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Review article

A systematic review of the influence of anti-TNF on infection rates in patients with rheumatoid arthritis

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ABSTRACT

Objective: The present article aims to provide a systematic review of the influence of anti-tumor necrosis factor (TNF) on infection rates in patients with rheumatoid arthritis (RA).
Method: Medline was searched to obtain quality control information on infection rates in RA patients treated with anti-TNF.
Results: A high proportion of RA patients are now established users of anti-TNF agents. Data from national registries in European countries of patients with RA treated with anti-TNF suggest that biological therapies are closely linked to sepsis. Although previous studies reported a higher risk of infections, there are now emerging data with longer duration of follow-up that suggested an adjusted hazard risk of 1.2. Elderly patients and those with longstanding disease may have a higher rate of serious infections compared to their counterparts who were younger with early disease. There are now emerging data to suggest that anti-TNF therapy is associated with the development of neutropenia shortly after the commencement of treatment. The biologic registries found that RA patients treated with monoclonal antibodies are at increased risk of tuberculosis (TB) compared to those on TNF receptor blockers. This risk of infection needs to be weighed against the established benefits of TNF blockers.
Conclusion: Current evidence suggests that anti-TNF treatment in RA is closely linked to infection. Patients need to be aware of the risk of infection together with the established benefits of TNF blockers in order to give informed consent for treatment.

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Análise sistemática da influência do antifator de necrose tumoral [anti-TNF] sobre as taxas de infecção em pacientes com artrite reumatoide

Palavras-chave:
Artrite reumatoide
Anti-TNF
Infecções

RESUMO

Resumo: O presente trabalho tem como objetivo fornecer uma análise sistemática da influência do anti-TNF sobre as taxas de infecção em pacientes com artrite reumatoide (AR).
Método: Pesquisamos na Medline para obter informações de controle de qualidade sobre as taxas de infecção em pacientes com AR tratados com anti-TNF.
Resultados: Atualmente, uma proporção elevada de pacientes com AR é usuária de agentes anti-TNF. Dados de registros nacionais em países da Europa de pacientes com AR tratados com anti-TNF sugerem que terapias biológicas estão intimamente ligadas à sepse. Apesar de estudos anteriores terem relatado um maior risco de infecções, atualmente há dados emergentes com maior duração de acompanhamento que sugerem um risco ajustado de 1,2. Os pacientes idosos e os com doença de longa data poderão apresentar uma taxa mais elevada de infecções graves em comparação às suas contrapartes mais novas com doença inicial. Hoje, há dados emergentes que sugerem que a terapia com anti-TNF está associada ao desenvolvimento de neutropenia logo após o início do tratamento. Os registros biológicos constataram que os pacientes com ARES tratados com anticorpos monoclonais apresentam aumento no risco de tuberculose (TB), em comparação aos tratados com bloqueadores dos receptores de TNF. Esse risco de infecção precisa ser ponderado em relação aos benefícios estabelecidos dos bloqueadores de TNF.
Conclusão: A evidência atual sugere que o tratamento com anti-TNF na AR está intimamente associado à infecção. Os pacientes precisam estar cientes do risco de infecção, assim como dos benefícios estabelecidos dos bloqueadores de TNF, para que possam fornecer o consentimento informado para o tratamento.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving synovial joints that affects over 400,000 people in the United Kingdom. Women are more than twice as likely to be affected compared to men.[1] In Brazil, RA affects up to 1% of the population with an estimated 1,300,000 sufferers.[2]

In 1972, O'Sullivan et al. reported the result of a population-based study where 72% of the RA patients who fulfilled the American Rheumatism Association (ARA) 1958 criteria had no clinical signs of RA at follow-up three to five years later.[3] It is not surprising, therefore, that the pyramidal approach[4,5] was widely adopted in the treatment of RA. This is based on the assumptions that RA is a benign condition and that disease-modifying antirheumatic drugs (DMARDs) have high incidence of toxicity. In this traditional treatment paradigm, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are used initially to control inflammation. DMARDs are offered to patients with more severe disease. Current evidence suggests that this has changed, and that disease-modifying treatments are started earlier rather than later in the management of RA.

Tumor necrosis factor alpha (TNF-α) is a potent inflammatory cytokine found in high titer in the synovial fluid of RA patients.[6] Anti-tumor necrosis factor (anti-TNF) therapies have revolutionized the way RA is managed. Evidence shows that patients treated early with anti-TNF therapies have less radiographic progression and better functional outcome.[7] With the availability of effective therapies, it is likely that, in the foreseeable future, many patients will be managed with TNF blockers.

One of the main concerns regarding anti-TNF treatment is the adverse consequences of TNF inhibition. TNF is a mediator in the normal inflammatory pathway[8] and has bactericidal properties.[9] Therefore, TNF blockers may cause severe immunosuppression.

Conversely, previous clinical trials have demonstrated that in patients with sepsis, anti-TNF may promote a small survival benefit.[10-12] However, these findings were not replicated in other studies.[13,14]

This study aimed to review the available clinical evidence on the influence of anti-TNF on infection rates in RA patients.

Methods

In this review, Medline (http://www.pubmed.gov) as the main search engine. If the number of hits exceeded 375, the review of articles would be restricted using the "core clinical journals" subset function and those published in the last ten years. The inclusion criteria were articles pertaining to human subjects and published in English language. The Medical Subject Headings [MeSH] database was consulted to search for the best keywords. The Boolean operator "AND" together with "OR" were used when combining two or three keywords. Only articles regarding the first generation anti-TNF agents with the highest level of evidence were selected

and reviewed in detail. The references of the retrieved articles were also consulted.

Infection in RA

("Infection" [MeSH] OR "Adverse effects") AND "Rheumatoid arthritis" [MeSH] AND "Risk factors"

Infection and anti-TNF in RA

a) ("Rheumatoid arthritis" [MeSH] AND "infliximab") then ("Rheumatoid arthritis" [MeSH] AND "etanercept") then ("Rheumatoid arthritis" [MeSH] AND "adalimumab").
b) ("Infection [MeSH]" OR "Adverse effects") AND ("infliximab" OR "etanercept" OR "adalimumab") AND "Rheumatoid arthritis" [MeSH].

