A retrospective, single-center cohort study on complications after dental extractions in patients taking biologic agents

Andres Davila, DMD; Rogan Magee, MD, PhD; Katherine France, DMD, MBE

Supplemental material is available online.

ABSTRACT

Background. Although biologic agents represent a growing class of therapeutics, little is known about how these agents affect the provision of dental treatment.

Methods. This retrospective case-control study analyzed patients undergoing dental extraction treated with biologic agents from 2017 through 2020. Complications within 30 days postextraction were recorded.

Results. One-hundred twenty-one patients were treated during 147 encounters. Fifteen patients experienced complications during 16 encounters. Notable or excessive pain was most common (14/16; 88%). Patients who experienced complications were treated with 7 biologic agents: dulaglutide, belimumab, adalimumab, aflibercept, tofacitinib, ranibizumab, and ixekizumab. Complication after extraction—specifically, pain—was elevated for patients receiving aflibercept and ranibizumab. When grouped by class, complications were more common with vascular endothelial growth factor antagonism.

Conclusions. The impact of biologics on the provision of and recovery after dental treatment remains unknown. Pain was most commonly reported. Patients treated with vascular endothelial growth factor antagonists experienced an elevated rate of complications.

Practical Implications. This study provides preliminary data on how patients taking biologic agents heal after dental extraction. It is limited by small sample sizes. Further work will build on this data to determine appropriate management of patients taking biologics in the dental setting.

Key Words. Biologic agents; biologics; dental extraction; postextraction complication; postextraction pain; medically complex dentistry.

JADA 2022:153(11):1060-1069
https://doi.org/10.1016/j.adaj.2022.07.009

A biologic agent (BA) is defined as "a substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases."[1] Biological sources for BAs include monoclonal antibodies—human (suffix "mab"), humanized (suffix "zumab"), or chimeric (mouse–human; suffix "ximab")—or variant fusion proteins (suffix "cept").[2]

BAs are an expanding class of therapeutics used in treatment of a variety of conditions, including cancer, neurologic diseases, dermatologic disorders, and endocrinopathies. They also have garnered favor in the management of inflammatory immune-mediated disorders.[3] As BAs have grown in number and application, an increasing number of patients receive them long term in outpatient settings. BAs also are used increasingly to treat oral mucosal diseases, including but not limited to pemphigus vulgaris and Sjögren syndrome.[4,5]

Despite their efficacy, BAs lead to both systemic and organ-specific adverse effects. Although oral adverse events are poorly characterized to date, systemic reactions are well characterized and include malignancy, infection, and infusion reactions.[6] In recognition of these risks, patient selection and pretreatment evaluation are essential. Preparation for biologic therapy includes suitability to treatment, pretherapy counseling, screening for latent infections, baseline laboratory tests, and maintenance of vaccination status. Candidacy for biologic therapy includes both evaluation of the

presence or severity of disease and identifying contraindications, including, but not limited to, severe, active, or untreated infection; uncontrolled heart failure; and neurologic conditions such as multiple sclerosis. Infection is a particularly important primary risk. Minimizing opportunistic infection and reactivation of latent infection is recommended through screening for tuberculosis, HIV, hepatitis B and C, and varicella zoster virus. Examples of baseline laboratory testing include basic metabolic panels, complete blood count with differential, liver function tests, varicella zoster antibody testing, and C-reactive protein.[7-9]

In recognition of these risks, impaired postsurgical healing is an active area of concern in patients taking BAs. Several investigations have attempted to characterize this risk in select medical settings, with variable reporting of associated risk.

A meta-analysis of the impact of various immunosuppressive agents on postoperative outcomes in Crohn disease revealed no difference in total postoperative complications in patients treated with BAs compared with patients treated with other medications. However, a trend toward higher postoperative complication with anti–tumor necrosis factor (TNF)-α treatment was observed.[10] Similarly, other studies have found a possible increased risk after abdominal and nonabdominal surgery for adults and children taking anti–TNF-α agents.[11-14] Contrarily, 2 retrospective studies analyzing postoperative infectious complications in adult patients with Crohn disease after major abdominal surgery treated with anti-TNF, vedolizumab (anti-integrin), or ustekinumab (interleukin antagonist) found that no class of biologic therapy independently increased the risk of postoperative infectious complications.[15,16] Although 1 meta-analysis found an increased risk of short-term postoperative complications in patients with ulcerative colitis undergoing surgery while taking infliximab,[17] a follow-up meta-analysis found that preoperative infliximab use did not increase the risk of early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery.[18]

Regarding surgical planning for irritable bowel disease in patients taking BAs, best practice includes considering the nature of the condition, the urgency of surgery, and, where relevant, preoperative anti-TNF levels. In patients with ulcerative colitis, it has been proposed that BAs can be continued owing to poor systemic bioavailability. However, higher anti-TNF levels (>3 mg/mL) appear to be associated with higher overall infectious complications in Crohn disease but seem noncontributory in ulcerative colitis.[19]

In rheumatoid arthritis, a cohort study evaluating adults undergoing total knee or hip arthroplasty who were taking abatacept, adalimumab, etanercept, infliximab, rituximab, or tocilizumab revealed a similar risk of prosthetic joint infection, in-hospital infection, and readmission after surgery.[20] Other evidence in this setting remains minimal.[21] BAs have also become established therapies for psoriasis and psoriatic arthritis, in which consensus recommendations suggest continuing BAs during minor surgical procedures but evaluating risks and benefits before higher-risk procedures.[22]

Despite some evidence of the impact of BAs on healing in surgical contexts, their effects on the safe delivery of dental treatment remain largely unknown. To date, limited evidence is available regarding the impact of biologic treatment on tolerance of or healing from dental treatment. As a result, no official recommendations exist to guide appropriate dental management of the treatment of these patients. Our research aimed to evaluate the rate and nature of outpatient oral surgical complications in patients taking BAs. Our study compared only patients taking BAs and did not compare these patients with healthy control patients or patients taking other medications. In so doing, this study attempts only to begin to estimate the rate and nature of complications after dental extraction in patients taking BAs. With this reporting, our study contributes to the safe and effective delivery of dental treatment in patients taking BAs, providing important expansion of a topic that has, to date, been poorly characterized in the medical literature.

METHODS

In this retrospective case-control study, we gathered all available data on healing or complications after dental extraction performed in outpatient clinics at University of Pennsylvania (Philadelphia, Pennsylvania) on patients taking BAs. The study was deemed exempt by the University of Pennsylvania Institutional Review Board (protocol 844617). All data were deidentified, and informed consent was not required per institutional review board review.

