

# Long Term Observation of Biologics in Germany – Safety Data after 6 Months

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## Introduction

In randomised controlled trials the efficacy of etanercept, infliximab, anakinra and adalimumab has been proven in patients with active rheumatoid arthritis (RA). Although evidence from these trials and from clinical experience so far is encouraging there is lack of information on the long-term safety of these agents. Therefore, in Germany as in other European countries a long-term register on patients treated with biologics was initiated. We used data of the German biologics register (RABBIT) to investigate the safety of biologic therapies in RA in comparison with controls on conventional DMARDs.

## Patients and Methods

Since May 2001, patients with RA and a new prescription of etanercept, infliximab, anakinra (since January 2003) or adalimumab (since September 2003) as well as control patients have been consecutively enrolled into the German biologics register (RABBIT). For better comparability with the patients on biologics, the control group consists of patients with RA who have a change in their DMARD therapy. The patients will be followed-up for five years. One hundred seventy two rheumatological units (private practices, outpatient departments of hospitals) from all parts of Germany participate. Data are shown for patients enrolled within the first two years: from May 2001 till May 2003.

Adverse events (AE) and serious AE (SAE) have been reported by the treating rheumatologists. They were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and assigned to system organ classes (SOC) of MedDRA by the study physician.

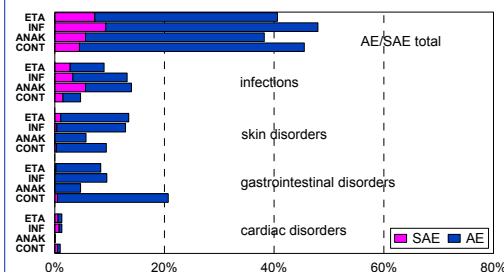
SAE were defined as fatal, life-threatening, leading to hospitalisation, miscarriage, congenital defect or significant disability.

## Results

Among the 1295 patients enrolled, 435 were on etanercept, 298 on infliximab, 59 on anakinra and 495 were control cases.

The percentage of patients with at least one AE within the first 6 months of observation ranged between 38% and 48%.

Fig.: Percent of patients with at least one AE/SAE



ETA: etanercept, INF: infliximab, ANAK: anakinra, CONT: controls.

Within the first 6 months of treatment the total incidence of infections (AEs) was significantly higher in the biologics groups than in the control group ( $p=0.002$ ). This was especially due to respiratory tract infections and skin and subcutaneous tissue infections (Tab. 1).

However, there was no significant difference in the incidence of serious infections (SAEs) ( $p=0.29$ ), and no significant difference in serious skin disorders ( $p=0.35$ ) or serious gastrointestinal disorders ( $p=0.49$ , Fig. 1).

Tab. 1: Percentage of patients with at least one infection within the first six months of therapy

Infections	Etanercept	Infliximab	Anakinra	Controls
Abscess	0.6	0.7	0.0	0.0
Herpes simplex/ zoster	1.3	3.3	0.0	0.6
Respiratory tract infection	3.6	7.1	8.4	1.4
Skin and subcutaneous tissue bacterial infection	1.3	0.0	0.0	0.4
Urinary tract infection	0.8	0.5	0.0	0.5
Other infections	3.0	3.3	5.6	1.8

Tab. 2: Percentage of patients suffering from at least one form of skin disorder within the first six months of therapy

Skin disorders	Etanercept	Infliximab	Anakinra	Controls
Alopecia	1.6	1.7	0.0	4.5
Dermatitis	1.2	3.3	0.0	1.0
Erythema	1.7	0.4	0.0	0.0
Exanthema	3.2	2.7	2.8	1.8
Pruritus	3.2	5.0	1.9	1.8
Increased sweating	0.7	0.4	0.0	0.7
Urticaria	0.3	1.7	0.0	0.5
Other skin disorders	4.0	1.6	3.8	0.2

There was a highly significant difference in the incidence of gastrointestinal disorders (AE total, diarrhoea, nausea) between the control group and the patients on biologics ( $p<0.0001$ , Tab 3).

Tab. 3: Percentage of patients experiencing at least one form of gastrointestinal disorder within the first six months of therapy

Gastrointestinal disorders	Etanercept	Infliximab	Anakinra	Controls
Abdominal pain/discomfort	2.1	0.5	0.0	2.4
Diarrhoea	1.2	2.1	1.9	6.6
Nausea	2.9	5.2	2.8	10.2
Oral soft tissue disorder	1.0	1.2	0.0	2.0
Other gastrointestinal disorders	2.5	1.5	0.0	2.5

Within 12 months, 10 deaths (5 ETA, 1 INF, 4 Control), 1 lung tuberculosis (INF), 1 malignoma (pancreatic carcinoma/Control), 1 demyelinating disease (ETA), and 1 lupus-like syndrome (INF) were reported.

## Conclusion:

After 6 months of observation, the incidence of infections was higher in the groups treated with biologics whereas the overall rate of AEs and SAEs was not different between patients treated with biologics and controls. It is important to notice that the patients in the biologics groups were more severely ill and that the numbers of cases so far enrolled are too small to adjust for disease severity, treatment history, co-morbidity, or co-medication.

## Disclosure:

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