Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders

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Objective. Patients may cease therapy with anti-tumour necrosis factor (TNF) agents due to inefficacy at 12 weeks (termed primary non-response) or later. Until now, the extent of this later secondary non-response has not been clearly defined. We followed-up a substantial single-centre cohort to determine kinetics of this secondary loss of response. The licensed dose of 3 mg/kg was used throughout.

Methods. Prospective data collection since anti-TNF therapy introduction in 1999 formed the basis of the analysis. Patients with rheumatoid arthritis who received infliximab as their first biologic agent, with at least 2 yrs follow-up were included. All relevant clinical data to calculate DAS-28 score and EULAR response were collected at 3, 6, 9, 12, 18 and 24 months. Reasons for cessation in those patients achieving a EULAR response at 3 months (secondary failures) were determined.

Results. Of a total of 309 patients commenced on infliximab, 290 received this as their first biologic agent.; 195 commenced ≥2 yrs ago. Efficacy data to identify EULAR responders at 3 months was available in 174 patients. Sixty-seven per cent achieved a ‘moderate’ or ‘good’ EULAR response; 25% failed to achieve a response, 8% developed toxicity within the first 12 weeks. Of the primary responders, over 55% subsequently ceased therapy in the first year, the predominant reason was a secondary loss of response; other reasons included high disease activity despite achieving a definable response, toxicity, and intercurrent illness. Subsequent loss of response in the second year was less pronounced.

Conclusions. This study of patients treated in clinical practice with infliximab demonstrated that secondary non-response occurred in around half the patients in the first year. The data highlight the need to continue development of other therapies as well as investigation of the underlying causes of this loss of response.

Key words: Infliximab, RA, Response, Outcome.

Introduction

Tumour necrosis factor (TNF)-antagonists are well established in the management of rheumatoid arthritis (RA) following the impressive clinical and radiological benefits observed in clinical trials. Nevertheless, it is apparent from both trial data and subsequent clinical experience that a certain proportion fails to respond from the outset [1]. The reasons underlying this primary non-response remain unresolved with several lines of investigation being pursued. In addition, it has also been demonstrated that a proportion of patients fail to maintain an initial response (termed ‘secondary’ non-response). There is a relative paucity of information on the time course and long-term outcome of such patients.

Several studies have sought to address the value of dose escalation of infliximab; both the ATTRACT [1] and ASPIRE [2] studies as well as those from clinical practice suggest additional efficacy to be gained from either higher dosage or increased frequency of infusions. A recently published study [3] from a large academic centre addressed these issues further, confirming substantial discontinuation due to inefficacy (clinical judgement) and the advantages of dose escalation. This study, however, included any patient receiving at least one infliximab infusion; in addition, distinction between primary and secondary non-responders specifically was not included.

In contrast, the objective of our analysis was to determine the duration of efficacy of infliximab treatment in patients with RA who had demonstrated initial response to infliximab at week 12 (primary responders), this being the usual time of assessment for initial therapeutic response; clinical data in the form of disease activity score and EULAR response throughout the follow-up period were available.

Patients and methods

Following the introduction of biologic therapies, we initiated prospective data collection. Data have been entered in our biologics database based at the Leeds Teaching Hospitals Resistant Rheumatoid Arthritis Clinic as per standard practice and reviewed using the Leeds Research Ethics Committee guidelines. Data include measurements for DAS-28 score and EULAR response as well as components of the American College of Rheumatology Criteria (ACR) core set of measures.

The Resistant RA Clinic is a tertiary referral centre for patients resistant to standard disease-modifying therapy. Over 550 patients attending the clinic from June 2000 to January 2005 have been treated with one or more biologic agents (over 700 treatment courses).

