Towards optimal care in inflammatory bowel disease

Thiopurines, tofacitinib and impact on working life

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Publication date
2023

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THESIS SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

THESIS SUMMARY

In this thesis we aimed to further optimize inflammatory bowel disease (IBD) care by focusing on efficacy and safety of 'old' (thiopurines) and 'new' (tofacitinib) immunomodulators and by evaluating disease impact on working life.

PART I: THIOPURINES FOR ULCERATIVE COLITIS – 'THE OLD'

In **chapter 2,** we critically reviewed the literature to determine the efficacy of conventional thiopurines (azathioprine and mercaptopurine) to treat ulcerative colitis (UC) patients. We showed that available literature to support the use of thiopurines for UC treatment is scarce, outdated and controversial. In general, no endoscopic outcomes were available, no therapeutic drug monitoring (TDM) was applied in case of drug intolerance or inefficacy and most studies lacked sufficient power or blinding of treatment allocation. We concluded that there is a need for solid evidence to support the use of thiopurines in UC patients in current clinical practice. Therefore, satisfying current standards using endoscopic end-points and applying TDM, in **chapter 3** we performed a randomized placebo-controlled trial to assess efficacy of optimized mercaptopurine treatment to achieve and maintain (combined) corticosteroid-free clinical remission and endoscopic improvement after one year. UC patients who were included in this study had active disease despite mesalazine maintenance treatment that required a corticosteroid remission-induction course. Due to recruitment problems, this study was stopped prematurely. Although a large proportion of patients (45%) in the mercaptopurine group stopped treatment before one year, a superior effect of mercaptopurine treatment was observed to achieve combined clinical remission and endoscopic improvement (48%) after one year compared to placebo (10%). Dose-adjustments were required in 76% of patients on mercaptopurine, yet TDM did not prevent drug-related adverse events in this study. By systematically reviewing existing literature, in **chapter 4** we assessed risk factors for thiopurine-induced leukopenia in IBD. We found strong associations between presence of thiopurine methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15)* gene polymorphisms and development of thiopurine-induced leukopenia. Gene polymorphisms may lead to changed (mostly decreased) enzyme activity and can thereby result in altered thiopurine metabolization. Trends towards an association between (very) high levels of 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) and thiopurine-induced leukopenia were observed, yet cut-off levels remain unclear.

PART II: TOFACITINIB FOR ULCERATIVE COLITIS – 'THE NEW'

Tofacitinib, a Janus kinase (JAK) inhibitor, has been shown to be a potent drug to treat UC. Yet, only few patients are eligible for inclusion into randomized controlled trials due to strict in- and exclusion criteria. In **chapter 5**, we therefore evaluated efficacy and safety of tofacitinib in a 'real-world' therapy-refractory UC cohort of 39 patients using tofacitinib carepath data. We showed combined corticosteroid-free clinical remission and endoscopic improvement in 39% of UC patients after one year. Although in our cohort patients continued tofacitinib in remission-induction dose (10 mg twice daily) for a relatively long period of time (median 14 weeks), tofacitinib was well tolerated.

Nine adverse events (incidence 0.4/patient-year) led to (temporary) tofacitinib withdrawal or dose reduction, including 2 herpes zoster infections. No cardiovascular adverse events (such as thromboembolic events and myocardial infarction) or malignancies were reported. In **chapter 6** we tried to fill a gap of knowledge concerning the potency of tofacitinib to reduce histological inflammation and to assess immunological changes in the colonic mucosa of UC patients before and after 8 weeks of treatment. We showed that most patients achieved histological response (85%) and remission (58%) after 8 weeks. Tofacitinib led to a substantial decline of total STAT1, STAT3 and STAT5 expression in the total patient cohort, showing JAK-STAT inhibition at a mucosal level. Significantly lower STAT1 levels were observed in responders after 8 weeks of treatment, which is presumably a reflection of the degree of histological inflammation. At baseline, (non-significant) trends towards higher JAK1, JAK2 and STAT4 and lower STAT6 levels were observed in *non*-responders compared to responders. Only for JAK2 this finding was confirmed in a subgroup analysis, showing highest baseline JAK2 levels for true non-responders, lowest for true responders and intermediate levels for partial responders. High JAK2 expression seemed associated with tofacitinib *non*-response and these patients might benefit from higher dosages or longer treatment duration in remission-induction dose.

