Extended Report:

Evidence for Differential Acquired Drug Resistance to Anti-TNF Agents in Rheumatoid Arthritis

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ABSTRACT

Objective: To study acquired drug resistance to anti-TNF agents in rheumatoid arthritis (RA).

Methods: Swiss health authorities requested continuous monitoring of patients receiving biologic agents. We analysed intensification of co-therapy with traditional disease modifying antirheumatic drugs (DMARDs), gradual dose escalation, and drug discontinuation rates in all patients receiving infliximab, etanercept or adalimumab, adjusting for potential confounders. Intensification of DMARD co-therapy and time to discontinuation of the three anti-TNF agents were analysed using proportional hazards models. Dose escalation and evolution of RA disease activity (DAS28) was analysed using a longitudinal regression model.

Results: A total of 1198 patients contributing 1450 patient-years of anti-TNF treatment met the inclusion criteria. The rate of intensification of traditional DMARD co-therapy over time was significantly higher with infliximab (HR: 1.73 [99% CI: 1.19 - 2.51]) compared to the two other agents. Infliximab also demonstrated significant dose-escalation over time, with an average dose increase of +12% (99% CI: 8% - 16%) after one year, and +18% (99% CI: 11% - 25%) after two years. No significant differences in the discontinuation rates were observed between the three anti-TNF agents (ANOVA, p = 0.67). The evolution of disease activity over time indicated a lower therapeutic response to infliximab (DAS28, p < 0.001) compared to etanercept, after 6 months of treatment.

Conclusions: In this population, infliximab was associated with a higher risk of requiring intensification of DMARD co-therapy compared to the other anti-TNF agents and a significant dose-escalation over time. Analysis of RA disease activity indicated a reduced therapeutic response to infliximab after the first six months of treatment, suggestive of acquired drug resistance.
INTRODUCTION

New disease modifying antirheumatic drugs (DMARDs) have become available since 1999. Biological agents, such as anti-Tumour Necrosis Factor \( \alpha \) (anti-TNF) agents, dramatically improve the signs and symptoms of RA refractory to conventional treatment \(^1\)\(^-\)\(^3\). The chemical structure, pharmacokinetic properties and specific mechanisms of TNF inhibition of available anti-TNF agents differ: Infliximab (INF) (Remicade®, Centocor INC., Malvern, PA) is a chimeric monoclonal anti-TNF antibody (human IgG\( \kappa \)/mouse F\( \nu \)); adalimumab (ADL) (Humira®, Abbott Laboratories, Illinois, USA) is a fully human monoclonal anti-TNF antibody; whereas etanercept (ETN) (Enbrel®, Amgen, Inc., Thousand Oaks, CA) is an engineered TNF receptor (humanized protein) acting as a competitive inhibitor of TNF-\( \alpha \) and \( \beta \). The unique pharmacological properties of these agents have been associated with different rates of opportunistic granulomatous infections \(^4\)\(^-\)\(^5\) and are thought to explain why some anti-TNF agents work in some chronic inflammatory conditions and not in others \(^6\)\(^-\)\(^7\). It is not known whether these differences affect their long-term therapeutic effectiveness or the potential development of drug resistance in RA.

In clinical practice, loss of effectiveness of long-term DMARD therapy is a common problem \(^8\). Acquired drug resistance or gradual drug failure has been described with most traditional DMARDs \(^8\)\(^-\)\(^11\) and is also starting to be recognized with anti-TNF agents \(^12\)\(^-\)\(^13\). Not all RA patients respond to standard dosage of anti-TNF agents \(^14\), 28% to 58% of all RA patients show little response to these drugs in large randomised trials \(^15\). Acquired resistance to DMARD therapy in RA has been measured by analysing use of additional DMARD co-therapy \(^18\), anti-TNF dose-escalation \(^11\) and drug discontinuation rates (‘drug survival’) \(^8\)\(^-\)\(^10\)\(^-\)\(^16\)\(^-\)\(^18\). These outcomes reflect common therapeutic options a physician has when faced with loss of DMARD effectiveness \(^19\). For patients not fully responsive to anti-TNF agents, physicians may increase co-therapy with traditional DMARDs, increase the anti-TNF dose, or decide to stop the current anti-TNF treatment and switch to other therapies. Dosage escalation has been observed with infliximab \(^19\)\(^-\)\(^25\), but this may not be a valid measure of drug resistance for anti-TNF agents without flexible dosing regimen (ETN, ADL), in which case intensification of traditional DMARD co-therapy and drug discontinuation might be more adequate outcomes.

