Five-year survival on infliximab in rheumatoid arthritis patients: analysis from an Italian registry (GISEA) by different calendar years

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Abstract

Objective

To assess long-term drug survival and effectiveness in biological drug-naïve patients with rheumatoid arthritis (RA), starting infliximab as first treatment, in the period 2000-2009, comparing different calendar years.

Methods

Patients with RA recorded in the GISEA registry beginning infliximab as first ever biological drug were enrolled, subdivided into periods 2000-2002, 2003-2005, and 2006-2009. We evaluated 5-year drug survival by Kaplan-Meier life analysis and 1-year EULAR responses based on the 28 joint count Disease Activity Score (DAS28), and baseline predictors, by multiple logistic regression analysis.

Results

Of 565 RA patients included in the analysis, 290 (51.3%) began infliximab in years 2000-2002, 167 (29.5%) in 2003-2005, and 108 (19.1%) in 2006-2009. At entry, DAS28-ESR was significantly lower in 2006-2009 (5.1±1.3) than in 2000-2002 (6.0±1.2) or 2003-2006 (6.0±1.0) (p=0.001). Significantly more RA patients attained a EULAR "good" response at 1 year in 2006-2009 (39.8%) than in 2000-2002 (23.1%, p=0.001). Nevertheless, the rate of drug survival at 5 years, roughly 40%, was not significantly different over the calendar periods. Co-administration of DMARDs was significantly correlated with drug survival (Odds Ratio (OR) 1.42, 95% Confidence Intervals (CI) 1.005–2.09, p=0.04), but not the period when starting treatment. Instead, a EULAR "good" response was significantly correlated with the period 2006-2009 (OR 2.24, 95% CI 1.37–3.65, p=0.02).

Conclusion

Our study shows that RA patients have similar drug survival on infliximab regardless of the period when they started. However, patients treated in more recent years tend to have less active RA and to more readily attain favourable clinical outcomes.

Key words

infliximab, anti-TNF, GISEA

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Introduction

It is nearly 15 years since infliximab, a chimeric monoclonal antibody targeting tumour necrosis factor-α (TNF-α), was licensed for therapeutic use in patients with rheumatoid arthritis (RA) (1, 2), and, later with ankylosing spondylitis, psoriasis, and inflammatory bowel diseases. Infliximab is the progenitor of the biological disease-modifying drugs and, in patients with RA, has amazingly reduced the disease severity and improved their functional ability. Several studies conducted in real-world clinical care settings have confirmed the results of the randomised clinical trials and provided evidence that infliximab enables the achievement of favourable clinical outcomes and slows, or even arrests, joint damage progression in RA (3-20). However, because of the different population selection, the clinimetric tools that are measurable in controlled trials settings are not fully applicable in daily clinical practice. A useful surrogate that may be helpful in assessing long-term outcomes of infliximab is the time of persistence on therapy, since the drug retention rate can be considered as a result of all the variables affecting treatment continuation, safety, effectiveness and tolerability, and may ultimately represent an indirect measure of the overall worth of a drug in long term routine care.

However, the possibility that the survival/effectiveness of infliximab may change over time was not taken in account in previous survey analyses. In the last decades, a growing body of evidence has shown that the best management of RA should be based on tight control of the patients, following a "treat to target" strategy and starting adequate treatment in the early stages of the disease (window of opportunity) (21). Consistently, the current approach of the rheumatology community is to begin aggressive treatment of patients with recent onset RA. Therefore, it is conceivable that the behaviour of rheumatologists, in the sense of either the selection of eligible patients or targeting different outcomes, may have changed over time, thus affecting the clinical responses to therapy. Indeed, it has been shown that early treatment with Infliximab plus methotrexate is more likely to succeed than if the same treatment is delayed until later in the course of the disease (22).

To our knowledge, only one recent study has focused on in this issue by comparing clinical characteristics and outcomes in RA patients starting infliximab across different calendar periods (17). The purpose of our study was to assess whether the profile of our RA population under treatment with infliximab has changed, in terms of 5-year drug survival or 1-year effectiveness, over time in different periods.

