Comparison of efficacy of first- *versus* second-line adalimumab in patients with rheumatoid arthritis: experience of the Italian biologics registries

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Abstract

Objective

Targeted drugs against key pathogenetic molecules such as TNF-alpha have significantly improved outcomes in rheumatoid arthritis (RA). They are widely used in clinical practice and drug registries give us information to support their use. Adalimumab (ADA) is able to induce a comprehensive disease control in RA by achieving clinical, functional and radiographic control.

Methods

By interrogating 2 Italian registries, LORHEN and GISEA, we analysed the efficacy of ADA in first- or second-line in a total of 2262 RA patients.

Results

Patients in 1st line were significantly older, with lower disease activity and HAQ scores compared to 2nd line. In 1st line, rates of DAS28-remission (DAS28rem) at 2 years were 34.4% while 26.5% in 2nd line (p=0.038). A normal HAQ score (HAQ≤0.5) was achieved in 53.5% after 2 years in 1st line versus 30.1% in 2nd (p<0.0001). DAS28rem+HAQ≤0.5, a combined parameter that we defined global clinical disease control, was reached in 20.7% in 1st line versus 13.3% in 2nd (p<0.01). Five-year-survival on therapy was higher for patients in 1st line (45.6% vs. 33.2%, p<0.0001). Discontinuation due to lack of efficacy was lower in 1st line (37.4 vs. 54.4%, p<0.0001). Rates of adverse events were similar.

Conclusion

Responses in 1st line are generally significantly better than after a first anti-TNF-alpha failure but patients in 2nd line have a worse clinical and functional profile. A global disease control with clinical and functional remission is an achievable target in both lines.

Key words

rheumatoid arthritis, adalimumab, remission, HAQ

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Introduction

Biological disease-modifying anti-rheumatic drugs (DMARDs) have changed the course of rheumatoid arthritis (RA) to a "curable" disease where remission or low disease activity (LDA) in most severe cases are feasible and achievable goals (1). More recently, the concept of comprehensive disease control (CDC) has been introduced as the sum of clinical (DAS28), functional and radiological remission, thus aiming to an even higher quality of response of the therapeutic strategy (2).

A large number of drugs with different targets involved in RA pathogenesis are approved on the market or in the pipeline of pharmaceutical companies (3). Current guidelines of RA management with DMARDs do not indicate a preference of one mechanism over another to start biologics after conventional DMARDs failure, but because the class of anti-TNF-alpha is the most long-lived, their larger and longer evidence leads *de facto* to a slight preference as first-line drugs (4). To date, beside the relatively large choice of pathogenic mechanisms to target and different molecular compounds against the same cytokine (monoclonal antibodies or soluble receptors), there are no general strategies in switching patients when a first biologic fails and in most cases this decision is left to the physician in charge of the patient (5). Ideally, to test whether there are major differences in efficacy and quality of response of a drug when used in first- or second-line could be very informative on its use in clinical practice.

Besides randomised clinical trials, there are a number of registries of biologic drugs across countries and these provide real-life data on large series of patients.

By looking at the data of the two largest Italian biological registries, the Lombardy Rheumatology Network (LORHEN) (6) and the Gruppo Italiano per lo Studio dell'early arthritis (GISEA) (7), we aimed to compare the efficacy, safety and tolerance of adalimumab (ADA) as a first- or second-line drug in RA patients.

Methods

Patients

Patients satisfying the 1987 ACR criteria for RA and consenting to adhere to the two registries, LORHEN and GISEA, and approved by the local ethics committees, were enrolled in the study. All patients on ADA therapy were treated according to current Italian guidelines (1). Data of the registries include demographic and clinimetric variables such as sex, age, body mass index (BMI), autoantibody status, disease duration, erythrocyte sedimentation rate (ESR) (mm/h), disease activity score (DAS28), health assessment questionnaire (HAQ), previous and current conventional DMARDs, previous corticosteroids (CCS) use. Patients' data were collected at baseline and at least every 6 months during follow-up. They were longitudinally followed up for a minimum of 12 months and reasons of discontinuation and side effects were recorded. Remission was considered achieved by the DAS28 criterion (DAS28 score <2.6), LDA as a DAS28 ≤3.2. EULAR response criteria were also applied based on the EULAR improvement criteria: good response was considered if a relative improvement of >1.2 points was obtained or a DAS28 ≤3.2, moderate responders were improved >0.6 and ≤1.2 or >1.2 but persisting in an active state of disease (>5.1) (8).

