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Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry

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Abstract

Objective—To examine the association of methotrexate (MTX) and tumour necrosis factor (TNF) antagonists with the risk of infectious outcomes including opportunistic infections in patients with rheumatoid arthritis (RA).

Methods—Patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry prescribed MTX, TNF antagonists or other disease-modifying antirheumatic drugs (DMARDs) were included. The primary outcomes were incident overall and opportunistic infections. Incident rate ratios were calculated using generalised estimating equation Poisson regression models adjusted for demographics, comorbidities and RA disease activity measures.

Results—A total of 7971 patients with RA were followed. The adjusted rate of infections per 100 person-years was increased among users of MTX (30.9, 95% CI 29.2 to 32.7), TNF antagonists (40.1, 95% CI 37.0 to 43.4) and a combination of MTX and TNF antagonists (37.1, 95% CI 34.9 to 39.3) compared with users of other non-biological DMARDs (24.5, 95% CI 21.8 to 27.5). The adjusted

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incidence rate ratio (IRR) was increased in patients treated with MTX (IRR 1.30, 95% CI 1.12 to 1.50) and TNF antagonists (IRR 1.52, 95% CI 1.30 to 1.78) compared with those treated with other DMARDs. TNF antagonist use was associated with an increased risk of opportunistic infections (IRR 1.67, 95% CI 0.95 to 2.94). Prednisone use was associated with an increased risk of opportunistic infections (IRR 1.63, 95% CI 1.20 to 2.21) and an increased risk of overall infection at doses >10 mg daily (IRR 1.30, 95% CI 1.11 to 1.53).

Conclusions—MTX, TNF antagonists and prednisone at doses >10 mg daily were associated with increased risks of overall infections. Low-dose prednisone and TNF antagonists (but not MTX) increased the risk of opportunistic infections.

Patients with rheumatoid arthritis (RA) have an increased risk of infection compared with the general population.[1, 2] Pharmacoepidemiological studies of the risk of infection—including opportunistic infections—in patients with RA have been limited, however, and have focused primarily on tumour necrosis factor (TNF) antagonists but not methotrexate (MTX).[3, 4]

Concerns for the risk of opportunistic infections associated with immunosuppressed populations have been raised for TNF antagonists, primarily from published case series.[5–8] Opportunistic infections that have been reported in the literature include *Mycobacterium tuberculosis, Histoplasma capsulatum and Listeria monocytogenes,* among other pathogens. In September 2008 the US Food and Drug Administration (FDA) circulated a warning regarding an increased incidence of opportunistic fungal infections in patients receiving TNF antagonists. In addition to TNF antagonists, case series of opportunistic infections developing in patients with RA treated with MTX have also been reported.[9–11] Recent evidence that the combination of MTX and biological agents has superior efficacy to monotherapy with either agent alone also suggests that the potential for an additive risk of infections may be present for MTX and TNF antagonist combination therapy.[12–16]

To investigate whether the risk of infection associated with the use of MTX, TNF antagonists and combination MTX/TNF antagonist therapy is increased compared with treatment with other non-biological disease-modifying antirheumatic drugs (DMARDs), we analysed data from a cohort of patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. We examined the association of MTX and TNF antagonists with the risk of infection overall, as well as the risk of opportunistic infection in this dataset.

METHODS

Study design

A prospective cohort study was conducted using data from the CORRONA registry. The study population included patients enrolled in CORRONA who met diagnostic criteria for RA.

Source population and database

Patients with RA at participating CORRONA rheumatology practices enrolled from 1 October 2001 to 30 September 2006 with at least one follow-up visit were included. A total of 76 sites including 56 community-based and 20 academic sites in the USA enrolled patients during this period. Details of the CORRONA registry have been previously published.[17] Briefly, both physicians and patients complete detailed clinical assessment forms at enrolment and follow-up visits, including standard measures of disease activity, functional status, medical comorbidities and updated DMARD and biological agent utilisation. Follow-up assessments are completed during visits and are requested every 3 months, at which time interim events are captured. In the registry there is no standard treatment protocol or algorithm imposed to mandate drug utilisation or diagnostic testing such as screening for latent tuberculosis.

