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ORIGINAL ARTICLE

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Nonsteroidal anti-inflammatory drug use in ankylosing spondylitis—a population-based survey

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Abstract The objective of the study is to describe the use, clinical efficacy, and toxicity of nonsteroidal anti-inflammatory drug (NSAID) therapy in patients with ankylosing spondylitis (AS). A cross-sectional population study of 1,080 AS patients was carried out by a written questionnaire in the year 2000. Seventy-eight percent of AS patients had regularly taken NSAIDs for their disease 12 months prior to the study. Most AS patients commonly used diclofenac and indomethacin. AS patients were generally rather satisfied with the efficacy of their therapy where 19.1% reported complete pain control, 26.8% reported pain reduction to one quarter, and a further 34.4% reported pain reduction to one half. However, over 20% of patients taking NSAIDs still reported insufficient pain control and more than 40% changed the NSAID due to lack of efficacy. One quarter of AS patients reported severe side effects from their treatment, most commonly abdominal pain, headache and dizziness, and nausea. There was no effect on age or duration of disease on the occurrence of NSAID-related side effects. Medications were commonly ceased or changed due to inefficacy or side effects. The percentage of AS patients reporting changing their NSAID due to side effects ranged from 10.5% for celecoxib to 31.4% for indomethacin. We conclude that NSAIDs are effective in the management of inflammatory symptoms of many, but not all, patients with AS. There is a significant side effect profile, which frequently results in medication change or cessation. Anti-tumor necrosis factor therapy may reduce the need for intensive long-term NSAID therapy in AS.

Keywords Ankylosing spondylitis · Nonsteroidal anti-inflammatory drugs · Population study

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Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory, rheumatic disease characterized by inflammatory back pain due to sacroiliitis and spondylitis, peripheral arthritis, and the formation of syndesmophytes leading to ankylosis, which has long been a therapeutic challenge for clinicians. Exercise and nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of symptom control [1–3], but there has until recently been a dearth of disease-modifying treatments. The advent of biological therapies has revolutionized the management of AS [4], but these therapies bring with them a significant cost and side effect profile. At this time, NSAIDs remain the standard therapeutic choice for AS. NSAIDs are well recognized as useful for symptom control and this efficacy has been one of the diagnostic criteria for AS specified in the Amor classification criteria [5, 6]. Symptoms recur on withdrawal [5], requiring prolonged or repeated therapy during the course of the disease. Problems arise with the recognized risk of gastrointestinal (GI) side effects in 10–60% [7] of patients, and a 2–4% risk of serious GI complications over 12 months of therapy [8]. The introduction of Cyclooxygenase-2 (Cox-2) inhibitors is thought to have brought a reduced risk of such side effects [9], but their efficacy and toxicity in the AS population has not been well described. This study aims to look at current practice such as patient preferences for NSAID preparations, including coxibs, in the management of AS and the incidence of self-reported side effects in this population with chronic disease.

Materials and methods

A population survey was carried out by way of a questionnaire published in the newsletters of the German AS Society (Deutsche Vereinigung Morbus Bechterew, DVMB) and the Austrian AS Society (Österreichische Vereinigung Morbus Bechterew, ÖVMB) in 2000. It was distributed to all of the 14,127 and 1,077 patient members of these societies, respectively. Baseline characteristics of the cohort and the wording of the questionnaire have been published previously [10, 11]. Individuals were asked to describe the use of NSAID as medication over the course of their disease: (1) how effective the medications were, (2) changes made to NSAID therapy, and (3) the occurrence of severe side effects due to this therapy. The term severe was not further defined and so reflects the patients' self-perception of how NSAID side effects affect their health.

The survey sample included all patients who gave their primary diagnosis as AS, with or without any other associated conditions. Patients who did not indicate that their diagnosis was arrived at or confirmed by a physician were excluded from the survey.

The significance of the percentage differences was determined by the chi-squared test for two-by-two tables, and odds ratios (OR) calculated for binary variables. The differences between means were tested by the *t* test. Logistic regression analysis was carried out using a backward method. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 11.0.