Statistical analysis

The differences between patients treated with ADA in the first line therapy and second line were analysed using the Kruskal-Wallis non-parametric test for continuous variables (mean values and standard deviations) and the chi-squared test for categorical variables (absolute numbers and percentages). Comparisons among the two lines of biologic therapy regarding baseline characteristics, assessment of response to therapy after 1 and 2 years and reasons of discontinuation of therapy at 3 and 5 years. Survival of adalimumab therapy was measured using the Kaplan-Meier life table method, and the log-rank test was used to compare the discontinuation rates between 1st and 2nd line therapy after 3 and 5 years. Multivariate analyses were performed using stepwise logistic regression models. The baseline variables taken into account were gender, age, disease duration, HAQ scores, the number of DMARDs prior to adali-

mumab, the concurrent use of MTX, year of biologic start and 1st line IFX *versus* 1st line ETA. The response variable was defined as DAS28 remission after 1 year and 2 years. Missing data were not replaced in the analysis. Statistical analysis was performed using SAS v. 9.2 (SAS Institute, Inc; Cary, NC), and a *p*-value of 0.05 or less was considered statistically significant.

Results

Patients' characteristics

A total of 2262 patients treated with ADA were analysed, gathered from a total of 30 Italian centres. ADA was the first line biologic therapy in 1780 (78.7%) subjects and second-line in 482 (21.3%). Baseline features are detailed in Table I.

Patients in ADA as the 2nd-line biologic were significantly younger (51.4±13.2 yrs *vs*. 53.3±13.1 yrs, p=0.01), with higher disease activity (DAS28 5.5±1.3 *vs*. 5.3±1.5, p=0.002) and HAQ scores (1.4±0.7 *vs*. 1.2±0.7, p=0.001) compared to patients receiving ADA as the first biologic drug. ESR levels at baseline of ADA therapy were higher in patients treated in 2nd line (37.1±23.9 *vs*. 33.8±22.5 mm/h, p=0.009). Patients in ADA 2nd line were also more frequently treated with concomitant DMARDs (90.5 *vs*. 85.8%, p=0.007). There were no differences in sex, disease duration, BMI, concomitant use of MTX, corticosteroids (CCS), RF or ACPA status between groups (see Table I).

Previous therapies

Patients in ADA 2nd-line had used a higher number of previous DMARDs (more than 1 in 73.9% *vs*. 64%, p=0.001) or previous steroids (92.6% *vs*. 88.2%, p=0.011) than 1st line patients.

First-line biologic therapy in patients switching to ADA 2nd line were prevalently other anti-TNF (etanercept (ETA) in 312 (65%) patients, infliximab (IFX) in 141 (29%), in 5 (1%) certolizumab, in 3 (0.6%) golimumab). Other first-line agents were tocilizumab (10 (2%) patients), abatacept (5 (1%)), anakinra (4 (1%)), and rituximab (2 (0.4%)).

