Differences in biologic dose-escalation, non-biologic and steroid intensification among three anti-TNF agents: evidence from clinical practice

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Abstract

Objectives
To evaluate prevalence of dose escalation among RA patients in normal clinical practice treated with etanercept, adalimumab or infliximab and to estimate its economic impact.

Methods
A retrospective observational study of 739 patients with RA receiving continuous treatment with etanercept (n=319), adalimumab (n=313) or infliximab (n=107) for 18 months. Dose escalation, intensification of concomitant DMARDs and risk of dose escalation were evaluated, as well as costs.

Results
Significantly more patients prescribed adalimumab (10%, p<0.001) or infliximab (35%, p<0.001) experienced dose escalation compared with patients treated with etanercept (3%). DMARD or steroid dose adjustment, when added as criteria of escalation, occurred more often among patients treated with adalimumab (28%; p=0.022) or infliximab (47%; p<0.001) than those prescribed etanercept (19%). Independent of confounding covariates, hazard of dose escalation was significantly higher for either infliximab (28.1-fold) or adalimumab (4.9-fold) relative to etanercept. Escalation among subjects treated with either infliximab or adalimumab incurred statistically significant increases in total cost of care compared with non-escalators whereas such differences observed for subjects treated with etanercept were not significant.

Conclusions
Patients receiving monoclonal antibody therapies, adalimumab or infliximab, had significantly higher rates of dose escalation than patients receiving the soluble TNF receptor, etanercept, and related costs were higher.

Key words
rheumatoid arthritis, TNF-α inhibitor, dose escalation, etanercept, infliximab, adalimumab

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Introduction

Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease affecting approximately 1% of adults (1). Because it is a progressive disease, patients with RA require effective early therapy to inhibit disease progression followed by long-term management with an effective and well-tolerated treatment regimen. The anti-tumour necrosis factor (TNF) agents, etanercept, infliximab, and adalimumab have been shown to be effective early and throughout the course of the disease (2-5).

Although infliximab, adalimumab and etanercept all target and neutralise TNF-α, there are structural differences among these agents; etanercept is a recombinant human soluble TNF receptor protein (6), and infliximab and adalimumab are anti-TNF monoclonal antibodies (2, 3). These differences in molecular structure may result in pharmacologic differences including immunogenicity profiles (7). Immunogenicity and subsequent development of anti-drug antibodies (8) is one of the contributing factors leading to loss of satisfactory therapeutic response (9-11). Infliximab, adalimumab and etanercept are all associated with production of antibodies although to differing degrees and with differing effects on therapeutic efficacy (8, 12, 13). In studies of infliximab, 29 to 61% of patients had anti-infliximab antibodies after one year of therapy (14-16). Adalimumab appears to be less immunogenic; cumulative incidence ranged from 6 to 17% (8, 17, 18). Although etanercept also elicits anti-etanercept antibodies, occurring in about 5% of patients, they are non-neutralising (12, 19). Previous studies have demonstrated that serum antibodies against infliximab or adalimumab are associated with either clinical non-response (17) or dose-escalation to maintain clinical response (13). However, dose escalation leads to increases in drug treatment costs, patient inconvenience and risk of adverse events (20, 21).

Previous European studies evaluating loss of efficacy and need for dose adjustments in patients with RA were generally single country or site studies and were mainly focused on infliximab (7, 9, 22-25). Several North American studies, mostly claims database reviews of infliximab use, have examined dose escalation (21, 24, 26-28). This latter group of studies do not afford an opportunity to examine either reasons or clinical outcomes of dose escalation. Specifically, it is not possible to identify whether differences in incidence of dose-escalation could be attributed to differences in disease severity.

Although a number of studies have examined incidence of dose-escalation in various RA populations it is not known whether biologic response modifier (biologic), non-biologic disease-modifying anti-rheumatic drug (DMARD) or steroid escalation is also required by subjects continuing treatment with anti-TNF agents for an extended period of time. It is also not known whether there are any systematic differences among the three anti-TNF agents in this population.

The DART (Drug utilisation and dosing patterns Assessment: a Retrospective observational study of subjects Treated for rheumatoid arthritis) study was designed to evaluate the nature and extent of dose-escalation occurring among RA patients who have continued treatment with their first anti-TNF agent infliximab, adalimumab or etanercept for at least 12 months and followed up for an additional 6 months. In a recent supplement, a high-level summary of 12-month results was reported (29). Here we present complete 18-month results. The retrospective observational study was conducted in five European countries in which patients were recruited consecutively. It provides insight into comparative incidence of biologic, DMARD and concomitant steroid escalation in routine clinical practice. The economic implications of dose escalation are also considered.