Table 1 NSAID use in AS and disc prolapse patients in the previous 12 months

NSAID	AS	DP	χ^2	*p*
Any NSAID	842 (78.0%)	74 (72.5%)	1.101	0.18
Number of NSAIDs			3.864	0.70
0	238 (22.0%)	28 (27.5%)		
1	627 (58.1%)	55 (53.9%)		
2	156 (14.4%)	12 (11.8%)		
3	48 (4.4%)	6 (5.9%)		
4 or more	11 (1.1%)	1 (1.0%)		
Celebrex	30 (2.8%)	5 (4.9%)	5.134	0.27
Up to 200 mg daily	15 (1.4%)	1 (1.0%)		
400 mg or more daily	15 (1.4%)	4 (3.9%)		
Diclofenac	394 (36.5%)	28 (27.4%)	25.316	<0.0001*
Up to 50 mg daily	127 (11.8%)	4 (3.9%)		
100 mg daily	163 (15.1%)	4 (3.9%)		
150 mg or more daily	104 (9.7%)	20 (19.6%)		
Ibuprofen	124 (11.5%)	31 (30.4%)	63.572	<0.0001*
Up to 600 mg daily	65 (6.0%)	8 (7.8%)		
1,200 mg daily	33 (3.1%)	5 (4.9%)		
1,800 mg or more daily	26 (2.4%)	18 (17.7%)		
Indomethacin	152 (14.1%)	8 (7.8%)	12.475	0.014
Up to 50 mg daily	68 (6.3%)	0 (0%)		
100 mg daily	47 (4.4%)	1 (1.0%)		
150 mg or more daily	37 (3.4%)	7 (6.9%)		
Meloxicam	59 (5.5%)	8 (7.8%)	3.585	0.47
Up to 7.5 mg daily	23 (2.1%)	2 (2.0%)		
15 mg or more daily	36 (3.5%)	6 (5.8%)		
Naproxen	22 (2.0%)	5 (4.9%)	13.38	0.004*
Up to 500 mg daily	17 (1.6%)	2 (2.0%)		
1,000 mg daily	2 (0.2%)	0 (0%)		
1,500 mg or more daily	3 (0.3%)	3 (2.9%)		
Piroxicam	90 (8.3%)	4 (3.9%)	8.16	0.043
Up to 10 mg daily	21 (1.9%)	2 (2.0%)		
20 mg or more daily	69 (6.4%)	2 (2.0%)		
Rofecoxib	119 (11.0%)	12 (11.8%)	6.03	0.11
Up to 12.5 mg daily	39 (3.6%)	1 (1.0%)		
25 mg daily	60 (5.6%)	6 (5.9%)		
50 mg or more daily	20 (1.9%)	5 (4.9%)		
Other	144 (13.3%)	1 (1.0%)	13.21	<0.0001*

*Statistically significant difference in proportions, $p<0.005$ (Bonferroni correction)