All patients commenced on biologic therapy have fulfilled the revised 1987 (ACR) [4] for a diagnosis of RA. Eligibility for TNF-blocking agents was as per the British Society of Rheumatology Guidelines [5] [failure of two previous disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) and a DAS-28 score > 5.1]. All patients commenced on infliximab are maintained on varying doses of MTX (ranging 5–25 mg weekly) as per prescribing guidelines. A small number of patients, however, were on concomitant leflunomide (10 or 20 mg daily) instead of MTX due to toxicity to the latter. Equivalent efficacy (but higher incidence of adverse events) of this combination has been previously reported by this group [7]. Infliximab was administered intravenously at 3 mg/kg at 0, 2, 6 and 14 weeks and 8 weekly thereafter (financial limitations only allowing 3 mg/kg dose with no dose escalation).
Results

A summary of numbers of patients at each time-point with EULAR response data is illustrated in Fig. 1. Figure 2 illustrates similar information as a bar chart to demonstrate progression over the 2 yrs.

Three hundred and nine patients were treated with infliximab (73% female, 27% male), mean (s.e.m.) age 57 (0.9) between July 1999 and December 2004. Of these 309, 290 received infliximab as their first biologic agent (biologic-naïve). One hundred and ninety-five of the 290 patients had commenced infliximab as their first biologic agent (i.e. biologic-naïve group) ≥ 2 yrs ago. DAS-28 change with subsequent EULAR response (‘moderate’ or ‘good’) has been used as the primary method of assessing response (as per national BSR guidelines) at week 12, the first, formal time-point for assessment of response to therapeutic intervention. The number of patients that discontinued infliximab having achieved a EULAR response at 3 months was calculated with reason for cessation recorded, providing evidence of the attrition rate over 2 yrs in week 12 responders. In addition, DAS-28 reduction with EULAR response at each of these time-points was also calculated.

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At 3 months, data were available on 174/195 patients. Of the 174, 116 (67%) achieved an EULAR response; 44 (25%) failed to achieve a EULAR response and 14 (8%) patients stopped due to toxicity.

Of the 116 achieving a EULAR response at 12 weeks, 72% comprised ‘moderate’ scores and 28% ‘good’. Mean DAS-28 reduction of 2.57 [from DAS-28 (s.e.m) of 6.53 (0.98)–3.96 (0.13)] was observed (P < 0.0005) (Fig. 3). Of the 116 patients, a further four did not continue due to concurrent toxicity and three stopped due to continued high disease-activity despite achieving a EULAR response. Therefore, 109 continued to week 24 analysis. Incomplete data prevented response calculation in 16 patients. Of the remaining 93 patients, 77 (83%) achieved a EULAR response (63% of these a ‘moderate’ and 37% ‘good’ EULAR response); 16 (17%) did not achieve a response. Reduction in the overall disease activity score to a mean DAS-28 (S.E.M) at week 24 of 3.72 (0.15) (P < 0.0005) was maintained (Fig. 3). Four of these patients, however, persisted with high-level of disease activity, deemed clinically unacceptable and hence, discontinued; two patients stopped due to new diagnosis of malignancy.

Of the 71 patients continuing to week 36, data were available for 66. Fifty-six out of 66 (85%) achieved a EULAR response (of these, 61% ‘moderate’ and 39% ‘good’ EULAR response).

The mean DAS-28 (S.E.M) was significantly reduced to 3.62 (0.21) from baseline (P < 0.0005) (Fig. 3). Three discontinued despite a response due to development of a rash, continued high disease activity (> 5.1) and loss to follow-up.

Of the 53 continuing to week 48, 40 (93%) achieved a EULAR response (58% ‘moderate’ and 42% ‘good’) with only 7% failing to achieve a response. Similar mean DAS-28 (s.e.m.) of 3.51 (0.3) compared with previous time-points was maintained (P < 0.0005) (Fig. 3). Two out of 40, however, did not continue; one due to clinically judged high disease activity whilst the other developed a malignancy.

Fig. 1. Flow diagram of outcome of patients initiated on infliximab at least 2 yrs ago having achieved a 3-month EULAR response (primary non-response group). Of the initial infliximab response group at 3 months, a notable proportion comes off therapy due to lack of sustained response. In addition, a number of patients cease therapy despite achieving an EULAR response due to persistent clinically active disease.

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Of the 27 continuing to week 96, all achieved a response deemed high disease activity; one patient planned to conceive (Fig. 3). Two of these did not continue, again, one due to clinically MTX (patients on concomitant leflunomide (n on concomitant leflunomide). Proportionately, more of the MTX continued to achieve a response and 4/29 (13.8%) patients this study, 87 were on concomitant MTX and 29 on concomitant difference between the two groups.

