LAVORO ORIGINALE

Switching between TNFα antagonists in rheumatoid arthritis: personal experience and review of the literature*

Passaggio ad altro antagonista del TNFα in pazienti con artrite reumatoide: esperienza personale e review della letteratura

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RIASSUNTO

Circa un terzo dei pazienti affetti da artrite reumatoide (AR) trattati con gli antagonisti del TNFα presenta una risposta inadeguata o effetti collaterali che costringono alla sospensione. Le differenze nella struttura e nel meccanismo d'azione tra i diversi anti-TNFα hanno suggerito che l'impiego di un secondo o terzo farmaco, dove il primo abbia fallito, possa rappresentare un'alternativa terapeutica possibile. Nel presente lavoro riportiamo i dati, raccolti prospetticamente dal 2000, dei nostri pazienti con AR trattati con un secondo anti-TNFα dopo aver sospeso il primo per inefficacia o eventi avversi, e li confrontiamo con quelli della letteratura, di cui forniamo una revisione.

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INTRODUCTION

The treatment of rheumatoid arthritis (RA) has evolved over the past decade with the introduction of anti-tumor necrosis factor (TNF) α agents, which allowed remarkable advances in controlling signs and symptoms of inflammation and in slowing joint destruction (1-3).

However, some patients do not respond or show suboptimal response to the currently available anti-TNFα agents (infliximab, etanercept, and adalimumab) used either as monotherapy or in combination with methotrexate. Furthermore, patients who respond initially may lose efficacy over time (4) or develop adverse events. Because significant differences exist among the three TNFα antagonists in terms of molecular structure, pharmacokinetics, interactions with TNFα, generation of antibodies, induction of apoptosis, and dosing regimen, switching from one anti-TNFα agent to another could represent an option in RA patients who fail or are intolerant to the first treatment (4). Overall, the available data suggest that trying another anti-TNFα agent may result in improved disease control, although the published studies widely vary in respect of population size, study design and outcomes (Tab. I) (5-26). In this paper, we report the results of an ongoing, longitudinal, observational study evaluating the clinical response after switching from one anti-TNFα agent to another in patients with RA within a "real-life" clinical setting. In addition, a review of the literature was made.

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PATIENTS AND METHODS

In this ongoing, longitudinal, observational study, we prospectively collected data since 2000 on efficacy and safety for patients starting biological treatments in our rheumatology unit.

Table I - Overview of the published studies on switching anti-TNFα antagonists.

Study	*Type of study*	*Switchers (N.)*	*Type of switching (N.)*	*Reason for switching (%*)*	*Mean follow-up (mo)*	*Outcomes*	*Clinical response after the switching*
Ang 2003 (5)	R	29	a. IFX-ETA (5) b. ETA-IFX (24)	a. IE (40), AEs (60) b. IE (50), AEs (42), other (8)	a. 8.2 b. 10	JC, ESR, CRP	69% of switchers maintained the second anti-TNFα
van Vollenhoven 2003 (6)	P	31	a. IFX-ETA (13) b. ETA-IFX (18)	a. AEs (85), other (15) b. IE (78), AEs (11), other (11)	a. 24 b. 24	DAS28, ACR	a,b: significantly better
Hansen 2004 (7)	R	20	a. ETA-IFX (20) vs IFX-naïve (73)	IE (85), AEs (5), other (10)	NOS	JC, ESR, CRP	Similar. Higher IFX dose in switchers
Haraoui 2004 (8)	P	25	IFX-ETA	IE (76), AEs (12), other (12)	3	ACR	ACR20/50/70: 64%/25%/13%
Gomez-Puerta 2004 (9)	P	12	IFX-ETA	IE	6	DAS28, EULAR	Significant mean DAS28 reduction; EULAR response: good 17%, moderate/good 83%
Bennett 2005 (10)	P	26 (29 treatments)	a. IFX (23) / ETA (5) / ANAKINRA (1)-ADA vs ADA-naïve (44)	LaE (27), LoE (45), AEs (21), other (7)	8.5 vs 7.5	DAS28, EULAR, HAQ	Mean DAS28 change a/controls: -1.7/-2.4; EULAR response a/controls: remission 8%/23%, good 19%/30%, moderate 46%/55%; Mean HAQ change a/controls: -0.31/-0.31
Wick 2005 (11)	P, C	36	a. IFX-ADA (27) b. ETA-ADA (9) vs ADA-naïve (26)	LoE	6	DAS28, ACR20	Similar mean DAS28 reduction and ACR20 improvement
Cohen 2005 (12)	R	38	a. IFX-ETA (24) b. ETA-IFX (14)	a. IE (67), AEs (33) b. IE (93), AEs (7)	a. 10.1 b. 13.9	DAS28, EULAR	a,b: significant mean DAS28 reduction and similar EULAR response at 3 months
Gomez-Reino 2006 (13)	P	385	a. IFX-ETA b. ETA-IFX c. IFX-ADA d. ETA-ADA	IE, AEs, other (NOS)	24	Survival curves	Probability of retaining the second anti-TNFα lower than the first one
Nikas 2006 (14)	P, C	24	IFX-ADA (24) vs ADA-naïve (25)	IE (37.5), AEs (62.5)	12	DAS28, EULAR, ACR20	Similar
Solau-Gervais 2006 (15)	R	70	a. mAb-ETA (32) b. ETA-mAb (30) c. mAb-mAb (8) d. all three drugs (20)	IE, AEs	3	DAS28	EULAR response a/b/c: good 45%/45%/33%
Hyrich 2007 (16)	P	856	IFX, ETA, ADA: first-time switchers, all possible combinations	IE (59), AEs (41)	6	Survival curves	73% of switchers remained on the second anti-TNFα