We included all data on adult patients (>18 years) taking BAs and receiving at least 1 dental extraction in any outpatient clinic at the University of Pennsylvania from July 1, 2017, through July

ABBREVIATION KEY

BA: Biologic agent.
BLyS: B lymphocyte stimulator.
CD: Cluster of differentiation.
CDT: Code on Dental Procedures and Nomenclature.
GLP-1: Glucagonlike peptide-1.
GM-CSF: Granulocyte-macrophage colony-stimulating factor.
HER2/neu: Human epidermal growth factor receptor 2/proto-oncogene neu.
IgE: Immunoglobulin E.
Il: Interleukin.
JAK: Janus kinase.
PCSK9: Proprotein convertase subtilisin/kexin type 9.
PD-1: Programmed cell death protein 1.
TNF: Tumor necrosis factor.
VEGF: Vascular endothelial growth factor.

1, 2020. Patients were identified if they had a BA included in their medication list (a list of BAs included in the search is in the Appendix, available online at the end of this article) and received an extraction according to Code on Dental Procedures and Nomenclature (CDT) codes corresponding to extraction procedures: D7140, D7210, D7250, D7111, D7220, D7230, D7240, and D7241.[23] Extractions were performed either alone by a licensed dentist or by an oral surgery resident or dental student under supervision of a licensed dentist. Given that we included all patients taking BAs across the institution, the data included each of these levels of service.

We excluded patients if they were no longer taking the BA on the date of the extraction, as confirmed by clinical notes. Additional exclusion criteria included patients with a history of osteonecrosis and osteomyelitis, given the independent risk factors associated with these conditions; patients for whom an extraction preceded biologic treatment; patients taking bisphosphonates and denosumab; and patients who had been treated with single-dose agents such as antidotes.

We gathered demographic data for all patients, including age on date of treatment, sex, and race (White, Asian, Black, Native Hawaiian or Other Pacific Islander, and unreported). We collected appointment dates for extractions and postoperative visits. We summarized BAs via number and agents taken by each patient during treatment rendered, mechanism of action, dose, and frequency.

We reviewed patient charts to determine any record of complication in the 30 days after each extraction. For each patient, we reviewed any visits within 30 days in detail, regardless of location of next visit, to determine if any complication with healing or other adverse reaction was noted. This included any notation of proper healing but also any objective or subjective evidence recorded relating to healing. We compiled and stratified any reported adverse events according to predefined major complications (bleeding, postsurgical abscess and infection, hematuria, lymph node tenderness) and minor complications (delayed wound healing, pain, swelling, alveolar osteitis, sensitivity, bony spicules). We also noted further descriptive data associated with each complication, including treatment rendered and outcome for any complication identified. We obtained all data directly from the electronic medical record system and gathered them using standardized Microsoft Excel spreadsheets created before data collection began. We did not collect any identifying data.

We compiled demographic and clinical data descriptively. We compared complications using Fisher exact test or *t* test according to demographic information. We defined significance as *P* value below .05 throughout. We completed statistical analysis in Excel and R software (R Foundation for Statistical Computing).

RESULTS

From July 1, 2017, through July 1, 2020, 121 patients treated with BAs received 309 dental extractions during 147 encounters (mean, 2.10 extractions per encounter). Mean (SD) age was 58 (12.9) years, and 65 (54%) patients were female. Although race was not recorded for every patient, at least 32% of the patients were Black, and 20% were classified as White.

Patients were treated with 28 different BAs: dulaglutide (Trulicity, Eli Lilly), adalimumab (Humira, AbbVie), infliximab (Remicade, Janssen), ustekinumab (Stelara, Janssen), evolocumab (Repatha, Amgen), etanercept (Enbrel, Amgen), ixekizumab (Taltz, Eli Lilly), tofacitinib (Xeljanz, Pfizer), collagenase (Santyl, BioSpecifics), interferon beta (Rebif, Pfizer; Avonex, Biogen), ranibizumab (Lucentis, Genentech), belimumab (Benlysta, GlaxoSmithKline), epoetin (Epogen, Amgen), nivolumab (Opdivo, Bristol Myers Squibb), tocilizumab (Actemra, Genentech), secukinumab (Cosentyx, Novartis), golimumab (Simponi, Janssen), omalizumab (Xolair, Genentech), bevacizumab (Avastin, Genentech; ^{Pr}Avastin, Roche), aflibercept (Eylea, Regeneron; Zaltrap, Regeneron), dornase alfa (Pulmozyme, Genentech), alirocumab (Praluent, Regeneron and Sanofi), filgrastim (Neupogen, Amgen), obinutuzumab (Gazyva, Genentech), pembrolizumab (Keytruda, Merck), trastuzumab (Herceptin, Genentech), daratumumab (Darzalex, Janssen), and rituximab (Rituxan, Roche). The most prescribed BA was dulaglutide (46 patients [38%] and 53 encounters [36%]), followed by adalimumab (17 patients [14%], 23 encounters [16%]) and infliximab (7 patients [6%], 8 encounters [5%]).

Fifteen patients in this study experienced 24 complications after extraction during 16 encounters, consisting of bleeding, postsurgical abscess, hematuria, pain, and delayed wound healing. This resulted in an overall rate of 12.3% of patients experiencing complications during 10.9% of encounters. Notable or excessive pain was the most common complication documented, occurring after 14 of 16 encounters (88%, accounting for 25 extractions), followed by delayed wound healing

Table 1. Data for patients undergoing dental extraction 2017-2020, demographics of the subpopulation who experienced a complication after extraction, and details of complications.

PATIENT DATA	TOTAL	WITH COMPLICATIONS
Events, No.		
Encounters	147	16
Unique patients	121	15
Total extractions	309	31
Average extraction per visit	2.1	1.9
Distinct biologics used	28	7
Demographics		
Age, y, mean (SD)	58 (13)	60 (13)
Sex, no. (%)		
Female	65 (54)	6 (40)
Race, no. (%)		
White	24 (20)	1 (6)
Black	39 (32)	6 (40)
Asian	4 (3)	0
Native Hawaiian or Other Pacific Islander	2 (2)	0
Other	5 (4)	1 (6)
Missing	47 (39)	7 (46)
Complications, No.		
Pain	–*	14
Postsurgical abscess	–	3
Delayed wound healing (including bone spicule, alveolar osteitis)	–	3
Swelling	–	2
Bleeding	–	1
Hematuria	–	1

* –: Not applicable.

