Safety profile of repeated rituximab cycles in unselected rheumatoid arthritis patients: a long-term, prospective real-life study

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Abstract

Objective

To evaluate the long-term safety of rituximab (RTX) in rheumatoid arthritis (RA) patients in daily clinical practice.

Methods

This was a multicentre (17 Greek Rheumatology sites), prospective, long-term, pharmacovigilance study of patients with moderate to severe RA and an inadequate response or intolerance to ≥1 anti-tumour necrosis factor (TNF) agents. Adverse events (AEs) were recorded and collected prospectively every 2-6 months.

Results

234 patients (mean age: 59±12.5, 79.5% women, mean DAS28: 5.35±1.32) were included and followed for 27.7 months (median). The overall AEs, serious AE (SAEs) and serious infection (SIEs) rate were 48.36, 6.68 and 2.53/100 patient-years, respectively. Three cases of hepatitis B virus (HBV) reactivation were recorded (two in chronic and one in past HBV infection). Withdrawals due to AEs (5.6%) occurred more frequently during the first cycles of RTX therapy while repeated RTX cycles were not associated with an increased risk of AEs. There were 3 deaths with an incidence rate of 0.69/100 patient-years. Age ≥65 years was associated with a higher incidence rate ratio of AEs and SAEs as compared to <65 years (1.53, p=0.002 and 2.88, p=0.005, respectively). Drug retention rate during 434.28 patient-years of follow-up was 57.3%. Factors associated with drug discontinuation by multivariate analysis included age, baseline swollen joint count and no use of concomitant methotrexate therapy.

Conclusion

Long-term RTX therapy in a real-life RA cohort, did not reveal any new safety issues. Advanced age was associated with increased risk of AEs and premature drug discontinuation.

Key words

rheumatoid arthritis, rituximab, biological therapy, disease-modifying anti-rheumatic drugs, safety.

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Introduction

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody that leads to B cell depletion is an established therapeutic agent for patients with rheumatoid arthritis (RA) that have failed therapy with anti-tumour necrosis factor (TNF) agents or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) under certain conditions (1, 2). Certain baseline factors have been recently identified as predictive to response to RTX therapy in RA patients (3, 4). A number of randomised controlled (RCTs) and their long-term extension studies (or trial extension studies-TES) (5) have demonstrated its efficacy and safety in such patients (6, 7). More specifically, data from the RTX global clinical trials program comprising 8 randomised placebo controlled trials in patients with moderately to severely active RA, demonstrated that the overall rates of adverse events (AEs) and serious AEs (SAEs), including serious infections (SIEs), were similar to those observed with methotrexate alone (MTX) (6, 7). Despite their usefulness, TES have certain limitations including patient selection bias, lack of generalisability (inclusion of patients who fulfill certain inclusion and exclusion criteria) and underreporting of rare adverse events (5). Similarly, although biologic registries have provided important real-life data, they are often limited by their heterogeneity in safety data collection and reporting (8).

The purpose of this long-term, pharmacovigilance study was to record systematically all side effects associated with long-term RTX administration in RA patients who were intolerant or had failed anti-TNF therapy and identify risk factors associated with AEs and drug discontinuation.

Materials and methods

Patients

The non-interventiona**L** s**A**fety study of rit**U**ximab in patie**N**ts with severe a**C**tive rheumatoid art**H**ritis (LAUNCH) trial was a multicentre, prospective, long-term, pharmacovigilance study initiated in 2006, soon after the market authorisation of RTX in Greece. Seventeen Rheumatology academic and non-academic hospital sites in Greece enrolled 234 adult patients with moderate to severe RA during a 5 year period (between 2006 to end of 2011). The patient population consisted of those who had been taking RTX according to their treating physicians judgment and its licensed indication for RA, *e.g.* patients with active RA and inadequate response or intolerance to at least one anti-TNF.