Patients and methods
Patients
A review of medical records from consecutive eligible RA patients taking one of three biologics, etanercept, adalimumab or infliximab, and who granted consent was undertaken in 44 centres in five European countries (France, UK, Germany, the Netherlands and

Italy). Medical charts were reviewed retrospectively for the 12–18 months after initiation of biologic therapy for all available demographics, clinical characteristics, drug dosing and frequency of administration data. RA patients treated continuously with an initial biologic for at least 12 months between January 1, 2003 and December 31, 2004 were eligible; those with any prior biologic therapy or suffering from another TNF-mediated illness (Crohn's disease, psoriasis, psoriatic arthritis, ankylosing spondylitis) or terminal illness (HIV, cancer) were excluded as were patients receiving any investigational drug within 28 days of index date or throughout the study. The eligibility dates were chosen to ensure at least 18 months of follow-up after initiation of anti-TNF agents. The requirement of continuous treatment with anti-TNF agents for 12 months ensured that study subjects were broadly similar in terms of clinical response.

Due to differences in mode of drug administration it was possible that differences in incidence of dose-escalation could potentially be attributed to tighter control due to infusion-related visits. Therefore, all subjects in the study were required to have at least three office visits.

Selection bias was avoided by enrolling successively treated subjects at each site. Written informed consent was obtained before each subject could participate in the study in accordance with relevant Institutional Ethics Committee and Institutional Review Boards. The study was conducted in accordance with guidelines for good clinical practice (GCP) and all applicable regulatory requirements, including the 1996 version of the Declaration of Helsinki.

Endpoints

Endpoints included the proportion of patients requiring dose escalation in each treatment group at 12 and 18 months. Dose escalation was defined as the first occurrence of any upward adjustment in dose or dosing frequency of each anti-TNF agent from the label-indicated starting dose and unit of time (etanercept 25 mg bi-weekly or 50 mg once weekly; adalimumab 40 mg every other week; infliximab 3 mg/kg every 8 weeks after the third infusion).

Alternative definitions of dose-escalation included the proportion of patients who switched to a different biologic after the 12-month qualifying period, those who intensified DMARD or steroid or both. DMARD intensification was defined as an increase in DMARD dose from baseline, addition of a new DMARD or switch to a new DMARD or a switch from oral to intravenous DMARD. Similarly, steroid intensification was defined as addition of a new steroid or an increase in prednisolone dose equivalent by a level (low: ≤10mg/day, medium 10.1 to 25 mg/day; high: >25mg/day) or a switch from oral to intravenous steroid.

The time ensuing before dose escalation was estimated as was the impact of various clinical or demographic factors on dose escalation. Disease activity scores (DAS-28) were collected as available but pre- and post-escalation outcome data, including DAS-28, were sparse. Only DAS-28 observed data were evaluated.

Investigators were surveyed to determine if there were any budgetary, legal or other restrictions that limited their decision to prescribe dose escalation and as to reasons behind those decisions.

Economic analyses, performed from the third-party payer's perspective, comprised RA-related medical resource utilisation extrapolated to average annual per patient amounts and included: outpatient visits, inpatient visits, surgical procedures, labs, diagnostics and medication costs. Annualised mean medication costs including administration were estimated for each cohort using published data in each country following implementation of a non-parametric bootstrap test in cases of skewed data or violation of equality of variance as appropriate (30).

Multiplying resource use by unit prices yielded annualised mean costs for each cohort (Euros). Resource valuation for outpatient and inpatient visits and cost of drug administration were made with standardised unit costs from the Dutch manual for costing in economic evaluations only in the absence of available data for individual countries and using appropriate purchasing power parity deflation (31). Skewed data or violation of equality of variance were dealt with as above (30).

Statistical methods

A two-group continuity corrected chi-square test (2-sided α=0.05) was used to establish sample size such that the study would be amply powered on the basis of rates of dose escalation perceived from published and unpublished reports to detect differences in the proportion of escalators. Those escalation rates were predicted to be 5, 12 and 40 percent for etanercept, adalimumab and infliximab, respectively. A total of 735 patients, sought in a 3:3:1 etanercept:adalimumab: infliximab ratio, were expected to have 85% power to detect expected differences in escalation proportion between etanercept and adalimumab cohorts through sequential pair-wise comparisons and 99% power to detect the difference in escalation proportion between etanercept and infliximab cohorts.

Unless otherwise stated, all statistical tests were 2-sided tests performed at a significance level of 0.05 and were performed with Statistical Analysis System (SAS) Version 8 software. In order to maintain an overall alpha of 0.05, the primary endpoint null hypothesis of no difference between treatment cohorts in the proportion of subjects was tested sequentially. First, equal rate of dose-escalation in etanercept- and infliximab- treated was tested. Conditional on this being rejected, equal rate of dose escalation in etanercept- and adalimumab groups was tested. All comparisons were prospectively protocol-specified.

Differences in subject characteristics among three cohorts were examined using Chi-square test for categorical variables and ANOVA model for continuous variables.

