

Effect of Anti-Tumor Necrosis Factor on Work Disability



Many studies have shown that work loss is a common outcome among patients with rheumatoid arthritis (RA). Factors associated with work loss include demographic features such as age and job type; however, work loss is also related to functional disability, likely as a surrogate marker for disease activity and joint damage^{1,2}. Not only are there social consequences of work loss for the patient and their family, but also major economic consequences, i.e., reduced income for the patient and high societal costs (indirect costs)^{3,4}.

Recently, a number of new biological therapies have been introduced for the treatment of RA. Compared to conventional disease modifying antirheumatic drugs (DMARD), these agents have been shown to be more effective in controlling disease symptoms. They have also been shown to improve disability and slow radiographic progression. Whether treatment with these therapies will result in better work prospects for patients with RA in the long term, thereby reducing indirect costs, remains unknown⁵.

In this issue of *The Journal*, as part of their study on work disability among patients with RA in the US, Wolfe and colleagues describe their investigation of the effect of anti-tumor necrosis factor (TNF) therapy on work disability⁶. Their study is of interest because studies investigating the association between anti-TNF therapy and work disability have been scarce. In a previously published study in 2003, Yelin, *et al* investigated the association between etanercept and employment status⁷; using data from an observational study as well as a clinical trial, they found a positive association between etanercept therapy and employment. Although in a randomized clinical trial no significant differences on actual employment rates were found between patients with early RA receiving methotrexate (MTX) plus placebo versus MTX plus infliximab, fewer workdays were lost in the MTX plus infliximab group⁸. In contrast, no substantial decrease in work disability costs was observed in a

Finnish study, in which work disability costs for patients with chronic inflammatory disease were calculated one year before and one year after commencement of infliximab⁹.

Data for the current study⁶ were obtained from the National Data Bank for Rheumatic Diseases (NDB), in which participants are recruited on an ongoing basis from the practices of US rheumatologists and followed prospectively with semiannual questionnaires. These investigators identified 1986 patients who were both simultaneously employed and receiving anti-TNF therapy at their first observation (mean disease duration 12.5 yrs) and 1900 patients who had never received anti-TNF therapy but who were also employed at their baseline screening for entry into the database (mean disease duration 14.1 yrs), for a total of 3886 patients. Work disability due to any cause, not just RA, was based on 2 definitions: (1) work-disabled by self-report (SR disability) and (2) US Social Security-disabled (SS disability). Conditional logistic regression analyses were used to estimate the effect of anti-TNF therapy on work disability.

In an unadjusted analysis, patients treated with anti-TNF therapy had an increased risk of SS disability [relative risk (RR) = 1.6; $p = 0.006$]. However, as patients in the anti-TNF group were younger and had fewer comorbid conditions compared to patients in the non-anti-TNF group, results from a multivariate model, which included demographic and comorbidity data, increased this RR for work disability to 1.9 ($p < 0.001$) for patients in the anti-TNF group versus patients who had never received anti-TNF. Comparison of RA-related factors between the 2 groups revealed large differences at first entry visit: patients in the anti-TNF group had considerably worse disease activity scores (i.e., Health Assessment Questionnaire score, Symptom Intensity scale, Rheumatoid Arthritis Disease Activity Index joint score and pain) and had used more disease modifying antirheumatic drugs (DMARD) than patients in the non-anti-TNF group;

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more patients in the anti-TNF group had also used prednisone in the past. Adjustment for all these RA-related factors in the model resulted in a nonsignificant RR of 1.2 ($p = 0.441$) for SS disability, but a significantly increased RR of 1.6 ($p = 0.014$) for SR disability, suggesting that anti-TNF therapy was still a significant predictor of SS disability.

Unfortunately, limitations to this study prevent one from concluding that anti-TNF therapy does not reduce work disability and unemployment in RA. It is known that a significant proportion of patients who start anti-TNF therapy will already be work-disabled at the start of therapy. Therefore, limiting this study to patients who were still employed at the time of anti-TNF therapy precluded analysis of whether treatment with anti-TNF may allow patients who were previously work-disabled to return to work after initiation of anti-TNF therapy. It is also not clear who were included in the analysis: all patients who were employed at the start of anti-TNF therapy, or only those who were still employed at the time they were registered with the NDB, thus possibly excluding patients who had originally been employed at the start of anti-TNF but who had stopped working prior to registration with the NDB, leading to an underestimation of the degree of new work disability among anti-TNF-treated patients. In addition, the authors did not provide any information on time until work disability, which may have been longer than that in the non-anti-TNF group. Finally, it is not clear, due to the intention-to-treat analysis, which patients within the anti-TNF group became work-disabled. It is thought that about 20%–30% of patients do not respond to anti-TNF therapy^{10,11}. Based on the results of this analysis, it is not clear if the new work disability was limited to those patients who were nonresponders, and whether, in fact, work outcomes among responders to this treatment may have been very good.

Their study has shown that disease activity at study entry is clearly entwined with the effect of anti-TNF and is associated with the risk of work disability; both groups differed with respect to disease activity and disease characteristics. To see the effect of anti-TNF on work disability, these effects and differences cannot simply be disentangled by statistical techniques. A selection of control patients matched for patient characteristics and disease severity may have helped to address this issue further. Ideally, however, the most methodologically sound investigation to evaluate the economic consequences of anti-TNF and other DMARD therapies would be a controlled trial, whereby randomization would eliminate confounding by indication. Preferably this should be a study with longterm followup, in which not only work disability is investigated, but also the number of days on sick leave, productivity level, and return to work. Of course, the main problem with such a randomized trial is feasibility.

The other conclusion of this study, that self-reported disability seems to be diminishing, possibly reflecting

improvements in RA therapy and better disease control, seems to be justified. In the years to come, more intensive treatment strategies will be used and biological agents will probably be prescribed in earlier stages of the disease^{12,13}. In the current study, patients in the anti-TNF group had long mean disease duration at first database entry and had already failed taking several DMARD. Since a significant proportion of patients with RA become work-disabled in the first few years after disease onset¹⁴, an earlier, aggressive therapeutic regimen, possibly including early biologic therapy, will hopefully result in less work loss for the patient and will reduce indirect costs to both the patient and society. Clearly this is an issue that requires further research.

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