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Management of biologics in oral surgery

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Abstract – Biologics have revolutionised the management of immune-mediated inflammatory disorders, and their growing use has resulted in increasing numbers of these patients presenting in oral surgery settings. While the efficacy of biologics has been well established, they are associated with numerous adverse effects. Several professional bodies have published recommendations on perioperative management of these agents to reduce complications. Currently no specific dental or oral surgery guidance exists. The aim of this paper is to review the current literature and guidance regarding the use of biologics in the perioperative period.

Introduction

Biological therapies, also referred to as targeted immunomodulator therapies, are currently the fastest growing class of therapeutic products [1]. They have revolutionised the management of conditions such as rheumatoid arthritis, psoriasis, inflammatory bowel disease and oncological diseases, as their use has led to high rates of efficacy and remission. The growing use of biological agents in clinical practice has resulted in increasing numbers of these patients presenting in dental and maxillofacial settings [2].

Most synthetic drugs are small molecules with a precise chemical structure and made by a chemical process. Conversely, biological therapies are manufactured in a living system such as a microorganism, plant or animal complex [3]. They are protein-based molecules, or mixtures of molecules, often produced using recombinant DNA. Unlike corticosteroids, which are non-discriminant and suppress numerous host immune processes, biologics target specific elements of proinflammatory pathways [4]. Most are administered by injection, however the latest class of biologics, JAK inhibitors, can be taken orally. JAK inhibitors have a shorter half-life, so may offer increased flexibility and lower infection risk. Classes of biologics, their trade names and half-lives are outlined in Table I.

Biological agents do carry a risk of immunosuppression and have the potential to increase the risk of infections and delayed wound healing by blocking the normal inflammatory response in the perioperative period. However, stopping biologics may lead to flare up of the underlying condition which can affect postoperative recovery. There is little information regarding oral surgery procedures and biological therapy. Establishment of perioperative guidelines in oral surgery is needed as the number of patients on these medications increase.

Materials and methods

A literature search using Medline was completed using the MeSH terms 'oral surgery' and 'biological products'. The search yielded 14 articles, none of which were relevant to management of biologics in the perioperative period. As there are currently no studies comparing interruption of biologics in oral and maxillofacial surgery, the search criteria was widened to assess perioperative management of biologics in all types of surgery. A search was performed using Medline and EMBASE databases with the following keywords: biologics, surgery, complications, postoperative outcomes, and perioperative interruption. This literature review was based on guidelines for the Preferred Reporting Items for systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [10]. Articles were systematically screened to exclude irrelevant titles then full texts were assessed for eligibility. Subsequent results are presented in a PRISMA diagram (Fig. 1).

Results

There are currently no studies investigating the perioperative management of biological therapy for patients undergoing oral and maxillofacial surgical procedures. The majority of published evidence originates from retrospective studies of the

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Table I. Mechanism of action, dosing intervals and half-lives of biological therapies [5–9].

Class	Target	Agent	Trade name(s)	Indication	Dosing interval	One half-life (days)
Cytokine inhibitor	TNF-α inhibitor	Adalimumab	Humira, Amjevita, Imraldi, Cyltezo	RA, IBD, PsA, PS, AS, JIA	2 weekly	14
		Certolizumab pegol	Cimzia	RA, IBD, PsA, AS	2 weekly	14
		Etanercept	Enbrel, Benepali, Erelzi	RA, PsA, PP, JIA, AS	Weekly or twice weekly	3
		Golimumab	Simponi	RA, PsA, IBD	4 weekly	14
		Infliximab	Remicade, Remsima, Renflexis, Inflectra	RA, IBD, AS, PsA, PP	4, 6, or 8 weekly	9
	IL-1 receptor antagonist	Anakinra	Kineret	RA	Daily	0.25
	IL-6 inhibitor	Sarilumab	Kevzara	RA	2 weekly	10
	IL-6 receptor inhibitor	Tocilizumab	Roactemra, Actemra	RA, JIA	IV 4 weekly	11
					SC weekly	13
	IL-12 and IL-23 inhibitor	Ustekinumab	Stelara	IBD, PsA, IBD, Ps	12 weekly	21
	IL-17 inhibitor	Ixekizumab	Taltz	PP, PsA	Monthly	13
		Secukinumab	Cosentyx	Ps, PsA, AS	Monthly	27
	IL-23 inhibitor	Guselkumab	Tremfya	PP, PsA	8 weekly	18
	Immune modulator	Apremilast	Otezla	PsA, PP	Daily	0.25
	JAK inhibitor	Baracitinib	Olumiant	RA	Daily	0.5
		Tofacitinib	Xeljanz	RA, PsA, AS, JIA, IBD	Twice daily	0.33
		Filgotinib	Jyseleca	RA, IBD	Daily	0.29
		Upatacitinib	Rinvoq	RA, PsA, IBD	Daily	0.17
		Abrocitinib	Cibinqo	AD	Daily	0.21
Cell-depleting agent	CD20 (peripheral B-cell depletion)	Rituximab	Mabthera, Rixathon, Truxima, Rituxan	NHL, CLL, RA, P, PV	Two doses 2 weeks apart every 6 months	18
Co-stimulation blocker	CD80 and CD86 (minimises T-cell activation)	Abatacept	Orencia	RA, PsA, JIA	IV monthly	14
					SC weekly	