(3 of 16 encounters [19%], 3 extractions), postsurgical abscess (3 of 16 encounters [19%], 4 extractions), and swelling (2 of 16 encounters [13%], 7 extractions). Less common complications were hematuria in the setting of opioid analgesic use after extraction (1 of 16 encounters [6%], 2 extractions) and bleeding (1 of 16 encounters [6%], 1 extraction). Percentages summed to greater than 100%, as in several cases, multiple adverse events were noted during a single 30-day course. Of patients who experienced complications, 9 (60%) were male, mean age was 60 years (range, 36-80), and 40% were Black, and a mean of 1.94 teeth were extracted during the encounter preceding the complication (Table 1). In 13 of 16 (81%) encounters, 26 teeth were removed via simple extraction (CDT D7140). In 2 encounters (13%), 3 teeth were removed surgically (CDT D7210), and in 1 encounter, 2 partial bony impacted teeth were removed (CDT D7230). The surgical extractions were completed in a 45-year-old woman taking adalimumab for psoriasis and a 71-year-old woman taking dulaglutide for diabetes. The partial bony impacted teeth were extracted from a 38-year-old man taking ixekizumab for psoriasis who experienced excessive pain after the procedure.

Patients who experienced complications were each treated with 1 of 7 BAs (dulaglutide, belimumab, adalimumab, aflibercept, tofacitinib, ranibizumab, ixekizumab) representing 6 mechanisms of action (glucagonlike peptide-1 agonists, B-cell activating factor antagonists, TNF antagonists, vascular endothelial growth factor [VEGF] antagonists, Janus kinase antagonists, interleukin-17 antagonists). Aflibercept and ranibizumab were administered intravitreally. All others were formulated for systemic uptake via injection (dulaglutide, belimumab, adalimumab, ixekizumab) or oral administration (tofacitinib). The complete list of BAs represented in this cohort and agents associated with complications are listed in Table 2.

Table 2. Details of biologic agents received by the total population and those who experienced complications.

BIOLOGIC AGENT*	TOTAL NO. OF PATIENTS†	PATIENTS WITH COMPLICATIONS	RATE, %
Ranibizumab (Lucentis)	2	2	100
Aflibercept (Eylea, Zaltrap)	1	1	100
Belimumab (Benlysta)	2	1	50
Ixekizumab (Taltz)	3	1	33
Tofacitinib (Xeljanz)	3	1	33
Dulaglutide (Trulicity)	46	7	15
Adalimumab (Humira)	17	2	12
Infliximab (Remicade)	7	0	0
Ustekinumab (Stelara)	5	0	0
Evolocumab (Repatha)	4	0	0
Etanercept (Enbrel)	4	0	0
Collagenase (Santyl)	3	0	0
Interferon beta (Rebif, Avonex)	3	0	0
Nivolumab (Opdivo)	2	0	0
Tocilizumab (Actemra)	2	0	0
Secukinumab (Cosentyx)	2	0	0
Golimumab (Simponi)	2	0	0
Omalizumab (Xolair)	2	0	0
Bevacizumab (Avastin, ^{Pr}Avastin)	2	0	0
Epoetin (Epogen)	2	0	0
Dornase alfa (Pulmozyme)	1	0	0
Alirocumab (Praluent)	1	0	0
Filgrastim (Neupogen)	1	0	0
Obinutuzumab (Gazvya)	1	0	0
Pembrolizumab (Keytruda)	1	0	0
Trastuzumab (Herceptin)	1	0	0
Daratumumab (Darzalex)	1	0	0
Rituximab (Rituxan)	2	0	0

* Manufacturers' names are listed in the text. † Two patients in this cohort were being treated with 2 biologic agents simultaneously, causing the number of patients taking each biologic to sum to 123 despite describing a cohort of 121 patients.

Patients who experienced complications were being treated with biologics for the following indications: 1 patient taking ranibizumab for macular degeneration, 1 patient taking ranibizumab for papilledema, 1 patient taking aflibercept for diabetic retinopathy, 1 patient taking belimumab for systemic lupus erythematosus, 1 patient taking ixekizumab and 2 patients taking adalimumab for psoriasis, 1 patient taking tofacitinib for rheumatoid arthritis, and 7 patients taking dulaglutide for type 2 diabetes mellitus (eTable 1, available online at the end of this article).

We also sought to understand whether medication interactions may have affected our results. For the 15 patients experiencing complications, we pooled other prescription medications to count overall rates of each medication (eTable 2, available online at the end of this article). The most common medication among patients experiencing complications was dulaglutide, with large percentages also prescribed aspirin (33% [5 of 15]), amlodipine, atorvastatin, gabapentin, metformin (4 patients or 27% each).

In our data set, 1 patient taking aflibercept experienced complications after 2 of 3 encounters (67%), and both patients taking ranibizumab experienced complications after extraction (1 encounter each, 100%) (Figure 1). When grouped by class (Figure 2), patients treated with