Anti-TNF and neutropenia

"Tumor Necrosis Factor-alpha/antagonists and inhibitors" [MeSH] e "neutropenia".

The results of the literature search are shown in Table 1.

Table 1 – Results of search.

	Number of hits	Number of articles reviewed in detail
Infection and anti-TNF in RA	171	6
a) RA and infliximab	345	4
RA and etanercept	281	4
RA and adalimumab	140	4
b) Infecção, anti-TNF e AR	244	26
Anti-TNF e neutropenia	22	5

RA, rheumatoid arthritis; TNF, tumor necrosis factor.

Results

Rheumatoid arthritis and risk of infections

In 2002, Doran et al.[15] reported the result of a population-based study where the frequencies of infection in RA patients were compared to controls. The participants were followed-up for over ten years. There were a total of 1,218 participants (609 RA and an equivalent number of non-RA subjects). The overall rate of infection requiring hospitalization was 9.57 per 100 person-years in RA patients compared to 5.07 per 100 person-years in non-RA subjects. The hazard ratio (HR) for infection requiring hospital admission was 1.83 (95% CI: 1.52-2.21), while that for objectively confirmed infection was 1.70 (95% CI: 1.42-2.03). The commonest sites of serious infection in RA patients were septic arthritis, followed by osteomyelitis and soft tissue. The same group found that increasing age, leucopenia, disease severity factors (i.e. rheumatoid factor positivity, rheumatoid nodules, raised ESR), and co-morbidities (i.e. diabetes and chronic lung disease) were predictors of serious infection.[16]

In the study by Edward et al.,[17] RA patients and their matched-controls were identified using the United Kingdom General Practice Research Database (GPRD). Participants were prospectively followed up for a median of seven years. There were a total of 34,250 RA patients and 102,747 controls: 321 septic arthritis cases were identified during the study period. Of these, 236 occurred in those after the diagnosis of RA compared to 85 in controls. One-third of the RA patients with septic arthritis were not on DMARDs or prednisone two months prior to the diagnosis of septic arthritis. The respective septic arthritis incidences for RA cases and controls were 1.31 (95% CI: 1.22-1.41) and 0.11 (95% CI: 0.09-0.12) per 1,000 person-years. Exploratory analysis found that the increased incidence of septic arthritis occurred even before the diagnosis of RA. Prednisolone was associated with increased risk of septic arthritis with incidence rate ratio of 2.94 (95% CI: 1.93-4.46).

In another study, Wolfe et al. found that each ten-year increase in age or disease duration, history of smoking, ischaemic heart disease, and each additional previous DMARD use was found to be a predictor of pneumonic hospitalization.[18] High-dose steroid was found to be associated with sepsis in a dose-dependent manner.[18,19] Bernatsky et al.[20] found that the relative risk (RR) of infections requiring hospitalization for glucocorticoid agents was estimated to be 2.56 (95% CI: 2.29-2.85).

Summary of evidence for risk of infection in RA patients

RA patients are at an inherently increased risk of infection due to immune dysfunction.[15,17] The available evidence demonstrates that the risk of infection in RA patients rises with increasing age, leucopenia, extra-articular features, and co-morbidities.[16] High dose steroids[17-20] and history of smoking[18] were found to be sepsis predictors. For patients managed with prednisone, dosage reduction should be considered in order to minimise the risk of infection. Bone, joint, skin, and respiratory tract are the commonest sites of infection.

Rheumatoid arthritis, TNF blockers, and infections

Randomised controlled trial (RCT)

Infliximab. In the Anti-TNF Trial in Rheumatoid Arthritis with Combination Therapy (ATTRACT) trial, 428 active RA patients refractory to methotrexate (MTX), were randomized to receive infliximab (3 or 10 mg/kg every four or eight weeks plus MTX); and the fifth group was treated with MTX and placebo for 54 weeks.[21] The frequency of serious infections was comparable between those that received MTX/infliximab and those treated with MTX.

The BeST study was designed to examine the effect of infliximab in early RA. 508 early RA patients were randomly assigned to sequential monotherapy, step-up combination therapy, step-down therapy, or infliximab with MTX.[22]. There were no significant differences in the number of adverse infectious events between the four groups during the first year of follow-up. Infections, predominantly in the upper respiratory tract, were observed in 4%, 7%, 8%, and 8% of subjects, respectively.

In a randomized placebo control trial (START), 1,084 patients with RA on MTX were randomized to receive in-

fliximab 3 mg/kg, infliximab 10 mg/kg, or placebo.[23] At 22 weeks, the relative risk of serious infection in those treated with the 3 mg/kg and 10 mg/kg dose of infliximab were 1 (95% CI: 0.3-3.1) and 3.1 (95% CI: 1.2-7.9), respectively. Infection of the respiratory tract was the commonest infectious adverse event.

In another large study, the Active controlled Study of Patients receiving infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE), 1,049 patients were randomized to receive infliximab 3 mg/kg, infliximab 6 mg/kg, or placebo. All patients received concomitant MTX.[24] Patients were followed-up for 54 weeks. There were significantly more serious infections in patients who were receiving a combination of MTX/infliximab 3 mg/kg and MTX/infliximab 6 mg/kg when compared to those treated with MTX alone, with respective P-values of 0.02 and 0.04.

Etanercept. Moreland et al. performed a long-term open-label study to examine the efficacy and safety of etanercept in patients with established disease.[25] The participants in this study were recruited from previous double-blinded controlled and open-label studies. There were a total of 628 patients treated for a median of 25 months. The infective rate was 4.8 per 100 patient-years in users of etanercept, which was comparable to those on placebo (5 per 100 patient-years).

In another study, Gernovese et al.[26] performed a randomized controlled study in early RA to investigate the effects of etanercept on both safety and efficacy. Patients with active disease were randomly assigned to receive MTX or etanercept at a dose of 10 mg or 25 mg twice weekly. At the beginning of the third year, patients on MTX and 10 mg of etanercept went on to treatment with etanercept 25 mg twice per week, while those on etanercept 25 mg twice per week continued on the same regime. A total of 632 patients participated at the start of the study and five-year data were available for 293 patients. The overall rate of serious infection was 2.6 events per 100 patient-years in those who received etanercept, which was comparable to MTX group (3.1 events per 100 patient-years) in the first year of the study.