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Study	*Type of study*	*Switchers (N.)*	*Type of switching (N.)*	*Reason for switching (%*)*	*Mean follow-up (mo)*	*Outcomes*	*Clinical response after the switching*
Di Poi 2007 (17)	P	18	IFX-ETA	LaE (61), LoE (39)	10.5	DAS28, EULAR	Significant mean DAS28 reduction; EULAR response: 72%
Iannone 2007 (18)	R	37	IFX-ETA	AEs	6	DAS44, ACR	Reduction of mean DAS44 (NS); ACR50/70: 73%/50%
Bombardieri 2007 (19)	P	899	a. IFX-ADA (591) b. ETA-ADA (188) c. both IFX and ETA before ADA (120)	a. LaE (19), LoE (44), AEs (23), other (14) b. LaE (33.5), LoE (25.5), AEs (21), other (20) c. not reported	3	DAS28, EULAR, ACR, HAQ	Considering the switchers altogether: ACR20/50/70: 60%/33%/13%; EULAR response: good 23%, moderate/good 76%; DAS28<2.6: 12%; HAQ <0.5: 13%
Buch 2007 (20)	P	95	IFX-ETA	LaE (36), LoE (40), AEs (24)	3	DAS28, EULAR, ACR	Significant mean DAS28 reduction; EULAR response: good 12%, moderate/good 61%; ACR20/50/70: 38%/24%/15%
Furst 2007 (21)	P, C, Ra, single- blind	13	a. ETA-IFX (13) vs ETA maintainers (14)	IE	4	DAS28, ACR, X-Ray, MRI	Mean DAS28% change a/controls: -31/-16; ACR20 a/controls: 61%/29%, ACR50 a/controls: 31%/14%; Similar X-Ray and MRI changes
Hjardem 2007 (22)	P	286	IFX, ETA, ADA: all possible combinations a. first-time switchers (235) b. second-time switchers (51)	a. IE (46), AEs (31), other (23) b. IE (61), AEs (16), other (24)	51	DAS28, survival curves	Significantly better with the second drug at 3 months, mostly in patients switching for IE; drug survival of the second higher
Karlsson 2008 (23)	P	373	IFX, ETA, ADA: all possible combinations a. first-time switchers (337) b. second-time switchers (36)	IE (46), AEs (46), other (8)	3	DAS28, EULAR, ACR	ACR20 a/b: 51%/35%, ACR50 a/b: 27%/18%; EULAR response a/b: good 25%/9%, moderate/good 71%/58%; DAS28 remission a/b: 16%/6%