Improvement criteria

Efficacy was assessed at 1 and 2 years in both ADA 1st and 2nd line of therapy (see Table II). DAS28 remission was induced in 322/1098 (29.3%) at 1 year and 246/716 (34.4%) patients after 2 years with ADA 1st line while in 69/326 (21.2%) and 52/196 (26.5%) in 2nd line. At both time points rates were significantly higher in 1st line. Similar trends were observed for all other clinical efficacy outcomes: LDA status in 1st line was achieved in 43.9% and 51.4% of patients at 1 and 2 years *versus* 31.9% and 38.3% in 2nd line (p<0.001 for both comparisons); good/moderate EULAR responses in 75.9% and 81% *versus* 64.7% and 68.9% (p<0.01 for both). Functional outcomes were checked as the percentage of patients achieving an HAQ ≤0.5, those who maintained this improvement during follow up and finally as the improvement in the HAQ score of 0.22 points. The percentages of patients with HAQ ≤0.5 were 49.9% and 53.5% after 1 and 2 years in 1st line *versus* 31% and 30.1% in 2nd (p<0.0001 for both). Once reached, HAQ ≤0.5 was stably maintained at 2 years in both groups in a similar percentage (189/226, 83.6%, in 1st line *vs*. 20/23, 87%, in 2nd line, p=0.67).

Patients who showed an improvement in HAQ ≥0.22 were 63.1% and 68.4% in 1st *versus* 60.9% and 61.1% in 2nd line and these frequencies were not significantly different.

We looked at the combined DAS28 and HAQ response (global clinical disease control, gCDC) and found 204/1203 (17%) of patients reaching it in 1st line *versus* 61/533 (11.4%) after 1 year (p<0.01), with numbers consolidating at 2 years with 168/811 (20.7%) in 1st line *versus* 42/315 (13.3%) in 2nd (p<0.01).

At the logistic regression analysis (see Table III), male sex (OR=2.8 95%CI 1.96-4.11), age (0.974 (0.96–0.985)) and basal DAS28 (0.671 0.58–0.776) were significantly (p<0.0001 for all) predicting remission at 1 year for patients in 1st line ADA therapy. In 2nd line patients, basal HAQ had a significant influence on rates of remission at 1 year (OR=0.573 95% CI 0.329–0.997, p=0.0487) and was the only significant predictor.

Figures were similar at 2 years with the exception that basal HAQ (OR 0.52 0.385–0.702, p<0.0001) showed a significant predictive value also in patients in 1st line.

Survival on treatment

After 3 years of follow-up, 1132/2262 (50%) patients were on ADA treatment. Of them, 938/1780 (52.7%) were in 1st and 194/482 (40.3%) in 2nd line (p<0.001, Fig. 1). After 5 years 972/2262 (42.3%) patients were still treated and proportion were higher in 1st line (812/1780, 45.6%) *vs*. 2nd line (160/482, 33.2%, p<0.0001).

Reasons for discontinuations after 3 years were available for 1153 patients in total, 862 in 1st line ADA and 291 in 2nd line (see Table IV): 370 (32.7%) patients were lost to follow-up with a

Table I. Patients' features according to time of ADA therapy.

	Total (all)	ADA		*p*-value
		1st Line (1780)	2nd Line (482)	
Age (mean ± SD)	52.9 ± 13.1	53.3 ± 13.1	51.4 ± 13.2	0.010
Sex (F) n (%)	1886 (83.4)	1478 (83)	408 (84.6)	0.399
Disease duration (mean ± SD)	8.5 ± 8.1	8.6 ± 8.2	8.1 ± 7.8	0.283
DAS28 (mean ± SD)	5.3 ± 1.4	5.3 ± 1.5	5.5 ± 1.3	0.002
ESR (mm/h) (mean ± SD)	34.4 ± 22.8	33.8 ± 22.5	37.1 ± 23.9	0.009
HAQ (mean ± SD)	1.2 ± 0.7	1.2 ± 0.7	1.4 ± 0.7	0.001
BMI kg/m^2 (mean ± SD)	24.8 ± 4.6	24.9 ± 4.6	24.5 ± 4.5	0.132
Seropositivity (RF or ACPA+) n (%)	1138 (58.2)	890 (57.3)	248 (61.7)	0.115
Baseline DMARDs n (%)	1963 (86.8)	1527	85.8	436
Baseline MTX n (%)	1202 (53.1)	933 (52.4)	269 (90.5)	0.007
Previous DMARDs n (%)				
0	238 (10.5)	199 (11.2)	39 (8.1)	
1	529 (23.4)	432 (24.8)	87 (18)	
1+	1495 (66.1)	1139 (64)	356 (73.9)	0.001
Baseline CCS n (%)	1152 (50.9)	904 (50.8)	248 (51.5)	0.795
Previous CCS n (%)	1695 (89.2)	1309 (88.2)	386 (92.6)	0.011

Table II. Response to therapy.

