

# PROJECTED PATTERNS OF COMPLIANCE ASSOCIATED WITH REMICADE (INFLIXIMAB) AND ENBREL (ETANERCEPT)

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The new biological agents etanercept (Enbrel) and infliximab (Remicade) are highly efficacious in the treatment of refractory rheumatoid arthritis (RA). However, the actual real world effectiveness of these compounds will depend on patient preferences and patient compliance. The issue is important, because compliance is a problem in RA. Etanercept is self-administered in twice-weekly subcutaneous (SC) injections, and infliximab is administered by a health care professional every other month as an intravenous (IV), two-hour infusion. Both medications are usually used in combination with methotrexate (MTX). A literature review was conducted to assess the expected compliance profiles of each drug. Four distinct MEDLINE searches were done on, (1) compliance in RA in general, (2) compliance with SC and IV injections, (3) compliance with MTX, and duration of treatment with MTX, and (4) the effects of reminder systems on compliance with scheduled medical appointments. Compliance in RA patients is poor within all medication categories. Compliance with assisted IV infusions in other illnesses is higher than compliance with self-administered SC injections. Injection anxiety and pain at the injection site appear to be obstacles to compliance with SC injections. Patients appear to prefer assisted IV infusions. Reminder systems do improve compliance with medical appointments separated by long delays. Compliance with infliximab is expected to be better than that of etanercept because, (1) compliance with etanercept may be limited by patients' general dislike of SC injections, as well as the pain and irritation at the injection site, (2) etanercept is administered more frequently than infliximab, (3) RA patients often have difficulty in handling secure medication containers, and patients tend to prefer the type of clinical assistance for injections that infliximab involves, and (4) a survey of Canadian RA patients indicated a preference for the infliximab IV regime over the etanercept SC regime. This study emphasizes the importance of monitoring infliximab and etanercept compliance, and taking corrective steps when necessary.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common, chronic, systemic inflammatory disease, associated with significant morbidity and premature mortality.<sup>15</sup>

**Infliximab:** a chimeric, anti TNF- $\alpha$  monoclonal antibody which is to be administered through bi-monthly intravenous (IV) infusions. Each infusion requires two hours, and is administered by a health care professional.

**Etanercept:** a non-specific bioengineered fusion protein of the p75 soluble TNF receptor which is to be self-administered via twice weekly subcutaneous (SC) injections.

This review assesses the potential patient compliance profiles of infliximab and etanercept, given the unique regimens associated with each of these drugs.

## METHODS

Four distinct MEDLINE searches were done on:

- compliance in RA in general;
- compliance with SC and IV injections;
- compliance with methotrexate (MTX) and duration of treatment with MTX, and
- the effects of reminder systems on compliance with scheduled medical appointments.

All searches excluded articles focussed on pediatric populations. Systematic search procedures were followed.

## RESULTS

### Compliance in RA

Our review of the literature over the past 20 years for all RA medications indicates remarkable similarity between different compliance measurement methods such as self-report, pill count, electronic monitoring, biological assays, and pharmacy refill rates.

Approximately 50% to 70% of RA patients are compliant.<sup>6-11</sup>

### Compliance with IV infusions, SC injections, and patient preference

Because of the different administration modes of infliximab and etanercept, we reviewed compliance with self-injected SC medications, and with IV infusions involving regular contact with a health care professional (see Table 1).

### Compliance with SC injections is poor:

- diabetic patients frequently miss injections<sup>12</sup>
- diabetic patients fail to obtain all of their prescribed insulin<sup>13</sup>
- injections are missed because of injection anxiety<sup>14</sup>
- patients are reluctant to self-inject<sup>15</sup>
- due to pain and irritation at the injection site<sup>16</sup>

### Compliance with IV infusions involving contacts with a health care provider appears to fare better:

- high levels of compliance are observed for assisted IV infusions<sup>17</sup>
- patients switched from self-administered SC to assisted IV infusions prefer the assisted IV<sup>18</sup>

### Compliance with MTX and duration of treatment

Toxicity leads approximately 30% of patients to discontinue the long term use of MTX therapy.<sup>19-27</sup>

This is important given that infliximab has been approved for concomitant use with MTX and etanercept appears to be extensively used in combination therapy with MTX.<sup>28</sup>