Patients and methods

Study design

The Gruppo Italiano Studio Early Arthritis (GISEA) registry was designed to prospectively collect real-world clinical data on patients with RA, psoriatic arthritis, spondyloarthritis treated with biological drugs, based on their routine care. Data are recorded at 24 hospitals or community-based rheumatology units throughout Italy, but the registry covers only those patients referred to a rheumatology centre. The local Ethics Committee approved the GISEA registry (Trial registry no. NCT01543594) and prior written informed consent to take part was obtained from all patients in compliance with the declaration of Helsinki.

Patient data were recorded at baseline and every six months thereafter. The collected data include age, gender, disease duration, body mass index, the intake of glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs), tender and swollen joints count, 28 joints-based Disease Activity Score (DAS28), C-reactive protein, the first hour erythrocyte sedimentation rate (ESR) (mm/1st hour), rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA), pain assessed by means of a visual analogue scale (VAS 0-100), functional ability by the Health Assessment Questionnaire Disability Index (HAQ-DI), side effects, biological drug discontinuation.

Study population

The study design involved the selection of patients with RA, diagnosed ac-

cording to the American Rheumatism Association 1987 revised criteria (23), beginning their first ever anti-TNF-α treatment with infliximab up to December 2009. Patients were censored on 31st August 2104. Patients previously treated with biological drugs were excluded from the study. Infliximab 3.0 mg/kg intravenously at weeks 0, 2 and 6, and every 8 weeks thereafter was given following the official guidelines. Patients for whom no follow-up data were available (approximately 10%) were excluded. A change in the DAS28 was used to assess the clinical response (modified EULAR response criteria), considering the response as "good" when the DAS28 improvement from baseline was >1.2, together with passage to a lower disease activity class. Disease remission was defined as a value of DAS28 ≤2.6 (24).

Table I. Patient demographics and baseline characteristics.

		Enrolment period			
	Overall n=565	2000-2002 (**A**) n=290	2003-2005 (**B**) n=167	2006-2009 (**C**) n=108	Between-groups *p*-value
Female (%)	574 (83.9%)	240 (82.8%)	142 (85.0%)	92 (85.2%)	0.68
Age, years	52.9 ± 12	53.3 ± 12	54.2 ± 12	50.0 ± 13	0.01 C *vs*. B 0.03 C *vs*. A
Disease duration, years	8.6 ± 7.8	9.3 ± 7.9	8.3 ± 7.9	6.9 ± 7.1	0.003 C *vs*. A
DAS28-ESR	5.8 ± 1.2	6.0 ± 1.2	6.0 ± 1.0	5.1 ± 1.3	0.001 C *vs*. A/B
ESR mm/hour	40.8 ± 24	41.6 ± 23	41.0 ± 24	38.2 ± 25	0.45
HAQ-DI	1.5 ± 0.7	1.6 ± 0.7	1.5 ± 0.6	1.3 ± 0.7	0.04 C *vs*. B 0.01 C *vs*. A
RF/ACPA (%)	83.2	85.2	84.2	76.6	0.12
DMARDs (%)	97.2	98.3	97.6	93.5	0.1
DMARD before	2.9 ± 1.4	3.3 ± 1.4	2.8 ± 1.4	2.0 ± 1.1	0.001 C *vs*. A/B 0.01 B *vs*. A

Values are the mean 1 SD unless otherwise indicated. ESR: erythrocyte sedimentation rate; DAS28: 28 joints Disease Activity Score; HAQ-DI: Health Assessment Questionnaire - Disability Index; RF/ACPA: rheumatoid factor/anti-citrullinated peptide antibody; DMARDs: disease-modifying antirheumatic drugs; BMI: body mass index.

Statistical analysis

The Kolmogorov-Smirnov test was used to check a normal distribution of continuous variables. Continuous variables were reported as means and standard deviations if normally distributed, while medians and interquartile range (IQR) were calculated for not normally distributed continuous variables. For categorical variables, counts and percentages were calculated. Differences in means for normally distributed continuous variables were compared by one-way analysis of variance and the Kruskal-Wallis test was used to compare not normally-distributed continuous variables. Differences in the distribution of frequencies were assessed by chi-squared test. Survival of therapy was measured using the Kaplan-Meier life table method, and the log-rank test was used to compare the discontinuation rates. Patients contributed to the survival models until the first discontinuation or censoring at 5 years of treatment. Multivariate logistic regression analysis was used to analyse predictors of clinical outcomes. The response variable was drug discontinuation (yes/no), a EULAR "good" response (yes/no) or DAS28-based remission (yes/no) and the baseline covariates were age, gender (female/male), disease duration, DAS28, use of DMARDs (yes/no) at entry, and calendar period (2000–2002 as reference). All the analyses were made using SAS version 9.2 (SAS Institute, Inc; Cary, NC), and a *p*-value of 0.05 or less was considered statistically significant. The data are expressed as percentages or mean values ±1 standard deviation (SD), unless otherwise indicated.

