

## Tumor Necrosis Factor Inhibitors

*A review of dosing patterns and related economic considerations*

*By Joseph Flood, MD, FACR*

*President, Musculoskeletal Medical Specialists Inc.;*  
*Clinical faculty member, The Ohio State University*  
*College of Medicine and Public Health, Columbus*

*With a managed care analysis by Douglas S. Burgoyne, PharmD*  
*President, Scrip World, Salt Lake City, Utah*

Supplement to

**M A N A G E D**  
**Care**

Volume 17, No. 10  
Supplement 11  
October 2008

*This publication is supported by Amgen*

# Tumor Necrosis Factor Inhibitors

## A review of dosing patterns and related economic considerations

**T**umor necrosis factor (TNF) inhibitors represent a major advancement in the treatment of rheumatoid arthritis (RA) (Furst 2007). All TNF inhibitors have been shown to be effective disease-modifying anti-rheumatic drugs; however, response to therapy and the dose needed to sustain response are difficult to predict in individual patients (van Vollenhoven 2007, Furst 2007). In fact, in RA, the recommended maintenance regimens for some of these agents accommodate dose adjustments for incomplete response. Although the use of etanercept (Enbrel) at a dose greater than the starting dose of 50 mg per week is not recommended, an infliximab (Remicade) dose can be increased up to 10 mg/kg or administered as often as every 4 weeks, and adalimumab (Humira) 40 mg can be increased to weekly versus every other week in patients who are not receiving methotrexate (Enbrel 2008, Remicade 2007, Humira 2008). Furthermore, numerous observational studies suggest that, at least in some instances, all TNF inhibitors may be used at doses that exceed the standard recommendations (Durez 2005, Edrees 2005, van Vollenhoven 2004). Given the economic implications of dose elevation, it is critical to understand the nature of dosing patterns. Principal considerations presented in this Clinical Brief are specific to the evaluation of dosing patterns in RA, but they can be also broadly applied to other indications.

### Key concepts in assessing dosing patterns and dose elevation

In general, dosing is affected by a number of factors that interact in a complex, dynamic pattern over time. It would be an oversimplification to assume that dose elevation is a dichotomous variable, or that there is a straightforward linear relationship between dosing changes and treatment costs. Hypothetical treatment scenarios, depicted in the accompanying Figure (page 2), demonstrate that in each patient exposed to therapy, dosing patterns can evolve uniquely along three key dimensions: the actual amount of drug administered; when in the course of therapy dosing changes occur; and the duration of dosing changes.

First, however, it is important to understand the initial dose; in particular, not to overlook whether treatment is initiated at a high dose. For instance, the Figure (page 2) shows that although dosing remained stable throughout a 10-week period for both Patient A and B, the initial dose administered to Patient B was elevated at twice the recommended starting dose, and subsequently the total dose was double that of Patient A.

The magnitude of dose escalation, which is determined by the amount of drug and the frequency of administration, can vary considerably among patients. For example, other things being equal, higher costs will result from a 100 percent dose increase observed with Patient D than from the 50 percent dose increase seen with Patient C. Further, the timing of dose increases has substantial cost implications. Patients who increase their dose early will incur significantly greater drug costs than patients with the same magnitude of increase later in treatment. Lastly, the duration of dose escalation also has substantial economic implications. The cost of a one-time dose increase (Patient E) would be insignificant compared with the cost of a dose increase of the same magnitude and timing that persisted throughout the course of therapy (Patient F).

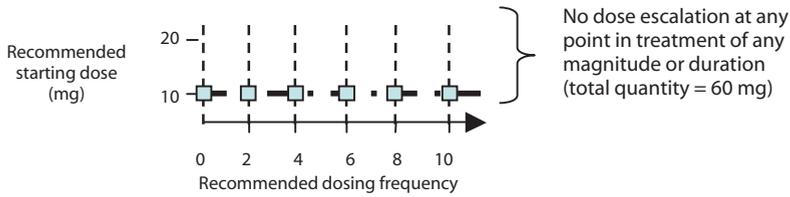
Different methods have been used for measuring dose elevation with the TNF inhibitors (Sidiropoulos 2004, Stern 2004, Harley 2003). However, most of these methods focus on the percent of patients who experience some form of dose escalation, which, in the absence of information on the above dimensions, can obscure the true extent of the incremental costs. The following is a brief overview of the limitations associated with the methods frequently described in the literature.