In the COmbination of MTX and Etanercept (COMET) study,[27] 542 RA patients with disease duration of less than 2 years who were MTX naïve were randomized to treatment with MTX or a combination of etanercept and MTX. Patients were followed-up for 24 months. Adverse events were similar between the two groups. Eight patients (3%) in the monotherapy group and five (2%) in the combination therapy group developed serious infections.

In another study (TEMPO trial) of three years duration, 682 RA patients with longer disease duration (mean disease duration of 6.8 years) were randomized to etanercept, MTX, or combination of etanercept with MTX.[28]. There were no differences in incidence of serious infections between the three groups.

Adalimumab. The Safety Trial of Adalimumab in RA (STAR) study was performed to investigate the safety and efficacy of adalimumab in RA patients treated with concomitant therapy.[29] In that study, 636 RA patients were randomized to treatment with adalimumab 40 mg every other week, or placebo for 24 weeks. Patients continued to receive their basic antirheumatic treatment. The mean age was 55.4 years, with mean disease duration of 10.4 years. Infectious adverse events were comparable between the two groups. The rate of serious infection was 0.028 patients per patient-year in the adalimumab group, while in the placebo group it was 0.046 patients per patient-year.

In the ARMADA study, 271 RA patients were randomly assigned to receive placebo or adalimumab 20 mg, 40 mg, or 80 mg every other week.[30] There were 271 RA patients with mean disease duration of 12.3 years and mean age of 55.5 years. The study period was 24 weeks. Infection rates were similar between those treated with adalimumab (1.55/patient-year) and those who received placebo (1.38/patient-year).

In the PREMIER study, 799 RA patients with disease duration of less than 36 months were randomized to a combination of MTX/adalimumab, monotherapy adalimumab, or oral MTX for a period of two years.[31] The rate of serious infections in the combination group was 2.9 events per 100 patient-years. This was significantly higher compared to the adalimumab monotherapy group, but not significantly different from the MTX monotherapy group.

Keystone at al. performed a double-blinded randomized placebo control trial where 619 RA patients were randomized to receive treatment with adalimumab plus MTX or MTX alone for 52 weeks.[32] The patients had inadequate response to MTX with mean disease duration of 10.9 years. There were significantly more patients treated with adalimumab who developed serious infections compared to placebo (3.8% *vs*. 0.5%, $P < 0.02$).

Non-randomized controlled trial

Wolfe et al.[18] performed a prospective cohort study where 16,788 RA patients were assessed semi-annually for 3.5 years (Table 2). The participants were patients identified from the National Data Bank for Rheumatic Diseases (NDB). This study showed no increase in pneumonic risk in patients treated with anti-TNF (hazard ratio [HR] infliximab, 1.2 [95% CI: 0.9 to 1.4]; etanercept, 0.8 [95% CI: 0.6 to 1], and adalimumab, 1.1 [95% CI: 0.6 to 1.8]). There was no increased risk of pneumonia amongst users of MTX and sulphasalazine. Again, the study found an increase in hospitalization for pneumonia in patients managed with prednisolone in a dose-response manner. The authors also reported a HR of 1.2 (95% CI: 1 to 1.5) for leflunomide.

In the United States, Schneeweiss et al.[19] performed a prospective cohort study on 15,597 RA patients aged 65 and over, where the risk of serious bacterial infections in those treated with TNF blockers was compared with users of other DMARDs. The results demonstrated that the risk of bacterial infections was similar in subjects receiving anti-TNF *versus* those treated with MTX. The rate of serious infections was more notable in the first 90 days after initiation of glucocorticoids and cytotoxic DMARDs. Treatment with glucocorticoids at a dosage of less that 5 mg was not associated with sepsis, but higher doses followed a dose-response relationship. Patients treated with anti-TNF were more likely to have undergone orthopedic surgery, indicating the severity of the rheumatoid process. However, this study was limited

Table 2 – National registries/observational studies of patients with rheumatoid arthritis treated with anti-TNF therapy.

First author, year of publication, journal title, country of origin	Type of study e.g.: RCT, cohort, case-control, cross sectional surveys, case report, reviews	Mean age (yrs)	Disease duration (yrs) (Mean unless otherwise stated)	Sample size	Duration of follow-up	Study population	Key findings	Serious infections rate per 100 PY(95 % CI) (unless otherwise stated)	Respiratory infection	Skin infection	Others
Wolfe et al. (USNDB), 2006,[18] Arthritis Rheum, United States	Prospective observational study	62	16.3	USNDB = 16,788, Non-registry = 9,619	3.5 years	Tx with anti-TNF versus DMARD versus prednisolone	No increase in pneumonia risk with anti-TNF	Overall: USNDB = 1.7 (1.6-1.9) Non-registry = 1.5 (1.3-1.6)	HR (95% CI) pneumonia: INF 1.2 (0.9-1.4) ETA 0.8 (0.6-1.1) ADA 1.1 (0.6-1.9)	_____	_____
Schneeweiss et al., 2007,[19] Arthritis Rheum, United States	Retrospective cohort study	76.5	_____	Anti-TNF = 469, Control (MTX) = 1,900	Mean years- Anti-TNF = 1.29, MTX = 0.58	Tx with anti-TNF versus MTX	No increase in serious infections reported between the two groups	Anti-TNF = 4.89 (3.15-6.62) MTX= 3.77 (2.64-4.90)	The RR* for pneumonia was 0.78 (0.28-2.13) when compared to treatment with MTX	____	The RR* for osteomyelitis was 0.9 (0.14- 5.79) when compared to treatment with MTX
Kievit et al., 2010,[33] Rheumatology, Nethelands	Prospective observational study	INF = 57 ADA = 54 ETA = 55	5.5-6.2	1,560	33 to 40 months	Tx with anti-TNF	The benefit to risk ratio for anti-TNF is favorable	Anti-TNF = 2.9	34 URTI	24 skin infections	Eight joint infections
Listing et al. (RABBIT) 2005,[34] Arthritis Rheum, Germany	Long-term prospective cohort study	INF = 53.6 ETA = 53.7 Control = 56.5	IFN = 8 ETA = 9 Control = 6	INF = 346 ETA = 512 Control = 601	12 months	Tx with INF or ETA versus traditional DMARD (control)	Infections occurred in 15%, 21%, and 6% of patients receiving ETA, INF, and traditional DMARD, respectively	DMARD = 2.28 (1.3-3.9) ETA = 6.42 (4.5-9.1) INF = 6.15 (4-9.5)	Exposed group = 14 cases of pneumonia (*versus* three in control). Exposed group = 32 upper respiratory tract infections (versus one in control)	Four, six, eight, and six patients developed erysipelas, furuncle, abscess, and paronychia (total 24), respectively, in the anti-TNF groups, compared to three in controls	Exposed group = six cases of septic arthritis (ETA = five, INF = one) compared to one in the control group

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Table 2 – National registries/observational studies of patients with rheumatoid arthritis treated with anti-TNF therapy *(continued)*.