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Study	Type of study	Switchers (N.)	Type of switching (N.)	Reason for switching (%*)	Mean follow-up (mo)	Outcomes	Clinical response after the switching
Van der Bijl 2008 (24)	P	41	IFX-ADA	LaE (36.6), LoE (51.2), AEs (12.2)	16	DAS28, EULAR, ACR, HAQ, CRP	Significantly better in all measures
Laas 2008 (25)	P	49	IFX-ETA	IE (42), AEs (12), other (46)	16	DAS28, ACR, survival curves	Better in switchers for AEs than in switchers for IE
Hyrich 2008 (26)	P	331	IFX, ETA, ADA: first-time switchers, all possible combinations vs stoppers (148) or stayers despite non-response (289)	IE	12	HAQ	Significantly better in switchers than in stoppers or stayers

*When specified; R: retrospective; P: prospective; C: controlled; Ra: randomized; lower cases (a, b, c, d) identify the different groups of switchers considered in each study; vs: versus; IFX: infliximab; ETA: etanercept; ADA: adalimumab; mAb: anti-TNFα monoclonal antibody; first-time switchers: patients having switched anti-TNFα once; second-time switchers: patients having switched anti-TNFα twice; LaE: lack of efficacy; LoE: loss of efficacy; IE: inadequate efficacy, when not specified if LaE or LoE; AEs: adverse events; JC: joint count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; DAS28: DAS 28 joints; ACR: ACR response criteria; NOS: not otherwise specified; EULAR: EULAR response criteria; HAQ: Health Assessment Questionnaire; MRI: magnetic resonance imaging; NS: not significant.

The present analysis was restricted to patients with a diagnosis of RA who switched from one TNFα antagonist to another, with a minimum of 6 months' follow-up (at least 3 months for each treatment) by the end of December 2007.
RA was classified according to the revised ACR criteria (27).
The choice of the biological agent was based on clinical considerations only; thus, these patients represent a 'real-life' sample of subjects undergoing TNFα antagonist treatment. Infliximab 3-5 mg/kg was administered intravenously at weeks 0-2-6, and every 6-8 weeks thereafter; etanercept (25 mg twice a week or 50 mg once weekly) and adalimumab (40 mg every fortnight) were given subcutaneously.

Clinical assessment

Each patient was evaluated by the same rheumatologist at baseline before starting TNFα antagonist, every 3 months, and at the last administration of the drug. Clinical and demographic data were collected into a standardized form previously described (28).
Clinical evaluation in RA patients included: swollen and tender joint count (0-28), patient and physician global assessment on a visual analogue scale (VAS, 0-100 mm), and Health Assessment Questionnaire (HAQ) (29).
Each patient underwent a blood drawing to evaluate erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).
Disease activity score (28 joint count, four variables, ESR-based; DAS28) was calculated and the clinical response (none, moderate, good) was evaluated according to the European League Against Rheumatism (EULAR) criteria (30). In addition, we measured the clinical remission defined as a DAS28 score of less than 2.6 and low disease activity as a DAS28 score equal to or less than 3.2 (31).
Drug discontinuation was based on the rheumatologist's opinion and the reason of withdrawal recorded as lack of efficacy (LaE) (patients who never reached a satisfactory response, i.e. primary failure), loss of efficacy (LoE) (patients who relapsed after an initial response, i.e. secondary failure), adverse events (AEs) or other.
The wash-out period between TNFα antagonists was 6 weeks.

Statistical analysis

Qualitative differences between subgroups were analysed by the chi-squared and Fisher's exact