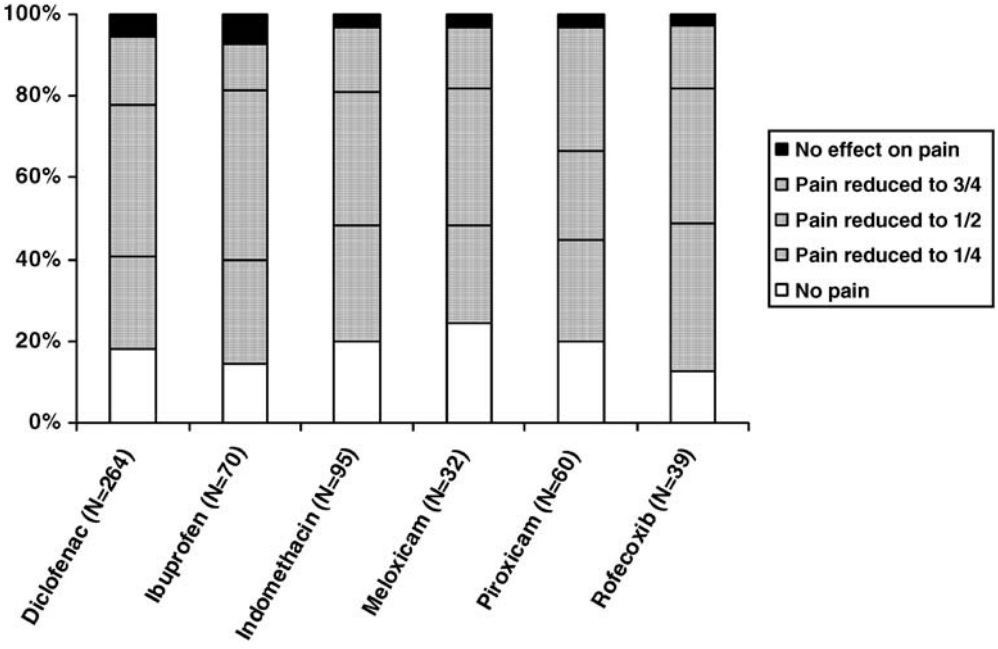

Fig. 1 Efficacy of different NSAID preparations (%) in AS patients

Results

The cohort had a mean age of 49.8 years (range 21–86 years), mean age on the onset of disease of 25.2 years (range 6–68 years), and mean disease duration of 24.6 years (range 0–66 years). As expected, most AS patients reported being human leukocyte antigen (HLA) B27 positive (79%), although a further 12.5% were unaware of their B27 status. Two-thirds reported they had peripheral arthritis (N=714, 66.1%) and 98 (9.1%) patients said they had concomitant inflammatory bowel disease. Sixty-four percent of the group were male (N=687).

Approximately three quarters of the study group reported using NSAIDs for their disease (N=843, 78.1%). Most had been treated for more than 4 years (N=602, 71.4%). The distribution of NSAID use in the past 12 months is given in Table 1. AS patients most commonly used diclofenac and indomethacin, and frequently used NSAIDs not specifically mentioned in our questionnaire.

NSAID therapy is rather effective in most patients with AS where 19.1% of the patients reported complete pain relief, 26.8% reported pain reduction to 25%, and a further 34.4% reported reduction to 50%. Only 3.6% reported no analgesia from current NSAID therapy. AS patients who reported a poorer result from NSAID therapy also reported more hours of pain each week (χ^2=173.99, p<0.0001) and more days of pain each year (χ^2=124.12, p<0.0001).

AS patients who were HLA B27 positive were as likely to respond to NSAIDs (pain reduced to half or less) as HLA B27 negative AS patients (χ^2=1.93, p=0.17) and NSAID response was not related to the presence of peripheral arthritis (χ^2=2.06, p=0.15).

There was no difference in NSAID efficacy between males and females (χ^2=0.61, p=0.43) in AS patients with a

Table 2 Odds ratios for efficacy (pain reduction of 50% or more) with different NSAID preparations

NSAID preparation	Comparison NSAID	Odds Ratio	95% CI	χ^2 statistic	p value
Indomethacin	Rofecoxib	0.94	0.37–2.41	0.00	1.00
	Diclofenac	1.23	0.69–2.21	0.30	0.58
	Ibuprofen	0.98	0.45–2.13	0.00	1.00
	Meloxicam	0.95	0.35–2.58	0.00	1.00
	Piroxicam	2.14	1.03–4.46	3.37	0.07
Rofecoxib	Diclofenac	1.32	0.56–3.06	0.17	0.68
	Ibuprofen	1.04	0.39–2.80	0.00	1.00
	Meloxicam	1.02	0.32–3.26	0.00	1.00
	Piroxicam	2.29	0.88–5.94	2.10	0.15
Diclofenac	Ibuprofen	0.79	0.41–1.53	0.21	0.60
	Meloxicam	0.77	0.31–1.91	0.10	0.75
	Piroxicam	1.74	0.95–3.18	2.63	0.11
Ibuprofen	Meloxicam	0.97	0.35–2.77	0.00	1.00
	Piroxicam	2.19	0.99–4.86	2.98	0.08
Meloxicam	Piroxicam	2.25	0.82–6.15	1.73	0.19

*Statistically significant difference in proportions, p<0.005 (Bonferroni correction)

