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Review

Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry

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ABSTRACT

Objective: To evaluate the risk of serious infections (SIs) in RA patients receiving anti-TNF therapy on the basis of the data included in the GISEA register.

Methods: The study involved 2769 adult patients with long-standing RA (mean age 53.2 ± 13.4 years; mean disease duration 9.0 ± 8.3 years) enrolled in the GISEA register, who had been treated for at least 6 months with TNF inhibitors or had discontinued therapy due to SI: 837 (30%) treated with infliximab (IFN), 802 (29%) with adalimumab (ADA), and 1130 (41%) with etanercept (ETN).

Results: 176 patients had experienced at least one of the 226 Sis during the 9 years of treatment with an anti-TNF agent, an overall incidence of 31.8/1000 patient-years (95% CI 25.2–38.3): 23.7/1000 patient-years (95% CI 13.1–34.2) on ADA; 12.8/1000 patient-years (95% CI 6.3–19.4) on ETN and 65.1/1000 patient-years (95% CI 48.4–81.8) on IFN. The risk was higher in the first than in the second year of treatment, but this difference was not statistically significant ($p = 0.08$) (38.9% of the SIs were recorded in the first 12 months of treatment). The risk of SI was significantly different among the three treatment groups ($p < 0.0001$). Multivariate models confirmed that the use of steroids ($p < 0.046$), concomitant DMARD treatment during anti-TNF therapy ($p = 0.004$), advanced age at the start of anti-TNF treatment ($p < 0.0001$), and the use of IFN or ADA rather than ETN (respectively $p < 0.0001$ and $p = 0.023$) were strong and statistically significant predictors of infection.

Conclusions: Anti-TNF therapy is associated with a small but significant risk of SI that is associated with the concomitant use of steroids, advanced age at the start of anti-TNF treatment, and the type of anti-TNF agent.

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Contents

1. Introduction

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory condition that can lead to significant disability and joint pain [1]. It is associated with increased mortality and comorbidity due to a number of causes including infection [2,3]. Infections are frequent in patients with rheumatic diseases (the incidence is almost double that observed in matched controls), and this may be related to the disease itself (altered immunological function, disability, immobility, joint surgery), extra-articular manifestations of RA and comorbidities or the drugs used to treat it (particularly immunosuppressants and steroids) [3–5]. Many trials have shown that anti-tumour necrosis factor (TNF) drugs significantly improve the signs and symptoms, function, radiographic progression and quality of life of patients with early or long-standing RA [6–9].

However, TNF also plays an important role in host defence [10], and the British Society for Rheumatology Biologics Register (BSRBR) initially found a 20% non-significant increase in the rate of serious infections (SIs) between TNF-treated patients and controls [11], even though there was an increase of infections due to intracellular bacterial species (e.g. Listeria, Salmonella) and more specifically *Mycobacterium tuberculosis* [11,12]. In a subsequent paper a small but significant overall risk of SI was observed [13]. The same has also been reported by the German and Swedish Biologics Registries [14,15]. The Lombardy Rheumatology Network (LORHEN) registry found that the overall rate of SI (35.9 per 1000 patient-years) was significantly lower than those reported in other post-marketing observational studies, but substantially similar to those reported in phase III randomized controlled trials (RCTs) [16]. The most frequent were lower respiratory tract infection, particularly pneumonia. There were no differences between the individual anti-TNF agents, but an increased risk was associated with age, the erythrocyte sedimentation rate (ESR) and the use of steroids [16].

The aim of this study was to evaluate the risk of SI in patients with RA treated with the three anti-TNF agents licenced in Italy between 2001 and 2005 (infliximab [INF], etanercept [ETN] and adalimumab [ADA]) using data from the GISEA (Gruppo Italiano Studio Early Arthritis) Register.

2. Methods

The nationwide GISEA registry, which started in 2008, records patients under TNFa blockers dating back to 1999, and prospectively all patients from 2008 onward [17]. It registers and monitors rheumatic patients treated with biological drugs on the basis of standard clinical care at hospital and community-based rheumatology units throughout Italy. The registry was approved by the local Ethics Committees, and patients aged ≥18 years were enrolled after giving their written informed consent.