tests. The Wilcoxon paired test was used to compare quantitative variables in the same group. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 692 anti-TNFα-naïve patients has been registered, of whom 395 with a diagnosis of RA. Among these, 253 (64%) started with etanercept, 115 (29.1%) with adalimumab, and 27 (6.8%) with infliximab.
Thirty-seven RA patients switched to another TNFα antagonist (mean age 50 years, range 17-78; mean disease duration 8.5 years, range 3-22) (Tab. II). The proportion of patients switching for LaE was 35.1%, LoE 40.5%, AEs 24.3%.
Three months after switching, the proportion of patients with remission, low disease activity, good and moderate/good EULAR responses grew from 0%, 2.7%, 0%, and 5.4% (baseline before switching) to 16.2%, 35.1%, 27%, and 62.2% ($p<0.05$, $p<0.001$, $p<0.001$, $p<0.000001$, respectively). Of the patients who switched because of LaE and LoE, a moderate/good EULAR response was achieved in 38.4% and 66.6%, respectively. Among subjects switching for AEs, a response was observed in 88.8% of patients.
During the follow-up 12 patients discontinued the second anti-TNFα, 7 patients for LaE, 4 patients for LoE, and 1 patient for AE (Tab. II). Mean treatment duration with the second anti-TNFα was significantly longer in patients switching for LoE (19.1 months, range 3-38) and AEs (19.1 months, range 4-28) than in those switching for LaE (11.0 months, range 3-47) ($p<0.05$).

Switchers stratified by sequence of drug

Switching from etanercept to adalimumab
Table II shows the clinical and therapeutic features of the 22 patients (mean age 51.6 years, range 17-78; mean disease duration 8.4 years, range 3-22) who received first etanercept and then adalimumab.
After 3 months of adalimumab all clinical parameters evaluated except ESR showed a significant improvement (Fig. 1). The mean duration of adalimumab was longer than the previous etanercept treatment (16.4 *vs* 12.6 months, NS).

Switching from adalimumab to etanercept
Table II shows the clinical and therapeutic features of the 12 patients (mean age 45.1 years, range 33-64; mean disease duration 8.5 years, range 3-17) who received adalimumab as first drug and etanercept as second.
After 3 months of etanercept physician global assessment, HAQ and all DAS28 components except swollen joints showed a significant improvement (Fig. 2).
The mean duration of etanercept was significantly longer than the previous adalimumab treatment (14.2 *vs* 8.8 months, $p<0.05$).

Switching from infliximab to etanercept
Table II shows the clinical and therapeutic features of the 3 patients (mean age 58.3 years, range 53-63; mean disease duration 10.3 years, range 4-19) treated first with infliximab and then with etanercept.
The mean duration of etanercept was longer than the previous infliximab treatment (23.7 vs 18 months, NS).

DISCUSSION

The findings of this longitudinal, observational, single center study on a selected population of RA patients confirm that the failure of a first anti-TNFα agent does not preclude the response to another. In addition, the probability of achieving a clinical response after the switching is higher in patients discontinuing the first treatment for secondary failure or adverse events in comparison with switchers for primary failure.
TNFα inhibitors have significantly changed the therapeutic approach to RA patients: the three available agents - adalimumab, etanercept, infliximab - have proven highly efficacious, especially when used in combination with methotrexate (32-34). Nevertheless, approximately one third of patients discontinue anti-TNFα treatment due to inefficacy or intolerance.
Because the TNFα antagonists differ in chemical structure, mechanism of action and safety profile, there is a rationale for switching from one to another.
Several reports, reviewed in Table I, support this possibility and switching to a different TNFα antagonist has now become a common practice in RA, although no published guidelines exist. Studies on switching among anti-TNFα agents are mostly limited by short trial duration, small sample size and lack of randomization or controls. Re-

Table II - Clinical and therapeutic features of the patients.