First author, year of publication, journal title, country of origin	Type of study e.g.: RCT, cohort, case-control, cross sectional surveys, case report, reviews	Mean age (yrs)	Disease duration (yrs) (Mean unless otherwise stated)	Sample size	Duration of follow-up	Study population	Key findings	Serious infections rate per 100 PY(95 % CI) (unless otherwise stated)	Respiratory infection	Skin infection	Others
Dixon et al. (BSRBR), 2006, [35] Arthritis Rheum, United Kingdom	Prospective observational study	Anti-TNF = 56, DMARD = 60	Anti-TNF = 12, DMARD = 6	Anti-TNF = 7,664 DMARD only = 1,354	Anti-TNF = 1.26 years, Controls = 0.94 years	Tx with anti¬TNF versus traditional DMARD	No significant differences in the risk of overall serious infections were observed. However, rate of serious skin and soft tissue infections was raised	INF = 6.89 (6.24-7.60) ETA = 6.17 (5.60-6.78) ADA = 5.42 (4.55-6.40)	The IRR for respiratory infection for anti-TNF patients was 0.77 (95% CI 0.46-1.11)	The IRR was 4.28 (95% CI: 1.06-17.17). There were 118 skin infections, of which four (3.4%) were reported within 30 days of surgery	The IRR for bone/ joint and urinary tract infections were 1.12 (95% CI: 0.32-3.88) and 1.70 (95% CI: 0.32-9.03), respectively
Salliot et al., 2007,[36] Rheumatology, France	Retrospective observational study	Anti-TNF = 45.9 Control = 46.5	Anti-TNF = 11.8, Control = 12.1	Anti-TNF (FU) = 709, Control (FU + control period) = 623	1.7 years	Anti-TNF = infection rates during Tx with anti-TNF Control = infection rates before and during Tx with anti-TNF	Infections are frequently observed with anti-TNF.	Incidence rates: Anti-TNF = 10.4+/-82.1 Control = Before =3.4+/-38.7 During = 10.5+/-86.9	_____	_____	_____
Inanc et al., 2006,[37] Rheumatol Int, Turkey	Prospective cohort study	Anti-TNF = 52 DMARD = 55	Anti-TNF= 14 (median) DMARD= 12 (median)	Anti-TNF= 48 DMARD=130	Median duration of Tx in anti-TNF = 19 months	Tx with anti-TNF *versus* DMARDs	Anti-TNF is associated with an increased risk of infections compared to DMARDs	Incidence: Anti-TNF = 17, DMARDs = 8.6	Incidence per 100 PY for pneumonia: Anti-TNF = 4 DMARDs = 0.7	Incidence per 100 PY for skin infection: Anti-TNF= 0 DMARDs = 0.2	Incidence per 100 PY for otitis media and sinusitis: Anti-TNF = 1.3 DMARDS = 0
Askling et al. (LORHEN), 2007,[38] Ann Rheum Dis, Sweden	Prospective observational study	___	Anti-TNF (ARTIS) = 12.1 Swedish inpatient RA register = 15	Anti-TNF= 4,167 Swedish inpatient RA register = 2,692 Control = 10,295	Anti-TNF group = 7,776 PY	Tx with anti-TNF *versus* controls	There was an increase risk of infection requiring hospitalisation in those treated with anti-TNF	TNF antagonists (crude incidence) = 4.7 (4.2-5.2)	The RR for respiratory infections on year 2 was 1.45 (95% CI: 1-2.09)	The RR for skin/ soft tissue infections was 1.01 (95% CI: 0.48-2.16)	The RR for joint sepsis was 0.17 (95% CI: 0.67-2.98)

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Table 2 – National registries/observational studies of patients with rheumatoid arthritis treated with anti-TNF therapy *(continued)*.

First author, year of publication, journal title, country of origin	Type of study e.g.: RCT, cohort, case-control, cross sectional surveys, case report, reviews	Mean age (yrs)	Disease duration (yrs) (Mean unless otherwise stated)	Sample size	Duration of follow-up	Study population	Key findings	Serious infections rate per 100 PY(95 % CI) (unless otherwise stated)	Respiratory infection	Skin infection	Others
Curtis et al., 2007,[39] Arthritis Rheum, United States	Retrospective cohort study	Anti-TNF group = 50, MTX only = 55	__	INF = 792 ETA = 1,201 ADA = 282	17 months, Observation time in anti-TNF group = 3,894 PY, MTX only = 4,846 PY	Tx with INF, ETA or ADA versus MTX	Risk of bacterial infection requiring hospitalization was two-fold higher overall in the exposed versus the unexposed group	Exposed group = 2.9 Unexposed group = 1.4	25 (29.09%) cases of pneumonia/ empyema occurred in those exposed to anti-TNF versus 23 (28.04 %) in the MTX group	23 (26.74%) and 17 (20.73%) cases of cellulitis/soft tissue infection occurred in those receiving anti TNF and MTX, respectively	Four cases of septic arthritis were observed in each group
Carmona et al. (BIOBADASER), 2007,[40] Ann Rheum Dis, Spain	Prospective observational study	BIOBADASER = 53, EMECAR = 52	_____	BIOBADASER= 67, EMECAR = 67	BIOBADASER = 2,644 PY, EMECAR = 2,269 PY	RA patients treated and not treated with TNF antagonists	Rate of serious infections is significantly higher in those treated with TNF antagonists (RR 1.6). However, the mortality rate ratio between the two groups was 0.52 (0.21-1.29)	IR: BIOBADASER = 4.3 (3.6-5.2), EMECAR = 2.8 (2.2-3.6)	_____	_____	_____
Takeuchi et al. 2008, [41] Ann Rheum Dis, Japan	Prospective post marketing surveillance study	55.1	9.9	5,000	2,359.34 PY	RA patients treated with infliximab	Tx with INF was well tolerated with low dose MTX	IR for: infection = 8.56 (8.44-8.68) "respiratory disorders" = 1.70 (1.65-1.75)	Bacterial pneumonia = 2.2%, PCP = 0.4%, TB = 0.3%, Interstitial pneumonitis = 0.5%	Serious ADR = 0.34 (0.32-0.36)	Serious ADR for musculoskeletal = 0.25 (0.23-0.27)
Favalli et al., 2009,[42] Autoimmunity Reviews, Italy	Retrospective cohort study	55.84	9.44	1,064	24.21 months	Tx with INF, ETA, or ADA	The IR of serious infections was 35.9 per 1,000 PY. Age, ESR, and use of steroids were predictors of infection	INF = 3.89 (2.71-5.07) ADA = 3.81 (2.14-5.49) ETA = 2.56 (1.05-4.07)	34.3% of infections involved the lower respiratory tract. Five patients developed active tuberculosis	There were 15 (20.5%) cases of skin and soft tissue infections	Seven (9.6%) cases of osteoarticular infections were observed