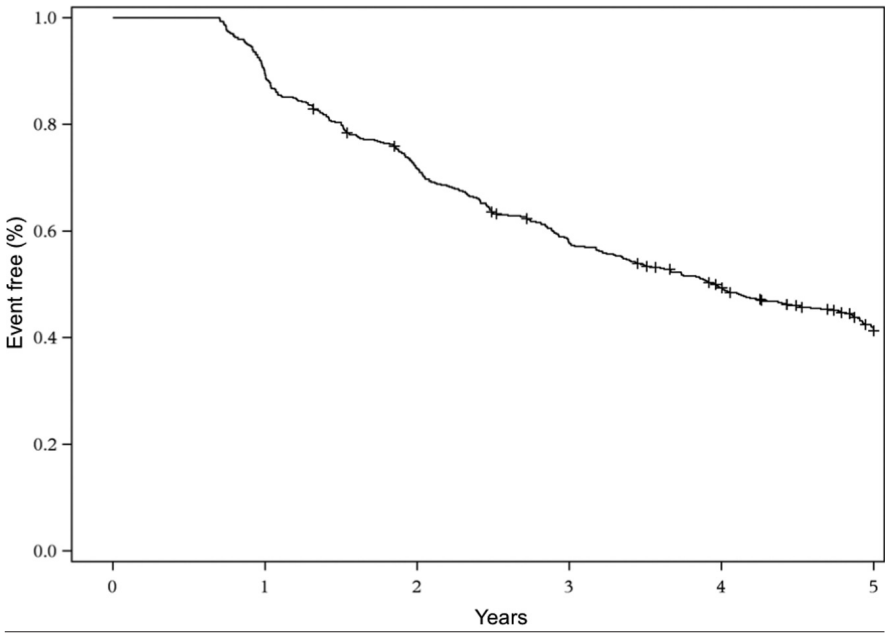
Results

Patient demographics

By August 2014, 565 biologic drug-naïve active RA patients registered in the GISEA met the criteria for analysis. Of these, 290 (51.3%) had received infliximab in 2000–2002, 167 (29.5%) in 2003–2005, and 108 (19.1%) in 2006-2009 (Table I). At entry, DAS28-ESR was significantly lower in 2006–2009 (5.1±1.3) than in 2000-2002 (6.0±1.2) or 2003–2005 (6.0±1.0) (p=0.001). Age at start of treatment with infliximab was significantly lower in RA patients in years 2006–2009 than in previous calendar periods (p=0.03). Yet, RA patents in years 2006–2009 had the shortest disease duration (p=0.01) and the lowest HAQ-DI (p=0.03). Interestingly, the number of DMARDs prior to starting infliximab was significantly lower (p=0.001) in 2006-2009 (2.0±1.1) than in previous periods (2000–2002: 3.3±1.4, 2003–2005: 2.8±1.4). There were no differences in terms of BMI, positivity of RF/ACPA or co-administration of DMARDs among the 3 groups at baseline.

Clinical outcomes

Persistence on therapy was assessed by Kaplan-Meier life table methods. The overall crude drug survival rate was 58.0% at 3 years and 41.1% at 5 years (Fig. 1). Considering each calendar period (Fig. 2), the rate of 5-years drug survival was 43.1% in 2000-2002, 41.9% in 2003–2005, and 39.8% in 2006–2009, with no statistically significant difference (log rank test, p=0.31). Clinical outcomes were assessed at 1 year by evaluating the EULAR "good" response, DAS28-based remission and functional improvement (HAQ ≥0.22 from baseline) (Table II). Crude DAS28 was significantly lower in 2006-2009 (3.4±1.4) than in the previous periods (2000-2002, 4.1±1.5; 2003–2005, 3.8±1.4). The highest percentage of EULAR "good" response was reached in patients in years 2006–2009 (39.8%) and the difference was statistical significant when compared to years 2000-2002 (23.1%, p=0.001). The percentage of EULAR "good" responses was also significantly higher in 2003–2005 (32.9%) than in 2000–2002 (p=0.002). Likewise, the percentage of DAS28-