Investigator assigned reasons for dose-escalation were tabulated and summarised for each of the 3 cohorts. Multivariate determination of factors that were independently and significantly associated with time to dose-escalation was estimated using a Cox proportional hazards model to control for right censoring of data. This model

took into account treatment group, country, number of erosions at index date, Charlson comorbidity index, disease duration, and other measures for all available data points. Adherence to labelled dose over time was estimated using Kaplan-Meier (K-M) techniques of Cox proportional hazard regression modelling.

Results

As previously reported, 739 patients were studied, 319 receiving etanercept, 313 receiving adalimumab, and 107 receiving infliximab (Table I) (29). The three cohorts were well-balanced in terms of demographic and clinical characteristics. The patient population was predominantly female (79%), with a mean age of 59 years and disease duration of 15 years. At baseline, subjects had highly active disease (DAS-28=5.9). There were significant differences among cohorts for inpatient visits, outpatient visits and disease-related laboratory tests. As shown in Figure 1, subjects in all 3 cohorts had similar improvement in disease activity as measured by DAS-28.

The significantly higher proportion of patients who received either adalimumab or infliximab requiring dose escalation over the 12-month period compared with patients treated with etanercept (29) was maintained through follow-up (Fig. 2A). The number of patients requiring a switch of biologic or an increased dose of either infliximab (34.6%, n=37, $p<0.001$) or adalimumab (9.6%, n=30, $p<0.001$) was significantly higher over the period including follow-up to 18 months compared with patients treated with etanercept (2.5%, n=8). Lack of or loss of adequate response was most often reported as the reason for escalation. Inadequate dose response was reported by 1% of patients in the etanercept group compared with 8% and 22% of patients in the adalimumab and infliximab groups, respectively.

The average magnitude of increase, among those whose prescription was augmented, is shown in Table II: etanercept dose went from two to three 25-mg injections per week; adalimumab dose was increased by going from every other week to weekly 40-mg injections; and

infliximab dose went from three to four mg/kg. Among subjects in each cohort whose dose increased, the net change from baseline in biologic drug use over the 12-month period was 50, 101.5 and 30.6% for etanercept, adalimumab and

infliximab, respectively (Table II). The average magnitude of increase during follow-up was lower than during the 12-month period for etanercept; that for the other two cohorts was basically the same.

Table I. Baseline characteristics of the three study cohorts*.

Mean characteristics	Etanercept (n=319)[†]	Adalimumab (n=313)[†]	Infliximab (n=107)[†]	*p*-value[‡]
DAS-28 (0–10)	5.7 (208)	5.9 (212)	5.9 (74)	0.099
Inpatient visits[§]	0.55 (313)	0.36 (302)	0.66 (74)	0.007
Outpatient visits[§]	4.6 (313)	4.9 (302)	5.2	0.018
Joint aspiration/injections[§]	0.6	0.5 (311)	0.6	0.946
Physiotherapy[§]	0.9	0.2 (311)	0	0.250
RA-related diagnostics[§]	2.3	2.3 (311)	2.2	0.141
RA-related labs[§]	18.1 (318)	18.8 (311)	23.0	0.005

DAS-28: Disease Activity Score; RA: rheumatoid arthritis; *Details of age, gender, disease duration and severity and treatment available in Moots, 2009 (29); [†](n) refers to number of subjects with valid data at baseline; [‡]*p*-value is for overall treatment comparisons. Continuous variables were analysed with a two-way ANOVA including treatment and country. Categorical variables were analysed with the Cochran-Mantel-Haenszel test controlling for country; [§]Annualised per patient per year rates based on 6-month utilisation before biologic initiation.
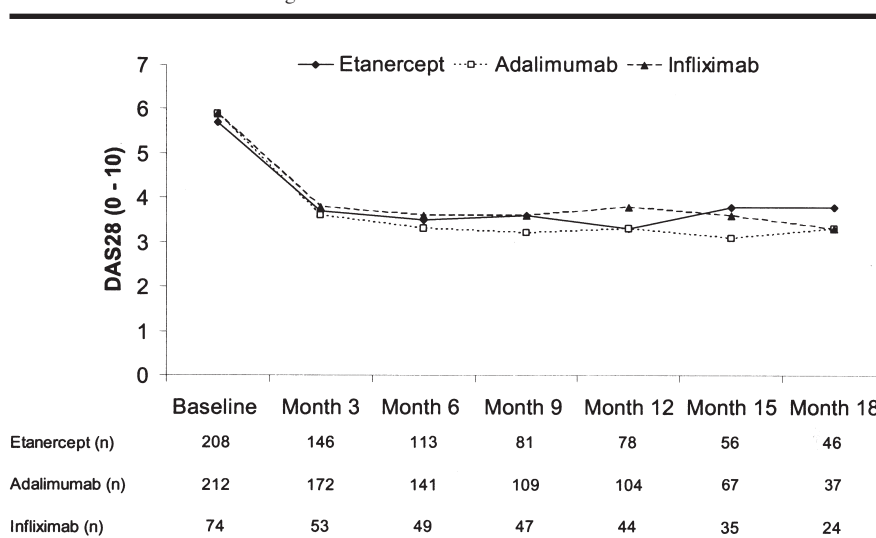

Etanercept (n)	208	146	113	81	78	56	46
Adalimumab (n)	212	172	141	109	104	67	37
Infliximab (n)	74	53	49	47	44	35	24

Fig. 1. DAS-28 scores over time (observed cases)

Table II. Average magnitude of dose escalation during the 12-month study and 18-month follow-up periods.

