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Original article

Clinical and economic burden of extra-articular manifestations in ankylosing spondylitis patients treated with anti-tumor necrosis factor agents

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Abstract

Objective:
To assess concomitant extra-articular manifestation (EAM) rates in patients with ankylosing spondylitis (AS) treated with anti-tumor necrosis factor (anti-TNF) agents and examine the economic burden of uveitis and inflammatory bowel disease (IBD) in French and German AS patients.

Methods:
Previous analyses of uveitis and IBD in AS patients treated with infliximab, etanercept or adalimumab were identified in PubMed/Medline (January 2000 to August 2011). A supplemental analysis incorporated more recent adalimumab clinical trial data (ATLAS [NCT00085644] and RHAPSODY [NCT00478660]). For resource utilization/costs associated with EAMs, the search was expanded to general spondyloarthritis (SpA) conditions (i.e., AS, reactive or psoriatic arthritis, psoriatic spondylitis, IBD and undifferentiated SpA). Direct and indirect yearly costs associated with AS-associated uveitis and IBD were estimated based on interviews with French and German clinicians and literature review.

Results:
The pooled average rate of anterior uveitis (AU) flares for patients treated with anti-TNF therapy in two meta-analyses and supplemental adalimumab clinical trials was 4.9/100-patient-years (PYs). AU rates (per 100-PYs) were 3.4, 3.7 and 5.7 for infliximab ($p = 0.26$ vs etanercept; $p = 0.86$ vs adalimumab), adalimumab ($p = 0.033$ vs etanercept) and etanercept, respectively. IBD flares (per 100-PYs) were 0.2 for infliximab ($p < 0.001$ vs etanercept; $p = 0.18$ vs adalimumab), 0.63 for adalimumab ($p = 0.009$ vs etanercept) and 2.2 for etanercept. No studies assessing EAM-associated resource utilization or costs in AS patients were found. Direct medical costs associated with IBD treatment ranged from €483 (Germany) to €6443 (France). Clinician-estimated AS-related uveitis direct medical costs were €1410 (Germany) and €1812 (France).

Conclusions:
Clinical data synthesis demonstrated significantly lower AU flare rates with adalimumab vs etanercept and significantly lower IBD rates with both adalimumab and infliximab vs etanercept. Economic analysis indicated substantial costs associated with AU and IBD flares secondary to AS in France and Germany. Future economic evaluations of anti-TNF agents should incorporate EAMs and subsequent treatment costs. Limitations include restricted availability of randomized, placebo-controlled clinical trial data, inclusion of data from open-label studies, lack of real-world (i.e., non-trial-based) EAM rates and a lack of EAM-specific direct and indirect costs with which to compare the results presented herein.

Introduction

Ankylosing spondylitis (AS) is a chronic, rheumatic disease primarily associated with pain, stiffness and disability at the axial skeleton and with peripheral joint

involvement in up to 70% of patients. AS is the most common and severe form of spondyloarthritis (SpA), with an estimated prevalence of 0.2–1.2%[1,2]. Although SpA conditions like AS often affect the locomotor system, extra-articular manifestations (EAMs) can occur in up to 40% of patients[3]. The common extra-articular sites involved are the eyes (e.g. acute anterior uveitis [AU]) and the gut (e.g. inflammatory bowel disease [IBD]). Other EAMs include cardiovascular, pulmonary, renal and neurological involvement[1,3]. It has been hypothesized that AS and EAMs are linked to a mechanism involving a level of HLA-B27 allele and/or as a consequence of uncontrolled systematic inflammation[1]. Between 20–40% of patients with AS experience at least one flare of AU during the course of their disease[4,5]. Although IBD is less common, it is a more costly EAM as it is associated with early onset, chronic maintenance therapy and possibly surgery[3,6].

Tumor necrosis factor (TNF), a cytokine known to mediate pro-inflammatory activities, plays an important regulatory role in the pathogenesis of AS, a role confirmed by the successful use of TNF inhibitors as treatment[7–9]. Four anti-TNF agents are currently used to treat AS: infliximab, etanercept, adalimumab and golimumab. Although no head-to-head trials have directly compared these agents in AS, indirect comparisons suggest that they may have broadly comparable efficacy in AS[6,7,10–12]. However, differences in the rates and types of EAMs during treatment with infliximab, adalimumab and etanercept have been reported[13–16]. For golimumab, which was recently approved for the treatment of AS, no published information is currently available on the rate of EAMs.