**Prevalence estimates.** Many observational studies report the percentage of patients who have met the study-defined criteria for dose escalation (Durez 2005, Edrees 2005, van Vollenhoven 2004). The limitation of this approach is that it does not specify the magnitude, timing, and duration of dose increases, making it difficult to understand the cost impact. These shortcomings are illustrated by the following definitions of dose escalation found in the literature.

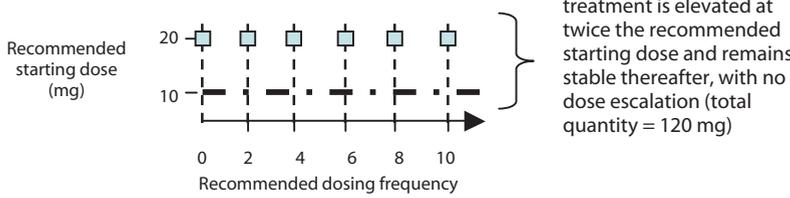
- Ending dose exceeds the initial dose – This definition ignores the vast period that lies between treatment initiation and the end of the study. It excludes patients whose dose increased during treatment and then returned to the same dose at treatment initiation, or those whose treatment was initiated at high doses. It also gives equal weight to all patients who meet the criterion, despite individual differences in magnitude, timing, and duration of dose increases, all of which collectively impact costs.
- Any dose that exceeds the initial dose – This definition can exclude patients with a high initial dose. It does not distinguish the magnitude, timing of inception, or the duration of dose increase.

**FIGURE**  
**Examples of dosing patterns\***

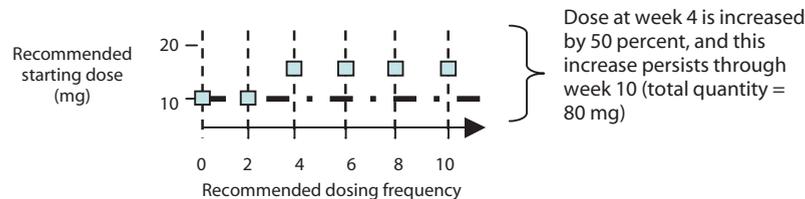
**Patient A**



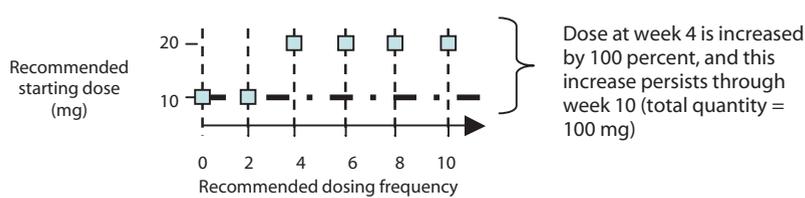
**Patient B**



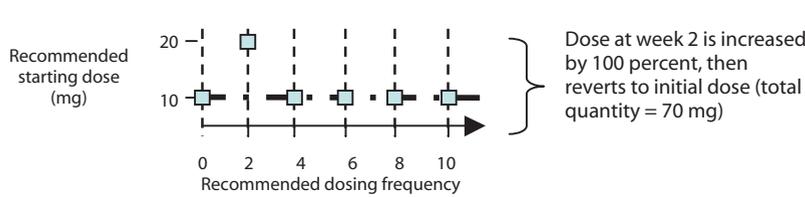
**Patient C**



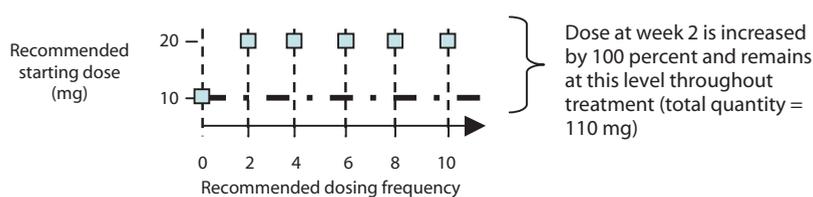
**Patient D**



**Patient E**



**Patient F**



\*Dotted horizontal line represents recommended dose in mg; dotted vertical line represents recommended dosing frequency; squares represent actual doses in hypothetical patient treatment scenario.