		Mean dose (dose escalators)*		
		Etanercept (mg qw)	Adalimumab (mg q2w)	Infliximab (mg/kg q8w)
12-month study period	Label	50	40	3.0
	Baseline	50	39.4	3.3
	Dose at escalation	75	78.7	4.3
	Percent change from baseline[†]	50	101.5	30.6
18-month follow-up period	Dose at escalation	59.4	74.9	4.2
	Percent change from baseline[†]	18.8	91.2	29.5

*Etanercept mean dose was in mg/week; adalimumab mean dose was in mg/once every other week; infliximab mean dose was in mg/kg every 8 weeks after the third dose.
[†]Mean of % changes differs slightly from % change of means.

Figure 2B shows the relative extent of dose escalation during 18 months when defined to comprise non-biologic DMARD intensification as well as increased biologic dose. By this expanded definition, a higher proportion of each cohort had dose augmentation, however the relative difference between cohorts was quite constant (7–8% between etanercept and adalimumab groups; 32% between etanercept and infliximab groups: Figure 2A vs. 2B). Significantly more patients treated with adalimumab (23%, n=71, p=0.010) or infliximab (47%, n=50, p<0.001) required an increase in biologic or DMARD or addition of another DMARD than among patients treated with etanercept (14%, n=46).

An increase in biologic, DMARD or steroid dose or addition of another DMARD or steroid to the treatment regimen was also compared among cohorts over the study and follow-up periods (Fig. 2C). The gap between the proportion of patients requiring such dose adjustments again remained similar between cohorts and significantly more patients taking adalimumab (28%, n=88, p=0.022) or infliximab (47%, n=50, p<0.001) required such an adjustment during the 18-month period compared with those taking etanercept (19%, n=62).

Figure 3 shows the adherence to labelled dose for the treatment groups over time. The survival curves demonstrate that adherence to labelled dose was significantly shorter for infliximab and adalimumab compared to etanercept (log rank p<0.001 for both groups). By 100 days into treatment, the three cohorts can be seen to diverge from each other in terms of proportion of patients requiring escalation. The survival curves for infliximab and etanercept continued to diverge for the study duration, while separation between etanercept and adalimumab flattened out at approximately 300 days.

A Cox proportional hazard model was used to estimate hazard of dose escalation according to several demographic and clinical characteristics as potentially contributing factors. For the 18-month study period, hazard of dose escalation relative to etanercept
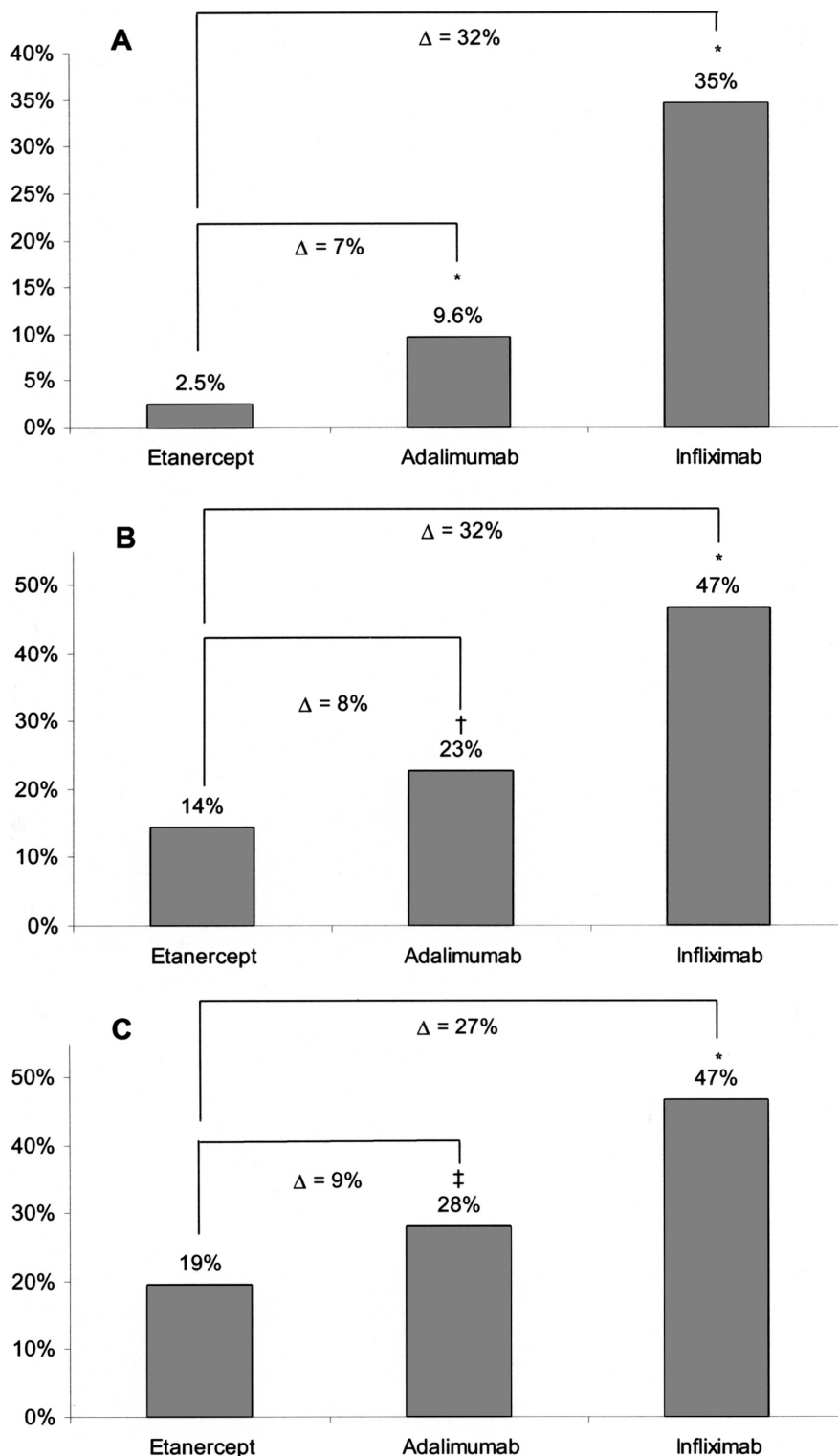

