Review

Burden of dose escalation with tumour necrosis factor inhibitors in rheumatoid arthritis: a systematic review of frequency and costs

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ABSTRACT

Objective. *Optimising therapy to minimise disease activity is the goal for treating rheumatoid arthritis (RA) today. In refractory disease requiring biologics, the ability to modify therapy may be limited. In the case of the most widely used biologics, the TNF inhibitors (TNFi), dose escalation consisting of increasing the dose and/or shortening the interval between doses is often reported.*

Methods. *We systematically searched PubMed, EMBASE, Cochrane and Centre of Disseminated Reviews for reports of dose escalation of TNFi in RA and the economic effects of such a practice.*

Results. *Of 41 publications, 36 reported dose escalation and a weighted proportion of dose escalators was calculated for each drug. The proportion of dose escalators varied widely (adalimumab 7.5% to 36%, etanercept 0% to 22%, and infliximab 0% to 80%) due to a variety of methods for defining dose escalation. Based on 33 studies, the weighted proportion of dose escalators was adalimumab 14.9%, etanercept 4.9% and infliximab 41.7%. Six studies reported economic data comparing dose escalators with non-dose escalators. Adalimumab drug costs increased 27% to 43%, with total costs increasing 28% to 34%; infliximab drug costs increased 14% to 71%, RA-related costs increased 25% to 54% and total costs increased 14% to 34% and etanercept drug costs increased 3.2% to 19%, RA-related costs increased 4.5% and total costs increased 2.2% to 15%.*

Conclusion. *Escalating the dose of TNFi in inadequate responders in RA is widespread, occurring most frequently with infliximab and least with etanercept. This practice not only increases drug costs, but also RA-related and total costs.*

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease typically affecting the synovial joints with symptoms of pain, stiffness, swelling and progressive joint destruction. Recommendations for the treatment of RA suggest early and dynamic treatment to suppress the underlying inflammation and inhibit the progression of joint damage and other complications that may otherwise develop soon after diagnosis (1-3). Over the past several years, biologic agents such as those that inhibit the action of tumour necrosis factor (TNF) have become efficacious alternatives or additions to therapeutic strategies using traditional disease-modifying anti-rheumatic drugs (DMARDS) (4). Biologic therapy is particularly recommended for patients with RA who are unresponsive or have a partial response to conventional DMARDs (1, 2).

TNF inhibitors currently approved for the treatment of RA are adalimumab, certolizumab, etanercept, golimumab and infliximab (1, 2). Although efficacious, over time, a proportion of patients remain unresponsive, have a partial response, or exhibit a diminished response to these inhibitors (5). The presence of anti-adalimumab or anti-infliximab antibodies has been associated with a reduced clinical response (6-8), implicating the presence of neutralising antibodies as a potential factor underlying loss of response to these agents. Data on the immunogenicity of certolizumab, etanercept and golimumab are limited (9), though research suggests that the anti-drug antibodies raised in response to etanercept treatment are non-neutralising and have no effect on clinical efficacy (10, 11).

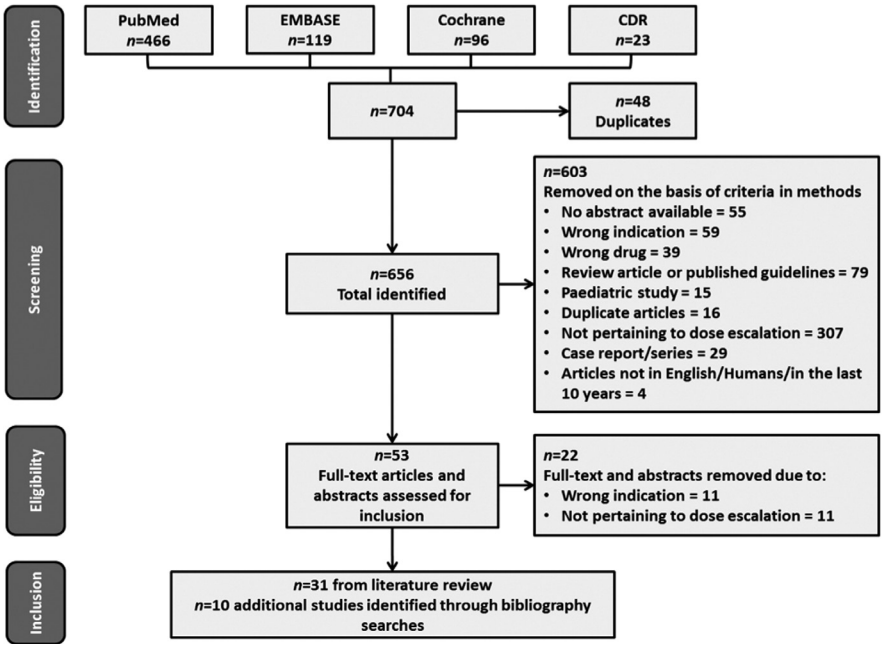
Data from both observational and interventional clinical studies have shown

