

Use of Synthetic and Biological DMARDs in Treatment of Ankylosing Spondylitis at a University Hospital

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Abstract

Aim: Sulphasalazine is used widely as a second-line treatment of ankylosing spondylitis (AS) after non-steroidal anti-inflammatory drugs (NSAIDs) in Finland. The objective of this study is to evaluate the use of disease-modifying anti-rheumatic drugs (DMARDs) and drug survival in incident AS patients at Helsinki University Central Hospital (HUCH).

Method: We identified all incident patients with AS in the hospital register from 1 Jan 2005 to 31 Dec 2009. The index day was defined as the date of AS diagnosis. Medication and clinical data were evaluated until the end of 2010.

Results: 176 patients were identified. For 165 of them a DMARD was started. In 9 patients with low disease activity the drug treatment consisted only of NSAIDs. Sulphasalazine was the first synthetic DMARD for 157 (95%) patients. No one was prescribed a biologic drug as the first DMARD. The mean follow-up time was 3.8 years. The mean synthetic DMARD survival was 80%. Bath AS Disease Activity Index (BASDAI) available from 46 patients was 4.1 (1.8) at baseline and decreased by 1.6 (95% CI 2.2-1.1, $p < 0.001$) during the DMARD treatment. Because of continuing disease activity, 28 (17%) patients became eligible for reimbursement of biological DMARDs and a TNF inhibitor was instituted. This was predicted by peripheral disease, higher ESR, and CRP at the baseline.

Conclusion: Most patients with incident AS do fairly well with synthetic DMARDs but the proportion of the patients needing biological DMARD treatment grows over time. Use of synthetic DMARDs may reduce or postpone the need for biological DMARD treatment in AS.

Keywords: Sulphasalazine; Methotrexate; Etanercept; Adalimumab; Ankylosing spondylitis

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease causing back pain due to inflammation in sacroiliac joints and spine. Peripheral joints are less frequently affected. When untreated, AS causes marked structural damage in spine and is also a threat to work productivity [1,2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for AS [3], and a significant proportion of AS patients cope with NSAIDs and non-pharmacological treatments.

The efficacy of either sulphasalazine or methotrexate is not well documented in AS [4]. Sulphasalazine has shown some effect especially in the AS patients with peripheral arthritis [5] but this has not been found in all [6,7] studies. Methotrexate has been tried in patients with AS [8], but generally it has not been an effective treatment of AS [9-11].

The biological drugs targeted to tumour necrosis factor (TNF) have proved to be very effective in AS, and have become an important albeit costly option during the 2000's [12]. In Finland, however, especially sulphasalazine is still widely used as a second line treatment in AS [13], if NSAIDs are not effective enough. This is partly due to the drug reimbursement regulations of the Social Insurance Institution (SII). The Finnish hospitals are responsible for financing intravenous medications such as infliximab, whereas the subcutaneous anti-TNF blockers are reimbursed by the SII after a medical examiner has verified the proper need of this treatment. To become eligible to reimbursement of a biological DMARD in mid-2000's a patient with AS had to have received at least two synthetic DMARDs with insufficient effect or side effects, but nowadays use of one synthetic DMARD is required before a biological DMARD can become reimbursed.

Published data on the usage of synthetic DMARDs in the treatment of AS in clinical practice are scarce. To diminish this shortage, we examined the use of synthetic and biological DMARDs in the treatment of AS in patients referred to the Helsinki University Central Hospital (HUCH).

Methods

Patient cohort

From the patient registry of HUCH we identified by the ICD-10 code of M45 all the patients with ankylosing spondylitis who visited the HUCH outpatient clinic of rheumatology between January 1st 2005 and December 31st 2009. We gathered the patients with newly diagnosed AS in our clinic. The diagnosis was based on and X-ray or MRI and clinical examination. The medication started for treatment of AS was assessed and followed up until December 31st 2010. We focused on synthetic and biological DMARDs.

In HUCH, the criterion to start a biological DMARD is active disease after a failure of prior DMARD(s). The activity is defined by the Bath AS Disease Activity Index (BASDAI) (at least 4/10) and by expert opinion based on clinical features and laboratory findings. The values of BASDAI were not routinely entered into the records of HUCH before 2007. Thus, treatment response with BASDAI was available only in a part of patients and analysed as a subgroup.

Statistical methods

The data are presented as means with standard deviations, medians with interquartile range or counts with percentages. The 95 per cent confidence intervals are given for the most important outcomes. Statistical comparison between the groups was performed by t-test, permutation test or chi-Square test, when appropriate. Analysis of drug survival was performed using the Kaplan-Meier method, with differences compared by the permutation type log-rank test. The 95% confidence bands for the Kaplan-Meier estimate were calculated using the bootstrap method. A Cox proportional hazards regression model with robust estimate of variance served to estimate hazard ratios (HR). The proportional hazard assumptions were tested using Schoenfeld residuals and natural logarithm of follow-up time.