This analysis was restricted to patients registered with the GISEA who had been diagnosed by a rheumatologist as having RA and who had received at least one infusion or filled a prescription for INF, ETN or ADA [18]. All of the patients were treated in accordance with the Italian Society of Rheumatology guidelines for the use of anti-TNF agents: a diagnosis of RA (ACR criteria); a failure to respond to at least one course of combined therapy with full-dose traditional DMARDs, one of which should always be methotrexate (MTX) unless contraindicated; and active disease as defined by a 28-joint disease activity score (DAS28) of >3.5 [19].

At the time an anti-TNF agent is started, the rheumatologist completes a standardised form indicating the patient's age, gender, diagnosis, disease duration and current disease activity, including swollen and tender joint counts (28 joints), the erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels, well as a patient global assessment. In addition to being evaluated individually, these measures were also used to compute the DAS28 and define whether the patient is a treatment responder on the basis of the EULAR criteria [20]. Details of the past and present anti-rheumatic therapies and current co-morbidities are also recorded, and the patient is asked to complete a separate questionnaire, including the Italian adaptation of the Health Assessment Questionnaire (HAQ) [21]. Data concerning changes in treatment, disease activity and the occurrence of adverse events are captured every 6 months, including all episodes of infections occurring during biological therapy that require medical care and are documented by a physician. All of the infections are classified as “serious” (defined as life-threatening, requiring hospitalisation and/or intravenous antibiotic therapy, or leading to significant disability/incapacity or a comparable significant risk) or “non-serious”, defined as any other infectious episode.

This study included all of the patients who had been treated for at least 6 months with TNF inhibitors or had discontinued therapy earlier due to SI. If the patients had switched to a second or subsequent anti-TNFα drug, only the time and adverse events data relating to their first drug was used in the analysis.

2.1. Statistical analysis

The incidence rates (IRs) and Poisson's 95% confidence intervals (CIs) were calculated from the observed number of events and the number of person-years at risk; the IRs and 95%CIs of all infections and tuberculosis (TB) cases were estimated in the population as a whole and on the basis of specific baseline characteristics (age at the start of therapy, disease duration, DAS28 score, HAQ score, concurrent use of DMARDs and steroids, the presence of comorbidities, and the first anti-TNFα treatment).

The uni- and multivariate analyses were made using Cox regression models to identify the independent predictors of the primary endpoint.

The Kruskal–Wallis test, the Mann–Whitney non-parametric test, Pearson's chi-squared test and Fisher's exact test were used to evaluate the differences in the continuous and categorical variables between the three treatment groups. All of the analyses were made

Table 1
Baseline demographic and clinical data of the RA patients in the GISEA Register.

	All patients 2769	Infliximab 837 (30.2%)	Adalimumab 802 (29.0%)	Etanercept 1130 (40.8%)	p
Age (years)	53.18 ± 13.35	52.98 ± 12.93	53.84 ± 12.65	52.85 ± 14.14	ns
Females	2277 (82.2%)	673 (80.4%)	672 (83.8%)	932 (82.5%)	ns
Males	492 (17.8%)	164 (19.6%)	130 (16.2%)	198 (17.5%)	ns
Disease duration (years)	9.02 ± 8.34	9.08 ± 8.06	9.07 ± 8.57	8.95 ± 8.40	ns
DAS28	5.63 ± 1.34	5.81 ± 1.26	5.41 ± 1.31	5.64 ± 1.40	<0.0001
DI-HAQ	1.40 ± 0.72	1.56 ± 0.69	1.16 ± 0.65	1.44 ± 0.74	<0.0001
RF positive	2008 (72.5%)	662 (79.1%)	559 (69.7%)	794 (79.1%)	0.0009
Comorbidity	1407 (50.8%)	475 (56.8%)	416 (51.9%)	516 (45.6%)	<0.0001
DMARD therapy	1174 (42.4%)	420 (50.2%)	326 (40.6%)	428 (37.9%)	<0.0001
Corticosteroid therapy	1130 (40.8%)	373 (44.6%)	309 (38.5%)	448 (39.6%)	0.02

DAS 28 = Disease activity score; DI-HAQ = Disability Index-Health Assessment Questionnaire; RF = Rheumatoid factor: DMARDs = Disease-modifying antirheumatic drugs. Continuous variables expressed as mean values ± SD. ns: not statistically significant.

using SAS version 9.2 (SAS Institute, Inc; Cary, NC), and a p value of 0.05 or less was considered statistically significant.

