IgA serum levels and disease activity in ankylosing spondylitis: a prospective study

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SUMMARY We investigated the possible association between serum IgA, IgM, and IgG and disease activity in a longitudinal study of 48 weeks' duration in 38 male patients with active ankylosing spondylitis receiving regular treatment with either phenylbutazone or diflunisal. Throughout the study serum IgA levels correlated most frequently with chest expansion and lumbar flexion index, and patients with extensive radiological changes also had the highest serum IgA levels. Likewise, changes in IgA, but not in IgM and IgG, correlated with changes in a composite index of disease activity (IDA). Changes in erythrocyte sedimentation rate (ESR) showed a similar correlation with changes in IDA, whereas changes in serum IgA and ESR showed no consistent correlation, suggesting that both parameters reflect different aspects of disease. Serum IgA, ESR, and IDA values all decreased during regular drug treatment, suggesting a disease modifying effect of the non-steroidal anti-inflammatory drugs (NSAIDs) studied. Regular measurement of serum IgA may be useful in the assessment of disease activity of ankylosing spondylitis.

Two observations have recently pointed to the possible importance of serum IgA levels in ankylosing spondylitis (AS). Firstly, IgA serum levels have been found to be disproportionately raised compared with other immunoglobulins in AS.¹⁻⁴ Secondly, disease activity in AS has been associated with the presence of *Klebsiella pneumoniae* in the faeces of patients with AS,⁵⁻⁷ though other studies have been unable to confirm these data.⁸⁻¹⁰ Since humoral immune responses in the gut are mainly of the IgA type,¹¹ several authors looked for and in fact found an association between serum IgA levels and disease activity in AS.^{2,3,12,13} If IgA serum levels are indeed a parameter for disease activity in AS, this would be helpful, because assessment of activity by clinical parameters is problematic in this disease, especially when peripheral arthritis is absent. Longitudinal studies on IgA serum levels and disease activity in AS have not so far been carried out.

The aim of the present study was to investigate in a prospective, longitudinal way the possible rela-

tionship between serum IgA levels and clinical disease activity in AS. This study was part of a clinical trial comparing the efficacy of two NSAIDs, phenylbutazone and diflunisal, against disease activity in AS. In addition we studied possible correlations between serum IgA levels and radiological features of the disease.

Patients and methods

The present study was part of a clinical trial in male patients with ankylosing spondylitis, comparing treatment with phenylbutazone and diflunisal. Thirty eight patients were studied aged between 18 and 55 years, with a diagnosis of ankylosing spondylitis according to the New York criteria¹⁴ confirmed by two or more of the following symptoms: back pain, morning stiffness, and progressive limitation of movement. Patients were admitted only when they showed a flare-up during or after a drug withdrawal period of maximally 14 days. A flare-up was defined as a worsening of the patient's condition in which pain and stiffness were essential components, requiring treatment. After this wash-out period patients were randomly allocated to receive either diflunisal (500 mg twice daily) or phenylbutazone

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(200 mg twice daily), resulting in two treatment groups of 19 patients each. The study covered a 12-week double blind period followed by an open extension period up to week 48. Nine patients dropped out: three in each treatment group due to side effects and one in each group due to lack of efficacy. Another one was lost to follow up. Of the parameters studied the following are relevant to the present report: dominant spinal pain (DSP; cervical, thoracic, or lumbar sacroiliac), scored by the patient using a five-point scale ranging from 0 (no pain) to 4 (very severe pain); morning stiffness (MS) in minutes since arising; chest expansion (CE)¹⁵; and lumbar flexion index (LFI),¹⁶ assessed by taking the maximum of two measurements.

Laboratory parameters included an ESR according to Westergren and serum immunoglobulins as assessed by the radial immunodiffusion method of Mancini, with standard commercially obtained immunodiffusion plates and standards (Behringer Werke, Marburg, West Germany).^{17 18} All measurements were made at baseline and at weeks 12, 24, 36, and 48 thereafter. In addition to the individual parameters we used an index of disease activity (IDA) to evaluate the response. The four components of this IDA and its gradings are shown in Table 1. The individual's mean of the four graded parameters was used as the IDA for that patient, being minimally 0 and maximally 4. During the study an x-ray of the vertebral column, the sacroiliac joints, and the chest was made. The radiographic findings were graded according to Rogan *et al.*,¹⁹ i.e., grade I: changes confined to sacroiliac joints; grade II: early changes in the spine and in sacroiliac

joints; grade III: well marked changes in the thoracic and lumbar spine, with some evidence of ankylosis, and changes in sacroiliac joints; grade IV: gross changes in sacroiliac joints and thoracic and lumbar spine. For comparison of immunoglobulin and ESR values we used baseline data from 14 male patients with rheumatoid arthritis (RA), obtained during a single blind study comparing auranofin and aurothioglucose.²⁰ Moreover, immunoglobulin levels of 40 healthy male blood donors, mean age 37 $\pm$ 12 years, were used as normal controls. Their mean serum immunoglobulin concentrations plus one standard deviation were considered normal values.