PART III – IMPACT OF INFLAMMATORY BOWEL DISEASE ON WORKING LIFE

In part III, we assessed the impact of IBD on daily life of patients, with a focus on working life. In collaboration with the Coronel Institute of Occupational Health, we started a prospective multicenter cohort study to collect and assess patient-reported outcome (PRO) data in an employed IBD population. In **chapter 7** we presented the cross-sectional baseline data of the WORK-IBD study. The majority (53%) of the included patients reported overall work productivity loss in the past week, mainly due to presenteeism (on-the-job work productivity loss, reported by 50%) and 18% reported absenteeism (absence from work). Severe work productivity loss was predominantly associated with disease activity and disease severity (in the article defined according to treatment classes; i.e. treatment naïve patients versus patients on 'third class' biologic treatment). Fatigue was the most frequently reported reason for both absenteeism (56%) and presenteeism (71%) by IBD patients. Higher fatigue scores and lower health-related quality of life (HRQL) scores were significantly associated with increased work productivity loss and lead to considerable indirect healthcare costs. In **chapter 8** we confirmed these findings in the longitudinal WORK-IBD cohort, in which patients were followed for 18 months. We found that fatigue and reduced HRQL were the strongest determinants for work productivity loss in IBD patients even after correction for disease severity and disease activity. While HRQL is a commonly used PRO in IBD nowadays, quality of working life (QWL) has never been assessed in this population. Therefore, in **chapter 9** we used the Quality of Working Life Questionnaire (QWLQ), developed for cancer survivors returning to work, to assess QWL in IBD patients. It was shown that IBD-related problems negatively influenced QWL with similar outcomes when compared to cancer-survivors. Again fatigue and reduced HRQL, but also work productivity loss were associated with a low QWL.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The care for inflammatory bowel disease (IBD) patients is challenging. The pathogenesis of IBD (including ulcerative colitis (UC) and Crohn's disease (CD)) is still largely unknown. IBD can lead to a broad spectrum of disease phenotypes and disease severity can vary immensely between patients. Although already great progress has been made in the field of IBD care, including for example the rapid development of new drugs and shifting treatment targets, this in turn also leads to new challenges to overcome. With new drugs, new side effects can occur and questions arise concerning treatment optimization and dosing (personalized care). In addition, the pursuit of complete absence of inflammation is still unattainable in many IBD patients. In this thesis, we aimed for further optimization of IBD care by evaluating efficacy and safety of 'old' and 'new' oral immunomodulators (thiopurines and tofacitinib) and by focusing on the disease impact on working life.

PART I: THIOPURINES FOR ULCERATIVE COLITIS – 'THE OLD'

Is there still room for thiopurines?

The use of thiopurine monotherapy is recommended in UC patients with 5-aminosalicylate (5-ASA) intolerance or with corticosteroid-dependent disease.[1] When a patient fails both 5-ASA and thiopurines, biologicals (i.e. anti-tumor necrosis factor (anti-TNF) agents, vedolizumab and ustekinumab) and Janus kinase (JAK) inhibitors (i.e. tofacitinib, filgotinib and upadacitinib) are available therapies. Due to limited and low-quality evidence of efficacy and due to anxiety regarding (potentially serious) adverse events, reluctance concerning the use of thiopurines in UC has arisen (**chapter 2**).[2] Azathioprine (AZA) and mercaptopurine (MP) have been used and studied since the 1960s. As over the years treatment targets have broadened from achieving clinical remission to endoscopic remission and due to the introduction of thiopurine metabolite measurement in daily clinical care, studies that investigated the effectiveness and safety of conventional thiopurines are outdated. The most recent Cochrane meta-analysis that included 7 RCTs of predominantly poor study quality showed superior effectiveness for thiopurines compared to placebo and to 5-ASA in sustaining maintenance of remission.[3] In line with these outcomes, we have shown that optimized mercaptopurine therapy (using TDM) is more effective than placebo when added to 5-ASA in order to maintain steroid-free clinical remission and endoscopic improvement after one year in UC (48% vs 10%, **chapter 3**).[4] The use of thiopurines in comparison to newer drugs remains a topic of discussion. Yet, the majority (>70%) of IBD physicians consider thiopurine monotherapy as an effective treatment option in UC and >50% of them agreed that conventional thiopurines will still be used both in monotherapy and combination therapy in the future.[5] Unfortunately, no head to head studies exist comparing conventional thiopurines to 'third step' therapies (biologicals and tofacitinib) with regard to maintenance of remission in UC. The comparison is difficult since thiopurines are only indicated as maintenance therapy, which is different from biologicals and JAK inhibitors that are used for both remission induction and maintenance of remission in UC. Therefore, indirect treatment comparisons using network meta-analysis usually disregard thiopurines.[6,7] To make any comparison: 35% of biologic-naïve patients using infliximab monotherapy and 42% of tofacitinib responders at 8 weeks had endoscopic improvement after one year.[8,9] These outcomes, however, are difficult to