The aim of this study was to investigate acquired drug resistance to anti-TNF therapies in a population-based observational cohort of RA patients. We examined intensification of DMARD co-therapy, progressive dose escalation and drug discontinuation rates of the three available anti-TNF agents. In addition, we explored underlying pathways leading to these therapeutic adjustments in relationship to RA disease activity.

PATIENTS AND METHODS

Study population.

Regulatory agencies in Switzerland have requested continuous monitoring of all patients receiving costly biologic agents \(^26\). The Swiss Clinical Quality Management of RA (SCQM) system \(^27\) was established by the Swiss Society of Rheumatology and selected to follow all RA patients started on anti-TNF agents. The patient’s rheumatologist or primary care physician are incited to enrol their patient in the SCQM by allowing them to deduct costs of anti-TNF drugs from their global treatment expenditure scrutinized by the health authorities, which contributes to a high enrolment rate. Based on a comparison with sales data from the industry, between 70 and 80% of all Swiss RA patients receiving anti-TNF agents are included in SCQM. Patients are enrolled at the initiation of anti-TNF therapy and
followed prospectively. The SCQM includes measurements of disease activity, radiographic damage, adverse drug reactions, and RA symptoms. Clinical information is collected systematically by the patient’s physician every 6 – 12 months and further updated at every significant change in antirheumatic therapy. The accuracy of medication data provided by the physicians - including start and stop dates - was confirmed against records from the pharmaceutical industry and participants self-reported information. Patients come from a wide variety of clinical settings: 40% private rheumatology practices, 30% non-academic centres and 30% academic centres. This analysis includes data collected between January 1998 and the end of September 2004. The inclusion criteria for this analysis were a diagnosis of RA by a rheumatologist and therapy with INF, ETN or ADL.

Outcomes.

We considered three outcomes that operationally define drug resistance: increase in concomitant DMARD therapy, dosage escalation in anti-TNF agents and interruption of the current anti-TNF therapy. Traditional DMARD co-therapy was defined as concomitant prescription of methotrexate, leflunomide, sulfasalazine, cyclosporine, hydroxychloroquine or azathioprine with an anti-TNF agent. Increase in concomitant DMARD therapy was defined by a rise in the weekly dose of traditional DMARDs or by the introduction of a new DMARD in addition to the current therapy. Replacement of one concomitant DMARD by another was not considered an increase in DMARD co-therapy. Dose escalation can occur either by increasing the dose of anti-TNF agent or by shortening the dispensation interval. To take into account both of these possibilities, we computed each patient’s average weekly dose of anti-TNF therapy [mg/week] at each time point. We examined drug retention of current anti-TNF therapies using the time until drug discontinuation, independently of the reason that led to drug interruption. Drug discontinuation rates or ‘drug survival rates’ reflect both the patients’ and doctors’ satisfaction with a given treatment and thus represent a summary measure of the overall treatment effectiveness and tolerability.

To link the therapeutic changes in anti-TNF therapy and/or in DMARD co-therapy with possible loss of drug effectiveness, we examined RA disease activity in a secondary analysis using the Disease Activity Score (DAS28). The DAS28 is a validated physician assessment of disease activity in RA, which includes number of swollen joints, the number of tender joints and the erythrocyte sedimentation rate. DAS28 ranges from zero to 10, where 10 represents maximum disease activity. Other important covariates such as the RA Disease Activity Index (RADA1), rheumatoid factor positivity, the Stanford Health Assessment Questionnaire (HAQ), previous failure on anti-TNF agents and disease duration - defined as the time between symptom onset and enrolment - were also extracted from the SCQM database.

Analysis.

Baseline disease characteristics were compared across the three anti-TNF agents. The significance of differences in mean values of continuous variables was assessed with one-way analysis of variance (ANOVA) for normally distributed variables and with the Kruskal-Wallis test for non-normally distributed variables. For dichotomous variables, Pearson’s Chi-square test was used. All statistical tests were two-sided and evaluated at the 0.05 significance level. To account for multiple pair-wise comparisons, Bonferroni’s procedure was used to adjust p values and confidence intervals (CI). The statistical analysis was performed with Stata v. 8.2 for Windows (Stata Statistical Software, Texas, USA).

