Supplementary Methods

Exclusion Criteria

Patients were also excluded if they were missing date of birth, were over age 85, were diagnosed with other indications for anti-TNF therapy (specifically, rheumatoid arthritis, psoriasis, psoriatic arthritis, or ankylosing spondylitis) within the 12 months prior to the first anti-TNF prescription, received more than 1 type of anti-TNF therapy at the time of first anti-TNF prescription, had more ulcerative colitis (UC) diagnoses than CD diagnoses in the available data prior to the first anti-TNF prescription, or had a diagnosis of UC on or immediately preceding the first anti-TNF prescription.

Covariates

Based on preliminary analyses, we categorized oral steroid use (prednisone or budesonide) into 3 groups: new initiation within 28 days prior to the start of anti-TNF therapy, at least 1 prescription for steroids between the period from 90 to 29 days prior to the start of anti-TNF therapy, and no prescriptions for steroids in the 90 days prior to the start of anti-TNF therapy. Because age and eligibility for Medicare due to disability were highly correlated, we combined these into a single variable. Patients under age 65 were all eligible mainly due to disability. We included 3 additional age categories: 60-69 with disability, 60-69 without disability, and 70 and older with or without disability. For the latter category, we combined those with or without disability due to small numbers when stratified by disability.

Outcome Measures

<u>Opportunistic Infections</u>

For aspergillosis, a prescription for posaconazole, itraconazole, or voriconazole was required within 90 days of the diagnosis. For blastomycosis, coccidioidomycosis, cryptococcosis,

histoplasmosis, and endemic mycosis, we also required a prescription for fluconazole, itraconazole, or voriconazole within 90 days of the diagnosis code. For tuberculosis, we required a prescription of pyrazinamide. For herpes zoster, we required a prescription of acyclovir, valacyclovir, or famcyclovir within 90 days of the diagnosis. For all other opportunistic infections, we did not require concomitant antimicrobial prescriptions.

Statistical Analysis

Propensity Score

The propensity score was calculated separately for patients receiving infliximab and adalimumab. We excluded patients in a particular therapy group with propensity scores at the extremes of the distribution such that there was no overlap with the other therapy group. Subsequently, we used 3:1 variable ratio balanced parallel matching between monotherapy and combination therapy patients and excluded patients who did not have a match. Covariate balance between the combination therapy and monotherapy groups was assessed by measuring the mean of the standardized difference weighted by the matched set size; values of $\leq$0.1 are consistent with minimal differences between the groups. Since not all users of combination therapy had 3 matches (i.e. some had only 1 or 2 matches), all analyses were initially conditioned on the number of matches.

Prespecified secondary and sensitivity analyses

Given that a substantial proportion of patients require dose escalation of anti-TNF therapy over time,[25,26] we evaluated the need for dose escalation and incorporated this as a combined outcome with time to discontinuation or surgery. Our definition of dose escalation was based on dispensed units of medication for infliximab and reimbursement amount per patient for adalimumab. We defined dose escalation as at least a 25% increase in the dose per unit time

on 2 consecutive dispensings for infliximab (which would capture patients receiving at least 5 mg/kg every 6 weeks) and at least a 50% increase above the expected dose of 40 mg per 14 days for adalimumab on 2 consecutive dispensings (which would capture patients receiving at least 40 mg every 10.5 days). To avoid difficulty calculating reimbursement for patients with both Medicare and Medicaid benefits, we limited this analysis to patients with Medicare benefits only.

For the surgery outcome, we repeated the analysis including as outcomes the surgeries that were excluded on manual review of the Medicare claims, as described previously.[19] For the hospitalization outcome, 2 alternative definitions were used: 1) allowing CD to be a secondary discharge diagnosis if the primary diagnosis were consistent with CD (e.g., abdominal pain); and 2) allowing CD or UC to be the primary or secondary discharge diagnosis. For the outcomes of serious infection and overall opportunistic infection, we performed time-updating adjustment for oral steroid use (prednisone or budesonide), in which exposure time to steroids was defined as the date of each prescription for steroids plus 60 days. We performed 2 sets of sensitivity analyses censoring follow-up. In the first, we censored follow-up after patients discontinued anti-TNF therapy (with end of follow-up defined as 60 days after the last dispensing of anti-TNF agent). In the second, we also censored follow-up after patients changed from combination therapy to monotherapy (with end of follow-up defined as 60 days after the last dispensing of immunumodulator), or vice versa (with end of follow-up defined as 60 days after the new dispensing of immunomodulator). Additionally, we performed a sensitivity analysis in which start of follow-up was the date of the first prescription for anti-TNF therapy rather than 120 days later. Because the majority of users of combination therapy initiated immunomodulator therapy $\geq$90 days prior to starting anti-TNF therapy, we performed an analysis restricted to these patients and their matched controls (i.e. excluding patients who initiated immunomodulators in the period 89 days before to any time after initiating anti-TNF therapy and their matched controls). Given that Medicare includes a large proportion of elderly patients, we