Fig. 2. Prevalence of dose escalation or adjustment among patients prescribed etanercept, adalimumab or infliximab 18 months after the index date. (**A**) Escalation of biologic; (**B**) Escalation of biologic or DMARD or addition of DMARD (**C**) Escalation of biologic or DMARD or steroid or addition of DMARD or steroid.
*p<0.001; †p=0.010; ‡p=0.022 relative to dose escalation in the etanercept group (chi-square).

for adalimumab patients was 4.6 times higher (p<0.0001) and 26 times higher for infliximab patients (p<0.001). Only monotherapy at index date, which in-

creased hazard of escalation 2.2-fold (p=0.004) was otherwise significant.
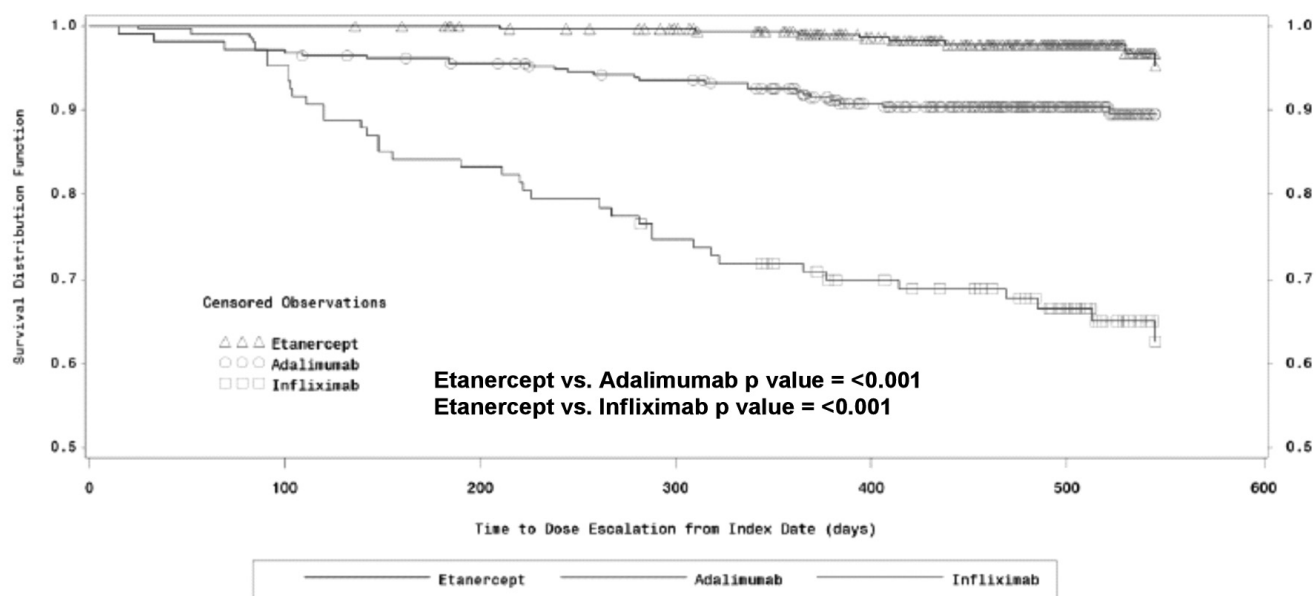To control for differences in treatment practice patterns, budgetary restrictions