compare with thiopurine trials due to a more treatment-refractory UC population that participate in biological and JAK-inhibitor trials. A different way to compare therapies is to assess treatment-associated healthcare costs for society. Thiopurines are considered a low-cost treatment option, since drug costs are low. But, healthcare costs consists of more than drug costs alone and can be divided into direct costs (i.e. drug costs and costs for hospitalization, disease assessment and TDM) and indirect healthcare costs, including work productivity loss.[10] For thiopurines in the biosimilar era, it was shown that initial AZA monotherapy comprised the lowest costs and utility in terms of quality adjusted life years (QALYs) compared to immediate infliximab monotherapy or combination therapy in Crohn's disease (CD).[11] Although in long-term, starting direct with combination therapy (infliximab and AZA) might be cost-effective in the future with expected further reductions in drug costs for biologicals. In this thesis, we did not assess direct healthcare costs. However, in **chapter 7** we did show that patients using first, second or third-line biologic treatment comprised the highest indirect costs due to work productivity loss when compared to patients that were treated with first-line immunomodulators or 5-ASA or compared to treatment-naïve patients.[12] Our results reveal that indirect healthcare costs can be attributed to disease severity, disease activity or treatment refractoriness rather than the specific type of therapy the patient uses.

Fear of thiopurines, is it fair?

Adverse events and toxicity hamper the use of thiopurines. Fear of thiopurine-induced adverse events leads to reduced thiopurine prescription in up to 45% of IBD physicians.[5] Frequent side-effects include dose-independent gastrointestinal complaints (mainly nausea) and dose-dependent bone marrow suppression (i.e. leukopenia and thrombocytopenia) and hepatotoxicity.[13] Other known intolerances comprise pancreatitis and hypersensitivity reactions (i.e. skin rash, fever and arthralgia).[13,14] The most feared complications to occur using thiopurines include malignancies, especially lymphomas.[15] IBD patients are at increased risk to develop lymphomas when using thiopurines, in particular when used in combination therapy with anti-TNF therapy, although the absolute risk remains very low.[16,17] Drug withdrawal is a major concern in IBD patients treated with thiopurines. Approximately 40% of IBD patients stop their thiopurines because of side-effects, with a peak one month after treatment initiation.[13,18] Overcoming the first period after thiopurine initiation is of great importance, since thiopurines continuation over 16 weeks leads to longer drug adherence.[19] In the OPTIC trial we observed high drug withdrawal rates (45%) in UC patients treated with MP, despite therapeutic drug monitoring (TDM), which was predominantly because of an adverse events (24%, **chapter 3**).[4] Indeed we observed an increased number of side effects one month after treatment initiation and after 6 months of therapy no significant differences in adverse events were observed between patients receiving MP versus patients in the placebo group. Nausea was the major reason for thiopurine-related treatment withdrawal (14%), which is already known from prior research.[13,20] Mild bone marrow suppression incidence rates have been described between 5 and 25% of UC patients using thiopurines.[21] Bone marrow suppression was the most frequently observed side effect in the OPTIC trial (16% of the MP treated patients, **chapter 3**), of which only one was considered severe. However, no patients had to discontinue treatment for this reason and no cases of febrile neutropenia were observed.[4]