		0 year	3 years	5 years	MST
All cohorts	Patients at risk	565	328	228	3.83 years
	Events	0	237	327	

MST: median survival time

Fig. 1. Five-year drug survival rate of infliximab in the whole RA cohort (n. 565 patients) is shown.

based remission was significantly higher in 2006–2009 (26.9%) than in 2000–2002 (15.9%, p=0.01), and in 2003–2005 (23.4%) than in 2000–2002 (p=0.04). The percentage of patients who attained an HAQ improvement was almost identical in the different calendar periods and was about 70%.

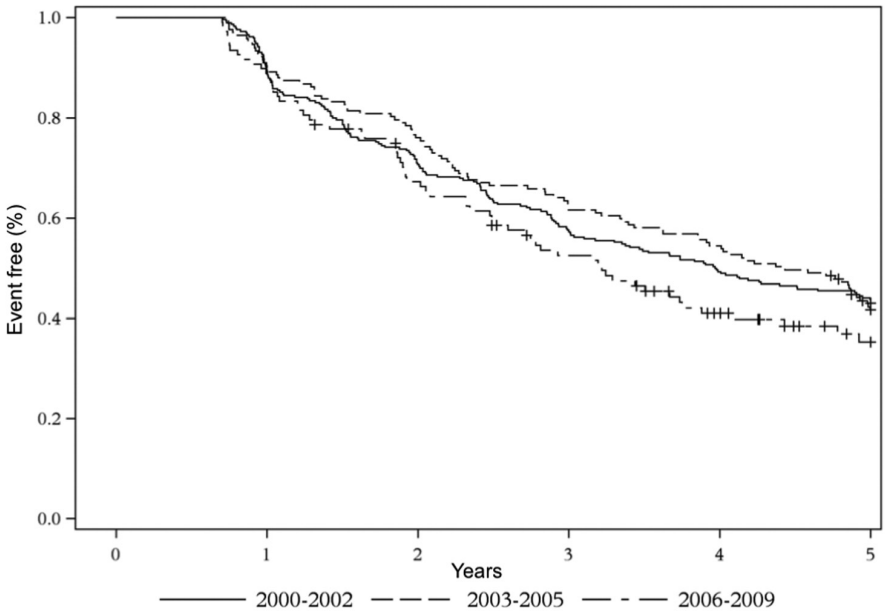
Analysis of predictors

Logistic regression models were used to search for possible predictors of clinical outcomes. The only predictor of 5-year survival on Infliximab was the combination therapy with DMARDs (OR 1.45, 95% CI 1.00 to 2.09, p=0.04), whereas the period when starting treatment was not correlated with drug persistence nor disease activity. Analyses of predictors of EULAR responses at 1 year are shown in Table III. RA patients beginning infliximab in 2003-2005 had a higher probability of attaining a EULAR "good" response at 1 year (OR 1.90, 95% CI 1.16 to 2.79, p=0.05), or DAS28-based disease remission at 1 year (OR 1.99, 95% CI 1.91 to 3.34, p=0.02) than those in years 2000–2002. RA patients in period 2006–2009 also had a significantly higher probability of attaining a EULAR "good" response at 1 year (OR 2.24, 95% CI 1.37 to 3.65, p=0.02), but the correlation with DAS28-based remission at 1 year (OR 1.56, 95% CI 0.86 to 2.82, p=0.68) was not statistically significant because of the wide CI. Baseline negative predictors of disease remission were age at the start of inflixmab treatment (OR 0.97, 95% CI 0.95 to 0.98, p=0.001), female gender (OR 0.40, 95% CI 0.23 to 0.67, p=0.0007) and DAS28 (OR 0.68, 95% CI 0.56 to 0.82, p=0.0001). No correlation with disease duration was found.

In Table IV, the causes of infliximab discontinuation periods are shown by calendar periods. During the 5 years of the survey, 165 patients (56.8%) discontinued treatment in 2000–2002, 97 (58.0%) in 2003–2006, and 65 (60.0%) in 2006–2009. There were no differences with regard to rates of ineffectiveness, adverse events or remission. Notably, the frequency of switching to a different biological drugs was 42.4% in years 2000–2002, 37.7% in 2003–2006, and 45.3% in 2006–2009, with no significant differences among groups (p=0.37).