Concomitant EAMs occurring during anti-TNF therapy for AS cause a substantial clinical burden to patients. Previous studies have attempted to compare the incidence of EAMs (whether paradoxically induced by therapy or not) using clinical trial[6,17,18] and real-world data[15,16]. Most studies included in these reviews were conducted before 2007 and had limited data for adalimumab. In addition, analyses of the economic burden associated with EAMs occurring concomitantly in AS are scarce. One early study of AS costs was conducted in three European countries (Netherlands, France and Belgium) but included no details on EAMs[19]. Most other recent European studies were from the UK[20–22]. No studies have evaluated medical resource utilization and costs associated with EAMs for French or German patients with AS[23].

The present study sought to (1) review and update estimates of concomitant uveitis and IBD in patients with primary AS treated with anti-TNF agents, (2) review economic studies of uveitis and IBD in general SpA (i.e., AS, reactive or psoriatic arthritis, psoriatic spondylitis, inflammatory bowel disease and undifferentiated spondyloarthritis) and (3) provide estimates of the medical resource utilization and costs associated with the treatment of these EAMs based on German and French experience.

Methods

EAM occurrence in AS

A literature search was conducted in PubMed/Medline (January 2000 to August 2011) to identify clinical trials, meta-analyses and reviews of anti-TNF clinical trials reporting the rate(s) of uveitis and/or IBD in patients with AS treated with infliximab, etanercept or adalimumab. The data derived from these studies were abstracted and synthesized into pooled averages. Search terms included *ankylosing spondylitis*, *IBD*, *inflammatory*, *uveitis*, *extra-articular*, *anti-TNF*, *etanercept*, *infliximab* and *adalimumab*. Studies were selected broadly if they included data with regard to patients with AS who were treated with anti-TNF agents and who had experienced one or more EAMs.

Specifically, the absolute risk reduction in the flare rates with confidence intervals was calculated for the pooled population between study drug (infliximab, etanercept or adalimumab) and placebo groups. Under the assumption that the number of events was Poisson distributed, the confidence intervals were obtained based on the relationship between the Poisson distribution and the chi-square distribution. This calculation is consistent with methods used in previously published meta-analyses[6,18,24].

Resource utilization and costs for EAMs in AS/SpA

The literature pertaining to resource utilization and the direct and indirect costs associated with EAMs in AS was also reviewed, with specific focus on IBD and uveitis. This search was supplemented by a more inclusive search of the economic burden of EAMs in non-AS SpAs (PubMed/Medline, 2000–2011) with the search terms of (cost OR 'resource utilization') AND 'extra-articular manifestation*' AND 'spondyloarthro*'. In addition to the supplemental search, individual searches were conducted whereby 'spondyloarthro*' was replaced by specific SpA indications (i.e., 'psoriatic arthritis', 'reactive arthritis', 'uveitis' or 'inflammatory bowel disease').

Given that the information on EAMs in AS/SpA was expected to be limited, a targeted literature review was also performed on resource utilization and/or costs associated with general uveitis and IBD outside of AS/SpA. This review was country-specific and focused on the literature in France and Germany.

Additionally, two French clinicians (one rheumatologist and one ophthalmologist) and one German rheumatologist with expertise in the management of AS-related

uveitis were consulted to provide detailed information on the resource use associated with the diagnosis, treatment and monitoring of patients with AS and uveitis. Responses were aggregated and then multiplied by country-specific unit costs. Direct costs per flare and yearly direct costs (assuming three flares per year per expert opinion) were estimated. The indirect cost per flare was also assessed based on the physician-estimated number of missed work days.

For cost-estimation, all cost values were adjusted and/or inflated to 2009–2010 Euros using country-specific exchange rates and healthcare components of the respective consumer price indices. Details on costing assumptions are presented in Table 1[19,25–29].

Results

EAM occurrence in AS

Ninety-nine articles were identified in the literature search. Of these, 35 were found to be potentially relevant following abstract review. Upon further assessment of the full retrieved articles of the 35 studies, three meta-analyses[6,18,24] provided the best summary of drug-specific uveitis and IBD rates and also included the relevant clinical trials found in these searches. Two recent clinical trials of adalimumab (ATLAS [NCT00085644][9] and RHAPSODY [NCT00478660][16]) provided additional information on rates of uveitis and IBD.