Fig. 3. Time to dose escalation among patients prescribed etanercept, adalimumab or infliximab over 18 months from the index date, estimated using the Kaplan-Meier techniques of Cox Proportional Hazard Regression Modelling.

or treatment guidelines, a risk factor associated with sites in Germany, Italy, the Netherlands and the United Kingdom (UK) was incorporated into the model, using France as a reference country. Compared with France, patients treated in Italy showed a 2.5-fold hazard of escalation (p=0.005) and in Germany the hazard was 2.0 times as great (p=0.071). The hazard of escalation among patients in the UK and the Netherlands was not significant relative to that in France. It should be noted that choosing France as a reference country was arbitrary but choice of another country as reference would not alter the finding that there were country-specific differences in incidence of dose-escalation.

There were very few DAS-28 data in the charts for both pre- and post-escalation. The scores were similar across the treatment groups but escalation had little if any effect on DAS-28: patients in the etanercept (3 of 8 escalators had pre- and post-escalation numbers) and adalimumab (13 of 30) had slight increases in score; infliximab-treated patients (14 of 37) showed a slight decrease (Fig. 1).

As reported previously, total annualised per patient medical costs accrued by the adalimumab cohort were significantly higher than those of the etaner-

cept cohort; those of the infliximab cohort, marginally so (29). Furthermore, among subjects treated with either infliximab or adalimumab, there were statistically significant differences in total cost of care between subjects with dose escalation compared with non-escalators. Such differences observed for subjects treated with etanercept were not significant (Table III).

Discussion

This retrospective study was designed to establish the nature and extent of dose adjustment among patients treated for RA and continuing treatment with anti-TNF agents for at least 12 months. Indeed, the data provide further evidence that etanercept, adalimumab, and infliximab are highly effective therapies and patients in all cohorts responded

equally well to treatment, as has been seen in recent registry studies (32, 33). However, during the initial 12-month period of study as well as during the 6-month follow-up period, a significantly higher proportion of patients receiving infliximab (35%) or adalimumab (9.6%) required an escalation of their anti-TNF dose to maintain effectiveness compared with etanercept (2.5%: p<0.001). Statistically significant differences among treatment groups were maintained when alternate definitions of dose adjustment were employed such as DMARD or steroid switches or intensification, biologic switches or 12- or 18-month weighted dose for study duration (data not shown) *vs*. label-recommended dose.

Although the study was retrospective in nature, cohorts were well balanced

Table III. Total cost of care per patient per year for subjects with dose escalation *vs*. non-escalators.

	Etanercept (n=319)	Adalimumab (n=313)	Infliximab (n=107)
Total cost of care for biologic dose escalators	€17,773	€23,300	€17,153
Total cost of care for biologic non-escalators	€15,507	€17,429	€15,028
Difference in total cost of care among escalators and non-escalators (95% CI)*	€2,266 (-878 – 5,410)	€5,872 (3,862 – 7,882)[†]	€2,126 (411 – 3,840)[†]

*CI: confidence interval; Linear model used to compute mean difference and confidence interval of mean difference. [†]p<0.001 relative to the etanercept group (chi-square).

in terms of demographic and clinical factors; thus our findings are relatively uninfluenced by known confounders. Through Cox proportional hazard modelling we were able to demonstrate that disease duration, number of previous DMARDs, age, DAS-28 score, presence of erosive disease and other comorbidities did not alter the finding of differences in incidence of dose-escalation among three cohorts. Our finding that initiation of monotherapy is associated with an increase in hazard for dose-escalation is similar to previous results reported by Breedveld and colleagues (4). In their study 25% of patients on adalimumab monotherapy underwent dosage escalation during year-1 as opposed to only 11% on adalimumab combination therapy.

Our results are consistent with previous reports in terms of the difference between biologics but the proportion of patients who underwent dose escalation was generally lower across the three cohorts than in published studies. Whereas 9.6% of patients in our adalimumab cohort required dose escalation, 18% of patients either on combination adalimumab methotrexate therapy (n=268) or monotherapy (n=274) followed during the PREMIER trial, required escalation (4). Studies of infliximab-use generally reported higher proportions of dose escalation than the 35% in our study, the exception being that of Durez *et al*. who reported that 22% of patients (n=482) required escalation at 22 weeks (9). In other reports (24, 26, 27, 34), involving as many as 1324 patients prescribed infliximab (27), the proportion of escalators ranged from 35% (of 124 patients) (34) to 62% (of 394 patients) (27). Escalation among patients prescribed etanercept (2.5% in our study) was also higher among patients in previously published studies. A longitudinal claims data study indicated escalation for 11% of patients prescribed etanercept (n=690, *vs*. 55% of 424 patients on infliximab) (20); an examination of costs to treat RA patients over age 65 reported escalation among 16% of 99 subjects on etanercept (*vs*. 37% of those receiving infliximab; n=181) (35).

