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Crohn's Disease Activity and Concomitant Immunosuppressants Affect the Risk of Serious and Opportunistic Infections in Patients Treated With Adalimumab

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OBJECTIVES: **Anti-tumor necrosis factor (TNF) drugs are commonly used to treat moderate-to-severe Crohn's disease (CD). Both the activity of CD and the concomitant immunosuppressants (corticosteroids and immunomodulators) used with anti-TNF drugs could increase the risk of infection. We determined the relative risk of serious and opportunistic infections associated with increasing disease activity and concomitant immunomodulators and corticosteroids in patients with CD treated with adalimumab.**

METHODS: **This pooled analysis identified incident treatment-emergent serious and opportunistic infections among patients with CD in clinical trials of adalimumab. Disease activity was assessed with the Crohn's Disease Activity Index (CDAI).**

RESULTS: **The analysis included 2,266 patients treated with adalimumab with median age 35 years. Higher disease activity was associated with significantly increased risks of both serious and opportunistic infections at 1 year, with each 100-point increase in CDAI associated with a >30% increased risk of each type of infection. Concomitant use of immunomodulators was associated with a significant >3-fold decreased risk of serious infection (hazard ratio (HR) 0.29 (0.08–0.98), *P*=0.045) by 1 year. Concomitant use of corticosteroids was associated with a significantly increased risk of serious infection by day 120 (HR 2.40 (1.33–4.35), *P*=0.004). Concomitant use of either category of immmunosuppressant was associated with numerically higher rates of opportunistic infection, 40% of which were due to herpes zoster, compared with adalimumab monotherapy.**

CONCLUSIONS: **Higher disease activity in CD is associated with significantly increased risks of both serious and opportunistic infections. In addition to corticosteroid-sparing strategies, consideration should be given to expanding herpes zoster vaccination guidelines to include younger patients.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Crohn's disease (CD), a type of inflammatory bowel disease, is a chronic relapsing disease for which there is no cure. Patients with moderate-to-severe CD are treated with immunosuppressants, which include corticosteroids, anti-tumor necrosis factor (anti-TNF) drugs, and immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), often in combination (1). Although effective for many patients, these medications are associated with risks, most notably infection and malignancy, with infection occurring far more commonly (2–6). It was recently

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demonstrated that the risk of serious infection has a stronger impact on patients' willingness to accept a therapy than the risk of lymphoma or the expected duration of symptom-free remission (7). As such, it is important to understand the factors that contribute to serious infections for patients with CD, particularly those receiving anti-TNF therapy.

Observational studies of infection risk with biologic and other immunosuppressant medications are potentially subject to confounding by indication if increased activity of CD is itself associated with an increased risk of infection. Unfortunately, the only available data regarding infection risk with increasing disease activity in CD is from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry, in which moderate-to-severe disease activity was independently associated with a >2-fold increased risk of serious infection (2). However, in TREAT, disease activity was assessed globally by the treating physicians and not by a quantitative disease activity index.

Also, there are limited data regarding the relative risk of infection in patients with CD receiving combination immunosuppressive therapy as compared with anti-TNF monotherapy. Several studies have suggested that the risk of serious infection may not be increased with combination anti-TNF and immunomodulator therapy compared with anti-TNF monotherapy (8–10). However, combination therapy has been associated with an increased risk of opportunistic infection overall and herpes zoster in particular (9).

The aims of this pooled analysis of clinical trial data in patients treated with adalimumab were twofold. First, we aimed to determine whether more highly active CD influenced the rate of serious and opportunistic infections independent of the concomitant medications used to treat the underlying disease. Second, we aimed to determine whether the concomitant use of immunomodulator therapy and/or corticosteroids increased the risk of these infections independent of disease activity.