	Total (all)		Line				*p*-value
			1st Line		2nd Line		
	n	%	n	%	n	%	
DAS28 remission							
After 1 yr	391/1424	27.5	322/1098	29.3	69/326	21.2	0.0037
After 2 yrs	298/912	32.7	246/716	34.4	52/196	26.5	0.0384
LDA							
After 1 yr	586/1424	41.2	482/1098	43.9	104/326	31.9	0.0001
After 2 yrs	443/912	48.6	368/716	51.4%	75/196	38.3	0.0011
EULAR response (moderate/good)							
After 1 yr	1044/1424	73.3	833/1098	75.9	211/326	64.7	0.0001
After 2 yrs	715/912	78.4	580/716	81	135/196	68.9	0.0003
HAQ≤0.5							
After 1 yr	592/1299	45.6	499/999	49.9	93/300	31	0.0001
After 2 yrs	420/868	48.4	362/675	53.6	58/193	30.1	0.0001
DAS28 remission + functional (HAQ) remission							
After 1 yr	265/1736	15.3	204/1203	17	61/533	11.4	0.0032
After 2 yrs	210/1126	18.6	168/811	20.7	42/315	13.3	0.0043

significantly higher proportion in 1st line (37.5% *vs*. 16.2%); lack of efficacy in 484, with a significantly lower percentage in 1st line (37.6% *vs*. 55%, $p<0.001$). No significant differences were noted in adverse events leading to drug discontinuation (204 patients: 16.6% in 1st line *vs*. 21% in 2nd); remission (23 patients: 2.3% *vs*. 1%), death (6 patients: 0.6% *vs*. 0.3%). Reasons of discontinuation after 5 years were available for 1324 patients in total, 995 in 1st line ADA and 329 in 2nd line (see Table IV): 422 patients were lost to follow-up, again in a higher proportion in 1st line (37.1% in 1st line *vs*. 16.1% in 2nd, $p<0.0001$), lack of efficacy was recorded in 551 patients with a lower percentage in 1st line (37.4 *vs*. 54.4%, $p<0.0001$). Rates were similar between groups for adverse events (234 patients: 16.7 in 1st line *vs*. 20.7% in 2nd), remission (34 patients: 2.7% *vs*. 2.1%) and death (7 patients: 0.6% *vs*. 0.3%).

Discussion

Our study compares the efficacy of ADA as 1st or 2nd line of therapy in RA patients of the 2 biggest Italian biologic registries, LORHEN and GISEA. In both lines of treatment ADA shows good rates of response: clinical, in terms of remission and EULAR response, and functional as evaluated by HAQ. We report for the first time in the comparison of ADA in 2 different lines of therapy the results of a "global clinical disease control" (gCDC) indicated by a combined clinical DAS28 remission and functional HAQ response. GCDC in our registries is reached in a remarkable percentage of patients: up to 20% in 1st line and 13% in 2nd maintained after 2 years with numbers consolidating from year to year. The entity of this response in both lines is particularly relevant in our real-life setting because the study includes patients with an active and already compromised longstanding disease and to our knowledge our group is the first to use the approach of such a combined analysis in patients of registries and not clinical trials (9). These goals were evaluated and considered good surrogates of response as EULAR guidelines themselves recommend less stringent measures for many patients who cannot attain stringent forms of remission (10). Furthermore, as our 2 registries (and most of biologic registries worldwide) do not include radiographic data the combination of the clinical (DAS28) and functional (HAQ) outcome is the best possible combination of response given that only the DAS28 remission does not guarantee that radiographic progression and disability are inhibited (2).