The overall lower incidence of escalation across the three cohorts may be an effect of study design, which required that subjects remain on one biologic for at least 12 months. This implied that patients in the study were responding fairly well to treatment. Indeed, 41, 47 and 31% of the etanercept, adalimumab and infliximab cohorts, respectively, were EULAR (European League against Rheumatism) good responders (compared with 18% of patients on etanercept or infliximab examined in a British Society for Rheumatology biologics registry study) (36).

Adherence to labelled dose (from K-M analysis) was longest for etanercept (followed by adalimumab and infliximab) and separation in survival curves occurred at 100 days and continued until about one year, consistent with loss of efficacy over time. Loss of clinical efficacy associated with these anti-TNF agents may be attributed to their immunogenicity profiles and their propensity to generate anti-TNF antibodies (7, 8, 13).

Surveyed investigators from our study indicated that dose escalation was the preferred treatment option for patients with inadequate response to recommended dose or loss of efficacy over time. A related question could be as to why the inadequate responders were not switched to another line of treatment. In this context, it is worth noting that perhaps inadequate response may not signify absolute lack of therapeutic response. Further, reimbursement guidelines require that biologic agents be available for patients who have failed multiple lines of prior treatment and therefore have limited recourse to other treatment options.

Although some difference in total cost of care can be attributed to variation in drug price across the five EU markets, it is noteworthy that escalation, where it occurred, was not significantly more costly for patients on etanercept whereas for those on adalimumab or infliximab, escalation resulted in significantly higher total cost of care.

This, as with any retrospective study, is limited by available data, particularly those of clinical efficacy which were often missing. Bias cannot be ruled out as it may have been introduced through unobserved variables. There has been greater clinical familiarity with escalating doses of infliximab and adalimumab compared to etanercept, which is more often switched to a different biologic rather than the dose increased, however, secondary endpoints of increase or addition of new DMARD and/or steroid was also consistently lower in our etanercept cohort. Persistence was not specifically addressed in our study as it has been by others who have shown that patients persist on etanercept at least as long as with adalimumab or infliximab (37-39).

An unavoidable limitation is that certolizumab could not be included as it was yet to be approved at the time of the study. Future work may examine dose escalation among all biologics, including soon to be licensed golimumab, when there are sufficient patient numbers using these drugs in normal clinical practice in Europe.

Charts were only reviewed for DAS-28 and HAQ scores as indications of efficacy. Rheumatoid arthritis is a constellation of many interrelated clinical, structural and functional symptoms. It is perhaps not entirely appropriate to assess the impact of dose-escalation solely in terms of its impact on clinical disease activity. Other clinical outcomes such as reduced morning stiffness or lessening of pain may have resulted from dose escalation but such data were not available. Therefore, we cannot rule out clinical benefits of dose-escalation in terms of functional or structural outcomes. Further, we cannot definitively rule out that our study is reflective of prescribing behaviour of rheumatologists linked to the label. As the study was being designed only the adalimumab label supported dose-escalation (40).

Despite the sparseness of outcomes data (DAS-28), they are in general agreement with those reported in the PREMIER study (adalimumab) (4) and that of van Vollenhoven *et al*. (infliximab) (34), that dose-escalation does not result in measurable benefits in terms of disease activity (6). However, because of small numbers, ours are not definitive findings and suggest need for further research.

Conclusion

Our investigation demonstrates that dose escalation is significantly <u>less frequently</u> observed with etanercept compared to the anti-TNF monoclonal antibodies, adalimumab and infliximab in real life practice consistent with the findings of others (41). Furthermore, the total cost of care associated with <u>dose escalation</u> was significantly higher for patients treated with the monoclonal antibodies but not for those treated with etanercept.

Acknowledgments

References

1. SILMAN A, HOCHBERG M, (Eds.). Epidemiology of the rheumatic diseases. New York: Oxford Medical Publications; 1993.
2. MAINI R, ST CLAIR EW, BREEDVELD F *et al.*: Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.
3. WEINBLATT ME, KEYSTONE EC, FURST DE *et al.*: Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; 48: 35-45.
4. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al.*: The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
5. VAN DER HEIJDE D, KLARESKOG L, LANDEWÉ R *et al.*: Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 3928-39.
6. WEINBLATT ME, KREMER JM, BANKHURST AD *et al.*: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.

