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## Economic Considerations of the Treatment of Ankylosing Spondylitis

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### Abstract

Ankylosing spondylitis (AS) is associated with both significant direct and indirect costs, which vary by country, and have generally increased dramatically since the introduction of anti-TNF therapy. The cost-effectiveness of biologic agents is controversial, although cost-effectiveness studies need to consider the potential impact of anti-TNF treatments on work ability. Alternatives to reduce costs associated with biologics have been examined, including on-demand dosing and lower dose alternatives. Other treatment measures, such as total hip arthroplasty and physical therapy, are also effective in reducing pain and improving function in patients with AS, although the optimal type or combination of physical therapy treatment modalities, the optimal frequency and duration of treatment, and whether therapy is equally effective in stable disease and uncontrolled AS needs to be determined. No studies have examined differences in patient outcomes based on subspecialty care. Establishing an evidence base for these questions would help inform policy decisions to design the most cost-effective measures to treat AS.

### Keywords

Spondyloarthritis; Ankylosing Spondylitis; Psoriatic Arthritis; Economics; anti-TNF Treatment

### The Rising Cost of Health Care

With the introduction of newer agents, especially biologics, the cost of care for patients with AS has risen considerably. Health-care economics is rapidly becoming the challenge that government and private insurers cannot afford to ignore any longer. This is particularly so in the United States, where national health expenditures as a percentage of gross domestic product have risen from 5.2% in 1960 to 15.9% in 2005, and are projected to climb to 21.3% by 2020 (Centers for Medicare and Medicaid Services, The Lewin Group). The U.S. leads the world in health-care spending per capita--\$6,714 in 2006 compared to \$3,678 in Canada and \$2,760 in the U.K.<sup>1</sup> This in no small part is accounted for by pharmaceutical spending, where again the U.S. leads developed countries (\$843 per capita compared to \$639 in Canada and \$500 in Germany). In most European countries and Canada, Australia and New Zealand, the overwhelming majority (90-100%) of the population have health insurance coverage through public (i.e., governmental) programs. In the U.S. in 2006 only 27.4% of the population had public insurance. In fact, most health-care coverage comes through private insurance, which has risen in cost considerably in the past several years.

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The burden this is placing on patients and their families is considerable and getting worse: In 1999, the average family insurance premium as a percentage of median family income was 11%. By 2010 it has risen to an estimated 18% and by 2020 it is projected to rise to 24% in the U.S.<sup>2</sup> These increases are, in part, explained by the aging of U.S. population and the increasing presence of comorbidities, which further complicate the care of the patient with AS. Likewise, patients with chronic conditions in the U.S. report significantly higher out-of-pocket medical costs (41% report spending >\$1,000 annually compared to 20% in Canada and 4% in the U.K.), which further complicates compliance with prescribed medications and health-care access. Not surprisingly, this has resulted in the U.S. ranking worst among countries in the Organisation for Economic Co-operation and Development (OECD) in the frequency of cost-related access problems and in medical care and medications in past two years<sup>1</sup>. Another problem is care for the uninsured; 37 million people in the U.S. alone had no health-care insurance in 2007<sup>3</sup>.

AS is associated with significant costs, both direct costs (medications, outpatient visits, hospitalizations, home help, and alternative treatments) and indirect costs (lost productivity in the workplace and disability)<sup>4-14</sup>. Ward identified a subset at risk for higher costs in the pre-anti-TNF era (>\$50,000 over five years)<sup>4</sup>, predicted by those with greater functional impairment and pain. The amount of direct and indirect costs vary by country (Table 1), and the direct costs have generally increased dramatically since the introduction of biologic therapy<sup>5-14</sup>. As a rule, the impact has been least in countries where anti-TNF therapy is least available. This is particularly so in Latin America, Africa and Asia<sup>11-14</sup>, where anti-TNF usage is not subsidized by public insurance and private insurance is not commonly encountered (Table 2).

## Cost-Effectiveness of Anti-TNF Medications

The added costs associated with new treatments such as biologics have led to the development of therapeutic guidelines to optimize the use of these expensive therapies with those patients who are most likely to need and benefit from these agents<sup>15</sup>. The cost-effectiveness of anti-TNF medications in AS is controversial. Neilson, et al.<sup>16</sup> found that the cost-effectiveness of etanercept in patients with severe AS in Germany varied with the cost perspective, and was comparable with reported cost-effectiveness of anti-TNF treatments in patients with RA, although costs were higher in Germany than in the UK. Kobelt, et al.<sup>17</sup> reported that infliximab therapy for patients with active AS should be cost-effective both from the societal perspective and from the perspective of the health-care system in Spain (ranges from EUR 5,300 to EUR 32,000 per quality-adjusted life year [QALY] gained). On the other hand, Boonen, et al.<sup>18</sup> reported an estimate of EUR 118,000 per QALY gained with etanercept and EUR 189,000 per QALY with infliximab treatment, with both estimates exceeding acceptability criteria. In a meta-analysis of trial results and economic evaluations through 2005, McLeod, et al.<sup>19</sup> concluded that the short-term economic assessment indicated that none of the three anti-TNF-alpha agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least cost-effective option.