Responses in 1st line are generally significantly better than after a first anti-TNF-alpha failure and our results are in line with the literature showing that anti-TNF alpha drugs work better when used in biological DMARDs naïve patients (11-13). Nevertheless, patients failing to respond to a first anti-TNF may still benefit from a switch to a second anti-TNF (14) but attention must be paid to the type of patients and the reason of discontinuation (13). Randomised controlled trials targeted to define the best switching protocol are lacking yet. Our data come from a real-life setting of national registries and unveil drug performances in different lines of therapy contributing to inform

Table III. Multivariate analysis of predictors of remission at 1 and 2 years.

Multivariate model	1 year-remission						2 year-remission					
	1st Line			2nd Line			1st Line			2nd Line		
	OR	95%CI	*p*-value	OR	95%CI	*p*	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Male sex	2.81	1.85-4.27	<0.001	1.98	0.69-5.65	0.2	2.24	1.38-3.62	0.001	0.94	0.23-3.83	0.93
Age	0.97	0.96-0.98	<0.001	0.98	0.95-1.01	0.39	0.97	0.96-0.99	0.0002	0.99	0.95-1.03	0.65
Disease duration (yrs)	0.99	0.97-1.01	0.49	1.04	0.98-1.11	0.15	0.98	0.96-1.01	0.29	1	0.94-1.08	0.84
Baseline HAQ	0.88	0.66-1.19	0.42	0.57	0.33-0.99	0.04	0.52	0.38-0.7	<0.0001	0.39	0.19-0.79	0.009
Previous DMARDs (1+ *vs*. 1)	1.07	0.74-1.55	0.7	1.34	0.43-4.2	0.61	1.11	0.72-1.7	0.63	0.65	0.18-2.41	0.52
Baseline MTX	1.06	0.76-1.48	0.71	0.61	0.27-1.4	0.24	1.04	0.71-1.51	0.82	0.47	0.16-1.33	0.15
Year of biologic start	0.98	0.93-1.05	0.7	1.03	0.88-1.19	0.71	0.98	0.9-1.06	0.66	1.04	0.86-1.24	0.69
1st line IFX *vs*. 1st line ETA	-	-	-	0.86	0.36-2.05	0.73	-	-	-	0.73	0.26-2.05	0.55

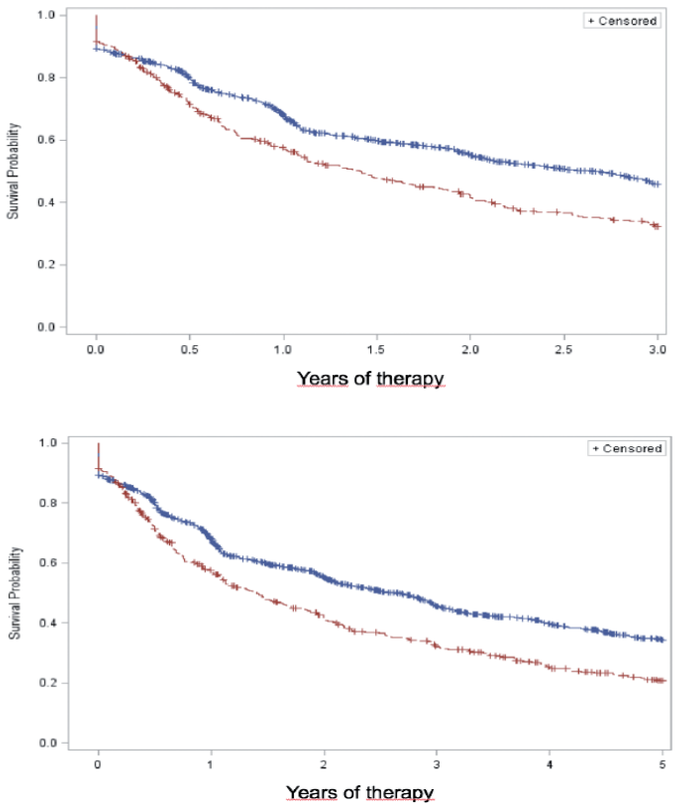

Fig. 1. Survival rates on ADA as 1st (blue line) or 2nd (red line) line biologic agent after 3 and 5 years.