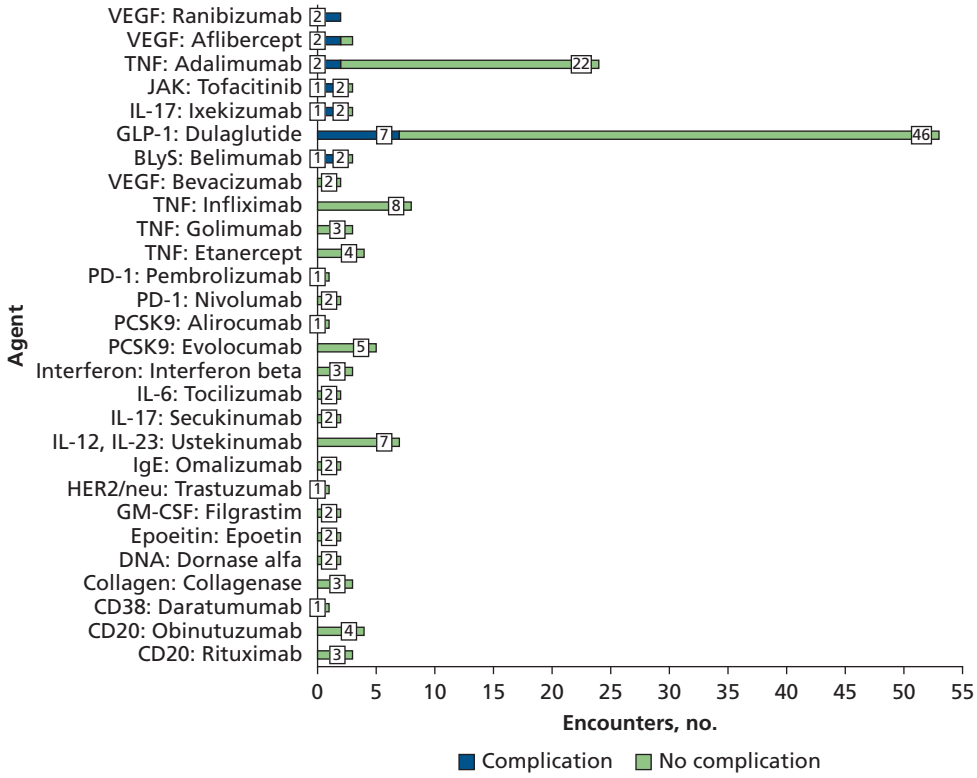

Figure 1. Number of encounters associated with each biologic agent, coded by those that did (blue) and did not (green) result in a complication after extraction (both values numerically labeled), with all agents labeled with both target of action and generic name, scaled according to number of patients receiving each agent. BLyS: B lymphocyte stimulator. CD: Cluster of differentiation. GLP-1: Glucagonlike peptide-1. GM-CSF: Granulocyte-macrophage colony-stimulating factor. HER2/neu: Human epidermal growth factor receptor 2/proto-oncogene neu. IgE: Immunoglobulin E. Il: Interleukin. JAK: Janus kinase. PCSK9: Proprotein convertase subtilisin/kexin type 9. PD-1: Programmed cell death protein 1. TNF: Tumor necrosis factor. VEGF: Vascular endothelial growth factor.

VEGF antagonists experienced the most complications. Specifically, 3 patients treated with VEGF antagonists noted excessive pain after 4 of 5 extraction events.

To further clarify the context in which these complications occurred, we explored the indication for BA treatment among the 15 patients experiencing complications and combined these indications with other medications each patient was taking and the complication experienced (eTable 1, available online at the end of this article). As above, aflibercept and ranibizumab were the only agents associated with an increase in complications, specifically, pain. In these patients, ranibizumab was prescribed for macular degeneration and papilledema, whereas aflibercept was prescribed for diabetic retinopathy.

No other individual BAs or mechanism classes were associated with an increased risk of complications. In addition, no individual agents or mechanisms were associated with an increased risk of infection after dental extraction. Furthermore, only 3 patients (2.5% of patients and 2.1% of encounters) were treated for postsurgical infection. There were also no significant differences in age (mean [SD], 60 [13.3] years in the cohort with complications; mean [SD], 58 [12.9] years in the cohort without; $P = .4019$) or sex (40% female in the cohort with complications vs 54% female overall; $P = .7962$; odds ratio, 0.84) among patients experiencing complications.

DISCUSSION

The purpose of this research was to estimate the rate of and describe the nature of postextraction complications in patients treated with BAs. To date, orofacial adverse effects of BAs, including oral lesions and development of orofacial infections, primarily have been reported through case reports and case series. Orofacial adverse effects of BAs have included oral ulcerations, mucositis, erythema multiforme, lichenoid reactions, and bacterial odontogenic infections.[24] However, to our knowledge, ours is the first study that examined surgical healing in dental cohorts.

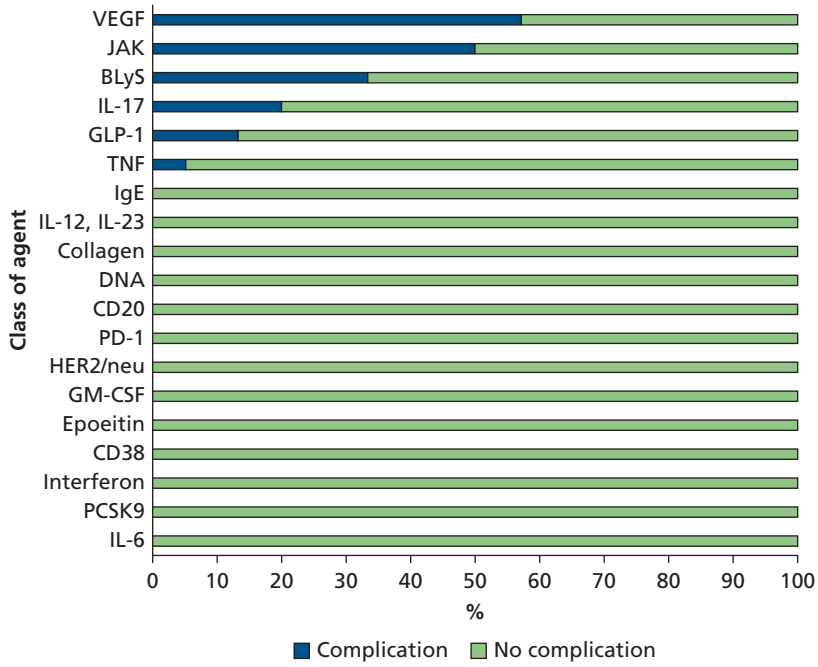

Figure 2. Percentage of encounters representing each class of biologic agents coded according to those that resulted in complications after extraction (blue) or did not (green). BLyS: B lymphocyte stimulator. CD: Cluster of differentiation. DNA: GLP-1: Glucagonlike peptide-1. GM-CSF: Granulocyte-macrophage colony-stimulating factor. HER2/neu: Human epidermal growth factor receptor 2/proto-oncogene neu. IgE: Immunoglobulin E. Il: Interleukin. JAK: Janus kinase. PCSK9: Proprotein convertase subtilisin/kexin type 9. PD-1: Programmed cell death protein 1. TNF: Tumor necrosis factor. VEGF: Vascular endothelial growth factor.

In our study population, patients exhibited few complications after dental extraction, with an overall complication rate of 11% and only 16 major and minor complications observed. These complications consisted primarily of pain (88% of major and minor complications). Patients who experienced complications were each treated with 1 of 7 BAs representing 6 mechanisms of action. When grouped by class, patients treated with VEGF antagonists experienced complications more frequently than those patients treated with other individual BAs or drug mechanisms.

Dysregulated VEGF signaling leads to unrestrained vascular proliferation and has been reported in tumor growth and metastasis, diabetic retinopathy, macular degeneration, and inflammatory processes (for example, rheumatoid arthritis).[25,26] Abnormal vascular proliferation contributes to interstitial hypertension, hypoxia, and acidosis in the microenvironment. VEGF antagonists and other antiangiogenic pharmaceuticals were designed to control vascular proliferation and normalize the microenvironment.[27,28]

In background literature, localized adverse events recorded after anti-VEGF intravitreal injections include infectious endophthalmitis, intraocular inflammation, rhegmatogenous detachment, acute intraocular pressure elevation, and ocular hemorrhage.[29] Adverse events reported with systemic administration of anti-VEGF agents include cardiovascular events, bleeding, delayed wound healing, and gastrointestinal complications.[28] Research has supported a connection between antiangiogenic agents (including intravitreal aflibercept) and medication-related osteonecrosis of the jaw.[30,31]

Our data reveal an increased rate of postextraction pain in patients receiving VEGF antagonists. Although the clinical or biological relevance of this observation is unclear, early reports regarding osteoarthritis and rheumatoid arthritis have described dysregulation of VEGF receptor 1 and VEGF receptor 2 as potential mechanisms contributing to progression and severity of pain.[32,33] Other reports have linked VEGFA to nociception in chronic neuropathic pain.[34,35] Further background suggests treatment with VEGF antagonists may hinder the normal proliferation of neurovascular supply during tissue regeneration.[25,26] Together, these observations raise the possibility that VEGF antagonism may increase the rate of postextraction pain mechanistically. Future work should aim to validate this observation and elucidate potential causal relationships.