that some patients require increased dose adjustment or shortened dose intervals to regain or maintain clinical response to some TNF inhibitors (12-14). In the real-world setting, the frequency at which dose escalation occurs is unclear and the impact it has on costs additional to direct drug costs is unknown. We hypothesised that there may be differences in the frequency of dose escalation between TNF inhibitors and that the practice of dose-escalation would result in additional costs in the treatment of RA. Thus, the purpose of this comprehensive review was to assess the frequency of dose escalation of TNF inhibitors in the treatment of RA and the economic impact of this practice to payers.

Methods

A search of PubMed, EMBASE, Cochrane and Centre of Disseminated Reviews was conducted for the five TNF inhibitors approved for the treatment of RA using an internal pre-specified search strategy document/protocol. Inclusion criteria consisted of articles pertaining to dose escalation with or without an economic component for the five biologics for the sole indication of RA. Search terms included the biologic agents, adalimumab, certolizumab, etanercept, golimumab and infliximab, and the general term "anti-TNF", the indication "rheumatoid arthritis" and immunogenicity "anti-drug antibodies" (and/or ADA). Searches for dose escalation included the following terms: "dose escalation", "dosage increase" and "dosing patterns". Searches for economic analyses included the following terms: "resource utilisation", "cost burden", "cost", "cost of illness", "healthcare costs", "cost benefit analysis", "drug costs" (MeSH, EMTREE), "economic" and "economic burden". In addition, bibliography review of the included articles was performed to capture any publications not identified in the formal literature search.

These searches were limited to results reported on human subjects, published in English in the last 10 years (2003 to 2013). Publications were excluded if no abstract was available, the article was a review or published guideline, studies were paediatric, pharmacokinetic or case-report, or were conducted in healthy subjects or in those with alternative indications. Figure 1 depicts a flow diagram incorporating the criteria for article selection. Informal sensitivity analyses were conducted by assessing dose-escalation rates reported by type of study (chart review, claims data, clinical study).



CDR: Centre for Disseminated Reviews

Fig. 1. Literature review flow diagram.

Table I. Summary of publication demographics and characteristics.

Characteristic	Number of studies[a]	Number of patients[a]
Study location		
Asia	1	327
Brazil	1	41
Canada	1	41
Europe	12	4886
Multi-continental	2	1128
USA	23	39968
Publication year		
2000–2004	9	6934
2005–2009	22	22195
2010–2013	9	17262
Study design		
Claims	17	37417
Clinical study	9	2668
Retrospective review	12	4941
Survey	2	1365
Drug		
Adalimumab	15	8142
Etanercept	19	17837
Infliximab	38	17316

[a]Does not include a systematic review; one publication reported two studies – each study is counted individually.

Publications were included if the patient population involved any adult patient with rheumatoid arthritis receiving adalimumab, certolizumab, etanercept, golimumab, or infliximab. The publication needed to contain information regarding dose escalation of these agents. Both comparative and non-comparative studies were included. The outcomes to be evaluated were type of dose escalation (dose *vs*. interval), time to dose escalation, and proportion of dose increase or interval decrease. Only direct medical costs were assessed for the economic studies with patient, hospital, or payer/societal perspectives being included. Data was independently extracted into tables by one reviewer, with verification by a second reviewer.