			Etanercept			*Adalimumab*				
Pt	*Sex*	*Disease duration (years)*	*Concomitant DMARD treatment*	*Treatment duration (months)*	*Reason for discontinuation*	*Concomitant DMARD treatment*	*EULAR response (at three months)*	*Treatment duration (months)*	*Patients currently on treatment*	*Reason for discontinuation*
1	F	84	-	3	LaE	-	None	3	No	LaE
2	F	144	-	26	LoE	-	Moderate	18	Yes	-
3	M	252	-	30	LoE	-	Moderate	18	Yes	-
4	F	264	-	7	LoE	-	None	28	Yes	-
5	F	60	-	3	LaE	LFN	Good	19	No	LoE
6	F	36	LFN	12	LoE	LFN	Moderate	12	Yes	-
7	F	108	MTX	3	LaE	MTX	Moderate	6	No	LoE
8	F	60	HCQ	13	AE*	MTX	Good	28	Yes	-
9	F	36	LFN	3	LaE	LFN	None	3	No	LaE
10	F	72	MTX	3	LoE	MTX	Moderate	36	Yes	-
11	F	48	MTX	3	LaE	MTX	Good	47	Yes	-
12	F	120	MTX	3	AE§	-	Moderate	4	No	AE§
13	F	60	-	3	LaE	-	None	12	Yes	-
14	F	72	MTX	33	LoE	MTX	None	3	No	LaE
15	F	48	MTX	5	LoE	-	Good	22	No	LoE
16	F	60	MTX	44	LoE	MTX	Moderate	8	No	LoE
17	F	36	MTX	11	LoE	MTX	None	23	Yes	-
18	F	204	MTX	46	LoE	MTX	Good	23	Yes	-
19	F	192	MTX	6	LoE	MTX	None	3	No	LaE
20	M	48	MTX	8	AE&	-	Good	24	Yes	-
21	F	48	LFN	6	LaE	LFN	None	3	No	LaE
22	F	180	-	7	LaE	-	Moderate	18	Yes	-
			Adalimumab			*Etanercept*				
23	F	96	LFN	20	LoE	LFN	Moderate	18	Yes	-
24	M	168	MTX	3	LaE	MTX	None	3	No	LaE
25	M	36	MTX	5	AE&	MTX	Moderate	16	Yes	-
26	F	144	MTX, HCQ	24	AE&	HCQ	Good	26	Yes	-
27	M	36	-	6	AE$	-	Good	22	Yes	-
28	M	168	MTX	3	LaE	MTX	None	5	No	LaE
29	F	36	-	10	LoE	-	Moderate	28	Yes	-
30	F	204	LFN	6	LaE	LFN	None	12	Yes	-
31	M	132	-	7	AE&	-	Moderate	4	Yes	-
32	M	84	MTX	6	AE&	-	Good	24	Yes	-
33	F	48	MTX	4	LaE	MTX	Moderate	4	Yes	-
34	F	36	MTX	3	LaE	MTX	None	8	Yes	-
			Infliximab			*Etanercept*				
35	F	48	MTX	3	AE#	-	None	24	Yes	-
36	F	96	MTX	34	LoE	MTX	Good	9	Yes	-
37	M	228	MTX	17	LoE	-	None	38	Yes	-

LaE: lack of efficacy; LoE: loss of efficacy; AE, adverse event; MTX: Methotrexate; LFN: Leflunomide; HCQ: Hydroxychloroquine.
*Injection-related reaction; §Hypertension; &Hypertransaminasaemia; $Skin infection; #Onset of ulcerative colitis.