Uveitis

To date, the most comprehensive AS-related uveitis assessment was a comparative meta-analysis conducted by Braun *et al.*[24] on the incidence of anterior uveitis flares in patients with AS enrolled in four placebo-controlled and three open-label clinical trials of infliximab and etanercept. This analysis compared the proportions of patients who experienced a flare of anterior uveitis, of whom 297 and 90 were being treated with etanercept or infliximab for a total exposure time of 430.0 and 146.4 patient-years (PYs), respectively (Table 2)[9,16,18,24]. Another meta-analysis conducted by Sieper *et al.*[18] reported uveitis rates for etanercept based on more recent etanercept clinical trials (Table 2). Unfortunately, neither study provided uveitis flare rates in patients with AS treated with adalimumab. Therefore, Table 2 also includes updated information with data from an open-label prospective evaluation of the effect of adalimumab on anterior uveitis flares in patients with AS (RHAPSODY)[16] and a randomized, placebo-controlled trial of adalimumab (ATLAS)[9]. These two studies had comparable key design features, including inclusion and exclusion criteria, baseline characteristics of the study cohorts (e.g., mean age of 42 vs 43 years, 76% vs 71% male, mean 11-year disease duration for adalimumab treatment arm] and patients with a history of uveitis [33% vs 22%].

Uveitis flare incidence rates were different across anti-TNF agents. The rates (per 100-PYs) of AU were similar between adalimumab and infliximab (3.7 [95% confidence interval (CI): 2.6–5.2] vs 3.4 [1.1–8.0]; $p = 0.86$) but were higher for etanercept (5.7 [4.6–7.0] vs infliximab [$p = 0.26$] and vs adalimumab [$p = 0.033$]). However, all anti-TNF agents were associated with a significantly lower overall incidence of uveitis flares compared with placebo, individually and when pooled ($p < 0.05$).

IBD

Braun *et al.*[6] provided the most comprehensive meta-analysis of the incidence of flares or new-onset IBD in patients with AS being treated with infliximab, etanercept or adalimumab. This analysis synthesized data from nine studies: seven placebo-controlled clinical trials and two open-label studies (Table 3)[6,9]. A total of 1130 patients were included in these trials[6]. Table 3 also includes the incidence of IBD flares, which was updated using results from the ATLAS trial[9].

Based on the results reported by Braun *et al.*[6], both adalimumab and etanercept had a greater incidence of IBD than placebo. Only infliximab was associated with significantly lower rates of IBD compared with placebo [0.2 flares/100-PYs (95% CI: 0.0–0.9) vs 1.3 flares/100-PYs (95% CI: 0.2–4.8); $p = 0.04$). When the adalimumab incidence rate was updated with the incidence observed in the ATLAS trial, it decreased from 2.3 to 0.63 flares per 100-PYs. After this update, both adalimumab and infliximab were associated with significant IBD rate reductions compared with etanercept (both $p < 0.01$) (Table 3).

The inclusion and exclusion criteria were similar between the studies included in the Braun 2007 meta-analysis and the ATLAS study[9]. One exception was that the use of certain disease-modifying anti-rheumatic drugs, such as sulfasalazine and methotrexate, was allowed in the two etanercept studies[10,30] included in the Braun 2007 meta-analysis and in the ATLAS study. Baseline characteristics (including age, sex, race and disease duration) of the study cohorts were comparable between the studies. The percentage of patients with concomitant sulfasalazine use varied from 13% in the adalimumab-treated patients (ATLAS study) to 24%[30] and 40%[10] in the etanercept-treated patients. The Braun 2007 meta-analysis reported that 6.3%, 6.9% and 5.6% of patients had a history of IBD among those who received infliximab, etanercept and adalimumab, respectively, compared with 3% (Crohn's disease) and 4% (ulcerative colitis) reported by the ATLAS study.

Table 1. Assumptions used in the uveitis costing.