- Any dose that exceeds the lowest standard recommended dose – This definition includes a meaningful threshold by referring to the product Prescribing Information, but has the same shortcomings as the other estimates.

**Magnitude estimates.** Three studies were reviewed that have measured the difference between the average ending dose and the initial dose of TNF inhibitors (Bullano 2006, Abarca 2004, Etemad 2005). This method discounts intervening dose increases, while it inflates the contribution of dosing changes that were noted at the end of the study, no matter how short-lived they were.

**Comparative estimates of dose elevation**

The preceding discussion becomes especially important when comparing dosing patterns among different treatments. Numerous analyses have compared dose elevations of TNF inhibitors in patients with RA (Ariza-Ariza 2007, Etemad 2005, Gu 2007). Since various methods have been used, study findings should be interpreted in the context of the conceptual framework presented in the previous section.

Ariza-Ariza (2007) conducted a systematic review to assess the prevalence of dose escalation in a pooled sample of 8,510 patients who were treated with etanercept or infliximab; studies of adalimumab dosing patterns did not meet the inclusion criteria. The investigators estimated the percentage of treatment cases with any dose exceeding the lowest standard recommended dose (e.g., infliximab doses >3 mg/kg every 8 weeks, etanercept doses >50 mg/week). According to this definition, the prevalence of dose escalation for etanercept was 17.5 percent (95 percent confidence interval [CI], 16 percent - 19 percent), and 53.7 percent for infliximab (95 percent CI, 51.88 percent - 54.64 percent). However, when focusing on the actual magnitude of the increase, etanercept was

**TABLE****Impact of dose escalation with TNF inhibitor therapy on rheumatoid arthritis (RA) costs**

Study	Etanercept-treated patients			Infliximab-treated patients		
	No dose escalation	Dose escalation*	% difference	No dose escalation	Dose escalation*	% difference
<i>Gilbert 2004</i>						
Percentage of affected patients (ratio)	82 percent (778/950)	18 percent (172/950)	n/a	42 percent (252/598)	58 percent (346/598)	n/a
Mean annual RA-related drug costs per patient	\$11,307	\$11,830	<b>4.6 percent</b>	\$11,224	\$17,148	<b>52.8 percent</b>
Mean annual RA-related health care costs per patient	\$13,865	\$14,482	<b>4.5 percent</b>	\$16,713	\$22,283	<b>25 percent</b>
<i>Ollendorf 2005</i>						
Percentage of affected patients (ratio)	-	-	-	38 percent (474/1236)	62 percent (762/1236)	n/a
Mean annual RA-related drug costs per patient	-	-	-	\$10,916	\$17,760	<b>63 percent</b>
Mean annual RA-related health care costs per patient	-	-	-	\$14,425	\$22,283	<b>54 percent</b>

\* Dose escalation with infliximab was defined as at least 1 or 2 occurrences [1 or more by Gilbert 2004 and 2 or more by Ollendorf 2005] per patient of an increase in the number of vials used for the initial maintenance dose, or 2 or more occurrences of infusions with an interval of fewer than 49 days; dose increase for etanercept was defined as 2 or more prescriptions per patient with the average daily dose exceeding the initial maintenance dose.

SOURCES: GILBERT 2004, OLLENDORF 2005

associated with insignificant changes in the actual dose, whereas increases from baseline in the infliximab dose ranged from 29 percent to 43 percent. However, these estimates do not reflect dosing fluctuations that occurred during the entire treatment period, limiting their utility from a cost analysis perspective.

A claims analysis of 4,426 members of a large health plan showed that the mean weekly dose of etanercept remained stable at 50 mg to 52 mg (Etemad 2005). In con-

trast, the average dose of infliximab was increased with each subsequent administration, from 282 mg with the first infusion to 383 mg with the eighth infusion. The benefit of this method is that it analyzed dosing patterns over the entire course of treatment.