The results were analysed by Student's *t* test, always two sided and when appropriate by paired testing. Correlations were assumed to be linear, and the significance of correlation coefficients was assessed by *t* testing.

Results

SERUM IMMUNOGLOBULIN LEVELS IN ACTIVE AS

Table 2 shows mean serum immunoglobulin levels in the active phase of AS, i.e., at baseline (week 0). Mean serum IgA levels were raised in both AS and RA, showing no significant difference. Serum IgM levels were higher in male patients with AS than in those with RA. In contrast, ESR values were significantly ($p < 0.001$) higher in male RA (54 ± 32 mm/h) than in male AS patients (26 ± 18 mm/h). A study of the raised serum immunoglobulin levels showed that IgA was the dominantly increased

Table 1 Grading of dominant spinal pain (DSP), morning stiffness (MS), chest expansion (CE), and lumbar flexion index (LFI) according to increasing severity

		0	1	2	3	4
DSP	(0-4)	0	1	2	3	4
MS	min	<10	10-30	31-60	61-120	>120
CE	cm	≥ 7	6.9-5.0	4.9-3.5	3.4-2.0	<2.0
LFI	cm	≥ 7	6.9-5.0	4.9-3.5	3.4-2.0	<2.0

The index of disease activity (IDA) of an individual patient is calculated as the mean of his score for the four respective components.

Table 2 Immunoglobulin levels (mean $\pm$ SD) in healthy controls (C), patients with ankylosing spondylitis (AS), and patients with rheumatoid arthritis (RA)

	Male C (n=40)	Male AS (n=38)	Male RA (n=14)	AS v C	RA v C	AS v RA
IgA (g/l)	2.17 $\pm$ 0.94	3.30 $\pm$ 1.53	3.73 $\pm$ 1.15	$p < 0.001$	$p < 0.001$	NS
IgM (g/l)	1.46 $\pm$ 0.85	1.85 $\pm$ 0.64	1.31 $\pm$ 0.56	$p < 0.05$	NS	$p < 0.01$
IgG (g/l)	11.06 $\pm$ 2.55	14.42 $\pm$ 3.63	16.80 $\pm$ 5.25	$p < 0.001$	$p < 0.001$	0.05 $< p < 0.1$

NS=not significant.

serum immunoglobulin in 38% of the patients. IgG and IgM were dominantly raised in 19% and 5% of the patients with AS respectively. 38% of the patients had no serum immunoglobulin increase at all.

DISEASE ACTIVITY AND SERUM IMMUNOGLOBULIN LEVELS

Table 3 shows correlations between serum immunoglobulin levels, ESR, and clinical parameters. Laboratory parameters frequently correlated with the objective clinical parameters, i.e., chest expansion and lumbar flexion index. Most correlations were found for IgA (nine times), followed by IgG (six times), ESR (five times), and IgM (three times). No consistent correlations were found between laboratory parameters and dominant spinal pain, morning stiffness, and the index of disease activity. Table 3 also shows a consistent and close correlation between ESR and IgA and, to a lesser extent, IgG.

Next we studied changes in laboratory parameters and clinical parameters during treatment. Since there were no consistent differences between the effects of both treatments, the two groups were taken together. Fig. 1 shows the mean serum immunoglobulin levels throughout the study, indicating the most significant changes in IgA at week 24 and thereafter. Table 4 shows correlations

Fig. 1 Mean immunoglobulin levels during the study for all patients completing the trial, and separately for those with a normal and a raised IgA serum level, respectively (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Table 3 Correlations between clinical and laboratory parameters throughout the study