METHODS

Analysis population

Patients with CD who had received at least 1 dose of adalimumab during randomized placebo-controlled or open-label trials of adalimumab for the induction or maintenance of remission or mucosal healing (CLASSIC I and II, GAIN, CHARM, EXTEND, CARE, ACCESS, and a Japanese study) (11–19) or during the corresponding open-label long-term extension study (ADHERE) (20,21) were included. Patients who initiated therapy with placebo in any of the above studies were excluded, as our aim was to examine the added infection risk with combination therapy given that the current standard of care for the treatment of moderate-to-severe CD is a combination therapy or anti-TNF monotherapy (1), and due to relatively low duration of exposure to placebo in the data set, the number of infections that occurred in patients receiving placebo was too low for any meaningful assessment. CLASSIC I was a blinded 4-week induction study from which patients could enter CLASSIC-II, a 56-week maintenance study with both blinded and open-label arms (11,12). GAIN was a blinded 4-week induction study in patients who had lost response or were intolerant to infliximab (13). CHARM was a 56-week maintenance study with a 4-week open-label induction phase followed by a blinded 52-week maintenance phase (14). Patients from GAIN and CHARM were allowed to continue open-label adalimumab as part of long-term monitored follow-up for up to an additional 204 weeks in the open-label extension study, ADHERE (20,21) due to the time frame of our analysis, ADHERE exposure was evaluated only for patients from GAIN. EXTEND was a 52-week endoscopic mucosal healing study with a 4-week open-label induction phase followed by a blinded 48-week maintenance phase (15). CARE was a 20-week single-arm open-label study in Europe (16). ACCESS was a 24-week single-arm open-label study in Canada (17). The Japanese study had a blinded induction phase lasting up to 8 weeks, followed by a blinded 52-week maintenance phase, followed by an open-label extension phase lasting up to additional 184 weeks (18,19). See **Figure 1** for a summary of the designs and timelines of these studies. This analysis pooled the prospectively collected data from these studies to determine the risk of serious and opportunistic infections in patients with treated with adalimumab.

Exposure definitions

Disease activity was assessed using the Crohn's Disease Activity Index (CDAI), which was measured at each visit in all included studies. Generally, CDAI was measured every 2–4 weeks in the early phases of the studies and every 6–12 weeks at later time points. Immunomodulator exposure was defined as use of either thiopurines or methotrexate, and corticosteroid exposure was defined as use of either oral systemic corticosteroids or oral budesonide at any dose.

For the analysis of risk of infection with higher disease activity, patients were followed for up to 1 year to allow for substantial variation in disease activity in order to study this exposure more completely, as some patients achieved remission while others remained with varying degrees of active disease. Because the follow-up time was relatively long, disease activity was treated as the time-updating exposure of interest and immunomodulators and corticosteroids were treated as time-updating covariates. For this analysis, the disease activity was categorized according to the CDAI recorded at each visit and held constant until the next visit when a new CDAI was calculated and the variable updated.

For the analysis of infection risk with concomitant immunomodulators or corticosteroids, we followed patients for shorter time periods, specifically until day 56 or 120, for our primary analysis in an attempt to completely avoid confounding by changing doses or discontinuing therapies. For these analyses, exposure to immunomodulators and corticosteroids was defined as use in the lead-in study at baseline and CDAI was considered a static covariate also measured at baseline. In a secondary analysis, we extended follow-up to 1 year; thus, since therapies were allowed to change by this time point in the studies, immunomodulators and corticosteroids were treated as time-updating exposures and disease activity was treated as a time-updating covariate.

Start of follow-up for all patients in our analyses was the first dose of adalimumab; thus, for exposure in ADHERE, start of