A comparison of the dosing patterns of adalimumab and etanercept was presented at the 2007 meeting of the International Society for Pharmacoeconomics and Outcomes Research. Recognizing that dosing patterns can be characterized along multiple dimensions, Gu (2007) used several methods to measure dose elevation. For example, based on the analysis of pharmacy claims for 1,830 patients, the investigators found that treatment was *initiated* at a higher-than-standard dose (etanercept 50 mg once weekly, adalimumab 40 mg every other week) in 11.9 percent of adalimumab patients versus 2.8 percent of etanercept patients ( $P < .001$ ). Further, across the entire 12-month treatment period, the average weekly doses of etanercept and adalimumab were above the standard recommended dose in 10.3 percent and 33.6 percent of patients, respectively. Although these examples do not capture all of the dimensions that have been discussed, they reinforce the importance of understanding the initial dose as well as analyzing dosing patterns over the entire course of treatment.



### About the Author

*Joseph Flood, MD, FACP, is a clinical rheumatologist and educator with more than 20 years of experience in musculoskeletal medicine. He is president of Musculoskeletal Medical Specialists Inc., and is a member of the clinical faculty of The Ohio State University College of Medicine and Public Health in Columbus. Flood teaches medical students in all four years of the medical school curriculum at OSU. He is a fellow of the*

**Joseph Flood, MD, FACP**

*American College of Rheumatology, board certified in Internal Medicine and Rheumatology, and a Certified Clinical Densitometrist.*

## Managed Care Considerations:

By Douglas S. Burgoyne, PharmD

President, Scrip World, Salt Lake City, Utah

**T**umor necrosis factor (TNF) inhibitors have significantly affected the care of members with rheumatoid arthritis. Their role as effective therapies in the course of this disease is well established, and I think it can be agreed upon that they provide tangible benefit to our member populations.

The cost associated with TNF inhibitors has always been of major concern for managed care organizations. This issue now is becoming more of a physician and member concern, as more and more expenses are now borne by members in the world of high-deductible health plans, health

reimbursement accounts, and health savings accounts. But beyond the price of the drug itself, the dose and dosing regimen of the medication has the greatest impact on the overall cost of an individual's drug therapy.



Douglas S. Burgoyne,  
PharmD

Dose escalation is a common practice in our society. The mentality exists that "if one is good then two must be better." This is not always the case in drug therapy management and may have an unintended

effect in terms of cost-effectiveness — two might just cost more without incremental benefit.

This may indeed be the case in RA treatment. Increasing the dose

of a TNF inhibitor may not provide greater therapeutic benefits for all members, and only increase the cost of the treatment. We must be aware of the cost of dosing fluctuations, and take these costs into account when reviewing TNF Inhibitors for formulary placement.

As stewards of medical and pharmacy budgets for our customers, managed care decision makers must take dosing and the total cost of therapy into account when evaluating drug regimens. A simple review of cost based on initial dosing or any one-time change in dose is insufficient — we must carefully consider dose escalation and fluctuation over time to determine the true cost of these medications.

### Economic impact

Several approaches have been used to explore the relationship between dose escalation and treatment costs in RA patients treated with the TNF inhibitors (Etemad 2005, Gilbert 2004, Ollendorf 2005). Etemad (2005) showed that the average ending dose of etanercept did not increase from the baseline dose of 51.3 mg, and the annual cost of therapy remained stable at \$17,818. In contrast, the average dose of infliximab increased from 280 mg at the start of treatment to 360 mg at the end of the study period. Although this finding by itself does not reveal the incremental cost impact, the authors did report that this 28.6 percent change in infliximab dose resulted in a 31 percent rise in the annual treatment cost (from \$17,799 to \$23,332).