All patients entered the study at the time of their first exposure to the drug. RTX (1 gm) was administered intravenously (IV) on the 1st and 14th day of each cycle and was repeated every 6-12 months. Follow up visits were performed every 2–6 months according to each investigator's site practice. The use of DMARDs and corticosteroids was also recorded during the duration of study.

Baseline data and information regarding safety were recorded in the study's Case Report Form (CRF). All AEs after the first RTX treatment were recorded using the Medical Dictionary for Regulatory Activities (MedDRA, v. 13.1). An AE was defined as any untoward medical occurrence in a patient administered the medication and which does not necessarily have to have a causal relationship with this treatment. AEs were classified with a five-grade scale in accordance with the NCI CTC grading system (Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated., Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living-ADL. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated, Grade 5: Death related to AE). All patients were asked for AEs in each visit and when no AEs were noted this was also recorded.

Serious adverse events (SAEs) were defined as events that were fatal, immediately life-threatening, required inpatient hospitalisation or prolongation of an

existing hospitalisation, were medically significant, or required intervention to prevent one of the above outcomes. During the 5-year duration period of the study, patients were followed up for a median time of 27.7 months (range: 0.5–40.3 months) leading to 434.28 patient-years of follow-up.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the laws and national regulations of Greece. Each participating site received approval from the institutional review board/Ethics Committee. Additionally all patients provided written informed consent prior to study participation and an updated informed consent throughout the study conduct.

The study was funded by F. Hoffmann-La Roche. The sponsor designed the study in collaboration with the lead authors. The sponsor collected, analysed and interpreted the data and wrote the clinical study report (CSR). All authors contributed to data interpretation, amended the manuscript, and attest to the accuracy and completeness of the reported data. The lead authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript.

Statistical analysis

The description of baseline characteristics is based on all recruited patients (n=234), whereas the analysis regarding the safety profile of RTX is based on the safety population comprised of all patients who received at least one infusion of RTX regardless of dose (n=233).

The safety analysis is based on the Treatment Emerged Adverse Events (TEAEs) defined as any AE with starting date after the first RTX infusion and within the 180 days after the last RTX infusion. Summary statistics of AEs were based on incidence rates, calculated as the number of new events divided by the sum of patient-time in the trial, expressed per 100 patient years, followed by the respective 95% confidence intervals (CI). AEs frequencies are also provided.

Kaplan Meier curves were employed to illustrate the time to discontinuation due to any AE (drug survival). Drug survival distribution curves were compared between groups of interest by the log-Rank statistic. Following this, the semi-parametric Cox's regression model of proportional hazards was employed in order to assess the simultaneous effect of variables that were statistically significant at the univariate analysis at α=0.1.

In order to address the safety of the elderly population, the AE incidence rates of the different age groups (cut off point = 65 years of age) were compared using the normal approximation as provided by the "epitools" package of R (http://cran.r-project.org). All tests were 2-sided whereas level of statistical significance was set at 0.05.

Results

Baseline characteristics and co-morbidities

Out of 234 RA patients recruited in the study during the study period, 233 received at least one dose of RTX. The mean age of patients was 59 years and the mean disease duration 14.3 years (Table I). The majority of patients were females (79.5%) and rheumatoid factor (RF) positive (75%). At baseline, the median swollen (SJC) and tender (TJC) joint count were 8 and 4, respectively while the median ESR and CRP level was 38 mm/h and 3.7 mg/L, respectively. Included patients had either moderate (38.4%) or severe (55.6%) disease activity (mean DAS28 score = 5.35±1.32) while the mean Health Assessment Questionnaire (HAQ) score was 1.1 (Table I). Patients were resistant to a high number of csDMARDs (mean number: 4.5±1.9) and/or biologic DMARDs (bDMARDs) (mean number: 1.8±0.9). At baseline, the majority of patients were also receiving corticosteroids (83.8%). Co-morbidities were common among this patient population including hypertension (29.8%), osteoporosis (13.9%), hyperlipidaemia (10.1%), diabetes mellitus (7.7%) and coronary artery disease (6.7%).

