Severe adverse drug reactions to biological disease-modifying anti-rheumatic drugs in elderly patients with rheumatoid arthritis in clinical practice

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Abstract

Objective

Biological DMARDs are widely used in the treatment of rheumatoid arthritis (RA) but their relationship with adverse drug reaction (ADR) is important. RA is now known to increase in incidence and prevalence with age. Our objective was to assess the incidence of severe ADR in the long term, compare safety between the different bDMARDs and identify other possible risk factors for severe ADR in elderly RA patients.

Methods

A 14-year retrospective longitudinal study was performed. RA patients followed in an out-patient clinic starting bDMARDs after the age of 65 were included. Primary outcome: discontinuation due to a severe ADR related to bDMARDs (etanercept, infliximab, adalimumab, rituximab, golimumab, certolizumab, abatacept and tocilizumab). Covariables: sociodemographic, clinical and therapy. Incidence rates of discontinuation were estimated using survival techniques and comparison between bDMARDs discontinuation rates and other associated factors were run by Cox regression models.

Results

We analysed 286 courses of bDMARDs therapy in 146 elderly patients (604 patient-years). 78% were women, with a mean age at diagnosis of 66.5±7 years, and a median time to the start of the first bDMARDs of 6±4 years. The incidence of discontinuation due to severe ADR estimated was 10.2% patient-years, with a median survival of around 7 years. The most frequent cause was infections. Etanercept had the lowest risk of severe ADR compared to other bDMARDs.

Conclusion

Our study reflects the 'real world' experience in elderly RA patients on bDMARDs, with non-selected patients for a 14-year follow-up.

Key words

rheumatoid arthritis, elderly, diverse drug reactions, bDMARDs

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Received on December 5, 2016; accepted in revised form on March 14, 2017.

Funding: this work was supported by an independent grant from Pfizer.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is now known to increase in incidence and prevalence up to approximately age 85. The prevalence of RA in persons 60 years of age and older is reported to be around 2% (1).

The main goal of treatment in RA patients is to prevent joint damage and disability, achieving "remission", or at least a state of low disease activity. It seems that the disease has a better prognosis due to the benefit from early diagnosis and the introduction of effective treatment strategies such as intensive management, full dose of disease-modifying anti-rheumatic drugs (DMARDs) in combination, and the emergence of biological disease modifying anti-rheumatic drugs (bDMARDs) (2).

In the treatment of RA with treat-to-target strategy, bDMARDs are indispensable and effective drugs, but they are also associated with the occurrence of adverse drug reactions (ADR) (3-6). ADR are defined by WHO (7) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function". We can classify ADR according to the Medical dictionary for Regulatory Affairs (MedDRA) (8) as moderate, when they force the suspension of the drug and severe when they require patient hospitalisation, develop permanent sequelae or cause death. The role of bDMARDs has been well established in middle-aged patients with RA.

However, information about the safety of bDMARDs in elderly RA patients in the long term is not well known yet. The treatment of RA in elderly patients requires particular vigilance, not only related to compromised host defense mechanisms, but also increasing comorbidities (mainly diabetes mellitus, renal disease, cardiovascular disease, chronic lung disease, and frailty), which may also increase the risk of infection. Since elderly patients may have an elevated risk for ADR, evaluating this risk in this population through observational studies is necessary, especially because despite the high incidence of this disease in the elderly, patients who are >65 years of age have been consistently underrepresented in clinical trials of arthritis treatments (9, 10).

Some observational studies indicated an increased risk for adverse events or infections in elderly patients treated with bDMARDs compared with younger patients (11, 12), while other studies reported a similar safety profile between the two groups of patients (13, 14). An observational study support their use does not increase bacterial infections in elderly patients (15). On the other hand, older age was a significant risk factor of infection or serious infection in patients with RA (16, 17). In summary, information about safety about bDMARDs in elderly RA patients in the long-term is not conclusive. In the next decade, a strategy suitable for elderly RA patients should be developed because the number of these patients is on the rise.