Parameter	French assumptions	German assumptions	Reference(s)
Diagnosis			
Laboratory	Directly from Literature and Expert Opinion	Directly from Literature and Expert Opinion	Expert opinion; Losch *et al.*[27]
Office visit	Cost is mean value (between societal and NHS costs of visit to ophthalmologist in France); frequency (1–2 visits/year) based on expert opinion	Cost is mean value (between societal and NHS costs of visit to ophthalmologist in Germany); frequency (1–2 visits/year) based on expert opinion	Expert opinion; Lafuma *et al.*[26]
Medication			
Dexamethasone	Per expert opinion	–	Expert opinion
Prednisolone acetate	Treatment duration based on expert opinion: 2–3 weeks per flare	Treatment duration based on expert opinion: 2–3 weeks per flare	Expert opinion
Rheumatrex	Per expert opinion: 5% of patients with uveitis will receive 5-mg methotrexate injection once a week for 12 weeks	Treatment for >8 weeks, assuming it will be given through the flare (2.5 months = 10 weeks)	Expert opinion
Decortin H	Per expert opinion: 20% of patients with uveitis will receive 1 mg/kg per day as initial dose and then decrease for 90 days	Treatment duration based on expert opinion: 2–3 weeks per flare	Expert opinion
Cyclosporin A	–	Per expert opinion: treatment for >8 weeks, assuming it will be given through the flare (2.5 months = 10 weeks); 2–5 mg/kg per day	Expert opinion
Azathioprine	–	Per expert opinion: treatment for >8 weeks, assuming it will be given through the flare (2.5 months = 10 weeks): 100 mg/day	Expert opinion
Monitoring			
Office visits	Per expert opinion: 2 ophthalmologic visits per flare for flare management	Per expert opinion: 2 ophthalmologic visits per flare	Expert opinion; Lafuma *et al.*[26]
Hospitalization	Per expert opinion: <10% of patients hospitalized and the average length of hospital stay is 7 days; average per day cost of hospital stay was literature based	Per expert: <10% of patients hospitalized and the average length of hospital stay is 7 days; average per day cost of hospital stay in a general ward was literature based	Expert opinion; Bonastre *et al.*[26] Expert opinion; Martin *et al.*[28]
Office visits for AEs	Per expert opinion: 10% of AEs are due to systemic immunosuppressant, with three additional ophthalmologist visits per year (i.e., one visit per flare) for AEs; cost was literature based	Per expert opinion: 10% of AEs are due to systemic immunosuppressant, with three additional ophthalmologist visits per year (i.e., one visit per flare) for AEs; cost was literature based	Expert opinion; Lafuma *et al.*[26]
In between flares	Per expert opinion: includes office visits and laboratory tests, assuming four additional office visits/laboratory tests per year for in-between flare monitoring for ⅓ of patients (~1.3 additional office visits/laboratory tests per flare assuming three flares per year)	Per expert opinion: includes office visits and laboratory tests, assuming four additional office visits/laboratory tests per year for in-between flare monitoring for ⅓ of patients (~1.3 additional office visits/laboratory tests per flare assuming three flares per year)	
Prophylactic treatment	Per EO expert opinion ⅓ of patients will additionally receive the same treatment listed under 'Medication'	Per expert opinion: ⅓ of patients will additionally receive the same treatment listed under 'Medication'	Expert opinion
Indirect costs			
Missed work days	Per expert opinion: 50% of patients will miss 3 days per flare; 50% will miss 9 days; wages lost per day was literature based	Per expert opinion: 50% of patients will miss 3 days per flare; 50% will miss 9 days; wages lost per day was literature based	Expert opinion; Boonen *et al.*[19] Expert opinion; Sohn *et al.*[29]

NHS, National Health Service.

Table 2. Summary of the incidence of anterior uveitis in anti-TNF studies.

Agent	*n*	Exposure (PY)	AU flares (*n*)	Flares/100-PYs (95% CI)*	Absolute rate reduction vs placebo (95% CI)*
Braun *et al.*[24] meta-analysis					
Placebo	190	70.5	11	15.6 (7.8–27.9)	
Infliximab	90	146.4	5	3.4 (1.1–8.0)	12.2 (4.5–19.9)
Etanercept	297	430	34	7.9 (5.5–11.1)	7.7 (0.1–15.2)
Anti-TNF total	387	576.4	39	6.8 (4.8–9.2)	8.8 (2.0–15.7)
ATLAS and RHAPSODY[9,16]†					
Adalimumab	1561	917	34	3.7 (2.6–5.2)	–
Sieper *et al.*[18] meta-analysis					
Placebo	249	83.0	10	12.0 (5.8–22.2)	
Etanercept	1074	1136.9	55	4.8 (3.6–6.3)	7.2 (2.1–12.4)
Summary of Braun *et al.*[24], ATLAS & RHAPSODY[9,16], and Sieper *et al.*[17]					
Total placebo	439	153.5	21	13.7 (8.5–20.9)	
Total infliximab	90	146.4	5	3.4 (1.1–8.0)	10.3 (3.6–16.9)
Total etanercept	1371	1566.9	89	5.7 (4.6–7.0)	8.0 (3.8–12.2)
Total adalimumab	1561	917	34	3.7 (2.6–5.2)	10.0 (6.1–13.8)
Total anti-TNF	3022	2630.3	128	4.9 (4.1–5.8)	8.8 (5.0–12.6)