Table I. The baseline patient characteristics of patients included in the study are shown.

Characteristics	
Age, years	59.0 ± 12.5
Females, n (%)	186 (79.5)
Caucasians, n (%)	232 (99.1)
Disease duration, years	14.3 ± 10
DAS 28	5.35 ± 1.32
HAQ	1.1 ± 0.7
Swollen joints count, median [range]	4 [0-28]
Tender joints count, median [range]	8 [0-28]
CRP (mg/L), median [range]	3.7 [0-308]
ESR (mm/h), median, [range]	38 [0.5-122]
Rheumatoid factor (+), n (%)	171 (75.3)
n of previous conventional synthetic DMARDS	4.5 ± 1.9
n of previous biological DMARDS	1.8 ± 0.9
Baseline corticosteroids, %	82.1%
Dose (mg/day)	5.6 ± 2.1 mg
Baseline methotrexate use, %	62%
dose (mg/week)	11.1 ± 3.2 mg
Co-morbidities	
Hypertension, n (%)	62 (29.8)
Osteoporosis, n (%)	29 (13.9%)
Hyperlipidaemia, n (%)	21 (10.1%)
Coronary artery disease, n (%)	14 (6.7%)
Diabetes mellitus, n (%)	16 (7.7%)

HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; DMARDs: disease-modifying anti-rheumatic drugs. Data are expressed as mean ± 1 standard deviation (SD), unless otherwise specified.

Study flow

In Figure 1, the flow of patients enrolled in the study is shown. During the observational period, 233 patients received up to 7 cycles of RTX over a median time of 27.7 months (total number of cycles: 910) with a total exposure time of 434.28 patient-years. Overall, 133 patients completed the observational period (56.8%, Fig. 1) while 101 (43.2%) patients discontinued treatment. The majority of withdrawals occurred after the first 2 cycles of therapy (25.6%, Fig. 1). In the safety population (n=233) and among patients who discontinued therapy (n=100), only 13 patients (5.6%) did so for safety reasons (see detailed analysis below). The majority of patients (n=87, 37.3%) discontinued treatment for "other" reasons including insufficient therapeutic response, refusal of treatment, lack of cooperation, consent withdrawal, loss during follow-up and physician's decision to withdraw. Patients who completed the study were censored at the time of study completion while patients who discontinued treatment for any reason (safety or "other" reasons) were censored at the time of drug dis-

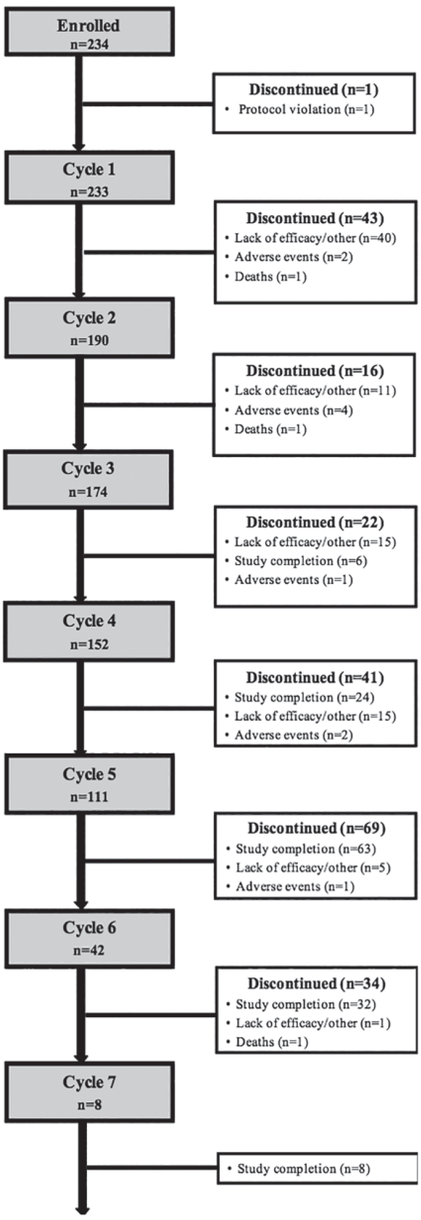

Fig. 1. A flow sheet showing patient disposition during rituximab therapy is depicted.