Towards personalized medicine

Different treatment strategies have been proposed to avoid thiopurine intolerance, toxicity and withdrawal and to improve effectiveness. In the Netherlands, reactive measurement of thiopurine metabolites including 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) is common practice in IBD patients with signs of intolerance, toxicity or non-response. Higher 6-TGN levels lead to increased treatment response, with a threshold target between 235 and 490 pmol/8 × 10^8 RBCs (measured using high-performance liquid chromatography (HPLC) in red blood cells by the Lennard method).[22,23] Using a different HPLC method (Dervieux method, which is applied in many laboratories in the Netherlands), usually a grade 2.6 conversion factor is applied leading to target levels between 600 and 1200 pmol/8 × 10^8 RBCs.[24] In contrast, higher 6-TGN levels, and also very high 6-MMP levels, are associated with higher risk of myelotoxicity as we have shown in our systematic review, yet ideal cut-off levels remain unclear (**chapter 4**).[25,26] High 6-MMP levels in combination with low 6-TGN levels (skewed metabolism) are especially associated with hepatotoxicity and higher risk of non-response. Pro-active TDM, even as early as one week after treatment initiation, is a widely researched strategy in order to overcome intolerance, toxicity and withdrawal and to improve efficacy.[27,28] However, superior effectiveness of pro-active TDM compared to reactive TDM has yet to be proven. Important shortcomings of TDM for thiopurines include interlaboratory differences, analytical pitfalls and the large amount of retrospective studies leading to discrepancies in 6-TGN targets.[29,30] In addition, thiopurine metabolites are measured in erythrocytes, while white blood cells are the treatment target in IBD and no distinction is made between active thioguanine nucleotides and its residual products.[30] Switching to low dose thiopurine with allopurinol co-treatment is found to be effective to overcome thiopurine intolerance, improve drug adherence and thereby effectiveness, especially in patients with skewed metabolism (preferential 6-MMP shunting).[31–33] Another effective strategy in skewers is to start thioguanine, an alternative thiopurine in which 6-MMP metabolization is bypassed.[34] In the OPTIC study we found a relatively high number of patients with 'skewed metabolism' which resulted in nearly half of the patients to switch to allopurinol co-treatment (switching to thioguanine was not allowed in the OPTIC trial, **chapter 3**).[4] Although this might have occurred due to a relatively high aimed weight-based dose, it might also have contributed to the considerable number of patients with steroid-free clinical remission and endoscopic improvement after one year.

Patients with thiopurine methyltransferase (*TPMT*) polymorphisms express lower TPMT enzyme activity resulting in metabolite imbalance with significantly higher 6-TGN levels. As a result, these patients are at higher risk of developing myelotoxicity (**chapter 4**).[25] In many countries pre-treatment TPMT assessment is therefore routinely applied resulting in lower dosing regimens in TPMT variant carries. As we have shown in **chapter 4**, numerous factors might be associated with thiopurine-induced leukopenia. Although TPMT variant carriers are at increased risk of myelotoxicity, pre-treatment TPMT genotyping was not found to prevent the occurrence of adverse drug reactions (TOPIC-trial).[35] Nudix hydrolase 15 (NUDT15) variant carriers (with decreased NUDT15 enzyme activity) are also at increased risk of developing thiopurine-induced myelotoxicity, presumably as a result of high 6-thioguanosine triphosphate (6-TGTP) levels, one of the 6-TGN (**chapter 4**).[25,36] Nevertheless, NUDT15 polymorphisms are predominantly found in the Asian population.[37] At this

moment, too little evidence exist for standard pre-treatment NUDT15 genotyping with regard to its cost-effectiveness in the Netherlands.

The future of thiopurines, to be continued…

Despite poor drug adherence and high numbers of intolerance, efficacy of conventional thiopurines as monotherapy therapy in UC in the biologic and JAK inhibitor era have been proven. Although pro-active measurement of thiopurine metabolites may not result in less drug withdrawal, reactive TDM still remains an attractive strategy to optimize thiopurine efficacy and reduce toxicity. Prospective studies comparing pro-active (starting one week after treatment initiation) and reactive TDM in IBD would be of great interest. New (non-invasive) biomarkers to predict thiopurine treatment response, toxicity and intolerance are more than welcome. An interesting first step might be further development and testing of a newly proposed pharmacodynamic marker panel including Ras-related C3 botulinum toxin substrate 1 and phosphorylated transcription factor signal transducer and activator of transcription 3 (Rac1/pSTAT3) measured in peripheral blood leukocytes.[38]

PART II: TOFACITINIB FOR ULCERATIVE COLITIS – 'THE NEW'

