Assessing the incidence of skin and soft tissue infection in patients on biologics

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Background: Biologic agents may predispose patients to skin and soft tissue infections (SSTIs). Guidelines recommend discontinuing the agent preoperatively; the true risk of infection is unclear.

Objectives: To assess the incidence of SSTIs in patients receiving biologic agents for all clinical indications. A secondary aim was to assess those undergoing surgery to determine postoperative SSTI risk.

Methods: A retrospective medical record review was conducted at 2 urban tertiary care hospitals. Biologic agent use ranged from June 2013 to June 2018. Data were extracted on biologic agent injections, surgical procedures, and patient characteristics.

Results: Hypertension, former smoking, and corticosteroid use were significantly associated with SSTI risk ($P < .05$). There was no increased SSTI risk among biologic agents ($P = .49$). Biologic therapy with concomitant corticosteroid use increased risk of SSTI ($P = .0049$). There was no difference in postoperative SSTI risk in patients who stopped biologic therapy before surgery and those who did not.

Limitations: This study is limited by its retrospective design.

Conclusions: There was no increased risk of either postoperative or nonperioperative SSTI risk among biologic agents. Concomitant corticosteroid use increased SSTI risk. Current guidelines regarding stopping biologic agents before surgery warrant re-evaluation, because there was no difference in SSTI risk in patients who did so. (J Am Acad Dermatol 2021;85:604-10.)

Key words: adalimumab; biologics; etanercept; immunosuppression; infliximab; postoperative; skin and soft tissue infections; surgery; ustekinumab.

Skin and soft tissue infections (SSTIs) are an important cause of sepsis, morbidity, and mortality, affecting 10% of hospitalized patients.[1] Biologic agents have revolutionized the treatment of autoimmune conditions, shifting the paradigm from escalating systemic therapies in parallel with disease to a more aggressive early treatment. The immunomodulating effects of these agents can theoretically predispose patients to infections such as SSTIs. SSTIs occur 3 times more frequently in patients with rheumatic arthritis compared to the general population,[2] which can be attributed to complications of the disease itself or to the use of immunosuppressive agents. Although the risk of opportunistic infections such as tuberculosis has been well defined,[3-5] the risk of SSTIs in patients using biologic agents both perioperatively and nonperioperatively has not been well elucidated.

One group from the United Kingdom found an increased risk of SSTIs in patients taking anti–tumor necrosis factor (TNF) agents compared to those taking disease-modifying antirheumatic drugs; however, patients in this study taking disease-modifying antirheumatic drugs had milder disease and were less likely take steroids, potentially confounding these findings.[6]

Patients treated with these agents may undergo surgical intervention during the course of their disease management. The risk of postoperative SSTIs while using biologic agents also has not been well

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defined. TNF-α promotes fibroblast and endothelial cell proliferation, which are essential to wound healing,[7] and may serve as a counterbalance to the immunosuppressive effects of these medications. Giles et al[8] describes an increased risk between anti-TNF biologics and risk of a postoperative orthopedic infection in patients with rheumatoid arthritis.[8] However, other studies do not show a significantly increased risk of postoperative infection associated with these agents.[9-12] Data regarding non–anti-TNF biologics are even more sparse, and currently, there are insufficient data to support the guideline recommendations for interleukin (IL) 12/23 therapy.[13]

CAPSULE SUMMARY

- Biologic agents are thought to increase the risk of skin and soft tissue infections (SSTIs). The true risk of infection is currently unclear.
- This study assessed the incidence of SSTIs in patients taking biologics both perioperatively and nonperioperatively, finding no increased risk of infection.

In light of this, several guidelines recommend discontinuing biologic agents before surgery[13,14]; however, different organizations suggest different discontinuation timeframes, and adherence to these guidelines is variable.[15] Given the lack of understanding of the true risk of infection associated with the use of these agents, it is difficult to ascertain if these guidelines are necessary. For example, George et al[16] found no increased risk of infection when infliximab was administered within 4 weeks of elective orthopedic surgery compared to withholding for longer time periods.[16] Because these agents are widely in use, it is essential to determine their true effect on postoperative complication risk.

