

Editorial

Key patient related factors in the management of inflammatory bowel disease

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Abstract

Background: Inflammatory Bowel Disease (IBD) is a lifelong illness typically starting during the teen years in patients with an appreciable negative impact on health-related-quality-of-life (HRQoL). However, more needs to be known about the effects of IBD on work productivity, daily activities and HRQoL to guide future decision making including priorities for resource allocation with an increasing prevalence of IBD as well as years with disability. In addition, concerns that indirect costs may not always be considered by payers within reimbursement and funding decisions. Methods: Survey among Austrian patients with IBD using robust instruments. Results and Conclusion: IBD does have a substantial burden reducing HRQoL and work productivity and increasing work absenteeism, with differences between those with ulcerative colitis and Chron's disease. Productivity reduction was associated with reduced HRQoL. Improved HRQoL should be a focus of future treatments and funding decisions, which is particularly important for patients with IBD. However, indirect costs may not always be a focus among reimbursement authorities.

Body of the review

As Walter *et al.* point out, inflammatory bowel disease (IBD) including Chron's disease (CD) and ulcerative colitis (UC) are lifelong conditions with a significant impact on the health-related-quality-of-life (HRQoL) of patients (1-7). In their systematic review, Knowles *et al.* (2018) showed that HRQoL was appreciably lower among patients with IBD when their disease was active and that mental functioning was particularly impacted (3). In addition, whilst patients with CD typically had lower HRQoL scores than those with UC, this difference was not significant, although patients with CD in remission had significantly lower, i.e. worse, mental health HRQoL scores (3). This is important as the prevalence of IBD is relatively high across Europe at 0.3% of the population and rising globally (8, 9), with the total number of IBD-related deaths world-wide also increasing with rates rising by 67.0% between 1990 and 2017. In addition, years lived with disability (YLD) attributed to IBD almost doubled during the same period (8). Alongside this, a recent study from King *et al.* (2020) in the UK based on a national patient level database suggests that these prevalence rates may be underestimates with current rates more than double previous estimates and rising (10). This increases the focus on managing IBD well across countries.

Alongside the disease burden associated with IBD in terms of HRQoL and YLD, Walter *et al.* also pointed out that IBD has a considerable economic burden further enhancing health authority focus. This includes indirect costs especially with IBD typically occurring during the teens and 20s for most patients and is lifelong (1, 11-13). Sick leave and unemployment is found to be significantly associated with a reduction in HRQoL in patients with IBD necessitating the need to address this (1, 7). However, in their recent study Lo *et al.* (2020) found that among 513 IBD patients in Denmark, and matched with a control group, there were no significant differences in indirect costs between those patients with either CD or UC and the control population (14). Consequently, studies such as those by Walter *et al.* are needed to provide further information on issues such as HRQoL, work productivity, and indirect costs in patients with IBD, to guide future decision making (1).

The biologics including the anti-TNF agents, e.g. infliximab and adalimumab, interleukin IL-12/ IL-23 (ustekinumab), and vedolizumab (15, 16), have appreciably expanded available treatments to manage patients with IBD resulting in a more curative approach (1, 17-19), which is welcomed. However, biologics have considerably added to the direct medical costs for treating patients with IBD, making them unaffordable in a number of lower- and middle-income countries (LMICs) including Central and Eastern European countries (20, 21). The advent of the biosimilars has started to change this with appreciable price reductions seen with infliximab and adalimumab and concomitantly with HUMIRA among European countries (22-26). The Norwegian Government's study with infliximab showing no differences in effectiveness and safety between the originator and biosimilars has helped address concerns with biosimilars, which has resulted in ongoing initiatives across countries to increase their use (27-30). Initiatives include physician education, prescribing targets for biosimilars as well as financial incentives among European and other countries (30-34). Typically, multiple initiatives are needed to aid price reductions and utilisation to achieve desired savings, with ongoing developments to enhance comparisons between countries to expedite this (35-37).