Thus, the aim of our study was to analyse the ADR related to bDMARDs, and specifically the severe ones in a cohort of elderly RA patients over a long period of time in real-life conditions. We wanted to assess the incidence of severe ADR in the long term, and compare safety between the different bDMARDs. Secondly, we also wanted to identify other possible risk factors for severe ADR, to help rheumatologist to choose the best therapeutic option.

Materials and methods

Study design, patient sample, and data collection

This study was carried out in one of the tertiary public health Hospitals of the Community of Madrid (Hospital Clínico San Carlos), covering a catchments area of approximately 400,000 people. An observational retrospective longitudinal study was performed. Subjects included all patients attending the rheumatology outpatient clinic of our centre, with medical diagnosis (according to ICD-10) of RA, aged ≥65 years when started treatment with bDMARDs between January 1st. 2000 and November 15th. 2012, until end of the study (December 15th. 2013).

The patient data in this project were obtained during routine clinical practice by the rheumatologists for 14 years

with the informed consent of patients to be treated in a service that has clinical assistance and research work. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, and was approved by the institutional ethics committee.

The investigators retrospectively reviewed all the medical records (MRs) to obtain the variables. For the period between 2000 to December 2006, MRs were on paper and after that period, they were recorded in a departmental electronic health record (MEDI <log>) used in our outpatient clinic (20).

Variables

The main outcome was the development of a severe ADR defined as an injury related to medical management that required discontinuation of the bDMARDs and hospitalisation or when the patient dies as a result of the ADR.

The independent variable was the type of BA (Anti-TNF: etanercept (ETN), golimumab (Goli), certolizumab (CTZ), infliximab (IFX) y adalimumab (ADA); other biologics: rituximab (RTX), abatacept (ABA), tocilizumab (TZL)).

The following predictive and confounding factors were considered: 1) Sociodemographic baseline variables including sex, age, marital status (*vs*. not married), education level (any study degree *vs*. no studies), job status (assessed as Active, Retired, Housewife, Student, Unemployment), and disability (permanent disability, support or need help). 2) Disease related variables, including the date of RA onset and diagnosis, disease duration, erythrocyte sedimentation rate (ESR) (defined as mean value during the first year before first bDMARDs therapy), positive rheumatoid factor (RF), positive antibodies directed against citrullinated proteins and peptides (ACPAs), DAS-28 and HAQ (both defined as mean value during the first year of the first bDMARDs therapy). 3) Comorbid baseline medical conditions (hypertension, hypercholesterolaemia, cardiovascular disease, diabetes mellitus, depression, renal failure, osteoporosis, chronic obstructive pulmonary disease (COPD)) 4) Other pharmacological variables including a) concomitant glucocorticoids, NSAIDs (both defined as yes or no during the first three months from the beginning of the bDMARDs; and b) number of previous DMARDs and concomitant DMARDs (during the whole follow-up of the study). (4) Calendar time: dividing the start time of each bDMARDs in 2-year intervals (from 1st Jan 2000 until 31st Dec 2001; 1st Jan 2002 until 31st Dec 2003; etc, until end of follow-up).

Table I. Cohort description.

Number of patients	146
Female, n (%)	112 (78.32)
Age at diagnosis (years), mean ± SD	66.53 ± 6.98
Married, (%)	46.5
No studies or primary school, (n=113, %)	91 (80.5)
Courses of BA treatment	286
Age at first bDMARD (years), mean ± SD	72.53± 5.19
Lag time to the first bDMARD (years), mean ± SD	6.5 ± 7
ESR (mm/h), median (p25-p75)	29.6 (19-51)
Positive RF, n (%) (n=146)	104 (71.2)
Positive ACPAs, (n=80, %)	44 (55)
DAS 28, median (p25-p75)	4.4 (3.9-5.3)
Comorbid conditions, %	
Hypertension	71.4
Hypercholesterolaemia	59.4
Congestive heart failure	19.5
Cardiovascular disease	17.8
Diabetes Mellitus	24.8
Depression	34.9
Cancer	11.2
Renal failure	3.7
Osteoporosis	64.6
Chronic obstructive pulmonary disease (COPD)	9.7
Liver disease	12
HAQ, median (p25-p75)	1.12 (0.5-1.7)
Corticoids, %	89
DMARDs, %	98
Number of DMARDs before BA, median (p25-p75)	3 (2-4)
Biologic agents, %	
Adalimumab	27.3
Etanercept	21.3
Infliximab	22.4
Rituximab	19.2
Other TNF-α	4.2
Other BA	5.6

Statistical analysis

A description of the sociodemographic and clinical characteristics of patients included were explored with frequency distribution and the mean and standard deviation or median and percentiles.

