Editorial

Predicting outcome in ankylosing spondylitis

Introduction

Ankylosing spondylitis (AS) has an estimated prevalence of 0.2–0.86% for adult Caucasian populations of western European extraction [1]. The ability of anti-TNF treatment to dramatically suppress symptoms in AS [2–4] and improve quality of life [5–7] is now beyond doubt. However, the high costs and potentially serious side-effects [8], combined with uncertainties over any long-term ‘disease modifying’ effects [9] make careful selection of patients for treatment absolutely critical if needless toxicity and expense are to be avoided. Inevitably, funding bodies are reluctant to commit huge funds to this relatively obscure and formerly ‘cheap’ disease; therefore, it is incumbent on rheumatologists to avoid exposing patients who will do well without biologic therapy to unnecessary risk.

In practice, most patients do well on anti-TNF treatment. However, there are very few guides to long-term prognosis [10]. Current approaches to patient selection are based on the severity of symptoms ‘now’ rather than taking into account likely longer term outcomes. While the current approach may turn out to be the right one, replacing short-term subjective criteria for treatment with outcome-based objective criteria is plainly a highly desirable goal. To achieve this we need to be able to predict which AS sufferers will do ‘well’ and which ‘badly’ if managed conventionally. As a secondary issue we also need to determine more precisely what the terms ‘well’ and ‘badly’ mean when placed in the cost–benefit balance [11].

The natural history of AS

The natural history of AS remains poorly documented. It has been a difficult area to study for two reasons. The heterogeneity of the disease, in particular with regard to the severity of the symptoms and radiographic progression, the slow speed of progression and the lack, until recently, of appropriate and validated outcome measures [12], has made studies technically difficult and necessarily long-term. In the absence of highly effective treatment, prior to the arrival of biologics, there was also little motivation to undertake or fund such work. Moreover, documentation of the early course of AS has been inhibited by the lack of suitable criteria for early diagnosis. Although the ‘modified New York criteria’ have been pivotal in the widespread recognition and study of AS, dependence on radiographic changes has meant that many patients still experience long delays before the diagnosis is made and many cases go unrecognized [13, 14].

Rudwaleit and colleagues [15] have pointed out that AS passes through three stages which, in reality, are a continuum. The earliest phase is ‘pre-radiographic’, objective evidence of the disease being principally symptoms and MRI abnormalities. Subsequently, symptoms and radiographic sacroiliitis combine to render the disease diagnosable by conventional criteria [16] though at a time when the disease is well established and irreversible, changes have already occurred. In the third phase, radiographic spinal changes—syndesmophytes and facet joint obliteration—indicate severity and chronicity. By this stage not only are changes irreversible, they may progress even if the biologic therapy is suppressed [17].

There is considerable individual variation in the pattern of progression of AS. Findings from two early prospective studies suggest that the pattern of AS within the first 10 yrs of disease usually indicates the likely subsequent course [18, 19]. In the study by Carette et al. [20] the natural course of AS was examined over a 23-yr period in 51 patients whose mean disease duration was 38 yrs. Seventy-four percent of the patients who had mild spinal restriction after 10 yrs did not progress to severe spinal involvement. In contrast, 81% of the patients who eventually had severe spinal restriction were severely restricted within the first 10 yrs [20]. Recently, Stone and colleagues [21] have demonstrated that the course of AS generally falls into one of the four patterns so far as persistence of disease activity is concerned, so that recognition of the disease pattern in early disease may help to predict future course.

In other rheumatic diseases, especially RA [22] valuable predictions of future course and outcomes can be based on a combination of clinical features and biomarkers. In this respect, AS has lagged behind but the need to tailor biologic treatment judiciously calls for urgent progress in predicting outcome.

What outcomes should be measured and predicted?

Subjective measures of symptom severity (Bath Ankylosing Spondylitis Disease Activity Index—BASDAI [23]) and functional ability (Bath Ankylosing Spondylitis Functional Index—BASFI [24]) are widely used along with standardized measurements of spinal mobility (Bath Ankylosing Spondylitis Metrology Index—BASMI) [25] and other clinically useful instruments. Less often objective radiological indices are used as outcome measures. Changes seen on spinal radiographs can be recorded objectively using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [26] and spinal MRI indices have also been devised [27].

However, in order to determine the true benefits of treatment, and hence to be able to balance them against the human and financial costs, clear data on the biological effects including the reduction or prevention of joint damage and ankylosis, changes in people’s well-being and productivity and personal and societal costs are essential. For these to be seen in proper context, the true natural history of ‘non-biologically’ treated AS needs to be known, bearing in mind the effects of associated comorbidities including spinal osteoporosis and fractures and the need for surgery. And for expensive and potentially dangerous treatments to be prescribed optimally we need to know whether the above and other measures will allow prediction of which individuals will have a bad outcome, such as to justify biologic treatment.