This study reviews retrospective data from 2 institutions regarding use of the biologic agents adalimumab, infliximab, etanercept, and ustekinumab for all clinical indications and assesses the incidence of SSTIs among these agents both outside the perioperative setting and in the postoperative period. The hypothesis is that the true risk of SSTIs is quite low and that it may be unnecessary for most patients to hold biologic agents perioperatively.

METHODS

Patient identification and data collection

A retrospective cross-sectional study was conducted of patients receiving biologic therapy at Massachusetts General Hospital and Brigham and Women's Hospital between June 2013 and June 2018. Patients were identified using the Partners Research Patient Data Registry, an electronic medical record database. Four biologic agents were included: adalimumab, infliximab, etanercept, and ustekinumab. Inclusion criteria included patients who were at least 18 years old, who received at least 2 consecutive injections at maintenance dose and intervals, and were treated with these agents for any clinical indication. A total of 827 male and female patients met the inclusion criteria. From each patient's chart, age at initiation of biologic, sex, race, and comorbidities for SSTI risk (including diabetes, obesity, corticosteroid use, smoking status, hypertension, past or current cancer, chronic obstructive pulmonary disease, and intravenous drug use status) were recorded. Corticosteroid use was defined by systemic treatment for at least 1 week, concurrent with the biologic agent in question. Each chart was also reviewed for occurrences of SSTI during biologic therapy and whether surgery was undertaken during this time period.

A subgroup analysis was performed of the 218 patients who had undergone surgery while taking the biologic agent. From the clinic and pre- and postoperative notes, surgery type, if the agent was held perioperatively, and the duration for which the agent was held were recorded. Postoperative SSTI was defined by skin infection within 90 days of the surgery necessitating antibiotic treatment. The study was approved by the Partners Health institutional review board.

Statistical analysis

Categorical variables are reported as percentages, and continuous variables are given as means and standard deviations (SDs). Demographic and risk factors were compared among patients who developed SSTIs at baseline. In the surgical subgroup, surgery type and risk factors were compared between patients who stopped biologics perioperatively and those who continued. Categorical variables were compared with Fisher's exact test for small sample sizes and chi-square test for larger sample sizes. Statistical significance was set at a 2-sided P of less than .05. Analyses were performed using GraphPad Prism software, version 8.2.1 (GraphPad, San Diego, CA).

RESULTS

Table I summarizes the characteristics of the 827 patients included in this study. The mean age differed significantly among biologic agents ($P < .0001$), with adalimumab having a mean age of 41.4 ± 16.1 years; infliximab, 38.9 ± 16.9 years;

Abbreviations used:

IL: interleukin
SD: standard deviation
SSTI: skin and soft tissue infection
TNF: tissue necrosis factor

etanercept, 50.1 ± 13.9 years; and ustekinumab, 40.9 ± 15.4 years. Sex also differed significantly by biologic agent ($P < .0001$), with greater prevalence in women: adalimumab, 55.0%; infliximab, 57.0%; etanercept, 64.2%; and ustekinumab, 51.9%. Comorbidities differed by agent used, with hypertension, obesity, former smoking, corticosteroid use, and cancer being significantly different ($P < .01$). The majority of patients in our cohort were treated for Crohn's disease (38.6%), followed by psoriasis (27.2%) (Supplemental Fig 1, available via Mendeley at http://doi.org/10.17632/8hxp4wyyhm.2).

The baseline patient risk factors in patients who developed an SSTI versus those who did not were are summarized in Table II. Hypertension ($P = .03$), former smoking status ($P = .01$), and corticosteroid use ($P = .0049$) were found to be significantly associated with patients who developed an SSTI.