Ethical considerations

The data were collected retrospectively from the records of HUCH and patients were not contacted. Thus, no legal requirement for approval by an ethics committee was needed.

Results

From January 1st 2005 to December 31st 2009, 176 incident patients with AS were found in the HUCH. Nine of them had low disease activity and were prescribed only NSAIDs. Thus, they were excluded from the further analysis. One patient was not compliant to any synthetic DMARD, and another refused to start synthetic DMARD due to a planned pregnancy. Thus 165 patients, 92 (56%) male and 73 (44%) female, were included and followed-up until December 31st 2010. Most patients (72%) had an axial disease. None started any biological drug at baseline. Sulphasalazine was the most common first synthetic DMARD (157 patients). We have no structured data on simultaneous use of NSAIDs.

The mean follow-up time was 3.8 years. Synthetic DMARD survivals (95% CIs) after 12, 24, and 60 months were 95% (91 to 98), 88% (82 to 93), and 80% (72 to 86), respectively (Figure 1A). The drug survival was worse in peripheral disease than in axial disease: at 12 months 93% (75 to 98) vs. 96% (90 to 98), at 24 months 77% (56 to 89) vs. 91 (84 to 95), at 60 months 49% (21 to 72) versus 86% (78 to 91) (p=0.004), respectively (Figure 1B). The initial synthetic DMARD was

switched to another in 49 patients. A combination of two DMARDs (sulphasalazine and methotrexate) was prescribed for 31 patients. The mean sulphasalazine dose prescribed was 2.1 g (SD 0.5), and methotrexate dose 18.7 g (SD 4.4).

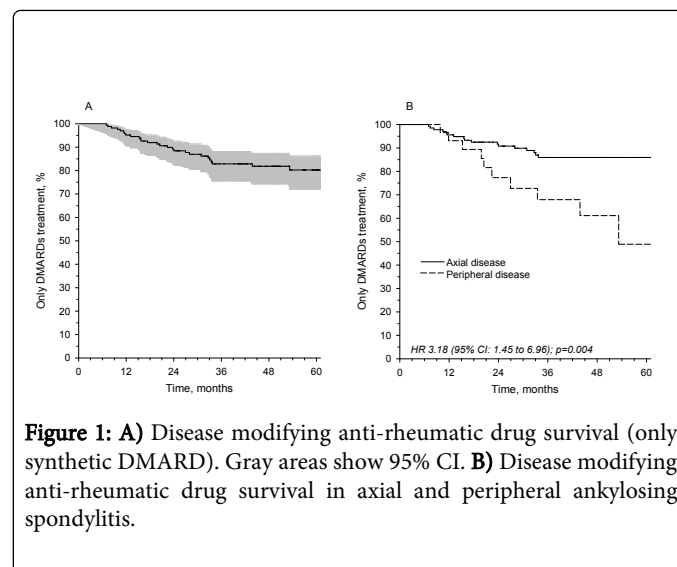


Figure 1: A) Disease modifying anti-rheumatic drug survival (only synthetic DMARD). Gray areas show 95% CI. **B)** Disease modifying anti-rheumatic drug survival in axial and peripheral ankylosing spondylitis.

	Synthetic DMARD n=137	Biological DMARD n=28	p value
Males (%)	74 (54)	18 (64)	0.32
Age, years, Mean (SD)	35 (10)	34 (10)	0.89
Duration of symptoms, years, median (IQR)	4 (2, 10)	5 (2, 10)	0.98
Peripheral disease, (%)	19 (14)	10 (36)	0.006
HLAB27 positive (%)	122 (89)	27 (96)	0.23
Previous iritis, (%)	36 (26)	6 (21)	0.59
ESR, mm/h, mean (SD)	16 (12)	23 (19)	0.011
CRP, mg/l, mean (SD)	9 (10)	23 (26)	<0.001
Schober test, cm, mean (SD)	4.0 (1.4)	3.4 (1.5)	0.092
Chest expansion, cm, mean (SD)	5.0 (2.1)	4.9 (1.9)	0.88
Medication started at baseline, (%)			0.11
Sulphasalazine	132 (96)	25 (89)	
Methotrexate	5 (4)	3 (11)	
Biological DMARD	0 (0)	0 (0)	

SD: Standard Deviation; IQR: Interquartile Range; DMARD: Disease Modifying Anti-Rheumatic Drug; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein

Table 1: Demographics and clinical data at baseline according to the need for only synthetic DMARDs and biological DMARD treatment during the follow-up

A biological DMARD was instituted to 28 (17%) patients (Table 1). Treatments at the time of switch to a biological DMARD are shown in Table 2. Every patient switched to a biological DMARD had received more than one synthetic DMARD. Lack of efficiency was the main reason for switch to a biological DMARD especially in peripheral disease (Table 2).