The time to intensification of DMARD co-therapy and the time to discontinuation of anti-TNF agents (‘drug survival’), were analysed with Cox proportional hazards models.
Survival curves of the time to intensification of DMARD co-therapy and the time to discontinuation of anti-TNF agents (‘drug survival’) were produced using the Kaplan-Meier product-limit method. Dose escalation of anti-TNF agents and evolution of disease activity were analysed using generalized mixed models for longitudinal data. Rheumatoid factor positivity, baseline disease activity (DAS28), baseline functional disability (HAQ), disease duration and failure on a previous anti-TNF agent were all considered confounders and forced into the models. We tested other covariates using a backward stepwise selection approach. Additional covariates were included in the model only if found to be significant predictors or substantial confounders, using the 10% change in estimate criteria. We also explored potential effect modification by co-therapy with traditional DMARDs and have reported subgroup analyses when significant effect modification was present. For the final estimates, a robust estimator of the variance was used. All patients receiving anti-TNF agents were included in the analysis, though patients without follow-up data only contributed information to baseline. Because incomplete follow-up was generally due to recent initiation of anti-TNF therapy, we assumed absent follow-up data to be missing at random.

RESULTS

A total of 1198 patients on anti-TNF treatment met the inclusion criteria, with assessments every four months on average. Some differences in baseline characteristics between the three groups were noted (Table 1), in particular ADL had a higher proportion of patients with previous failure on another anti-TNF agent \((p < 0.001)\), slightly lower disease activity, and less functional disability (HAQ) at baseline.
Table 1: Baseline characteristics of patients at initiation of anti-TNF therapy

<table>
<thead>
<tr>
<th>Disease characteristics *</th>
<th>Adalimumab (ADL) (N=317)</th>
<th>Infliximab (INF) (N = 362)</th>
<th>Etanercept (ETN) (N = 519)</th>
<th>p °</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF dose, median</td>
<td>40 [mg/2 wk] (IQR: 40 - 40)</td>
<td>3.2 [mg/kg*8 wk] (IQR: 3.0 – 3.75)</td>
<td>50 [mg/wk] (IQR: 50 – 50)</td>
<td></td>
</tr>
<tr>
<td>Female [%]</td>
<td>74</td>
<td>75</td>
<td>74</td>
<td>0.89</td>
</tr>
<tr>
<td>Age [years]</td>
<td>53.0 (CI: 51.4 – 54.7)</td>
<td>53.1 (CI: 51.7 – 54.5)</td>
<td>54.4 (CI: 53.2 – 55.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Disease duration [years], median</td>
<td>10.1 (IQR: 5.6 – 17.5)</td>
<td>10.2 (IQR: 5.0 – 16.5)</td>
<td>10.3 (IQR: 5.7 – 15.9)</td>
<td>0.97</td>
</tr>
<tr>
<td>Rheumatoid Factor + [%]</td>
<td>82%</td>
<td>81%</td>
<td>78%</td>
<td>0.33</td>
</tr>
<tr>
<td>Follow-up [Mo] †, median</td>
<td>10.7 (IQR: 5.8 - 12.3)</td>
<td>18.8 (IQR: 11.5 - 28.3)</td>
<td>23.7 (IQR: 12.6 - 35.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous failure on anti-TNF agent [%]</td>
<td>39</td>
<td>12</td>
<td>7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Disease activity score (DAS28)</td>
<td>4.19 (CI: 4.02 - 4.36)</td>
<td>4.54 (CI: 4.38 - 4.7)</td>
<td>4.72 (CI: 4.59-4.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RA Disease Activity Index (RADAI)</td>
<td>4.02 (CI: 3.6 – 4.5)</td>
<td>4.59 (CI: 4.37 – 4.81)</td>
<td>4.85 (CI: 4.67 – 5.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Function disability (HAQ)</td>
<td>1.25 (CI: 1.18 – 1.33)</td>
<td>1.37 (CI: 1.29 – 1.44)</td>
<td>1.37 (CI: 1.31 – 1.43)</td>
<td>0.04</td>
</tr>
<tr>
<td>Concomitant DMARD use</td>
<td>53</td>
<td>93</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>- Methotrexate [%]</td>
<td>37</td>
<td>70</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>- Leflunomide [%]</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>- Sulfasalazine [%]</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>- DMARD else [%]</td>
<td>2</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid use [%]</td>
<td>41</td>
<td>56</td>
<td>60</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Legend Table 1:

