Cost of dose escalation in people with rheumatoid arthritis treated with tumour necrosis factor inhibitors across Europe

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Abstract

Objective

The aim of this study was to calculate the marginal cost of dose escalation in people with rheumatoid arthritis treated with tumour necrosis factor (TNF) inhibitors across Europe.

Methods

The proportion of people who escalate their dose of TNF inhibitor and the average percentage increase in TNF inhibitor cost associated with escalators versus non-escalators was calculated from previously published estimates, weighted by the sample size for each study. The number of people with rheumatoid arthritis treated with TNF inhibitors and the corresponding total drug sales were obtained for five European countries from Decision Resources' Pharmacor Market Forecast. Method 1 assumed that total sales of a TNF inhibitor represented the cost of an escalator multiplied by the number of escalators plus the cost of a non-escalator multiplied by the number of non-escalators. Method 2 assumed that the drug cost per day used to forecast total sales was calculated using the dose of TNF inhibitor used by non-escalators. The marginal cost of TNF inhibitor dose escalation was estimated by multiplying the difference in cost between escalators and non-escalators by the number of escalators.

Results

The estimated increase in TNF inhibitor costs associated with dose escalation in people with rheumatoid arthritis across five European countries (Germany, France, UK, Spain and Italy) was €51.5–54.4 million for adalimumab, €44.8–52.8 million for infliximab and €5.8–5.9 million for etanercept.

Conclusion

Dose escalation of the TNF inhibitors adalimumab, etanercept and infliximab in people with rheumatoid arthritis has resulted in an increase in TNF inhibitor costs across five European countries.

Key words

TNF inhibitor, rheumatoid arthritis, dose escalation, cost, Europe, etanercept, adalimumab, infliximab

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S.E. Holden is employed by, and C.J. Currie is a director of Pharmatelligence, a research consultancy receiving funding from ELM Medical for the submitted work and from other healthcare-related organisations;
M. Lennon is owner of ELM Medical and consults to many healthcare-related organisations;
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Introduction

Rheumatoid arthritis is a chronic, systemic disorder characterised by inflammation of the synovial joints leading to progressive joint destruction, pain, swelling and stiffness. Biologic disease-modifying anti-rheumatic drugs (bDMARDs) are efficacious therapies for the management of rheumatoid arthritis (1) and are used alongside or instead of conventional DMARD therapy (2, 3).

Adalimumab, etanercept, infliximab, certolizumab and golimumab belong to a class of biologic agents that inhibit tumour necrosis factor (TNF), a cytokine shown to play an important role in the development of rheumatoid arthritis (4). Although TNF inhibitors are effective, a proportion of people fail to respond adequately, or they lose their response to the specific TNF inhibitor over time (5). The development of antibodies against adalimumab or infliximab has been linked to a reduction in drug concentration and a reduced response (6-9). However, although antibodies to etanercept have been documented, they appear to be non-neutralising and have no effect on clinical activity (10).

A recent systematic review conducted by Moots and colleagues found that the practice of escalating the dose of TNF inhibitors in order to improve or achieve an adequate response in people with rheumatoid arthritis is common, where the weighted proportion of dose escalators treated with adalimumab, etanercept and infliximab was 15%, 5% and 42%, respectively (11). Dose escalation, through increased dose or decreased dose-interval, was associated with an increase in TNF inhibitor-related drug acquisition costs, rheumatoid arthritis related treatment costs and thus total health costs (11). However, the cost of dose escalation at the population level remains unquantified. The aim of this study was to calculate the marginal cost of dose escalation in people with rheumatoid arthritis treated with TNF inhibitors across Europe.

Materials and methods

From a review conducted by Moots and colleagues (11), three studies provided relevant data on TNF inhibitor drug costs for dose escalators and non-dose escalators in people with rheumatoid arthritis: Harrison *et al.* (12), Gilbert *et al.* (13) and Ollendorf *et al.* (14). These studies were carried out in the US, where drug cost and healthcare provision may differ from Europe. Therefore, from these data, the average percentage increase in TNF inhibitor cost associated with escalators versus non-escalators for each individual TNF inhibitor (adalimumab, etanercept and infliximab) was calculated, weighted by the sample size for each study. An estimate of the proportion of people who escalated their dose of TNF inhibitor was taken as the weighted average calculated by Moots and colleagues in their recently published systematic review (adalimumab 15%, etanercept 5% and infliximab 42%) (11).