tested for interaction by age (<65 vs. ≥65 years) for all primary analyses. Finally, in order to increase the likelihood that patients were first-time users of anti-TNF therapy, we conducted a sensitivity analysis restricted to patients with at least 2 years of data prior to the first prescription for anti-TNF therapy.

Post-hoc analysis

As a post-hoc analysis, we investigated whether any of the results changed due to dose of thiopurines or use of methotrexate. Given our sample sizes, we created a 4-level exposure variable as follows: 1) anti-TNF monotherapy (reference group); 2) combination therapy with low-dose thiopurines; 3) combination therapy with high-dose thiopurines; and 4) combination therapy with methotrexate. Low-dose and high-dose thiopurine groups were determined as follows: first, converting all thiopurine prescriptions to 6MP dose equivalents (where AZA dose = 2.08 x 6MP dose), during the 120 days after start of anti-TNF therapy; second, computing the average daily dose for each patient; third, determining the median average daily dose among all patients; and finally, defining low-dose as less than or equal to the median and high-dose as greater than the median average daily dose. Of note, patient weight or thiopurine methyltransferase (TPMT) genotype/activity were not accounted for when considering thiopurine dosing. The methotrexate group was very small, which prohibited meaningful dose stratification, and was analyzed as part of the 4-level exposure variable.

Supplementary Table 1. Primary and secondary analyses with follow-up censored after discontinuation of anti-TNF therapy or also after change from combination to monotherapy or vice versa.

	Infliximab			Adalimumab			Combined Anti-TNF
Outcome	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**	**Adjusted HR* (95% CI)**
Censor after discontinue anti-TNF							
Surgery							
With manual review	4.8	3.9	1.22 (0.49-3.05)	3.9	6.1	0.55 (0.18-1.65)	0.89 (0.44-1.78)
Without manual review	5.2	4.3	1.22 (0.50-2.94)	3.9	7.1	0.46 (0.16-1.33)	0.82 (0.42-1.61)
Hospitalization							
CD as 1º diagnosis	7.0	9.0	0.79 (0.38-1.63)	7.9	13.1	0.60 (0.27-1.35)	0.71 (0.41-1.21)
CD as 1º or 2º diagnosis	13.4	14.3	0.86 (0.50-1.49)	13.2	21.6	0.68 (0.35-1.31)	0.80 (0.52-1.21)
CD or UC as 1º or 2º diagnosis	14.4	14.5	0.96 (0.55-1.65)	13.2	21.9	0.68 (0.35-1.31)	0.85 (0.56-1.29)
Serious infection							
Without time-varying steroid adjustment	8.0	7.7	0.95 (0.47-1.91)	8.2	6.5	1.20 (0.47-3.07)	1.03 (0.59-1.81)
With time-varying steroid adjustment	8.0	7.7	0.94 (0.47-1.91)	8.2	6.5	1.13 (0.44-2.94)	0.99 (0.56-1.75)
Opportunistic infection							
Without time-varying steroid adjustment	4.3	1.8	**7.86 (2.69-23.0)**	3.3	1.5	3.20 (0.54-18.8)	**6.09 (2.36-15.7)**
With time-varying steroid adjustment	4.3	1.8	**7.45 (2.55-21.8)**	3.3	1.5	2.70 (0.48-15.2)	**5.55 (2.17-14.2)**
Herpes zoster	3.2	1.0	**12.8 (3.69-44.7)**	2.6	0.9	3.25 (0.43-24.5)	**8.58 (2.85-25.8)**
Censor also after change from combination therapy to monotherapy or vice versa							
Surgery							
With manual review	4.8	3.9	1.10 (0.34-3.54)	5.1	6.0	0.84 (0.21-3.38)	1.00 (0.42-2.39)
Without manual review	4.8	4.3	1.14 (0.36-3.61)	5.1	7.0	0.68 (0.17-2.67)	0.91 (0.38-2.15)
Hospitalization							
CD as 1º diagnosis	7.8	8.6	0.66 (0.27-1.59)	10.5	13.1	0.80 (0.30-2.15)	0.74 (0.38-1.42)