A weighted proportion of dose escalators was calculated for each drug as an alternative to reporting ranges. This calculation comprised multiplying the number of patients reported in the study for each drug by the proportion of patients experiencing dose escalation. This number was then totalled and divided by the number of patients for that drug. For studies reporting more than one calculation method, timeframe or

Table II. The proportion of dose escalators by study.

Study	Adalimumab	Etanercept	Infliximab
Agarwal *et al*. 2005 (29)			69%
Ariza-Ariza *et al*. 2007 (15)		17.4%	53.2%
Berger *et al*. 2005 (24)			33% to 50%
Blom *et al*. 2010 (30)	12%	7.6%	35.6%
Bonafede *et al*. 2012 (57)	8.7% to 17.5%	0.8% to 2.1%	22.9% to 57.6%
Breedveld *et al*. 2006 (42)	25%		
Durez *et al*. 2005 (40)			22%
Edrees *et al*. 2005 (41)			32.7%
Etemad *et al*. 2005 (19)		11%	55%
Favalli *et al*. 2008 (25)			0% to 59%
Geborek *et al*. 2002 (64)			57%
Gilbert *et al*. 2004 (34)		18%	58%
Gu *et al*. 2010 (35)	8%	3.4%	
Haraoui *et al*. 2006 (14)			63%
Harley *et al*. 2003 (21)		22%	36.9%
Harrison *et al*. 2010 (36)	9% to 10%	1% to 3%	24% to 26%
Huang *et al*. 2010 (65)	7.8% to 33.6%	3.4% to 10.3%	
Moots *et al*. 2011 (18)	9.6%	2.5%	34.6%
Nair *et al*. 2009 (37)			45.4%
Ogale *et al*. 2011 (47)	21.7% to 24.1%	11.1% to 15.9%	61.2% to 80.2%
Ollendorf *et al*. 2005 (32)			61.7%
Ollendorf *et al*. 2009 (31)	8.5% to 11.4%	4.7% to 7.6%	32.1% to 36.31%
Radstake *et al*. 2009 (51)	36%		20%
Rahman *et al*. 2007 (52)			30.4%
Schabert *et al*. 2012 (38)	7.5% to 12.5%	0 to 1.4%	10.8%
Scheinberg *et al*. 2008 (26)			68%
Sidiropoulos *et al*. 2004 (33)			73%
Stern R, Wolf F 2004 (27)			56% to 61%
van Vollenhoven *et al*. 2004 (43)			35%
Wendling *et al*. 2005 (66)			12%
Weycker *et al*. 2005 (22)		16%	37%
Wu *et al*. 2008 (23)	8.3%	3.3%	35.1%
Yazici *et al*. 2009 (48)	18%		40%

population, the reported proportions of patients for all methods/assessments were included.

Results

A total of 41 publications were identified following elimination of duplicates and the application of exclusion criteria (Table I). The majority of these publications originated from the USA (n=23) and were published between 2005 and 2009, a large proportion of which were claims database analysis studies. Publications included studies with adalimumab (15), etanercept (19) and infliximab (38) (Table I). No studies with certolizumab or golimumab were identified.

Dose escalation

Among the 41 publications identified, 36 studies reported values for dose escalation, one of which was a systematic review and meta-analysis of dose escalation studies (15). Dose escalation was defined as an increase in dose and/or an increase in the frequency of administration (decreased interval). However, a variety of definitions and methods for evaluating dose escalation were used depending on the study. Variations included reporting on first to last dose, first to subsequent dose or average dose, different timeframes – 12 months, 24 months, any dose increase or predefined dose-increase criteria (115%, 130%, 150% (12)) and different populations – naïve (initial), continuing (maintenance). Variations in the methods used for calculating the proportion of patients undergoing dose escalation led to a wide range of reported results (Table II). The proportion of dose escalators ranged from 7.5% to 36% for adalimumab, 0% to 22% for etanercept and 0% to 80% for infliximab (Table II).