3. Results

The clinical records of 2769 adult patients with long-standing RA (mean age 53.2 ± 13.4 years; mean disease duration 9.0 ± 8.3 years) were analysed: 837 (30%) treated with infliximab (IFN), 802 (29%) with adalimumab (ADA), and 1.130 (41%) with etanercept (ETN) (Table 1).

One hundred and seventy-six patients had experienced at least one of the 226 SIs during the 9 years of treatment with an anti-TNF agents. Table 2 shows their clinical characteristics. Their mean age was 57.39 ± 11.6 years, and the mean duration of RA was 10.75 ± 8.92 years; 121 (68.5%) were positive for rheumatoid factor (RF), and 85 (48.3%) had comorbidities, including diabetes mellitus (n = 13), chronic obstructive pulmonary disease, asthma or pulmonary interstitial fibrosis (n = 14), chronic nephropathy (n = 1), and chronic hepatitis (n = 6). In combination with the biological drug, 109 (61.9%) of the patients received steroids (mean dose 5.80 ± 3.78 mg/day) and 117 (66.5%) at least one DMARD (63.6% methotrexate at a median dose of 11.02 ± 2.92 mg/week).

The overall incidence was 31.8/1000 patient-years of follow-up (95% CI 25.2–38.3): 23.7/1000 patient-years (95% CI 13.1–34.2) among those treated with ADA; 12.8/1000 patient-years (95% CI 6.3–19.4) among those treated with ETN; and 65.1/1000 patient-years (95% CI 48.4–81.8) among those treated with IFN. The risk was higher during the first 12 months of treatment (38.9% of all of the SIs were recorded in the first 12 months) than during the second 12 months, but the difference was not statistically significant (p = 0.08).

The most common sites of infection were upper and lower respiratory tract infections (nearly 50%, including 32 cases of pneumonia and one of *Legionella pneumophila* pneumonia), urinary tract infections (13.3%), skin infections (11.95% including 12 *Herpes zoster* infections [44.4%] and 15 bacterial infections [55.6%]) (Table 3). Nine patients developed active tuberculosis (TB): six pulmonary TB, one subcutaneous disseminated tubercular infection, and two extrapulmonary TB. Bacteria were responsible for 75.7% of the infectious events, viruses for 11.1% fungi for 1.77%, and mycobacteria for 3.98%; one parasitic infection was recorded, but the micro-organism was not identified in 4.42% of cases. The infections led to one death. There was no correlation between the SIs and comorbidities. The risk of SI was significantly different in the three treatment groups (p<0.0001). However, as shown in Table 1, the patients treated with IFN showed significantly greater disease activity (DAS28) and disability (DI-HAQ) at the time of the start of anti-TNF treatment than those treated with ADA or ETN.

Univariate analysis showed the use of steroids (p<0.0001), age at the start of anti-TNF treatment (p<0.0001), the HAQ score (p = 0.002), concomitant DMARD treatment during anti-TNF therapy (p<0.0001), and the use of IFN or ADA rather than ETN (p<0.0001 and p = 0.007) were associated with a risk of SI (Table 4); disease duration and the DAS28 score did not seem to be predictive. Multivariate models confirmed that the use of corticosteroids (odds ratio [OR] 1.633; 95%CI: 1.01–2.644) (p = 0.046) and concomitant DMARD treatment during anti-TNF therapy (OR 2.14; 95%CI: 1.28–3.595) (p = 0.004), age at the start of anti-TNF treatment (OR 1.036; 95%CI: 1.02–1.053) (p<0.0001), were statistically significant predictors of infection. The other factors independently associated with an increased risk of SIs were the use of INF (OR 4.916; 95%CI: 2.71–8.906; p<0.0001) or ADA (OR 2.22; 95%CI: 1.12–4.42; p = 0.023) rather than ETN.

Table 2
Baseline demographic and clinical data of RA patients with serious infections.