The 'new' kid on the block

The registration of the oral small molecule tofacitinib for therapy refractory UC patients was a welcome addition to the biological treatment arsenal, since biologicals need to be administered intravenously or subcutaneously. Tofacitinib, a JAK inhibitor, is an effective drug to treat UC. In a refractory UC cohort remission rates of ~18% after 8 weeks and up to 41% after one year have been observed (OCTAVE trial).[9] However, the difficulty of these well-designed and complex registration trials is that the data is hard to extrapolate to the individual patient, due to stringent eligibility criteria, protocols and dosing regimens. Therefore, we investigated the efficacy of tofacitinib in a 'real world' refractory UC cohort using care path data and found comparable efficacy rates of 22% after 16 weeks and 39% after one year (**chapter 5**).[39] Evidence is accumulating positioning tofacitinib as first-line treatment after failing conventional therapies (5-ASA and thiopurines) before biologicals. Also, tofacitinib has been suggested as effective treatment option in acute severe colitis leading to high short-term colectomy-free survival.[40] A network meta-analysis showed highest maintenance efficacy rates for upadacitinib and tofacitinib in comparison to biologicals including anti-TNF, ustekinumab and vedolizumab in UC.[6] In Japan, first-line tofacitinib in biological-naïve UC patients was found to be cost-effective compared to first-line infliximab in terms of quality adjusted life years (QALYs).[41] Another advantage of JAK inhibitors over biologics is the absence of immunogenicity and the possibility of re-initiation after loss of response (OCTAVE SUSTAIN and OPEN trials).[42] In comparison, we observed a need for dose re-escalation to 10 mg BID in ~40% of patients in our real world cohort (**chapter 5**).[39] In one third of these patients the dose was again reduced to 5 mg BID, thereby suggesting reobtained clinical response after loss of response. Achieving histological remission in addition to absence of macroscopic inflammation of the mucosa in UC has been shown to reduce the risk of relapses and neoplasia development in long-standing UC.[43,44] Although it has not been introduced as treatment target in daily care yet, few studies have already shown feasibility

of certain drugs to achieve histological remission in UC.[45] In **chapter 6** we showed that tofacitinib led to histological response in the majority of UC patients and even led to complete disappearance of neutrophils in more than half of the patients.

The flip side of the coin

JAK inhibition leads to downregulation of signal transducer and activator of transcription (STAT) phosphorylation and thereby reduces cytokine release. Tofacitinib targets all members of the JAK family, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), with a preferential selectivity for JAK1 and JAK3.[46] The JAK-STAT signaling pathway is involved in many processes, such as immunity, inflammation and cell differentiation (i.e. cell division, cell death and tumor formation). Therefore, as a reasonable result, JAK inhibition by tofacitinib can lead to unwanted side effects. For tofacitinib these side effects include infections (especially viral infections such as herpes zoster), non-melanoma skin cancer (NMSC). More rarely major cardiovascular events (MACE) and malignancies (other than NMSC) have been described. The latter two have been discussed extensively and are for some gastroenterologists a reason for caution to start tofacitinib. Evaluating latest evidence, the risk of major adverse events due to tofacitinib has to be downgraded. Recent meta-analyses revealed no increased overall cancer risk or higher risk for MACE in patients using JAK-inhibitors.[47,48] In addition, no significant higher risk for developing overall (serious) adverse events was observed for tofacitinib compared to biologicals and other JAK inhibitors.[6,7] In our real world cohort with a relatively short follow- up period of one year, we did not observe MACE or cancer (**chapter 5**).[39] However, (mild) infections were often reported, including two patients with herpes zoster for which tofacitinib had to be stopped temporary. The risk to develop herpes zoster is higher when using higher dosages of tofacitinib and in patients over the age of 65 years old.[49] Older aged IBD patients are also at increased risk to develop NMSC and other malignancies when treated with tofacitinib, but in the general population this risk is also accumulating with higher age.[49] In therapy refractory elderly UC patients with a history of varicella zoster infection a varicella zoster vaccine is advised before tofacitinib is initiated. This was challenging up until very recently, since the only available vaccine in the Netherlands before July 2020 was a live attenuated vaccine after which tofacitinib initiation had to be postponed for 4 weeks. Since higher tofacitinib dosages are associated with higher risk of adverse events, the duration of remission induction using tofacitinib high dose (10 mg BID) in UC is usually confined to 8 weeks and can be extended to 16 weeks. In our cohort patients were treated with high dose tofacitinib (10 mg BID) for a relatively long period of time (~14 weeks, **chapter 5**).[39] Extended tofacitinib induction treatment (≥16 weeks 10 mg BID) is overall well tolerated and safety outcomes are comparable to short induction treatment (8 weeks 10 mg BID).[39,50] Both the OCTAVE trial data and real-world data reveal a substantial benefit of extended tofacitinib induction treatment (≥16 weeks) leading to ~50% of initial non-responders to achieve a clinical response or remission after one year.[39,50]