Pharmacor at Decision Resources analyses and forecasts the current and future earning potential of drugs on the market and in research and development. The Pharmacor Market Forecast by Decision Resources provided an estimate of the number of people with rheumatoid arthritis treated with each prescribed TNF inhibitor in five European countries (Germany, France, UK, Spain and Italy) for 2014 (15). These estimates were multiplied by the percentage of people who escalate to provide the number of escalators and non-escalators by TNF inhibitor type for each European country.

The Pharmacor report creates a bottom-up forecast of 2014 market sales for each TNF inhibitor by country through the multiplication of estimates of drug price per treated day, the number of treated days (365 days), compliance rates and the number of people treated with each drug. In order to provide a more accurate estimate of the price paid by the health service provider, ex-manufacturer drug prices per treated day were substituted with values derived from 2014 retail (inclusive of value-added tax) or wholesale prices obtained separately from Decision Resources. For the five European countries overall, average drug price per treated day was weighted by the number of drug-treated rheumatoid arthritis patients from each country. The cost of dose escalation for each of the five European countries was es-

timated using two methods. Method 1 was based on the assumption that the TNF inhibitor cost per day provided by Decision Resources was based on the average person (including both dose escalators and non-escalators). Method 2 assumed that the drug cost per day represents the average cost for non-escalators.

Costs were converted from dollars to Euros using the exchange rate provided in the Pharmacor Market Forecast.

Method 1

It was assumed that people with rheumatoid arthritis prescribed a TNF inhibitor were either a dose escalator or a non-dose escalator. Therefore, the estimated total sales of a TNF inhibitor taken from the Pharmacor Market Forecast represents the cost of an escalator multiplied by the number of escalators plus the cost of a non-escalator multiplied by the number of non-escalators. From this, the cost of one non-escalator was calculated by dividing total sales by the sum of the number of escalators and non-escalators plus the number of escalators multiplied by the percent increase in cost of an escalator. The marginal cost of dose escalation was then estimated by subtracting the cost of a non-escalator multiplied by the total number of patients prescribed the TNF inhibitor from total sales.

Method 2

The cost of a non-escalator was calculated by dividing total sales by the number of patients prescribed the TNF inhibitor. The cost of an escalator could then be calculated by multiplying the cost of a non-escalator by one, plus the percentage increase in cost of an escalator. The marginal increase in TNF inhibitor cost for dose escalation was estimated by multiplying the difference in cost between escalators and non-escalators by the number of escalators.

Results

The weighted average percentage increase in TNF inhibitor cost associated with escalators when compared with non-escalators was 38% for adalimumab, 13% for etanercept and 42% for infliximab (Table I).

Table I. Average percentage increase in TNF inhibitor cost associated with escalators *versus* non-escalators.

TNF inhibitor	Published study	Cost of escalator*	Cost of non-escalator*	Sample size	% increase in cost of escalators	Weighted % increase in cost of escalators
Adalimumab	Harrison (Continual) (12)	€ 28,050	€ 19,663	538	43%	31%
	Harrison (Naive) (12)	€ 22,072	€ 17,434	203	27%	7%
	Gilbert (13)	-	-	-	-	-
	Ollendorf (14)	-	-	-	-	-
	Total/year	€ 26,413	€ 19,053	741		38%
	Cost per day	€ 72.36	€ 52.20			
Etanercept	Harrison (Continual) (12)	€ 21,697	€ 18,401	1,496	18%	10%
	Harrison (Naive) (12)	€ 19,806	€ 16,651	282	19%	2%
	Gilbert (13)	€ 13,399	€ 12,979	950	3%	1%
	Ollendorf (14)	-	-	-	-	
	Total/year	€ 18,612	€ 16,332	2,728		13%
	Cost per day	€ 50.99	€ 44.74			
Infliximab	Harrison (Continual) (12)	€ 28,183	€ 24,795	1,749	14%	6%
	Harrison (Naive) (12)	€ 23,121	€ 14,874	360	55%	5%
	Gilbert (13)	€ 20,557	€ 12,850	598	60%	9%
	Ollendorf (14)	€ 20,992	€ 12,301	1,236	71%	22%
	Total/year	€ 17,729	€ 14,306	3,943		42%
	Cost per day	€ 48.57	€ 39.19			

*Costs were published in dollars and conveted to Euros using the exchange rate provided in the Pharmacor Market Forecast.