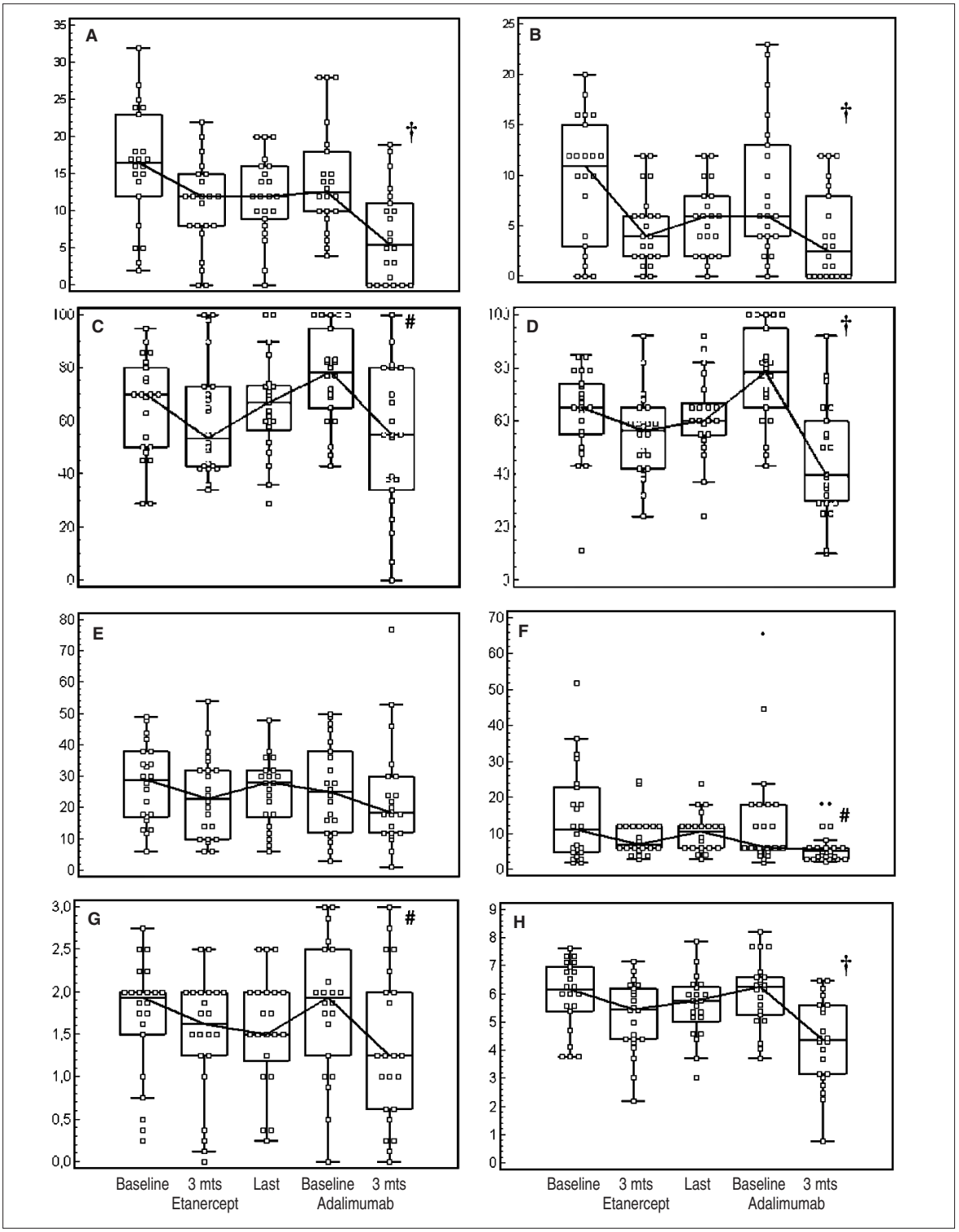

Figure 1 - Clinical parameters of patients who switched from etanercept to adalimumab (N=22). Box and whiskers plot (median, quartiles, range and possible extreme values) of (A) tender joint count, (B) swollen joint count, (C) patient and (D) physician global assessment (VAS), (E) ESR (mm/h), (F) CRP (mg/dl), (G) HAQ, (H) DAS28. Values shown are the mean values at baseline (before etanercept treatment), after 3 months of etanercept treatment, at last visit while on etanercept, at baseline (before adalimumab treatment) and after 3 months of adalimumab treatment. # $p<0.05$, † $p<0.001$ versus baseline before adalimumab treatment.