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Table 2 – National registries/observational studies of patients with rheumatoid arthritis treated with anti-TNF therapy *(continued)*.

First author, year of publication, journal title, country of origin	Type of study e.g.: RCT, cohort, case-control, cross sectional surveys, case report, reviews	Mean age (yrs)	Disease duration (yrs) (Mean unless otherwise stated)	Sample size	Duration of follow-up	Study population	Key findings	Serious infections rate per 100 PY(95 % CI) (unless otherwise stated)	Respiratory infection	Skin infection	Others
Galloway et al. (BSRBR), 2011, [43] Rheumatology, United Kingdom	Prospective observational study	Anti-TNF = 56, DMARD = 60	Anti-TNF = 11, DMARD = 6	Anti-TNF = 11,798, nbDMARD = 3,598	Anti-TNF = 36,230 PY, nbDMARD = 9,259 PY	Tx with anti-TNF *versus* traditional DMARD	There is a small significant risk of serious infections for patients treated with anti-TNF. ↑ age was an independent risk factor for sepsis in both groups. The adjusted hazard risk was 1.2 (95% CI 1.1-1.5), and the risk was highest in the first 180 days of treatment	Anti-TNF = 4.2 (4-4.4) nb DMARD = 3.2 (2.8-3.6)	_____	_____	_____
Komano et al. (REAL), 2011,[44] J Rheumatol, Japan	Prospective hospital-based observational study	Exposed = 58.3 Unexposed 61.4	Exposed = 9.5 Unexposed = 9.2	Exposed = 646 Unexposed = 498	Exposed = 592.4 PY Unexposed = 454.7 PY	Tx with anti-TNF *versus* nb DMARD	Anti-TNF is associated with increased risk of serious infections in comparison to traditional DMARD	Anti-TNF = 6.42, Traditional DMARD = 2.64	Exposed = 23, Unexposed= 9. The crude IRR was 1.96 (0.91-4.24)	Exposed = 9, Unexposed = 1	Bone and joint (one for each)
Titton et al. (BiobadaBrasil), 2011, [45] Rev Bras Reunmatol, Brazil	Prospective observational study	47.3	Biologic = 10.8 DMARD = 9.6	1,037	2.09 years	Tx with biological agent *versus* traditional DMARD	Higher frequency of infections in the group treated with biological agent	_____	Exposed = 28.6%	Exposed =18.9%	Urinary tract = 27.6%

DMARD, disease-modifying antirheumatic drug, URTI, upper respiratory tract infection; HR, hazard ratio; RR*, rate ratio; IRR, incidence rate ratio; INF, infliximab; ETA, Etanercept; ADA, adalimumab; FU, follow up; RR, relative risk; PY, patient-years; IR, incidence rate; PCP, pneumocystis jiroveci pneumonia; TB, Tuberculosis; ADR, adverse drug reaction; IR, incidence rate; ESR, erythrocyte sedimentation rate.

by the short duration of follow-up; in addition, infection of the respiratory tract, urinary system, and diverticular abscess which were more common in the elderly, were excluded from the definition of serious bacterial infection.

Kievit et al.[33] recently performed a multi-center data registry (DREAM) of RA patients treated with anti-TNF. The study included 1,560 patients, and the mean follow-up was 33 to 40 months. 174 patients were followed-up for at least five years. The mean disease duration range was 5.5 to 6.2. The incidence rate of serious infections was 2.9 per 100 patient-years. This was lower than that reported in other registries.

Conversely, in 2005 Listing et al.[34] performed a 12-month prospective observational cohort study using the German biologic register (RABBIT), where 858 patients treated with anti-TNF were compared to controls on conventional DMARDs. The authors reported a more than two-fold increase in serious infections for patients treated with etanercept (RR: 2.2) and infliximab (RR: 2.1). The risk persisted even after adjustment for predictors of infection (i.e. age, CRP, RF positivity, and disability). There were significantly more respiratory tract and skin infections in the anti-TNF cohort.

A year latter, Dixon et al.,[35] on behalf of the British Society for Rheumatology Biologics Register (BSRBR) compared the infective risk in 8,659 RA patients treated with anti-TNF with 2,170 patients on non-biologic treatment. There were significantly more skin and soft tissue infections. However, the overall risk was similar between those receiving anti-TNF and traditional DMARDs. Again, this study showed that increases in true infective risk peaks in the first three months of anti-TNF treatment.

In another retrospective cohort study, Salliot et al. compared the incidence of serious infection in the same group of patients (n = 709) pre- and post-TNF inhibitor treatment.[36] Approximately 60% of patients had RA. During the treatment and control period, the incidence rate of serious infection was 10.5 ± 86.9 and 3.4 ± 38.7 per 100 patient-years, respectively. Previous joint surgery and steroids were found to be risk factors for infection.

