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Original article

Initiation of rheumatoid arthritis treatments and the risk of serious infections

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Abstract

Objective. In clinical trials of RA patients on traditional DMARDs, the addition of TNF-α antagonists increased infections compared with addition of placebo. Our objective was to compare serious infections following initiation of different RA regimens. Prior comparative studies of DMARD initiation have yielded conflicting results.

Methods. We estimated hospitalization rates for infections following initiation of TNF-α antagonists, other DMARDs and oral glucocorticoids in Tennessee Medicaid-enrolled RA patients (1995–2005). Exposure time was measured using pharmacy information and infections were identified using validated definitions. Initiation of RA regimens was compared using Cox regression models with MTX as the reference. Sensitivity analyses excluded glucocorticoid users, applied a first exposure carried forward approach, restricted observations to 2002–05 and first episodes of use and explored effects of unmeasured confounders.

Results. We identified 28 906 new episodes of medication use, including TNF-α antagonists (8%), MTX alone (15%) and glucocorticoids alone (57%). Compared with MTX initiation, TNF-α antagonist initiation did not significantly increase the risk of hospitalizations for pneumonia [adjusted hazard ratio (aHR) 1.61; 95% CI 0.85, 3.03] or any infection (aHR 1.31; 95% CI 0.78, 2.19). Initiation of LEF, SSZ or HCQ did not increase serious infections, compared with MTX. Both initiation and concurrent glucocorticoid use were associated with a dose-dependent increase in serious infections. Sensitivity analyses showed consistent results.

Conclusions. Compared with initiation of MTX alone, initiation of TNF-α antagonists was not associated with a large increase in the risk of serious infections. Glucocorticoid use was associated with a dose-dependent increase in the risk of these infections.

Key words: Rheumatoid arthritis, Biologic therapies, Epidemiology, Infections.

CLINICAL SCIENCE

Introduction

Although the introduction of TNF-α antagonists revolutionized the treatment of RA, concerns about the safety of these medications remain. Serious infections have been reported among users of TNF-α antagonists. Pooled data from nine randomized clinical trials of either adalimumab or infliximab found that the odds of serious infections were two times higher among RA patients randomized to TNF-α antagonists than among those randomized to placebo or MTX alone [1].

The use of TNF-α antagonists has been associated with relatively rare systemic opportunistic infections and tuberculosis [2–4]. However, the association of these medications with more common serious infections, such as pneumonia, remains debatable [5–10].

Safety information from clinical trials is limited because few trials had sufficient power to assess safety outcomes conclusively. Moreover, the selected populations

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participating in the trials warrant caution in extrapolation of safety results. Although placebo-controlled trials are widely used to study medications efficacy, placebo is not the most clinically applicable comparator when making decisions about treatment for RA. Nevertheless, few trials have provided safety data comparing initiation of TNF-α antagonists with initiation of other DMARDs [11–13].

Several randomized controlled trials of TNF-α antagonists added either placebo or TNF-α antagonists to ongoing MTX regimens [14–16]. Thus, initiators of TNF-α antagonists were compared with placebo initiators among prevalent users of MTX. Patients enrolled in these trials had disease insufficiently controlled with their current MTX regimen. In administrative databases without detailed clinical information, patients whose disease is poorly controlled are best identified by the initiation of a new therapeutic regimen. Moreover, the study of initiators (i.e. 'new users') is of interest because it avoids known selection bias in observational studies [17]. Hence, similar to the design of three other clinical trials [10–12], we compared the initiation of TNF-α antagonists with the initiation of MTX or other DMARDs on the risk of serious infections among RA patients enrolled in TennCare, the managed-care Medicaid programme in Tennessee.

Methods

TennCare provides health-care insurance to those who are Medicaid eligible and those who are uninsured or lack other access to health care. We assembled a retrospective cohort of RA patients, who were identified with one or more RA-coded (ICD9-CM: 714.**, except Juvenile Rheumatoid Arthritis [714.3*]) health-care encounters and a prescription filled for a DMARD. RA was also defined by two or more RA-coded encounters (⩾30 days apart) and an oral glucocorticoid prescription filled [18].