Existing cost-effectiveness studies project future disease progression based on functional limitations or symptoms, but have not considered the potential impact of anti-TNF treatments on work ability. Reduced symptoms due to effective use of anti-TNF treatment may improve work ability, reduce sick days, and decrease the risk of permanent work disability. However, at present there are limited data on the effects of anti-TNF treatment on work outcomes in patients with AS<sup>20, 21</sup>. If treatment with anti-TNF medications were demonstrated to reduce work disability, the associated reduction in indirect costs would help

offset the increase in direct medical costs due to these medications, and would lead to more favorable cost-effectiveness estimates.

### Use of On-Demand Regimens

One alternative to reduce costs is to give biologics only when they are acutely needed (i.e., during active disease or a flare). Fautrel, et al.<sup>22</sup> determined the incremental cost-effectiveness ratios (ICERs) of q6 week dosing vs. an on-demand regimen of infliximab in 230 patients with active AS. The administration of infliximab every 6 weeks was found to be cost-effective compared to the on-demand regimen; however, the ICER was close to the acceptability threshold of EUR 50,000 for one QALY gained.

### Use of Low-Dose Regimens

Another method to reduce costs is to try lower dose alternatives. One early study<sup>23</sup> used a 3mg/kg/infusion of infliximab in 16 psoriatic arthritis (PsA), 12 AS, and 2 undifferentiated SpA patients and found that the majority required subsequent dose adjustment upward to 5mg/kg/infusion. Three more recent reports in larger series of AS and PsA patients<sup>24-26</sup>, however, found the lower dose of infliximab was generally safe, effective and well-tolerated in the treatment of AS, with different proportions of patients requiring dose escalation.

The same holds for etanercept. One study of 16 patients<sup>27</sup> found that AS patients in clinical remission can use low doses of etanercept (tapered individually) without increasing disease activity. Another report<sup>28</sup> showed that 25 milligrams of etanercept per week is effective enough to maintain remission in AS in most patients. A report of even lower etanercept dosing (25mg/2 weeks) had an acceptable safety and effectiveness profile in four individuals with AS. Despite potential clinical and cost benefits, use of low-dose regimens is not common, and on-demand treatment regimens remain investigational.

Current guidelines also suggest that anti-TNF medications be switched or discontinued in patients who have an inadequate symptom response<sup>15</sup>, although it is not known how often this recommendation is followed in clinical practice. In a poll of SPARTAN members, there was no clear consensus on the degree of improvement or the duration of treatment needed before judging primary non-response to an anti-TNF medication. Tapering and eventual discontinuation of anti-TNF medications in patients in clinical remission is another way to decrease costs of care. However, two small observational studies found that almost all patients had symptom relapse within 24 weeks of discontinuation of anti-TNF medication<sup>30, 31</sup>. Therefore, this option may be viable for only a minority of patients.

### Surgery and Physical Therapy

Total hip arthroplasty is the most common orthopedic surgery performed for the treatment of AS-related joint damage, with 5% to 10% of patients having the procedure<sup>32, 33</sup>. Total hip arthroplasty is extremely effective in reducing pain and improving function in patients with AS and hip arthritis<sup>32</sup>. Even considering the possible need for subsequent revision arthroplasty in younger patients, the clinical benefit and episodic nature of the intervention certainly make the procedure a good value, although formal cost-effectiveness studies have not been done<sup>34, 35</sup>.

Physical therapy is another commonly-used treatment in patients with AS, with 10% to 20% of U.S. patients receiving therapy in any year<sup>4</sup>. Rates of use are much lower in the U.S. than in western Europe<sup>6, 36</sup>. Although both individual and group physical therapy is effective in improving symptoms and flexibility in the short term, several questions remain about how physical therapy can best be used to treat AS<sup>37</sup>. These include the optimal type or

combination of treatment modalities, the optimal frequency and duration of treatment, and whether therapy is equally effective in stable disease and uncontrolled AS<sup>37</sup>. It is also not clear if all patients with AS require physical therapy at the time of diagnosis, if the need for physical therapy changes with the stage of AS, and if the advent of anti-TNF medications has broadened or reduced the role of physical therapy<sup>38</sup>. Physical therapy can serve the important function of educating patients about movement, posture and exercise, and is viewed as a fundamental component of AS treatment, although whether structured therapy improves long-term outcomes over that of recreational exercise is uncertain<sup>39</sup>. Knowing these answers will greatly help evaluate the cost-effectiveness of physical therapy in AS.