Across all studies, the weighted proportion of dose escalators for each drug was adalimumab 14.9%, etanercept 4.9% and infliximab 41.7% (Fig. 2). For comparative studies, results consistently reported the frequency of dose escalation as highest for infliximab, followed by adalimumab, with etanercept-treated patients having dose escalations least often. In patients receiving infliximab, dose escalations included both increases in dose and decreases in the dose interval. Overall, dose increases were reported more frequently than dose-interval decreases. In patients undergoing dose escalation, dose increases ranged from 2.9% to 53%, whereas interval decreases ranged from 8.3% to 42.6%. In studies reporting change in dose over time, the percent increase in dose varied from no significant change (16), 11.2% (17) and 101% (18) increase for adalimumab; no significant change (19) to 7.4% (17, 20-23) and 50% increase (18) for etanercept; and 11.2% to 41.3% increase (16-22, 24-28) for infliximab.

Mean or median time to dose escalation was reported in seven studies (25, 27, 29-33). Time to dose escalation was 10.5 months (30) and 5.8 months (31) in two studies of adalimumab, 9 months (30) and 5.6 months (31) in two studies of etanercept, and 4.4 months to 8.5 months in the seven studies all reporting on infliximab.

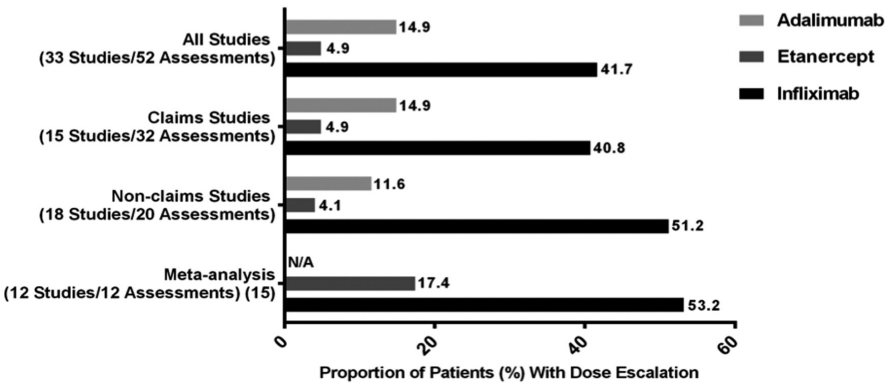


Fig. 2. Weighted proportion of patients undergoing dose escalation.

Table III. Summary of economic studies.

Study	Measure	Dose escalators	Adalimumab Non-dose escalators	% increase	Dose escalators	Etanercept Non-dose escalators	% increase	Dose escalators	Infliximab Non-dose escalators	% increase
Gilbert 2004 (34)	Number of patients				172/950 (18.1%)	778/950 (82%)		346/598 (57.9%)	252/598 (42%)	
	TNF inhibitor costs (mean cost/patient/year)				$10 427	$10 100	3.2%	$15 998	$10 000	60% (p<0.0001)
	Total RA-related costs (mean cost/patient/year)				$14 482	$13 865	4.5%	$20 915	$16 713	25% (p<0.0001)
	Total outpatient costs				1225	1261		2251	2167	3.8%
	Hospitalisation costs				1428	1298	10%	1516	3323	
	Non-RA related costs				3955	4178		5370	6104	
	Total costs (mean cost/patient/year)				$18 437	$18 043	2.2%	$26 285	$22 818	15% (p<0.0001)
[a]Gu 2010 (35)	Number of patients	131/461 (28%)	330/461 (72%)		146/1369 (11%)	1223/1369 (89%)				
	Average annual total medical costs	$19 059	$14 905	28% (p<0.001)	$15 100	$14 417	4.7% (p<.001)			
[a]Harrison 2010 (36)	Number of naïve patients – comparing the first to last prescriptions	18/203 (10%)			86/282 (26%)			4/360 (1%)		
	Number of continuing patients – comparing the first to last prescriptions	43/538 (9%)			443/1496 (24%)			48/1749 (3%)		
	Naïve – mean annual TNF inhibitor costs	$17 177	$13 567	27%	$15 413	$12 958	19%	$17 993	$11 575	55%
	Continual – mean annual TNF inhibitor costs	$21 829	$15 302	43%	$16 885	$14 320	18%	$21 932	$19 296	14%
Moots 2011 (18)	Number of patents	30/313 (9.6%)			8/319 (2.5%)			37/107 (34.6%)		
	Total cost of care/patient/ year	€23 300	€17 429	34%	€17 773	€15 507	15%	€17 153	€15 028	14%
[b]Nair 2009 (37)	Commercial group patients							761/1678 (45.4%)		
(Total pharmacy costs)	Medical-eligible group patients							242/616 (39.3%)		
	Commercial medical costs/member/year							$32 255	$21 011	54%
	Commercial pharmacy costs/member/year							$3462	$2072	67%
	Medical-eligible medical costs/member/year							$27 520	$15 967	72%
	Medical-eligible pharmacy costs/member/year							$4106	$2380	75%
Ollendorf 2005 (32)	Number of patients							762/1236 (61.7%)	474/1236 (38.3%)	
	TNF inhibitor costs							$16 336	$9573	71%
	RA-related costs annualised							$22 283	$14 425	54% (p<0.001)
	Non-RA related costs							$7816	8010	
	Total costs annualised							$30 099	$22 435	34% (p<0.001)