The cohort was restricted to RA patients with new episodes of DMARD use, which should reduce bias related to the inclusion of prevalent users in the study of medication effects [17]. A new episode of DMARD use started when an RA patient filled a prescription for a DMARD or glucocorticoid (t_0) from 1995 to 2005, and had no prescription filled for the medication of interest during the 180 days preceding the fill date (baseline). As of t_0, cohort members were aged ⩾18 years, had at least 180 days of continuous enrolment in TennCare and had filled one or more prescriptions for any medication during baseline (to assure active use of pharmacy benefits and active medical surveillance).

Since some medical conditions could reduce follow-up and/or increase the risk of infections regardless of medication exposure, we excluded patients with solid organ transplantation, HIV/AIDS, cancer and serious kidney, liver or respiratory diseases, identified at baseline. We also identified and excluded patients who had two or more health-care encounters (⩾30 days apart) coded for JRA, SLE, Crohn's disease or ulcerative colitis during baseline (although some of these patients would receive DMARDs, their risk of infections could be different from RA patients).

New episodes of use began on t_0 and continued through the earliest of the following dates: death, loss of enrolment, study outcome or 180th day of follow-up. We restricted the follow-up to 180 days because previous research suggested an increased risk of infections during the first months of use of TNF-α antagonists [5, 8, 10]. Moreover, a previous study in this population indicated short persistence on initial DMARD regimens [19], making the long-term classification of exposure person-time problematic. This strategy allowed the isolation of follow-up time after initiation of DMARD use and the assessment of study outcomes and medication adherence. Patients who left the cohort could subsequently re-enter and contribute new episodes of medication use if they fulfilled selection criteria.

Exposures

Study DMARDs included TNF-α antagonists (etanercept, infliximab and adalimumab), LEF, SSZ, HCQ and MTX. New episodes of DMARD use were identified applying a hierarchical algorithm to maximize the identification of newer and less frequently used study DMARDs in TennCare. This hierarchy was: TNF-α antagonists, LEF, SSZ, HCQ and MTX [20]. We also identified new episodes of use of oral glucocorticoids. This last group was stratified according to the estimated average daily dose of prednisone equivalents that the patient was initiating [⩽7.5 (low), 7.5–30 (medium) and >30 mg (high)] [21, 22]. For each new episode of use, the 180 person-days following initiation were included as part of a defined follow-up time. Once identified, these person-days could not be included as part of new use of another medication group.

To calculate person-time exposed to a study medication, we aggregated the person-time from t_0 through the earliest of: end of the episode, death, loss of enrolment, occurrence of a study outcome, switch to another DMARD regimen or the discontinuation of the current regimen (defined as 14 days without medication). This approach reduced the potential misclassification introduced by concurrent use of other non-study DMARDs and allowed a short gap in which outcomes identified after drug supply exhaustion could be related to the most recent exposure. The TNF-α antagonist group allowed the concurrent use (continuation or addition) of MTX; all other exposure episodes ended with the addition of another DMARD [6, 8, 20]. Concurrent use of glucocorticoids was allowed among initiators of DMARDs, but initiation of DMARDs ended a glucocorticoid episode.

Outcomes

Study outcomes were serious infections that required hospitalization [5, 6, 23]. These infections were identified using computerized definitions based on principal discharge diagnoses [6, 24, 25]; and pneumonia, the most common serious infection in our cohort, was assessed separately; whereas, due to small number of events, all serious infections were aggregated into a

composite outcome. Based on medical-chart reviews, computerized definitions for serious infections showed high positive predictive value in identifying study outcomes among TennCare RA patients [24]. The identification of systemic opportunistic infections is challenging in administrative databases and those rare infections were not included in this study.