Biomarkers for treatment response; is it you JAK2?

Choosing the right drug for the right patient remains a challenging task in IBD. It may take years to find an effective drug and ideally prognostic biomarkers for therapy response are discovered. A few

attempts have been made to find predicting biomarkers for tofacitinib response in UC patients. An interesting potential predictor for tofacitinib response is a mucosal hub gene with 100% accuracy.[51] Using peripheral blood DNA methylation, a panel of 53 differentially methylated positions (DMPs) was identified with acceptable discrimination between responders and non-responders to tofacitinib.[52] In **chapter 6** we assessed JAK-STAT signaling in colonic mucosa of UC patients before and 8 weeks after tofacitinib initiation and observed a reduction in total STAT1, STAT3 and STAT5 expression in both responders and non-responders (**chapter 6**). Reduced STAT3 phosphorylation (pSTAT3) was observed in colonic mucosa of UC patients treated with tofacitinib, without an association with treatment response.[53] Lower pSTAT3/STAT3 ratios after tofacitinib initiation were associated with response to tofacitinib, but baseline pSTAT3/STAT3 ratios were not predictive for treatment response.[54] Interestingly, in a rheumatoid arthritis (RA) cohort higher baseline pSTAT1, pSTAT3 and pSTAT5 expression measured in peripheral blood monocytes was seen in tofacitinib responders compared to non-responders, which was not applicable to total STAT1 and STAT3 levels.[55] In RA conflicting data exists between *in vitro* and *in vivo* findings of JAK-STAT signaling, which can also be applicable to UC. In addition, differences in serum and mucosal JAK-STAT levels can exist. Another observation we made in **chapter 6** was a trend towards higher baseline JAK1, JAK2 and total STAT4 levels and lower total STAT6 levels in colonic mucosa of tofacitinib non-responders. In particular for JAK2 a gradual association was observed with highest JAK2 levels for true non-responders, lower levels for partial responders and the lowest levels were found for true responders. To our knowledge, this was not found in previous *in vivo* studies in UC patients before. *In vitro* assays show that tofacitinib has only moderate affinity for JAK2 and therefore it is suggested that JAK2 only plays a minor role in the efficacy of tofacitinib in UC. Our exploratory work might suggest that patients with higher JAK2 expression in colonic mucosa are potential non-responders to tofacitinib. Certain patients might benefit from higher tofacitinib dosage or longer treatment duration. Preliminary findings by Verstockt et al. have already shown that higher mucosal tofacitinib levels are associated with treatment response.[51]

Tofacitinib in the future

It can be concluded that tofacitinib is an effective treatment option for (especially younger) therapy refractory UC patients, with the advantage of absence of immunogenicity. Tofacitinib can be re-initiated (in a higher dose) after withdrawal or dose-reduction. The safety profile of tofacitinib is acceptable given its efficacy and in comparison to other available therapies in UC. In the future, tofacitinib and other JAK inhibitors might be considered as first-line treatment option after failing conservative therapies before biologicals, since network meta-analyses show highest efficacy rates for upadacitinib and tofacitinib. Head to head trials comparing different strategies in UC will contribute to optimization of the UC treatment algorithm. Further research should focus on finding predictive biomarkers for tofacitinib response and exploration of JAK-STAT signaling in colonic mucosa and peripheral blood is needed.

