

Extra-articular manifestations and comorbidities in spondyloarthritis : epidemiological and clinical aspects

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VALORISATION ADDENDUM

Valorization is the process of “translating academic wisdom to societal benefit”. In this thesis we focused on the epidemiology and measurement of extra-articular manifestations (EAMs) and comorbidities in patients with spondyloarthritis (SpA) and ankylosing spondylitis (AS). This addendum describes the societal relevance of the present findings.

Prevalence of SpondyloArthritis

Data on the prevalence of SpA were limited available, but increasingly important. In the last decade, more treatments have become available for SpA; in particular the introduction of anti-TNF-alpha therapy dramatically changed the outcome of patients with SpA. However, anti-TNF-alpha therapy is expensive and may have large impact on health budgets when frequently prescribed. In this thesis we have shown that SpA and its subtypes are a relatively common disease. The pooled prevalence of SpA was 0.54% (0.36-0.78) and that of AS 0.25% (0.18-0.33) in Europe. These numbers can be used in budget impact analyses to estimate the financial consequences for society for example when new biologicals or biosimilars will become available in the near future.

Extra-articular manifestations in Ankylosing Spondylitis

AS is the prototype of the SpA group and is characterized by inflammation of the sacroiliac joints and the vertebrae, causing pain and stiffness in the back and/or buttock area. Patients with AS may also suffer from other manifestations belonging to the SpA concept, such as peripheral arthritis, enthesitis, or EAMs comprising acute anterior uveitis (AAU), psoriasis, and inflammatory bowel disease (IBD). All these clinical symptoms and subsequent disease progression result in substantial functional limitations and lower quality of life.

Symptoms associated with AS usually start in the 2nd or 3rd decade of life when development of a personal career and raising a family life are important social roles. In several studies it has been shown that patients with AS have lower employment rates, incur more official work disability, and experience more absences from work than the general population [1, 2]. The clinical burden of disease leads to significant direct and indirect costs for patients and society [3]. In order to decrease both the burden of disease for patients and costs for society, appropriate and early treatment is needed. Early treatment is particularly important, since several observations suggests that early effective treatment may influence radiographic outcome [4].

Importantly, in order to provide early treatment, patients should be diagnosed early and patients with poor prognosis should be identified. The tools available for rheumatologists to diagnose patients with axial SpA (axSpA) have improved substantially in the last years, for example with the introduction of MRI to detect sacroiliitis. However, the diagnosis of

AS is often delayed as a result of late recognition of patients. This may be caused by the insidious onset of symptoms, the heterogeneous picture, and the limited knowledge on manifestations belonging to the concept of SpA by general practitioners (GPs) and other referring physicians. Many patients present to GPs with back pain and not all patients with axSpA suffer from the typical inflammatory back pain. This makes it difficult for GPs to refer the right patients to rheumatologists.

One of the fundamental aspects to improve early recognition of SpA patients is knowledge and recognition of disease patterns by GPs and other physicians [5]. These patterns include axial symptoms, peripheral symptoms and EAMs. In this thesis, we showed that EAMs are frequently present before the diagnosis of AS. More than 11% of patients had an episode of AAU, more than 4% had psoriasis, and almost 4% had IBD before AS was diagnosed. These findings prove the relevance of EAMs in the early phase of SpA. The EAMs may particularly help to recognize patients who present with chronic back pain and possibly have SpA. Actively asking about other SpA features in these patients is needed. Further, in this thesis we showed that half of the patients with IBD who reported articular SpA features were never referred to a rheumatologist by their gastroenterologist. Education and increasing awareness of GPs and other specialists who see patients with a possible SpA about features belonging to SpA, including EAMs, is therefore warranted.

It is also important to realize that half of the patients develop an EAM after the diagnosis of AS. This is particularly important for AAU, because AAU needs immediate treatment by an ophthalmologist to prevent possible visual impairment. It is important to educate patients about the symptoms of AAU and about the fact that a first episode of AAU can also present some decades after the diagnosis of AS.

The presence of EAMs are also important in light of the choice of treatment. Most TNF-blocking agents are effective both for SpA and refractory uveitis, psoriasis, and/or IBD, although differences may exist among the available agents [6]. Since anti-TNF medication is expensive and economic evaluations showed substantial direct and indirect costs associated with AAU and IBD flares in patients with AS, it is important to take EAMs into account when selecting the most appropriate treatment.