Potential confounders

To control for potential confounders, we measured covariates during baseline including demographics: age, gender, race, residence (urban, suburban and rural), nursing home/community dwelling and calendar year; generic markers of comorbidity: number of hospitalizations, outpatient and emergency-room visits, enrolment in TennCare based on disability, number of different medication classes filled; surrogate markers of disease severity: extra-articular manifestations of disease, number of IA and orthopaedic procedures, number of laboratory tests ordered for inflammatory markers and days of drug supply for other DMARDs, oral glucocorticoids, NSAIDs and narcotics [5, 6, 18, 20, 26]; and risk factors for infections: previous hospitalization due to infection, chronic obstructive pulmonary disease (COPD), diabetes and previous use of antibiotics [6]. Among DMARD initiators, the average daily dose of oral glucocorticoids at t_0 was categorized as described above.

Statistical analysis

Since MTX is considered to be the cornerstone of RA treatment and was the most prevalent DMARD used [20], initiation of MTX served as the reference for all comparisons [27, 28]. Cox proportional hazard regression models assessed the association between medication exposure and outcomes. Person-time of continuous exposure (including <14-day gaps) represented time at risk. Since patients could contribute one or more episodes of new use (with an updated set of covariates), we accounted for this clustering of observations using patient's study numbers to define clusters and accounted for this additional intra-group correlation using the Huber–White 'sandwich' variance estimator and calculated robust S.E. for all estimates [29]. The proportional hazard assumption was verified using generalized linear regressions of Schoenfeld residuals on functions of time [30].

Because of limited number of outcomes by exposure group, we summarized the distribution of covariates using propensity scores. A multinomial logistic regression model was fitted to estimate the probability of initiating use of each study medication regimen using MTX as the reference [31]. The visual inspection of the distribution of predicted probabilities across exposure groups indicated appropriate overlap. Calendar year and the average daily dose of glucocorticoids among DMARD initiators were not included in the propensity score model, but were added to the final outcome models to assess their effects independently.

Specific measurements of RA disease severity were not available in our data. Although our strategies accounted for constructs that correlated with RA disease severity, residual confounding could persist. Hence, we explored the potential effect of an unmeasured confounder, using an array-based sensitivity analysis [32, 33]. All analyses were done in Stata 10.1, and this study was approved by the Vanderbilt University IRB and by the Bureau of TennCare.

Results

There were 21 981 TennCare enrollees who met our RA definition. After application of selection criteria, our cohort encompassed 14 586 (66%) RA patients (Fig. 1). These RA patients contributed 28 906 new episodes of medication use, including TNF-α antagonists with or without MTX (8%), LEF (4%), SSZ (4%), HCQ (12%), MTX (15%) and glucocorticoids (57%).

Initiators of TNF-α antagonists had more orthopaedic procedures, inflammatory markers assessed and joint aspirations performed during baseline than other groups. Moreover, the baseline use of DMARDs, NSAIDs and narcotics was consistently higher among initiators of TNF-α antagonists, suggesting higher disease severity, compared with other groups. Initiators of TNF-α antagonists were also more likely to be enrolled in a TennCare disability category and to be urban residents than initiators of other regimens (Table 1).

Initiators of LEF, MTX or glucocorticoids were older than other groups. Initiators of MTX or glucocorticoids were also more likely to be nursing-home residents, and had more hospitalizations and emergency department visits, suggesting more frailty than other groups. Patients initiating MTX were the most likely of all groups to be using high doses of glucocorticoids at t_0. Initiators of glucocorticoid regimens were more likely to have a history of smoking-related diseases, COPD, a previous infection

Fig. 1 Selection criteria and cohort assembly. RA TennCare cohort, 1995–2005.