Medication data

DMARD and TNF antagonist drug utilisation data were collected prospectively at each study visit. DMARD and TNF antagonist use was categorised into the following four mutually exclusive categories for each time interval based on the treatment indicated by the rheumatologist at the beginning of that interval: (1) MTX use without TNF antagonists; (2) TNF antagonist use without MTX; (3) combination MTX and TNF antagonist use; and (4) use of other non-biological DMARDs without MTX or TNF antagonists. The three TNF antagonists adalimumab, etanercept and infliximab were considered as a class for purposes of this analysis; separate analyses for the individual TNF antagonists were not conducted. Individual patients could contribute patient-years of exposure in different drug categories over time, but drug exposure for each study interval was assigned to only one of the four categories as described above. Prednisone use was examined as a separate variable. Non-MTX non-biological DMARDs including azathioprine, cyclosporine, gold, hydroxychloroquine, leflunomide, penicillamine and sulfasalazine were grouped together for analysis; most of the use of non-biological DMARDs other than MTX was contributed by hydroxychloroquine, sulfasalazine and leflunomide.

Infection outcomes

The primary outcome of this study was physician-reported infections. Prespecified categories included infectious arthritis/bursitis, cellulitis, pneumonia (pyogenic and non-pyogenic), sepsis, sinusitis, upper respiratory infection (URI), urinary tract infection (UTI) and other infections. Rheumatologists were also asked to report opportunistic infections as a separate category and specify the infectious organism. Prespecified categories included *Cryptococcus neoformans*, varicella zoster, *Histoplasma capsulatum*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Pneumocystis jiroveci (carinii)* and other opportunistic infections.

Covariates

We selected covariates based on known risk factors for infection and factors associated with utilisation of TNF antagonists. The covariates included age, gender, race, body mass index, alcohol use, smoking history, education, duration of RA, individual American College of Rheumatology (ACR) core dataset measures (tender joint count, swollen joint count, patient global assessment, physician global assessment, patient pain score, modified Health Assessment Questionnaire and erythrocyte sedimentation rate) and ACR functional class, as well as a past history of diabetes mellitus, chronic lung disease, liver disorder, ischaemic heart disease and use of prednisone.

Statistical analysis

For each time interval between visits, patients were assigned into groups based on mutually exclusive categories defined above. If a patient discontinued a drug treatment during the interval, the portion of that interval after the discontinuation was still assigned to the category based on the treatment prescribed at the beginning of that interval. Patients could switch to a different group if their treatment changed during a subsequent interval. Person-years of exposure were calculated either from enrolment or from the time of drug initiation until drug discontinuation or the end of the study period, whichever occurred first. Rates of infection are presented as events per 100 person-years with 95% CIs. Unadjusted and adjusted incident rate ratios (IRRs) were calculated using generalised estimating equation (GEE) Poisson regression models to account for within-patient correlation due to the use of multiple time intervals for each patient. Adjusted models incorporated covariates with unadjusted associations in univariate analysis with either drug exposure or risk of infection, as well as drug interaction terms. Adjusted rates are based on the best fit Poisson regression model. All covariates other

than drug use category are fixed at the average value in the population and the incidence rates were estimated based on this model. Several sensitivity analyses were performed. First, we derived separate propensity scores for TNF antagonist use and MTX use and repeated the multivariable GEE Poisson regression models adjusting for propensity scores. In these analyses we did not include the individual ACR core set measures as covariates as their effect is subsumed within the propensity scores. Second, we considered the possible effect of channelling due to a history of prior infection and adjusted for this as a covariate. Third, we stratified on the history of prior infection and ran models for each stratum individually. Fourth, we limited the analysis to only the first exposure interval for each patient in order to eliminate any potential bias due to an order effect of changing treatments. Finally, we limited the analysis to new drug starts (incident users). All analyses were performed using Stata Version 9 (Stata Corporation, College Station, Texas, USA).