	Axial disease N=18	Peripheral disease N=10	All N=28
Reasons for switch, n (%)			
Lack of efficiency	14 (78)	10 (100)	24 (86)
Adverse event	4 (22)	0 (0)	4 (14)
Previous drugs, n (%)			
Sulphasalazine	8 (44)	8 (80)	16 (57)
Methotrexate	13 (72)	5 (50)	18 (64)
Leflunomide	0 (0)	2 (10)	2 (7)
Hydroxychloroquine	0 (0)	1 (10)	1 (4)
Treatment strategy, n (%)			
Single therapy	15 (54)	5 (50)	20 (71)
Combination therapy	3 (17)	5 (50)	8 (29)
DMARD: Disease Modifying Anti-Rheumatic Drug			

Table 2: Reasons for synthetic DMARD switch to a biological DMARD and treatment before switch to a biological DMARD

Switch to a biological DMARD was predicted at baseline by higher ESR [HR=1.03 (95% CI: 1.01 to 1.05)], higher CRP [HR =1.03 (95% CI: 1.02 to 1.05)], and the presence of peripheral disease [HR=2.43 (95% CI: 1.04 to 5.71)] (Table 1). Among those who were prescribed a biological agent 19 patients received adalimumab and 9 etanercept. The median follow up from the start of synthetic biological DMARD was 20 (IQR 12, 32) months. After a 6-month biological DMARD treatment ESR and CRP had significantly declined from baseline (Figure 2).

BASDAI, being available for 46 patients who started synthetic DMARD treatment, decreased from 4.1 (SD 1.8) by 1.6 (95% CI 2.2-1.1, $p < 0.001$) during the treatment. In case of DMARD failure, BASDAI was 5.6 (SD 1.2) before biological DMARD treatment and decreased by 3.1 (95% CI 4.4-1.8, $p < 0.001$).

Discussion

This register study shows that sulphasalazine was prescribed to almost all AS patients in the 2010s in HUCH, the only secondary referral centre in the Metropolitan area for 595,000 inhabitants of Helsinki. Methotrexate was much less used and none received biological agents as the first DMARD. The survival of synthetic DMARDs was 80%. Only 17% of the cohort patients were prescribed a biological DMARD during the average follow-up of 3.8 years.

The natural course of AS is typically variable. Inflammatory back pain may persist for decades, but it is probable that most of the structural damage takes place early in the 10 first years of the disease [14,15]. Sulphasalazine has no disease modifying effect on

radiographic progression of the disease [16]. Anti-TNF drugs suppress the bone oedema in the spine in patients with early axial spondylarthropathy [17] as well as in full-blown ankylosing spondylitis [18].

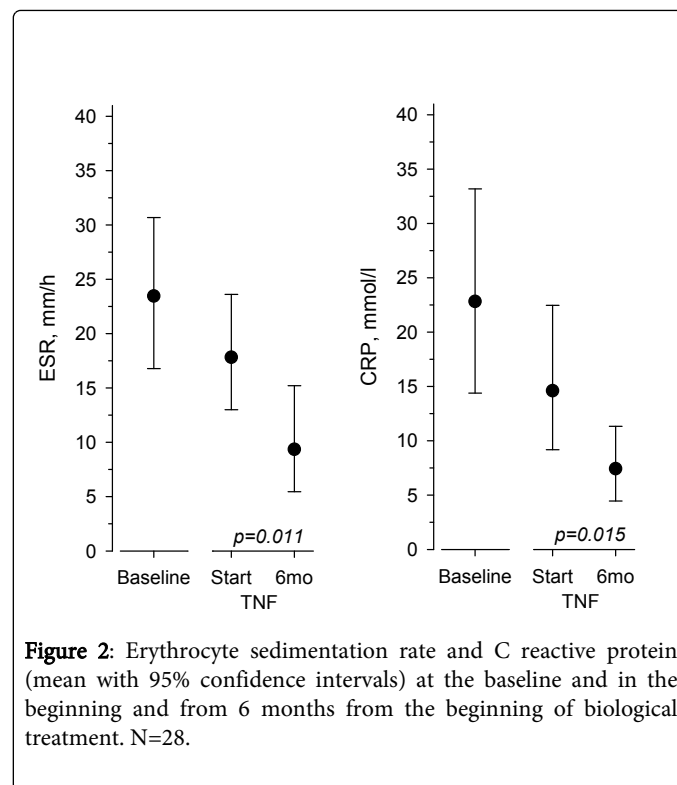


Figure 2: Erythrocyte sedimentation rate and C reactive protein (mean with 95% confidence intervals) at the baseline and in the beginning and from 6 months from the beginning of biological treatment. N=28.