Concomitant treatments that may have influenced SSTI rates in our cohort were further evaluated (Supplemental Table I, available via Mendeley at http://doi.org/10.17632/8hxp4wyyhm.2). A significant number of patients (41.8%) who developed SSTIs were simultaneously treated with systemic corticosteroids compared to those who did not develop SSTIs (28.0%) ($P = .0049$). When the patients who were concomitantly treated with steroids were compared to those who were treated with the biologic alone (Supplemental Table II, available via Mendeley at http://doi.org/10.17632/8hxp4wyyhm.2), the SSTI rate was 10.1% in patients taking biologics alone and 18.6% in those who were also treated with steroids ($P = .0012$). Within this total rate, all 4 agents showed an increased risk of SSTI with concomitant steroid use, although this association was only significant in adalimumab ($P = .027$) and etanercept ($P = .03$). Although a greater percentage of patients who developed SSTIs were also concomitantly taking the nonbiologic immunosuppressive agents methotrexate (17.3%) and azathioprine (3.6%), this association was not found to be statistically significant. Furthermore, there was no

Table II. Baseline risk factors and predictors of skin and soft tissue infection in our cohort, n (%)

Baseline risk factors	SSTI (n = 110)	No SSTI (n = 717)	*P* value
Age, >65 y	15 (13.6)	81 (11.3)	.48
Female	69 (62.7)	400 (55.8)	.17
Diabetes mellitus	11 (10)	56 (7.8)	.43
Hypertension	**44 (40)**	**212 (29.6)**	**.03**
Obesity	30 (27.3)	156 (21.8)	.19
Former smoker	**41 (37.3)**	**186 (25.9)**	**.01**
Current smoker	12 (10.9)	49 (6.8)	.12
COPD	6 (5.5)	25 (3.5)	.31
Corticosteroid	**46 (41.8)**	**201 (28.0)**	**.0049**
Cancer	17 (15.5)	64 (8.9)	.06
IVDU	5 (4.5)	14 (2)	.11
Former IVDU	4 (3.6)	11 (1.5)	.12

Values in bold reached a significance level of $P < .05$.
COPD, Chronic obstructive pulmonary disease; *IVDU,* intravenous drug use.

Table I. Baseline characteristics of patients (N = 827)

Characteristic	Adalimumab (n = 322)	Infliximab (n = 228)	Etanercept (n = 148)	Ustekinumab (n = 129)	*P* value
Age, y, mean ± SD	41.4 ± 16.1	38.9 ± 16.9	50.1 ± 13.9	40.9 (15.4)	<.0001
Female sex, n (%)	177 (55)	130 (57)	95 (64.2)	67 (51.9)	<.0001
Ethnicity, n (%)					
White	276 (85.7)	199 (87.3)	129 (87.2)	122 (94.6)	.074
Black	8 (2.5)	10 (4.4)	2 (1.4)	6 (4.7)	.25
Comorbidities, n (%)					
Diabetes mellitus	27 (8.4)	15 (6.6)	15 (10.1)	10 (7.8)	.2
Hypertension	97 (30.1)	67 (29.4)	67 (45.3)	27 (20.9)	.0001
Obesity	84 (26.1)	49 (21.5)	38 (25.7)	15 (11.6)	.007
Former smoker	82 (25.5)	49 (21.5)	55 (37.2)	41 (31.8)	.005
Current smoker	28 (8.7)	14 (6.1)	11 (7.4)	8 (6.2)	.67
Corticosteroid use	92 (28.6)	63 (27.6)	29 (19.6)	54 (41.9)	.001
COPD	13 (4)	4 (1.8)	10 (6.8)	4 (3.1)	.09
Cancer	22 (6.8)	20 (8.8)	29 (19.6)	10 (7.8)	.0002
IVDU	10 (3.1)	2 (0.9)	4 (2.7)	3 (2.3)	.38

COPD, Chronic obstructive pulmonary disease; *IVDU,* intravenous drug use.

Table III. Characteristics of 218 surgical procedures among 180 patients*

Surgical procedures (n = 218)	Total, n (%)	Adalimumab, n (n = 66)	Infliximab, n (n = 68)	Etanercept, n (n = 49)	Ustekinumab, n (n = 35)
Abdominal†	83 (38.1)	24	35	3	21
Orthopedic‡	62 (28.4)	16	15	25	6
Cardiovascular§	9 (4.1)	2	1	4	2
Head and neck surgery‖	13 (6.9)	7	4	1	1
Neurosurgery¶	9 (4.1)	1	0	6	2
Urologic/gynecologic#	18 (8.3)	9	3	5	1
Breast surgery	6 (2.8)	2	2	2	0
Skin excisions	9 (4.1)	1	4	3	1
Infectious**	9 (4.1)	4	4	0	1