To explore severe ADRs, we included all the patients with RA and the time of exposure comprised the period from the baseline visit (starting date of bDMARD therapy) until the occurrence of any of the following cut-off points: lost of follow-up, main outcome, or the end of the study (Dec. 2013). It is important to note that real life conditions use complicated patterns of drug therapies. Thus, patients were included in different time-periods and contributed with patient-years at risk to severe ADR.

Kaplan-Meier curves were set to account for ADRs over time. Incidence rates (IR) of ADRs were estimated using survival techniques, and results were expressed per 100 patient-years with their respective 95% confidence interval (CI).

Cox bivariate analyses were done to assess differences between sociodemographic, clinical covariables and the main outcome. Cox multivariate regression analyses were run to compare the different bDMARDs in the development of severe ADRs. In multivariate analysis we included age, sex, calendar time, and all variables with a $p<0.2$ in the bivariate analysis, to adjust for confounders. Results were expressed by hazard ratio (HR) or relative rate of se-

Table II. Characteristics of the severe adverse drug reactions (ADRs). Results are expressed as number (n) and percentage (%).

	Severe ADR	
bDMARDs		
- ETN	**6**	**(9.68)**
- GOLI	1	(1.61)
- CERTO	0	
- IFX	**28**	**(45.16)**
- ADA	**15**	**(24.19)**
- RTX	**11**	**(17.74)**
- ABT	1	(1.61)
- TOCI	0	
Causes of severe ADR		
- Cancer	4	(6.45)
- Ischaemic cardiopathy	3	(4.84)
- General	1	(1.61)
- Congestive heart failure	5	(8.06)
- Infection	**32**	**(51.61)**
- Mucocutaneous	1	(1.61)
- Exitus	**16**	**(25.81)**

vere ADRs, and CI. Regarding missing data, for categorical variables a dummy category for such missing observations with the value "no data" was included, so those subjects could be included in the analysis.

Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. All analyses were performed in Stata v. 12 statistical software (Stata Corp., College Station, TX, USA). A two-tailed *p*-value under 0.05 was considered to indicate statistical significance.

Results

Patient's baseline characteristics

146 patients were included in the study who began 286 different courses of BA treatment, with a total follow-up of 604 patients-year. Table I includes a wide cohort description. Most of the patients were women with a mean age at diagnosis of 66.5±7 years, and the mean time to the first bDMARDs of 6±4 years. At the beginning of the study, most of the patients had at least moderate disease activity, with a medium level of disability. Most of the patients had at least one basal comorbid medical condition with hypertension, hypercholesterolaemia, osteoporosis, hypercholesterolaemia and depression the most prevalent ones. 71% of the patients had positive rheumatoid factor and half of patients ACPA positive. Almost all patients were taking DMARDs at the beginning of study (98%) and 89% of the patients were taking glucocorticoids, with a median dose of 9.1 (p25–75: 7.5–10) mg/day and a maximum of 20 mg/day. The BA most frequently used was ADA, followed by IFX, ETN, and RTX.

We found a total of 62 discontinuations due to severe ADRs (21.7%), 16 of which resulted in exitus (Table II). The most frequent cause was infections, mainly respiratory, tuberculosis and herpes zoster. The second main cause was exitus mostly due to infections and cancer.

The median time to development of a severe ADR was 7.3 years, and the retention rate for the bDMARDs related to discontinuation due to severe ADRs was 73% at 6 months, 60% at 12 months, 29% at 3 years, and only a 5% at 10 years. Table III shows the incidence rates (IR) of severe ADR, which

Table III. Incidence rate (IR) of severe ADRs in eldery RA patients with bDMARDs, by sex, diagnostic period, and therapy.