The role of sulphasalazine in the treatment of patients with AS has remained controversial. In placebo-controlled trials, sulphasalazine significantly improved chest expansion, morning stiffness and inflammatory markers, especially in patients with peripheral disease [5] but improvement of these parameters has been found also in patients with axial disease [19]. Braun et al. [7] showed that sulphasalazine had effect on some AS patients without peripheral disease, but not in the whole study population. In 2006, an extensive literature review by Zochling et al. [4] concluded that there is an inconclusive level IA evidence favouring sulphasalazine in AS.

In a recent study, etanercept was compared to sulphasalazine in a randomized, placebo-controlled 16-week study in patients with active AS [20]. Both groups responded to the short treatment, but the response was higher in the etanercept group: ASAS20 response was achieved by 52.9% in the SSA vs. 75.9% in the etanercept group ($p < 0.0001$), and mean BASDAI decreased from a mean of 5.9 to 3.21 vs. to 2.78, respectively ($p < 0.0001$). Despite the superiority of etanercept, this study showed significant disease activity suppression also in patients on sulphasalazine. The sulphasalazine dose was slowly escalated over 4 weeks from 0.5 g/day to 3 g/day or maximal tolerated dose. Consequently, the period of optimal dosage lasted only 12 weeks, which may be a time too short for a full effect of sulphasalazine. We have previously shown that AS patients on sulphasalazine continue to get better up until 20 weeks [21]. Lack of a placebo treatment arm [20] leaves the interpretation of the true effect of sulphasalazine uncertain.

Few studies with methotrexate are based on small number of patients, and the evidence in favour of methotrexate in AS was not convincing. Methotrexate is generally not considered to be effective in

AS [9-11]. Five of our patients continued methotrexate without need for anti-TNF treatment, but the number is too small to draw conclusions. In addition to patients intolerant to sulphonamides and patients with peripheral disease, [8] it is possible that in cases of active iritis [22] methotrexate is more beneficial than sulphasalazine. Thus, methotrexate appears to be a treatment option at least for a selected minority of AS patients.

Despite being considered as the first-line drugs in AS, the NSAIDs as monotherapy were the treatment strategy for very few of our patients. Practically all patients were prescribed NSAIDs already in primary care, and there was a need for a more efficient treatment. Although ASAS/EULAR recommendations [3,12] do not support any obligatory use of synthetic DMARDs before anti-TNF treatment in patients with axial disease, especially sulphasalazine and methotrexate are frequently prescribed in clinical practise [13,23]. A Turkish cross-sectional study [24] showed that 77.5% of 216 AS patients were receiving sulphasalazine, 15% methotrexate and only 9.9% anti-TNFs. A recent study [25] provides additional evidence that AS patients may benefit from sulphasalazine and combination of sulphasalazine and methotrexate.

Due to the Finnish reimbursement regulations, practically all patients with AS not responding to NSAIDs have had to undergo at least one synthetic DMARD treatment before a biological drug is considered. Thus, all patients in the present study received more than one synthetic DMARD before a TNF inhibitor. In subgroup analysis, the BASDAI scores available mainly from patients 2008 onwards showed low disease activity in patients treated with synthetic DMARDs. The results are in line with our recent nationwide data from Finland, based on the drug reimbursement register [13].

During the study period, etanercept, adalimumab, and infliximab were the TNF inhibitors available for the treatment of active AS, but none of our patients received infliximab. This may be explained by the responsibility of hospitals for the costs of intravenous drugs in Finland. The patients responded well to a biological DMARD with a considerable decrease in ESR, CRP, and BASDAI.

In summary, this study shows that synthetic DMARDs, especially sulphasalazine, are widely used in the treatment of AS at a large university hospital. The long drug survival and the relief of symptoms as shown by the improvement of BASDAI suggest that the synthetic DMARDs may have a favourable impact on AS, and they may be an alternative to biological DMARDs also in axial AS. Even postponement of the expensive biological DMARDs may have considerable economic implications. In addition, the patients who were prescribed biological DMARDs after synthetic DMARD treatment seemed to respond well. Register studies from other countries could give more information about the use of DMARDs in AS.

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