*Updated statistical comparisons (*p*-values were calculated using chi-square tests) were infliximab vs total placebo: $p = 0.0025$; Total etanercept vs total placebo: $p = 0.0002$; Total adalimumab vs total placebo: $p \leq 0.001$; Total infliximab vs total etanercept: $p = 0.26$; Total infliximab vs total adalimumab: $p = 0.86$; and total etanercept vs total adalimumab: $p = 0.033$. Adalimumab 95% CI was calculated based on the normal distribution.
† For adalimumab only, including the ATLAS study[9] (1.9 flares/100-PYs with a cumulative exposure of 622-PYs) and RHAPSODY study[16] (7.4 flares/100-PYs with a cumulative exposure of 295-PYs). Placebo uveitis data were not reported in these two studies.

Table 3. Summary of the incidence of IBD in anti-TNF studies.

Agent	*n*	Exposure (PY)	IBD flares (*n*)	Flares/100-PYs (95% CI)	Absolute rate reduction vs. placebo (95% CI)*
Braun *et al.*[6]					
Placebo	434	150.4	2	1.3 (0.2–4.8)	
Infliximab	366	618	1	0.2 (0.0–0.9)	1.2 (0.1–2.3)
Etanercept	419	625.4	14	2.2 (1.2–3.8)	−2.0 (–5.1–1.1)
Adalimumab	295	132.3	3	2.3 (0.5–6.6)	−0.9 (−4.0–2.2)
Anti-TNF total	1080	1375.7	18	1.3 (0.8–2.1)	0.0 (−1.9–1.9)
Updated with ATLAS[9]†					
Adalimumab	606	794.3	5	0.63 (0.2–1.5)‡	0.7 (−0.8–2.2)
Anti-TNF total	1391	2037.7	20	1.0 (0.6–1.5)	0.3 (−1.3–2.0)

*Updated statistical comparisons (*p*-values were calculated using chi-square tests) were infliximab vs placebo: $p = 0.04$; etanercept vs placebo: $p = 0.49$; adalimumab vs placebo: $p = 0.68$; infliximab vs etanercept: $p < 0.001$; infliximab vs adalimumab: $p = 0.18$; and etanercept vs adalimumab: $p = 0.009$.
†For adalimumab only. Placebo IBD data were not reported in the ATLAS study[9].
‡95% CI was calculated based on the Poisson distribution.

Resource utilization and costs for EAMs in AS/SpA

Although reviews were available on the clinical burden of EAMs in patients with AS, no studies specifically evaluated the economic burden of EAMs associated with AS. A supplemental review of EAM-associated resource utilization and costs in other SpAs identified more than 200 studies. However, none of these studies was ultimately included due to insufficient information on EAMs. EAMs were rarely discussed and the resource utilization/costs related to EAMs were not quantified.

Boonen *et al.*[19] conducted an analysis of expenditures related to AS treatment in France, Belgium and the Netherlands. Although EAMs were not the focus of the analysis, 6%, 15% and 4% of patients in the Netherlands ($n = 71$), France ($n = 68$) and Belgium ($n = 53$), respectively, were being treated for concomitant uveitis during the study. However, only drug costs for uveitis were considered. Additionally, 10% and 8% of patients with AS in the Netherlands and Belgium, respectively, reported concomitant IBD. Having comorbid IBD was associated with greater total direct AS costs (HR: 1.89 [95% CI: 1.09–3.23]). However, IBD-specific costs were not reported.

Resource utilization and cost of uveitis and IBD in France and Germany

Literature review results

Given that no studies specifically evaluating the resource utilization and costs of uveitis and IBD associated with AS

Table 4. Direct and indirect costs associated with an IBD event in AS patients (in 2010 Euros).

