Infections in RA patients treated with infliximab or etanercept

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RABBIT

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Introduction

To investigate the long-term safety, effectiveness and costs of biologic therapies in rheumatoid arthritis (RA) the German Society of Rheumatology invited all rheumatologists to contribute to a national prospective cohort study in 2001. The study is known as **RABBIT** which is a German acronym for: **r**heumatoid **a**rthritis – o**b**servation of **bi**ologic **t**herapy.

The data were used to estimate the incidence rates of serious and non-serious infections in RA patients treated with etanercept or infliximab and to contrast these rates to those observed in patients treated with conventional DMARDs.

Patients and Methods

Patients

- RA patients enrolled into the German biologics register RABBIT
- new prescription of etanercept or infliximab
- new prescription of a DMARD after at least one DMARD failure (control group).

Assessments

- Treating rheumatologists assessed adverse events (AE) and serious adverse events (SAE) according to the ICH guidelines.
- MedDRA v. 7.0 was used to code the adverse events.

Statistical analysis

- Inclusion of all AE/SAEs experienced within the first 12 months.
- AE/SAE rates per 100 observed patient years were calculated.
- Propensity score methods were applied to estimate which part of the increase was attributable to differences in patient characteristics.
- The following risk factors were included in the propensity (logistic regression) model: age, number of DMARD failures, rheumatoid factor, disease activity score (DAS28), CRP, and disability measured by the Hannover functional questionnaire (FFbH). These factors indicate a higher likelihood of being treated with biologics as well as a higher susceptibility to infections.
- By this method subgroups of patients with a comparable likelihood of being treated with biologics were identified and Poisson regression was applied to calculate adjusted relative risks based on these subgroups.

Results

1,459 patients were enrolled between May 2001 and September 2003. As expected, the patients in the biologics groups had significantly more active disease and more previous DMARD failures (Tab. 1).

Tab. 1: Patient characteristics

Patients enrolled till September 2003	Etanercept	Infliximab	Controls
N	512	346	601
Age	53.7	53.6	56.5
Disease duration (median, years)	9.0	8.0	6.0
Swollen joint count (0-28)	10.5	10.8	7.7
DAS 28	6.1	6.0	5.4
FFbH (mean % of full function)	52.7	53.9	63.4
No. Previous DMARDs	3.6	3.4	2.0
Comorbid conditions (%)			
Chronic lung disease	9.5	6.1	8.2
Diabetes	8.1	7.6	7.9

Values are means if not otherwise specified.

The dropout rate was low (11.1%). In total 483, 325, 571 patient years of follow up were available for patients from the etanercept, infliximab, and control group respectively.

The infection rates per 100 patient years were for etanercept, infliximab, and control group 22.6 (95% CI: 18.7 – 27.2), 28.3 (23.1 – 34.7), 6.8 (5.0 – 9.4) (p<0.0001) respectively.

Tab. 2: Infections / 100 patient years

Adverse events	Etanercept	Infliximab	Control
Respiratory tract infections (RTI)	7.0	11.4	1.8
among them: Pneumonia	1.2	2.5	0.5
Tuberculosis	0	0.3	0
other lower RTI	2.7	2.2	0.9
Influenza like illness	2.7	4.0	0.7
Herpes viral infections	1.9	3.4	1.4
Bacterial skin and subcut. tissue infect.	3.7	4.0	1.2
Gastrointest. and oral soft tissue infect.	1.5	2.1	0.4
Other	5.8	3.4	1.3
AE total	22.6	28.3	6.8
Among them: moderate/severe AEs	15.7	20.6	5.1

Significant differences were also found for serious infections (etanercept: 6.4 [4.5-9.1], infliximab 6.2 [4.0 – 9.5], control group 2.3 [1.3 – 3.9]). Higher rates in the biologics groups were especially found for lower respiratory tract infections, bacterial skin infections, bone and joint infections.

Tab. 3: Serious infections / 100 patient years

Serious adverse events	Etanercept	Infliximab	Control
Lower respiratory tract infections	1.9	3.4	0.7
Herpes viral infections	0.6	0.6	0.4
Bacterial skin and subcut. tissue infect.	1.5	1.2	0.4
Bone and joint infections	1.0	0.3	0.2
Sepsis	0.6	0	0.4
Other	0.8	0.6	0.4
SAE total	6.4	6.2	2.3

However, the higher risk in the biologics groups could only partly be attributed to the drugs themselves. The different predispositions of the patients had to be taken into account.

Adjusted for differences in patient case mix by propensity score methods the relative risk of infections in comparison to the controls decreased for serious and non-serious infections by nearly one third (Tab 4).

Tab. 4: Relative risk (RR) of infections compared to the control group

	Etanercept		Infliximab	
	Unadj. RRs	95% CI	Unadj. RRs	95% CI
Infections total	3.3	2.3 - 4.8	4.1	2.8 - 6.0
Serious infections	2.8	1.4 - 5.9	2.7	1.3 - 5.9
	Adjusted RRs		Adjusted RRs	
Infections total	2.3	1.4 - 3.9	3.0	1.8 - 5.1
Serious infections	2.2	0.9 - 5.4	2.1	0.8 - 5.5

Conclusion:

Patients treated with biologic agents have a higher a-priori risk of infections. However, our data suggest that this risk is further increased by the treatment with TNF inhibitors.

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