In two analyses of large claims databases, RA-related costs were stratified by the presence of dose escalation (Gilbert 2004, Ollendorf 2005). Gilbert (2004) compared treatment costs in 1,548 patients treated with etanercept and infliximab during a 12-month follow-up. Ollendorf (2005) evaluated costs in 1,236 patients followed for an average of 15 months after the start of infliximab therapy. Rates of dose escalation reported in these analyses were consistent with overall pooled estimates (Table, page 3). In the Gilbert (2004) study, RA-related drug costs were higher among patients who experienced dose escalation

than among those who did not; however, the gap between these groups was substantially greater with infliximab. Namely, in the infliximab cohort, RA-related drug costs were 53 percent higher among patients who experienced some form of dose increase than among their counterparts who did not experience a dose increase. In contrast, in the etanercept cohort, patients who experienced some form of dose increase incurred drug costs that were only 5 percent higher than their counterparts who did not experience an increase. Similar trends were observed with overall RA-related health care costs (Table, page 3). If the entire cohort of infliximab-treated patients described by Gilbert (2004) received a stable dose at the average drug cost seen in infliximab patients without dose escalation, RA drug costs would be reduced by 23 percent. In the etanercept cohort, an analogous assumption would result only in an 0.8 percent savings.

Finally, dosing elevations can substantially influence the cost-effectiveness of the TNF inhibitors (Wailoo 2008). A decision-analytic model was developed to inform the Agency of Healthcare Research and Quality and the Centers for Medicare and Medicaid Services of the comparative cost-effectiveness of the TNF inhibitors. The results revealed that if all products were administered consistently according to the standard recommended dosing, the cost-effectiveness of these agents was similar. However,

based upon evidence of dose escalation with infliximab, the report concluded that infliximab was significantly less cost-effective than the remaining TNF inhibitors.

## Conclusion

Effective management of the TNF inhibitors requires a thorough understanding of their dosing patterns. However, some methods used to measure dose elevation may not fully capture the economic implications. Many studies report the percentage of patients who experience some form of dose increase, based upon study-defined criteria. This approach is limited by its inability to determine the magnitude, timing, and duration of these dosing fluctuations. These issues are especially important based upon economic analyses showing that the incremental costs associated with dose elevation can vary substantially among the TNF inhibitors.

## References

- Abarca J, Malone DC, Armstrong EP, et al. Longitudinal analysis of the use of etanercept versus infliximab determined from medical chart audit. *J Manag Care Pharm.* 2004;10:538–542.
- 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;46:529–532.
- Bullano MF, McNeeley BJ, Yu YF, et al. Comparison of costs associated with the use of etanercept, infliximab, and adalimumab for the treatment of rheumatoid arthritis. *Manag Care Interface.* 2006;19:47–53.
- 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;44:465–468.
- Edrees AE, Misra SN, Abdou NI. Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions. *Clin Exp Rheumatol.* 2005;23:469–474.
- Enbrel (etanercept). [prescribing information]. Thousand Oaks, Calif: Immunex Corp. June 2008.
- Etemad L, Yu EB, Wanke LA. Dose adjustment over time of etanercept and infliximab in patients with rheumatoid arthritis. *Manag Care Interface.* 2005;18:21–27.
- Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. *Ann Rheum Dis.* 2007;66(suppl 3):2–22.
- Gilbert TD, Smith D, Ollendorf DA. Patterns of use, dosing, and economic impact of biologic agent use in patients with rheumatoid arthritis: a retrospective cohort study. *BMC Musculoskelet Disord.* 2004;5:36.
- Gu NY, Huang XY, Globe D, Fox KM. Methods for measuring dose escalation in TNF antagonists for rheumatoid arthritis patients treated in routine clinical practice. Presented at the 12th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); May 19–23, 2007; Arlington, Va.
- 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 6):S136–S144.
- Humira (adalimumab). [prescribing information]. North Chicago, Ill.: Abbott Laboratories. February 2008
- 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;11:383–393.
- Remicade (infliximab). [prescribing information]. Malvern, Pa.: Centocor, Inc. April 2007.
- Sidiropoulos P, Bertsias G, Kritikos HD, et al. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: dose adjustments are common but not always sufficient to assure sustained benefit. *Ann Rheum Dis.* 2004;63:144–148.
- Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol.* 2004;31:1538–1545.
- van Vollenhoven RF. Switching between anti-tumour necrosis factors: trying to get a handle on a complex issue. *Ann Rheum Dis.* 2007;66:849–851.
- 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;63:426–430.
- Wailoo A, Bansback N, Brennan A, et al. Biologic drugs for rheumatoid arthritis in the Medicare program: a cost-effectiveness analysis. *Arthritis Rheum.* 2008;58:939–946.