7. SIDIROPOULOS PI, BOUMPAS DT: Differential drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 701-3.
8. ANDERSON PJ: Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005; 34 (Suppl. 1): 19-22.
9. DUREZ P, VAN DEN BOSCH F, CORLUY L *et al.*: A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. *Rheumatology* (Oxford) 2005; 4: 465-8.
10. FINCKH A, SIMARD JF, GABAY C, GUERNE PA: Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 746-52.
11. GEBOREK P, CRNKIC M, PETERSSON IF, SAXNE T: Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002; 61: 793-8.
12. FOERDER CA, ROGGE MC: Enbrel (etanercept). *Dev Biol* (Basel) 2002; 109: 99-102.
13. HARAOUI B, CAMERON L, OUELLET M, WHITE B: Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. *J Rheumatol* 2006; 33: 31-6.
14. BAERT F, NOMAN M, VERMEIRE S *et al.*: Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348: 601-8.
15. DE VRIES MK, WOLBINK GJ, STAPEL SO *et al.*: Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. *Ann Rheum Dis* 2007; 66: 1252-4.
16. WOLBINK GJ, VIS M, LEMS W *et al.*: Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 711-5.
17. BARTELDS GM, WIJBRANDTS CA, NURMOHAMED MT *et al.*: Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 921-6.
18. VAN DE PUTTE LB, ATKINS C, MALAISE M *et al.*: Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; 63: 508-16.
19. KLARESKOG L, MORELAND L, COHEN S *et al.*: Safety and efficacy of over 8 years of continuous etanercept therapy in patients with rheumatoid arthritis in North America and Europe. *Ann Rheum Dis* 2006; 65 (Suppl. II): 326.
20. ETEMAD L, YU EB, WANKE LA: Dose adjustment over time of etanercept and infliximab in patients with rheumatoid arthritis. *Manag Care Interface* 2005; 18: 21-7.
21. HARLEY CR, FRYTAK JR, TANDON N: Treatment compliance and dosage administration among rheumatoid arthritis patients

receiving infliximab, etanercept, or methotrexate. *Am J Manag Care* 2003; 9 (Suppl.): S136-S143.
22. BUCH MH, BINGHAM SJ, BRYER D, EMERY P: Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. *Rheumatology* (Oxford) 2007; 46: 1153-6.
23. ELLIS M, ZWAAN F, HEDSTROM U *et al.*: Recombinant human interleukin 11 and bacterial infection in patients with [correction of] haematological malignant disease undergoing chemotherapy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; 361: 275-80.
24. FITZCHARLES MA, CLAYTON D, MENARD HA: The use of infliximab in academic rheumatology practice: an audit of early clinical experience. *J Rheumatol* 2002; 29: 2525-30.
25. KRISTENSEN LE, GEBOREK P, SAXNE T: Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment: observational results from the South Swedish Arthritis Treatment Group register. *Rheumatology* (Oxford) 2009; 48: 243-5.
26. OLLENDORF DA, MASSAROTTI E, BIRBARA C, BURGESS SM: Frequency, predictors, and economic impact of upward dose adjustment of infliximab in managed care patients with rheumatoid arthritis. *J Manag Care Pharm* 2005; 11: 383-93.
27. STERN R, WOLFE F: Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 1538-45.
28. YAZICI Y, KRASNOKUTSKY S, BARNES JP *et al.*: Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. *J Rheumatol* 2009; 36: 907-13.
29. MOOTS RJ: Real life usage of biologics. *BMJ Satellites* 2009; 22-5.
30. BARBER JA, THOMPSON SG: Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med* 2000; 19: 3219-36.
31. OOSTENBRINK JB, KOOPMANSCHAP MA, RUTTEN FF: Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics* 2002; 20: 443-54.
32. PAVELKA K, FOREJTOVA S, STOLFA J *et al.*: Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. *Clin Exp Rheumatol* 2009; 27: 958-63.
3.3 SARAUX A, COMBE B, BLIN P *et al.*: Survey of the therapeutic management of rheumatoid arthritis in France: the OPALE study. *Clin Exp Rheumatol* 2010; 28: 325-32.
34. VAN VOLLENHOVEN RF, BRANNEMARK S, KLARESKOG L: Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. *Ann Rheum Dis* 2004; 63: 426-30.
35. WEYCKER D, YU EB, WOOLLEY JM, OSTER G: Retrospective study of the costs of care during the first year of therapy with etanercept or infliximab among patients aged > or =65 years with rheumatoid arthritis. *Clin Ther* 2005; 27: 646-56.

36. HYRICH KL, WATSON KD, SILMAN AJ, SYMMONS DP: Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford) 2006; 45: 1558-65.

37. BROCQ O, ROUX CH, ALBERT C *et al.*: TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. *Joint Bone Spine* 2007; 74: 148-54.

38. DU PAN SM, DEHLER S, CIUREA A *et al.*: Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum* 2009; 61: 560-8.

39. DUCLOS M, GOSSEC L, RUYSSEN-WITRAND A *et al.*: Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. *J Rheumatol* 2006; 33: 2433-8.

40. Adalimumab label. 2005. http://www.emea.eu.int/humandocs/Humans/EPAR/humira/humira.htm. (Accessed 5 Aug 2005).

41. ARIZA-ARIZA R, NAVARRO-SARABIA F, HERNANDEZ-CRUZ B *et al.*: Dose escalation of the anti-TNF-alpha agents in patients with rheumatoid arthritis. A systematic review. *Rheumatology* (Oxford) 2007; 46: 529-32.