Week	Parameter	DSP*	MS	CE	LFI	IDA	ESR
0	IgA	-0.05	0.05	-0.28	-0.47‡	0.31	0.65§
n=38	IgM	-0.02	0.37‡	-0.32	-0.31	0.44‡	0.01
	IgG	-0.08	0.07	-0.33‡	-0.44‡	0.28	0.39‡
	ESR	0.16	-0.15	-0.14	-0.43‡	0.34‡	
12	IgA	-0.07	-0.29	-0.34‡	-0.53‡	0.28	0.50‡
n=32	IgM	-0.13	0.11	-0.24	-0.38‡	0.28	-0.03
	IgG	-0.31	-0.29	-0.30	-0.47‡	0.05	0.39‡
	ESR	0.26	-0.20	-0.16	-0.28	0.20	
24	IgA	-0.02	0.08	-0.47‡	-0.61‡	0.34	0.70§
n=29	IgM	0.13	0.08	-0.26	-0.40‡	0.40‡	0.09
	IgG	-0.20	-0.28	-0.31	-0.47‡	0.08	0.59§
	ESR	-0.01	-0.29	-0.24	-0.45‡	0.13	
36	IgA	-0.12	-0.32	-0.51‡	-0.49‡	0.25	0.61§
n=29	IgM	0.01	0.02	-0.11	-0.51‡	0.21	0.08
	IgG	-0.26	-0.25	-0.38‡	-0.39‡	0.06	0.59§
	ESR	-0.06	-0.30	-0.39‡	-0.43‡	0.15	
48	IgA	0.15	-0.33	-0.45‡	-0.48‡	0.25	0.72§
n=29	IgM	0.36	-0.07	-0.13	-0.33	0.27	0.09
	IgG	0.10	-0.38	-0.24	-0.34	0.08	0.63§
	ESR	0.08	-0.21	-0.27	-0.47‡	0.20	

*Abbreviations as in Table 1.
‡ $p<0.05$. † $p<0.01$. § $p<0.001$.

Table 4 Correlations of changes as compared with baseline between parameters during the study

Weeks	Parameter	DSP*	MS	CE	LFI	IDA	ESR
0-12 n=32	IgA	0.11	0.25	0.05	-0.33†	0.38‡	0.28
	IgM	0.18	0.28	-0.23	-0.43‡	0.36‡	0.10
	IgG	0.20	0.17	-0.03	-0.25	0.18	0.10
	ESR	0.39‡	0.23	-0.13	-0.03	0.42‡	
0-24 n=29	IgA	0.24	0.35†	0.01	-0.46‡	0.54§	0.13
	IgM	0.31	0.18	-0.12	-0.10	0.37‡	0.06
	IgG	0.14	0.14	-0.14	-0.05	0.28	0.09
	ESR	0.30	0.28	-0.03	-0.16	0.56§	
0-36 n=29	IgA	0.29	0.32†	0.00	-0.37‡	0.41‡	0.45‡
	IgM	0.05	0.00	0.22	-0.08	-0.12	0.16
	IgG	0.17	0.21	0.06	0.01	0.06	0.07
	ESR	0.39‡	0.20	-0.07	-0.15	0.39‡	
0-48 n=29	IgA	-0.03	0.12	-0.11	-0.33†	0.34†	0.58§
	IgM	0.06	-0.14	-0.09	-0.28	0.14	0.04
	IgG	0.02	0.13	-0.07	-0.12	0.29	0.02
	ESR	0.07	0.05	0.02	-0.05	0.17	

*Abbreviations as in Table 1.
†0.05<p<0.1. ‡p<0.05. §p<0.01.

Fig. 2 Radiological gradings of the axial skeleton¹⁹ and serum IgA levels at baseline.

between changes during treatment. This table indicates that, so far as immunoglobulins and index of disease activity are concerned, most correlations are found for IgA, followed by IgM. Correlations of ESR with index of disease activity were comparable with those of IgA, though correlations between IgA and ESR became significant only after 36 and 48 weeks. Of the individual IDA components only lumbar flexion index changes showed correlations with immunoglobulin changes, most frequently with IgA: twice significant and twice close to significance (0.05<p<0.1).

RELATION BETWEEN SERUM IGA LEVELS AT BASELINE AND RADIOLOGICAL FEATURES
Since radiological features at least partly reflect disease activity, we studied serum immunoglobulin levels in the various radiological categories. As shown in Fig. 2 radiological grades II, III, and IV differ significantly from grade I in mean serum IgA level (p<0.01). No such differences were found for IgM and IgG.

