Complications After Dental Extractions in Patients Taking Biologic Agents

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INTRODUCTION

Biologic agents are an expanding class of therapeutics employed in treatment of cancer, autoimmune conditions, neurologic diseases, and more. As these agents have grown in number and application, an increasing number of patients receive them for treatment in outpatient contexts, often chronically. While impacts of biologic agents on healing have been elucidated in specific surgical contexts[1,2], their effects on the safe delivery of dental treatment remain unknown. This research aimed to estimate the rate of surgical complications in patients receiving therapy with biologic agents and to describe the complications observed. In doing so, this study contributes to the safe and effective delivery of dental treatment in this population and expands on a topic that has to date been poorly characterized in the medical literature.

METHODS & MATERIAL

- Retrospective case-control study
- Penn Dental Medicine patients treated with biologics who underwent dental extraction between July 1, 2017 – July 1, 2020
- Analysis of complications within 30 days of extraction
- Demographic data were compiled descriptively
- Complications were compared using Fisher's exact test and multivariate logistic regression.

RESULTS

- 1 July 2017 - 1 July 2020: 121patients treated with biologics received 217 dental extractions during 147 encounters.
- 15 patients experienced 16 complications, consisting of: bleeding, post-surgical abscess, hematuria, pain, delayed wound healing, swelling, and alveolar osteitis.
- Notable or excessive pain was most commonly documented (14 of 16 cases; 88%).
- Complication after extraction was significantly more common in patients receiving aflibercept (67 vs. 33%; p = 0.03) and ranibizumab (100 vs. 0%; p = 0.01)
- Neither sex (p = 0.80) nor age (p = 0.85) were not significantly associated with complication.
- When grouped by class, reported complication after extraction – specifically, excessive pain - was significantly elevated in patients treated with VEGF antagonists (67 vs. 33%; p = 0.0010).
- Multivariate logistic regression on complications combining drug treatment status (including only n=7 drugs with observed complications) with age and sex was not significant overall ($\chi^2(8) = 14.50$, p = 0.07

Patient data				**Biologic agent**	**Total**	**Complications**	**Rate (%)**
Population (n)	**Total**	**Complications**		Dulaglutide (trulicity)	46	7	15%
Encounters	147	16		Adalimumab (humira)	17	2	12%
Unique patients	121	15		Infliximab (remicade)	7	0	
Total # extractions	217	31		Ustekinumab (stelara)	5	0	
Average # of extractions on date of service	1.8	1.9		Evolocumab (repatha)	4	0	
# of distinct biologic agents (see right)	28	7		Etanercept (enbrel)	4	0	
				Ixekizumab (taltz)	3	1	33%
Demographics	n=121	n=15		Tofacitinib (xeljanz)	3	1	33%
Age (Mean (St. Dev))	58 (13)	60 (13)		Collagenase (santyl)	3	0	
Female (n (%))	65 (54)	6 (40)		Interferon beta (rebif/avonex)	3	0	
Race (n (%))				Ranibizumab (lucentis)	2	2	100%
White	24 (20)	1 (6)		Belimumab (benlysta)	2	1	50%
Black or African American	39 (32)	6 (40)		Epoetin (epogen)	2	0	
Asian	4 (3)	0		Nivolumab (opdivo)	2	0	
Native Hawaiian or Other Pacific Islander	2 (2)	0		Tocilizumab (actemra)	2	0	
Other	5 (4)	1 (6)		Secukinumab (cosentyx)	2	0	
Missing	47 (39)	7 (46)		Golimumab (simponi)	2	0	
				Omalizumab (xolair)	2	0	
Complication		n=16		Bevacizumab (avastin/pravastin)	2	0	
Pain		14		Aflibercept (eylea/zaltrap)	3	2	67%
Bleeding		1		Dornase alfa (pulmozyme)	1	0	
Swelling		2		Alirocumab (praluent)	1	0	
Hematuria		1		Filgastim (neupogen)	1	0	
Post-surgical abscess		3		Obinutuzumab (gazyva)	1	0	
Delayed wound healing		3		Pembrolizumab (keytruda)	1	0	
No additional detail		1		Trastuzumab (herceptin)	1	0	
Alveolar osteitis		1		Daratumumab (darzalex)	1	0	
Bone spicule		1		Rituximab (rituxan)	1	0	

Table: Patient data for the population of patients undergoing dental extraction at Penn Dental Medicine 2017-2020, demographics of the subpopulation who experienced a complication after extraction, and details of complications (left). Details of biologic agents received by the full population and those that experienced complications (right).