Inanc et al. found an increased risk of infection in a small cohort of patients (n = 48) on TNF inhibitor compared to those on traditional DMARDs (n = 130).[37] The incidence of serious infection prior to and during treatment were 7/100 patient-years and 17/100 patient-years, respectively.

In 2007, Askling et al. performed a similar study using data from the Swedish biologic (ARTIS) and inpatient registers, with 4,167 and 44,496 RA patients, respectively.[38] Cross-referencing methods were applied to calculate the relative risk of infection requiring hospitalization. The risk of infection was 1.43 (95% CI: 1.18 to 1.73), 1.15 (95% CI: 0.88 to 1.51), and 0.82 (95% CI: 0.62 to 1.08) in the first, second, and third year of TNF antagonist exposure, respectively.

In the United States, Curtis et al.[39] conducted a retrospective study of RA patients comparing the bacterial infections in those treated with a TNF inhibitor (n = 2,393) with those who received MTX (n = 2,933). Medical records of possible bacterial infections were identified and examined by physicians for evidence of definite sepsis. The rates of hospitalization in those treated with anti-TNF and MTX were 2.7% and 2%, respectively. In the multivariate analysis, bacterial infection was respectively two- and four-fold higher overall and in the first 180 days in patients treated with anti-TNF *versus* those who were treated with MTX alone.

Carmona et al. compared RA patients (n = 4,459) in the Spanish biologic registry (BIOBADASER) with another RA cohort (n = 789).[40] The relative risk of serious infection in the anti-TNF group was significantly higher when compared to the other cohort (RR: 1.6).

Takeuchi et al.[41] reported the results of a postmarking surveillance study where 5,000 RA patients started on infliximab were prospectively monitored for six months. The mean age of patients was 55.1 years, with mean disease duration of 9.9 years. Bacterial pneumonia occurred in 108 subjects, whose mean age was 63.5 years. No pneumonic complications were observed in patients under 40 years old. Multiple logistic regression identified the age range of 60 to 70 years as one of the risk factors for pneumonia.

In 2009, Favali et al. performed a 24-month prospective observational study using the Italian register (LOHREN) with 1,064 RA patients.[42] Comparisons were made between users of different types of TNF blockers. The incidence rate was 35.9 per 100 patient-years. Baseline ESR, use of steroids, and age at commencement of anti-TNF therapy were identified as predictors of infection.

More recently, Galloway et al. reported the updated BSRBR results in which the risk of serious infection in 11,798 patients treated with anti-TNF therapy was compared with 3,598 patients on traditional DMARDs.[43] The adjusted hazard risk was 1.2 (95% CI: 1.1 to 1.5), and the risk was highest in the first 180 days of treatment. Although the relative risk of infection did not differ between different age groups, the number needed to treat in the first six months for one additional serious infection was 25 in those aged under 65 years (95% CI: 20 to 31) compared to 19 (95% CI: 16 to 23) in subjects over 65 years.

In Japan, Komano et al.[44] performed a prospective hospital-based observational cohort study (REAL) on 1,144 RA patients, comparing the risk of serious bacterial infections in patients treated with TNF blockers *versus* users of non-biologic DMARDs. The crude incidence rate ratio of serious infections in the exposed group as compared to the unexposed group was 2.43 (95% CI: 1.27 to 4.65).

In 2011, Titton et al.[45] reported the preliminary results of the Brazilian biologic registry, where 1,037 patients treated with biological therapy were compared to 287 controls on conventional DMARDs. 72% of the patients were female, with mean age of 47.3 years. The mean exposure to treatment was 2.09 years. Of the 723 RA patients, 466 were treated with biological therapy while 257 were treated with non-biologic DMARDs. 37%, 31%, and 15% of RA patients were receiving infliximab, adalimumab, and etanercept, respectively. 8%, 6%, and 4% were treated with abatacept, rituximab, and tocilizumab, respectively. Overall, infection occurred in 23% of those treated with biological agents. Upper respiratory tract, urinary tract, and soft tissue were the commonest sites of infection. There were three cases of active TB: one pulmonary and two disseminated.

The characteristics of the included studies are displayed in Table 2.

Meta-analysis

A recent meta-analysis[46] of randomized controlled trials of the safety of TNF blockers in over 8,800 RA patients did not identify an increase risk of serious bacterial infection in the normal recommended dose (Table 3). However, a dose response increase in sepsis was observed with high dose biological therapy. The odds ratio for serious infection with anti-TNF agents was 2.08 for studies of 12 weeks duration compared with 0.97 for those with follow-up of 104 weeks. Another meta-analysis by Alonso-Ruiz et al.[47] demonstrated that the relative risk of serious infections while being treated with TNF antagonist was 1.4 (95% CI: 0.8 to 2.2).

Conversely, a systematic review and meta-analysis by Bongartz et al.[48] found an odds ratio of 2 (95% CI: 1.3 to 3.1) for serious infections in RA patients treated with anti-TNF (infliximab and adalimumab) *versus* placebo patients. The number needed to harm was 59 (95% CI: 39 to 125) for one additional infection within a follow-up period of three to 12 months. In the meta-analysis of observational studies by Bernasky et al.[49] the investigators reported the pooled adjust relative risk of 1.37 (95% CI: 1.18 to 1.61) for infection in RA patients on biologic therapy.

Table 3 presents the meta-analysis of randomized/observational studies on the risk of infection with anti-TNF therapy.

Table 3 – Meta-analysis of randomized/ observational studies on the risk of infection with anti TNF therapy.

First author, Year of publication, Journal title, Country of origin	Method	Anti-TNF agents	Pooled odds ratio (OR) (95% CI) (unless otherwise stated)
Leombruno et al., 2009,[46] Ann Rheum Dis, Canada	Meta-analysis of RCT	INF, ETA, ADA	High dose *versus* placebo = 2.1 (1.3-3.3) Recommended dose versus placebo = 1.2 (0.9-1.6)
Alonso-Ruiz et al., 2008,[47] BMC Musculoskelet Disord, Spain	Meta-analysis of RCT	INF, ETA, ADA	Relative risk of: Serious infections = 1.4 (0.8-2.2) Infection = 1.9 (0.9-1.2)
Bongartz et al., 2006,[48] JAMA, United States	Meta-analysis of RCT	INF, ADA	High dose *versus* placebo= 2.3 (1.5-3.6) Low dose *versus* placebo= 1.8 (1.1-3.1)
Bernatsky et al., 2010, [49] J Rheumatol, Canada.	Meta-analysis of observational studies	____	Pooled risk ratio = 1.37 (1.18-1.60)

TNF, tumor necrosis factor; RCT, randomized controlled trials; INF, infliximab; ETA, etanercept; ADA, adalimumab.