It is likely that prices of biosimilars will continue falling mirroring the situation with oral generics; however, not to the same extent in view of higher production and clinical trial costs. In view of this, it is important to investigate further the impact of biologics and other treatments on key issues such as HRQoL, work productivity and the extent of indirect costs among IBD patients currently being treated with a full range of conventional medicines and biologics in Europe to guide future decision making. This was the objective of Walter *et al.* (1). We appreciate that only a relatively limited number of European countries consider indirect costs in their reimbursement decisions (1, 38); however, measures such as the impact of diseases on HRQoL, productivity, and mental health are considered important outcome measures across disease areas. The focus on the impact of different diseases and treatment options on mental health will grow with the advent of COVID-19 and the appreciable impact this pandemic is having, and will continue to have, on the prevalence of mental disorders across populations (39-42).

Published studies have shown that biologics improve productivity and employment in patients with UC whilst reducing disability-pension payments, and similarly with patients in remission (43, 44), which is welcomed. However, Walter *et al.* wanted to build on this by seeking to determine the extent of impaired work productivity, reduced daily activities and associated loss of HRQoL attributable to IBD to help guide future decision making (1). In addition, breaking down the findings into CD versus UC patients as well as those on conventional versus biologic therapy. We have seen other authors show differences in factors such as disability between CD and UC patients (6). The authors used robust methodologies among 510 patients with IBD, with the questionnaire circulated by the Austrian Crohn's Disease/ UC Association similar to other studies (11, 21, 45). For instance, HRQoL was measured via the SIBDQ (Short Inflammatory Bowel Disease Questionnaire), which has been widely used in other studies (5, 46).

Not surprisingly, first line biologics were the anti-TNF agents (84.1%), with appreciable differences in HRQoL between patients in relapse versus those in remission (1). However, there were differences between UC and CD, different to the study of Christiansen *et al.* (2019) (7), which may be due to differences in the observation period (1). Having said this, Argyriou *et al.* (2017) had previously demonstrated significant differences in disability between UC and CD patients (6). Patients on first line biologics also evaluated their HRQoL significantly higher than those in the following lines. Encouragingly, the HRQoL of patients did not differ significantly between those on conventional therapy, which tend to have milder symptoms, reflecting the authors' belief regarding the effectiveness of biologics in patients with IBD (1). The authors also found differences in the effect of

different biologics on HRQoL similar to other studies (47-51), which needs further investigation to guide future treatment strategies. This includes whether any therapeutic drug monitoring (TDM) takes place as under-dosing impacts on their effectiveness in practice (52-55). We are seeing developments in approaches to monitor blood levels of biologics in practice since the ideal situation would be for patients to be tested during follow-up clinics rather than being recalled sometime later to review treatment strategies (56), and we will be reporting on these in the future. In any event, TDM is likely to grow as more biosimilars become available with an increased imperative to ensure patients are treated well first time with biosimilars before going onto more expensive patented biologics, with second line biologics typically less effective than first time treatments (1).

Unsurprisingly, a relapse was associated with reduced productivity, greater than those in remission (1), with sick leave lower than seen in previous studies; however, like other studies absenteeism and sick leave was higher in CD vs. UC patients and higher than seen in the general population (1, 57). There is a concern though that patients with IBD seem reluctant to miss work even with severe symptoms. Consequently, the correlation between HRQoL and everyday activities was stronger than the correlation with paid work (1).

In conclusion, whilst more studies are needed in this area including potentially new metrics that might better capture patients' preferences for specific treatments, the authors have shown that IBD reduces HRQoL, with differences between those patients in relapse and remission, as well as appreciably impacting on work productivity. Treatments that improve the HRQoL of patients with IBD, and with it work productivity, are welcomed. However, we will continue to see differences in the inclusion of indirect costs in reimbursement decisions across countries. Such differences may be exacerbated post the COVID-19 pandemic with its envisaged increase in unemployment levels especially in the short term.

Conflicts of interest

No conflicts of interest to declare.

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