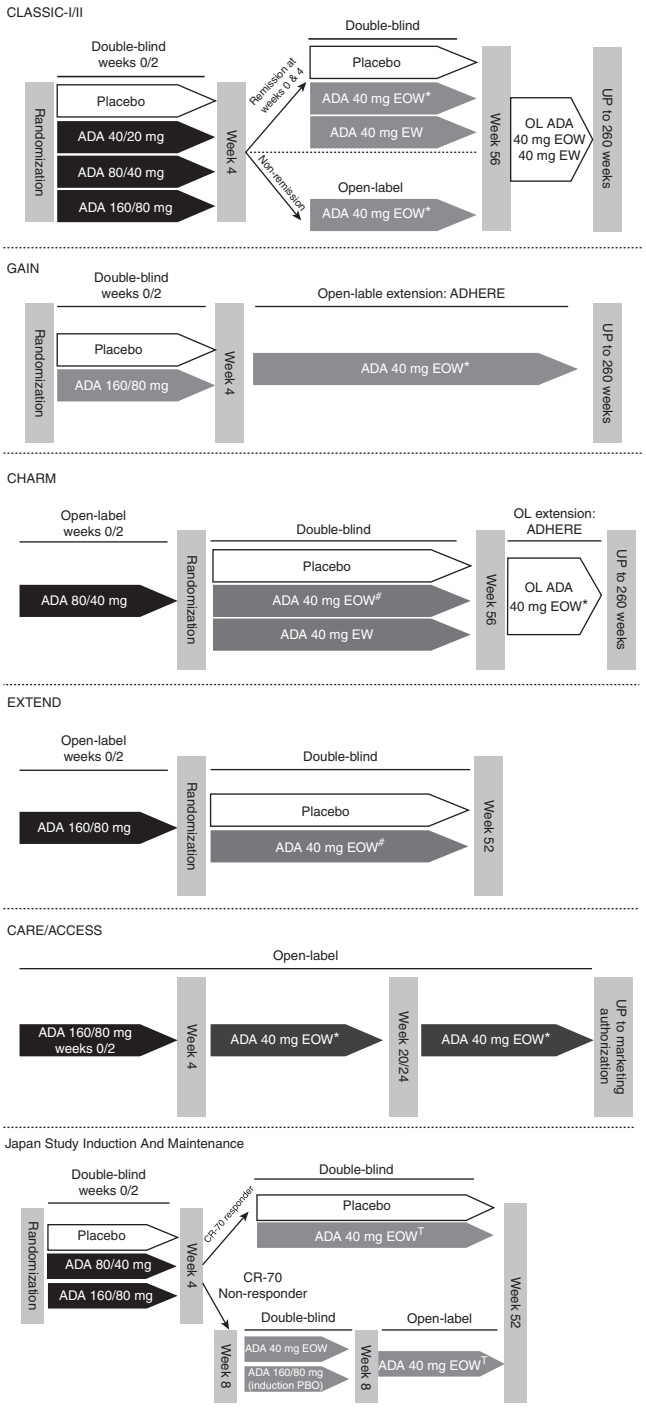

Figure 1. Design of the included studies of adalimumab for Crohn's disease (CD). ADA, adalimumab; EOW, every other week; EW, weekly; OL, open-label. *Patients experiencing flare or non-response could move to open-label adalimumab 40 mg weekly. #Patients experiencing flare or non-response could move to open-label adalimumab 40 mg every other week at or after week 12 in CHARM or week 8 in EXTEND, followed by 40 mg weekly for continued flare/non-response. TPatients experiencing flare or non-response receiving blinded 40 mg every other week dosing could move to open-label adalimumab 40 mg every other week, followed by 80 mg every other week for continued flare/non-response. Patients receiving open-label adalimumab 40 mg every other week could move to 80 mg every other week for flare or non-response.

follow-up was the first dose of adalimumab in GAIN. In all of the studies except ADHERE and CARE, concomitant CD medication use at baseline was to remain stable for the duration of the trials, with the exception of corticosteroids which could be tapered at the discretion of the investigator (generally beginning at week 8). In ADHERE, patients rolling over from GAIN were allowed to taper corticosteroids after 8 weeks of open-label adalimumab and to adjust other concomitant CD medications after 3 months of open-label adalimumab. In CARE, modifications in CD-related concomitant treatments were allowed beginning at week 8. Of note, in all studies, corticosteroids were allowed as rescue therapy for loss of response only in patients who were receiving them at baseline and were not to be initiated in those who were not taking them at baseline.

Outcome measures

The primary outcome measures in this analysis were treatment-emergent serious infections and opportunistic infections as reported by the investigators. Serious infections were defined as infectious adverse events that were classified as "serious" based on the Food and Drug Administration guidance for clinical trials and included an infection that met at least 1 of the following: (1) caused significant disability; (2) was life-threatening; (3) resulted in death; (4) required medical or surgical intervention in order to prevent serious outcome; or (5) required hospitalization (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32). CD-related serious infections were defined as abdominal or anorectal/perineal abscesses. Opportunistic infections were defined as in prior studies and included infection with the following organisms: *Aspergillus*, *Blastomyces*, *Candida*, *Coccidiodes*, *Cryptococcus*, *Histoplasma*, *Pneumocystis*, *Actinomyces*, *Legionella*, *Listeria*, *Norcardia*, *Salmonella*, tuberculous and non-tuberculous mycobacteria, *Toxoplasma*, herpes zoster, and JC virus (9,22).

Covariates

Other covariates were measured at lead-in study baseline and included demographic data, specifically age, sex, body mass index, and smoking history, and medical history data, specifically duration of CD, presence of fistulae, and history of diabetes mellitus, chronic obstructive pulmonary disease, and asthma. Diabetes mellitus was included as a covariate given increased risk of infection in this population (23). Chronic obstructive pulmonary disease and asthma were included as we expected the majority of non-gastrointestinal serious infections to be pneumonias or other respiratory infections (24).

Statistical analysis

Initial descriptive statistics included the baseline demographic and medical history covariate data above. The primary outcomes in this pooled analysis were: (1) the risks of serious infections and opportunistic infections at 1 year with higher disease activity in patients treated with adalimumab; and (2) the short-term risks of serious infections and opportunistic infections (at day 56 or 120 of follow-up) with immunomodulator or corticosteroid use

when combined with adalimumab, compared with adalimumab monotherapy.