RESULTS

A total of 7971 patients with RA were followed for 15 047 patient-years. The study cohort was 74.5% female, mean (SD) age was 58.9 (13.4) years and 72.1% were rheumatoid factor (RF) positive. The baseline characteristics of the patients in the four cohorts are summarised in table 1. There were 4206 patients prescribed MTX at a mean (SD) dose of 13.2 (6.6) mg/week; 1804 patients were prescribed TNF antagonists; 2855 patients were prescribed MTX and TNF antagonist combination therapy; and 1274 patients were prescribed non-biological DMARDs other than MTX. There were 3286 patients (41.2%) prescribed oral prednisone with a mean (SD) daily dose of 5.5 (2.5) mg. Concomitant non-biological DMARDs were also prescribed in 29.5% of patients in the MTX group, 36.8% of patients in the TNF antagonist group and 15.1% of patients in the combination MTX/TNF antagonist group. Statistically significant differences ($p<0.001$) between the four groups were observed for all baseline characteristics except race, body mass index and RF status. Patients prescribed TNF antagonists and combination therapy were generally younger, more likely to be women and had higher disease activity and lower levels of physical function.

The mean (SD) follow-up period for each patient was 1.4 (0.9) years; there was no significant difference in mean follow-up time between the categories. The median (interquartile range) number of analytical intervals per patient was 3 (2, 6) and was not significantly different among groups. Only 15% of patients changed their medication category during follow-up; of these, approximately 80% had only one change.

The number and rate (per 100 person-years) of infections for the four drug exposure groups are shown in table 2. Adjusted rates of infection were significantly higher for MTX (30.9 per 100 person-years, 95% CI 29.2 to 32.7), TNF antagonists (40.1, 95% CI 37.0 to 43.4) and combination MTX/TNF antagonist therapy (37.1, 95% CI 34.9 to 39.3) than for those receiving only other DMARDs (24.5 per 100 person-years, 95% CI 21.8 to 27.5). The results were similar when further adjusted for history of previous infection (data not shown).

The distribution of infections by type of organism (opportunistic vs non-opportunistic) and site of infection is shown in table 3. The most frequent opportunistic infection was varicella zoster virus, with 56 infections in the MTX/TNF antagonist group, 32 infections in the MTX group, 26 infections in the TNF antagonist group and 7 infections in the other DMARD group. The second most common opportunistic infection was *Pneumocystis jiroveci (carinii),* with four cases in the TNF antagonist group and three cases equally distributed across the other three groups. Of note, there were three active tuberculosis infections in the MTX group and one each in the TNF antagonist group and the MTX/TNF antagonist combination group.

In the multivariable adjusted model (table 4), independent predictors of risk of overall infection included current TNF antagonist use (IRR 1.52, 95% CI 1.30 to 1.78) and current MTX use (IRR 1.30, 95% CI 1.12 to 1.50) compared with the risk associated with other non-biological DMARDs (referent group). A significant two-way interaction between use of MTX and TNF antagonists was observed (IRR 0.75, 95% CI 0.62 to 0.89, p = 0.001), indicating that the combined use of MTX and TNF was not associated with the expected multiplicative risk based on the individual risk contributions. The only ACR core set measure that was independently associated with an increased risk in the adjusted model was tender joint count.

Although low-dose prednisone use overall was not associated with risk of infection, in a multivariable model with prednisone use categorised as a daily dose of <5 mg, 5–10 mg and >10 mg, we found that prednisone use above 10 mg daily was independently associated with risk of infection (IRR 1.30, 95% CI 1.11 to 1.53, p = 0.001).

We conducted sensitivity analyses to further examine our study findings. Similar risk estimates were obtained for TNF antagonists (IRR 1.52, 95% CI 1.30 to 1.78) and MTX (IRR 1.29, 95% CI 1.12 to 1.50) in separate models incorporating propensity scores for treatment with TNF antagonists and MTX, respectively. Similar risk estimates were also obtained when analyses were limited to new (incident) users (TNF antagonists: IRR 1.46 (95% CI 1.14 to 1.86) and MTX: IRR 1.25 (95% CI 0.96 to 1.62)), albeit with wider confidence intervals. A history of infection was a significant predictor of subsequent infection (IRR 2.31, 95% CI 2.13 to 2.51). The inclusion of this variable in the base multiple variable model did not alter the results for MTX and TNF antagonists. Furthermore, in separate multivariable models stratified on history of prior infection, the use of TNF antagonists and MTX were both significantly associated with increased risk of infection (data not shown). Similar results were also noted when analyses were limited to the first drug treatment interval (data not shown).