Adapted from Table, Flood 2008 (67). [a]Dose escalators included patients with high index dose. [b]Reported as patients with increase dose, no increase dose and decrease dose. Only increase dose (dose escalators) and no increase dose (non-dose escalators) are reported here.

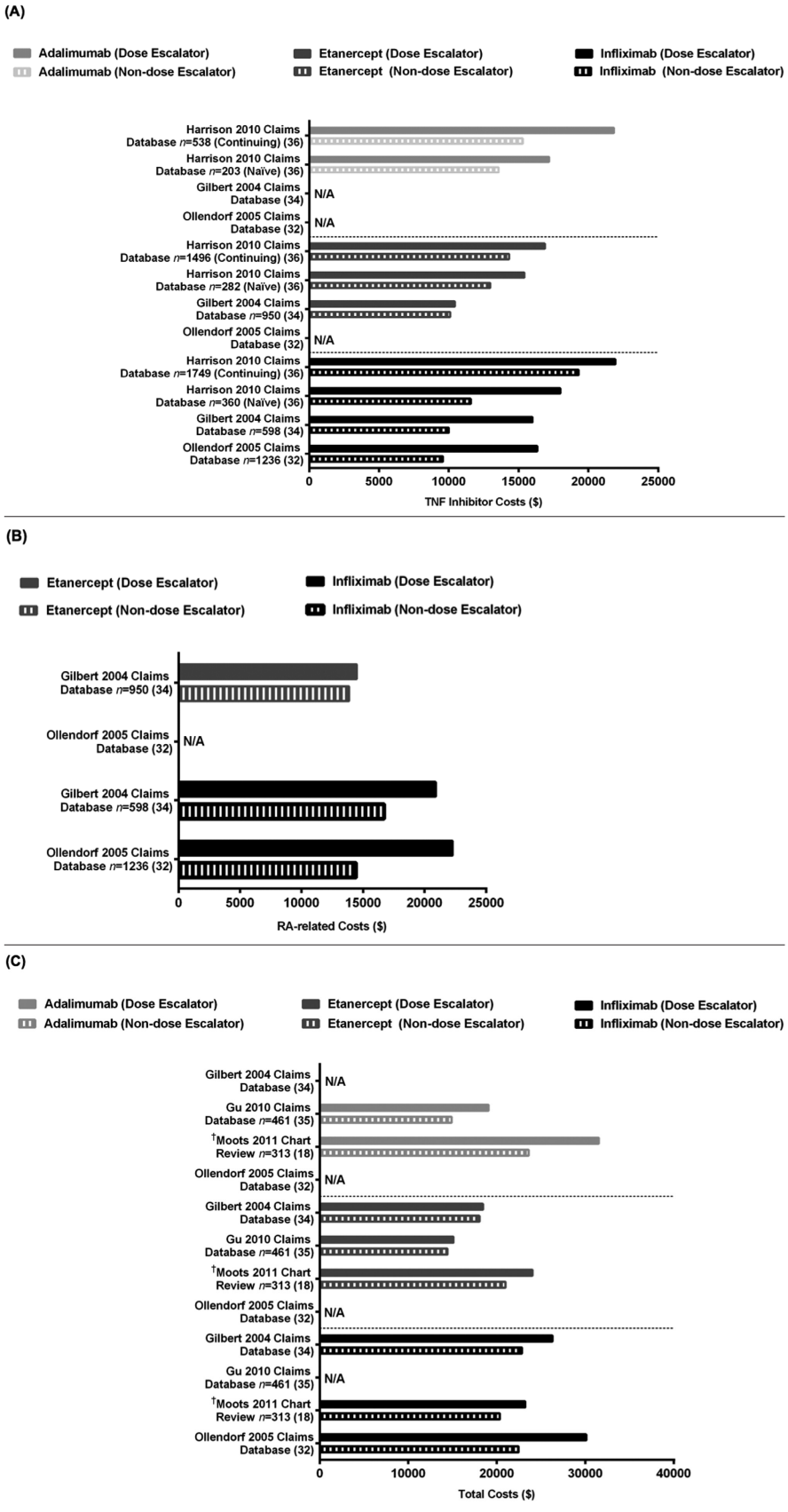


Fig. 3. TNF inhibitor (**A**), RA-related (**B**) and total costs (**C**) associated with dose escalators and non-dose escalators.

Economic analysis

Economic information of some kind was reported by 13 studies; however, only six of these (18, 32, 34-37) reported economic data comparing dose escalators with non-dose escalators. Of these six studies, five were based on US claims databases (32, 34-37), while one was a retrospective observational study of centres across Europe (18). Cost measures were variable, but regardless of the measure used, costs were higher in dose-escalators compared with non-dose escalators for TNF inhibitor, RA-related and total costs (Fig. 3). One study (37) reported pharmacy- and medical-eligible costs, which increased by 67% to 75% and 54% to 72%, in dose-escalators respectively, but did not specifically itemise biologic costs (Table III; data not shown in Fig. 3).

Increases in TNF inhibitor, RA-related and total costs were less for etanercept compared with adalimumab and infliximab (Table III). Adalimumab drug costs increased 27% (mean annual) (36) to 43% (continual annual) (36), while total costs increased 28% (35) to 34% (18). In these studies, total RA-related costs were not reported for adalimumab. Etanercept drug costs increased 3.2% (34) to 19% (36), RA-related costs increased 4.5% (34) and total costs increased 2.2% (34) to 15% (18). For infliximab, drug costs increased 14% (36) to 71% (32), RA-related costs increased 25% (34) to 54% (32) and total costs increased 14% (18) to 34% (32). Blom *et al*. reported that dose increases of 12%, 8% and 36% in patients receiving adalimumab, etanercept and infliximab, respectively, would result in increases of 40% to 80% of total TNF inhibitor costs (30).

Discussion

The practice of dose escalation to regain or maintain clinical response to TNF inhibitors is undoubtedly associated with increased drug costs. However, the frequency of this practice and the impact it has on indirect costs is unknown. This review is the first attempt to understand and summarise the real-world economic outcomes with dose escalation.

Our findings suggest that costs in addition to the direct drug costs increase

with dose escalation and that there are differences in the frequency of dose escalation among biologics of the same drug-class.

This literature review identified a number of dose-escalation studies involving the biologic agents, adalimumab, etanercept and infliximab. A variety of definitions and methods were used in these studies, which reported a wide range of results. Despite the various methods used to define dose escalation, using a weighted proportion calculation, studies consistently demonstrated greater dose escalation with infliximab, followed by adalimumab, and then etanercept. Only one study by Schabert *et al*. reported that patients receiving adalimumab experienced dose escalation more frequently than those receiving infliximab (38). However, dose escalations with adalimumab were only more frequent in the first 12 months of treatment, after which infliximab dose escalations occurred more frequently. Since completion of this literature review, the results of a pharmacy benefit management database study have also demonstrated that across five different methods used to estimate dose escalation, patients receiving etanercept had significantly lower rates of dose escalation than patients receiving adalimumab (39).

