Devolving therapeutic pyramids

In a recent article, Axel Finckh and colleagues assessed the potential cost-effectiveness of the major therapeutic strategies for very early (that is, symptom duration of less than 1 month) rheumatoid arthritis (Finckh, A. *et al. Ann. Intern. Med.* **151**, 612–621; 2009). For each of the different therapeutic strategies, the investigators compared radiographic evidence of joint damage with functional disability at various time points—toxicity, treatment initiation or discontinuation, or death. Estimates of lifetime costs and benefits were expressed as quality-adjusted life years (QALYs) and a decision analytic model with probabilistic sensitivity analyses applied. The primary comparison was between the pyramid strategy—initial treatment with NSAIDs, patient education, exercise, pain management, low-dose glucocorticoids as needed and disease-modifying anti-rheumatic drugs (DMARDs; leflunomide, sulfasalazine, hydroxychloroquine or methotrexate) for nonresponders at 1 year—and two early, aggressive treatment strategies, which consisted of either methotrexate within 12 weeks of symptom onset (early DMARD strategy) or methotrexate plus a biologic agent (early biologic strategy). The clinical outcomes were assumed to be unpredictable at presentation and included drug-free remission, a mild disease course with slow disease progression, or rapid disease progression. Additional outcomes included QALYs and direct and indirect costs.

The model predicted that early DMARD or biologic therapy delayed functional disability progression by 2–4 years and influenced both QALYs and costs by reducing the use of resources (for example, for joint replacements and hospitalizations) and preventing “...deterioration in health status.” The early DMARD strategy was more cost-effective over a lifetime than the pyramid strategy, by incorporating indirect costs such as lost productivity. Similarly, during the first 10 years of treatment, the early biologic strategy offered the most benefit compared with the pyramid strategy; however, owing to predicted conversion to treatment with DMARDs, patients who received early biologic therapy had less benefit, over time, compared with patients who received biologic agents later in the disease course. Hence, despite the ‘early’ benefits of biologic therapy, maximum cost-effectiveness was achieved by utilizing the early DMARD strategy and reserving biologic therapy for nonresponders.

In his editorial on the work of Finckh *et al.*, Maarten Boers describes many aspects of rheumatoid arthritis that are similar to Crohn’s disease (Boers, M. *Ann. Intern. Med.* **151**, 668–669; 2009). They are both “...multisystem

disease[s] characterized by chronic inflammation and, ultimately, destruction of joints [or transmural complications that] ... left unchecked ... [lead] to a high burden of disease, early loss of work capacity, major morbidity, and [in the case of rheumatoid arthritis] increased mortality.” However, there is good evidence in the setting of rheumatoid arthritis that “...early and aggressive treatment...” can prevent many of the long-term consequences of the disease. In contrast to Crohn’s disease, different combinations of drugs that have disease-modifying activity in rheumatoid arthritis have been systematically evaluated, demonstrating both short-term and long-term benefits. Furthermore, the end points used to evaluate DMARDs include quantifiable radiographic measures as well as standardized quality of life assessments that do not necessarily parallel measurements of disease activity. By contrast, in Crohn’s disease we do not have a gold-standard measure of structural damage and there is a strong correlation between clinical activity scores (Crohn’s Disease Activity Index) and quality of life scores (Inflammatory Bowel Disease Questionnaire).

The most striking finding in the modeling of early intervention in rheumatoid arthritis is the relative clinical comparability between the early DMARD strategy and early biologic strategy, with cost being the major difference in the cost-effectiveness analysis. As Boers points out, however, “...trials that compare a biologic head-to-head with optimum conventional treatments are rare, because the industry has no impetus to fund such trials and financial and organizational hurdles are rapidly becoming insurmountable for nonindustry sponsors.” The same is the case for Crohn’s disease therapy. Even the SONIC trial, which compared azathioprine monotherapy, azathioprine combination therapy plus infliximab, and infliximab monotherapy, failed to optimize azathioprine therapy—the most efficacious maintenance treatment after steroid-induced remission (Sandborn W. J. *et al. ACG Annual Scientific Meeting*, Abstract 29; 2008).

Nonetheless, there are important and relevant messages from the rheumatoid arthritis studies that are applicable to Crohn’s disease. First, the therapeutic pyramid based on severity of illness that was first employed for rheumatoid arthritis should fall by the wayside. An early, aggressive approach towards disease-modifying therapies was most effective in nonselected patients presenting with early disease. Second, recognizing the heterogeneity of both rheumatoid arthritis and Crohn’s disease and identifying predictors of disease progression and treatment responsiveness will improve the cost-effectiveness of more expensive therapies when

“We eagerly await ... well-designed comparative effectiveness trials in IBD...”

Stephen B. Hanauer is the Editor-in-Chief of *Nature Reviews Gastroenterology & Hepatology*.

Competing interests

The author declares an association with the following companies: Abbott Labs, Alevan, Amgen, Astellas Pharma Global, Astra Zeneca, Bristol Myers Squibb, Centocor, Chemocentryx, Elan, Ferring, Genentech, GSK, McNeil PPC, Millennium Pharmaceuticals, Novartis, Pfizer, Prometheus, Salix, Shire, Takeda, Therakos, UCB Pharma and Warner-Chilcott. See the article online for full details of the relationships.

applied to individual patients (that is, by identifying who would achieve the greatest benefit from early aggressive disease modification with conventional agents and biologic agents). Yet, the message rings clear that, in rheumatoid arthritis, the 'step-up' or pyramid strategy for patients with early disease does not prevent disease progression and is not cost-effective. Boers argues for early referral to rheumatologists for early, aggressive DMARD (or biologic) therapy. The Institute of Medicine has listed the "Compared effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease,

ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis" in its final list of priority topics (IOM, 2009). We eagerly await prospective studies that will delineate appropriate predictors of progression and response and well-designed comparative effectiveness trials in IBD, as we follow our rheumatology colleagues in their deconstruction of severity-based treatment strategies and move towards early, aggressive strategies that will probably continue to include conventional agents along with biologic agents.

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