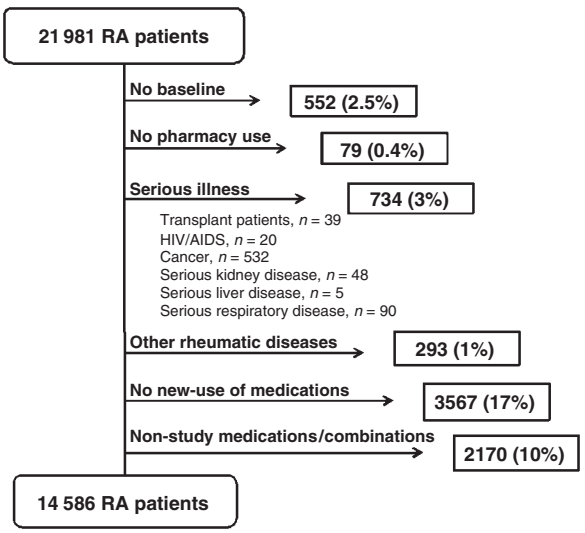

TABLE 1 Characteristics of RA patients initiating new episodes of medication use, RA TennCare cohort, 1995–2005

New episodes of use, *n*	TNF-α antagonists 2192	LEF 1097	SSZ 1283	HCQ 3398	MTX 4355	GC (low dose) 2058	GC (medium dose) 11 117	GC (high dose) 3406	*P*-value
Age, median (IQR), years	54 (45–62)	56 (48–64)	52 (42–61)	52 (43–62)	55 (45–64)	57 (47–67)	55 (45–65)	55 (45–64)	<0.001
Female	74.86	77.03	68.04	81.11	76.21	77.75	76.38	75.60	<0.001
Race									<0.001
White	83.90	84.32	84.88	79.64	80.60	80.47	84.72	84.44	
Black	12.73	13.49	12.70	18.01	16.67	17.15	13.28	13.30	
Other	3.38	2.19	2.42	2.35	2.73	2.38	2.01	2.26	
Residence									<0.001
Rural	47.40	50.41	54.25	52.77	51.76	59.52	59.64	55.23	
Sub-urban	27.14	25.80	23.54	24.51	26.80	19.97	22.39	24.05	
Urban	25.46	23.79	22.21	22.72	21.45	20.51	17.97	20.73	
Disability	69.75	67.37	61.26	58.92	60.16	62.15	64.08	65.27	<0.001
Nursing home resident	0.64	0.82	0.62	1.12	1.65	3.50	1.91	1.88	<0.001
Markers of disease activity									
RA visit in baseline	87.18	88.61	71.78	63.39	70.47	41.11	36.20	33.35	<0.001
Extra articular disease	1.23	3.01	1.56	2.24	1.19	0.92	0.88	1.06	<0.001
Orthopaedic surgeries	26.55	25.34	23.30	20.42	20.94	20.31	18.71	18.32	<0.001
Inflammatory markers	42.11	34.28	33.20	37.26	32.61	17.15	14.99	13.83	<0.001
Joint aspirations	21.44	20.42	19.02	15.92	16.74	15.74	13.73	13.12	<0.001
Concurrent GC use on t_0									<0.001
⩽7.5 mg/day	70.26	67.91	74.67	77.02	70.31	–	–	–	
7.5–30 mg/day	25.36	28.08	21.67	19.39	24.52	–	–	–	
>30 mg/day	4.38	4.01	3.66	3.59	5.17	–	–	–	
No. of inj. GC									<0.001
0	77.83	83.68	83.40	81.61	80.53	78.43	81.51	82.41	
1	8.67	6.93	8.42	8.59	8.01	6.46	8.30	7.57	
⩾2	13.50	9.39	8.18	9.80	11.46	15.11	10.19	10.01	
No. of days on DMARDs, median (IQR)	160 (56–180)	101 (0–180)	0 (0–97)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	<0.001
No. of days on NSAIDs, median (IQR)	59 (0–162)	52 (0–155)	37 (0–128)	30 (0–118)	39 (0–120)	30 (0–136)	30 (0–125)	30 (0–125)	<0.001
No. of days on narcotics, median (IQR)	78 (7–180)	44 (0–142)	15 (0–99)	19 (0–105)	22 (0–97)	30 (0–157)	30 (0–141)	37 (0–153)	<0.001
Other risk factors for infections									
Diabetes	12.86	11.21	10.37	10.92	12.33	11.37	10.07	10.80	<0.001
Infection	5.20	5.56	3.27	4.91	5.30	6.22	6.29	5.96	<0.001
No. of days on antibiotics, median (IQR)	25 (5–104)	30 (5–107)	16 (0–56)	10 (0–30)	10 (0–38)	16 (0–51)	17 (1–47)	16 (2–45)	<0.001
Smoking-related disease	7.62	7.38	6.00	5.50	6.22	7.34	7.48	9.45	<0.001
COPD	9.67	11.85	9.98	10.18	10.75	14.63	16.48	19.64	<0.001
Health-care utilization									
Baseline hospitalizations									<0.001
0	81.25	79.31	82.00	80.40	78.92	76.87	76.84	75.69	
1	13.37	14.13	13.17	13.39	14.26	14.87	15.52	16.24	
⩾2	5.38	6.56	4.83	6.21	6.82	8.26	7.65	8.07	
Baseline ED visits									<0.001

