Editorial

The Challenges of Measuring Adherence to Clinical Treatment Recommendations in Spondyloarthritis

Clinical t*f*featment recommendations are intended to provide evidence-based guidance to healthcare practitioners about appropriate care for specific clinical situations, with the goal of using that guidance to improve patient care. Unfortunately, translating treatment recommendations from the library literature review to routine clinical care can present a significant challenge. Many groups may propose treatment recommendations for the same disorder, and in some cases these recommendations may be contradictory. Further, the number of treatment recommendations that emerge at a steady pace make it difficult for the clinician to keep up to date. In 2017 so far, the American College of Rheumatology has already published 2, and the European League Against Rheumatism has published 6 sets of treatment recommendations. Despite the frequency of recommendations, it is difficult to assess whether they are being applied routinely to clinical care. In this issue of *The Journal*, Harvard, *et al*[1] address this problem by evaluating a system to define adherence to anti-tumor necrosis factor (TNF) use recommendations in spondyloarthritis (SpA). Additionally, they evaluate how adherence to anti-TNF use recommendations in SpA affects economic and health outcomes, while controlling for adherence to other SpA recommendations.

Harvard, *et al*'s study included 469 patients who met the Assessment of Spondyloarthritis international Society (ASAS) criteria for SpA[2] in the large, prospective, longitudinal DESIR (Devenir des Spondylarthropathies Indifférenciées Récentes) cohort[1]. The included patients were relatively early in their disease process (≤ 3 yrs)[1]. Adherence to treatment recommendations was defined based upon the 2010 update of the international ASAS recommendations for the treatment of SpA[3], with patients divided into 4 groups (Table 1). Economic evaluation of adherence to treatment recommendations was calculated using total costs, nonbiologic costs, and quality-adjusted life-years (QALY) over a 1-year observation period[1].

The analysis yielded intriguing results. In the main analysis, the "timely anti-TNF users" and "late anti-TNF users" were revealed to have the same total and nonbiologic costs, as well as the same QALY[1]. Essentially, there was no demonstrated cost savings to treating patients early, aggressively, and according to treatment recommendations. Remarkably, a separate sensitivity analysis, which used an alternate definition of adherence, contradicted the results of the main analysis. With the modified definition, nonadherence to treatment recommendations contributed to higher nonbiologic costs (in late anti-TNF users) and worse QALY (in those with unmet anti-TNF need)[1].

Regrettably, Harvard, *et al* were not able to evaluate reasons for anti-TNF nonuse because of missing data. Was the decision to not use anti-TNF drugs the physician's choice, the patient's, or were the recommendations simply not used? This information is relevant because a key component of the 2010 ASAS treatment recommendations is the recognition that "expert opinion" is needed before the initiation of anti-TNF therapy. The authors try to account for this expertise by including a physician's global assessment (PGA) of disease activity. However, there are many clinical situations in which a patient may have high disease activity, but "expert opinion" would suggest avoiding anti-TNF therapy (for example, active infection). These cases cannot be appropriately accounted for by PGA alone.

This study demonstrated no cost savings with adherence to treatment recommendations for anti-TNF use in SpA over 1 year of observation, but it is important to interpret this finding in the greater context of the disease's natural history. SpA in general is a very slowly progressing disease, with progression from nonradiographic axial SpA (nr-axSpA) to ankylosing spondylitis (AS) meeting New York criteria in only about 12% of patients over 2 years[4]. Progression is also slow in the spine, where 20% of those with AS progressed over 2 years, and only 7.4% of patients with nr-axSpA had significant changes[4]. Further complicating the issue is that it is still unknown whether patients' symptoms and function are affected more by radiographic progression versus potentially reversible spinal inflammation[5].

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Table 1. Definition of adherence to anti-TNF use recommendations in the DESIR cohort[1].

	Meets Recommendations Criteria for anti-TNF	Does Not Meet Recommendations Criteria for anti-TNF
Prescribed anti-TNF	Adherent Users (timely use of anti-TNF)	Nonadherent Users (late use of anti-TNF)
Not prescribed anti-TNF	Nonadherent Nonusers (unmet anti-TNF need)	Adherent Nonusers (no anti-TNF need)

TNF: tumor necrosis factor; DESIR: Devenir des Spondylarthropathies Indifférenciées Récentes.

Further, the cost analysis performed by Harvard, *et al* does not account for unemployment, early retirement due to SpA, or loss of work productivity, which have been previously shown to be significant contributors to overall cost, in addition to absenteeism alone[6]. It is imperative that future studies examining cost outcomes consider the effect of this disease on all aspects of a patient's life, including domains such as leisure and loss of work productivity.

Harvard, *et al*'s finding that appropriate early intervention with anti-TNF agents in SpA does not improve cost or QALY could be used to support greater restrictions to these very expensive but effective medications. In Canada, for example, biologic treatments for chronic inflammatory disease dominate the pharmaceutical market, with costs of these drugs representing the largest portion of drug costs nationwide[7]. Policy makers could use findings that suggest there is no economic or QALY benefit with early intervention with anti-TNF drugs to argue that we are spending money on those who do not need it. This could in turn significantly affect patients' ability to access appropriate treatment. For this reason, it is imperative that future studies investigate the cost of treatment in the context of the slow natural history of SpA.

The discrepancy between this study's main and sensitivity analyses also emphasizes that how adherence is defined directly affects the outcomes regarding cost and patient quality of life in SpA. The authors note that while cost benefits were not noted with the original definition of adherence to recommendations, a slight modification in definition produced contradictory results[1]. They also note that the definition of adherence used in the main analysis potentially misclassifies some subsets of patients with SpA, such as those who use anti-TNF prematurely and those who adhere to recommendations but remain in a high disease activity state[1]. This suggests that measuring the effect of adherence to treatment recommendations is highly dependent upon which definition of adherence is used.

This study highlights the ongoing challenges of translating treatment recommendations to actual clinical practice. Treatment recommendations are an effective method of providing current evidence-based guidance to busy practitioners; however, it is still difficult to understand whether following them benefits patients. Further studies are needed to determine the best way of measuring adherence to recommendations, and how that affects patient care, before conclusions may be drawn regarding the effect of their use.

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