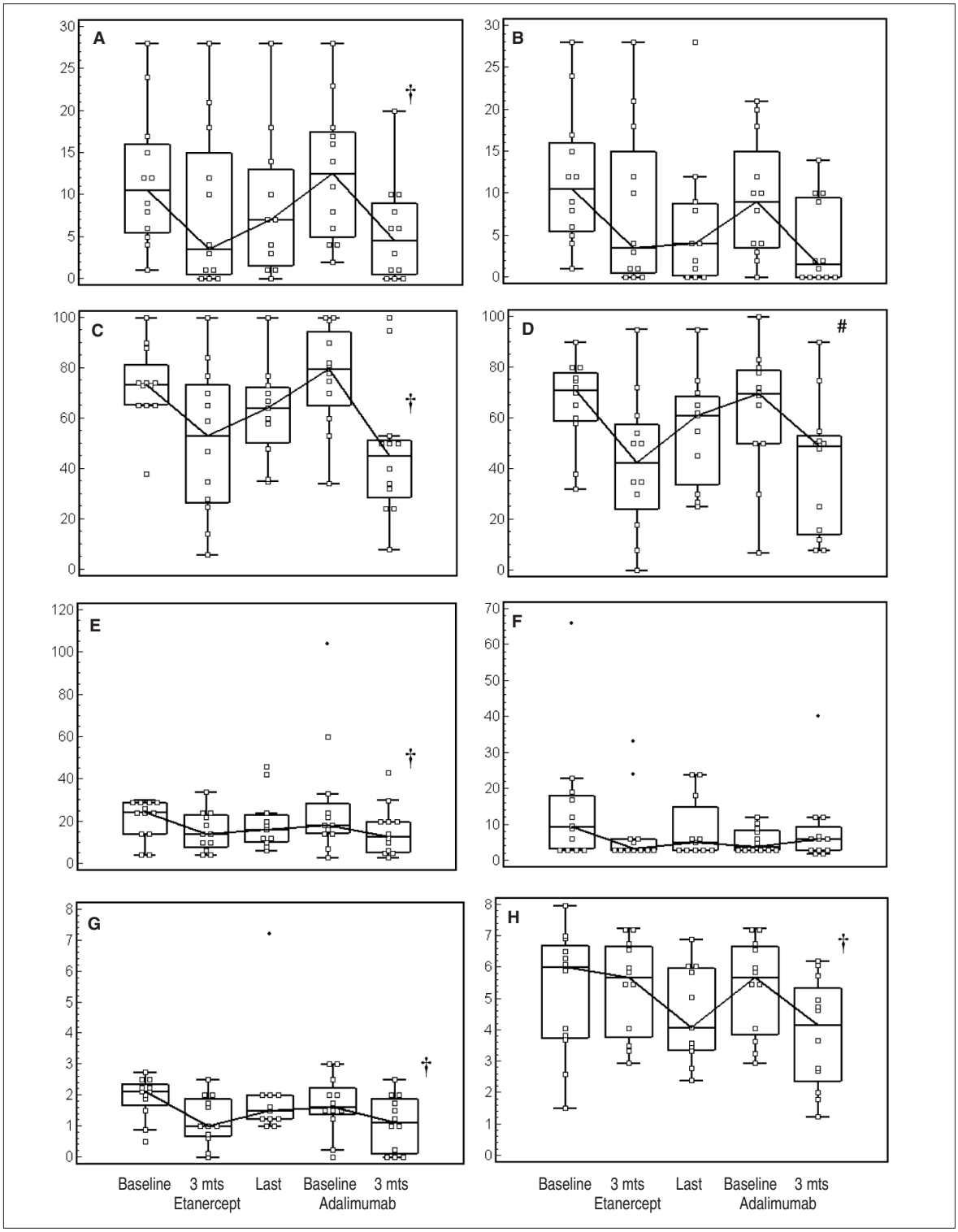

Figure 2 - Clinical parameters of patients who switched from adalimumab to etanercept (N=12). Box and whiskers plot (median, quartiles, range and possible extreme values) of (A) tender joint count, (B) swollen joint count, (C) patient and (D) physician global assessment (VAS), (E) ESR (mm/h), (F) CRP (mg/dl), (G) HAQ, (H) DAS28. Values shown are the mean values at baseline (before adalimumab treatment), after 3 months of adalimumab treatment, at last visit while on adalimumab, at baseline (before etanercept treatment) and after 3 months of etanercept treatment. #p<0.05, †p<0.001 versus baseline before etanercept treatment.

garding the reason for switching, it has rarely been specified whether the inefficacy was primary or secondary, and sometimes only selected groups of switchers have been considered. In addition, only few studies have included all the three available drugs (Tab. I).

The results from the earlier reports, mostly considering the switching between etanercept and infliximab, have shown that the response to the second drug, irrespective of the first one employed, may significantly ameliorate the outcome measures with a good safety profile (5-9).

The subsequent availability of adalimumab offered a further opportunity in the practice of switching anti-TNFα agents, and led to sustain the previous findings reporting a good clinical response after the failure of the first treatment.

Our data, in which all the three available TNFα antagonists were considered, confirm the beneficial effect of the second drug.

Moreover, in our patients, both the clinical response and the treatment duration with the second anti-TNFα were more favourable when LoE or AEs, respect to LaE, caused the discontinuation of the first.

As a matter of fact, only 38.4% of patients who never reached a satisfactory response with the first TNFα antagonist responded to the second, whereas higher percentages of patients showed a satisfactory response after discontinuing the first agent for secondary failure (66.7%) or adverse events (88.9%).