To examine whether the increased risk of infection associated with MTX and TNF antagonist treatment was significantly different from one another, we repeated the analysis using MTX as the comparator drug (rather than other DMARDs). In this analysis we found that both TNF antagonist use (IRR 1.18, 95% CI 1.05 to 1.32) and combined MTX/TNF antagonist use (IRR 1.13, 95% CI 1.03 to 1.25) were associated with increased risk compared with MTX without a TNF antagonist.

We also modelled risk factors for incident opportunistic infections (table 5). Independent predictors of opportunistic infection included prednisone use (IRR 1.63, 95% CI 1.20 to 2.21, p = 0.002), smoking history (IRR 1.64, 95% CI 1.17 to 2.29, p = 0.004) and diabetes mellitus (IRR 1.88, 95% CI 1.19 to 2.97, p = 0.027). The risk estimate for TNF antagonists was also increased (IRR 1.67, 95% CI 0.95 to 2.94), but the confidence intervals were wider owing to small numbers of events. The only ACR core set measure independently associated with the risk of opportunistic infection in the adjusted model was physician global assessment. In sensitivity analyses, a history of prior opportunistic infection was a significant predictor of a subsequent opportunistic infection (adjusted IRR 2.24, 95% CI 1.48 to 3.40).

DISCUSSION

We examined the rate of infection in patients with RA enrolled in a large US cohort receiving one of four commonly prescribed treatment regimens and used both physician- and patient-derived data to determine the marginal effects of MTX and TNF antagonists compared with other DMARDs. We report five major findings: (1) patients treated with MTX had a higher rate of infection than those treated with other non-biological DMARDs; (2) there was an increased risk of both overall infection and opportunistic infection in patients prescribed TNF antagonists compared with other DMARDs; (3) use of low-dose prednisone was associated

with an increased risk of opportunistic infection and doses of >10 mg/day were associated with an increased risk of overall infection; (4) combination therapy with MTX and TNF antagonists was not associated with a synergistic risk compared with either agent prescribed alone; and (5) both smoking and diabetes—potentially modifiable health and lifestyle conditions—are independent risk factors for infections, including opportunistic infection, in patients with RA.

One of the primary challenges of pharmacoepidemiological studies is identifying imbalances between the treatment regimens and accounting for these differences. We addressed this issue using several approaches. First, because of the large sample size and number of infectious events, we were able to adjust for a broad array of demographic variables, clinical risk factors for infection and RA disease activity and severity variables. Unlike administrative databases, the CORRONA registry collects detailed measures of RA disease activity and severity at each study visit, thereby allowing us to control for these variables. Second, we incorporated propensity scores into our multiple variable models, predicting risk of incident infections to further account for confounding by indication. Third, we incorporated a history of prior infection to account for possible channelling bias. Our findings were robust using all of these methods.

The finding of an increased risk of incident infections for patients prescribed MTX is supported by some, but not all, previous studies.[2, 18–22] In a cohort study from the Netherlands, the risk of infection for patients with RA prescribed MTX was comparable (RR 1.52, 95% CI 1.04 to 2.22) to our study.[18] In addition, a nested case-control study from Quebec observed an increased risk of pneumonia associated with MTX use.[21] Other studies, however, have reported either the absence of an increased risk of infection with MTX[20, 22] or a reduced risk with MTX for hospitalised infection.[2] Differences in the results may be related to lower MTX dosing used in earlier decades[20, 22] and different cohort definitions. In the study by Smitten and colleagues, cases were derived from a large managed care database that lacked information on duration of disease and disease activity and severity.[2] While there was a lower proportion of MTX use among patients with RA with serious infectious episodes than among RA controls, the patients were very different from those enrolled in CORRONA and less than one-third were using any DMARD.