* Values are given as means with 95 % Confidence Intervals (CI) if not otherwise indicated. When not normally distributed, variables medians and interquartile ranges (IQR) are reported. ° One-way analysis of variance (ANOVA) of means or medians for continuous variables. Chi square test for dichotomous variables. † For patients with follow-up data only, respectively N=107, N=425, N=295. DAS28 = Disease Activity Score based on 28 joints; RADAI = Rheumatoid Arthritis Disease Activity Index; HAQ = Health Assessment Questionnaire; DMARD = classical Disease Modifying Antirheumatic Drug; Rheumatoid Factor + = Proportion of rheumatoid factor positive patients.
Intensification of DMARD co-therapy. The rate of intensification of traditional DMARD co-therapy was significantly different between the three therapies (ANOVA, \( p = 0.006 \)) (Figure 1). The hazard ratio (HR) of increasing traditional DMARD co-therapy over time with INF was 1.73 (99% CI: 1.19 - 2.51) compared to the other anti-TNF agents, while there was no significant difference between ADL and ETN (Bonferroni, \( p = 0.82 \)). The difference in DMARD co-therapy intensification between anti-TNF agents started to become statistically different only after 1.2 years of treatment. Significant predictors of DMARD intensification were previous failure on another anti-TNF agent (HR = 2.14, 95% CI: 1.42 - 3.23), rheumatoid factor positivity (HR = 1.64, 95% CI: 1.07 - 2.51) and disease duration (HR = 0.98, 95% CI: 0.96 – 0.99). As expected, starting INF without concomitant DMARDs increased significantly the need for subsequent intensification of co-therapy (HR = 4.51, 95% CI: 2.64 – 7.71), but not so with ETN or ADL. No difference was observed between anti-TNF agents in glucocorticoid intensification or glucocorticoid reduction. Various sensitivity analyses with different definitions of DMARD co-therapy intensification, accounting for simultaneous changes in glucocorticoid dose, provided very similar results.

Dose escalation. Dose escalation was also significantly different between the three anti-TNF agents (ANOVA, \( p < 0.001 \)), with only INF demonstrating a significant change in dosage over time (Figure 2). The average dose escalation was 3.01 mg/week (99% CI: 2.0 – 4.03) after the first year of INF treatment, which represents an average increase of 24 mg per two-month period or +12% in INF dose. Furthermore, the average INF dose continued to escalate significantly after the first year of treatment and reached 4.60 mg/week (99% CI: 2.84 – 6.36), which represents an average increase of 37 mg per two-month period or +18% in INF dose. Dose escalation of INF was significantly higher in patients without concomitant DMARD therapy (5.5 mg/week at 1 year, 99% CI: 1.9 – 9.01). No statistically significant change in dose from baseline was apparent with ETN (Bonferroni, \( p = 0.08 \)) or with ADL (Bonferroni, \( p = 0.06 \)). However, progressive dose escalation may not be a valid measure of drug resistance for anti-TNF agents not commonly used with a flexible dosing regimen (ETN, ADL). Of the other covariates, only RF positivity significantly influenced changes in dose (\( p = 0.025 \)).

Discontinuation of therapy. The discontinuation rates were not significantly different between the therapies (ANOVA, \( p = 0.67 \)) (Figure 3). A total of 1450.5 patient-years of anti-TNF therapy and 300 cases of treatment interruption were examined. The overall discontinuation rate of anti-TNF agents was relatively low with a median drug survival of 3.21 years (IQR: 1.43 – 4.52). The hazard ratio (HR) of discontinuing therapy was 1.11 (99% CI: 0.89 – 1.40) for INF compared to ETN and ADL, 0.97 (99% CI: 0.71 – 1.15) for ADL compared to INF and ETN, and 0.91 (99% CI: 0.71 – 1.15) for ETN compared to INF and ADL. Significant predictors of discontinuation were increased disability at baseline as measured by the HAQ (HR: 1.22, 95% CI: 1.00 – 1.48) and calendar year of treatment initiation (HR: 2.01, 95% CI: 1.71 - 2.36), which reflects the increasing proportion of patients starting biologics after having failed on previous anti-TNF agents and a greater availability of therapeutic alternatives favouring treatment switches over time. As expected, previous failure on another anti-TNF agent increased the rate of drug discontinuation by 77% (HR: 1.77, 95% CI: 1.23 - 2.54) in a crude analysis. In a subgroup analysis, we explored the effect of DMARD co-therapy on anti-TNF discontinuation: In patients starting anti-TNF agents with concomitant DMARDs, discontinuation rates were significantly lower with ETN (HR = 0.66, 99% CI: 0.45 - 0.98) compared to INF or ADL.