Early versus longstanding disease

In early RA patients, the respective rates of serious infection in those treated with etanercept[26] and adalimumab[31] were 2.6 and 2.9 events per 100 patient-years, respectively. However, for those with established disease, the rates for etanercept[25] and adalimumab[32] were 4.8 and 6 events per 100 patient-years, respectively.

Elderly RA patients

Previous studies found that increasing age in RA patients is a risk factor for sepsis.[16,18] Takeuchi et al.[41] found an increased rate of bacterial pneumonia in those with mean age of 63.5 years and none in those less than 40 years old. Galloway et al.[43] reported that in the first 180 days of TNF inhibitor treatment, the number needed to harm in subjects over 65 years was 19, compared to 25 in subjects under 65 years. However, the result was not confirmed by Schneeweiss et al.[19]

Types of TNF inhibitor and infections

Infliximab was found to have a preferential risk of TB when compared to other TNF blockers. Although Curtis et al.[39] found a stronger association between infliximab and serious bacterial infections (RR: 2.4; 95% CI: 1.2 to 4.7) when compared to etanercept (RR: 1.6; 95% CI: 0.8 to 3.8, this finding was not confirmed by the German[34] and Italian[42] biologic registries.

Summary of evidence for infection in rheumatoid arthritis patients treated with anti-TNF

The results of published studies in RA patients on the influence of anti-TNF on infection rates are conflicting. Some studies suggest that there is a link between anti-TNF[24,31-32,34-43,48-49] and infections in RA, while other studies yielded the opposite result.[18-19,21-30,46-47] The biology of TNF,[8,9] the dose response relationship between TNF blockers and infection,[23,46] and the higher risk of serious infection at the start of treatment[35,38,39,43] would suggest that biological therapies are likely to be linked with sepsis. On balance, the results suggest that infection in RA patients treated with TNF blockers is not always due to the pre-existing disease process but rather to symptoms that are due to TNF blockers.

Although previous studies reported a higher relative risk of infections,[34,39] there are now emerging data with longer duration of follow-up from the entire United Kingdom that suggest an adjusted hazard risk of 1.2.[43] These, considered together with other studies that found no increased risk, would lead to the conclusion that the magnitude of the risk is unlikely to be as high as previously anticipated.

Elderly patients[41,43] and those with longstanding disease[25,32] may have a higher rate of serious infections compared to their younger counterparts with early disease.[26,31] Similarly, national registries reported a higher serious infection rate in those with longer disease duration who were exposed to anti-TNF[34-38,41-44] compared to patients with early disease.[33]

Rheumatoid arthritis, anti-TNF, and neutropenia

Rajakulendran et al.[50] found that in their cohort of 133 RA patients treated with anti-TNF, 19 patients (14.3%) devel-

oped neutropenia (< 2 × 10^9/L). The median time for the development of neutropenia after the initiation of biological therapy was three months. However, most patients did not require any changes to their anti-TNF treatment. Baseline neutrophil count and neutropenia on previous DMARDs were found to be predictors of low neutrophil count.

Hasting et al.[51] recently reported a retrospective cohort study examining the relationship between neutropenia, baseline demographics, and clinical features in patients with inflammatory arthritis receiving anti-TNF therapy. There were a total of 367 patients, of whom 81.2% had RA. 18.8% of patients had at least one episode of neutropenia (< 2 × 10^9/L) while on anti-TNF. 3% had severe neutropenia (< 0.5 × 10^9/L). These patients were on stable doses of MTX. Serious infection due to neutropenia occurred in four patients (6%). Baseline neutrophil count and previous neutropenia were predictors of neutropenia on anti-TNF therapy. The time taken for the development of neutropenia after the commencement of a TNF inhibitor was 17 weeks. However, most patients (81%) were able to remain on their original treatment.

In the previously discussed STAR study, the mean white blood count (WBC) and neutrophil count both decreased during treatment with adalimumab.[29] However, the observed changes in WBC were small. Similarly, Keystone et al. found that treatment with adalimumab was associated with a fall in mean WBC.[32]

The current British Society for Rheumatology guidelines recommend regular monitoring of full blood counts in RA patients treated with TNF blockers.[52]

Summary of evidence for neutropenia in patients with inflammatory arthritis on anti-TNF therapy

Anti-TNF therapy can be associated with development of neutropenia shortly after the commencement of treatment.[50,51] Most anti-TNF related neutropenia were not complicated by sepsis and did not require any alteration in anti-TNF treatment.

Rheumatoid arthritis, TNF blockers, and tuberculosis

Results were presented recently from the British biologic register of the risk of TB in RA patients receiving TNF antagonist.[53] In this prospective cohort study, 10,712 anti-TNF treated patients were compared with 3,232 RA patients on traditional DMARDs. The duration of follow up in the anti-TNF group was 3.21 years compared to 2.30 years in the DMARDs. There were 40 cases of TB, all of which occurred in the anti-TNF treated patients. 38% (15 cases) were pulmonary while 62% (25 cases) were extra-pulmonary. Of the 40 cases, 13 occurred within three months of treatment discontinuation. The incidence rate ratio (IRR) with etanercept at baseline was 4.2 (95% CI: 1.4 to 12.4) and 3.1 (95% CI: 1 to 9.5), respectively for adalimumab and infliximab. Patients of Asian origin had a six-fold higher risk of TB compared to their white counterparts. The number needed to harm was 600 in the monoclonal antibodies group (adalimumab) compared to TNF receptor blockers (etanercept).

In the French Research Axed on Tolerance of Biotherapies (RATIO) registry, 69 cases of TB were identified.[54] Of these, 40 patients had RA. The results showed that the standardized incidence ratio for infliximab (18.6 [95% CI: 13.4 TO 25.8) and adalimumab (29.3 [95% CI: 20.3 to 42.4]) were higher compared to etanercept (1.8 [95% CI: 0.7 to 4.3]).