IV = intravenous, SC = subcutaneous, RA = rheumatoid arthritis, IBD = inflammatory bowel disease, PsA = psoriatic arthritis, PP = plaque psoriasis, JIA = juvenile idiopathic arthritis, AS = ankylosing spondylitis, Ps = psoriasis, AD = atopic dermatitis, NHL = non-Hodgkin's lymphoma, CLL = chronic lymphocytic lymphoma, P = polyangiitis, PV = pemphigus vulgaris.

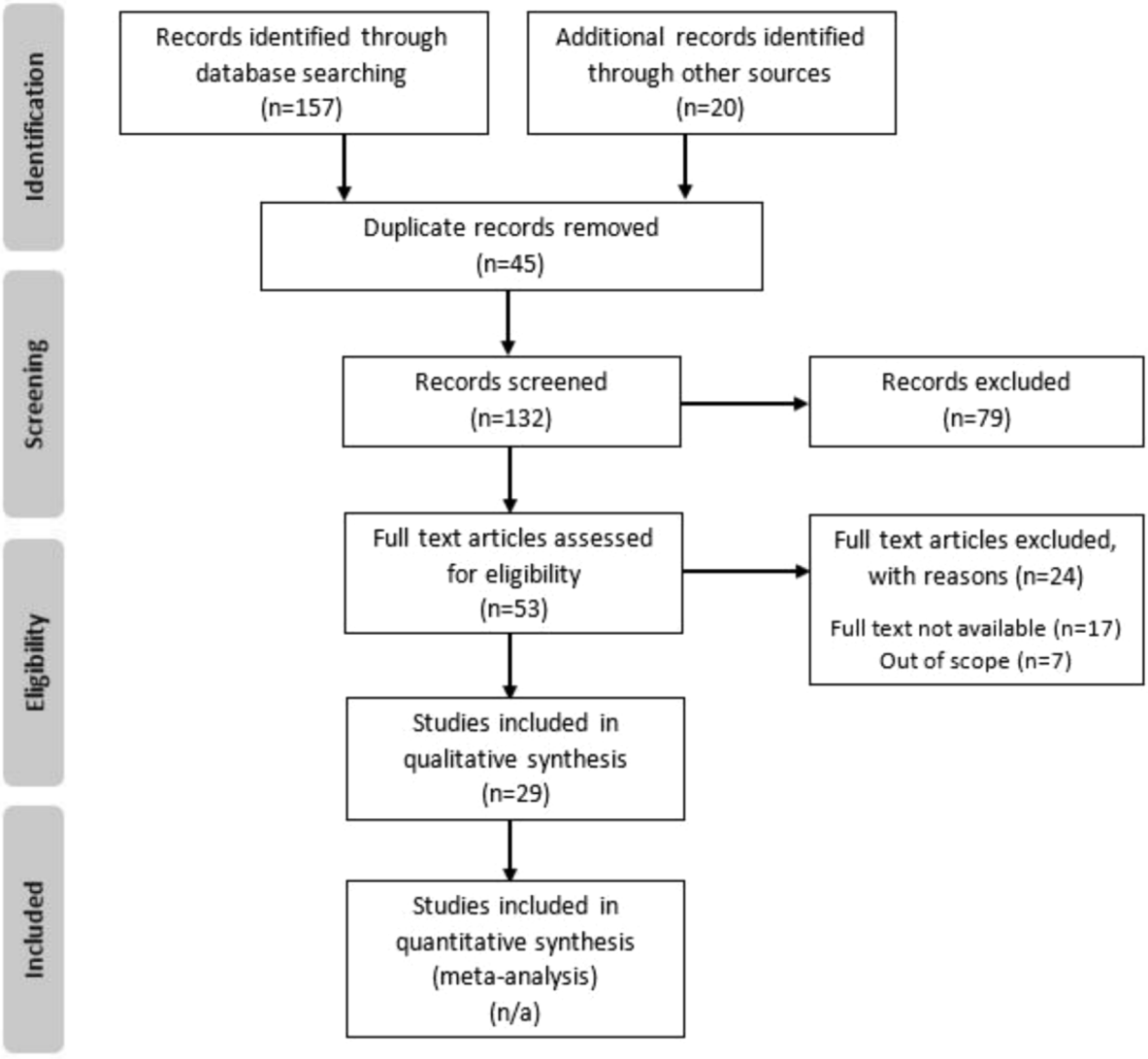

Fig. 1. PRISMA flow diagram demonstrating the screening and eligibility process during literature review.

rheumatoid arthritis population undergoing orthopaedic procedures. Of the 29 studies to date, 5 show statistically significant increased risk of infection when continuing biologics in the perioperative period, and 22 studies show no difference in postoperative outcomes (Tab. II).

The largest study to date was a retrospective study conducted by George *et al*. to assess postoperative infection following orthopaedic procedures in patients with rheumatology, dermatology and gastroenterology diseases [11]. The study compared patients who continued biological therapy in the perioperative period versus patients whose therapy was interrupted and found that administration of TNF-α inhibitor infliximab within four weeks of elective hip or knee arthroplasty was not associated with an increase in infection within 30 days.

One study investigated the impact of preoperative serum TNF-α inhibitor drug levels on postoperative outcomes in inflammatory bowel disease patients. It found that infectious complications were significantly higher in patients with therapeutic TNF-α inhibitor drug levels [12].

Most studies are retrospective, with heterogeneity of study methodologies, varying comparator groups and inconsistent outcome measures. These differences lead to variability in the association of infection with continued biological therapy in the perioperative period.