ADR	Patient-years	Severe ADR		
		n	IR	95% CI
	604	62	10.2	7.9-13.1
By sex				
Women	505	51	10.08	7.6-13.2
Men	94	11	11.6	6.4-21.1
By Calendar time				
2000-2001	32.48	8	7.54	3.7-15
2002-2003	278	6	13.3	5.9-29.6
2004-2005	455.2	9	11.5	5.9-22.1
2006-2007	378.1	10	7.9	4.2-14.8
2008-2009	172.4	16	13.03	7.9-21.2
2010-2011	161.4	8	8.9	4.4-17.4
2012-2013	99.7	5	13.3	5.5-32.8
By bDMARDs:				
Infliximab	176.7	28	15.8	10.9-22.9
Adalimumab	185.4	15	8.08	4.8-13.4
Etanercept	117.1	6	5.12	2.3-11.3
Rituximab	91.6	11	12	6.6-21.6
Other TNF-α	33.4	2	3.2	1.4-23.9

n: events; IR: incidence rate per 100; CI 95%: confidence interval.

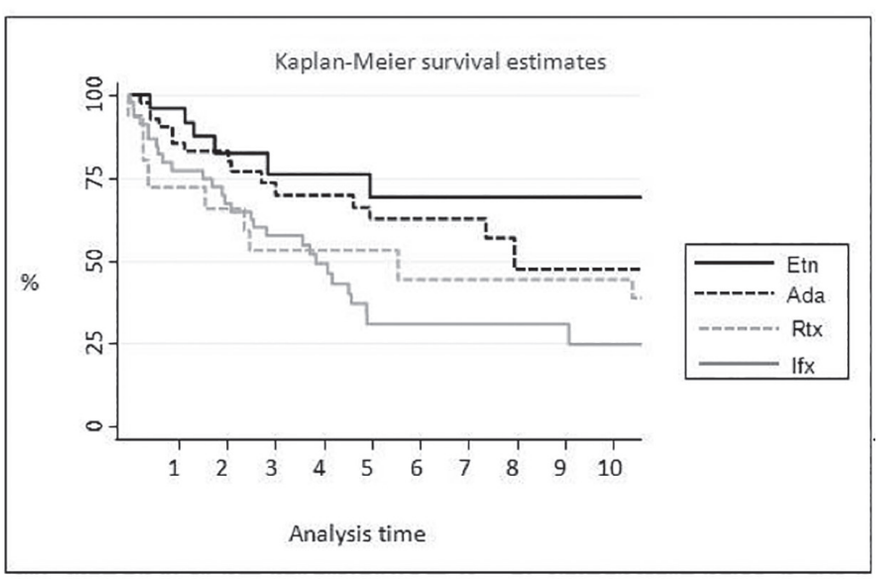

Fig. 1. Incident rates for etanercept, adalimumab, rituximab and infliximab.

Table IV. bDMARD discontinuation due to adverse drug reactions (ADR): bivariate analysis.