What evidence is already available?

Demographic factors

Gender and age at onset clearly have some prognostic significance. Male sex [28] and early age at disease onset [29] are associated with a poor prognosis. In women, AS is generally milder [30], begins later [31] and is more often associated with extra-sparinal involvement, especially peripheral arthritis and uveitis [32]. A recent study by Lee et al. [33], which examined the differences between the genders in terms of severity of AS concluded that in patients with long-standing disease, men tend to have more severe radiographic spinal changes while women had more peripheral joint arthritis but there was no difference in functional disability as measured by BASFI and the HAQ-S [34] between them. Although women had less severe radiological involvement of the thoracic and lumbar spine as evidenced by lower Bath Ankylosing Spondylitis Radiology Index.
symptoms showed significantly worse BASDAI and BASFI scores reported constant symptoms rather than variable or intermittent results, in that ‘bad disease begets bad disease’ [21]. Patients who patients and observed the associations with disease-specific health [21], which examined the disease activity patterns reported by AS [21] that in patients with AS both psoriasis and IBD increased severity of disease in terms of function and disease activity. In a related study, the presence of iritis was associated with restricted mobility of the spine, more widespread spinal disease and more radiological damage [39].

Musculoskeletal features

The early development of hip arthritis in particular [36], and peripheral arthritis in general [19, 36, 37] correlate with poor prognosis in AS. Amor et al. [36] identified hip involvement or the presence of any three of the following:

- ESR >30 mm/h,
- NSAID unresponsiveness,
- limitation of lumbar spine movements,
- sausage-like finger or toe and
- oligoarthritis,

within 2 yrs of onset of SpA or in individuals with onset at ≤16 yrs as predictive of severe disease (specificity 97.5%) and poor outcome (sensitivity 50%). Hip arthritis was associated with a 23-fold increase in the risk of severe disease. The absence of any of these features during the first 2 yrs of the disease was predictive of a better outcome (sensitivity 92.5%; specificity 78%). Regardless of age at onset, hip involvement (arthritis) is a risk factor for radiographic spinal progression. Furthermore, hip involvement is more common in patients with juvenile onset disease (18% vs 8% for adult onset; P < 0.001). The absence of hip disease in juvenile onset AS confers a good prognosis.

Extra-articular factors

The presence of extra-articular features is linked to a worse outcome. A study by Brophy et al. [38], which explored the nature of the inter-relationship between AS, psoriasis and IBD concluded that in patients with AS both psoriasis and IBD increased severity of disease terms of function and disease activity. In a related study, the presence of iritis was associated with restricted mobility of the spine, more widespread spinal disease and more radiological damage [39].

Disease activity and functional disability

One longitudinal study [12] of a cohort of hospital attenders with AS over a 5-yr period concluded that the BASDAI and BASFI scores may allow prediction of a more severe disease course, and therefore may be useful in identifying patients requiring intensive treatment and follow-up. More recently, a study by Stone et al. [21], which examined the disease activity patterns reported by AS patients and observed the associations with disease-specific health status measures notably the BASDAI and BASFI showed similar results, in that ‘bad disease begets bad disease’ [21]. Patients who reported constant symptoms rather than variable or intermittent symptoms showed significantly worse BASDAI and BASFI scores than those with intermittent symptoms alone.

Socio-economic and lifestyle factors

Several studies have investigated the influence of socio-economic status and lifestyle factors on outcome. Cigarette smoking has been associated with worse clinical, functional and radiological outcome in AS [40–42], suggesting that encouraging patients not to smoke may help to preserve function or that socio-economic factors linked to smoking predispose to poor outcome. Patients with lower educational status, in lower socio-economic groups [19, 28] and those with more physical occupational activities [43] have been noted to have a poorer prognosis. Recent studies, however, have found little evidence to substantiate the role of socio-economic factors in determining the severity of outcome in AS and suggest that disease severity might be largely controlled by genetic factors and hormonal influences, as suggested by the predictive value of male gender [44, 45].

Family and genetic markers

Susceptibility to AS. Genetic factors play a major role in susceptibility to AS. Heritability in twins is estimated to be >90% [46], and genes of the MHC, in particular HLA-B27, have been demonstrated, by both linkage and association methods to be heavily involved [47]. Genome-wide association studies have implicated two new non-B27 genes: IL-23r (interleukin receptor) and ARTS 1 (Type1 TNF receptor shedding aminopeptidase receptor) in the pathogenesis of AS [48]. Whilst the high prevalence of HLA-B27 in AS limits its value as a prognostic marker the potential of IL-23r, ARTS 1 and other associated genes in predicting susceptibility to disease and outcome has yet to be fully explored.