(continued)

Table 1 Continued

New episodes of use, *n*	TNF-α antagonists 2192	LEF 1097	SSZ 1283	HCQ 3398	MTX 4355	GC (low dose) 2058	GC (medium dose) 11 117	GC (high dose) 3406	*P*-value
0	69.75	68.55	68.28	63.48	65.26	61.71	57.61	53.02	
1	19.16	18.69	18.39	20.48	18.81	20.60	22.38	24.16	
2	5.38	6.47	5.77	7.89	7.51	7.29	9.21	10.13	
⩾3	5.70	6.29	7.56	8.15	8.43	10.40	10.80	12.68	
No. of different drugs, median (IQR)	14 (10–20)	13 (9–18)	11 (7–16)	12 (7–17)	11 (7–17)	13 (8–19)	13 (8–19)	14 (9–20)	<0.001
No. of outpatient visits, median (IQR)	6 (4–9)	6 (3–9)	5 (3–8)	5 (3–8)	5 (3–8)	5 (2–8)	5 (2–8)	5 (2–8)	<0.001

Values indicate percentages unless otherwise specified. GC: glucocorticoid (low dose: <7.5 mg; medium dose: 7.5–30 mg; high dose: >30 mg of prednisone equivalents per day); ED: emergency department; IQR: interquartile range.

Table 2 HRs for pneumonia and any infection requiring hospitalization, RA TennCare cohort (1995–2005)