Discussion

This study presents evidence that serum IgA levels, more than those of IgM and IgG, are associated with disease activity in ankylosing spondylitis. Firstly, absolute values of serum IgA were found to correlate with the objective disease parameters lumbar flexion index and chest expansion throughout the study. Secondly, and probably most important, changes in serum IgA correlated with changes of

disease activity expressed as an index of disease activity (IDA). Finally, mean serum IgA levels increased as the radiological changes became more severe. It should be stressed that these data apply only to the group studied, i.e., male patients with ankylosing spondylitis without peripheral arthritis who showed a flare up of pain and stiffness after a drug-free period.

Serum immunoglobulin levels have been found to be raised in ankylosing spondylitis by several authors, the most significant rise being that of serum IgA.¹⁻⁴ A few studies have indicated that serum IgA levels may be related to disease activity.^{2,3,12,13} However, no longitudinal studies have previously been done. The present study is the first to show that changes in serum IgA levels parallel changes in disease activity of ankylosing spondylitis. Similar changes were not found for the other immunoglobulins studied.

Evidence that serum IgA levels are somehow related to disease activity in ankylosing spondylitis may be important in several respects. A number of studies have indicated that other HLA-B27 related disorders, e.g., Reiter's syndrome and reactive arthritis, can be precipitated by an enteric infection.²¹⁻²³ Since IgA is the predominant immunoglobulin produced by the gastrointestinal mucosa,¹¹ association of IgA serum levels and disease activity as found in the present study may point to the localisation of a causative pathogen in the gut.^{2,6,7} In fact Ebringer *et al.*⁵ have reported evidence of the association between the presence of *Klebsiella pneumoniae* in the faeces of patients with ankylosing spondylitis and active disease. Other groups, however, have been unable to confirm these data.⁸⁻¹⁰ Another interesting observation was that serum IgA levels decreased during regular treatment with NSAIDs. Since changes in serum IgA were paralleled by changes in disease activity, these observations suggest that NSAIDs may have a disease modifying effect in ankylosing spondylitis. The observation in our study that there was also a decrease in ESR during treatment is compatible with this view. In this respect it is interesting that one previous study presents evidence of delayed ossification of the lumbar vertebral column in ankylosing spondylitis due to phenylbutazone treatment.²⁴

It is of practical importance that the present data justify the use of serum IgA levels as another parameter of disease activity. At present ESR and acute phase proteins such as C-reactive protein (CRP) are most frequently used as laboratory parameters of disease activity.^{2,25} However, the value of the latter parameters has been questioned in AS.^{3,26,27} In any case the serum IgA levels may

give valuable additional information, as suggested by our finding that especially in the earlier part of the trial there was no correlation between changes in ESR and those in IgA serum levels. In our group of patients the mean serum IgA levels were related to the extent of radiological abnormalities. The latter at least partly reflects disease severity, though duration of the disease admittedly also plays a part. If as suggested by our data serum IgA levels reflect disease activity, this would mean that patients with persistently raised serum IgA levels are most at risk of developing extensive axial inflammation and therefore ankylosis and flexion deformity. This group should be considered for regular treatment with NSAIDs, especially when this type of treatment has a disease modifying effect as our data suggest.

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Book review

Research. How to Plan, Speak and Write About It. Eds. Clifford Hawkins and Marco Sorgi. Pp. 184. £8.75. Springer: Berlin. 1985.

This book encapsulates in one volume the various aspects of research involvement and is particularly concerned with presenting its results. Of the eight chapters, the editors have contributed to three. The contents include chapters on: Research: why do it?; Planning and protocol; Searching the literature; Speaking at meetings; What the critical reader looks for in an original article; A guide for writers; Illustrating talks or articles; A guide to statistical methods; Publication. In addition, the work is most usefully supplemented by a series of appendices, including notes on the MD thesis, advice on using a dictating machine, and lists of needless and verbose words. There are also appendices on American and British usage in spelling, abbreviations of journal titles, and guidelines for putting up poster displays.

The book is intended to be an aid for anyone starting out

in research or someone who is already undertaking it. The intention of the editors is fully met by this work, which will provide embryo or established researchers with a wealth of useful information.

The coverage offers a good balance between verbal and visual aspects of communication, and throughout the reader is given the benefit of much practical experience from the editors and contributors. This is, therefore, a theory-and-practice approach, making the volume all the more valuable.

Anyone writing in this field to some extent exposes their style of presentation to scrutiny more than usual. However, these authors have strongly upheld the 'practice what is preached' philosophy, and the book throughout is clearly and pleasingly written. It is strongly recommended.

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