Table II. Marginal cost of dose escalation across Europe.

			Marginal cost of dose escalation (in millions of Euros)				
	TNF inhibitor	Total	UK	France	Spain	Italy	Germany
a) Method 1	Adalimumab	51.5	7.8	8.5	8.5	9.1	17.7
	Etanercept	5.8	1.1	1.0	0.9	1.1	1.7
	Infliximab	44.8	5.6	12.0	9.9	6.3	11.1
	Total	102.2	14.4	21.5	19.2	16.5	30.5
b) Method 2	Adalimumab	54.4	8.2	8.9	8.9	9.7	18.7
	Etanercept	5.9	1.1	1.0	0.9	1.1	1.8
	Infliximab	52.8	6.6	14.2	11.6	7.4	13.0
	Total	113.1	15.9	24.1	21.4	18.2	33.5

The estimated increase in TNF inhibitor cost associated with dose escalation across five European countries (Germany, France, UK, Spain and Italy) was €51.5–54.4 million for adalimumab, €5.8–5.9 million for etanercept and €44.8–52.8 million for infliximab (Table II). The lowest figure corresponds to the increase in TNF inhibitor cost calculated using Method 1 and the highest figure is calculated using Method 2.

The estimated marginal cost in Euros of dose escalation across the five European countries was 0.8–0.8 million for adalimumab, 0.1–0.1 million for etanercept and 2.1–2.5 million for infliximab per 1000 treated patients (Fig. 1a-b). The corresponding figures were 0.5–0.6 million, 0.1–0.1 million and 1.7–2.0 million for the UK; 0.6–0.6 million, 0.1–0.1 million and 1.5–1.8 million for France; 0.7–0.8 million, 0.1–0.1 million and 2.2–2.5 million for Spain; 1.1–1.1 million, 0.1–0.1 million and 3.0–3.5 million for Italy; and 1.2–1.2 million, 0.1–0.1 million and 3.3–3.9 million for Germany.

Discussion

The estimated increase in TNF inhibitor costs associated with the dose escalation in people with rheumatoid arthritis across five European countries (Germany, France, UK, Spain and Italy) was €51.5–54.4 million for adalimumab, €44.8–52.8 million for infliximab and €5.8–5.9 million for etanercept. As

63% of the population of the European Union live in these five European countries (16), this equates to an increase in TNF inhibitor cost of €81.7–86.3 million for adalimumab, €71.1–83.8 million for infliximab and €9.2–9.4 million for etanercept for the European Union as a whole. This is based on the assumption that the five European countries included in this study are representative of the countries included in the European Union in terms of the percentage of the population receiving biologics and drug cost per day. However, studies have shown that access to biologics may differ across Europe (17-19).

Two methods were used to estimate the marginal cost of dose escalation. Method 1 is likely to be a more accurate estimate of the cost associated with dose escalation for people with rheumatoid arthritis prescribed infliximab, because the cost per day estimated by Decision Resources in Pharmacor Market Forecast is estimated using a range of infliximab doses. Conversely, the cost per day estimated for etanercept and adalimumab was calculated using standard doses and dosing intervals. Therefore, Method 2 may be a more accurate calculation of the cost of dose escalation in Europe for people using etanercept and adalimumab.

Dose escalation could take the form of an increase in dose or a decrease in dose interval or both. In patients undergoing dose escalation, dose interval decreases have been reported to occur in 8.3%–42.6% of patients (11). Increased cost associated with dose escalation in people treated with infliximab is likely to be an underestimation. In the UK, infliximab is administered intravenously over a two-hour period by a healthcare professional at an estimated annual cost of £777 or £5,551 depending on whether the drug is administered on an outpatient or day case basis (20, 21). Conversely, adalimumab or etanercept can be administered subcutaneously in the home environment by the patient or carer. Any dose interval decreases for infliximab will result in a corresponding increase in administration costs. These costs have not been taken into account in our estimation because the exact decrease in the dosage interval was not known.

