparability of cases and control/exposed and non-exposed	Exposure			Total score/9
	Adequate cases definition	Representativeness of the cases	Selection of the controls	Definition of the controls/ non-exposed		Ascertainment of exposure	Same for cases and controls ?	Non-Response rate	
Ribeiro J. et al., 2005 [72]	yes, with independent validation *	consecutive or obviously representative series of cases *	hospital controls	no description of source or not concerned#	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	5
Zhao X et al., 2018 [73]	yes, eg record linkage or based on self reports	potential for selection biases or not stated	no description	no description of source or not concerned#	study controls for the most important factor + other factor **	interview not blinded to case/control status	yes *	rate different and no designation	3

Stars (*; **) indicate the scale items providing points; the final score corresponds to the sum of responses providing one (*) or two stars (**)

Table 10 Newcastle–Ottawa quality assessement scale for the cohort study included in the review

Selection						Outcome			Total score/12
Reference	**Representativeness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Ascertainment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	
Kobayashi T et al., 2014 [77]	somewhat representative of the average population in the community*	drawn from the same community as the exposed cohort*	structured interview*	yes*	study did not control for the factors	independent blind assessment*	no	no statement	5

Stars (*; **) indicate the scale items providing points; the final score corresponds to the sum of responses providing one (*) or two stars (**)

response related to the duration of surgery, its invasiveness and the extent of tissue injury [11]. The growing use of biological agents in clinical practice has resulted in increasing numbers of these patients presenting in dental and maxillofacial settings, but currently no specific dental or oral surgery guidance for the management of these patients exists [78].

This scoping review highlights that a relatively large number of complications were reported in the literature in patients with IMIDs under immunosuppressive treatment, especially in those with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases and vasculitis. In these studies, patients were mainly on methotrexate as cDMARDs, anti-TNF alpha (infliximab, adalimumab and etanercept) as bDMARDs, and complications occurred after invasive oral care.

Articles

Of the articles included in this scoping review, approximately half were less than 10 years old, and three-quarters were written by dentists or specialists in oral care, demonstrating the growing interest of practitioners in these treatments and the concerns related to the management of patients with IMIDs on immunosuppressant drugs presenting in oral surgery settings. The majority (80%) were case reports or series of cases, with methodological quality assessed as moderate or poor for 79% of them. Comparative studies, RCT or cohort studies were few in number and had low to moderate methodological quality, and high risk of bias.

Patients

Two-thirds of patients, representing half the studies in the review, presented with rheumatoid arthritis, which may be explained by the predominance of this condition among the immune-mediated inflammatory diseases studied here [79]. The most prescribed drugs were methotrexate, GCs and anti-TNF alpha, often in associations, which is once again explained by the preponderance of rheumatoid arthritis in this review [80].

Interventions

This review allows us to analyze a large panel of invasive oral procedures, of which tooth extractions accounted for approximately two-thirds. A significant number of studies (particularly comparative ones) focused on minimally or low invasive procedures such as periodontal probing or non-surgical periodontal treatments (dental scaling, root planing), which are less likely to cause complications [81]. Moreover, it's quite possible that in the two case-reports identified [20, 56], the MRONJs existed prior to dental scaling, without having been diagnosed beforehand. Dental scaling procedures would then have created the opportunity to diagnose these pathologies.

Outcomes and follow-up

Complications were reported in approximately one-third of articles, especially in women, and patients aged 50 or more, probably related to the prevalence of rheumatoid polyarthritis among these patients. Complications were more frequent in patients with multiple medications (combination of two or three treatments, including b/cDMARDS and/or GCs). The duration of treatment could be a risk factor for complication occurrence, but it was not possible to assess this important parameter, as information was lacking in two-thirds of articles.

Complications aroused mostly secondary to procedures requiring bone and mucosa healing (particularly tooth extractions in approximately two-third of cases), which is in line with what dentists reported in a recent French national survey on post-operative complications in patients on bDMARDs [82]. They were majorly local: osteonecrosis of the jaw (in half of cases), occurring always in a context of tooth extractions, delayed surgical site healing and local infections. Complications mainly concerned patients with IMIDs on immunosuppressive drugs having in addition a history of bisphosphonate use, unhealthy lifestyle habits and chronic diseases such as diabetes, which were previously described as related to post-operative complications following tooth extraction [83]. Few cases of osteonecrosis of the jaw were reported in patients on GC, cDMARD and/or bDMARD alone, in the absence of recognized factors as antiresorptive drugs intake [84, 85]. Therefore, immunosuppressive drugs should be considered as important risk -but not causative-factors of jaw osteonecrosis in these patients [86–88].