Cox regression was used for all analyses to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Follow-up time was censored when either the outcome of interest occurred or when patients discontinued the study to account for the possibility that concomitant medications could change after that point. All analyses were performed without and with adjustment for covariates. For selection of the final multivariable models, covariates were included as potential confounders if the *P*-values representing the association of those variables and the outcomes were <0.25 on univariable analysis (25). Of note, we were not able to adjust for adalimumab dose (e.g., cumulative or average exposure) in our analyses due the multitude of different treatment pathways that patients could undergo based on the various induction and maintenance doses as well as various open-label dosing and dose escalation schedules, both of which could occur at different time points, in the included studies. For the outcome of infection risk with higher disease activity, the mathematical nature of the association of CDAI with this outcome (i.e., linear vs. non-linear) was assessed by including both a linear and quadratic term for CDAI in the model and testing for significance.

A number of pre-specified secondary analyses were also performed. For infection risk with higher disease activity, the analyses were repeated with follow-up censored at day 56. For infection risk with concomitant immunomodulator or corticosteroid use: (1) all analyses were repeated extending follow-up to 1 year as described above; (2) the proportions of CD-related and non-CD-related serious infections were calculated; (3) the proportions of overall serious infections by baseline corticosteroid type/dose (prednisone or equivalent ≥20 mg/day, prednisone or equivalent <20 mg/day, or budesonide at any dose) were calculated; and (4) the proportions of opportunistic infections due to oral Candida, all Candida, and herpes zoster were calculated. For the latter three of these analyses, the number of outcomes was too low to perform multivariable analysis.

RESULTS

There were 2,266 patients treated with adalimumab who were included in this pooled analysis. More than 75% of patients were 45 years of age or younger with a median age of 35 years (interquartile range 27–44 years), 60% were women, 37% were current smokers, and 27% had fistulae (**Table 1**). The median baseline CDAI in each of the included studies ranged from 283 to 324. At lead-in study baseline, 1,073 patients (47%) were receiving concomitant immunomodulators (871 (81%) of these with thiopurines and 210 (19%) with methotrexate; 8 of these patients had received both agents) and 890 (39%) were receiving concomitant corticosteroids (521 (59%) of these with prednisone or equivalent ≥20 mg/day, 121 (14%) with prednisone or equivalent <20 mg/day, and 220 (25%) with budesonide at any dose without prednisone; 28 patients had prednisone dose not quantifiable). Combined, 739 patients (33%) received adalimumab monotherapy, 637 (28%) received adalimumab combined with immunomodulators but without corticosteroids, 454 (20%) received adalimumab combined with corticosteroids but without immunomodulators, and 436 (19%) received triple immunosuppression.

Table 1. Baseline characteristics of the study population (*n*=2,266)

Characteristic	Value
Age (y): *n* (%)	
≤25	436 (19)
>25 to 35	738 (33)
>35 to 45	585 (26)
>45	507 (22)
Female sex: *n* (%)	1,356 (60)
BMI: *n* (%)	
<18.5	226 (10)
18.5 to <25	1,193 (53)
25 to <30	513 (23)
≥30	326 (14)
Smoking status: *n* (%)	
Never	881 (39)
Past	538 (24)
Current	846 (37)
Duration of CD: mean y (s.d.)	10.3 (8.4)
Fistula(e): *n* (%)	614 (27)
Diabetes mellitus: *n* (%)	637 (28)
COPD: *n* (%)	446 (20)
Asthma: *n* (%)	544 (24)
Concomitant immunosuppressants: *n* (%)	
Corticosteroids	890 (39)
Prednisone or equivalent ≥20 mg/day	521 (23)
Prednisone or equivalent <20 mg/day	121 (5)
Prednisone dose not quantifiable	28 (1)
Budesonide	220 (10)
Immunomodulators	1,073 (47)
Thiopurines	871 (38)
Methotrexate	210 (9)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; *n*, number of patients; y, years.

Association of disease activity with infection risk

After 1 year of follow-up, 84 patients (3.7%) had developed serious infections, of which 30 (1.3% overall) were CD related (**Table 2**). Higher disease activity was associated with a significantly increased risk of serious infection, even after adjustment for concomitant corticosteroids and immunomodulators, with each 100-point increase in CDAI linearly associated with a 39% increased risk (HR 1.39 (1.19–1.63), *P*<0.001; **Table 3**). Thus, a

Table 2. Types of and numbers of patients with serious and opportunistic infections during follow-up

Infection type	Day 1–56 (*n*=2,266)	Day 57–120 (*n*=2,053)	Total, day 1–120	Day 121–365 (*n*=1,889)	Total, day 1–365
Serious infections					
CD related	9	13	22	8	30
Abdominal abscess	5	5	10	2	12
Anorectal abscess	4	8	12	6	18
Non-CD related	12	13	25	29	54
Respiratory	3	3	6	4	10
Clostridium difficile	3	1	4	2	6
Other gastrointestinal	5	2	7	8	15
Other	1	7	8	15	23
Total	21	26	47	37	84
Opportunistic infections					
Candida	12	6	18	7	25
Oral Candida	7	2	9	3	12
Non-Candida	5	10	15	10	25
Herpes zoster	4	9	13	7	20
Total	17	16	33	17	50

CD, Crohn's disease.