Intravitreal injection is the primary therapeutic route of delivery of VEGF antagonists used in retinal disease. Despite the localized entry of intravitreal anti-VEGF agents, there have been detectable levels of all available formulations in systemic circulation, ruling in the possibility of systemic adverse events caused by intravitreal agents.[36]

To further understand potential confounding factors, we pooled the medications prescribed to patients experiencing complication. The most commonly prescribed non-BAs were aspirin (33%) and amlodipine, atorvastatin, gabapentin, and metformin (27% each). Aspirin may independently increase the risk of postextraction bleeding, given its antiplatelet activity. Our data set included only 1 patient who experienced increased bleeding after extraction. Although this patient was not taking aspirin, the patient was treated independently with warfarin, which may have contributed to the increased bleeding, calling into question the connection between the patient's belimumab treatment and complication of bleeding. Gabapentin is commonly used to treat neuropathic pain and was given in our cohort to 4 patients, of whom 3 experienced increased pain. Despite the pain-relieving properties of gabapentin, given the link between VEGF antagonism and pain, the possibility of interaction between BAs and gabapentin or of decreased efficacy of gabapentin given BA administration is not excluded, and this possible connection should be explored in future work. Metformin is prescribed to treat diabetes, which may independently increase the risk of postextraction complication.

We also explored original indications for BA prescription among patients experiencing complications. Ranibizumab and aflibercept were the only BAs associated with increased rates of pain. Ranibizumab was prescribed for macular degeneration, whereas aflibercept was prescribed for diabetic retinopathy. Although no clear link between macular degeneration and altered nociception exists, diabetic retinopathy is a microvascular complication of diabetes. Diabetic neuropathy is also a microvascular complication of diabetes, with a complex pathophysiology ultimately rooted in DNA damage and mitochondrial dysfunction leading to apoptosis in neurons, glia, and vascular endothelial cells.[37] Given similar mechanisms underlying diabetic retinopathy,[38] the possibility of coexisting neuropathy in patients treated for retinopathy is not excluded. This raises the possibility that increased neuropathic pain after extraction was not related to BA treatment but rather to existing disordered nociception. Future work should explore whether coexisting neuropathy confounds the potential link between VEGF antagonism and worse postextraction pain.

Owing to the retrospective nature of our study, available data were limited and inconsistent across the patient population. Unfortunately, the sample sizes for patients undergoing dental extractions were small. Future work should include larger cohort sizes to assess for significant differences in complication rate among groups. Larger sample sizes may further clarify rates of postextraction pain in these patients and any other tendency toward complications. In addition, our study focused only on patients treated at all clinics within 1 institution. This may limit the external validity of our findings.

Our study only compared patients taking BAs undergoing surgical treatment and did not compare results in this population with other populations treated at our institution. This only allowed us to estimate the rate of complication in this cohort and limited our ability to compare our data with other populations. Complication rate after extraction has been reported as ranging from 0.5% through 30% or more, with rates tending to increase after extraction of third molars and with age and medical comorbidity.[39-43] However, to our knowledge, no systematic and large-scale estimate of postextraction complication rate has yet been completed. The rates we reported (12.3% of patients, 10.9% of encounters) fall within this wide range. In addition, population factors such as medical comorbidity, demographics, and practitioner experience may have increased the complication rate observed in our study. We are unable to conclude how the observed rate of complication in our population differed from a more general group.

We also gathered data on all patients regardless of underlying disease or specific BA, increasing heterogeneity in the health status and possible complications present. Although any visits within 30 days were reviewed in detail, multiple patients were lost to follow-up. Because of the study's retrospective nature, there was also no standardization in how complications were recorded clinically. We were unable to conduct analysis by race, given that self-reporting was not recorded for 47 patients (39%). Seven recorded complications (46%) occurred in patients missing data on race. Further research may seek to assess the contribution of race.

To date, limited evidence is available on the impact of biological treatment on patients' ability to withstand or heal from dental treatment. Thus, associated complications remain an area of much-needed focus. Our study sought to describe these impacts by means of reporting on complications in the dental setting. With increased production and use of BAs, the dental clinician is more likely to encounter possible adverse effects associated with these agents. The need for more reporting, studies, and, ultimately, establishment of guidelines for dental management in the setting of BAs is dire. Until guidelines are established, the dental clinician may choose to include the patient's health care providers, primarily those mediating BA care, when considering surgical intervention. Providers may also choose to monitor these patients carefully after extraction for any of the noted complications. Once established, guidelines will support the planning and execution of safe treatment in patients taking BAs.

CONCLUSIONS

As the number of BAs developed and approved continues to increase, associated adverse effects in medical and dental settings also may increase. The impact of BAs on the 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 taking biologics. Complications during postsurgical follow-up in this cohort included bleeding, postsurgical abscess, hematuria, delayed wound healing, swelling, alveolar osteitis, and pain. Pain was most commonly reported. Patients treated with VEGF antagonists experienced an elevated rate of complications.

Dental clinicians will continue to encounter patients treated with BAs during daily practice and must be aware of associated adverse effects or risk factors. In turn, further evidence must be gathered on treatment course and healing of these patients to inform clinical decisions. To date, there are no official guidelines for managing the treatment of patients taking BAs who are undergoing invasive dental treatment. It is imperative that guidelines be established for this ever-growing population. This study provides preliminary evidence on the healing course after dental extraction as a first step to establishing recommendations in dental medicine. Further study may build on this data and determine appropriate cross-disciplinary care management, pre- and postsurgical recommendation, and risk stratification for managing the care of patients taking BAs in the dental setting. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2022.07.009.

Dr. Davila is a resident, Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA.

Dr. Magee is a resident, Department of Neurology, Penn Medicine, University of Pennsylvania, Philadelphia, PA.

Dr. France is an assistant professor, Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA. Address correspondence to Dr. France, 240 S 40th St, Philadelphia, PA 19104, email kfrance@upenn.edu.

Disclosures. None of the authors reported any disclosures.

The authors thank the staff, dental assistants, and clinicians involved in the patients' care, as well as the electronic record management team for their assistance in data gathering. They are grateful to the Center for Clinical and Translational Research at Penn Dental Medicine for invaluable assistance in shaping this project.