Several studies identified that baseline disease activity was higher in those undergoing dose escalation, which may provide a rationale for the practice of dose escalation (27, 33, 34, 38, 40, 41). However, the effectiveness of this practice appears to be minimal, if at all, and may only provide benefit to patients who are non- or partial-responders (18, 30, 42). Van Vollenhoven *et al*. reported that the clinical response to infliximab dose escalation was similar but not superior to best outcomes reported in infliximab and etanercept non-dose escalators, suggesting that dose escalation occurs when patients with high disease activity undergo clinical worsening (43). However, this improvement may not necessarily be related to a dose increase but may be a result of the normal course of the disease (43). The effect of disease course could not be ruled out in other studies (33, 40).

Many reasons for dose escalation are suggested in the literature. Approved dose increases in the product labelling for infliximab (44) and adalimumab (45) could result in prescribers being more comfortable with dose escalation of these drugs compared with etanercept. This practice may explain less dose escalation with etanercept; however, one would therefore expect a higher rate of switching or discontinuation of etanercept compared with infliximab or adalimumab. In a claims study by Schabert *et al*., the proportion of patients with a second biologic during follow-up, an indication of biologic-switch, was adalimumab 13.5%, etanercept 6.3% and infliximab 10.4% (38). Blom *et al*. reported the discontinuations 3–6 months after dose increase: adalimumab 13.6% and 25%, etanercept 12.5% and 15.6%, and infliximab 7% and 17.4%, respectively (30). In clinical practice, retention rates for adalimumab, etanercept and infliximab were 31, 45 and 23 months, respectively (46). Though a limited number of studies in this review reported switching/discontinuation data – where available – adalimumab had a higher proportion of switches or discontinuations compared with etanercept or infliximab (30, 38, 47, 48) suggesting that this is not a major contributor for lower dose escalation with etanercept. It should be noted however that this observation is not universal and that some studies do report higher persistence with adalimumab *versus* etanercept after 1 year (65% *vs*. 57%) (49) or 2 years (70% *vs*. 80%) (50).

The production of neutralising anti-infliximab (8, 10, 14, 51) and anti-adalimumab (6, 7, 10, 51) antibodies could also result in the need for dose escalation. Patients who develop neutralising anti-antibodies to infliximab and adalimumab have been shown to have significantly lower levels of the corresponding drugs (10). Edrees *et al*. reported that patients with higher disease activity and higher levels of TNF-alpha that were not suppressed by standard dosing were more likely to benefit from increased drug infusion frequency, possibly due to the presence of neutralising antibodies against infliximab (41). Haraoui *et al*. detected anti-infliximab antibodies in 47% of patients undergoing dose escalation and in 27% of patients maintained at a standard dose (3 mg/kg every 8 weeks) and suggested that the presence of anti-infliximab antibodies may reduce clinical efficacy (14). Lastly, Rahman *et al*. reported that patients requiring dose escalations generally had lower pre-infusion serum concentrations of infliximab than non-dose escalators, which may have contributed to an inadequate response (52). This was consistent with data from Finkch *et al*., reporting that low residual infliximab concentrations or high infliximab antibodies were present in 42% of patients with acquired infliximab resistance (13). However, other factors may be involved in resistance to treatment.

Across the six studies comparing costs between dose escalating patients and non-dose escalating patients, total TNF inhibitor and RA-related costs were higher in dose escalators than non-dose escalators. Generally, the cost increases were lower with etanercept compared with adalimumab or infliximab. The outcome of a decision-making analytic model revealed that while cost-effectiveness of the three biologics was similar when administered according to standard recommended dosing, dose escalation of infliximab made it significantly less cost-effective (53).