	Infliximab			Adalimumab			Combined Anti-TNF
CD as 1º or 2º diagnosis	14.9	14.2	0.76 (0.39-1.48)	18.4	21.5	0.96 (0.44-2.09)	0.87 (0.52-1.45)
CD or UC as 1º or 2º diagnosis	15.9	14.4	0.85 (0.44-1.66)	18.4	21.6	0.96 (0.44-2.09)	0.93 (0.56-1.54)
Discontinuation or surgery	70.7	56.3	1.32 (0.96-1.81)	81.3	71.5	1.05 (0.71-1.53)	1.19 (0.94-1.52)
Serious infection							
Without time-varying steroid adjustment	6.9	7.4	0.83 (0.33-2.13)	10.5	5.6	1.86 (0.59-5.93)	1.14 (0.55-2.38)
With time-varying steroid adjustment	6.9	7.4	0.80 (0.31-2.05)	10.5	5.6	1.85 (0.58-5.88)	1.11 (0.53-2.31)
Opportunistic infection							
Without time-varying steroid adjustment	5.7	1.9	**13.2 (3.42-51.1)**	3.4	1.6	2.79 (0.27-28.7)	**8.69 (2.63-28.7)**
With time-varying steroid adjustment	5.7	1.9	**13.0 (3.33-50.5)**	3.4	1.6	2.25 (0.25-20.0)	**7.59 (2.36-24.4)**
Herpes zoster	4.0	1.0	**24.7 (5.07-120)**	3.4	0.9	3.66 (0.29-45.7)	**13.8 (3.46-54.8)**

*Adjusted for prior immunomodulator use

Abbrevations: E, events; PY, person-years; HR, hazard ratio; CI, confidence interval

Supplementary Table 2. Primary analyses with change in start of follow-up to date of first prescription for anti-TNF therapy.

	Infliximab			Adalimumab		
Outcome	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**
Surgery	6.5	5.0	1.13 (0.67-1.89)	4.5	6.6	0.79 (0.38-1.67)
Hospitalization	12.8	11.4	1.17 (0.79-1.72)	13.0	16.4	0.97 (0.60-1.55)
Discontinuation or surgery	49.4	51.1	1.17 (0.93-1.47)	44.1	59.0	0.96 (0.71-1.31)
Serious infection	7.7	9.5	0.90 (0.58-1.40)	8.2	7.9	1.23 (0.65-2.34)
Opportunistic infection	2.8	1.6	**2.62 (1.16-5.95)**	1.8	1.5	1.51 (0.40-5.71)
Herpes zoster	2.0	1.0	**3.21 (1.24-8.28)**	1.2	0.8	2.18 (0.39-12.3)

*Adjusted for prior immunomodulator use

Abbrevations: E, events; PY, person-years; HR, hazard ratio; CI, confidence interval

Supplementary Table 3. Primary analyses excluding patients who initiated immunomodulators in the period 89 days before to any time after initiating anti-TNF therapy.

	Infliximab			Adalimumab		
Outcome	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**
Surgery	5.2	4.1	0.96 (0.41-2.28)	5.1	5.8	1.13 (0.39-3.27)
Hospitalization	7.7	9.5	0.59 (0.31-1.13)	12.2	13.0	1.20 (0.57-2.53)
Discontinuation or surgery	46.1	58.2	0.98 (0.65-1.45)	51.2	66.1	0.95 (0.63-1.45)
Serious infection	6.3	7.5	0.78 (0.37-1.63)	10.0	6.9	1.23 (0.45-2.81)
Opportunistic infection	2.5	1.8	3.27 (0.42-25.6)	3.2	1.3	2.28 (0.79-6.62)
Herpes zoster	1.8	1.1	**2.26 (1.18-18.4)**	2.3	0.7	2.63 (0.69-10.1)

*Adjusted for prior immunomodulator use

Abbrevations: E, events; PY, person-years; HR, hazard ratio; CI, confidence interval

Supplementary Table 4. Primary analyses restricted to patients with at least 2 years of data prior to first prescription for anti-TNF therapy.