Complications were generally controlled after prolonged course of antibiotic (prescribed in two-thirds of cases) and antiseptic use and surgical procedures (in half of complications) in case of osteonecrosis of the jaw, which are classical treatment procedures [89]. The course of complication was generally favorable after these treatments. However, the length of follow-up was not provided for approximately one-third of complications. Focal or general complications seem to be very rare.

Prevention on complications in patients with IMIDs under immunosuppressant drugs

Preventing the risk of infection during invasive oral care for patients with IMIDs on b/cDMARDs is a complex and topical issue. Analysis of recommendations from scientific societies shows differences between national, European or American societies, as well as recommendations based on studies not specific to oral care, and not regularly updated. For example, for IBD, no information concerning oral care for patients on bDMARDs (e.g. anti-TNFalpha) has been found in the French SNFGE (Société Nationale Française de Gastro Entérologie) / GETAID

(Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif) and the ECCO (European Crohn's and Colitis Organisation) recommendations [90, 91]. As far as the AGA (American Gastroenterological Association) is concerned, we did not find any information on the risk of infection associated with invasive oral procedures in the guidelines on the use of methotrexate, and anti–TNFα biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease [92]. For inflammatory rheumatisms such as RA, there is no information in the SFR (French Society of Rheumatology) as well as the EULAR (European League Against Rheumatism) websites and guidelines [6, 93]. The French CRI (Club Rhumatisme et Inflammation) provides detailed recommendations for a number of bDMARDs, including anti-TNFalpha drugs, which are regularly reviewed (2013; 2020). It recommends prophylactic antibiotic therapy for invasive oral procedures, and discontinuation of the anti-TNF-alpha according to its half-life (at the exception of root planing) [94]. Our work highlights the fact that complications depend on the patient's profile and the nature of the oral invasive procedure performed. However, with the exception of two articles, the publications included in the scoping review did not detail the perioperative management protocol to prevent complications (prescription regimen for mouthwash and antibiotics, doses and durations; eventual communication between the surgical team and the prescribing physician to ensure management of immunosuppressant drugs in the perioperative period). It therefore supports the importance of carrying out clinical studies to clarify the infectious risk of these patients during oral care, in order to base and harmonize recommendations on data from the oral environment and reduce the unnecessary use of antibiotics [95]. Establishment of perioperative guidelines in oral surgery is needed as the number of patients on these medications increase.

Study's strengths and limitations

The main strength of this work is the relatively large number of articles on a very specific subject, enabling us to perform analyses according to the type of disease, the type of immunosuppressive treatment, a wide range of invasive procedures performed in the oral sphere, and the type of complications occurred.

Regarding the main limitations of the present study, the majority of the included studies are case reports or series of cases, with an overall average level of quality. We are certainly faced with publication bias, given that case reports generally describe adverse events and therefore certainly report cases of complication [96], whereas many patients with IMIDs and on c/bDMARDs and/or GCs surely undergo invasive oral care without any complication. Moreover, numerous studies lack information such as lifestyle factors (tobacco and/or alcohol use), comorbidities (e.g. diabetes mellitus, renal failure, cancer), bone-modifying medications (bisphosphonates, denosumab), or local factors (poor oral hygiene, hyposialia). Finally, it should be noted that in the other studies than case reports, as the primary outcome was not the presence of complications following oral invasive procedures, it is possible that information on these complications are missing.

Conclusion

This scoping review has shown that local infections or jaw osteonecrosis could occur after invasive oral procedures, mainly tooth extractions, in patients with IMIDs on b/cDMARDs and/or GCs, often in presence of comorbidities and concurrent medications such as bone-modifying agents known to impair bone and mucosa healing and to increase the risk of oral complications. This work raises the question of the need for best practice guidelines, detailing protocols for the oral care of these patients in the perioperative period, in order to achieve optimal outcomes from their management. These protocols need to be based on dental studies, with a high level of evidence, which still to be developed.

Supplementary Information

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Supplementary Material 1.

Authors' contributions

L.R. and M.G. identified the theme of the subject. L.R., M.K. and M.G. carried out the scoping review (in accordance with the description of the work notified in the journal) and drafted the main text of the manuscript. L.R. and M.G. prepared Figs. 1 and tables 1,2, 3,4, 5, 6, 7, 8, 9 and 10. L.R. and M.G. have modified the manuscript in revision. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

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Not Applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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