256-point increase in CDAI would be associated with a doubling of serious infection risk. Nearly identical results were seen when excluding CD-related infections. When censoring follow-up at day 56 in this analyses, higher disease activity was associated with a similarly increased risk of serious infection (adjusted HR 1.51 (1.15–2.00), *P*=0.003, per 100-point increase in CDAI).

By 1 year of follow-up, 50 patients (2.2%) had developed opportunistic infections, half of which were due to Candida and 40% of which were due to herpes zoster (**Table 2**). The five non-Candidal non-herpes zoster infections were one patient each with tuberculosis (on concomitant corticosteroids), coccidioidomycosis (on concomitant immunomodulator), nocardiosis (on concomitant immunomodulator), salmonellosis (on concomitant immunomodulator), and cytomegalovirus (on adalimumab monotherapy). Higher disease activity was also associated with a significantly increased risk of opportunistic infections, independent of concomitant use of corticosteroids and immunomodulators, with each 100-point increase in CDAI linearly associated with a 31% increased risk (HR 1.31 (1.04–1.64), *P*=0.020; **Table 3**). Thus, a 323-point increase in CDAI would be associated with a doubling of opportunistic infection risk. In the first 56 days of follow-up, higher disease activity was not associated with risk of opportunistic infection (adjusted HR 1.16 (0.77–1.75), *P*=0.479, per 100-point increase in CDAI).

Table 3. Risk of serious and opportunistic infection with increasing disease severity by follow-up day 365

Infection type	HR (95% CI) for each 100-point increase in CDAI
Serious infection total	
Univariable analysis	1.41 (1.20–1.65), *P*<0.001
Multivariable analysis[a]	1.39 (1.19–1.63), *P*<0.001
Serious infection non-CD related	
Univariable analysis	1.39 (1.14–1.70), *P*=0.001
Multivariable analysis[a]	1.41 (1.15–1.73), *P*<0.001
Opportunistic infection	
Univariable analysis	1.31 (1.05–1.62), *P*=0.014
Multivariable analysis[b]	1.31 (1.04–1.64), *P*=0.020

BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; HR, hazard ratio.

[a]Adjusted for BMI, smoking status, and presence of fistulae, based on univariable *P*<0.25, and time-dependent immunomodulator and corticosteroid use, irrespective of univariable *P*-value; of note, the other covariates had univariable *P*>0.25 and therefore did not qualify to be included in the final model.

[b]Adjusted for age, smoking status, duration of CD, and presence of fistulae, based on univariable *P*<0.25, and time-dependent immunomodulator and corticosteroid use, irrespective of univariable *P*-value; of note, the other covariates had univariable *P*>0.25 and therefore did not qualify to be included in the final model.

Association of concomitant immunosuppressant medication use with infection risk

By day 56 and 120 of follow-up, 21 (0.9%) and 47 (2.1%) patients developed serious infections, respectively, of whom 9 (0.4%) and 22 (1.0%) developed CD-related serious infections, respectively (**Table 2**). The rates of serious infection overall, CD-related, and non-CD-related by day 56 and 120 were numerically lowest in

Table 4. Rates of serious and opportunistic infections with adalimumab alone or combined with immunomodulators and/or corticosteroids by follow-up day 56 and 120

Group	Overall SI *n* (%)	CD-related SI *n* (%)	Non-CD-related SI *n* (%)	Overall OI *n* (%)	OI excluding oral candida *n* (%)
Day 56					
ADA monotherapy (*n*=739)	7 (0.9)	3 (0.4)	4 (0.5)	3 (0.4)	3 (0.4)
ADA+IM (*n*=637)	2 (0.3)	1 (0.2)	1 (0.2)	4 (0.6)	2 (0.3)
ADA+CS (*n*=454)	8 (1.8)	4 (0.9)	4 (0.9)	3 (0.7)	2 (0.4)
ADA+IM+CS (*n*=436)	4 (0.9)	1 (0.2)	3 (0.7)	7 (1.6)	3 (0.7)
Day 120					
ADA monotherapy (*n*=739)	12 (1.6)	7 (0.9)	5 (0.7)	5 (0.7)	5 (0.9)
ADA+IM (*n*=637)	6 (0.9)	2 (0.3)	4 (0.6)	9 (1.4)	6 (0.9)
ADA+CS (*n*=454)	16 (3.5)	8 (1.8)	8 (1.8)	8 (1.8)	6 (1.3)
ADA+IM+CS (*n*=436)	13 (3.0)	5 (1.1)	8 (1.8)	11 (2.5)	7 (1.6)

ADA, adalimumab; CD, Crohn's disease; CS, corticosteroids; IM, immunomodulator; OI, opportunistic infections; *n* number of patients; SI, serious infections.