	France[31] ($n=258$)* Mean per-patient cost over 6 weeks	Germany[32] ($n=483$)† Mean per-patient cost over 4 weeks
Total direct medical cost	€6443	€483
Diagnosis	€3222	NR
Outpatient physician consults	€100	€42
General practitioner	€48	NR
Gastroenterologist	€52	NR
Non-physician consults	NR	€14
Hospitalization	€3095	€77‡
Planned	€747	NR
Unplanned	€2374	NR
Medications	NR	€314
Special diet	NR	€15
Other medical products	NR	€18
Other expenditures	NR	€3
Indirect costs	€176‡	€877
Short-term productivity losses	€176‡	€238
Long-term productivity losses	NR	€639
Direct non-medical costs	NR	€52
Household support	NR	€18
Patient activities	NR	€19
Transportation	NR	€18

NR, not reported.
*For France, 30% of respondents had been hospitalized and/or were inpatients.
†For Germany, costs were estimated based on an outpatient survey.
‡Measured retrospectively for the previous 3 months.

were identified, resource utilization data for a general uveitis and IBD diagnosis (i.e., not limited to patients with concomitant AS) were extracted from the literature. Country-specific unit costs were applied accordingly to obtain cost estimates.

Few relevant articles that assessed resource utilization/costs in France and Germany on IBD irrespective of AS were identified[31,32]. Treatment costs for French patients were based on an analysis by Rolland *et al.*[31] of patients with IBD (Crohn's disease, ulcerative colitis and chronic unclassifiable colitis); the proportion with AS was unknown (Table 4)[31,32]. Questionnaires ($n=258$) were collected from patients, general practitioners and gastroenterologists.

German costs were estimated based on a 2006 analysis of outpatient-reported cost diaries reported by Stark *et al.*[32] (Table 4). As in the sample of French patients with IBD, the proportion of patients with AS in the German sample was unknown, although Stark *et al.*[32] reported that 8% of patients with IBD had rheumatologic disease, including AS, psoriasis and arthritis.

Costs were notably different between French and German sources, owing to the different cost components included and possible differences in IBD severity (i.e., as indicated by proxy with hospitalization rate) between the study populations (Table 4). The cost differential also may reflect changes in the management of IBD over time, as the analysis by Rolland *et al.*[31] was conducted before the introduction of biologic therapies. Based on the French analysis, diagnostic and hospital costs were the cost drivers; high inpatient costs suggested that the costs related to inpatient surgical procedures contributed greatly to the total[31]. In the German report, only outpatients were sampled and inpatient costs were retrospectively estimated[32]. In addition, the German estimate of indirect IBD costs included wages lost, productivity lost and costs related to early retirement, whereas the French IBD-related indirect cost estimate included only wages lost. Accordingly, the German estimate of indirect IBD costs was considerably higher.

Cost of uveitis based on expert opinion

Table 5 summarizes the uveitis-related resource utilization and costs per year estimated by French and German physicians. Responses and overall uveitis-related diagnosis, medication and indirect costs were consistent between countries. Differences in non-drug medical costs were driven by the greater unit costs for hospitalization and office visits in Germany. Medication costs were minimal, contributing less than 5% of the total direct cost.

Discussion

To date, the anti-TNF-related EAM burden in patients with AS has not been studied in great detail. The current review updated previous meta-analyses by including data from more recent clinical trials of adalimumab and by estimating the resource utilization and subsequent treatment costs associated with IBD and uveitis treatment. These findings highlight differences in rates of uveitis and IBD across anti-TNF medications used to treat AS and the substantial costs associated with these EAMs.

Based on the most recent adalimumab trials[9,16], the present analysis revealed that the incidence of AU among patients with AS treated with infliximab was 3.4 flares/100-PYs [95% CI: 1.1–8.0], which is comparable to that with adalimumab (3.7 flares/100-PYs [95% CI: 2.6–5.2]. The incidence of AU in adalimumab-treated patients was significantly lower than that observed in etanercept-treated patients (5.7 flares/100-PYs [95% CI: 4.6–7.0]; $p=0.033$). The pooled sample size of infliximab ($n=90$) is notably smaller than the sample sizes for etanercept ($n=1371$) and adalimumab ($n=1561$), which may explain why the rate of uveitis flares with infliximab was not significantly different compared with etanercept. With respect to IBD, the cumulative follow-up time used to calculate IBD rates for etanercept and infliximab was more than 4-times greater than for adalimumab-treated patients

Table 5. Resource use and cost for patients with AS treated for uveitis (per flare) in France and Germany.*