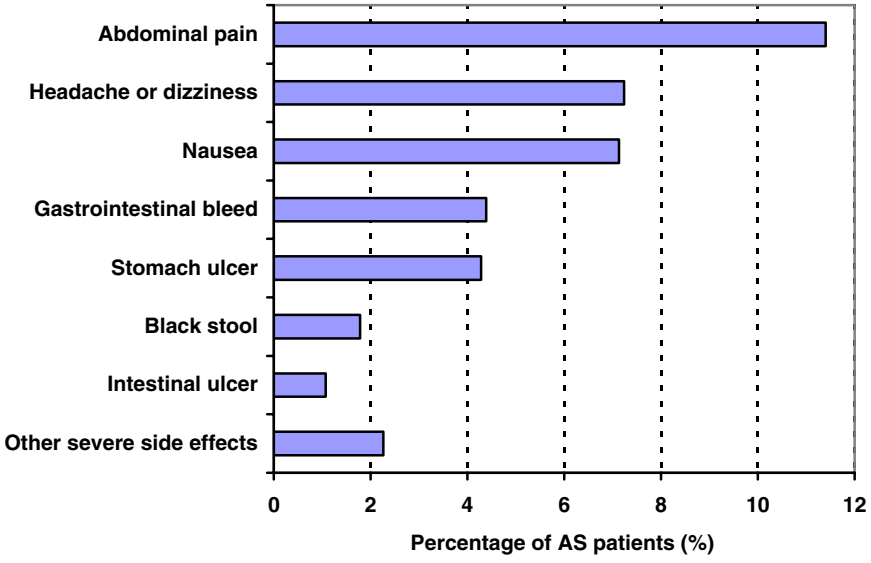

Fig. 2 Distribution of severe side effects due to NSAIDs therapy in AS (*N*=842)

similar proportion of males and females reporting improvements in symptoms of 50% or more. AS patients who reported effective pain relief from their NSAIDs were of similar age (mean difference: 0.8 years, 95% confidence interval (CI): 1.6 to 3.2 years, p=0.5) and had a similar disease duration (mean difference: 0.3 years, 95% CI: 2.3 to 2.8 years, p=0.8) compared to those who reported minimal pain relief. The distribution of pain relief with different NSAID preparations is shown in Fig. 1. Naproxen (*N*=13) and celecoxib (*N*=11) are not shown due to the small number of patients.

The relative efficacy of each NSAID preparation is shown in Table 2 where 'efficacy' is measured as an improvement in pain of 50% or more. There are no significant differences in efficacy between NSAID preparations in this study. Naproxen and celecoxib were not significantly different from any of the other preparations (all p>0.2), and have again not been shown due to the small number of patients. There was no significant difference in the efficacy between nonselective NSAIDs and the newer Cox-2 inhibitors celecoxib and rofecoxib, although the number of patients was quite small and was not able to show small differences.

Distribution of side effects

One quarter (24.9%) of AS patients who have taken NSAIDs for their disease (*N*=842) reported 'severe' side effects due to their medication. The distribution is shown in Fig. 2.

Female AS patients were more likely to report severe side effects from NSAID therapy than male AS patients (OR: 1.6, 95% CI: 1.2–2.2, p=0.004). HLA B27 positive status did not confer an increased risk of side effects (OR: 0.8, 95% CI: 0.5–1.4, p=0.57). There was no significant difference in age (mean difference: 1.4 years, 95% CI: 0.4–3.28, p=0.13) or disease duration (mean difference:

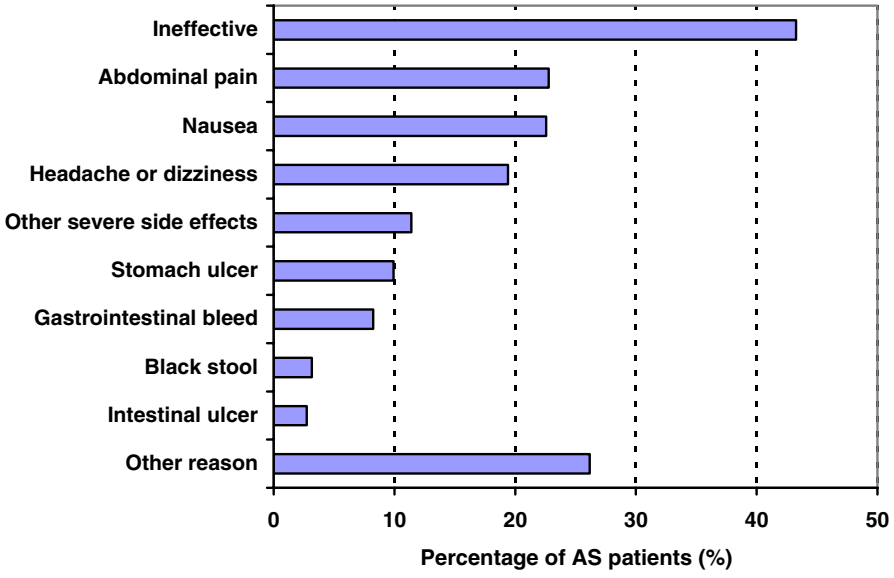

Fig. 3 Distribution of reasons for NSAID therapy change (*N*=474)

Table 3 Proportion of AS patients changing one NSAID preparation for another in the year prior to the study

Number of AS patients	Changing from NSAID	Changing due to severe side effects	Remaining on therapy	Proportion changing therapy (%)	Proportion changing due to side effects (%)
Celecoxib	8	4	30	21.1	10.5
Diclofenac	219	140	394	35.7	22.8
Ibuprofen	96	55	124	44.0	25.0
Indomethacin	135	90	152	47.0	31.4
Meloxicam	46	28	59	43.8	26.7
Naproxen	15	10	22	40.5	27.0
Piroxicam	72	39	90	44.4	24.1
Rofecoxib	39	25	119	24.7	15.8

1.7 years, 95% CI: 0.2–3.6, p=0.08) between AS patients reporting NSAID side effects and those who did not report any side effect.