Table 5. Risk of serious and opportunistic infection with adalimumab concurrent with immunomodulators or corticosteroids, relative to adalimumab monotherapy, by follow-up day 56 and 120

Exposure	Serious infection total HR (95% CI)	Serious infection non-CD-related HR (95% CI)	Opportunistic infection HR (95% CI)
Immunomodulators			
Univariable analysis			
Day 56	0.44 (0.17–1.13), *P*=0.087	0.49 (0.15–1.58), *P*=0.232	2.02 (0.75–5.45), *P*=0.167
Day 120	0.69 (0.38–1.25), *P*=0.225	0.85 (0.39–1.87), *P*=0.684	1.59 (0.79–3.22), *P*=0.197
Multivariable analysis[a]			
Day 56	0.43 (0.17–1.11), *P*=0.081	0.49 (0.15–1.59), *P*=0.235	
Day 120	0.68 (0.38–1.24), *P*=0.211	0.87 (0.39–1.92), *P*=0.725	
Corticosteroids			
Univariable analysis			
Day 56	2.02 (0.85–4.81), *P*=0.110	1.78 (0.60–5.28), *P*=0.302	2.16 (0.82–5.68), *P*=0.118
Day 120	2.34 (1.30–4.23), *P*=0.005	2.26 (1.02–5.03), *P*=0.046	1.93 (0.96–3.88), *P*=0.065
Multivariable analysis[a]			
Day 56	2.07 (0.87–4.92), *P*=0.099	1.83 (0.61–5.46), *P*=0.278	
Day 120	2.40 (1.33–4.35), *P*=0.004	2.40 (1.07–5.38), *P*=0.033	

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; HR, hazard ratio.
[a]Adjusted for baseline CDAI and presence of fistulae, based on univariable *P*<0.25 at either day 56 or 120; of note, the other covariates had univariable *P*>0.25 at both time points and therefore did not qualify to be included in the final model.

patients receiving adalimumab combined with immunomodulators but without corticosteroids and numerically highest in patients receiving adalimumab combined with corticosteroids but without immunomodulators (**Table 4**). Patients receiving triple immunosuppression or adalimumab monotherapy had rates of serious infection that were intermediate between these. The majority of serious infections among users of corticosteroids occurred in those taking prednisone or equivalent ≥20 mg/d, with higher rates in patients taking prednisone or equivalent at any dose compared with users of budesonide (**Supplementary Table S1** online).

In multivariable analysis, the risk of serious infection was numerically lower in concomitant users of immunomodulators by day 56 and 120 (**Table 5**). In contrast, the risk of serious infection was significantly higher with concomitant use of corticosteroids by day 120 (HR 2.40 (1.33–4.35), *P*=0.004); the HR was similar

by day 56 (HR 2.07 (0.87–4.92), *P*=0.099; **Table 5**). The point estimates at these time points were similar when excluding CD-related infections. In secondary analysis, we extended follow-up to 1 year at which point multivariable analysis revealed that users of concomitant immunomodulators had a significant >3-fold lower risk of serious infection (HR 0.29 (0.08–0.98), *P*=0.045), whereas concomitant corticosteroid use had no effect on this risk (HR 1.01 (0.36–2.87), *P*=0.98). Interestingly, when excluding CD-related infections, concomitant immunomodulator use was associated with a significant nearly 8-fold lower risk of serious infection (HR 0.13 (0.02–0.98), *P*=0.048), while concomitant corticosteroid use was not significantly associated with this risk (HR 1.42 (0.42–4.75), *P*=0.57).

By day 56 and 120 of follow-up, 17 (0.8%) and 33 (1.5%) patients developed opportunistic infections, with Candida and herpes zoster occurring most commonly (**Table 2**). Of note, there were no cases of mycobacterial or non-Candidal fungal infections by these time points. The rates of overall opportunistic infections by day 56 and 120 were numerically lowest with adalimumab monotherapy and highest with triple immunosuppression, with intermediate rates among users of either immunomodulators or corticosteroids combined with adalimumab; when excluding oral Candida, the rates of opportunistic infection remained numerically highest with triple immunosuppression (**Table 4**).

In univariable analysis, concomitant use of immunomodulators or corticosteroids was associated with a numerically increased (approximately twofold) risk of opportunistic infection by day 56 and day 120 (**Table 5**). In secondary analysis, we extended follow-up to 1 year and found that neither use of concomitant immunomodulators (HR 1.24 (0.45–3.41), *P*=0.68) nor corticosteroids (HR 0.80 (0.22–2.93), *P*=0.73) affected this risk. Multivariable analysis was not performed for any of these analyses due to the low number of outcomes relative to the number of covariates with *P*<0.25 in univariable analysis.