Second, our study strengthens existing evidence of an increased risk of infection with TNF antagonists. Conflicting evidence has emerged from clinical trials and observational studies of TNF antagonists. Although a meta-analysis of randomised controlled trials of adalimumab and infliximab demonstrated an increased risk of serious infections, these findings have been criticised due to the unbalanced duration of exposure for patients treated with placebo versus active drug.[23, 24] Moreover, two recent observational studies from the UK and a US administrative database contradict these findings, reporting no increased risk.[25, 26] In contrast to these studies, our study results are consistent with the meta-analysis, as well as other observational studies from both a European registry and US administrative databases.[27, 28] As demonstrated by Askling and colleagues,[29] differences in risk estimates for infections for patients prescribed TNF antagonists may also be attributable to differences in duration of follow-up.

Our third principal finding was that patients prescribed either low-dose prednisone or TNF antagonists had increased risk estimates of opportunistic infections compared with users of other DMARDs. The most common opportunistic infection was varicella zoster virus. Patients with RA have an almost twofold increased risk of acquiring this infection compared with the age- and sex-matched general population.[30] Smitten and colleagues, using administrative data, found that use of non-biological DMARDs, biological DMARDs and prednisone were all associated with increased risk of varicella zoster infection in patients with RA.[30] Previous studies on risk factors of opportunistic infections in patients with RA have focused primarily

on the association of TNF antagonists with *M tuberculosis.*[3, 4] The consensus recommendations of the American Thoracic Society and the Centers for Disease Control and Prevention indicate that use of prednisone at doses >15 mg daily for ≥1 month is a risk factor for *M tuberculosis.*[31] However, a recent study of more than 2.7 million patients showed that use of prednisone doses of <15 mg daily was also associated with a twofold risk of tuberculosis.[32] Our data extend these findings to an RA population examining the risk of opportunistic infection overall.

Our fourth principal finding was that combination therapy with MTX and TNF antagonists was not associated with a multiplicative risk of infection in this cohort. This observation is consistent with some, but not all, results from randomised controlled trials on the combination of MTX with TNF antagonists or other biological agents.[12, 13, 33, 34] Although the mechanisms of action of MTX and TNF antagonists remain incompletely defined, there is evidence that both can inhibit inflammatory mediators that play important roles in host defence.[35–37] The absence of a synergistic risk of infection for MTX and TNF antagonist combination therapy in our study is particularly noteworthy in light of the evidence that a combination of two biological therapies imparts an increased risk of infection.[33, 34]

One strength of our study is the size of the cohort of patients with RA with detailed clinical and drug information followed in the registry. To ensure that our findings were robust, we also integrated propensity scores into our models and performed a series of sensitivity analyses that did not alter our findings. A further strength of this study was the collection of data on all types of infections in the registry, improving our ability to detect relatively small effect sizes with greater precision. Finally, the reporting of the actual infectious organisms in the registry by the treating rheumatologist allowed us to investigate determinants of opportunistic infections as well.

Limitations of our study include the possible underestimation of mild infections occurring between study intervals. Complete on-site monitoring is probably beyond the means of any large patient registry.[28] It is also possible that we underestimated the rate of serious infections if these infections resulted in death. Although serious infections including those requiring hospitalisation or intravenous antibiotics were included in these analyses, earlier versions of the CORRONA data collection forms categorised infections based on the site of infection and type of organism (opportunistic versus non-opportunistic) rather than severity of infection. Hence, comparison of rates of serious infections with previous studies, including those reports from European registries, is not possible. However, any degree of over- or under-reporting of infections was likely to occur at random and would be unlikely to systemically bias the study. Indeed, the rates of overall infection reported in this study are slightly lower than those reported by Doran and colleagues from an inception cohort of patients with RA from Rochester, Minnesota.[1] Misclassification of infections to drug exposure intervals is another potential limitation. In addition, the possibility of confounding by indication and channelling bias cannot be entirely excluded. Our inclusion of both physician- and patient-reported measures of disease activity and severity in both the multivariable and propensity adjusted models reduces the likelihood of residual confounding by indication. Furthermore, inclusion of a history of infection, another potential reason for channelling, failed to alter the results. Finally, the statistical models assumed a constant risk of infection over time. Indeed, it is possible that the risk of infection varies with the duration of treatment with TNF blockers; this could lead to time-varying relative risks that would not have been examined in the current analyses.

