

Health and economic outcomes in axial spondyloarthritis

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Chapter 11

Impact paragraph

Summary of main findings

The overarching objective of this thesis was to investigate health and economic outcomes of axial spondyloarthritis (axSpA) from a patient and societal perspective (**Chapter 1**). We conducted eight studies, resulting in a number of findings. Gender was shown to affect quality of life and spinal damage of patients with axSpA, with male patients having better quality of life, yet also more spinal damage (**Chapter 2**). Mastery, defined as the sense of control over life and disease, was revealed to be a key determinant of symptoms of depression in axSpA ('comorbid depression') (**Chapter 3**). In addition, infliximab, a biological disease-modifying antirheumatic drug (bDMARD) commonly used in the treatment of axSpA, also reduced comorbid depressive symptoms in these patients, mainly by improving symptoms of axSpA. Importantly, we observed no signs of a direct effect of inflammation on depressive symptoms (**Chapter 4**). Regarding work outcome in axSpA, patients with axSpA were still less often employed when compared to the general population (**Chapter 5**) and frequently reported sick leave. Importantly, sick leave itself predicted future sick leave, and thus was concluded to be a warning signal (**Chapter 6**). In the setting of a willingness-to-pay study, which is an alternative approach to value the benefit of treatments, the majority of patients would hypothetically be willing to pay for infliximab, especially if they responded well to this drug (**Chapter 7**). In a cost-effectiveness study of algorithms meant to guide diagnosis of axSpA, the currently recommended algorithm ('Modification 2'), was confirmed to also be the most cost-effective option. However, this algorithm was not perfect, and it was revealed that a better algorithm could cost much more, yet still be worth its cost (**Chapter 8**). Finally, we successfully developed and implemented a new registry ('SpA-Net'), designed to monitor patients with SpA, in several hospitals in the Netherlands (**Chapter 9**).

Implications for research

Two studies in this thesis provided additional insights into the origin and treatment of the impact of axSpA on mental health, in particular depressive symptoms. 'Contextual factors', i.e. the personal and environmental factors that are not part of axSpA itself but influence how axSpA affects patients' functioning, likely play a larger role than axSpA-related factors themselves in comorbid depression. Future studies should therefore investigate whether prevention and management of comorbid depression could benefit more from a generic approach (incorporating context) instead of an axSpA-specific one. Also, the central role of mastery in comorbid depression suggests that mastery and related factors, such as self-efficacy, deserve attention in future research. It would be helpful to know if, and how, mastery could be improved in these patients, and whether this would also improve mental

health. In addition, we observed no direct link between comorbid depressive symptoms and inflammation - hypothesized to be the main mechanism behind comorbid depression. In the future studies that are necessary to confirm this finding, inflammatory biomarkers other than C-reactive protein (which was used in this thesis) should be included. These studies could also explore whether certain subgroups with comorbid depression, for example those with higher levels of inflammation, are more likely to benefit from infliximab and similar drugs. Finally, many contradictory findings in this area of research remain, also between this thesis and other published studies, partly as a consequence of clinical and methodological heterogeneity across studies. Future studies need to be designed with clearly formulated study objectives and hypotheses on comorbid depression, provide a clear definition of what constitutes 'depression' and take relevant determinants of depression into account.

In another study in this thesis, we asked patients how much they would be hypothetically willing to pay for treatment with infliximab. This 'willingness-to-pay' (WTP) approach is used to express changes in health due to treatment in monetary terms. It is an alternative approach to the traditional methods for measuring treatment benefits, which are based on measuring symptoms of disease or overall health. WTP studies are at risk of bias, however, as patients might state they would not be willing to pay out of protest (against the idea of paying for drugs), even when it is stated explicitly that it concerns a purely hypothetical situation. In this thesis, this problem was overcome by specific statistical methods that allow for identification of those never willing to pay, i.e. the 'protesters'. We recommend that future WTP studies in axSpA and other diseases adopt similar methods.

Up till now, cost-effectiveness research in axSpA was focused on drug treatments. Our cost-effectiveness study was the first to investigate (mis)diagnosis of axSpA, and demonstrated that it is feasible to estimate the consequences of misdiagnosis, i.e. to what extent a wrong diagnosis can lead to more costs and loss of quality-adjusted life-years (QALYs). Also, we conducted an analysis to assess the expected value of a perfect diagnosis, revealing the hypothetical room for improvement in monetary terms. This type of modelling can support researchers to understand in which position (in the diagnostic process or treatment decision) innovative tools, often biomarkers, would be most beneficial for patients and society. This calls for a stronger integration of health technology assessment in basic/translational research.

Implications for society

The findings in this thesis on reduced employment and substantial sick leave among patients with axSpA indicate that valuable human capital is lost for society. This suggests that there is room for improvement, i.e. to increase employment rates and reduce sick leave in axSpA, thereby increasing patients' productivity and reducing costs for society.