Reasons for cessation

Four hundred and seventy-four AS patients (57.3%) reported changing their NSAID during the course of treatment. Of these, 268 (56.5%) changed due to severe side effects and 205 due to inadequate pain relief (43.2%). The distribution of side effects and other factors necessitating therapy change is shown in Fig. 3.

Changing NSAID therapy for any reason was not related to gender or HLA B27 status (all p>0.1). AS patients reporting changing NSAID therapy were younger (mean difference: 1.7 years, 95% CI: 0.04–3.37 years, p=0.045) and had a shorter duration of disease (mean difference: 1.7 years, 95% CI: 0.03–3.41 years, p=0.046) than those AS patients who did not change therapy. The proportion of AS patients who reported changing NSAID since the beginning of their therapy is given in Table 3.

The Cox-2 inhibitors celecoxib and rofecoxib showed the lowest proportion of AS patients developing severe side effects leading to cessation of medication. The odds of developing severe side effects were significantly higher

Table 4 Odds ratios for severe side effects requiring cessation of therapy with different NSAID preparations

NSAID preparation	Comparison NSAID	Odds Ratio	95% CI	χ^2 statistic	p value
Indomethacin	Celecoxib	5.58	1.99–15.58	10.82	0.0001*
	Rofecoxib	3.50	2.12–5.76	24.12	<0.0001*
	Diclofenac	2.69	1.95–3.72	36.24	<0.0001*
	Ibuprofen	1.97	1.32–2.95	10.28	0.001*
	Meloxicam	1.81	1.09–2.99	4.73	0.03
	Naproxen	1.77	0.83–3.79	1.65	0.20
	Piroxicam	2.07	1.33–3.24	9.65	0.002*
Celecoxib	Rofecoxib	0.63	0.21–1.85	0.33	0.57
	Diclofenac	0.40	0.15–1.09	2.48	0.12
	Ibuprofen	0.35	0.13–1.00	3.07	0.08
	Meloxicam	0.32	0.11–0.96	3.31	0.07
	Naproxen	0.32	0.10–1.08	2.36	0.12
	Piroxicam	0.37	0.13–1.07	2.59	0.11
Rofecoxib	Diclofenac	0.64	0.40–1.01	3.27	0.07
	Ibuprofen	0.56	0.34–0.95	4.11	0.04
	Meloxicam	0.52	0.28–0.95	3.96	0.047
	Naproxen	0.51	0.22–1.16	1.85	0.17
	Piroxicam	0.59	0.34–1.03	2.91	0.09
Diclofenac	Ibuprofen	0.89	0.62–1.27	0.31	0.58
	Meloxicam	0.81	0.51–1.30	0.53	0.47
	Naproxen	0.80	0.38–1.67	0.15	0.70
	Piroxicam	0.93	0.62–1.40	0.05	0.82
Ibuprofen	Meloxicam	0.92	0.54–1.55	0.04	0.85
	Naproxen	0.90	0.42–1.95	0.003	0.95
	Piroxicam	1.05	0.66–1.68	0.008	0.93
Meloxicam	Naproxen	0.98	0.43–2.25	0.000	1.00
	Piroxicam	1.15	0.66–2.01	0.11	0.74
Naproxen	Piroxicam	1.17	0.53–2.60	0.03	0.87

*Statistically significant, p<0.005 (Bonferroni correction)

with indomethacin than with either of the Cox-2 inhibitors (p=0.0001), but comparisons of different nonselective NSAID preparations did not reach statistical significance (Table 4).

Discussion

This large population-based study of NSAID use in AS is of interest because NSAID therapy is the main treatment for AS patients and data on daily care of such patients are limited. It is well documented that NSAID and Cox-2 inhibitor therapy is effective for spinal symptoms in AS [12–14]. Response to NSAIDs is sufficiently reliable to be included in the Amor classification criteria for AS [5] with a positive predictive value of 34% and a negative predictive value of 97% [6].