Currently no formal guidance on management of these patients perioperatively in dental or maxillofacial setting exists, but principles can be drawn from other specialties guidance. Several professional bodies have issued formal recommendations for management of patients receiving

Table II. Summary of studies comparing risk of postoperative infection in patients on biological therapy [9, 11–38].

Study	Population	Sample size	Biologic therapy	Type of surgery	Comparator groups	Results
Abou Zahr *et al.*[20] (2015)	Rheumatoid arthritis	896	Various	Various	Continued TNF inhibitor Discontinued TNF inhibitor	Increased infection rates with continued biologics but did not reach statistical significance
Bafford *et al.*[21] (2013)	Crohn's disease	196	Various	Abdominal	Preoperative biologic use No preoperative biologic use	Similar infection rates
Bakkour *et al.*[10] (2016)	Psoriasis, psoriatic arthritis	42	ADA, ETN, INF	Orthopaedic, cardiovascular, skin	Continued biologic therapy Interruption to biological therapy	Similar infection rates
Bibbo *et al.*[22] (2004)	Rheumatoid arthritis	31	ETN, INF	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
Bongartz *et al.*[23] (2008)	Rheumatoid arthritis	50	ETN, INF, ADA	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
den Broeder *et al.*[24] (2007)	Rheumatoid arthritis	196	ETN, INF, ADA	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates but increased risk of wound healing complication with continued biologics (OR 11.2, 95% CI 1.4-90)
Cohen *et al.*[25] (2019)	Inflammatory bowel disease	955	Various	Abdominal	Biologic use within 12 weeks of surgery/ detectable anti-TNF levels No biologic use within 12 weeks of surgery/ undetectable anti-TNF levels	Similar infection rates
Gainsbury *et al.*[26] (2011)	Ulcerative colitis	81	INF	Abdominal	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
George *et al.*[6] (2017)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease	4288	INF	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates

Table II. (continued).