Notably, 71.4% of patients who discontinued the second drug for LaE had stopped the first one for the same reason.

These observations appear in agreement with some of the published reports.

The ReAct analysis, performed in 899 patients who switched to adalimumab, demonstrated a better response rate in patients who replaced previous treatments for LoE and AEs than in those who presented primary failure (19).

Similarly, in a smaller study in which 18 patients were treated with etanercept after infliximab failure, the clinical improvement was higher in patients switching for LoE than in those experiencing LaE with the first agent, whereas patients who had withdrawn for AEs were not considered (17).

Recently, a report from the GISEA study group has shown that all the 37 RA patients who began etanercept after developing intolerance to infliximab reached a clinical response according to EULAR and ACR criteria (18).

Finally, another open-label study on 41 patients who switched from infliximab to adalimumab confirmed a clinically meaningful improvement mostly in patients who had ceased the first treatment for LoE or AEs (24).

However, the issue of whether the reason for switching may influence the response to the other anti-TNFα has not still completely defined.

Indeed, a recent study yielded a different conclusion: the clinical response to a second anti-TNFα agent was irrespective of the reason for stopping the prior treatment, although a better outcome was admitted in patients showing primary inefficacy with the first drug (20).

In our patients, the mean treatment duration with the second anti-TNFα was significantly longer than with the first one.

Our results concur with those emerging from a Danish national register of biological treatments, where the survival of the second anti-TNFα in RA patients was longer than the first (22).

Conversely, the analysis of the national Spanish register showed a reduction in the survival of the second anti-TNFα agent, although it was longer in patients who switched for AEs (13).

There are some limitations to our study. First, the observational design with no randomisation of treatment options.

Second, being a "real-life study", the decision to replace one TNFα antagonist with another depended merely on the treating physician's judgement. However, our data, based on the application of the EULAR response criteria, on the whole support the possibility of trying another anti-TNFα in RA patients failing the first place treatment.

In conclusion, the results of this study suggest that RA patients may be successfully treated with another TNFα antagonist especially those withdrawing for secondary failure or adverse events.

Conversely, for patients stopping anti-TNFα treatment due to primary failure, different biological drugs, such as rituximab and abatacept, might offer a greater chance of therapeutic success.

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SUMMARY

Objective: To evaluate the clinical response after switching to another TNFα antagonist in patients with rheumatoid arthritis (RA) and provide a review of the literature on this topic.

Methods: In this ongoing, longitudinal, observational study we have prospectively collected data of patients starting biological treatments since 2000. The present analysis is restricted to RA patients who switched to another anti-TNFα due to lack of efficacy (LaE), loss of efficacy (LoE), or adverse events (AEs) by the end of December 2007. Disease activity score (ESR-based DAS28) was calculated and the clinical response (none, moderate, good) was evaluated according to the European League Against Rheumatism (EULAR) criteria. Clinical remission (DAS28 <2.6) and low disease activity (DAS28 ≤3.2) were also evaluated.

Results: A total of 692 anti-TNFα-naïve patients has been registered, of whom 395 with a diagnosis of RA. Thirty-seven RA patients switched to another TNFα antagonist. Three months after switching, the proportion of patients with remission, low disease activity, good and moderate/good EULAR responses grew from 0%, 2.7%, 0%, and 5.4% (baseline before switching) to 16.2%, 35.1%, 27%, and 62.2% ($p<0.05$, $p<0.001$, $p<0.001$, $p<0.000001$, respectively). Of the patients who switched because of LaE, LoE, and AEs a moderate/good EULAR response was achieved in 38.4%, 66.6%, and 88.8% of patients, respectively. Mean treatment duration with the second anti-TNFα was significantly longer in patients switching for LoE and AEs than in those switching for LaE ($p<0.05$).

Conclusions: The findings of this study suggest that RA patients may be successfully treated with another TNFα antagonist, especially those withdrawing for LoE or AEs.

Parole chiave - Artrite reumatoide, antagonisti del TNFα, terapie biologiche.

Key words *- Rheumatoid arthritis, TNFα antagonists, biological treatment, switching.*

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