DISCUSSION

There are sparse data in CD with respect to the risk of infection with increasing disease activity as well as few studies examining the relative risk of infection with combination therapy compared with anti-TNF monotherapy. In addition, confounding by indication is always a concern in observational studies investigating infection risk with immunosuppressant use if increased disease activity is independently associated with infection risk. In particular, quantitative measurements of disease activity are rarely available in longitudinal studies. This study took advantage of the serial measurement of disease activity on an individual patient basis using the CDAI in the included clinical trials. This unique data set allowed us to clearly identify that independent of medical therapy, greater disease activity is associated with significantly increased risks of both serious and opportunistic infections by 1 year, with each 100-point increase in CDAI associated with a >30% increased risk of each type of infection. We also identified that patients treated with concomitant immunomodulators, the majority of which were thiopurines, had a significant >3-fold decreased rate of serious infection by 1 year independent of disease activity, with numerically lower rates in the short term. In contrast, those treated with concomitant corticosteroids had a significantly increased risk of serious infection by day 120. Concomitant use of either category of immunosuppressants in this relatively young population was associated with numerically higher short-term rates of opportunistic infections, many of which were due to herpes zoster, which warrants notice as the majority of these patients would not be candidates for herpes zoster vaccination under current national vaccination guidelines (26).

The notion that increasing disease activity in CD is a risk factor for serious infection was put forth from the TREAT registry, in which disease activity was categorized according to a non-quantitative physician global assessment (2). Our analysis confirmed this hypothesis using a rigorous quantitative measurement of disease activity, which was assessed frequently in the pooled studies. In rheumatoid arthritis, higher disease activity has also been shown to be an independent risk factor for serious infection in several studies, with a 27–42% increase in risk for every unit increase in the Disease Activity Score in 28 joints (27,28) and a 7.7% increase in risk for every five-unit increase in the Clinical Disease Activity Index (29).

Our finding of an increased risk of opportunistic infection with higher disease activity at 1 year, independent of the effects of concomitant immunosuppressive medication, is novel in immune-mediated disease. Although this observation needs to be confirmed in other studies, we hypothesize that higher disease activity may render the body more vulnerable to the effects of opportunistic pathogens over time. As earlier treatment (duration of CD <2 years) with adalimumab has been shown to be potentially more efficacious than later treatment (30) and early combination therapy with infliximab and azathioprine has demonstrated impressive rates of corticosteroid-free remission in two randomized trials (8,31) it is possible that early aggressive treatment of CD could lead to a reduction in the rates of both serious and opportunistic infections over time by improving disease control, given the results of our analysis.

Our results demonstrating a significantly decreased 1-year risk of serious infection with concomitant immunomodulators, which was numerically lower in the short term, is similar to data reported in the SONIC trial, in which numerically lower rates of serious infection were observed in users of combination therapy with infliximab and azathioprine than in users of either agent alone (8). Interestingly, in our analysis a numerically lower incidence of serious infection was seen in both CD-related and non-CD-related infection. Thus, combination therapy may offer the potential for improved disease control, which may itself lead to lower rates of infection, coupled with a potentially lower risk of serious infection independent of disease activity, thereby possibly helping to alleviate concerns regarding adverse events for treating physicians who are contemplating aggressive immunosuppressive treatment for their patients with CD.

In contrast, the concomitant use of immunomodulators in our analysis was associated with a numerical increase in the risk of opportunistic infection in the short term. The disparity in the risk

of serious and opportunistic infections with concomitant immunomodulators in our analysis is not surprising given the specific opportunistic infectious agents observed. Thiopurines have been shown to be a risk factor for the development of herpes zoster and Candida whether used as monotherapy or concomitantly with anti-TNF agents in CD (3,4,9). We surmise that the lack of increased risk with immunomodulator use by 1 year was perhaps an underestimate of the risk, as patients who developed an early opportunistic infection may have dropped out of the study in which they were enrolled and thus those who remained on study were more likely to be tolerant of their immunomodulator.