Table IV. Reasons of discontinuation of therapy at 3 and 5 years.

Reasons for discontinuation	3 years					5 years				
	1st Line		2nd Line		*p*-value	1st Line		2nd Line		*p*-value
	n	%	n	%		n	%	n	%	
Lost to FU	323	37.5	47	16.2	0.0001	369	37.1	53	16.1	0.0001
Adverse events	143	16.6	61	21	0.0910	166	16.7	68	20.7	0.1004
Lack of efficacy	324	37.6	160	55	0.0001	372	37.4	179	54.4	0.0001
Remission	20	2.3	3	1	0.1738	27	2.7	7	2.1	0.5603
Death	5	0.6	1	0.3	0.6279	6	0.6	1	0.3	0.5167
Other	47	5.5	19	6.5	0.4942	55	5.5	21	6.4	0.5631
Total (all)	862	100	291	100		995	100	329	100	

the clinician in the daily practice. Furthermore, anti-TNF-alpha are no longer the only drugs that in many countries can be prescribed as first line biological DMARDs. Other targets may be explored first thus leaving anti-TNF as a subsequent step. To explain our results, patients treated in 2nd line in our study are significantly younger and show higher disease activity (DAS28) and functional scores (HAQ) compared to ADA 1st line. As a consequence, they are more frequently treated with ongoing DMARDs (other than MTX), have failed more DMARDs in the past and used steroids in a higher percentage. Despite these features, about 20% of patients in 2nd line achieves remission at 1 year with incremental rates (up tp 26%) at year 2. In patients of this severity response is probably better evaluated with the outcome LDA, a slightly more realistic goal of therapy in this real-life setting (15), our data show that the rate of LDA response rises to 30% in 2nd line after 1 year and again has incremental figures (38%) at year 2. As for the functional response, the HAQ improvement in absolute terms does not differ in both groups (delta HAQ >0.22) but HAQ ≤0.5 is achieved, and increased from year 1 to year 2, in a higher percentage of 1st line patients. In 2nd line HAQ ≤0.5 is obtained in around 30% of subjects, a stable percentage at both time points. As an indicator of the quality of this response we examined whether patients in functional remission maintained this outcome after 12 and 24 months and, despite numbers of this analysis were low, percentages of patients in stable remission were above 80% in both lines. HAQ is a crucial determinant of prognosis *quoad vitam* and disability in RA (16) and our study shows it is a significant predictor of remission at 1 and 2 years in patients treated with ADA in 2nd line and of remission at 2 years in 1st line. Baseline HAQ was very high in both groups, but significantly higher in patients who already failed a first biological DMARD and this probably explains its negative impact on remission. Feuchtenberger *et al*. showed that ADA treatment response, as evaluated by DAS28, EULAR response criteria and the functional measure Funktionsfragebogen Hannover (FFbH), was negatively influenced by use of prior biologic therapies with lower responses in patients having failed ≥2 drugs (17). Our results are in line with this report but analyse for the first time a combined outcome of clinical and functional response, the gCDC, along with other single clinical measures (DAS28, EULAR response, etc).

Survival in our registries was longer for patients in ADA 1st line than for those coming from a first anti-TNF failure in line with data coming from other national registries (12). Overall the survival we report, which is around 50% after 3 years and 40% after 5 years, are slightly higher than in other registries (18) and this is an indirect indication of the quality of our data.

In the study of Feuchtenberger *et al*. discontinuation rates were similar in the groups of patients with 0 or 1 previous biologic DMARD but they had a shorter follow-up and data were not obtained by registries but from a single-arm, multicentred non-interventional study therefore the two cohorts are not entirely comparable.