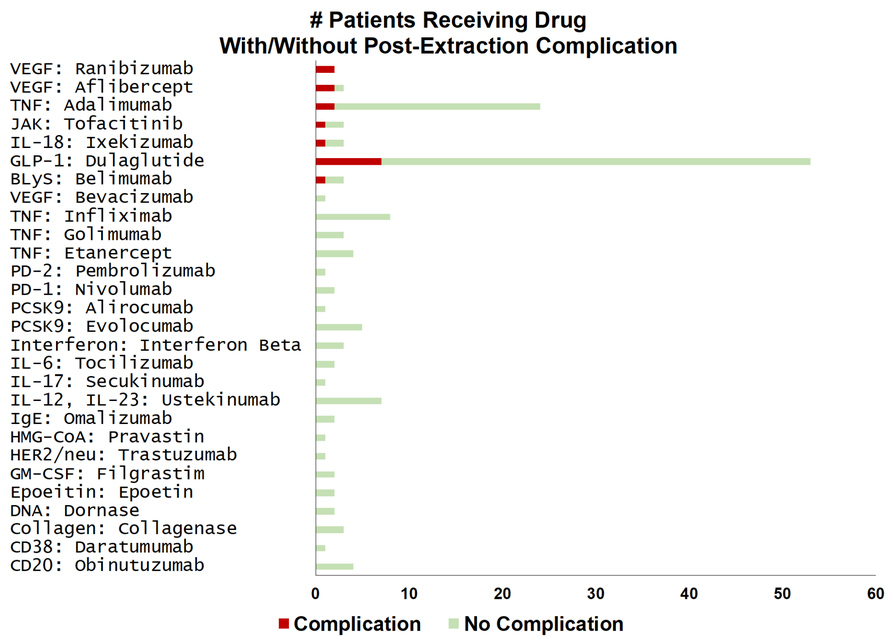

Figure 1: Number of patients receiving each biologic agent coded by those that did (red) and did not (green) experience a complication after extraction with all agents labeled with both mechanism of action and generic name, scaled according to number of patients receiving each agent.

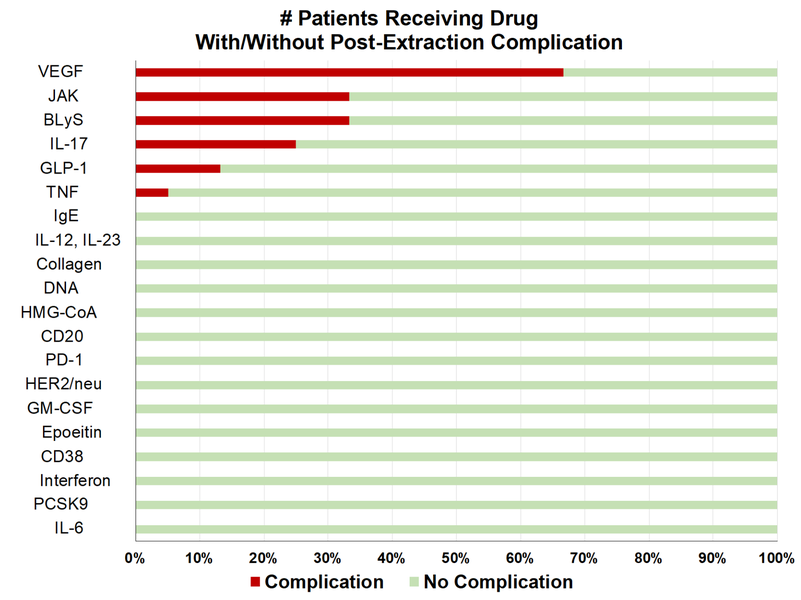

Figure 2: Percentage of patients treated with biologic agents in each class of agents who experienced complications after extraction (red) or did not (green).

CONCLUSIONS

As the number of biologic agents developed or approved has increased, the adverse effects associated with these agents have also increased. Orofacial adverse effects of biologic agents, including oral lesions and development of orofacial infections, have primarily been reported through case reports and case series[4]. The impact of biologic agents on provision of and recovery after dental treatment remains unknown. To the best of our knowledge, this is the first study on surgical complications after dental extractions in patients on biologics. Complications during post-surgical follow-up in this cohort included: bleeding, post-surgical abscess, hematuria, delayed wound healing, swelling, alveolar osteitis, and pain. Pain was the most reported complication. Notably, patients treated with VEGF antagonists experienced a significantly elevated rate of complications. While the clinical or biological relevance of a connection between VEGF antagonism and pain is unclear, early reports have investigated dysregulation of VEGF1R and VEGFR2 as a mechanism contributing to progression and severity of pain in osteoarthritis and rheumatoid arthritis[5,6]. Other reports have linked VEGF-A to nociception in chronic neuropathic pain[7,8]. In this cohort, it is unknown whether these mechanisms caused the observed relationship with increased post-surgical pain.

RELEVANCE TO PATIENT CARE

Pharmacotherapeutic management with biologic agents has proven successful in many systemic diseases. Dental clinicians will encounter patients treated with biologic agents during their daily practice and must monitor for associated adverse effects or risk factors. Evidence must be gathered on treatment course and healing of these patients to inform these clinical decisions.

To date, there are no official guidelines for the management of patients on biologic agents undergoing invasive dental treatment. Further research will continue to elucidate any drug- or class-associated adverse events and allow for establishment of such guidelines. This study provides preliminary evidence of the healing course after dental extraction as a first step to establishing recommendations for the dental clinician. Further study may build on this data and determine appropriate cross-disciplinary care management, pre/post-surgical recommendation, and risk stratification for managing patients on biologic agents in the dental setting.

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