Discussion

In this study we provided evidence that demographics and clinical characteristic of biological drug-naïve RA patients, recorded in the GISEA registry, starting treatment with infliximab, may have somewhat changed across calendar periods. The study span was subdivided into 3 periods, 2000–2002, 2003–2005, and 2006–2009, and patients beginning their first ever treatment with infliximab in years 2006–2009 had the shortest mean duration of disease (6.9 years), the lowest disease activity (mean DAS28 5.1), and the least impaired functional ability (mean HAQ-DI 1.3); they were younger (mean age 50 years), and had taken the lowest number of synthetic DMARDs (n.2) before starting infliximab. These findings are largely in agreement with the recently published data from the Biologic Treatment Registry Across Canada (17). In the latter study, Canadian patients with RA starting infliximab as first or second line biological drug showed a decrease in DAS28 (4.3), disease duration (9.6 years), or HAQ-DI (1.4), in the more recent years, 2008–2011. Like in our cohort, the authors also observed a trend to treat patients with a fewer number of DMARDs prior to beginning Infliximab. Similar results emerged from the register of the South Swedish Arthritis Treatment Group (25). In the latter, the authors assessed the profile of RA patients beginning a biological drug across years 1999–2006 and showed that biological drug-naïve patients had a significant negative trend in baseline disease duration, DAS28, and HAQ over time. The decrease in age and disease duration of biological starter patients over time would imply a trend to treat RA patients at earlier stages. Indeed, a reduction in age was seen only in our study, but not in the Canadian (17) or Swedish (25) reports. However, some differences among these studies should be taken into account. In the Swedish survey, all biological drugs were included and the years of analysis were less recent (up to 2006), whereas in the Canadian study RA patients initiating infliximab as second line biological drug were also included, thus possibly increasing the mean of



		0 year	3 years	5 years	MST
2000-2002	Patients at risk	290	167	125	3.97 years
	Events	0	123	165	
2003-2005	Patients at risk	167	103	70	4.43 years
	Events	0	64	97	
2006-2009	Patients at risk	108	58	43	2.8 years
	Events	0	50	65	

MST: median survival time

Fig. 2. Five-year drug survival rates of infliximab in RA patients by calendar period. The number of patients on therapy (patients at risk) and the number of withdrawals (events) at baseline, 3 and 5 years are shown.

Table II. Clinical outcomes: percentages of RA patients on infliximab achieving a "good" EULAR response, disease remission, or functional improvement at 1 year over time.

	Enrolment period			
	2000-2002 (**A**) n=290	2003-2005 (**B**) n=167	2006-2009 (**C**) n=108	Between-groups *p*-value
DAS28-ESR	4.1 ± 1.5	3.8 ± 1.4	3.4 ± 1.4	0.001 C *vs*. A 0.03 C *vs*. B 0.02 B *vs*. A
	n (%)	n (%)	n (%)	
EULAR "good" (Δ DAS28 ≥ 1.2)	67 (23.1%)	55 (32.9%)	43 (39.8%)	0.001 C *vs*. A 0.002 B *vs*. A
DAS28 remission (DAS28 ≤ 2.6)	46 (15.9%)	39 (23.4%)	29 (26.9%)	0.01 C *vs*. A 0.04 B *vs*. A
Function improvement (Δ HAQ-DI ≥ 0.22)	204 (75.6%)	119 (77.3%)	64 (71.1%)	0.57

DAS28: 28 joints Disease Activity Score; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire - Disability Index.

age when starting treatment. Altogether, this suggests that rheumatologists are complying with the recent official guidelines (26) and tend to prescribe infliximab earlier in RA patients with less severe disease. Moreover, this seems to be happening throughout the world, in faraway countries (17, 25), confirming the utility of releasing shared recommendations for the management of RA. In addition, in our opinion, this bears witness to the view that rheumatologists are becoming more confident with biological drugs and tend to prescribe them earlier.