PART III: IMPACT OF INFLAMMATORY BOWEL DISEASE ON WORKING LIFE

IBD patients are frequently diagnosed at adolescence or early adulthood, the same period people often initiate a study and start their carriers and families. It is not difficult to imagine that IBD patients experience problems in daily life related to IBD. IBD patients experience reduced health-related quality of life (HRQL) and increased disability, especially in periods of active disease.[56] Lower employment rates and higher work disability rates are found in the IBD population compared to the healthy population.[57,58] Work productivity loss can be measured in terms of absence from work (absenteeism) and on-the-job productivity loss (presenteeism). The latter is an underestimated problem in IBD, leading to high costs for society (**chapter 7**).[12,59] Absenteeism and presenteeism are not only related to disease activity and severity. Also patients with quiescent disease can experience problems leading to work productivity loss. Reduced HRQL and severe fatigue are important predictors for work productivity loss, especially in CD patients (**chapter 7 and 8**).[12,60] When you ask the IBD patient about the main reasons for their work productivity loss, fatigue is the foremost self-reported problem (**chapter 7**).[12] While drug costs are still considered the main driver of healthcare costs for society in IBD and healthcare costs are increasing,[61] indirect healthcare costs are significant and should be included in socioeconomic analyses (**chapter 7**).[12,62]

Quality of working life

While the incidence of IBD is rising globally, the number of working persons with one of these chronic illnesses is growing. Restoration of quality of life and disability (return to normal life) is often proposed as the highest achievable goal in IBD. It seems reasonable that an important part of normal life in young IBD patients is a normal working life and career. Work tends to signify 'normalcy and control' and being able to work adds to quality of life.[63] In **chapter 9** we showed as one of the first that quality of working life is diminished in IBD patients.[64] The outcomes resemble the outcomes of cancer survivors returning to work for which the questionnaire was initially developed.[65] Measuring quality of working life in IBD might be considered an important addition to the currently available PROs and should be studied in further detail. By using QWL monitoring, we can gain insights in different aspects of QWL and thereby identify certain patients that might benefit from additional supportive care or interventions in the workplace.[66]

Fatigue, an underestimated problem without a simple solution

Although it was not the main scope of this thesis, the disabling impact of fatigue needs a paragraph on its own. The negative impact of fatigue in the daily life of IBD patients is tremendous. In all our studies, fatigue was identified as an important or main predictor of negative health outcomes in IBD, even when the disease is in remission. It leads to significant work productivity loss (both absenteeism and presenteeism) and thereby to high costs for society (**chapter 7 and 8**).[12,60] Fatigue was strongly associated with a decreased quality of working life, which in turn is associated with a decreased HRQL (**chapter 9**).[64] Results of a large survey in patients, their caregivers and physicians revealed the number one research priority for children and young adults with IBD is to answer the question: 'what are the causes of fatigue in children and young adults with IBD, and what steps can they take

to reduce their fatigue levels?"[67] IBD patients tend to establish a 'new normal' by coping with fatigue aiming for a similar level of work as their non-diseased co-workers.[68] In addition, they often prioritize their daily tasks at the expense of social activities, which in turn negatively influences quality of life. Currently many trials are running to solve the fatigue problem in IBD. However, at this moment no effective therapies have been identified that specifically target fatigue.[69] Future studies should focus on finding therapies to treat fatigue in IBD patients, especially in those without disease activity. Ideally, we find the pathophysiological link(s) between IBD and fatigue.

HOW TO WORK FROM HERE…

Over the years, 'personalized medicine' is pursued in order to optimize IBD care aiming to find the right drug (or surgery) for the right person, to optimize safety and efficacy of drugs and to reduce the disease burden for patients and costs for society. Personalized medicine is already intertwined in daily clinical care. We can no longer treat our IBD patients with thiopurines or biologicals without applying TDM and we know that certain patients might benefit from accelerated step-up (patients with a more aggressive disease course) or top-down approach (patients with for example CD solely confined to the ileum). Still, it can be a bumpy road to find an effective and safe therapy for IBD patients. Ideally predictive biomarkers are identified for treatment response and safety. Head to head trials might help us to adjust the rigid treatment algorithm that is available at this moment. Addition of absence of disability and restoration of quality of life to other important treatment targets (including absence of mucosal disease and clinical remission) is a valuable development in IBD care. To my opinion these two outcomes should be included in current clinical care in a more prominent way. Harmonization of PROs is key in order to achieve this goal. Lastly, a major challenge in IBD care is recognition, understanding and treatment of fatigue, also in patients with quiescent disease.

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