	Infliximab			Adalimumab		
Outcome	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**	**Rate in Combination Therapy (E/100 PY)**	**Rate in Mono-therapy (E/100 PY)**	**Adjusted HR* (95% CI)**
Surgery	5.4	5.8	0.95 (0.33-2.69)	2.3	8.0	0.24 (0.04-1.33)
Hospitalization	7.0	12.9	0.70 (0.29-1.67)	5.2	18.5	**0.30 (0.09-0.98)**
Discontinuation or surgery	53.0	59.8	1.25 (0.81-1.91)	39.2	71.8	0.75 (0.42-1.35)
Serious infection	9.9	10.0	0.86 (0.41-1.79)	5.0	9.1	0.52 (0.13-2.08)
Opportunistic infection	1.7	1.6	1.24 (0.22-6.90)	2.3	2.3	1.84 (0.18-19.1)
Herpes zoster	0.57	1.1	0.53 (0.04-6.62)	1.1	0.9	1.62 (0.06-43.2)

*Adjusted for prior immunomodulator use

Abbrevations: E, events; PY, person-years; HR, hazard ratio; CI, confidence interval

Supplementary Table 5. Primary analyses stratified by type/dose of immunomodulator.

	Infliximab		Adalimumab	
Outcome	**Rate (E/100 PY)**	**Adjusted HR* (95% CI)**	**Rate (E/100 PY)**	**Adjusted HR* (95% CI)**
Surgery				
Monotherapy	3.9	Reference	6.1	Reference
Low-dose thiopurine	7.8	1.75 (0.90-3.41)	4.0	0.75 (0.26-2.17)
High-dose thiopurine	4.7	1.04 (0.47-2.32)	5.4	1.01 (0.37-2.80)
Methotrexate	4.2	0.97 (0.22-4.26)	6.2	1.10 (0.23-5.20)
Hospitalization				
Monotherapy	9.8	Reference	14.4	Reference
Low-dose thiopurine	11.5	0.96 (0.57-1.63)	9.2	0.79 (0.38-1.64)
High-dose thiopurine	6.1	0.49 (0.25-0.95)	13.1	1.03 (0.51-2.07)
Methotrexate	8.9	0.75 (0.26-2.16)	12.5	1.06 (0.31-3.64)
Discontinuation or surgery				
Monotherapy	55.9	Reference	70.8	Reference
Low-dose thiopurine	63.2	1.34 (0.99-1.80)	55.4	1.00 (0.67-1.49)
High-dose thiopurine	41.0	0.97 (0.69-1.37)	47.7	0.81 (0.52-1.24)
Methotrexate	78.2	1.73 (1.04-2.89)	48.4	0.88 (0.43-1.79)
Serious infection				
Monotherapy	8.0	Reference	7.4	Reference
Low-dose thiopurine	6.4	0.74 (0.40-1.37)	6.8	0.96 (0.39-2.34)
High-dose thiopurine	7.2	0.90 (0.48-1.70)	9.3	1.26 (0.53-2.98)
Methotrexate	6.6	0.76 (0.23-2.55)	16.5	2.24 (0.77-6.56)
Opportunistic infection				
Monotherapy	1.6	Reference	1.3	Reference
Low-dose thiopurine	2.7	2.47 (0.88-6.92)	4.9	4.51 (1.13-18.1)
High-dose thiopurine	1.2	1.33 (0.32-5.43)	0.9	0.80 (0.08-7.88)
Methotrexate	12.4	13.3 (3.87-45.7)	0.0	0.00

	Infliximab		Adalimumab	
Herpes zoster				
Monotherapy	1.0	Reference	0.7	Reference
Low-dose thiopurine	2.3	3.33 (1.03-10.7)	4.0	5.38 (1.03-28.1)
High-dose thiopurine	0.8	1.39 (0.25-7.71)	0.0	0.00
Methotrexate	9.9	16.1 (3.92-66.5)	0.0	0.00

*Adjusted for prior immunomodulator use

Abbrevations: E, events; PY, person-years; HR, hazard ratio; CI, confidence interval