	Number of episodes	Time, median (IQR), days*	Events	Crude HR (95% CI)	Age, gender-adjusted HR (95% CI)	PS-adjusted HR[a] (95% CI)
Pneumonia						
MTX	4355	60 (41–133)	32	1.00 (reference)	1.00 (reference)	1.00 (reference)
TNF-α antagonists	2192	68 (27–168)	19	1.17 (0.67, 2.05)	1.28 (0.73, 2.24)	1.61 (0.85, 3.03)
LEF	1097	43 (20–114)	11	1.64 (0.79, 3.39)	1.64 (0.79, 3.39)	1.65 (0.77, 3.54)
SSZ	1283	43 (28–51)	3	0.47 (0.14, 1.53)	0.51 (0.16, 1.68)	0.60 (0.19, 1.97)
HCQ	3398	43 (43–120)	27	1.11 (0.67, 1.85)	1.20 (0.72, 2)	1.24 (0.73, 2.08)
Glucocorticoids (low dose)[b]	2058	34 (23–43)	17	2.00 (1.1, 3.64)	1.71 (0.94, 3.1)	2.30 (1.2, 4.41)
Glucocorticoids (medium dose)	11 117	19 (19–23)	53	2.08 (1.31, 3.3)	1.92 (1.22, 3.01)	2.36 (1.44, 3.87)
Glucocorticoids (high dose)	3406	19 (18–25)	30	3.91 (2.31, 6.62)	3.67 (2.19, 6.15)	4.33 (2.49, 7.54)
Any infection						
MTX	4355	60 (41–133)	55	1.00 (reference)	1.00 (reference)	1.00 (reference)
TNF-α antagonists	2192	67 (27–167)	29	1.04 (0.66, 1.64)	1.12 (0.71, 1.77)	1.31 (0.78, 2.19)
LEF	1097	43 (20–114)	16	1.39 (0.78, 2.48)	1.39 (0.78, 2.48)	1.48 (0.81, 2.69)
SSZ	1283	43 (28–51)	9	0.82 (0.4, 1.66)	0.89 (0.44, 1.8)	1.03 (0.51, 2.1)
HCQ	3398	43 (43–119)	44	1.06 (0.71, 1.56)	1.13 (0.76, 1.67)	1.20 (0.81, 1.79)
Glucocorticoids (low dose)[b]	2058	34 (23–43)	21	1.46 (0.88, 2.43)	1.28 (0.77, 2.13)	1.62 (0.94, 2.78)
Glucocorticoids (medium dose)	11 117	19 (19–23)	90	2.12 (1.47, 3.05)	1.98 (1.38, 2.83)	2.39 (1.63, 3.51)
Glucocorticoids (high dose)	3406	19 (18–25)	43	3.37 (2.19, 5.19)	3.21 (2.1, 4.9)	3.72 (2.37, 5.84)

[a]PS-adjusted HRs accounted for all study covariates. [b]Low dose: <7.5 mg; medium dose: 7.5–30 mg; high dose: >30 mg of prednisone equivalents per day. PS: propensity score; IQR: interquartile range.

hospitalization and to be residents of rural areas. Initiators of glucocorticoids had less extra-articular disease, orthopaedic surgeries, assessments of inflammatory markers or joint aspirations than other groups. By definition, glucocorticoid initiators were non-users of these drugs during baseline (Table 1).

Pneumonia hospitalizations

There were 3842 person-years of follow-up and 192 pneumonia hospitalizations, yielding five pneumonia hospitalizations per 100 person-years. Compared with initiators of MTX, the risk of pneumonia hospitalizations was not significantly increased among initiators of TNF-α antagonists [adjusted hazard ratio (aHR) 1.61; 95% CI 0.85, 3.03]. Similarly, the risk of pneumonia was not increased among initiators of LEF, SSZ or HCQ compared with MTX. However, the risk of pneumonia hospitalizations was consistently increased with initiation of glucocorticoids (aHR 2.30, 2.36 and 4.33 for low, medium and high doses, respectively) (Table 2). In addition, baseline use of medium and high doses of glucocorticoids were

associated with increased pneumonia risk compared with low doses or no use (aHR 1.92; 95% CI 1.25, 2.95 and aHR 3.56; 95% CI 1.85, 6.85 for medium and high doses, respectively).

Serious infections hospitalizations

For the serious infections composite outcome, there were 3831 person-years of follow-up and 307 hospitalizations yielding eight serious infection-related hospitalizations per 100 person-years. Serious infections included 192 (63%) cases of pneumonia, 27 (9%) sepsis/septicaemia, 44 (14%) pyelonephritis, 37 (13%) cellulitis, 2 (1%) septic arthritis, 1 (0.3%) endocarditis, 1 (0.3%) meningitis and 3 (1%) osteomyelitis.