Our present study has some limitations. Data were obtained from real-life patients and in a setting where the thera-

peutic strategy is based on the physician judgment and not on a specified protocol. Data entry in the registries is on a voluntary basis and this constitutes a selection bias. Furthermore, there are some missing data that may increase the bias and lastly rates of patients lost to follow-up are high (above one third of patients), especially in 1st line. One strength of our observations is that the design of our study is retrolective, therefore data were collected prospectively before the design of the study and analyses were set up before the query of the database (12). In evaluating comprehensive disease control, because we lacked structural information of the radiographic progression in these patients, we concentrated our outcomes on clinical and functional endpoints and *ad hoc* referred to *g*CDC, a measure that needs further validation in further independent and prospective studies.

References

1. CAPORALI R, CONTI F, ALIVERNINI S *et al*.: Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology I. Efficacy. *Clin Exp Rheumatol* 2011; 29 (Suppl. 66): S7-14.
2. EMERY P, KAVANAUGH A, BAO Y, GANGULI A, MULANI P: Comprehensive disease control (CDC): what does achieving CDC mean for patients with rheumatoid arthritis? *Ann Rheum Dis* 2015; 74: 2165-74.
3. CAVAGNA L, SAKETKOO LA, SCHWARTING A, CAPORALI R: Biotechnological drugs: the breakthrough in autoimmune rheumatic conditions. *Biomed Res Int* 2014: 481973.
4. SMOLEN JS, LANDEWÉ R, BREEDVELD *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
5. ATZENI F, SARZI-PUTTINI P, GORLA R, MARCHESONI A, CAPORALI R: Switching rheumatoid arthritis treatments: an update. *Autoimmun Rev* 2011; 10: 397-403.
6. CAPORALI R, PALLAVICINI FB, FILIPPINI M *et al*.: Treatment of rheumatoid arthritis with anti-TNF-alpha agents: a reappraisal. *Autoimmun Rev* 2009; 8: 274-80.
7. IANNONE F, GREMESE E, ATZENI F *et al*.: Longterm retention of tumor necrosis factor-alpha inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J Rheumatol* 2012; 39: 1179-84.
8. MAKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005. 64: 1410-3.
9. IANNONE F, SINIGAGLIA L, FAVALLI EG *et al*.: 2016. Drug survival of adalimumab in patients with rheumatoid arthritis over 10 years in the real-world settings: high rate remission together with normal function ability. *Clin Rheumatol* 2016; 35: 2649-56.
10. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
11. HYRICH KL, LUNT M, WATSON KD, SYMMONS DP, SILMAN AJ, AND BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS, R: Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007; 56: 13-20.
12. FRAZIER-MIRONER A, DOUGADOS M, MARIETTE X *et al*.: Retention rates of adalimumab, etanercept and infliximab as first and second-line biotherapy in patients with rheumatoid arthritis in daily practice. *Joint Bone Spine* 2014; 81: 352-9.
13. CAPORALI R, SARZI-PUTTINI P, ATZENI F *et al*.: Switching TNF-alpha antagonists in rheumatoid arthritis: the experience of the LORHEN registry. *Autoimmun Rev* 2010; 9: 465-9.
14. LLOYD S, BUJKIEWICZ S, WAILOO AJ, SUTTON AJ, SCOTT D: The effectiveness of anti-TNF-alpha therapies when used sequentially in rheumatoid arthritis patients: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2010; 49: 2313-21.
15. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al*.: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
16. NORTON S, FU B, SCOTT DL *et al*.: Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. *Semin Arthritis Rheum* 2014; 44: 131-44.
17. FEUCHTENBERGER M, KLEINERT S, SCHARBATKE EC *et al*.: The impact of prior biologic therapy on adalimumab response in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 321-9.
18. DU PAN SM, SCHERER A, GABAY C, FINCKH A: Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients. *Ann Rheum Dis* 2012; 71: 997-9.