Table II. Various factors associated with rituximab discontinuation were tested by uni- and multi-variate Cox regression analysis and *p*-values and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. *p*-values <0.05 are shown in bold.

	Univariate analysis* *p*	Multivariate analysis** *p*	HR (95% CI)
Age (continuous)	0.074	**0.044**	**1.02 (1.001-1.04)**
Sex	0.695	0.149	
Disease duration	0.562	0.211	
DAS28	0.263	0.908	
HAQ	0.621	0.563	
SJC	**0.026**	**0.020**	**1.045 (1.01-1.09)**
TJC	0.717	0.415	
CRP	0.774	0.598	
ESR	0.648	0.892	
RF (+)	0.711	0.649	
n of previous synthetic DMARDs	0.613	0.910	
n of previous biologic DMARDs	0.794	0.646	
Steroid use at baseline	0.591	0.651	
Analgesic use at baseline	0.545	0.087	
COX-2/NSAID use at baseline	0.244	0.425	
Methotrexate use during therapy	**0.008**	**0.002**	**0.452 (0.27-0.75)**

*log-Rank statistic. **Cox's proportional hazard regression model.
DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; DMARDs: disease-modifying anti-rheumatic drugs; Y: yes; N: no; COX: cyclooxygenase; NSAIDs: Non-steroidal anti-inflammatory drugs.

Table III. All adverse events (AEs) and serious AEs (serious AEs) recorded during the observation period are shown.

	Incidence rate [95% CI]
AEs/100 patient-years	48.36 [42.04-55.36]
SAEs/100 patient-years	6.68 [4.47-9.59]
Infusion related reactions	4.61 [2.81-7.11]
Infections/100 patient-years	17.73 [13.99-22.16]
Serious infections/100 patient-years	2.53 [1.26-4.53]
Respiratory infections/100 patient-years	9.67 [6.97-13.07]
Serious respiratory infections/100 patient-years	1.38 [0.51-3.01]
Urinary tract infections/100 patient-years	3.68 [2.11-5.98]
Serious urinary tract infections/100 patient-years	0.23 [0.01-1.28]
Cerebrovascular accidents/100 patient-years	1.15 [0.37-2.69]
Malignancies/100 patient-years	0.46 [0.06-1.66]
Deaths/100 patient-years	0.69 [0.14-2.02]
Discontinuation due to AEs/100 patient-years	2.99 [1.59-5.12]

continuation (see RTX drug survival at Supplemental Fig. 1).

Factors associated with RTX discontinuation

Using univariate and multivariate analysis, a number of factors were explored as predictive of RTX discontinuation, including age, sex, disease duration, baseline DAS28, HAQ, SJC, TJC, ESR and CRP, RF positivity, number of previous cs- or bDMARDs, steroid or analgesic use at baseline and MTX use during therapy (Table II). By multivariate analysis, only age (*p*=0.044, hazard ratio-HR=1.02, 95% confidence intervals-CI: 1.001–1.04), SJC at baseline (*p*=0.02, HR=1.045, 95% CI: 1.01–1.09) and no use of MTX during RTX therapy (*p*=0.02, HR=0.452, 95% CI: 0.27–0.75) were statistically significantly associated with RTX time to discontinuation.