Hospitalizations due to serious infections were not significantly increased among initiators of TNF-α antagonists (aHR 1.31; 95% CI 0.78, 2.19), compared with initiation of MTX. Initiation of LEF, SSZ and HCQ did not increase serious infections, compared with MTX. Initiation of oral glucocorticoids was consistently associated with an increased risk of serious infections (aHR 1.62, 2.39 and 3.72 for low, medium and high doses, respectively). Furthermore, baseline use of medium and high doses of glucocorticoids were associated with increased serious infections risk compared with low doses or no use (aHR 1.78; 95% CI 1.26, 2.52 and aHR 3.72; 95% CI 2.26, 6.13, respectively).

Sensitivity analyses

Our findings were robust to a number of planned sensitivity analyses. After exclusion of patients initiating glucocorticoids with prescriptions of <30 days supply (14 565 episodes), the association of glucocorticoid initiation and the risk of serious infections remained (e.g. aHR 1.59; 95% CI 0.82, 3.10; aHR 2.23; 95% CI 1.31, 3.80; and aHR 1.69; 95% CI 0.51, 5.57 for low, medium and high doses, respectively). Furthermore, the daily dose of glucocorticoid used at the time of DMARD initiation was consistently associated with the study outcomes in all analyses and after exclusion of all glucocorticoid exposure groups from the analyses. Restricting analyses to episodes that started in 2002–05 (14 672 episodes excluded) showed similar patterns. Restricting the analyses to the first episode per patient (14 320 episodes excluded) and analyses using propensity scores quintiles also yielded similar results. Finally, analyses of drug initiation without regard to subsequent regimen changes (first exposure carried forward) yielded similar conclusions although most HRs were closer to the null (Table 3).

Since RA disease severity would increase the risk of infections [34] and TNF-α antagonist initiators had more surrogates of disease severity than other groups, our study HRs comparing initiation of TNF-α antagonists with initiation of MTX would overestimate the real HR [6]. Thus, the fully adjusted HR, accounting for RA disease severity, would be closer to the null (for a quantitative sensitivity analysis, see supplementary data available at *Rheumatology* Online).

Table 3 Sensitivity analyses exploring the HR of serious infections associated with initiation of TNF-α antagonists use, RA TennCare cohort, 1995–2005

Sensitivity analysis	Serious infection, PS-adjusted HR[a] (95% CI)
Main analysis	1.31 (0.78, 2.19)
Excluding GC initiators with <30 days supply	1.20 (0.68, 2.13)
Excluding all GC initiators	1.39 (0.79, 2.44)
Restricted to 2002–2005	1.33 (0.69, 2.56)
Restricted to first episode per subject	1.23 (0.50, 3.03)
Adjustment using PS quintiles	1.19 (0.71, 1.99)
First exposure carried forward[b]	1.15 (0.83, 1.60)

[a]All HRs considered MTX as reference. PS-adjusted HRs accounted for all study covariates. [b]Based on initiation of medication use only. GC: glucocorticoids; PS: propensity scores.

Discussion

Our findings indicate that among RA patients enrolled in TennCare, initiation of TNF-α antagonists was not associated with a large increase in the risk of serious infections requiring hospitalization compared with initiation of MTX. However, compared with MTX, the initiation of glucocorticoid regimens increased the risk of serious infections.

Although most randomized clinical trials reported effects of TNF-α antagonists compared with placebo in patients who continue traditional DMARDs, few trials provided information on the risk of serious infections comparing initiation of TNF-α antagonists with initiation of MTX. Available data suggested that infliximab increased the risk of serious infections compared with initiation of MTX [11], whereas initiation of either adalimumab [12] or etanercept [13] did not. A pooled estimate of these three randomized trials comparing initiation of TNF-α antagonists with initiation of MTX yielded an overall risk ratio of 1.48 (95% CI 0.93, 2.35), encompassing the estimates reported in this study.