There is suggestion of yet further improvement into the second year, possibly analysis. The degree of reduction in DAS-28 score observed in patients achieving represents the baseline score for the whole cohort included for the 2-yr period. The analysis suggests significant loss of response and subsequent discontinuation in the first year (~50%) of treatment.

For this study’s aims, only patients who had commenced infliximab a minimum of 2 yrs ago were included. Patient selection for analysis was kept as ‘clean’ as possible to minimize any ‘noise’ from a more heterogeneous case-mix. Our cohort was confined to patients with RA and only those receiving infliximab as a first biologic agent were included; response and long-term outcome could be different in already established biologic failures (as could these patients treated very late in the disease after multiple DMARD failures). Several points of interest are identified from this analysis.

First, the week 12-response rate was high with 67% of patients achieving a EULAR response. This is comparable with other studies, possibly higher than those in which ACR response has been employed. Indeed, applying ACR response criteria, only 50% achieved an ACR 20 response.

Second, it is clear that the majority of those patients ceasing infliximab due to toxicity did so within the first 12 weeks, with it quite uncommon thereafter. Eleven per cent of the cohort starting infliximab developed toxicity; of these patients, 79% suffered their toxicity within the first 12 weeks. Consistent with findings reported by Bingham et al. [7], a greater proportion of patients on leflunomide and infliximab had an adverse event compared with MTX and infliximab. Analysis of timing of infusion reactions at this centre has confirmed its occurrence mainly within the first 2–4 infusions [9]. Nevertheless, continued vigilance for potential atypical infection, including in patients well established on anti-TNF therapies, is paramount.

One of the most interesting features is the continuation over time of ‘secondary’ non-response, i.e. following achievement of response to infliximab at week 12, a certain proportion of patients at subsequent time-points fail to maintain this response. The trend suggests this occurs maximally within the first year. This latter point is not altogether surprising. It seems intuitive that with the cumulative ‘drop-off’ of subjects, a sub selected group of the best responders remain. This is further suggested by the overall, mean

Thus, this analysis included 195 of the 290 patients commenced on infliximab to date as a first biologic agent ≥2 yrs ago. Of those achieving a EULAR response, response data was unavailable in a total of 33 patients, and therefore excluded from further analyses. Table 1 summarizes the discontinuations with reason for cessation.

**Discussion**

Infliximab is a well-established biologic agent in the management of RA [8]. Despite almost 6 yrs since its introduction, however, little information exists on the ‘longevity’ of the treatment for those patients demonstrating an initial response. In this study, the key objective was to evaluate the durability of response in those patients who were already established responders on the standard, licenced 3 mg/kg dosage at a tertiary centre cohort over a 2-yr period. The analysis suggests significant loss of response and subsequent discontinuation in the first year (~50%) of treatment.

Chi-square analysis comparing disease duration (divided into ≥10 yrs and <10 yrs disease duration) and frequency of secondary non-response within the first year did not elicit any significant difference between the two groups.

Of the 116 response patients who formed the basis of analysis in this study, 87 were on concomitant MTX and 29 on concomitant leflunomide. At week 96, 20/87 (23%) patients on concomitant MTX continued to achieve a response and 4/29 (13.8%) patients on concomitant leflunomide. Proportionately, more of the patients on concomitant leflunomide (n = 6) compared with MTX (n = 8) stopped therapy due to toxicity at week 12.

**Table 1**. Number of reasons for discontinuation from a cohort of 174 patients commenced on infliximab

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
</tr>
<tr>
<td>MTX intolerance</td>
<td>3</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3</td>
</tr>
<tr>
<td>Other (patient moved, lost to follow-up, etc.)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

Longevity of infliximab response in RA

**Fig. 2**. Outcome of patients initiated on infliximab at least 2 yrs ago having achieved a 3-month EULAR response. The status of each patient is summarized in the following bar chart. Absolute numbers achieving or failing to achieve a response is shown; cumulative numbers, however, are shown for those patients having ‘stopped previously’ and patients for which ‘other/incomplete data’ (moved, missing data, etc.) applies to grasp progression of patients over the 2 yrs. Clear ‘drop-off’ of patients due to a loss of response (secondary non-response) is observed, most marked in the first year.