## Work Disability

Work disability affects 10% to 20% of patients with AS, most often in those with physically demanding jobs<sup>40-42</sup>. Lost income and lost productivity due to work disability represent major burdens to both families and society. Tools to identify at-risk patients have been developed, but better interventions are needed to prevent work disability. Vocational rehabilitation may help patients remain employed, but often may be used too late to be maximally effective. For patients with physically active jobs, counseling at the time of diagnosis, with an aim of sustaining employability over the next 30 or 40 years, may be appropriate.

## Role of Rheumatologists

Outpatient care and medications are the major contributors to the direct costs of AS<sup>4, 5</sup>. The nature and composition of outpatient care of patients with AS has received little attention. Although rheumatologists are often involved in the diagnosis of AS and in the ongoing management of patients with severe symptoms, no studies have examined differences in patient outcomes based on subspecialty care, what is the most appropriate balance of rheumatologist care vs. generalist care, what is the most appropriate frequency of rheumatology visits, or how these considerations may vary with the severity or stage of AS. Recommendations for young patients with active AS may not be the same as those for older patient with stable inactive AS. These considerations may be most relevant in resource-limited areas, where access to rheumatologists to treat patients with AS must be balanced against needs to treat patients with other rheumatic diseases. Establishing an evidence base for these questions would help inform policy decisions in areas with a limited supply of rheumatologists, but would also help in designing more efficient models of care for areas where access to rheumatologists is not limited.

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Table 1

## Direct and Indirect Costs of Ankylosing Spondylitis by Country

Country (ref)	Year(s)	Total	Direct	Indirect	Comments
U.S. (4)	1994-1999	\$6353	27%	33%	High total cost subset-functional disability and pain most important predictors
Belgium (6)	1996-1997	394€	75%	25%	Poor physical function increases patient's costs and time consumption. Loss of income is associated with lower QoL.
France (6)	1996-1997	252€	44%	56%	
Netherlands(7)	2009*	9374€	50%	50%	Productivity costs constitute the largest part of the total cost-of-illness of AS reflecting the high burden of the disease on work participation.
U.K.(8)	2003-2004	1852£	27%	73%	The most severely affected patients incur 50% of the total costs, and physiotherapy accounts for 32% of the total health-care costs in the UK.
Spain (9)	2008*	20328€	23%	77%	Costs increased significantly with worsening disease, in particular diminishing physical function, covering a range between EUR 5000 and EUR 75,000 per patient and year.
Sweden (10)	2005-2007	\$12365	47%	53%	The patients with AS treated with biological therapy constituted 80% of the total drug cost, but just 40% of the cost for disability pension.
Mexico (11)	2008*	n.a.	\$2289	n.a.	From the patient's perspective, the cost of AS represents 25% of direct medical costs.
Brazil (12)	2010*	\$4597 USD	45%	55%	The average monthly household income for the group was US \$520
Tunisia (13)	2006	546€	266€	280€	Most of the factors associated with higher costs were related to greater disease activity.
Hong Kong (14)	2005-2006	\$9120 USD	38%	62%	Costs of technical examinations represented the largest proportion of total cost. Patients with AS reported significantly impaired QoL. Functional impairment became the major cost driver of direct costs and total costs.

\* Year of publication



**Table 2**

TNF utilization in AS or SpA in Different Countries

Country	Year	AS	PsA
Belgium (5)	2009	44%	n.a.
Canada (Toronto) *	2011	48%	n.a.
Hong Kong (16)	2005-2006	0%	n.a.
Portugal (43)	2011	58%	52%
Spain (9)	2004-2005	17%	12%
Turkey (44)	2010	16.4%	n.a.
United States *	2011	50-55%	n.a.
Argentina (45) **	2008	10.4% *	
Brazil (45) **	2008	5.4% *	
Chile (45) **	2008	0% *	
Costa Rica (45) **	2008	10.4% *	
Mexico (45) **	2008	12.1% *	
Peru (45) **	2008	1.7% *	
Uruguay (45) **	2008	0% *	
Venezuela (45) **	2008	27% *	

\* Unpublished data from the Toronto and PSOAS Registries.

\*\* Total SpA