Therapeutic effectiveness on RA disease activity. The evolution of RA disease activity (DAS28) over time differed significantly between anti-TNF agents (ANOVA \( p < 0.001 \))
During the first 6 months of treatment, rates of improvement in disease activity varied little between the three groups, but thereafter the curves separated and the DAS28 stabilized or increased with INF: DAS28 worsened by 0.14 (99% CI: 0.01 - 0.27) during the following year, compared to a non-significant improvement of 0.13 (99% CI: - 0.03 - 0.27) with ETN during the same period. Data for ADL were insufficient beyond one year of treatment to allow reliable comparisons. After the first year of treatment, the DAS28 had improved by 0.68 (99% CI: 0.30 – 1.07) with ADL, 0.82 (99% CI: 0.61 – 1.03) with INF, and 1.05 (99% CI: 0.87 – 1.23) with ETN. Depending on the absolute level of disease activity, DAS28 improvements between 0.6 and 1.2 are considered moderate therapeutic responses and improvements greater than 1.2 are considered good therapeutic responses (EULAR response criteria) 34. After the first year of treatment, 47% (99% CI: 35% - 59%) of patients were classified as having a moderate or good response to ADL, 53% (99% CI: 44% - 61%) to INF and 66% (99% CI: 59% - 72%) to ETN.

**DISCUSSION**

We studied operational features of drug resistance to anti-TNF agents in RA by analysing intensification of DMARD co-therapy, gradual dose escalation, and drug discontinuation rates in a population-based cohort of 1198 RA patients on INF, ADL or ETN. Intensification of traditional DMARD co-therapy over time was significantly higher with INF compared to the other anti-TNF agents and progressive dose escalation was evident for INF, but not for ETN or ADL. No significant difference in discontinuation rates was observed. Analyses of RA disease activity over time indicated a lower therapeutic response to INF after the first six months of treatment compared to the other anti-TNF agents. With INF, lower therapeutic responses on the DAS28 were significantly associated with dose escalation and higher risk of concomitant DMARD intensification. Overall, these data suggest a gradual decrease of INF’s therapeutic effectiveness or the development of drug resistance occurring after the first half-year of treatment.

The rate of intensification of DMARD co-therapy was significantly higher with INF than with ETN or ADL (HR: 1.73 (99% CI: 1.19 - 2.51)). A recent RCT has established that ETN with concomitant MTX is more efficacious than ETN alone 36, and observational studies have confirmed that anti-TNF agents with concomitant DMARD therapy are more effective in preventing radiographic damage progression than anti-TNF agents alone 37. Intensification of concomitant DMARD therapy can thus represent an alternative to dose escalation of anti-TNF agents and be a proxy for acquired drug resistance, 18 in particular for biological agents whose dose is not commonly modified (ETN, ADL).

Not all patients with RA respond to the suggested initial INF dose of 3 mg/kg. Higher serum levels of INF in the ATTRACT trial were associated with increased clinical response, reduction in C-reactive protein levels, and reduced radiographic joint damage progression, which suggested a dose-response relationship 14. Subsequently, a flexible dosing regimen had been accepted for INF in some countries including Switzerland, which allows dose increases up to 10 mg/kg and reductions in dosing interval to every 4 weeks. Gradual dose escalation of INF has since been observed in several RA cohorts 19-25. The amount of dose increase in an American cohort was 36% at one year 21, significantly more than in our cohort (12%), which might reflect a difference in clinical practice and in patient population. It is not clear whether this dose escalation reflects initial dose adjustments of INF therapy or acquired drug resistance to this agent. In this study and in others 21, dose escalation of INF was steepest during the first year of treatment, but continued to increase in the second year at a slower rate.
suggesting that both phenomena may be involved. Because of the price of anti-TNF therapy, these results have important economic and clinical implications. It has been estimated that INF therapy incurred a 25% increase in one-year costs representing an average of $4200 per patient per year in the US
24. Higher INF dosage may also carry an increased risk of side effects
20 35.