Our finding that patients receiving corticosteroids with adalimumab had a higher short-term risk of serious infection than those receiving adalimumab alone is not surprising, as prior studies in other immune-mediated diseases have reported similar findings (24,32). Specifically, concomitant use of corticosteroids at a dose equivalent of 10 mg per day or more of prednisone with anti-TNF therapy has been associated with a threefold increased risk of serious infection in rheumatoid arthritis (24), juvenile idiopathic arthritis (32), and psoriasis and spondyloarthropathies (24). Our results demonstrating a numerically higher short-term risk of opportunistic infections with corticosteroids in adalimumab-treated patients is consistent with a prior study in a combined cohort of anti-TNF-treated patients with rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, and ankylosing spondylitis, in which additional corticosteroid use increased the risk of non-viral opportunistic infections by 2.5-fold (22). Combined, these results emphasize the continued need for corticosteroid-sparing medications and strategies for the treatment of CD. We hypothesize that the lack of increased risk of infection with concomitant corticosteroid use by 1 year may be due to 2 factors: (1) since corticosteroids were tapered in most of the included studies starting at week 8–12, any association between infection and corticosteroids at later time points would likely be reflective of lower corticosteroid dose; and (2) patients may have dropped out of their studies after early events, as 56 and 66% of serious and opportunistic infections occurred within the first 56 and 120 days of follow-up, respectively, thus leaving those who were less likely to develop these events.

An important issue highlighted by our results is the need for vaccination in patients with CD. Consistent with prior studies documenting that corticosteroids, thiopurines, and anti-TNF therapy all increase the risk of herpes zoster infection (4–6), the majority of non-Candida opportunistic infections in our analysis were due to herpes zoster. Vaccination against herpes zoster is highly effective, even among patients receiving anti-TNF drugs in whom it may also be safe (33), and is recommended for patients age 60 years or older (26). Given that nearly all patients in this study were under 60 years of age, these results argue for earlier vaccination against herpes zoster in patients with CD, ideally prior to commencement with immunosuppressive therapy.

This analysis has several potential limitations. Despite the large sample size, serious and opportunistic infections were relatively rare events. As such, only univariable analyses were possible for some outcomes. In addition, lack of statistical significance for certain outcomes may be the result of low statistical power rather than indicating true safety. We did not control for adalimumab dose in our analyses due to technical issues. However, we do not expect that lack of adjustment for this would have changed the risk of infection with concomitant immunosuppressants. With respect to disease activity, while patients with more severely active disease may have dose-escalated to weekly adalimumab, without the knowledge of adalimumab drug levels and anti-drug antibodies (which were not collected in the majority of these studies), it was not possible to accurately assess the impact of differential adalimumab dosing on infection risk associated with active disease. Moreover, in CHARM patients randomized to blinded weekly maintenance adalimumab did not have higher rates of infection than those randomized to blinded every other week maintenance adalimumab (14). Finally, we did not have consistent data in all included studies regarding comorbidities other than diabetes mellitus, chronic obstructive pulmonary disease, and asthma to be included as covariates in our analysis. However, although potentially associated with the risk of infection, it is unlikely that unmeasured comorbidities would be differentially associated with our exposures and thus be true confounders.

In conclusion, we found that higher disease activity in CD was independently associated with an increased risk of both serious and opportunistic infections. We also found that concomitant use of immunomodulators was independently associated with a lower risk of serious infection at 1 year, whereas concomitant use of corticosteroids was independently associated with an increased short-term risk of serious infection. Given that a substantial proportion of observed opportunistic infections in this relatively young population were due to herpes zoster, consideration should be given to expand herpes zoster vaccination guidelines to include patients under the age of 60.

CONFLICT OF INTEREST

Guarantor of the article: Mark T. Osterman, MD, MSCE.
Specific author contributions: Mark T. Osterman: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. William J. Sandborn: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Jean-Frederic Colombel: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Laurent Peyrin-Biroulet: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Anne M. Robinson: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Qian Zhou: analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis. James D. Lewis: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Writing Assistance: We thank Kristina Kligys, PhD, of AbbVie for assistance in preparing the figure.
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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Anti-tumor necrosis factor (TNF) therapy is commonly used with immunomodulators and/or corticosteroids for the treatment of moderate-to-severe Crohn's disease (CD).
- ✓ Disease activity and immunosuppressant medications may increase the risk of serious and opportunistic infections.
- ✓ There are scant data regarding the risk of infection with increasing disease activity in CD.
- ✓ There are few studies examining the relative risk of infection with combination therapy compared with anti-TNF monotherapy in CD.

WHAT IS NEW HERE

- ✓ Higher disease activity in CD was associated with a significantly increased risk of both serious and opportunistic infections, independent of concomitant medical therapy, in patients treated with adalimumab.
- ✓ Concomitant use of immunomodulators was associated with a significantly decreased risk of serious infection at 1 year, independent of disease activity.
- ✓ Concomitant use of corticosteroids was associated with a significantly increased risk of serious infection at day 120, independent of disease activity.
- ✓ As a substantial proportion of opportunistic infections in our young population was due to herpes zoster, consideration should be given to expand herpes zoster vaccination guidelines to include younger patients.

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