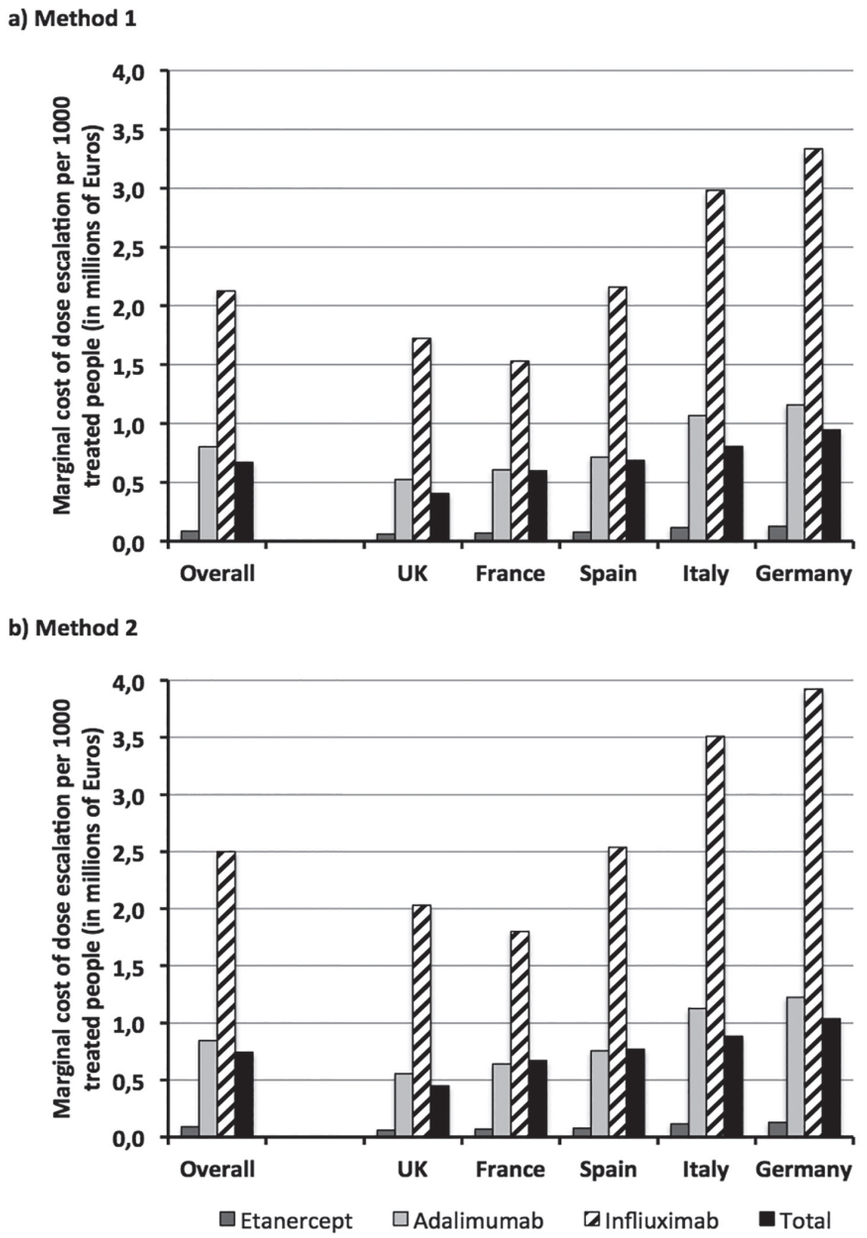

Fig. 1. Marginal cost of dose escalation per 1000 treated people.

Previously published costs have been estimated at the patient level rather than the population level. TNF inhibitor costs were greater for escalators *versus* non-escalators for all estimates included in this study (12-14). Total rheumatoid arthritis related costs and total healthcare costs have also been reported to be higher for escalators when compared with non-dose escalators (13, 14, 22, 23). Nevertheless, several studies have shown that dose escalation provides minimal clinical benefits (23-25). Conversely, other studies have shown some increased efficacy associated with dose escalation (26-28). The limited availability of evidence relating to clinical efficacy of dose escalation results from the sources of data being mainly claims databases, retrospective medical records reviews and observational studies.