	Severe ADRs		
	HR	95%CI	*p*-value
Age at diagnosis, years	1.01	0.96-1.05	0.646
Age at first bDMARD, years	1.05	1.00-1.10	0.024
Gender, male	1.03	0.55-1.93	0.9
Disease duration, years	1.03	0.98-1.07	0.168
Married	1.04	0.57-1.9	0.8
No studies or primary school	1.02	0.4-2.5	0.9
Calendar time, year intervals:			
2000-2001	1	-	-
2002-2003	1.4	0.39-3.2	0.8
2004-2005	1.7	0.7-4.1	0.2
2006-2007	0.96	0.35-2.6	0.9
2008-2009	1.6	0.6-4.5	0.33
2010-2011	1.9	0.5-7.1	0.33
2012-2013	1.46	0.4-5.2	0.56
Positive ACPAs	1.5	0.6-3.7	0.4
Positive RF	1.10	0.63-1.96	0.7
DAS 28	1.03	0.79-1.34	0.81
HAQ >1.5	1.70	0.9-3.2	0.08
Baseline Comorbid conditions			
Hypertension	1.17	0.53-2.56	0.69
Hypercholesterolemia	1.19	0.66-2.15	0.54
Congestive heart failure	1.96	1.12-3.43	0.018
Cardiovascular disease	2.04	1.14-3.63	0.015
Diabetes Mellitus	1.21	0.57-2.55	0.608
Cancer	2.13	0.83-5.46	0.1
Depression	1.26	0.71-2.25	0.42
Renal failure	0.46	0.13-.1.57	0.21
Osteoporosis	1.63	0.88-3.02	0.115
COPD	1.61	0.75-3.42	0.215
Liver disease	2.71	1.03-7.13	0.043
NAIDs	0.83	0.37-1.85	0.651
Corticosteroids (mg/day)	4.0	1.4-11.6	0.001
Concomitant DMARDs	0.79	0.58-1.07	0.133
Previous bDMARDs (Yes)	0.88	0.45-1.72	0.713
bDMARDs:			
Infliximab	1	-	-
Etanercept	0.32	0.13-8.16	0.018
Adalimumab	0.51	0.24-1.11	0.093
Rituximab	0.92	0.43-1.99	0.845
Other bDMARDs (Abata/Tzl)	0.29	0.03-2.27	0.243
Other TNF- antagonists (Ctz/Goli)	0.67	0.10-4.31	0.680

are estimated at 10.2 per 100 patient-years regardless the cause. The IR for ADR secondary to infections were estimated in 5.2 (3.7–7.5), and for exitus was 2.65(1.6–4.3). The IR due to severe ADRs had fluctuations over time. We also show the IR for the different bDMARDs (Fig. 1), infliximab being the drug with the highest IR.

Bivariate analysis

Table IV displays the bivariate analysis. We found statistical differences among bDMARDs, concomitant corticoids and severe ADRs. Regarding sociodemographic and clinical baseline characteristics of the patient, age of bDMARD onset, congestive heart failure, cardiovascular disease and liver disease, achieved statistical significance.

Multivariate analysis

The multivariate analysis is shown in Table V. Finally, it was adjusted by age, sex and calendar time, Etn had the lowest risk of severe ADR compared to other bDMARDs, achieving statistical signification for IFX, and RTX. With this model and modifying the type of bDMARD as reference category, in order to see differences between them, we have found that the HR of severe ADR development in ETN, ADA, and RTX compared to IFX was 0.18 (0.05–0.5), (p=0.004); 0.4(0.19–1.2), (p=0.1); and 0.7 (0.34–1.6), (p=0.4) respectively. The hazard for severe ADR of RTX compared to the rest of the bDMARDs, except for ETN, did not achieve statistical signification.

Other interesting findings were that patients with comorbidity had more probability of developing severe ADRs, specifically with congestive heart failure, cardiovascular disease or liver disease. We also found that taking glucocorticoids as well as age at first bDMARD increased the risk severe ADR. Interestingly, having positive ACPAs showed a trend for higher probability to severe ADR. HAQ and DAS 28 dropped from the model as well as concomitant DMARDs. The proportionality of the regression model was tested using the Schoenfeld and the scaled Schoenfeld residuals. In all models, p-values were ≥0.45.

Discussion

This study contributes to enhance the knowledge of the severe adverse drug reactions in the long term that occur in rheumatoid arthritis elderly patients receiving bDMARDs in real life conditions. We have estimated the incidence of the discontinuations due to severe ADR; we have conducted a direct comparison on safety between the different bDMARDs, demonstrating that ETN seems to be the safest in terms of development of severe ADRs compared to the rest of them.

The incidence of discontinuation due to severe ADR estimated in our study was 10.2 (events/ 100 patient-years) with a median survival of around 7 years, similar to other bDMARDs studies (19, 20). As in other previous studies (3-5, 18), the most frequent cause of severe ADRs was infections, showing an IR similar to our results (15, 21). Interestingly, the IR of severe ADRs in the whole cohorts of RA, is superior in elderly compared to younger patients (4, 22), reflecting the complexity of RA management in old, comorbid patients. Regarding the incidence in the different treatment regimens studied, we found that for the severe ADRs, IFX had the highest risk of ADR development compared to other bDMARDs, and ETN

Table V. bDMARD discontinuation due to severe adverse drug reactions (ADR): multivariate analysis.