No significant difference in discontinuation rates was observed between the three anti-TNF agents \( p = 0.67 \), after adjusting for confounders. This corroborates results of other studies on retention rates of anti-TNF agents \( 38-40 \). Drug discontinuation rates represent a useful summary measure of overall effectiveness of a treatment, even if the rate is influenced by the availability of therapeutic alternatives or the incidence of adverse drug reactions. Anti-TNF agents had relatively low discontinuation rates and median drug survival of 3.21 years (IQR: 1.43 – 4.52) in this population. Severe adverse drug reactions were relatively infrequent in this cohort \( 41 \), suggesting that drug discontinuation denoted mostly unsatisfactory treatment response
21.

In usual clinical practice, concomitant DMARD co-therapy or anti-TNF agents are increased only if disease activity is not satisfactorily controlled and tapered only when disease activity is adequately reduced. To link the therapeutic adjustments with clinically important outcomes, we examined RA disease activity over time in the three treatment groups using an independent outcome measure. The average effect size of the DAS28 response to anti-TNF agents was moderate with an overall improvement of 0.92 (95% CI: 0.81 – 1.03) after the first year
34. Similar values of DAS28 improvement have been observed in other cohorts: in Swedish RA patients, INF treatment was associated with median DAS28 improvement of 0.6 after one year
20. However, the course of disease activity differed significantly between INF and the other anti-TNF agents. After a similar initial improvement, RA disease activity tended to slow or increase with INF after the first 6 months of treatment compared to ETN. Smaller therapeutic responses on RA disease activity were associated with dose escalation and concomitant DMARD therapy intensification in INF treated patients. While the mechanisms of resistance to INF or other anti-TNF agents are still poorly understood, the presence of antibodies to INF has been shown to reduce clinical response to this drug in patients with Crohn’s disease
12 42 and are also thought to contribute to the loss of response over time in some RA patients. Unique pharmacological properties of anti-TNF agents have been associated also with differences in the incidence rates of opportunistic granulomatous infections
4 5 or the efficacy profiles in other chronic inflammatory conditions
6 7. Further research is needed to understand the mechanisms leading to loss of drug effectiveness with anti-TNF agents.

Some potential limitations inherent to the analysis of observational data need discussion. Firstly, in this study, there was no control over the treatment assignment. Because no rationale exists for favouring one anti-TNF agent over the other in terms of efficacy
7, major confounding by indication between these agents is unlikely. However, ADL had a higher proportion of patients with a previous failure on another anti-TNF agent, slightly lower disease activity and less functional disability (HAQ) at baseline. These differences probably reflect the fact that ADL was the latest of the three anti-TNF agents to come on the market and that indication for these drugs has widened with time. While we were able to adjust our analysis for potential confounding by levels of disease activity, functional disability, rheumatoid factor positivity, previous failure on anti-TNF agents or time trends, we cannot exclude the possibility of confounding by unmeasured factors. For example, we could not adjust for concomitant rheumatic diseases or for auto-medication use such as analgesics. While potential unmeasured confounding is always a concern, we have no
evidence for a systematic bias, which would imply a differential prevalence of comorbidities or of co-medications use between anti-TNF agents. Intensification or reduction of concomitant glucocorticoid therapy was not significantly different between anti-TNF agents. Secondly, missing data is another concern with observational studies. To address this, we checked the accuracy of medication data provided by the physicians – including start and stop dates – against records from the pharmaceutical industry and participants’ self-report. However, some residual non-differential misclassification is possible, which would tend to bias the results towards the null 43. We included all RA patients receiving anti-TNF agents since 1999, but for some patients (31%, Table1) no follow-up data were available yet allowing these patients to only contribute baseline information. The median follow-up of patients on ADL, in particular was only 10.7 (IQR: 5.8 – 12.3) months because it is the last to be introduced, which limited the ability to examine its potential drug resistance. By far, the most frequent reason for incomplete follow-up was a recent initiation of anti-TNF therapy, with insufficient time for follow-up measurements. Baseline disease characteristics of patients without complete follow-up were similar to those included in the present analysis (data not shown) suggesting that the subjects in the analysis were a representative sample of the whole population.