Adverse events

Among patients who received ≥1 RTX cycle, 110 (47.2%) experienced 210 AEs, leading to an AE incidence rate of 48.36/100 patients-years (95% CI: 42.04-55.36, Table III). Infections were the most common AEs (37%, 77/210 events) with an incidence rate of 17.73/100 patient-years. The most frequent infections in this study were respiratory tract infections (13.73%), followed by urinary tract infections (4.29%). The majority of AEs (80%) were of mild/moderate severity (grade I/II). Infusion related reactions (IRR) were noted in 20 patients (8.6%) with one anaphylactic reaction. The majority of infusion reactions occurred during the first 2 cycles (15/20, 75%).

Table IV. The incidence ratio of all adverse events (AEs), serious AEs (SAEs), infections and serious infections recorded during the observation period in patients older or younger of 65 years of age was calculated and compared between the two groups. *p*-values <0.05 are shown in bold.

	Incidence rate [95% CI]		Incidence rate ratio	*p*
Age	< 65 years	> 65 years		
Exposure (patient-years)	285.00	144.10		
AE/100 patient-years	40.35 [33.35-48.44]	61.76 [49.6-76.00]	1.53 [1.16-2.02]	**0.002**
SAEs/100 patient-years	3.86 [1.93-6.91]	11.10 [6.35-18.03]	2.88 [1.34-6.21]	**0.005**
Infections/100 patient-years	15.44 [11.32-20.73]	22.21 [15.19-31.35]	1.44 [0.91-2.27]	0.116
Serious Infections/100 patient-years	2.11 [0.77-4.58]	3.47 [1.13-8.10]	1.65 [0.50-5.40]	0.404

Table V. Safety data from long-term rituximab trials in the literature.

Authors Journal (year) (reference)	Vassilopoulos D Current study	van Vollenhoven RF *Ann Rheum Dis* (2013)* and *J Rheum* (2015)** (6,7)	Wendler J *Arthritis Res Ther* 2014 (17)	Payet S *Arthritis Care Res* 2014 (18)	Richter A *Arthritis Res Ther* 2014 (16)	Cobo-Ibanez T *Rheumatol Int* 2014 (15)	Soliman MM *J Rheumatol* 2012 (14)	Vander Cruyssen B *Arthritis Res Ther* 2012 (13)	Gottenberg JE *Arthritis Rheum* 2010 (12)
Name of study (country)	LAUNCH (Greece)	8 RCTs, 2 TES, 1 open label prospective (International)	GERINIS (Germany)	AIR (France)	RABBIT (Germany)	BIOBADASER 2 (Spain)	BSRBR (UK)	MIRA (Belgium)	AIR (France)
n	234	3595**	2484	1709	907	75	646	401	1303
Follow-up (months)	27.7 (median)		14.7 (median)	84	36 (mean)		6	17.5 (mean)	14.4 (mean)
Age, years	59 ± 12	51.5 (mean)*	56 ± 12		56-59		59 ± 12	59 (mean)	58 ± 13
Females, %	79	81*	77	77	78		77	76	78
Disease duration, years	14.3 (mean)	8.3 (mean)*	11.7 (mean)	14-17 (median)	13.7-14.7		14 (mean)	12 (mean)	15.5 (mean)
Previous DMARDs, n	4.5 (mean)	2.2 (mean, excluding MTX)*	3 (median)		3 (mean)		4.2 (mean)		3.2 (mean)
Previous biologics, n	1.8 ± 0.9	0.7*	1.4±1 (anti-TNF)	1-2 (median)	1.5-1.6				
RF+ (%)	75	78*	77	67	84		66	81	78
Swollen joint count (SJC)	4 (median)	20 (mean)*					9 ± 6		9 ± 6
Tender joint count (TJC)	8 (median)	31 (mean)*					14 ± 8		
DAS28	5.35 ± 1.32	6.64 (mean)*	5.7 ± 1.2	5.5-5.7 (mean)	5.3-5.7		6.2 ± 1.1	6 (mean)	5.7 ± 1.2
CRP (mg/dL)	3.7 (median)	2.8 (mean)*		1.4-2 (median)			3.4 ± 3.8		3.1 ± 3.5
HAQ	1.1 ± 0.7		1.6 ± 0.7				2 ± 0.6		
Corticosteroids (%)	84			78			46		80
Daily dose, mg	5.6 ± 2.1								10 ± 10
Exposure (pt-yrs)	434	14816**				146			1629
AEs, n (%)	110 (47.2)		532 (21.4)						
AEs (/100 pt-yrs)	48.36	239**	11.4						
SAEs, n (%)	25 (10.7)								
SAEs (/100 pt-yrs)	6.68	13.82**	3.62						
Infections (/100 pt-yrs)	17.73	75.7**	11.4						
Serious infections (%)				12					
Serious infections (/100 pt-yrs)	2.53	3.76**				16			
Deaths, n (%)	3 (1.3)	78 (2.1)**	9 (0.4)	74 (4.3)					
Deaths (/100 pt-yrs)	0.69	0.53**							
Drop-outs, n (%)	100 (42.9)			572 (33%)	179 (19.7)			30 (7.5)	
Kaplan-Meier, % survival	57.1			67	60.8				