Table 1. Compliance with IV Infusions, SC Injections, and Patient Preference

	Filippini et al. (1996)	Olivieri et al. (1992)	Barclay et al. (1993)	Tercyak et al. (1998)	Zambanini et al. (1967)	Morris et al. (1997)	Nicoletta et al. (2000)
Country	Italy	Canada	Australia	USA	UK	UK	USA
Illness	Osteoporosis	Thalassemia major	Hemodialysis induced anemia	Diabetes	Diabetes	Diabetes dialysis	Peritoneal
Drug	Cyclical clodronate	deferroxamine	erythropoietin	Insulin	Insulin	Insulin	erythropoietin
Measure	Treatment continuation	Doses taken as prescribed	Anecdotal	Self-report	Self-report	Pharmacy refill rates	Pharmacy refill rates
Regimen	every 3 weeks	twice / week	n / a	bid	bid / qid	bid / qid	n / a
Delivery	IV infusion	IV infusion	SC injection / IV infusion	SC injection	SC injection	SC injection	SC injection
Patients	279	9	13	11	115	89	55
Non-compliance	15.8% <sup>a</sup>	7% <sup>b</sup>	note <sup>c</sup>	45% <sup>d</sup>	14% <sup>e</sup>	28% <sup>f</sup>	55% <sup>g</sup>

<sup>a</sup> Defined as the percentage of patients who withdrew from the study within the first year for noncompliance.  
<sup>b</sup> Defined as the percentage of doses not administered as prescribed. The authors anecdotally reported high levels of patient satisfaction with the IV regimen.  
<sup>c</sup> Most patients preferred the IV administration of erythropoietin due to discomfort at the site of the SC injection.  
<sup>d</sup> Defined as the percentage of patients who indicated missing at least one injection per typical week.  
<sup>e</sup> Defined as the percentage of patients who reported avoiding injections secondary to anxiety.  
<sup>f</sup> Defined as the percentage of patients who did not collect enough insulin for their recommended daily use over one year.  
<sup>g</sup> Defined as the percentage of patients who obtained less than 90% of their prescribed dose.

Table 2.

	Infliximab	Etanercept
Compliance Advantage	<ul style="list-style-type: none"> <li>• Medication infusions every 2 months are more convenient</li> <li>• does not require self-injection</li> <li>• causes minimal pain and irritation at the injection site.</li> <li>• patients prefer clinical assistance for injections</li> </ul>	<ul style="list-style-type: none"> <li>• does not require clinical visits</li> <li>• some patients prefer self-injection</li> </ul>
Compliance Disadvantage	<ul style="list-style-type: none"> <li>• it may be difficult for patients to remember the treatment due to the 2 month delay between appointments</li> <li>• requires clinical visits</li> </ul>	<ul style="list-style-type: none"> <li>• pain and irritation at the injection site</li> <li>• injection anxiety</li> <li>• reluctance to self-inject</li> <li>• frequency and complexity of administration may cause difficulties with severe RA</li> </ul>

### Effects of reminder systems on compliance with medical appointments

Infliximab therapy requires an IV infusion, and long intervals between infusions. These lengthy intervals could make it difficult for patients to integrate infliximab administration into their daily routine.<sup>29</sup>

Overall, compliance with appointments without reminder systems varied between 33% and 88% in the studies included in this review. Reminder systems (e.g., telephone prompts and mail reminders of scheduled appointments) have been shown to produce a 6% to 10% improvement in appointment attendance, a statistically significant difference.<sup>30-40</sup>

Although infliximab compliance may be compromised by the long delay between appointments, this review shows that an appointment reminder system may effectively address this concern.

## CONCLUSIONS

Compliance is expected to be better with infliximab than with etanercept (see Table 2) because:

- Compliance with etanercept may be limited by patients' general dislike of self-administered SC injections, and pain and irritation at the injection site.
- Etanercept is administered more frequently than infliximab.
- RA patients have difficulty in handling secure medication containers<sup>41,42</sup>, and patients tend to prefer the type of clinical assistance for injections that infliximab involves.
- The results cited above are supported by a survey of 141 Canadian RA patients who indicated a preference for the infliximab IV regime over the etanercept SC regime (see Figure 1). Convenience was cited more frequently as a reason for preference by patients who preferred the IV regimen, rather than patients who preferred the SC regimen. The majority of patients who preferred the etanercept SC regimen would prefer not to self-inject.<sup>43</sup>

This review emphasizes the importance of monitoring infliximab and etanercept compliance and taking corrective steps when necessary. The conclusions reached in this review should be confirmed with empirical data.

Figure 1. Patient Preference for SC Injection and IV Infusion Administration Methods