*Mean number of surgeries, 1.34 (range, 1-5).
†Abdominal procedures: colectomy (n = 62), hernia repair (n = 6), appendectomy (n = 2), gastric sleeve (n = 2), cholecystectomy (n = 4), lysis of adhesions (n = 7).
‡Orthopedic procedures: joint replacement (n = 43), urgent cases (open reduction and internal fixation of fractures) (n = 10), tendon surgery (n = 9).
§Cardiovascular procedures: coronary artery bypass grafting (n = 5), mitral valve replacement (n = 1), vascular procedure (n = 2), bronchoscopy (n = 1).
‖Head and neck surgery: sinus surgery (n = 4), thyroidectomy (n = 6), tonsillectomy (n = 1), neck exploration (n = 1), cataract surgery (n = 1).
¶Neurosurgery procedure: vertebral surgery (n = 6), craniotomy (n = 2), spinal cord stimulator (n = 1).
#Urologic/gynecologic procedures: hysterectomy (n = 8), nephrectomy (n = 1), cystoscopy (n = 7), cesarean birth (n = 2).
**Incision and drainage of perineal or pelvic abscess (n = 9).

statistically significant difference in SSTI rate across the 4 biologics (P = .49), although etanercept was found to have highest rate of SSTIs (13.7% when looking at biologic agent use alone, compared to 8.2% in patients receiving ustekinumab, the lowest incidence of the 4 agents).

Table III summarizes the characteristics of 218 surgical procedures among 180 patients. Abdominal (38.1%) and orthopedic surgeries (28.4%) represented the most common procedures. A total of 20 SSTIs at the surgical site were identified postoperatively, of which 9 were diagnosed as cellulitis and 11 as abscesses. Of these cases, 6 were treated in the outpatient setting, 8 were treated in the emergency department, and 6 were admitted to the hospital. The mean time from surgery to development of an SSTI was 36.6 days (SD, 29.6).

To characterize the postoperative SSTIs in the surgical cohort, risk factors and procedures were evaluated in those who developed postoperative SSTIs compared to those who did not (Table IV). Of note, patients who developed postoperative SSTIs had been treated with their respective biologic agent for a mean of 11.4 months (SD, 11.2) compared to a mean of 30.5 months (SD, 37.8) in those who healed without complications. Concomitant corticosteroid use was found to be associated with development of postoperative SSTIs (60.0% vs 34.3%; P = .029). Age, obesity, and diabetes were not found to be significantly associated with postoperative SSTI. The majority (70%) of these infections occurred after abdominal procedures. After stratifying by surgery type, specific surgery was a statistically significant risk factor for postoperative SSTIs (P = .029), occurring after 33.3% of breast surgeries, 16.9% of abdominal surgeries, and 11.1% of neurosurgeries. Orthopedic and urology and gynecologic procedures had a relatively lower 3.2% and 5.6% rate of postoperative SSTIs, respectively. Furthermore, of the 43 joint replacement procedures, only 1 case resulted in a postoperative peri-prosthetic joint infection with corticosteroid and etanercept use.

Among the 218 surgical procedures, the characteristics of patients who held biologic therapy perioperatively and those who continued biologic therapy before surgery are described in Table V. There was no significant difference in patient characteristics between these 2 groups. The outcome of holding or continuing biologic therapies did not significantly vary across the different types of surgeries or clinical indications (P = .29 and .89, respectively). Postoperative SSTIs occurred in 14.5% of patients who stopped biologics compared to 6.3% of patients who continued perioperatively; this association approached but did not reach significance (P = .08). There was no significant difference in either noninfectious surgical site complications (such as wound dehiscence or delayed healing) or SSTI outside of the postoperative period between patients who stopped versus continued biologic agents before surgery (P = .16 and .25, respectively). Furthermore, there was no significant difference in development of postoperative SSTIs among clinical indications (P = .35), although