We also evaluated the persistence on therapy at 3 and 5 years as a surrogate of the global effectiveness and safety of infliximab, and found no differences over time. However, the overall survival rate on infliximab was quite high, being 58.0% at 3 years and 41.1% at 5 years, as already reported in other anti-TNF-α drugs (27). This survival rate was a little higher than the rate reported in a cohort of RA patients from southern Sweden, 36% (27), or from the Swedish Biologics Registry (ARTIS), 38% (14), but almost identical to that of a Belgian survey (9), from the Nationwide Danish DANBIO Registry (10), and of a cohort of rheumatoid patients in the Lombardy Rheumatologic Network (LOHREN) Registry (28). Furthermore, the only positive predictor of survival on Infliximab at 5 years was the association with DMARDs, as already reported in previous studies (12, 14, 16, 27, 29). We expected to find some divergence in the frequency of switching biological drug across periods, but although there was higher trend in 2006-2009 this was not significant. This would suggest that the wider spectrum of biological drugs available in more recent years does not seem to influence the rheumatologist's decision to change treatment with infliximab.

Therapy with infliximab was effective and reduced disease activity in the whole RA cohort, but there were some differences across the years. The percentages of patients achieving DAS28-based remission or a EULAR "good" response at 1 year progressively increased over time and were significantly higher in the more recent years in comparison with the previous calendar periods. We also searched for possible baseline covariates correlating with clinical responses. Multiple regression analysis showed that the odds to attain a EULAR "good" response were twice as high in patients starting infliximab in 2003–2005 and even higher in those of 2006–2009, considering the 2000–2002 period as reference. Nevertheless, RA

Table III. Odds of baseline covariates to predict 1-year EULAR "good" response or 1-year DAS28-based disease remission in the whole RA patients cohort in therapy with Infliximab, as evaluated by multivariate logistic regression analysis.

	1-year EULAR "good"			1-year disease remission		
Baseline covariates	OR	95% C	*p*-value	OR	95% CI	*p*-value
Age	0.97	0.96-0.99	0.005	0.97	0.95-0.98	0.001
Disease duration	1.01	0.98-1.03	0.31	1.00	0.97-1.03	0.88
DAS28-ESR	1.11	0.92-1.34	0.26	0.68	0.56-0.82	0.0001
Calendar years						
2000-2002	1			1		
2003-2005	1.80	1.16-2.79	0.05	1.99	1.91-3.34	0.02
2006-2009	2.24	1.37-3.65	0.02	1.56	0.86-2.82	0.68
DMARDs						
No	1			1		
Yes	1.45	1.00-2.09	0.04	0.70	0.42-1.17	0.17
Gender						
Male	1			1		
Female	0.87	0.55-1.39	0.58	0.40	0.23-0.67	0.0007

EULAR: European League Against Rheumatism; DAS28: 28 joints Disease Activity Score; DMARDS: disease-modifying anti-rheumatic drugs; OR: odds ratio; CI: confidence intervals.

Table IV. Causes of infliximab discontinuation at 5 years.

	Enrolment period			
	2000-2002 (A) n=290	2003-2005 (B) n=167	2006-2009 (C) n=108	Between-groups *p*-value
	n (%)	n (%)	n (%)	
Adverse events	42 (14.4)	28 (16.7)	15 (13.8)	0.34
Ineffectiveness	58 (20)	35 (20)	19 (17.5)	0.76
Lost to follow-up	25 (8.6)	19 (11.3)	9 (8.3)	0.45
Remission	6 (2.0)	2 (1.1)	3 (2.7)	0.23
Others	34 (11.7)	13 (7.8)	20 (18.5)	0.01 C *vs*. B

patients on infliximab from 2003–2005 had double the odds of achieving a DAS28-based remission, while there was not significant correlation for the 2006–2009 period despite the high OR, maybe due to the wide 95% CI range. Furthermore, patients on combination therapy with DMARDs had a 50% higher possibility of achieving DAS-28 based remission.

Despite the longitudinal data collection, our study has the drawbacks of being a retrospective analysis, necessarily excluding patients without adequate data, and lacking radiographic evaluation of the progression of joint damage. Nor can we be sure that there was no creeping dose of infliximab over time. Nevertheless, our study reconfirms the tendency over time of rheumatologists to start therapy with Infliximab in RA patients with a shorter disease duration, younger age, and less severe disease. The latter, in particular, seems to be correlated with a higher probability of attaining disease remission in more recent years. This treatment strategy seems to be successful in terms of clinical outcomes and, luckily, seem to be being pursued by rheumatologists all over the world in real-life settings. Pharmacoeconomic analysis would be useful to see whether this may also yield more favourable economic outcomes.

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