ORCID Numbers. Andres Davila: https://orcid.org/0000-0001-9263-8949; Katherine France: https://orcid.org/0000-0002-8787-9972. For information regarding ORCID numbers, go to http://orcid.org.

1. Definition of biologic agent: NCI Dictionary of Cancer Terms. National Cancer Institute. 2021. Accessed July 24, 2021. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/biologic-agent

2. Farah CS, Balasubramaniam R, McCullough MJ. *Contemporary Oral Medicine: A Comprehensive Approach to Clinical Practice*. Springer International Publishing; 2019.

3. Georgakopoulou E, Scully C. Biological agents: what they are, how they affect oral health and how they can modulate oral healthcare. *Br Dent J*. 2015;218(12):671-677.

4. Mays JW, Carey BP, Posey R, et al. World Workshop of Oral Medicine VII: a systematic review of immunobiologic therapy for oral manifestations of pemphigoid and pemphigus. *Oral Dis*. 2019;25(suppl 1):111-121.

5. Gueiros LA, France K, Posey R, et al. World Workshop on Oral Medicine VII: immunobiologics for salivary gland disease in Sjögren's syndrome—a systematic review. *Oral Dis*. 2019;25(suppl 1):102-110.

6. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;2:CD008794.

7. Findeisen KE, Sewell J, Ostor AJK. Biological therapies for rheumatoid arthritis: an overview for the clinician. *Biologics*. 2021;15:343-352.

8. Chebli JM, Gaburri PD, Chebli LA, et al. A guide to prepare patients with inflammatory bowel diseases for anti-TNF-α therapy. *Med Sci Monit*. 2014;20:487-498.

9. Kane SV. Preparing for biologic or immunosuppressant therapy. *Gastroenterol Hepatol (N Y)*. 2011;7(8):544-546.

10. Ahmed Ali U, Martin ST, Rao AD, Kiran RP. Impact of preoperative immunosuppressive agents on postoperative outcomes in Crohn's disease. *Dis Colon Rectum*. 2014;57(5):663-674.

11. Yung DE, Horesh N, Lightner AL, et al. Systematic review and meta-analysis: vedolizumab and postoperative complications in inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(11):2327-2338.

12. Law CCY, Narula A, Lightner AL, McKenna NP, Colombel JF, Narula N. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis*. 2018;12(5):538-545.

13. Kotze PG, Ma C, Mckenna N, et al. Vedolizumab and early postoperative complications in nonintestinal surgery: a case-matched analysis. *Therap Adv Gastroenterol*. 2018;11:1756284818783614.

14. Lightner AL, McKenna NP, Alsughayer A, et al. Anti-TNF biologic therapy does not increase postoperative morbidity in pediatric Crohn's patients. *J Pediatr Surg*. 2019;54(10):2162-2165.
15. Lightner AL, McKenna NP, Alsughayer A, et al. Biologics and 30-day postoperative complications after abdominal operations for Crohn's disease: are there differences in the safety profiles? *Dis Colon Rectum*. 2019;62(11):1352-1362.
16. Shah RS, Bachour S, Jia X, et al. Hypoalbuminaemia, not biologic exposure, is associated with postoperative complications in Crohn's disease patients undergoing ileocolic resection. *J Crohns Colitis*. 2021;15(7):1142-1151.
17. Yang Z, Wu Q, Wu K, Fan D. Meta-analysis: preoperative infliximab treatment and short-term postoperative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther*. 2010;31(4):486-492.
18. Yang Z, Wu Q, Wang F, Wu K, Fan D. Meta-analysis: effect of preoperative infliximab use on early postoperative complications in patients with ulcerative colitis undergoing abdominal surgery. *Aliment Pharmacol Ther*. 2012;36(10):922-928.
19. Zaghiyan K, McGovern D, Fleshner P. Should biologic agents be stopped before surgery for inflammatory bowel disease? *Expert Rev Gastroenterol Hepatol*. 2015;9(3):269-272.
20. George MD, Baker JF, Winthrop K, et al. Risk of biologics and glucocorticoids in patients with rheumatoid arthritis undergoing arthroplasty: a cohort study. *Ann Intern Med*. 2019;170(12):825-836.
21. Diaper R, Wong E, Metcalfe SA. The implications of biologic therapy for elective foot and ankle surgery in patients with rheumatoid arthritis. *Foot (Edinb)*. 2017;30:53-58.
22. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
23. CDT. Code on Nomenclature (CDT) Code. American Dental Association. Accessed August 30, 2022. https://www.ada.org/publications/cdt
24. Georgakopoulou EA, Scully C. Orofacial adverse effects of biological agents. *J Investig Clin Dent*. 2015;6(4):252-260.
25. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. *Cell*. 2019;176(6):1248-1264.
26. Stanca Melincovici C, Boşca AB, Şuşman S, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol*. 2018;59(2):455-467.
27. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005;307(5706):58-62.
28. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell*. 2014;26(5):605-622.
29. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)*. 2013;27(7):787-794.
30. Eguia A, Bagán-Debón L, Cardona F. Review and update on drugs related to the development of osteonecrosis of the jaw. *Med Oral Patol Oral Cir Bucal*. 2020;25(1):e71-e83.
31. Zarringhalam P, Brizman E, Shakib K. Medication-related osteonecrosis of the jaw associated with aflibercept. *Br J Oral Maxillofac Surg*. 2017;55(3):314-315.
32. Takano S, Uchida K, Inoue G, et al. Vascular endothelial growth factor expression and their action in the synovial membranes of patients with painful knee osteoarthritis. *BMC Musculoskelet Disord*. 2018;19(1):204.
33. Hamilton JL, Nagao M, Levine BR, Chen D, Olsen BR, Im HJ. Targeting VEGF and its receptors for the treatment of osteoarthritis and associated pain. *J Bone Miner Res*. 2016;31(5):911-924.
34. Hulse RP. Role of VEGF-A in chronic pain. *Oncotarget*. 2017;8(7):10775-10776.
35. Llorián-Salvador M, González-Rodríguez S. Painful understanding of VEGF. *Front Pharmacol*. 2018;9:1267.
36. Csaky K, Do DV. Safety implications of vascular endothelial growth factor blockade for subjects receiving intravitreal anti-vascular endothelial growth factor therapies. *Am J Ophthalmol*. 2009;148(5):647-656.
37. Callaghan BC, Cheng H, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurology*. 2012;11(6):521-534.
38. Wong TY, Cheung CMG, Larsen M, Sharma S, Simo R. Diabetic retinopathy. *Nat Rev Dis Primers*. 2016;2:16012.
39. Bui CH, Seldin EB, Dodson TB. Types, frequencies, and risk factors for complications after third molar extraction. *J Oral Maxillofac Surg*. 2003;61(12):L1379-L1389.
40. Dallaserra M, Poblete F, Vergara C, Araya I, Yanine N, Villanueva J. Infectious postoperative complications in oral surgery. An observational study. *J Clin Exp Dent*. 2020;12(1):e60-e70.
41. Dyer TA. A five-year evaluation of an NHS dental practice-based specialist minor oral surgery service. *Community Dent Health*. 2013;30(4):219-226.
42. Chuang SK, Perrott DH, Susarla SM, Dodson TB. *J Oral Maxillofac Surg*. 2007;65(9):1685-1692.
43. Kumbargere Nagraj SK, Prashanti E, Aggarwal H, et al. Interventions for treating post-extraction bleeding. *Cochrane Database Syst Rev*. 2018;33:CD011930.