**Fig. 3**. Mean DAS-28 scores at each time-point. DAS-28 score at month 0 represents the baseline score for the whole cohort included for the 2-yr analysis. The degree of reduction in DAS-28 score observed in patients achieving an EULAR response at month 3 is maintained in this response group over the 2 yrs. There is suggestion of yet further improvement into the second year, possibly reflecting a sub selected group of the best responders. Significant reduction in DAS-28 (P < 0.0005).

At week 72, data were available on 36/38 patients. Twenty-nine out of 36 patients (81%) achieved a EULAR response (of which 52% ‘moderate’ and 48% ‘good’ EULAR response). Mean DAS-28 (s.e.m.) of 2.97 (0.35) was observed (P < 0.0005) (Fig. 3). Two of these did not continue, again, one due to clinically deemed high disease activity; one patient planned to conceive. Of the 27 continuing to week 96, all achieved a response (52% ‘moderate’ and 48% ‘good’). Continued low, overall, mean DAS-28 (s.e.m.) with reduction to 2.98 (P < 0.0005) was noted (Fig. 3).

Chi-square analysis comparing disease duration (divided into ≥10 yrs and <10 yrs disease duration) and frequency of secondary non-response within the first year did not elicit any significant difference between the two groups.
DAS-28 scores at each time-point with a ‘fall’ to <3.0 in the second year.

The overall discontinuation rate therefore is high in the first year (55%), predominantly due to secondary non-response as discussed earlier. The ATTRACT trial [1] reported 21% discontinuation after the first year; the cohort described by Agarwal et al. [3] demonstrated similar discontinuation rate to our study (48%)—it is important to remember that our discontinuation rate is for a cohort who have responded to infliximab at week 12 (excluding the 25% week-12 primary non-response group). The reason for such a high rate is unclear but may relate to the characteristics of this patients cohort. High average disease duration of 16 yrs was noted (with over 30–40 yrs in a proportion), also reflected by the large number of conventional DMARDs employed before biologic use. It is likely that the consequences of such severe and long-standing disease have contributed to sub-optimal response with an earlier than expected dropout, and contrast with our experience in early disease [10].

In this study, a standard dose was given to all the patients with no dose ‘creep’. This approach has the advantage that it allows analysis of the kinetics of response without variability of changing dose, but has the disadvantage that the opportunity to reverse the loss of response by a higher dose was lost. Clearly the lower dose received following the initial ‘induction regimen’ may be a factor in loss of response. Finally, whilst the majority of patients received MTX (with the remaining on leflunomide), which should reduce the prevalence of human anti-chimeric antibodies (HACA), these may still have contributed to the secondary loss of response.

Of interest, a small but notable proportion of the discontinuations were despite achieving an EULAR response. In these patients, a continued high disease activity compelled a change in strategy. This illustrates that when a disease activity is high, a definable response to anti-TNF therapies is on occasions sub optimal and provides evidence that for individual patients a DAS-28 score (absolute) is perhaps more relevant than an ACR improvement (relative). Nevertheless, it is debatable how best to manage a patient demonstrating improvement but with high clinically evident disease activity; particularly with the structural benefits reported ‘across the board’ in a TNF-antagonist-treated group. Continuing therapy in a symptomatic patient would seem difficult to justify; dose escalation (if feasible) may be a more attractive option in this scenario.

In summary, evaluation of non-response to date, has concentrated on primary failure. This study represents the first large-sized cohort utilized to examine attrition rate in infliximab responders with particular emphasis on the issue of secondary non-response. Our findings clearly highlight this as a significant problem especially early on, and emphasize the continued need for therapeutic options in such subjects. The basis for such non-response remains unclear although HACAs and overall reduced dose after the first 3 months may be contributory. Availability and outcome of a fully human monoclonal antibody should clarify the role of HACAs in this secondary loss of efficacy.

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References