Multimorbidity

In addition to EAMs, many patients with AS suffer from other chronic diseases, which may or may not be related to AS. The World Health Organization (WHO) defines chronic diseases as diseases of long duration and generally slow progression [7]. According to the WHO, chronic diseases are the leading cause of mortality and morbidity in Europe. The prevalence of chronic diseases and also of combinations of chronic disease rises. Clinical population studies showed that multimorbidity is common and in the Dutch general population, 29.7% suffer from multimorbidity [8]. A systematic literature review showed a prevalence of 60% of multimorbidity among people aged 55 to 74 [9]. Although its

prevalence increases with age, it is not a problem limited to the elderly population. Multimorbidity is associated with high mortality, reduced functional status, and increased use of both inpatient and ambulatory health care [10]. In the USA, approximately 80% of Medicare spending is devoted to patients with 4 or more chronic diseases, with costs exponentially increasing with higher multimorbidity [11]. In this thesis, we showed that many patients with AS suffer from multimorbidity and that having more than one disease in addition to AS resulted in lower quality of life, impaired function and more work disability.

The findings in the literature and of the present thesis have several implications for society and organization of care. Traditionally, health care and treatment strategies mainly focused on single-diseases without considering the broader context of multiple risk factors and co-occurring chronic conditions. Most evidence based medicine guidelines are not developed for patients with multimorbidity and do not consider related consequences such as polypharmacy. Strategies to manage different chronic diseases create a growing burden for patients [12]. Different clinicians offer care, which may lead to uncoordinated prescriptions and polypharmacy, increasing treatment costs, side effects, and unintended drug interactions. To optimize care of patients with multimorbidity, health care services are needed that are coordinated at the patient level. In patients with SpA, for example, multidisciplinary consultation hours in which rheumatologists, dermatologists, gastroenterologists, and ophthalmologists are working together may improve care and decrease the burden of treatment for patients.

In light of prevention, it is important to learn more about which diseases are more prevalence or which patients are at risk to develop specific comorbidities. In this thesis we investigated the risk of cardiovascular disease in patients with AS. Cardiovascular disease is one of the leading causes of death and loss of quality of life worldwide. Understanding the underlying association between AS and cardiovascular disease may help determine the targets of prevention. The cardiovascular risk is now well established in patients with rheumatoid arthritis. In this thesis it was shown that the increased risk of cardiovascular disease was only higher in women with AS, but this was mainly explained by NSAID use in this group. In particular, the risk of ischemic heart disease was increased in patients who used a COX-2 inhibitor. The risk of acute myocardial infarction, however, was not increased in patients with AS. Therefore, it seems that there is no need to include patients with AS in large cardiovascular prevention programs, as is the case with rheumatoid arthritis. There is probably more potential in carefully selecting the appropriate class of NSAIDs in the lowest possible dose.

Mental health problems are often an underestimated comorbidity in patients with chronic diseases, such as in patients with AS. These conditions may have large impact both on patients and society. It has been shown that comorbid depression is often associated with a more severe course of the physical disorder, partly because of non-adherence to

treatment regimens in depressed patients [13]. Further, it has been shown that improvement in depression outcome was associated with decreased somatic symptoms without improvement in physiologic measures [14]. In AS, only limited information is available about the prevalence and treatment of depressive symptoms. In this thesis, we showed in a subgroup analysis of a randomized controlled trial that depressive symptoms were commonly present and improved with anti-TNF-alpha therapy. This study was a first step in the research on the effects of treatment of depression among people with AS and further larger studies are warranted.

In summary, SpA and AS as a subgroup, are common diseases with a significant burden on patients and society. Because AS usually starts at a young age and AS may have large impact on functioning, the socioeconomic impact of the disease can be high. With the introduction of anti-TNF-alpha treatment, effective treatment has now become available for SpA. Anti-TNF-alpha treatment, however, is expensive and reliable estimates of the prevalence of SpA and AS are useful for health care budgets. Since remission rates are highest in the early stages of disease, early recognition of SpA is important. In particular improving knowledge of GPs and other physicians about disease patterns of SpA and including EAMs will help to achieve this. As many patients suffer from EAMs or comorbidities, reorganization of health care delivery for these patients is important to improve quality of care.

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