APPENDIX

Biologics searched for were abatacept, abciximab, adalimumab, adalimumab-atto, ado-trastumuzumab emtansine, anakinra, aflibercept, agalsidase beta, albiglutide, aldesleukin, alemtuzumab, alglucosidase alfa, alirocumab, alteplase, asfotase alfa, asparaginase, atezolizumab, basiliximab, becaplermin, belatacept, belimumab, bevacizumab, bezlotoxumab, blinatumomab, brentuximab vedotin, canakinumab, capromab pendetide, cetuximab, collagenase, daclizumab, certolizumab pegol, daratumumab, darbepoetin alfa, denileukin diftitox, dinutuximab, dornase alfa, dulaglutide, ecallantide, eculizumab, elosulfase alfa, elotuzumab, etanercept, etanercept-szzs, evolocumab, filgrastim, filgrastim-sndz, galsulfase, golumumab, ibritumomab tiuxetan, idursulfase, interferon alfa-2b, interferon alfa-n3, interferon beta-1a, interferon beta-1b, interferon gamma-1b, ipilimumab, ixekizumab, laronidase, mepolizumab, infliximab, methoxy polyethylene glycol-epoetin beta, metreleptin, natalizumab, necitumumab, nivolumab, rituximab, tocilizumab, tofacitinib, upadacitinib, epoetin, epoetin alfa, Obinutuzumab, ocriplasmin, ofatumumab, olaratumab, omalizumab, oprelvekin, palifermin, palivizumab, panitumumab, parathyroid hormone, pegaspargase, pegfilgrastim, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon beta-1a, pegloticase, pembrolizumab, pertuzumab, ramucirumab, ranibizumab, rasburicase, reteplase, rilonacept, romiplostim, sargramostim, sebelipase alfa, secukinumab, siltuximab, tbo-filgrastim, tenecteplase, trastuzumab, ustekinumab, vedolizumab, ziv-aflibercept, remdesivir, pralsetinib, azacytidine, brodalumab, elosulfase alfa, idursulfase, iaronidase, becaplermin, and reslizumab.

Brand names of these medications were also included in the search: Orencia, Humira, Kineret, Cimzia, Enbrel, Simponi, Inflectra, Remicade, Rituxan, Actemra, Xeljanz, Rinvoq, ReoPro, Amjevita, Kadcyla, Eylea, Fabrazyme, Tanzeum, Proleukin, Campath, Lemtrada, Myozyme, Lumizyme, Praluent, Activase, Strensiq, Elspar, Erwinaze, Tecentriq, Simulect, Regranex, Nulojix, Benlysta, Avastin, Zinplava, Blincyto, Adcetris, Ilaris, ProstaScint, Erbitux, Santyl, Xiaflex, Zenapax, Darzalex, Aranesp, Ontak, Unituxin, Pulmozyme, Trulicity, Kalbitor, Soliris, Vimizim, Empliciti, Erelzi, Repatha, Neupogen, Zarxio, Naglazyme, Simponi, Simponi Aria, Zevalin, Elaprase, Inflectra, Intron A, Alferon N, Avonex, Rebif, Betaseon, Extavia, Actimmune, Yervoy, Taltz, Aldurazyme, Nucala Mircera, Myalept, Tysabri, Portrazza, Opdivo, Gazyva, Jetrea, Arzerra, Lartuvo Xolair, Neumega, Kepivance, Synagis, Vectibix, Natpara, Oncaspar, Neulasta, Pegasys, PegIntron, Sylatron, Plegridy, Krystexxa, Keyruda, Perjeta, Cyramza, Lucentis, Elitek, Cinqair, Retavase, Arcalyst, Nplate, Leukine, Kanuma, Cosentyx, Sylvant, Granix, TNKase, Herceptin, Stelara, Entyvio, Zaltrap, Gavreto, Onureg, Siliq, Amjevita, Vimizim, Elaprase, Aldurazyme, Regranex, Epogen, and Procrit.

eTable 1. Further characterization of patients who experienced complications after extractions, detailing age, sex, tooth extracted and associated diagnostic code, all medications prescribed to each patient, biologic agent taken and indication for biologic therapy, and the complication experienced after dental extraction.