We considered some of the methodological challenges that could explain differences in results of observational studies in this area [35]. Previous research suggested a time-dependent risk of infections after initiation of TNF-α antagonists [5, 8, 10]. To assure comparability of exposure groups, we applied a new-user design and focused on the period immediately after treatment initiation [17]. We reduced exposure misclassification by using pharmacy data to classify each day of follow-up during the new episodes of medication use. To reduce outcome misclassification, we identified infections using algorithms that had previously shown high positive predictive values in our population [24]. Furthermore, although direct measurements of disease severity were not available, adjustment for measured covariates (including surrogates

for disease severity) was performed and the potential role of unmeasured confounders was examined.

In our study, patients initiating TNF-α antagonists had an increased prevalence of surrogates for severe RA, suggesting channeling of patients with severe disease to these medications. However, TNF-α antagonists initiators were younger and had more baseline exposure to DMARDs than MTX initiators, suggesting that TNF-α antagonist initiators were less frail than MTX initiators. Adjustment for these latter factors resulted in increased HRs for TNF-α antagonists initiators. Although residual confounding could not be ruled out, our sensitivity analyses indicated that improving our imperfect adjustment for disease severity would reduce our HR within the confidence intervals of our estimate (see supplementary data available at *Rheumatology* Online) [6, 35].

Glucocorticoid use increased the risk of serious infections requiring hospitalizations consistently and in a dose-dependent manner, compared with MTX initiation. Although glucocorticoid use could also be a surrogate for severe RA, these associations persisted after adjustment for measured confounders and in a number of sensitivity analyses. Furthermore, these findings are consistent with results from randomized clinical trials and from previous observational studies [5–7, 36].

A retrospective cohort study of 609 RA patients reported 3.1 pneumonia hospitalizations per 100 person-years, but was not restricted to patients exposed to DMARDs [37]. Although our crude pneumonia hospitalization rate was 5/100 person-years, this likely reflects a sicker population of RA patients enrolled in a Medicaid plan and initiating DMARDs or glucocorticoids and observed during the initial months of medication use, when the risk for infections is considered to be the highest [5, 6, 8].

Since several DMARD therapies require months to achieve a satisfactory response, we hypothesized that studying medication effects during a short, defined follow-up time after initiation would maximize the potential for complete persistence. However, both stopping and switching were common shortly after initiation of a new DMARD [19]. We reduced the potential effects of changes in exposure categories by studying new episodes of medication use and by truncating the exposure follow-up when an original study regimen was changed. A sensitivity analysis based on initiation of regimens ignoring subsequent regimen changes showed results consistent with our main findings.

Our study has several limitations. First, although pharmacy files provide excellent information on medications dispensed through TennCare and they are virtually free of information bias [38], the actual use of these medications is unknown. Even though use of medications filled outside the system could not be ruled out, we consider this unlikely because cohort members had full access to TennCare pharmacy benefits and because some medications, such as TNF-α antagonists, are expensive. Secondly, we relied on coded information to identify study outcomes. Misclassification makes it more difficult to demonstrate true associations [5, 24]. However, we minimized outcome misclassification by using computerized definitions that were previously validated in our population [24]. Thirdly, we had insufficient numbers to evaluate the role of specific TNF-α antagonists on serious infections. Furthermore, the relatively short, exposed person-time during episodes of medication use limited our power to detect small increases in the risk of serious infections. Indeed, our findings are also consistent with up to a 2-fold increased risk of serious infections hospitalization. Finally, TennCare enrollees may not be representative of the general population.

In conclusion, we found no increased risk of hospitalizations due to serious infections among initiators of TNF-α antagonists compared with initiators of MTX. Although we could not rule out small increases in risk or differences between TNF-α antagonists, our results were robust to a number of sensitivity analyses and we did not observe significant increases in the risk of infections among other DMARD regimens commonly used in our population. However, our study demonstrated a strong association between glucocorticoid use (especially at high doses) and the risk of serious infections requiring hospitalization among RA patients.

Rheumatology key messages

- TNF-α antagonist initiation was not associated with a large increase in serious infections, compared with MTX.
- Glucocorticoid use was associated with a dose-dependent increase in the risk of serious infections.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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