Study	Population	Sample size	Biologic therapy	Type of surgery	Comparator groups	Results
George *et al.*[27] (2018)	Rheumatoid arthritis	1537	ABT	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
Giles *et al.*[28] (2006)	Rheumatoid arthritis	91	ETN, INF, ADA	Orthopaedic	Continued TNF inhibitor Continued conventional DMARDs	Increased risk of infection with continued biologics ($p<0.05$) OR 5.3 CI 1.1-24.9
Godot *et al.*[29] (2013)	Rheumatoid arthritis	140	RTX	Various	Postoperative complications No postoperative complications	Similar infection rates
Hirano *et al.*[30] (2009)	Rheumatoid arthritis	44	TCZ	Orthopaedic	Continued TNF inhibitor Continued conventional DMARDs	Similar infection rates
Hirano *et al.*[31] (2010)	Rheumatoid arthritis	113	ETN, INF	Orthopaedic	Discontinued TNF inhibitor Continued conventional DMARDs	Similar infection rates
Holubar *et al.*[32] (2021)	Inflammatory bowel disease	1562	Various	Abdominal	Biologic use within 60 days of surgery No biologic use within 60 days of surgery	Similar infection rates
Kawakami *et al.*[33] (2010)	Rheumatoid arthritis	128	ETN, INF	Orthopaedic	Continued TNF inhibitor Continued conventional DMARDs	Increased risk of infection with continued biologics ($p<0.05$) OR 21.8 CI 1.23-386.1
Kim *et al.*[34] (2018)	Ulcerative colitis	315	Various	Abdominal	Preoperative biologic use No preoperative biologic use	Similar infection rates
Kubota *et al.*[35] (2012)	Rheumatoid arthritis	554	INF, ETN, ADA, TCZ	Orthopaedic	Patients on biological therapy Patients not on biological therapy	Similar infection rates
Kunitake *et al.*[36] (2008)	Crohn's disease, ulcerative colitis	413	INF	Abdominal	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
Kulaylat *et al.*[37] (2021)	Crohn's disease	2364	Various	Abdominal	Biological therapy No biological therapy	Increased postoperative infection (OR 1.6; 95% CI, 1.2– 2.0)

Table II. (continued).

Study	Population	Sample size	Biologic therapy	Type of surgery	Comparator groups	Results
Latourte *et al.*[38] (2017)	Rheumatoid arthritis	263	ABT	Various	Postoperative complications No postoperative complications	Similar infection rates
Lau *et al.*[7] (2015)	Inflammatory bowel disease	331	INF, ADA, CTZ	Abdominal	Total serum level of TNFα inhibitor drug detected $\geq$ 0.98 g/mL	Infectious complications significantly higher in the $\geq$ 3 g/mL group (OR = 3.0, P = 0.03)
Marchal *et al.*[39] (2004)	Crohn's disease	79	INF	Abdominal	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
Mitsuya *et al.*[40] (2019)	Inflammatory bowel disease	62	INF, ADA, VDZ	Abdominal	Preoperative biologic use No preoperative biologic use	Similar infection rates
Momohara *et al.*[41] (2011)	Rheumatoid arthritis	420	ENT, INF, ADA	Orthopaedic	Continued TNF inhibitor Continued conventional DMARDs	Increased risk of infection with continued biologics ($p<0.05$) OR 5.69 CI 2.07-15.6
Ruyssen-Witrand *et al.*[42] (2005)	Rheumatoid arthritis, spondyloarthropathies, other	101	ETN, INF, ADA	Orthopaedic, abdominal, gynaecological	Discontinued TNF inhibitor <2 HL Discontinued TNF inhibitor 2-5 HL Discontinued TNF inhibitor >5 HL	Increased infection rates with continued biologics but did not reach statistical significance
Talwalker *et al.*[43] (2005)	Rheumatoid arthritis, psoriatic arthritis	16	ETN, INF, ADA	Orthopaedic	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates
Waterman *et al.*[44] (2013)	Inflammatory bowel disease	473	Various	Abdominal	Preoperative biologic use No preoperative biologic use	Similar infection rates
Wendling[45] (2007)	Rheumatoid arthritis	50	ETN, INF, ADA	Orthopaedic, abdominal, head and neck	Continued TNF inhibitor Discontinued TNF inhibitor	Similar infection rates

ABT = abatacept, ADA = adalimumab, CTZ = certolizumab pegol, ETN = etanercept, HL = half-life, INF = infliximab, OR = odds ratio, RTX = rituximab, TCZ = tocilizumab, VDZ = vedolizumab.

biological therapy in the perioperative period. The British Society for Rheumatology (2019) and the British Association of Dermatologists (2020) both agree on stopping biologic therapy for three to five times the half-life of the drug prior to major surgical procedures, and only restarting therapy postoperatively when there is no evidence of infection and wound healing is satisfactory [5,13]. The British Society for Rheumatology emphasise that the potential benefit of minimising postoperative infections should be balanced against a significant risk of flare in disease activity, as has been shown in some studies [39].

