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Not Better, But Quite Good: Impact of Combination Therapy for RA with and without Biologic Agents on Work

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Treatments for rheumatoid arthritis (RA) are far more effective now than even two or three decades ago. The usage of disease modifying agents (DMARDs), both traditional and biological, is largely responsible for this improvement, especially when initiated after onset of disease. In populations with good access to experienced providers, the appearance of extra-articular manifestations and joints with profound deformities is becoming less common, if not rare, and the goal has shifted to induction and maintenance of low disease activity states from the more limited aim of dampening a steep downward slope of symptoms and function.

For individuals with RA, expectations of limited symptoms and almost unlimited capacity to maintain activities now seem possible. For society, the improvements in treatment puts the goal of limiting the costs associated with RA within reach. To achieve that goal, however, requires reducing the prevalence of work loss, the single largest cost category in RA. A related issue is whether the considerable expenditure required for biologic agents redounds in reduced work loss costs, let alone whether such agents – averaging \$20,000 per year – can “pay” for themselves by reducing disability payments by a greater amount (Clearly, they have other benefits that must be incorporated in any cost calculations).

In this issue of JAMA-Internal Medicine, Eriksson and colleagues¹ have taken advantage of a well-done clinical trial of the combination of biologic agents and traditional DMARDs vs. combinations of traditional DMARDs among persons with early RA² to study the effects on work loss. The results of the original clinical trial showed that combinations including biologic agents were more efficacious with respect to radiological-verified damage than combinations without such agents.

For there to be any chance that work loss can be reduced, if not forestalled, aggressive treatment using DMARDs must be initiated early because, in the absence of aggressive treatment, ten percent will stop working within a year of diagnosis and half will do so by a decade; close to 90 percent will stop working before a normal retirement age³. Thus, the use of data from a clinical trial of persons with symptoms of RA of less than a year’s duration provided as sensitive a test of the effect of combination therapy including biologics as could be envisioned.

Furthermore, the study by Eriksson and colleagues took advantage of the fact that Sweden has a single source of data on all forms of reimbursement for work loss, incorporating both sick days, a measure of short-term disability, and disability pensions, a measure of long-term or permanent disability. In the U.S., in contrast, individuals experiencing work loss may receive private short-term and long-term disability pensions or public payments, including

Social Security Disability Insurance (if eligible and meeting stringent criteria for entitlement), Supplemental Security Income, state disability benefits, or other forms of welfare. Generating objective data would be extremely difficult with the fractionated disability compensation system here. The costs of generous social welfare systems garner a lot of media attention; the benefits of having centralized data sources for epidemiological and outcomes studies does not.

The analysis by Eriksson and colleagues indicates that the use of combinations of agents results in a reduction of about four days per month in sick days and disability pensions when measured 12 months after randomization. However, the form of the combination did not matter; that is, both those on combinations including biologic agents and those on combinations of traditional DMARDs experienced a similar reduction in the number of days with sick leave or disability pension benefits (4.1 for the former group, 4.0 for the latter, ns, using the primary method of intent-to-treat analysis). At twenty-one months after randomization, the two groups still did not differ significantly in the number of days, although there was a trend favoring the group with combinations that included biologic agents.

The authors' conclusion that work outcomes may be more refractory to medical intervention than clinical and radiological outcomes is based on combining the results of the original clinical trial with those from this use of the trial data to study work outcomes. As noted, the original trial reported that the combination including biologics resulted in a lower rate of radiographic progression at 24 months while the present study about work outcomes showed no difference in objectively measured work loss. The employment effects in their study are broadly consistent with the now substantial literature on work disability in RA^{4,5}. They are also consistent with the model of disablement first advocated by SaadNagi⁶ more than three decades ago in which pathology is less predictive of distal outcomes such as work capacity or actual labor force participation than of more proximal ones, such as impairment in joint function. Finally, the study resolves some of the issues identified in a systematic study of the impact of biologic agents on employment in RA, including, most importantly, subjective or varying outcome measures⁷. The implication is that employment is determined by a complex set of factors, including the severity of disease, but extending to the demographic background of the individual, the nature of his or her work, and the state of the economy at large.

However, that may be too conservative a conclusion to draw from the study findings. While it is true that combinations including biological agents were no more effective in reducing sick or pension benefit days, *both* reduced the number of days by about a quarter. Treating to a target of low disease progression by any means does reduce the work impacts of RA whatever the treatment strategy. Given how refractory employment is to intervention, that is a positive impact indeed.

Clinical trials are conducted differently than actual clinical care. In the real world in which payors limit access to biologic agents to those who have failed a regimen limited to traditional DMARDs, the fact that combinations including biologics may have an acceptable employment outcome even when initiated *after* traditional DMARDs have proven insufficient may be the true implication of the study. In the real world situation of sequential use of combinations first excluding and only after that including biologic agents, one might find that the employment outcome may not be equal as it was in after simultaneous randomization but the fine study by Eriksson and colleagues indicates that it may be good enough.

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