	% Utilization		Units/Flare		Cost/Unit (€)*		Cost (€)	
	France	Germany	France	Germany	France	Germany	France	Germany
Diagnosis								
Laboratory	100	100	1.0	1.0	734.34	762.75	734.34	762.75
Office visit	100	100	1.0	1.0	34.38	44.44	34.38	44.44
Subtotal	–	–	–	–	–	–	768.72	807.19
Medication								
Dexamethasone	100	NA	3.0	NA	2.57	NA	7.71	NA
Prednisolone acetate	20	95	360.0	1.0	0.23	14.88	16.67	14.14
Rheumatrex	5	5	12.0	10.0	2.27	35.20	1.36	17.60
Decortin H	NA	5	NA	25.0	NA	0.50	NA	0.63
Cyclosporin A	NA	5	NA	686.0	NA	1.11	NA	37.92
Azathioprine	NA	5	NA	140.0	NA	0.53	NA	13.15
Subtotal	–	–	–	–	–	–	25.74	83.44
Non-drug medical services								
Office visits	100	100	2.0	2.0	34.38	44.72	68.76	89.44
Hospitalization	5	5	7.0	7.0	554.63	1247.77	194.12	436.72
Office visits for AEs	10	10	1.0	3.0	34.38	44.44	3.44	13.33
In between flares	33	33	1.3	1.3	768.72	807.19	338.24	346.29
Prophylactic treatment	33	33	1.3	1.3	25.74	83.44	11.04	35.61
Subtotal	–	–	–	–	–	–	615.60	921.39
Indirect costs								
Missed work days†	50	50	3	3	104.74	105.09	157.10	157.64
	50	50	9	9	104.74	105.09	471.31	472.92
Direct costs subtotal	–	–	–	–	–	–	1410.06	1812.02
Indirect costs subtotal	–	–	–	–	–	–	628.41	630.56
Direct and indirect costs total	–	–	–	–	–	–	2038.47	2442.58

NA, Not applicable; AE, adverse event.
Utilization refers to patients with AS diagnosed with concomitant uveitis. Totals may not sum owing to rounding.
*Details on costing assumptions are presented in Table 1.
†Assuming 50% of patients missed 3 days and 50% missed 9 days based on expert opinions.

with AS (625.4 and 618.0 PYs vs 132.3 PYs, respectively) in the previous meta-analysis conducted by Braun *et al.*[6]. Once the ATLAS study was included, follow-up time for adalimumab increased and allowed for more balanced comparisons of IBD rates per 100-PYs in which the rate for adalimumab-treated patients more closely approximated that observed for infliximab. The difference between the estimate of IBD associated with adalimumab as reported by Braun *et al.*[6] and the estimate generated when data from the ATLAS study was included highlight the importance of carefully interpreting treatment-specific EAMs, particularly when the length of follow-up is vastly different between study medications.

The efficacy of TNF inhibitors in EAMs/comorbid conditions appears to vary among agents. The updated findings on IBD occurrence are consistent with the literature. The lack of efficacy of etanercept in IBD is acknowledged in the Assessment of SpondyloArthritis International Society consensus statement for the use of anti-TNF agents[33]. In the 2011 recommendations for management for AS[34], the Society in conjunction with the European League Against Rheumatism acknowledged that, despite similar efficacy on musculoskeletal manifestations, the monoclonal antibodies work better than the fusion protein for clinically symptomatic IBD. These recommendations are consistent with the approved treatment indications; infliximab is approved for both Crohn's disease and ulcerative colitis, adalimumab is approved for Crohn's disease and data are not yet available for golimumab. This line of thinking may be extrapolated to consider other EAMs/comorbid conditions[1]. Etanercept appears to have less effect on uveitis compared with infliximab and adalimumab. In contrast, the incidence of flares for both IBD and uveitis appears to be reduced with infliximab[3,24,35–38] and adalimumab[6,15,24] treatment for AS. The differences in the mechanisms of action for these agents may explain the differences in their clinical profiles[1,39–41]. The findings on the uveitis and IBD incidence rates are biologically plausible, given the similarity between the mechanisms of action for infliximab and adalimumab[42,43].

Within real-world treatment settings, the occurrence of EAMs likely impacts treatment patterns, leading to patients discontinuing or switching medications. Although large, randomized trials assessing anti-TNF switching patterns related to EAMs have not been conducted, a number of case reports describing patients who stop or switch anti-TNF agents due to extra-articular uveitis, IBD and/or psoriasis suggest the possibility of paradoxical effects with anti-TNF agents[43–47]. The results of these

case report studies should be interpreted with caution, due to the small number of cases overall, and more research is warranted to understand immune-mediated injury induced by anti-TNF agents.