	All patients 176	Infliximab 109 (61.9%)	Adalimumab 38 (21.6%)	Etanercept 29 (16.5%)	p
Age (years)	57.39 ± 11.60	57.75 ± 11.69	56.36 ± 10.89	57.19 ± 12.43	ns
Females	145 (82.4%)	95 (87.2%)	29 (76.3%)	21 (72.4%)	ns
Males	31 (17.6%)	14 (12.8%)	9 (23.7%)	8 (27.7%)	ns
Disease duration (years)	10.75 ± 8.92	11.05 ± 8.25	7.90 ± 8.06	13.33 ± 11.52	0.028
DAS28	5.81 ± 1.05	5.92 ± 0.98	5.55 ± 1.06	5.67 ± 1.35	ns
DI-HAQ	1.69 ± 0.65	1.84 ± 0.57	1.21 ± 0.63	1.65 ± 0.73	<0.0001
RF positive	121 (68.5%)	79 (72.4%)	23 (61.5%)	21 (72.2%)	ns
Comorbidity	85 (48.3%)	61 (56.0%)	17 (44.7%)	7 (24.1%)	0.008
DMARD therapy	117 (66.5%)	85 (78.0%)	19 (50.0%)	13 (44.8%)	0.0002
Corticosteroid therapy	109 (61.9%)	78 (71.6%)	16 (42.1%)	15 (51.7%)	0.0026

DAS 28 = Disease activity score; DI-HAQ = Disability Index-Health Assessment Questionnaire; RF = Rheumatoid factor: DMARDs = Disease-modifying antirheumatic drugs. Continuous variables expressed as mean values ± SD. ns: not statistically significant.

Table 3
Frequency of serious infections by infection site sub divided according to the type of the anti-TNF agent used.

	ALL	Infliximab	Adalimumab	Etanercept
	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Any serious infection	226	151 (66.8)	42 (18.6)	33 (14.6)
Site of infections				
Skin and soft tissue	27 (12.0)	10 (6.6)	10 (23.8)	7 (21.2)
Lower respiratory tract	33 (14.6)	15 (9.9)	12 (28.6)	6 (18.2)
Upper respiratory tract	83 (36.7)	67 (44.4)	11 (26.2)	5 (15.2)
Urinary tract	30 (13.3)	28 (18.5)	1 (2.4)	1 (3.0)
Osteoarticular	10 (4.4)	6 (4.0)	1 (2.4)	3 (9.1)
Intra-abdominal	8 (3.5)	3 (2.0)	1 (2.4)	4 (12.1)
Sepsis	3 (1.3)	2 (1.3)	0	1 (3.0)
Cardiovascular	2 (0.9)	0	1 (2.4)	1 (3.0)
Ocular	6 (2.7)	5 (3.3)	0	1 (3.0)
Tuberculosis	9 (4.0)	6 (4.0)	2 (4.8)	1 (3.0)

4. Discussion

The overall rate of SIs in our cohort (31.8/1000 patient-years of follow-up; 95% CI: 25.2–38.3) is similar to the data of German biologics register (RABBIT) [15], but is significantly lower than those reported in other observational studies. Salliot et al. [22] found an incidence of 105 ± 86.9/1000 patient-years during a first TNFα blocker course, and Dixon et al. [11] an overall incidence of 53.2 (95%CI: 48.9–57.8) per 1000 patient-years during anti-TNF treatment among the 7664 patients in the BSRBR. This difference can probably be explained by the under reporting of self-reported adverse events in the GISEA register, but differences between European National Health Systems, and doctors' education, culture and ethical groups are likely to be the other significant contributing factors. The Italian National Health System and guidelines are slightly different from those of other European countries, in addition the drug is given at different times and the timing of clinical evaluation could be rather different. A review of observational research designs has revealed a higher risk of infections in the first few months of anti-TNF treatment, followed by a progressive reduction [23].

We found that the risk was higher in the first 12 months of treatment (when 38.9% of the infections occurred) than in the second 12 months, although the difference was not statistically significant ($p = 0.08$). However, the findings of a recent meta-analysis of newly diagnosed RA patients starting anti-TNF therapy [24] conflict with those of our observational database.

Furthermore, our findings also suggest that uncontrolled inflammation not increases infection risk.

Table 4
Univariable and multivariable predictors of serious infections.