RCTs: randomised controlled trials; TESs: trial extension studies; DMARDs: disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor; RF: rheumatoid factor; AEs: adverse events; SAEs: serious AEs; pt: patient; yrs: years.
*Data from ref. 6 in 3194 patients. **Data from ref. 7 in 3595 patients.

Serious adverse events

SAEs were recorded in 25 patients (10.7%) who experienced 29 SAEs with an incidence rate of 6.68/100 patient-years (see Supplemental Table I). Serious infections occurred at a rate of 2.53/100 patient-years; most frequent were those of the respiratory tract (n=6, 1.38/100 patient-years).

During the observation period there were 3 cases of hepatitis B virus (HBV) reactivation (two have been previously published as case reports) (9, 10). The first case was that of a 61 year old male with chronic HBV infection (HBsAg+) who developed HBV reactivation after the first cycle of RTX (not screened at baseline). The patient was successfully

treated with tenofovir. The second case was a 56 year old female with known chronic HBsAg infection for 6 years who had failed different biologic and cs-DMARDs. The patient while on chronic antiviral therapy with lamivudine, developed HBV reactivation (AST/ALT: 111/150 U/L, HBV DNA levels: >1.1x10^8 IU/mL) 84 days after the first cycle of rituximab. Tenofovir was added to lamivudine with rapid control of HBV reactivation (10). The third case was that of a 64-year-old female with resolved HBV infection (HBsAg-, anti-HBc+, anti-HBs+) who demonstrated HBV reactivation (HBsAg+, elevation of AST/ALT: 501/565 U/L and HBV DNA levels: 1.1 x 10^8 IU/mL) after 2 years of treatment with rituximab (5 cycles) and methotrexate (9). RTX was discontinued and she was treated successfully with entecavir (1 mg/d).

A 73 years old female developed pneumonitis and encephalitis from West Nilus Virus (WNV) during a summer outbreak in the same geographical region (11) and recovered fully without any neurologic deficits. Another 73 years old male developed gradual deterioration of his cognitive function and bilateral impaired vision while on treatment with RTX (after the 5th cycle). An MRI of his brain showed occipital and parietal subcortical white matter lesions suggestive of ischaemic leucoencephalopathy. Further work-up for progressive multifocal leucoencephalopathy (PML) including PCR for JC virus in the cerebrospinal fluid was negative. The patient had a progressive neurological course and died (no autopsy was performed).

There were two cases of cancer (one metastatic liver cancer and one small cell lung carcinoma), one case of septic arthritis and five cerebrovascular accidents (2 transient ischaemic attacks and 3 strokes) and one case of pericardial tamponade.

Deaths

Three deaths were recorded during the study period (one due to pericardial tamponade, one due to small cell lung carcinoma and one due to leucoencephalopathy) with an incidence rate of 0.69 deaths/100 patient-years (0.14–2.02).