Dose escalation has been shown to occur less frequently in people with rheumatoid arthritis treated with etanercept when compared to those treated with adalimumab or infliximab (weighted average 5% *vs*. 15% and 42%, respec-

tively) (11). In two recently published observational studies, it was reported that patients treated with etanercept had significantly lower rates of dose escalation when compared with adalimumab (29-31) and infliximab (30, 31). The weighted percentage increase in TNF inhibitor cost associated with dose escalation was also lowest for etanercept (13% versus 38% and 42%, Table I). Therefore the corresponding marginal cost associated with dose escalation across the five European countries was lowest for etanercept, even though more people with rheumatoid arthritis were predicted to receive treatment with etanercept when compared with adalimumab or infliximab.

The reasons why clinicians increase the dose of a TNF inhibitor include no initial response, inadequate initial response and loss of initial response. Unfortunately most studies have not reported the reasons why patients escalated.

The differences in reported rates of dose escalation could be for a number of reasons. It has been proposed that the development of antibodies against adalimumab or infliximab may lead to a reduced response (6-9), which may then trigger an escalation in dose. Non-neutralising antibodies to etanercept have been reported, which have not been associated with any discernible effect on clinical activity (10), although studies that used an ELISA technique reported that antibodies to etanercept could not be detected (32), unlike the monoclonal antibodies (9). Clinical response to adalimumab and infliximab have been reported to correlate strongly with drug levels and antibody formation in RA (9): adalimumab antibodies have also been shown to affect clinical response in psoriasis (33), psoriatic arthritis (34) and ankylosing spondylitis (35). It should be noted that the order of dose escalation and antidrug antibody formation are the same, which may indicate that this is the most likely explanation. An additional possible reason for lower dose escalation rates seen with etanercept could be that, unlike infliximab and adalimumab, the product labelling for etanercept does not advocate any flexibility in the recommended dose (25 mg twice weekly or 50 mg once weekly) (36). This may discourage prescribers escalating the dose in patients treated with etanercept. The substantial increased costs across Europe reported here have important implications for health care budgets that are under increasing pressure given that clinical improvement may be limited. Payers and clinicians should consider whether this expenditure is a cost effective use of these limited resources when evidence indicates that switching to an alternative biologic may be effective (37). Recent evidence from Sweden suggests that switching between TNF inhibitors is a viable option, particularly from infliximab to etanercept for secondary inefficacy, which may be due to antibody formation (38).

Limitations

Several limitations should be taken into account when interpreting the results from this study. Total sales have been calculated using a bottom-up approach, using estimates for the number of treated people with rheumatoid arthritis, the compliance rate and the cost per day. The Moots review and its component studies (11) were conducted prior to the market forecasts and the proportion of dose escalators and their corresponding costs could have changed over time. In addition, differences between the studies included in the review conducted by Moots and colleagues may exist, including different definitions of dose escalation (11). In addition, different studies may report the proportion of people escalating over different time periods (11).

Differences between the populations may also exist. All studies providing TNF inhibitor costs for escalators and non-escalators were carried out in the US (12-14). The studies reporting TNF inhibitor costs for escalators and non-escalators included patients who were treatment naïve or on maintenance therapy (12-14). These figures were applied to the general population, who are likely to be a mixture of treatment naïve and those taking maintenance therapy. In addition, a proportion of people in the general population are likely to have progressed beyond their first-line TNF inhibitor therapy. It has been reported that switching to a second TNF inhibitor after failure of the first line therapy can produce good clinical results (38). However, the frequency of dose escalation of second-line therapy was not investigated (38). In addition, dose de-escalation is also possible but was not investigated here. Down-titration of TNF inhibitor doses due to disease remission has been reported to be uncommon (39). However, a more recently published Cochrane Systematic review reported that non-disease activity guided down-titration of etanercept doses in people with a minimum of 12 months of low disease activity was as effective in terms of disease activity and functional outcomes as continuing with standard doses (40). Evidence supporting down-titration of TNF inhibitors may have further encouraged this practice.

Conclusion

Dose escalation of the TNF inhibitors adalimumab, etanercept and infliximab in people with rheumatoid arthritis has resulted in an estimated increase in TNF inhibitor costs of €102.2–€113.1 million across five European countries. As the clinical response to dose escalation may be limited, clinicians should consider other alternative therapeutic strategies.

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