It requires careful thinking, however, how to support patients in healthy and sustainable workforce participation, to maximize societal health, wealth and welfare. Work-focused care and healthy workplaces could play an important role in this. Regarding sick leave, short-term sick leave often will actually promote recovery and thus protect patients from long-term sick leave or work disability. Society would not necessarily benefit most from averting all sick leave. We should also realise that gainful employment likely is not possible for all patients, or might not be possible in all phases of their life or disease-course.

Our cost-effectiveness study on diagnosis of axSpA investigated which diagnostic algorithm would be most cost-effective for society. This is important, as resources are scarce and healthcare budgets are limited. Decision-makers can spend money only once, meaning they should do so wisely and improve health in an efficient manner. This study revealed which algorithm would result in most value, in terms of both costs and quality of life, when implemented in current practice. In addition, the results also suggest that more accurate - but also more expensive - diagnosis of axSpA could still be 'worth it'. However, more accurate diagnosis likely requires new diagnostic tests, some of which are still in development. Both public funding bodies and private companies have to make investment choices: which technologies should we further invest in, and which should we abandon? Future studies could use the economic model that was developed for this thesis to answer such questions. If the expected benefits of a new technology are deemed to be too low, it could be considered to stop development and instead invest in other technologies that show more promise. This approach could help maximize the 'return on investment' for society.

In line with the above, society would benefit from transparency on health outcomes and costs of healthcare. Such transparency would help to identify areas for improvement in healthcare, but requires that relevant outcomes are measured in a regular and comprehensive manner. SpA-Net, a registry that is integrated in daily rheumatology practice as an electronic medical record, allows for monitoring of patients with SpA. The outcomes collected in SpA-Net can help inform the Dutch government, insurers and healthcare organisations on how to deliver efficient care and minimize any unwarranted variation in healthcare utilisation between practices.

Implications for patients

The findings on comorbid depression in this thesis are of value for patients. First, mental health problems, and specifically depressive symptoms, were quite common in patients with axSpA - and likely more common compared to the general population - which should make patients aware of this additional risk. It should also prompt them to discuss negative feelings with their healthcare provider. Second, patients should be aware of the factors associated with depression. In this thesis, axSpA-related disease activity contributed to depressive

symptoms, indicating a need for treatment adherence in order to control disease activity. Also, mastery had a central role, indicating that interventions aimed at increasing mastery and related factors, such as self-efficacy, could be beneficial. It should be noted that, as stated above, it is unknown whether improving mastery and self-efficacy actually improves depressive symptoms. Third, treatment with infliximab improved depressive symptoms in the majority of patients with active axSpA. Other bDMARDs would be expected to give similar results. This provides a promising outlook for patients in practice with active axSpA and depressed feelings. However, these patients should be aware that there is a chance that they do not experience such benefit, and that other therapies are necessary.

Our findings that patients with axSpA were less often employed compared to the general population, and that sick leave was recurrent, indicate that patients fall behind when work is concerned. This is relevant for patients, as they themselves perceive 'work' as one of the most important roles they can fulfill in society. Patients should be aware that, once they experience sick leave due to axSpA, they are at increased risk for additional future sick leave. This suggests that sick leave is not only a warning signal, but also a potential starting point for interventions to prevent future sick leave. These findings should stimulate patients to discuss work-related matters with those who can support them in their work role, such as their healthcare provider, but also an occupational physician and their employer.

Patients will also benefit from the successful development and implementation of SpA-Net. Patients participating in SpA-Net can access their records, see the results of outcome measures and leave notes for care providers. They could benefit directly by gaining insight into their disease and its course, and by becoming empowered and more involved in the care they receive. This was supported by interviewed patients, who considered SpA-Net to be of additional value to current care. Future studies need to confirm these benefits for patients. Patients not involved in SpA-Net, for example because their centre is not participating, might benefit in the future when these centres adopt similar systems.

Implications for healthcare professionals

As a result of this thesis, healthcare professionals should become more aware that not only disease-related but also contextual factors affect the outcomes of their patients with axSpA. Patients are at risk of being not employed, especially when disease activity is high and mastery is low. They will incur sick leave, in particular when educational attainment is low and disease activity and functional impairment are high. Patients are also more likely to feel depressed, and low income, low satisfaction with role participation and high disease activity that mainly contribute to these feelings. Treatment with bDMARDs in those with active disease can alleviate these dismal feelings, yet a notable proportion of patients will maintain clinically relevant depressive symptoms despite bDMARD treatment. Female

patients will likely experience lower health-related quality of life compared to male patients, independent of other factors. Some (perhaps most) of these relationships mentioned above are not easy to modify, or modifiable at all. However, appropriate awareness of outcomes outside disease activity - such as depression and work - and factors associated with these outcomes could help identify patients at risk for worse outcome and guide individualized disease management. Healthcare providers should discuss these outcomes with their patients. Systems such as SpA-Net help to monitor these patients in a comprehensive way, assessing such outcomes systematically, but also give patients a voice in care decisions, promoting shared-decision making. Finally, based on this thesis, healthcare providers should prefer Modification 2 over the alternative algorithms for diagnosis of axSpA, as this will provide the greatest benefits to patients and society.