Repeated cycles are not associated with increased risk of AEs

The percentage of patients that experienced any AEs was higher during the first two cycles (cycle 1: 21%, cycle 2: 19.5%) and decreased over the subsequent cycles (Supplemental Fig. 2). The same pattern was observed regarding the SAEs and infections throughout the cycles (data not shown). Low IgG levels were found in 5 patients in the entire cohort (2.1%); one of these patients had low IgG levels before starting RTX therapy, thus indicating a low overall rate of hypogammaglobulinaemia (1.71%) during long-term RTX treatment. No infections were recorded in these five patients.

Safety profile in elderly patients

The safety profile of RTX was compared between patients younger or older of 65 years of age (Table IV). In general, patients older than 65, had a statistically significant higher incidence rate of AEs and SAEs compared to younger patients (Incidence rate ratios: 1.53, 95% CI: 1.16-2.02, p=0.002 and 2.88, 95% CI: 1.34-6.21, p=0.005, respectively). Although, infections and SIEs were also more common in older patients the difference was not statistically significant (Table IV).

Discussion

This multicentre prospective study of patients with moderate to severe RA resistant or intolerant to anti-TNF therapy who received RTX in real-life clinical settings, confirms the long-term safety profile of RTX. At the same time, the study emphasises the need for close monitoring of treated patients especially those older than 65 years of age.

Our study is one of the few in the literature that focused on safety providing prospectively collected, detailed data regarding the long-term safety of RTX use in daily clinical practice. Safety and efficacy data regarding RTX in RA have been derived from RCTs and their TES [reviewed in ref. (6, 7)], national registries or multicentre routine practice based studies (12-18). The majority of these studies have focused either on RTX efficacy (13, 14, 16, 18) or its infectious complications (12, 15, 18) during long-term use. Only one recent study from Germany (GERINIS) (17) has collected prospectively data regarding long-term drug safety, but the follow-up was shorter compared to our study (median: 14.7 *vs*. 27.7 months). In Table V, all long-term published studies of RTX (including the current study) with safety data available are shown.

The present study was a long-term, multicentre, prospective post authorisation study in RA patients, treated with successive RTX cycles in the routine clinical setting. Safety data were prospectively collected and analysed. In general, our patient characteristics were closer to those reported in registries or multicentre studies compared to the RCTs (6, 7). These were older patients (mean age: 59 *vs*. 51 years), with a longer disease duration (mean: 14 *vs*. 8.3 years) and lower disease activity at baseline (mean DAS28: 5.35 *vs*. 6.6) compared to the patients included in the RCTs (6). They had been also exposed to more csDMARDS (4.5 *vs*. 3.2) and biologic DMARDs (mainly anti-TNF, 1.8 *vs*. 0.7). Co-morbidities like hypertension, osteoporosis, hyperlipidaemia, diabetes mellitus and coronary artery disease were common in this aged population. The majority of patients (82%) were also taking low dose steroids.

Although this was mainly a safety study, the retention of RTX after 3 years of treatment by Kaplan-Meier estimate was 57.3% which is close to what has been reported recently in the RABBIT registry from Germany (60.8% after 3 years) (16). Most withdrawals occurred after the first few cycles of therapy and only 13% of them were due to AEs. This is in agreement with the results of the RCTs where 30% of the withdrawals occurred following the first 2 cycles of therapy (6). A number of factors were investigated as potential predictors to drug discontinuation. Among them by multivariate analysis advancing age, a high swollen joint count at baseline and no use of MTX, were associated with drug discontinuation.

The rate of AEs was 48.36/100 patient-years which overall is much lower than that reported in RCTs (239/100 patient-years) (7) and closer to that reported in the GERINIS registry study from Ger-

many (39.58/100 patient-years) (17). Similarly, the incidence of SAEs was 6.68/100 patient-years compared to 13.82/100 patient-years from the RCTs and their TES (7) and 3.62/100 patient-years in the GERINIS study (17) while the rate of SIEs was 2.53/100 patient-years which is lower to that reported in the RTX RCTs and their TES (3.76/100 patient-years) (7).