	Severe ADRs		
	HR	95%CI	*p*-value
Gender, male	1.5	0.6-3.8	0.34
Age at first bDMARD, years	1.07	1.01-1.14	0.01
Calendar time: 2000-2013	1.2	1.03-1.4	0.01
Comorbid conditions:			
Congestive heart failure	1.96	0.98-4.1	0.07
Liver disease	4.3	1.6-11.3	0.003
Cardiovascular disease	2.3	1.12-4.9	0.02
Concomitant corticosteroids	3.8	1.6-8.8	0.001
Positive ACPAs	2.45	0.87-6.8	0.08
bDMARDs:			
Etanercept	1	-	-
Infliximab	5.5	1.7-17.7	0.004
Adalimumab	2.7	0.7-9.9	0.1
Rituximab	4.1	1.4-12.3	0.01
Other bDMARDs	1.6	0.4-7.3	0.5

the lowest. This data is confirmed by the multivariate analysis. There are few data comparing the safety of the different biologics in elderly RA patients. It is important to take into account that most of the RCTs in RA exclude commonly used clinically relevant patient subgroups as elderly patients. Moreover, they evaluate in the short term and the scope, environment is different from day-to-day clinical practice. All of these diminish the ability to make an extrapolation of the trial results on daily practice (23, 24).

A wide arsenal of therapy options for RA actually exist, but knowledge on the optimal use of different drugs in elderly patients in typical day-to-day practice still remains scarce. In this sense, only few studies have been conducted in clinical practice, with direct comparisons between different drugs in this specific population, showing similar results to our study (4, 25).

Several factors may contribute to severe ADRs (26-28). In this sense, we have corroborated the role of baseline comorbidities, concomitant use of glucocorticoids and also severity disease variables. Regarding the latest, the presence of positive ACPAs seemed to influence in the discontinuation due to severe ADR. In relation with comorbidities, recent studies have shown that patients with RA have a higher likelihood of developing congestive heart failure and cardiovascular disease (29-32). These problems may well be related to the chronic inflammation associated with RA (29).

Age at first bDMARD, as expected, also emerged as an independent factor for severe ADR. It is consistent with findings reported in other recent study (33). Physiological and immunological changes of elderly and decreased compliance in patients with multimedication might play a role in this. In the elderly, infections are more difficult to prevent than in young people, as vaccination is less effective, and infections are the most frequent ADR in patients treated with bDMARDs. Rather, elderly RA patients require enhanced vigilance in the management of their pharmacotherapy and comorbidities. In our study, a highest risk was found for concomitant glucocorticoid use, with a trend for an increasing risk at higher doses. Recently, concerns have emerged regarding glucocorticoids and both serious infections (15, 18, 34, 35). Regarding anti-TNF relation to infections, some studies had observed an approximately 2-fold increase in risk of serious infection amon6).

A limitation of our study can be related to the own design, that is a retrospective observational study. However, the main variable is not underestimated and is well registered in our electronic medical record in an easy and structured manner. A weakness is the follow-up length for some of the bDMARDs, mainly in those more recently commercialised. Although we had a longer follow-up, the sample size was not big enough to establish any specific conclusion in those. Despite these pitfalls, we think our study reflects the 'real world' experience in elderly RA patients on bDMARDs, and it is performed in non-selected patients, and takes into account many covariates on multiple potential confounders extracted from routine clinical practice.

This study has shown that etanercept seems be the safest regarding severe ADRs compared with the rest of bDMARDs in elderly RA patients in clinical practice. Our results confirm the bDMARDs should be chosen on the basis of patient characteristics, in order to ensure treatment successfulness. Caution and close monitoring is also advised in elderly RA patients ACPA positive treated with glucocorticoids, with congestive heart failure, cardiovascular disease or liver disease. Applying the recommended screening before using bDMARDs helps to reduce adverse events related to the therapy. All of these results give important information to the researchers and clinicians, and perhaps can be considered the starting point for other more specific studies to address the ongoing challenge in the super-aging society.

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