Discussion

By potentially inhibiting key molecules in normal inflammatory pathways, biologics may pose at least a theoretical risk of perioperative infection and delayed wound healing. The immune response plays an essential role during acute wound healing. The activation of immune cells and factors initiate the inflammatory process, facilitate wound cleansing and promote subsequent tissue healing [40]. Four overlapping phases are identified in acute wound healing; haemostasis, inflammation, proliferative phase and remodelling [41]. During the inflammatory phase TNF-α is expressed, and it includes stimulation of angiogenesis, fibroblast proliferation, and increasing collagenase and prostaglandin synthesis [42].

Perioperative interruption to biologics may reduce postoperative complication rates, but there is a need to balance the potential risk of infection with the risk of disease flare up and the potential that it may prove more difficult to re-establish disease control when a treatment has been temporarily withdrawn. Prediction of infectious or healing complications remains a challenge in these patients. There is an array of confounding factors which affect post-operative complications, including disease severity and flare up, comorbidities and immunosuppressive medications, and the type of surgery and the surgical stress response.

Disease severity and risk of flare up

The use of biologics is associated with high rates of improvement in disease signs and symptoms, but interruption to biological therapy can result in significant decline in disease control, which may require steroid therapy [5,42]. For patients with severe disease flare up, the consequences of this may outweigh the risk of post-operative infection, especially for minor procedures.

Comorbidities and immunosuppressive medications

Use of concurrent immunosuppressants (particularly corticosteroids and DMARDs), and the presence of other comorbidities may contribute significantly to post-operative infection. Concurrent glucocorticoid use was associated with an increased risk of infection postoperatively [11]. Patients with comorbidities which cause immunosuppression, such as diabetes mellitus or cancer, will be at increased risk of complications and the management of their biological therapy requires careful consideration.

Surgery stimulates a stress response in the body, in which physiological neuro-endocrine and inflammatory-immune responses occur [43]. The degree of stress response will depend on the duration of surgery, its invasiveness and the extent of tissue injury. The greatest stress response is elicited from procedures such as total joint replacement, major abdominal, open vascular or cardiac surgery [44,45]. Minimally invasive surgical techniques, such as laparoscopic surgeries, reduce the inflammatory response and associated tissue injury. Stress response is one means of quantifying the relative risk of a procedure, within which many oral and maxillofacial surgeries could be considered lower risk.

Recommendations

Management of biologics should be an individualised decision, taking into account disease activity, risk of flare up, comorbidities, concurrent immunosuppressive therapy, the type of surgery and patient preference. Following patient assessment, elective procedures can be either scheduled at the end of the dosing interval where the immunosuppressive effects of the drugs would be at their lowest, or biological therapy can be interrupted for three to five times the half-life before surgery based on dosing interval and half-life of the individual drug. When making this decision, it is advisable to liaise with the patient's prescribing physician and the patient on the best course of action.

When biologic therapy is interrupted, it can be restarted postoperatively if wound healing is satisfactory, sutures and staples are removed, and there are no clinical signs of infection. An outpatient review should be arranged approximately fourteen days following surgery for a clinician to assess healing. With regards to emergency surgery, scheduling and therapy interruption are not possible, so patients should be closely monitored for infection or other complications postoperatively.

Conclusion

Biologics are increasingly being used for management of immune-mediated inflammatory disorders. Management of these agents around the time of surgery requires balancing the risk of infection and delayed wound healing against the risk of disease flare up. Guidelines have provided a starting point to minimise perioperative risk, but recommendations should be considered in the context of the individual. Good communication between the surgical team and the prescribing physician is required to ensure management of biologics in the perioperative period carries optimal outcomes for patients. Further research is required to determine the implications of biologics on postoperative infection in oral surgery and a position paper is necessary to shape professional guidance.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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Ethical approval

Ethical approval will not be required because this study retrieved and synthesised data from previously published studies.

Informed consent

As this study systematically reviewed previously published studies, no new informed consent was required but ethical principles were followed.

Authors contributions

Sophie Mills, Patrick Ryan and Karl Gaffney contributed equally to the manuscript, with Sophie Mills writing the first draft and all authors participating in the editing process and approving the final version.

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