The safety pattern of long-term RTX use did not differ to that observed from the long-term use of other biologic agents such as anti-TNFs. Overall, the rate of SAEs and SIEs was comparable to those reported recently by the Hellenic Registry of Biologics after long-term anti-TNF use (infliximab, adalimumab and etanercept) in Greece (19). In that study, the rate of SAEs and SIEs ranged between 3.5–8.5/100 patient-years (compared to 6.68 /100 patient-years for RTX) and 2.1–4/100 patient-years (2.53/100 patient-years for RTX), respectively (19). This is an important finding taking into account that RTX treated patients had been already resistant to previous treatment with anti-TNF agents.

In our study, three cases of HBV reactivation were recorded; two in patients with chronic and one in a patient with past HBV infection. In the first case a patient with chronic HBV infection developed HBV reactivation, 3 months after the initiation of RTX therapy, emphasising the need for HBV screening at baseline prior to the initiation of biologic therapy (20). Appropriate initiation of oral antiviral therapy with tenofovir led to patient improvement. In the second case, HBV reactivation occurred despite chronic antiviral therapy with lamivudine. Most likely this was due to the emergence of a lamivudine-induced resistant HBV strain (as it has been reported previously) (21), highlighting the need for utilising antiviral agents with low rates of resistance like tenofovir or entecavir for prophylaxis (20, 22, 23). In the last case, HBV reactivation appeared in a patient with past HBV infection (anti-HBc+/anti-HBs+). In both cases prompt initiation of antiviral treatment with the new oral antiviral agents led to biochemical and virological remission. Although, viral reactivation has been reported in patients with past HBV infection treated with RTX and chemotherapy for hematological diseases (lymphomas) at a rate ranging between 3 to 25%, its frequency in RTX-treated patients with rheumatic diseases is probably limited (20). In two recent prospective studies of patients with past HBV infection treated with RTX, no HBV reactivation was recorded (24, 25). Despite the limited data available for rheumatic patients, most experts recommend frequent monitoring for HBV reactivation (by ALT and HBV DNA) during RTX treatment and initiation of antiviral therapy if reactivation is documented (20, 23, 26).

Data regarding the role of advancing age in the risk for AEs and infectious complications in RTX treated patients are limited (17, 27). In our study, patients older than 65 years demonstrated a statistically significant higher rate of AEs and SAEs compared to younger patients. Infections and SIEs were also more common in this age group but the difference was not statistically significant. Recent data from the French Registry (AIR) demonstrated an increased risk of severe infections and deaths in elderly RA patients treated with RTX (18). On the contrary, Wendler *et al*. in the GERINIS study from Germany did not find a higher rate in adverse drug reactions or deaths in patients older than 60 years of age compared to younger patients (17).

In anti-TNF treated patients, age was a major risk factor for serious infections both in the Hellenic Registry (19) as well as in a number of observational studies (27-30). Nevertheless, other studies have not found such an increased rate of serious infections in elderly patients (31, 32). More data are needed before a definite conclusion regarding the influence of advanced age in the risk of AEs or serious infections in patients treated with RTX can be made.

Malignancies (2 events, 0.46/100 patient-years) and cerebrovascular accidents (5 events, 1.15/100 patient-years) were rather uncommon in our study and not much different from has been reported in long-term extension studies of RCTs (6).

In conclusion, the LAUNCH study is one of the few, prospective, long-term, real-life studies confirming the safety of repeated RTX administrations in an unselected refractory RA population. These results are in accordance to the safety data obtained from RCTs and their long-term TES and do not differ from the safety profile observed in long-term treatment with anti-TNF agents. Caution is needed in patients with advancing age receiving RTX, although more data are needed in that direction while appropriate screening and monitoring for HBV reactivation in patients with chronic or past HBV infection is required.

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