In terms of the economic burden of EAMs, no previous publications have evaluated the cost of EAMs within AS or even more broadly within SpA. Previous AS economic studies rarely have included the resource utilization and costs associated with EAMs or included only the medication costs. Based on this literature review and the supplementary survey of clinicians in France and Germany, medication costs may account for only a small portion of the total, with the medical costs related to diagnosis, monitoring and hospitalization as primary drivers. A more detailed cost assessment for EAMs should be conducted in economic studies of AS to obtain a complete picture of AS burden.

The country-specific costs presented in this review reflect literature-based inpatient and outpatient costs for French patients with IBD and outpatient costs in German patients with IBD. Country-specific uveitis costs were based on experts' opinions, which are more outpatient-based as well. Differences between outpatient and inpatient costs would be particularly important to discern, particularly in IBD, for which inpatient surgical procedures can contribute greatly to overall cost. The disparity in direct IBD-related medical costs between French and German patients was likely due to the differences in the inclusion/exclusion of medical cost components and unit costs, as well as the difference in the prevalence of EAMs. Further collection of country-specific information on EAM-associated costs in a real-world setting is an area that would benefit from further research.

The present research also has implications for economic evaluations of treatments for AS. The incremental costs of EAMs have been largely overlooked or under-estimated in previous evaluations of the cost-effectiveness of anti-TNF agents for AS treatment. Furthermore, models that fail to address the effects of EAMs on treatment adherence and switching patterns and costs might not accurately reflect real-world clinical practice. Future models should incorporate as much information as possible on the full burden of EAMs in AS, given the potential high treatment costs associated with EAMs and differences in EAM rates across anti-TNF agents.

Limitations of the present analysis include that few studies were available for review and comparison and the available studies may have been under-powered to detect differences in EAM rates between anti-TNF agents. Use of clinical trial data also is likely to impact estimates of EAM rates because patients who may be pre-disposed to EAMs, which are somewhat prevalent in real-world treatment settings, are often excluded from clinical trials of anti-TNF agents in AS. Also, it would have been optimal to use clinical data derived solely from randomized, placebo-controlled clinical trials. However, such data are scarce and it was necessary (in this analysis and previously published analyses[18,24]) to supplement placebo-controlled data with data from observational, case-controlled and open-label studies. Should more placebo-controlled data become available in the future, the results and conclusions presented herein should be compared to assess possible skewedness. Similarly, it is likely (because the present analysis was based on the pooling of previous meta-analyses) that some studies may have been counted more than once (i.e. one study was included by both Braun *et al.*[24] and Sieper *et al.*[18]). The effect of this double counting would be limited to the confidence intervals presented. Additionally, this research focused on only two of the EAMs that occur with AS, uveitis and IBD. Other conditions, such as psoriasis and enthesitis, were not included due to very few data existing in the literature. The impacts of EAMs on quality-of-life and treatment discontinuation and/or switching were not captured in the present analysis. It should also be noted that the present analysis with respect to costs associated with concomitant uveitis was based largely on expert opinion given the lack of published data. Although expert opinion is not the optimal method of selecting and generating inputs, it is commonly used and was the only option available for this portion of the analysis. All of these limitations may under-estimate the clinical and economic burden of EAMs in patients with AS. Many of these limitations could be addressed in future research. Large, randomized, head-to-head trials of anti-TNF agents would provide the most rigorous evaluation of the incidence of EAMs and differential treatment effects of the various anti-TNF agents used to treat AS. Furthermore, evaluations of the downstream impact of EAMs on treatment patterns would provide a fuller picture of the trajectory and pharmacoepidemiology of AS.

In conclusion, this data synthesis of previous meta-analyses updated with more recent clinical trial data demonstrated differences in EAM incidence rates among anti-TNF agents. AU flare rates with adalimumab were significantly lower than with etanercept and IBD rates for both adalimumab and infliximab were significantly lower than with etanercept. Further, economic evaluations revealed substantial direct and indirect costs associated with uveitis and IBD flares secondary to AS in France and Germany. The clinical and economic burden of EAMs among patients with AS may be substantially under-estimated. The potential exists to differentiate anti-TNF agents on the basis of EAM incidence and related treatment costs. Therefore, future economic

evaluations of anti-TNF agents should incorporate EAMs and subsequent treatment costs.

Transparency

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