The Brazilian Society of Rheumatology's guidelines[55] state that all patients should have baseline chest X-ray and tuberculin skin test (PPD) prior to treatment with biologic DMARDs. The guidelines also state that patients with PPD ≥ 5 mm with previous TB on chest X-ray or those who had close contact with subjects with active TB should be treated with a six months course of isoniazid. This treatment should be started one month prior to treatment with anti-TNF therapy.

In 2007, Gomez-Reino et al.[56] found that prior to the implementation of the Spanish Society of Rheumatology's recommendations for TB prevention, the IRR was 19 (95% CI: 11 to 32) in RA patients treated with anti-TNF. However, with strict adherence to these recommendations, the IRR fell to 1.8 (95% CI: 0.28 to 7.1).

Summary of evidence for tuberculosis

The biologic registries found that RA patients treated with monoclonal antibodies are at increased risk of TB compared to those on TNF receptor blockers. However, with strict adherence to guidelines for prescribing TNF-α blockers, the IRR of TB fell and approached that of the normal population.

Health technology appraisals

The current American College of Rheumatology (ACR)[57] guidelines state that biologic agents should not be initiated in those with active bacterial infection and in patients with non-healing skin ulcers. The ACR guidelines also recommend that biologic agents should be withheld prior to surgery. The recently updated British Society of Rheumatology's guidelines[52] indicated that TNF blockers should not be initiated in the presence of sepsis, and that these agents should be discontinued in those with active infections. TNF antagonists should be used with caution in those with previous septic arthritis (native or prosthetic), longstanding infected leg ulcers, bronchiectasis and persistent chest infection. In Asia, the Japanese College of Rheumatology's guidelines on the use of biological therapies states that treatment with TNF blockers should be withheld in those with sepsis.[58] Similarly, the Brazilian Society of Rheumatology[55] recommends that anti-TNF agents should not be initiated in those with active infection or at high risk of developing infections.

Discussion

TNF antagonists have revolutionized the management of RA patients. However, the use of anti-TNF may lead to increased risk of sepsis. Emerging data from national registries appear to show an increased risk of serious infection in RA patients on TNF blockers.[37,38,40,42,43]

Previously, the higher risk of infective complications in RA has been explained by the use of steroids.[59] In the current era of anti-TNF with less use of steroids, national reg-

istries still reported an increased risk of sepsis that could not be explained solely by the inherent risk of RA. These, taken together with national guidelines would reinforce the notion that infection is closely linked to biological therapy. Furthermore, previous studies have shown that RA patients are at an inherently increased risk of infection due to immune dysfunction.[15,27]

In United Kingdom, the National Institute of Clinical Excellence (NICE) and the British Society of Rheumatology state that, in order to be eligible for anti-TNF therapy, RA patients must have had an adequate trial of two DMARDs, one of which should be MTX, and have disease activity score (DAS) > 5.1.[60] It follows that only patients with more severe and refractory disease are given anti-TNF. Patients with established disease on anti-TNF may have a higher rate of serious infections[25,32] when compared to those with early disease.[26,31] When considered together, this subset of patients may need to be carefully monitored for infectious complications of biologic therapy. The recently updated British Society of Rheumatology's guidelines[61] recommends the use of anti-TNF in RA patients with DAS > 3.2.

RA patients with shorter disease duration are more likely to remain in remission after TNF blocker discontinuation when compared to their counterparts with established disease.[22,62,63] Patients with longstanding disease on TNF blockers[25,32] may have a higher rate of serious infections compared to younger patients with early disease.[26,31] The inference that follows is that the earlier introduction of anti-TNF may allow for its successful withdrawal after remission, hence maximizing the benefit to risk ratio.

The use of anti-TNF may affect the production of protective antibodies following immunization. However, vaccinations other than live attenuated vaccines should be given to patients treated with biologic therapy.[64] The ACR guidelines recommend yearly *Influenza* and periodic pneumococcal vaccinations in those treated with biologic therapy.[57]

There is a body of evidence on the causal link between steroids and sepsis.[17-20] It is therefore important to consider steroid dosage reduction when remission is achieved. NICE recommends the use of steroids for managing flares and to only continue treatment when the long-term complications of steroids have been discussed. When the disease is stable, the DMARDs dosages need to be reduced.[65]

There are now emerging data on the relationship between anti-TNF and neutropenia.[50,51] RA can also be complicated by Felty's syndrome, which is characterized by splenomegaly and neutropenia. The presence of neutropenia should alert physicians to the need for tighter monitoring.

The British[53] and French[54] registries showed that RA patients treated with monoclonal antibodies are at increased risk of TB when compared to those on TNF receptor blockers. Therefore, prior to the initiation of anti-TNF, specific history of tuberculosis infection, physical examination for a BCG scar, and screening tests (Mantoux/chest X-ray) need to be performed.[61] More recently, the T-Spot and QuantiFERON-TB Gold tests are available to detect TB infection.[66] These tests have higher specificity compared to PDD, which can be falsely positive due to previous BCG vaccination. The British Thoracic Society Standards of Care Committee has issued guidelines for the management of *Mycobacterium tuberculosis* infections in patients due to commence TNF blockers.[67]

Different duration of anti-TNF treatment is likely to be a possible explanation for conflicting results observed in studies. National registries rather than RCTs may be more suitable for evaluating adverse side effects due to their longer duration of follow-up. Furthermore, observational studies are more reflective of clinical practice due to less stringent criteria. However, interpretation of observational studies is limited by their non-randomized nature and is subject to allocation bias.

The UK guidelines are such that patients with more severe disease are given anti-TNF. In other countries, the guidelines for the use of these drugs may allow for earlier or later treatment with TNF blockers. This could account for the differences in infection rates observed in published studies. A possible weakness of this review is the unavoidable publication bias that might ensue due to the higher publication rates of positive rather than negative results.

In conclusion, TNF blockers have revolutionized the way RA is managed. However, current evidence suggests that anti-TNF treatment in RA is closely linked to infection. Patients need to be aware of the risk of infection together with the established benefits of TNF blockers in order to give informed consent for treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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