Table IV. Characteristics of patients with postoperative SSTIs in our cohort

Characteristics	Postoperative SSTIs (n = 20)	No postoperative SSTIs (n = 198)	*P* value
Age at operation, mean (SD)	38.9 (16.5)	44.3 (16.7)	.17
Time on biologic, months, mean (SD)	11.4 (11.2)	30.5 (37.8)	**.025**
Obesity, n (%)	3 (15.0)	55 (27.8)	.29
Diabetes mellitus, n (%)	2 (10.0)	17 (8.6)	.83
Corticosteroid use, n (%)	12 (60.0)	68 (34.3)	**.029**
Type of surgery, n (%)			
Abdominal (n = 83)	14 (16.9)	69 (83.1)	**.029**
Orthopedic (n = 62)	2 (3.2)	60 (96.8)	
Urological and gynecologic (n = 18)	1 (5.6)	17 (94.4)	
Neurosurgery (n = 9)	1 (11.1)	8 (88.9)	
Cardiac (n = 9)	0 (0)	9 (100)	
Breast (n = 6)	2 (33.3)	4 (66.7)	
Head and neck (n = 13)	0 (0)	13 (100)	
Incisions over an infected area (n = 9)	0 (0)	9 (100)	
Skin excisions (n = 9)	0 (0)	9 (100)	

Values in bold reached a significance level of $P < .05$.
SD, Standard deviation; *SSTI,* skin and soft tissue infection.

Table V. Discontinuation of biologic therapy, patient characteristics, and complication rates

	Stopped biologic (n = 76)	Continued biologic (n = 142)	*P* value
Age at operation, mean (SD)	44.6 (16.4)	42.7 (16.6)	.15
Time on biologic, months, mean (SD)	28.2 (39)	27.9 (34.5)	.95
Hypertension, n (%)	36 (47.4)	49 (34.5)	.08
Obesity, n (%)	26 (34.2)	32 (22.5)	.07
Diabetes mellitus, n (%)	7 (9.2)	9 (6.3)	.45
Corticosteroid use, n (%)	26 (34.2)	49 (34.5)	.92
Former smoker, n (%)	31 (40.8)	49 (34.5)	.39
Cancer, n (%)	10 (13.2)	22 (15.5)	.61
Postoperative SSTI, n (%)	11 (14.5)	9 (6.3)	.08
Nonperioperative SSTI, n (%)	19 (25)	24 (16.9)	.16
Noninfectious complications, n (%)	2 (2.6)	1 (0.7)	.25
Clinical indication, n (%)			
Rheumatoid arthritis	24 (31.6)	40 (28.2)	.64
Crohn's disease	15 (19.7)	33 (23.2)	.53
Ulcerative colitis	30 (39.5)	54 (38)	.89
Psoriasis	13 (17.1)	32 (22.5)	.33
Psoriatic arthritis	12 (15.8)	20 (14.1)	.84
Hidradenitis suppurativa	3 (3.9)	5 (3.5)	.99

SD, Standard deviation; *SSTI,* skin and soft tissue infection.

patients with inflammatory bowel disease made up 80% of postoperative SSTIs compared to 10% and 5% of those with psoriasis and psoriatic arthritis, respectively (Supplemental Table III, available via Mendeley at http://doi.org/10.17632/8hxp4wyyhm.2).

The effect of time of preoperative biologic cessation on development of postoperative SSTI was evaluated. As summarized in Supplemental Table IV (available via Mendeley at http://doi.org/10.17632/8hxp4wyyhm.2), there was no statistically significant difference in postoperative SSTIs among patients who stopped their biologic therapy at fewer than 3 half-lives before surgery (6.7%), 3 to 5 half-lives before surgery (14.9%), or more than 5 half-lives before surgery (21.4%) ($P = .52$). There was also no significant difference between SSTI risk in patients who stopped their biologic therapy within each of the aforementioned time frames by type of surgery ($P = .29$). A risk of holding treatment is disease flaring, and this occurred once when biologics were stopped at fewer than 3 half-lives before surgery, 3 times when stopped at 3 to 5 half-lives before surgery, and once when stopped more than 5 half-lives before surgery ($P = .99$).