In conclusion, we observed that both MTX and TNF antagonists were associated with an increased risk of infection compared with the use of other non-biological DMARDs. Use of low-dose prednisone and TNF antagonists, but not MTX, were risk factors for incident opportunistic infections. We also observed that combination MTX and TNF antagonist therapy

was not associated with a synergistic risk of infection compared with TNF antagonist monotherapy. Our study indicates that vigilance for the development of infections is indicated for patients with RA prescribed MTX, TNF antagonists and corticosteroids. Rheumatologists should continue to follow published recommendations regarding vaccination, screening for tuberculosis in patients to be treated with TNF antagonists as well as prophylaxis against other opportunistic infections, where appropriate, in order to reduce the burden of infections in patients with RA.[38]

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Table 1

Baseline characteristics of study cohort by current treatment of rheumatoid arthritis

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Female %	73.8	76.0	77.7	74.1
Age (years)	59.7 (13.4)	56.8 (13.5)	57.9 (13.2)	60.1 (13.3)
Race (white) (%)	86.8	86.7	86.2	88.2
Body mass index (kg/m^2)	29.1 (7.0)	28.9 (7.3)	29.1 (7.0)	28.6 (6.7)
College education (%)	45.7	54.6	51.4	47.5
Duration of RA (years)	9.5 (9.8)	11.4 (9.6)	11.1 (9.6)	10.1 (9.8)
RF positive (%)	71.1	72.1	74.7	72.2
Functional class >1 (%)	57.5	64.6	67.7	45.8
Physician disease activity	25.6 (21.0)	27.6 (22.0)	27.6 (21.2)	22.5 (19.8)
MHAQ score	0.3 (0.4)	0.4 (0.5)	0.4 (0.4)	0.3 (0.4)
Patient disease activity	30.5 (26.1)	32.5 (25.9)	30.9 (24.9)	28.5 (24.8)
Patient pain score	33.0 (25.9)	35.5 (26.0)	33.7 (25.6)	30.1 (24.4)
Swollen joint count (28)	5.4 (6.1)	5.1 (5.8)	5.9 (6.5)	4.1 (5.1)
Tender joint count (28)	4.2 (5.7)	4.8 (6.1)	4.7 (6.1)	3.6 (5.3)
Chronic liver disease (%)	2.3	6.0	2.8	4.1
Diabetes mellitus (%)	7.1	7.8	5.9	7.5
Smoking history (%)	19.1	19.4	17.9	22.5
Chronic lung disorder (%)	6.2	9.0	5.0	11.2
Ischaemic heart disease (%)	7.1	5.8	6.1	8.6
Current prednisone (%)	39.3	40.9	38.3	36.6
Previous other DMARDs (%)	46.6	69.4	57.1	85.7

Except where otherwise indicated, values are mean (SD).

DMARD, disease-modifying antirheumatic drug; MHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumour necrosis factor.

Table 2

Risk of infection stratified by current treatment of rheumatoid arthritis

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Number of infections	1714	890	1514	447
Person years of follow-up	5141	2130	4031	1663
Unadjusted rate/100 person-years	33.3	41.8	37.6	26.9
Adjusted rate*/100 person-years	30.9 (29.2 to 32.7)	40.1 (37.0 to 43.4)	37.1 (34.9 to 39.3)	24.5 (21.8 to 27.5)

* Adjusted rates are per 100 person-years estimated with 95% CI in parentheses. Rates were adjusted for age, gender, race, education, duration of rheumatoid arthritis, modified Health Assessment Questionnaire, functional class, physician global, patient global, patient pain, swollen and tender joint counts, body mass index, disability status, liver disorder, lung disease, diabetes, ischaemic heart disease, alcohol use, smoking and prednisone use.

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumour necrosis factor.