In patients with RA in The Netherlands, another economic model attempted to quantify the costs incurred due to dose escalation related to the development of antibodies to adalimumab, etanercept or infliximab (54). The analysis demonstrated that starting patients on therapies with lower risk of neutralising antibody formation (etanercept rather than adalimumab or infliximab, due to the non-neutralising nature of the antibodies raised against etanercept (55)), resulted in the highest proportion of patients still in first-line therapy after 5 years. This strategy also resulted in the lowest proportion of patients experiencing treatment failure and the highest quality-adjusted life years. From a national perspective, the potential cost of wastage due to loss of efficacy with the TNF-inhibitor agents was 5–15 million euros (approximately $7–20 million) over a 5-year timespan (54).

Our literature review results from real-world studies, along with economic models, suggest that dose escalation is an important economic issue for healthcare payers. However, it is important to note that changes in the use of the different TNF inhibitors may have an impact on the potential number of patients that require dose escalation, as some agents raise more neutralising anti-drug antibodies than others, and may therefore be more likely to require dose escalation (54, 55). In 2009, etanercept (20%) was the most commonly used biologic for RA in the US, followed by infliximab (10%), adalimumab (9%), and abatacept (6%) (56). In this example and others, prescription rates of infliximab are lower than for etanercept, thus fewer patients may undergo dose-escalation with the associated economic implications to payers (56, 57). Changing usage patterns over time must therefore be considered in all economic projections.

Our study also revealed that overall costs in addition to direct drug costs were higher in patients undergoing dose escalation. This may suggest that dose escalation is not the most cost-effective approach to treatment and that patients may benefit from alternative treatment strategies, including switching to a different biologic therapy with a different mode of action. SWITCH-RA was a prospective, global observational study in which the comparative effectiveness of rituximab (an ant-CD20 B-cell depleting therapy) *versus* an alternative TNF inhibitor was assessed in real-life practice (58). In this study, switching to rituximab was associated with significantly improved clinical effectiveness compared with other TNF-inhibitors. Indeed, guidelines recommend that patients switch to a biologic with a different mechanism of action if they still have moderate or high disease activity after 3 months of TNF-inhibitor biologic therapy due to a lack or loss of benefit (1). The economic consequences of this practice appear promising, but head-to-head trials comparing cost-effectiveness are needed to assess the full economic impact (59). While a switch to a biologic with an alternative mechanism of action may be cost-effective compared with switching between TNF-inhibitors (60), there is little evidence to support the cost-effectiveness of switching between biologics of the same drug class (61). In addition, the need to switch TNF-inhibitors may be higher in those with neutralising antibodies against a first-line TNF-inhibitor. Concomitant use of methotrexate with TNF-inhibitors may reduce the formation of these antibodies and preserve TNF-inhibitor efficacy (62, 63). Therefore, combination therapy, or initiation with a drug that does not produce neutralising antibodies such as etanercept, could reduce the need for switching or dose escalation.

Several limitations with the data collection methods were identified in the studies included in this literature review. These included potential selection bias, the use of vials billed for infliximab (practitioners only bill for whole vials even though infliximab dosing is weight-based), payer limits for dose escalation, ICD-9 and drug coding errors typical in claims databases, and scheduling availability for infliximab. There was also no data collection of outcomes or reasons for dose escalation, or the ability to determine if the patient actually took the medication. However, this is the most extensive review of dose-escalation to date, and provides an overview of dosing patterns and the economics of dose-escalation in a variety of real-world settings. Future steps to combine outcome data with economic consequences could include meta-analysis.

Conclusion

Pooled results demonstrated that dose escalation occurred most frequently in patients with RA treated with infliximab and least frequently with etanercept. Although a variety of definitions and methods were used to calculate dose escalation with biologics, the results are consistent with individual comparative studies. Not only were biologic costs increased, but also RA-related and total costs. Etanercept was associated with the lowest cost increases. Effective management of TNF inhibitors requires a thorough understanding of their dosing patterns and the consequences of dose escalation. Studies of real-world treatment patterns can help to inform payers and healthcare providers of the utility and cost-effectiveness of dose-escalation.

Key messages

- Dose escalation of TNF inhibitor to retain clinical response is widely practiced.
- Escalating TNF inhibitor dose is associated with increased RA-related and total costs in addition to biologic costs.
- Dose escalation of adalimumab is associated with the highest costs, followed by infliximab, then etanercept.

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