The definition of acquired therapeutic resistance for antirheumatic therapy is less characterized than for antimicrobial therapy for example 18. Acquired resistance to DMARD therapy has been measured by analysing the use of additional DMARD co-therapy 18, anti-TNF dose-escalation 11 and drug discontinuation rates 8 10 16-18, which are only indirect measures of this concept. Further research is needed to understand the mechanisms of drug resistance to DMARDs and define outcome measures of drug resistance in RA. Moreover, we could not adjust this study’s longitudinal analyses for changes in time-dependent confounders such as simultaneous variations in dose of glucocorticoid or DMARD co-therapy, because this would have introduced biases 44. We accounted for changes in dose of glucocorticoid and DMARD co-therapy by examining intensification or reduction of these treatments over time independently. Strengths of this analysis include a true population-based cohort as all RA patients receiving anti-TNF agents are requested to be enrolled by the Swiss authorities and a systematic prospective ascertainment of a wide variety of disease characteristics.

In this population, INF was associated with a higher risk of requiring intensification of DMARD co-therapy and a significant dose-escalation compared to the other anti-TNF agents. Analyses of the evolution of RA disease activity indicated a reduced therapeutic response to INF after the first 6 months of treatment, suggesting gradual drug resistance to this therapy. Further research is needed to study the mechanisms of drug resistance to INF and other anti-TNF agents.
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**Legend Figure 1:**
The Kaplan-Meier curve for time to intensification of concomitant traditional DMARD therapy after anti-TNF initiation (dosage increase of an existing DMARD or initiation of an additional DMARD). Survivor curve was adjusted for rheumatoid factor positivity, baseline disease activity scores (DAS28), level of functional disability at baseline (HAQ), and failure on previous anti-TNF agents. ADL = adalimumab; INF= infliximab; ETN = etanercept.

**Legend Figure 2:**
Anti-TNF dose is represented in mg per week for all anti-TNF agents to allow comparison. The vertical lines represent the 99% confidence interval of the mean. The evolution of the mean dose is adjusted for the proportion of rheumatoid factor positivity, baseline disease activity (DAS28), baseline levels of functional disability (HAQ), age and failure on a previous anti-TNF agent. The evolution of ADL dose is not represented after 1 year because of scarce data. INF= infliximab; ETN = etanercept; ADL = adalimumab.

**Legend Figure 3:**
The Kaplan-Meier curve for time to discontinuation of anti-TNF agents (‘drug survival’). Survivor curve was adjusted for rheumatoid factor positivity, baseline disease activity scores (DAS28), level of functional disability at baseline (HAQ), year of initiation and failure on previous anti-TNF agents. ADL = adalimumab; INF= infliximab; ETN = etanercept.

**Legend Figure 4:**
The evolution after initiation of anti-TNF agents of 2 measures of RA disease activity is displayed. Figure 4 represents change from baseline in the Disease Activity Score (DAS28), which ranges from 0 to 10, where 10 represents maximum disease activity. The vertical bars represent the 99% confidence interval for the mean. Results are adjusted for rheumatoid factor positivity, baseline disease activity score (DAS28), level of functional disability at baseline (HAQ), and failure on previous anti-TNF agents. ADL = adalimumab; INF= infliximab; ETN = etanercept.
REFERENCES


37. The effectiveness of anti-TNF therapy in preventing progressive radiographic joint damage in Rheumatoid Arthritis. A population based study. ACR Scientific meeting; 2004; San Antonio. *Arthritis & Rheumatism.* 50 (S), manuscript submitted.


Time to intensification of concomitant DMARD therapy

% patients without change in concomitant DMARDs

ANOVA, $p = 0.006$

Time [year]

- ADL
- ETN
- INF

0 1 2 3 4
Change from baseline in anti-TNF dose

[Graph showing change in dose over time for different groups (NF, ETN, ADL). ANOVA, p < 0.001.]
Change from baseline in Disease Activity Score (DAS28)