DISCUSSION

Biologic agents have revolutionized the treatment of immune-mediated diseases. The proportion of patients taking biologic agents undergoing surgery has been increasing,[9] highlighting the need for further study regarding the risk of SSTI in patients using these medications. In this study, we examined risk factors for SSTI development while taking biologic agents, treatments that may have influenced SSTI risk, and characteristics of postoperative SSTIs.

Baseline risk factors for the development of SSTI were identified as hypertension, smoking history, and corticosteroid use. These factors likely contribute by way of impaired immune defenses and wound healing and by serving as surrogates for overall poor health status. Surprisingly, age older than 65 years, diabetes mellitus, obesity, and current smoking status were not found to be significant risk

factors in our cohort, in contrast with previously documented risk factors for development of cellulitis. It is paradoxical that current smoking status was not associated with SSTI risk but former smoking was. A possible explanation is that current smokers tended to be younger in our cohort. Perhaps this is related to the cumulative effect of nicotine on patients with a former smoking history, but this remains to be elucidated.

Concomitant treatment with systemic corticosteroids approximately doubled rates of SSTI compared to treatment with a biologic agent alone. This increased infection risk seen in glucocorticoids compared to biologic agents has also been reported in other studies.[16] Of the agents, ustekinumab represented the lowest baseline SSTI incidence (8.2%), likely because of its increased specificity compared to the adalimumab and infliximab (human anti-TNF monoclonal antibodies) and etanercept (a soluble TNF receptor fusion protein). Ustekinumab binds to the p40 subunit of both IL-12 and IL-23, blocking the subsequent inflammatory pathways. Etanercept has been previously associated with decreased risk of tuberculosis and general infections compared to adalimumab and infliximab, possibly because of differing mechanisms of action.[17] In our study, no statistically significant differences in SSTI risk were found among these 4 agents.

Furthermore, we found no difference in postoperative SSTI rate between patients who held their biologic agent before surgery and those who continued, regardless of how many drug half-lives had passed. Treatment with systemic corticosteroids led to an increased postoperative SSTI in this analysis, implying that corticosteroid use may be the significant factor in predisposing patients to SSTIs while taking biologics, not the biologic agent itself. Interestingly, the association between stopping the biologic before surgery and SSTI showed a trend toward more SSTIs the longer the drug had been stopped before surgery, but this did not reach statistical significance. Disease severity has been found to be associated with increased infection risk in patients with rheumatoid arthritis,[18] and thus, stopping a biologic agent and developing a subsequent flare may actually increase the risk of infection more so than continuing the agent. There has been shown that there were lower infection and postoperative complication rates in patients who continued methotrexate before surgery in contrast to patients who stopped.[19] Similarly, a longer duration of taking the biologic agent was associated with not developing SSTIs. In all, this suggests that, rather than stopping the biologic agent before surgery, it may be more efficacious to focus efforts on minimizing corticosteroid use and other concomitant risk factors. Given the risk of disease flare if a biologic agent is discontinued, which may contribute to inability to participate in rehabilitation,[15] it may be prudent to reconsider the current guideline recommendation of stopping biologic agents before surgery.

This study is limited by the fact that data were gathered through retrospective chart review. Our definition of a postoperative SSTI was based on provider documentation. However, misdiagnosis of cellulitis is prevalent,[20] and it is possible that some of these patients were misdiagnosed as having an SSTI but did not. Furthermore, the reason patients held their biologics before surgery was often not documented. The biologic agents examined in this study do not include many of the currently available classes, such as IL-23 and IL-17 inhibitors, limiting its generalizability to other agents. Finally, this study was limited to 2 large academic medical centers in 1 geographic area (Boston, Massachusetts), which may limit generalizability because surgical practices and patient populations may differ between institutions.

In conclusion, our study shows no relationship between the 4 biologic agents studied and risk of postoperative SSTI. These data are an important step in further elucidating the relationship between biologic agents and SSTIs. Given the paucity of data on SSTI and biologic use (especially non—anti-TNF agents), further prospective study is warranted. In the end, a case-by-case approach should be taken when evaluating these patients before surgery, keeping in mind that discontinuation of biologic therapies may not be necessary.

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