The data of this study indicate that anti-inflammatory therapy is effective for symptom control associated with patient satisfaction in about 80% of the reports received. This percentage is likely to be an overestimate as efficacy was reported by those patients who indicated they had only used one NSAID in the previous year, thus, excluding patients who may have tried multiple NSAID preparations because of inefficacy over that time. It needs to be recognized that a large proportion of patients reported insufficient pain relief from one or more of their medications during the course of their NSAID therapy, and many patients change therapy because of lack of efficacy. Furthermore, a high proportion of AS patients suffers relevant side effects, necessitating a change of NSAID therapy. These factors contribute to the burden of disease AS patients are carrying [15, 16].

To our knowledge, this is the first study to look at patient preferences for NSAID use in AS. It is quite certain that the preparations each patient used are in part determined by their physicians' prescribing preferences, but the high rate of NSAID switching and the availability of over-the-counter NSAIDs dilutes this effect as patients find the most effective therapy for their needs.

We have described a significant rate of self-reported GI toxicity associated with NSAID therapy in AS patients. In general, up to 50% of patients taking NSAIDs report nonserious GI intolerance [17] and 1–4% of chronic NSAID users experience a potentially life-threatening peptic ulcer complication [18]. The duration of NSAID therapy is more important than the preparation used in determining GI toxicity [19], although indomethacin is associated with the highest risk and was preferred by our cohort for pain relief. Patients taking Cox-2 inhibitors reported similar pain relief to patients taking nonselective NSAIDs, and the reported incidence of GI side effects was significantly lower than for many nonselective NSAIDs. AS patients can anticipate many years of NSAID therapy, and it is important to assess other factors contributing to GI toxicity such as older age, higher doses, and concomitant corticosteroid use [20] when individualizing therapy.

The strengths of this study lie in its size, the novel approach of describing patient preferences for therapy, and self-reported side effects, which brings relevance to everyday practice. The number of questionnaires returned represents only a relatively small proportion of the AS population sampled, but demographic data were consistent with a previous DVMB membership survey [20–22] where 20% of the population were sent personal mailings and the response rate was much higher at 54%, supporting the generalizability of the current results. Compared to other European studies on AS, our cohort showed a similar mean age on the onset of disease [23, 24] and prevalence of HLA B27 positivity [25], but was overrepresented by female respondents, the more common male to female ratio being 4:1 to 5:1 [26, 27].

There remains the problem of responder bias inherent to any population survey, which may bring a disproportionate number of patients who have experienced side effects returning the questionnaire. However, the survey encompassed many different aspects of AS, diluting the specific bias toward those unhappy with NSAID therapy. Similarly, there is the possibility of left censorship as those patients suffering the worst side effects (e.g., fatal GI bleeding or current hospitalization) may have failed to respond. Self-reported side effects are problematic as they have not been verified by a physician and it may be that the 'severe' events reported seemed severe to the patient but do not fulfill the accepted medical definition of what is 'serious' (requiring hospitalization or causing significant disability) used in classical drug trials and adverse event reporting. This study is a survey of patient experiences, nevertheless, the reported incidence of serious GI toxicity is consistent with previous studies with stricter event definitions, supporting the validity of our results.

Illness cognition theory draws on three models of coping with chronic disease: helplessness, acceptance, and perceived benefits [28]. In light of this, depending on the individual coping mechanisms employed, a patient with AS might overemphasize the negative aspects of disease such as lack of medication efficacy and severity of side effects, or focus on positive features such as pain relief. Both reactions will impact on the results of this study, causing biases in opposite directions, and without detailed information on illness behavior and expectancy in AS, it is not possible to assess the magnitude of these biases. This opens a new avenue of research into the effect of AS on the individual.

Recent advances in the therapy of AS have moved away from symptomatic control and toward disease modification. The advent of tumor necrosis factor (TNF) therapy is exciting, being the first group of drugs proven to have a dramatic effect on the underlying disease process [29, 30]. This brings the potential to minimize the NSAID requirements in AS, and subsequently reduce the incidence of NSAID-related complications. At present the cost of anti-TNF therapy is a major barrier to its everyday use, and it is likely that NSAIDs will continue to have an important role in the management of patients with AS. The ASsessment in AS recommendations for anti-TNF treatment in AS [31] have already pointed out that the tolerability of high NSAID doses, which are required in severely affected

patients may be limited, and that anti-TNF therapy should be considered earlier in such patients.

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