	Univariate				Multivariate			
	HR[a]	95% CI[b]		p	AHR[c]	95% CI[b]		p
Age at start of anti-TNF treatment	1.03	1.02	1.04	<.0001	1.036	1.02	1.053	<.0001
Disease duration	1.009	0.99	1.03	0.3	1.004	0.98	1.025	0.709
DAS28	1.055	0.94	1.19	0.381	0.946	0.81	1.107	0.49
DI-HAQ	1.443	1.15	1.81	0.002	1.156	0.85	1.576	0.358
Etanercept	1				1			
Adalimumab	1.942	1.2	3.15	0.0007	2.224	1.12	4.421	0.023
Infliximab	4.291	2.84	6.47	<.0001	4.916	2.71	8.906	<.0001
DMARDs	2.178	1.59	2.98	<.0001	2.145	1.28	3.595	0.004
Corticosteroids	1.849	1.36	2.51	<.0001	1.633	1.01	2.644	0.046
Comorbidity	0.899	0.67	1.21	0.479	1.246	0.87	1.791	0.234

DAS 28 = Disease activity score; DI-HAQ = Disability Index-Health Assessment Questionnaire; DMARDs = Disease-modifying antirheumatic drugs.
[a] HR: hazard ratio.
[b] 95% CI: 95% confidence interval.
[c] AHR: adjusted hazard ratio.

TNF plays an important role in controlling infection [10]. TNF release by macrophages seems to be crucial in the formation and maintenance of granulomas, and plays a critical role in defending intracellular organisms against invasion. TNF is also involved in leukocyte trafficking and immune complex (IC) clearance [25,26]. RA patients are at increased risk because of the disease process itself, and anti-TNF therapies may have beneficial effects by reducing their intrinsic abnormalities in immunity.

Bacterial infections have always been the most common infections in our immunocompromised patients receiving anti-TNF therapy [4,5].

Severe infections occur more frequently in elderly patients than in adults aged less than 65 years: two series have showed no increased risk of infections, whereas an Italian registry study found that the risk in patients treated with biologics was significantly associated with the risk of discontinuing anti-TNF agents [27]. Our results confirmed that advanced age at the start of treatment and steroid use were both associated with a higher risk of adverse events. The total number of comorbidities was high, but the SI risk did not correlate with chronic lung disease, diabetes mellitus or other associated diseases. Although the risk of TB during anti-TNF therapy seems to apply to all three agents, it has been suggested that monoclonal antibodies carry a higher risk than ETN because of their different effects on the structure of tubercular granulomas and macrophage activation [28,12]. ADA was licenced later, and so the patients receiving it may have already received one or both of the other anti-TNF drugs. Some risk of TB may be carried over from the previous drug. Other factors that may have influenced the drug-specific rates include the calendar year of drug start and the increasing Italian background population rate of TB and the changing Italian guidelines for TB screening [19].

The differences in infection rates and predictability to develop a SI of our study have supported by previous data of St Clair et al. and Listing et al. [29,15]. However, it needs to be remembered that we did not compare the three agents and a number of biases may be involved [30–33]. First of all, the drugs were marketed at different times (IFN first, followed by ETN and then ADA) and they were used in patients with different disease characteristics. At the start of therapy, the patients treated with INF had a significantly greater disease activity (DAS28) and disability (DI-HAQ). Secondly, and for the same reason, the number of patients receiving INF was much higher, and the follow-time significantly longer. Thirdly, the choice of drug may have been influenced by various confounding factors (e.g. compassionate availability and physician preference). Furthermore, a recent meta-analysis has shown that the type of anti-TNF agent does not influence infectious complications in younger patients with recent-onset RA because of their smaller number of associated co-morbidities, whereas our patients had long-standing RA [24].

In line with other studies, we found that the risk factors for infections were age at the time of starting anti-TNF therapy and the concomitant use of steroids. The risk of infection associated with steroid therapy is dose dependent, although it is not clear whether there is a threshold below which glucocorticoid therapy is safe [27,4]. Comparisons with the risk associated with other traditional DMARDs suggest that glucocorticoid therapy leads to a higher risk of serious and non-serious infections [34–37]. This emphasizes the importance of minimizing exposure to corticosteroids in RA patients, as this represents one of the modifiable risk factors.

Potential limitations of our study include all bias related to observational studies based on administrative data. Although we adjusted for all known risk factors for infection in our database, the results could still be affected by unmeasured or unknown counfounders [38].

In conclusion, our data suggest that anti-TNF therapy is associated with a small but significant risk of SI that is associated with the concomitant use of steroids and DMARDs and advanced age at the start

of anti-TNF treatment. The risk of SI also depends on the type of anti-TNF agent.

Competing interest

None

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Take-home messages

- The risk of serious infections in longstanding RA patients receiving anti-TNF therapy is increased.
- The risk of serious infections is associated with different risk factors such as concomitant use of steroids and DMARDs.
- This increase depends also on the type of anti-TNF agent.

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