Genetics and disease severity

A study by Hammersma et al. [44] demonstrated that in AS, disease severity is largely genetically determined and that environmental factors play a very limited role in determining either disease activity or functional capacity. No environmental component was found to be associated with either BASDAI or BASFI, age at disease onset, disease duration or severity. This study also concluded that disease severity and functional impairment show a consistent pattern within families so that the severity of disease in secondarily affected family members can be roughly predicted from the severity of disease in previously affected family members. More comprehensive genetic studies of determinants of clinical risk and manifestations such as those of the Technology Assessment in Social Context (TASC) group (consortium of Australian, British and North American investigators) study should provide more insight in the near future.

Imaging

Follow-up of 137 AS patients from the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort showed that radiological damage at baseline, male gender, hip arthritis and extra-spinal manifestations such as uveitis correlated with radiological progression of spinal disease after 4 yrs [49]. The course of spinal inflammation associated with AS can be well demonstrated by MRI [50] and many anti-TNF treatment trials in AS have assessed clinical response to these drugs in terms of short-term MRI radiological response. However, no long-term data are available to demonstrate whether or how such MRI changes relate to conventional radiographic changes. It is clear that more research, including long-term trials are needed to document early radiological factors that may predict severity of disease and response to treatment.

Laboratory parameters

There are no specific laboratory tests for AS in general. However, the strong association of HLA-B27 with AS (80–95%) and its rather low prevalence in most populations (5–14%) in Europe and the USA—with no increase of HLA-B27 in patients with mechanical low back pain [15]—makes testing for HLA-B27 a useful adjunct for diagnosis only. Laboratory markers of disease such as ESR and CRP levels, so useful in other inflammatory arthritides, have not been shown to be reliable indicators of disease activity or outcome in AS [51].

Predicting the outcome of biologic treatment

Most people with active AS respond to anti-TNF therapy. However, predicting who will respond well and who will only modestly is as important as predicting who will not respond for accurate targeting of use of these drugs. Baseline CRP levels have
been identified as a predictor of response [52, 53]. Rudawalet et al. [54] identified that shorter disease duration, younger age, lower BASFI and higher BASDAI also predict response to anti-TNF treatment. How this translates into clinical practice remains to be elucidated.

Anakinra, an IL-1 receptor antagonist, has been found to be effective in the IL-1-mediated disease [57]. IL-1 is a key pro-inflammatory cytokine and appears to be up-regulated in AS. Bennett et al. [58] report that in their cohort of patients treated with anakinra, ~40% had high baseline CRP levels, indicating that high serum markers of inflammation may be predictive of response to treatment with anakinra as well.

Identification of predictive biomarkers is of key importance. In one recent study, high levels of IL-6 and CRP were associated with a good clinical response to infliximab treatment [59]. Early reductions in IL-6 were significantly associated with improvements in disease activity and the spiral inflammation detected by MRI. There is an urgent need to expand the biomarker repertoire in AS.

Conclusions

Our knowledge of the natural history of AS remains far from complete. Some people with AS have severe disease whilst others seem to live without even being cognisant of the condition [60]. Some have severely impaired lives with considerable suffering and substantial personal and societal costs whilst others, with apparently severe disease do not. We do not know who will progress radiographically, whether progression is linear or episodic, whether established disease can be halted and how objective spinal and peripheral disease relates to personal and socio-economic outcome. Only the sketchiest basis currently exists on which to base prediction of future job loss, deformity and long-term suffering, and yet these are absolutely vital to our patients and to those who fund treatment. In comparison with RA those with an interest in AS have a great deal of catching up to do.

Future research needs to focus on the development of prognostic markers for severe disease and response to treatment, especially now that we have effective treatments for AS. This can only be achieved by setting up large, broadly based inception cohorts of AS patients with long-term follow-up data. Some such cohorts are now in existence but the task is huge and the need for more, and more detailed, information is urgent.

Disclosure statement: K.G. has received honoraria and participated in advisory boards for Abbott, Wyeth and Schering-Plough Pharmaceuticals. Their Rheumatology Department at Norwich has received research grants from Abbott, Wyeth and Schering-Plough Pharmaceuticals. A.K. has received honoraria for attending ad hoc boards, speaking at sponsored meetings and financial support for attending meetings from Abbott, Schering-Plough and Wyeth.

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1 Accepted 14 April 2008

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