PATIENT	AGE, Y	SEX	TOOTH EXTRACTED (DIAGNOSTIC CODE)	MEDICATIONS	BIOLOGIC	INDICATION	COMPLICATION
1	64	Female	No. 28 (D7140)	Ranibizumab (Lucentis), cyclobenzaprine, gabapentin, ibuprofen, simvastatin	Ranibizumab	Macular degeneration	Pain
2	63	Male	No. 30 (D7140)	Ranibizumab (Lucentis), amlodipine, haloperidol	Ranibizumab	Papilledema	Pain
3	80	Male	Nos. 9 and 6 (D7140) (visit 1); Nos. 1, 3, 4, 12, 21 (D7140) (visit 2)	Aflibercept (Eylea), amphetamine-dextroamphetamine, aspirin, insulin glargine (Lantus), losartan, methylphenidate HCl, repaglinide, rosuvastatin, albuterol (Ventolin HFA)	Aflibercept	Diabetic retinopathy	Pain (visits 1 and 2)
4	36	Female	No. 2 (D7140)	Belimumab (Benlysta), amlodipine, chloroquine phosphate, coumadin, cyclosporine, esomeprazole magnesium, methotrexate, sildenafil	Belimumab	Systemic lupus erythematosus	Bleeding, delayed wound healing
5	38	Male	Nos. 17 and 32 (D7230)	Ixekizumab (Taltz)	Ixekizumab	Psoriasis	Hematuria, pain
6	61	Female	No. 31 (D7140)	Tofacitinib (Xeljanz), alprazolam, cetirizine, duloxetine, fluticasone propionate, leflunomide, simvastatin	Tofacitinib	Rheumatoid arthritis	Postsurgical abscess, pain, delayed wound healing
7	59	Male	No. 30 (D7140)	Dulaglutide (Trulicity), amlodipine, aspirin, atorvastatin, cetirizine, levemir, losartan–hydrochlorothiazide, metformin, metoprolol succinate, nortriptyline, omeprazole, tamsulosin, topiramate	Dulaglutide	Type 2 diabetes mellitus	Postsurgical abscess, pain
8	68	Female	Nos. 7, 8, 9, 10, and 11 (D7140)	Dulaglutide (Trulicity), aspirin, cyclobenzaprine, gabapentin, hydrochlorothiazide, hydroxyzine, metformin, naproxen sodium, sertraline, sitagliptin, valsartan, vitamin B_{12}	Dulaglutide	Type 2 diabetes mellitus	Swelling
9	65	Male	Nos. 18 and 19 (D7140)	Dulaglutide (Trulicity), alprazolam, amoxicillin, aspirin, atorvastatin, bupropion, clopidogrel, insulin aspart (Novolog), insulin glargine (Toujeo), losartan, levemir, meloxicam, multivitamin, nitroglycerin, oxycodone, ranitidine, vitamin B_6, zinc	Dulaglutide	Type 2 diabetes mellitus	Pain
10	68	Male	Nos. 2, 14, and 32 (D7140)	Dulaglutide (Trulicity), insulin glargine (Lantus)	Dulaglutide	Type 2 diabetes mellitus	Pain
11	68	Male	No. 4 (D7140)	Dulaglutide (Trulicity), aspirin, atorvastatin, hydrochlorothiazide, insulin aspart (Novolog), insulin detemir, levothyroxine, lisinopril, metformin, metoprolol succinate, olopatadine, omeprazole	Dulaglutide	Type 2 diabetes mellitus	Pain
12	72	Male	Nos. 27 and 28 (D7140)	Dulaglutide (Trulicity), fluticasone propionate/salmeterol, amlodipine, atorvastatin, carvedilol, chlorthalidone, diclofenac sodium, gabapentin, insulin aspart (Novolog), insulin glargine (Lantus), losartan, morphine, omeprazole, oxycodone/paracetamol, pravastatin, roflumilast, tiotropium bromide, varenicline, albuterol (Ventolin HFA), vitamin B_3	Dulaglutide	Type 2 diabetes mellitus	Pain
13	71	Female	No. 29 (D7210)	Dulaglutide (Trulicity), allopurinol, amitriptyline, Bimatoprost, esomeprazole magnesium, gabapentin, glipizide, hydrochlorothiazide, meloxicam, nifedipine, nortriptyline HCl, pravastatin	Dulaglutide	Type 2 diabetes mellitus	Pain, delayed wound healing
14	49	Male	No. 1 (D7140)	Adalimumab (Humira), fluticasone propionate, ibuprofen, montelukast	Adalimumab	Psoriasis	Pain
15	45	Female	Nos. 2 and 31 (D7210)	Adalimumab (Humira), baclofen, benztropine, desvenlafaxine succinate, divalproex sodium, doxycline hyclate, escitalopram, ketamine, levothyroxine, metformin, multivitamin, n-acetyl cysteine, norethindrone, pantoprazole, trifluoperazine	Adalimumab	Psoriasis	Postsurgical abscess, pain, swelling

eTable 2. Details of medications received by the total population of patients experiencing complications by number of patients treated with each medication and percentage of the group who experienced complications.

MEDICATION	TOTAL TREATED, NO.	PATIENTS EXPERIENCING COMPLICATIONS, %
Dulaglutide (Trulicity)	7	47
Aspirin	5	33
Amlodipine	4	27
Atorvastatin	4	27
Gabapentin	4	27
Metformin	4	27
Hydrochlorothiazide	3	20
Insulin Aspart (Novolog)	3	20
Insulin Glargine (Lantus)	3	20
Losartan	3	20
Omeprazole	3	20
Albuterol (Ventolin HFA)	2	13
Adalimumab (Humira)	2	13
Ranibizumab (Lucentis)	2	13
Alprazolam	2	13
Cetirizine	2	13
Cyclobenzaprine	2	13
Esomeprazole Magnesium	2	13
Fluticasone Propionate	2	13
Ibuprofen	2	13
Levemir	2	13
Levothyroxine	2	13
Meloxicam	2	13
Metoprolol Succinate	2	13
Multivitamin	2	13
Nortriptyline	2	13
Pravastatin	2	13
Simvastatin	2	13
Aflibercept (Eylea)	1	7
Belimumab (Benlysta)	1	7
Ixekizumab (Taltz)	1	7
Tofacitinib (Xeljanz)	1	7
Allopurinol	1	7
Amitriptyline	1	7
Amoxicillin	1	7
Amphetamine-Dextramphetamine	1	7
Baclofen	1	7
Benztropine	1	7
Bimatoprost	1	7
Bupropion	1	7
Carvedilol	1	7
Chloroquine Phosphate	1	7

eTable 2. Continued

MEDICATION	TOTAL TREATED, NO.	PATIENTS EXPERIENCING COMPLICATIONS, %
Chlorthalidone	1	7
Clopidogrel	1	7
Coumadin	1	7
Cyclosporine	1	7
Desvenlafaxine Succinate	1	7
Diclofenac Sodium	1	7
Divalproex Sodium	1	7
Doxycycline Hyclate	1	7
Duloxetine	1	7
Escitalopram	1	7
Fluticasone Propionate/Salmeterol	1	7
Glipizide	1	7
Haloperidol	1	7
Hydroxyzine	1	7
Insulin Detemir	1	7
Insulin Glargine (Toujeo)	1	7
Ketamine	1	7
Leflunomide	1	7
Lisinopril	1	7
Losartan–Hydrochlorothiazide	1	7
Methotrexate	1	7
Methylphenidate	1	7
Montelukast	1	7
Morphine	1	7
N-acetyl Cysteine	1	7
Naproxen Sodium	1	7
Nifedipine	1	7
Nitroglycerin	1	7
Norethindrone	1	7
Olopatadine	1	7
Oxycodone	1	7
Oxycodone/Paracetamol	1	7
Pantoprazole	1	7
Ranitidine	1	7
Repaglinide	1	7
Roflumilast	1	7
Rosuvastatin	1	7
Sertraline	1	7
Sildenafil	1	7
Sitagliptin	1	7
Tamsulosin	1	7
Tiotropium	1	7
Topiramate	1	7

eTable 2. Continued

MEDICATION	TOTAL TREATED, NO.	PATIENTS EXPERIENCING COMPLICATIONS, %
Trifluoperazine	1	7
Valsartan	1	7
Varenicline	1	7
Vitamin B_{12}	1	7
Vitamin B_3	1	7
Vitamin B_6	1	7
Zinc	1	7