Table 3

Rate of specific types of infection by treatment group

	MTX (n = 4206)	TNF antagonists (n = 1804)	MTX + TNF antagonists (n = 2855)	Other DMARDs (n = 1274)
Site of infection				
URI	660 (12.8)	303 (14.2)	522 (13.0)	148 (9.0)
Sinusitis	370 (7.2)	166 (7.8)	331 (8.2)	71 (4.3)
Urinary tract	157 (3.1)	81 (3.8)	111 (2.8)	32 (2.0)
Cellulitis	59 (1.3)	49 (2.3)	71 (1.8)	18 (1.1)
Non-pyogenic pneumonia	51 (1.0)	40 (1.9)	61 (1.5)	16 (1.0)
Pyogenic pneumonia	49 (1.0)	22 (1.0)	46 (1.1)	22 (1.3)
Bursitis	9 (0.2)	5 (0.2)	7 (0.2)	3 (0.2)
Infectious arthritis	9 (0.2)	5 (0.2)	5 (0.1)	2 (0.2)
Septicaemia	8 (0.2)	8 (0.4)	10 (0.3)	4 (0.2)
Other	342 (7.0)	211 (9.9)	350 (8.7)	131 (7.9)
Type of infectious organism				
Opportunistic	84 (1.6)	63 (3.0)	101 (2.5)	28 (1.7)
Non-opportunistic	1436 (27.9)	734 (34.5)	1245 (30.9)	378 (22.7)
All types of infection	1714 (33.3)	890 (41.8)	1514 (37.6)	447 (26.9)

Frequencies listed with crude rates per 100 person-years in parentheses. Totals differ as there were individual visits and intervals in which multiple infections were reported.

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; TNF, tumour necrosis factor; URI, upper respiratory infection.

Table 4

Adjusted risk of infection in patients with rheumatoid arthritis (RA)

	Adjusted IRR (95% CI)	p Value
Current RA treatments		
TNF antagonists	1.52 (1.30 to 1.78)	<0.001
MTX	1.30 (1.12 to 1.50)	<0.001
Prednisone	1.05 (0.97 to 1.15)	0.251
Other DMARDs	Reference	–
Clinical variables		
Smoking (ever)	1.52 (1.38 to 1.67)	<0.001
Chronic lung disease	1.31 (1.15 to 1.50)	<0.001
Diabetes mellitus	1.33 (1.15 to 1.52)	0.001
Tender joint count	1.01 (1.00 to 1.02)	0.009
ACR functional class	1.23 (1.12 to 1.34)	<0.001
Body mass index	1.01 (1.00 to 1.02)	0.002

The interaction term for MTX and TNF antagonist combination therapy was significant (p = 0.001), indicating that patients on combination therapy had a reduced risk (IRR 0.75, 95% CI 0.62 to 0.89) compared with the expected multiplicative risk based on individual risk contributions.

The multivariable model included demographic variables (age, gender, race and education level) as well as the treatment and clinical variables listed in the table. Female gender (IRR 1.43, 95% CI 1.28 to 1.60) and age (IRR 0.995, 95% CI 0.99 to 1.00) were both significantly associated with the risk of infection in this model; race and education were not.

DMARD, disease-modifying antirheumatic drug; IRR, incident rate ratio; MTX, methotrexate; TNF, tumour necrosis factor.

Table 5

Adjusted risk of opportunistic infection in patients with rheumatoid arthritis (RA)

	Adjusted IRR (95% CI)	p Value
Current RA treatments		
TNF antagonists	1.67 (0.95 to 2.94)	0.077
MTX	0.93 (0.54 to 1.60)	0.781
Prednisone	1.63 (1.20 to 2.21)	0.002
Other DMARDs	Reference	–
Clinical variables		
Smoking history (ever)	1.64 (1.17 to 2.29)	0.004
Physician global assessment	1.01 (1.00 to 1.02)	0.027
Diabetes mellitus	1.88 (1.19 to 2.97)	0.027

The interaction term for MTX and TNF antagonist combination therapy was not significant (p = 0.876).

The multivariable model included demographic variables (age, gender, race and education level) as well as the treatment and clinical variables listed in the table. Other non-significant variables included were body mass index, ischaemic heart disease, chronic lung disease, duration of rheumatoid arthritis, ARA functional class, modified Health Assessment Questionnaire score, patient global score, patient pain score, swollen joint count, disability status, liver disorder and alcohol use.

DMARD, disease-modifying antirheumatic drug; IRR, incident rate ratio; MTX, methotrexate; TNF, tumour necrosis factor.