Quality of Life in Patients with Immune-Mediated Inflammatory Diseases

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ABSTRACT. There is no doubt that patients with immune-mediated inflammatory diseases (IMID) have a significantly impaired quality of life (QOL). Pain and disability often leave these patients helpless and frustrated. The recognition that addressing physical and psychological functioning plays a significant role in an overall treatment approach led to the inclusion of QOL measures as secondary outcomes in clinical trials with IMID patients. To that end, both generic and disease-specific instruments have been utilized. Measurement of health-related QOL (HRQOL) and patient-reported outcomes (PRO) in a controlled manner allows for better understanding of the correlation between different aspects of disease activity and QOL. In addition, the effects of different therapeutic options on HRQOL-related outcomes can be further evaluated. This 3-part section describes key QOL-related complaints of patients with IMID affecting joints, skin, or gut. An overview of the strengths and weaknesses of various commonly used HRQOL instruments is provided. Finally, the influence of anti-tumor necrosis factor-α agents on HRQOL outcomes, as assessed in recent clinical trials, is highlighted. (J Rheumatol 2011;38 Suppl 88:7–19; doi:10.3899/jrheum.110899)

Key Indexing Terms:
QUALITY OF LIFE OUTCOME ASSESSMENT RHEUMATOID ARTHRITIS
INFLAMMATORY BOWEL DISEASES PSORIASIS PSORIATIC ARTHRITIS

The management of chronic conditions, including immune-mediated inflammatory diseases (IMID), is becoming increasingly patient-oriented. Although the majority of patients affected by these recurrent, disabling conditions have a normal life expectancy, most of them experience effects on their daily activities, attitudes, and beliefs. Numerous studies have demonstrated that patients with IMID have a significantly worse quality of life (QOL) compared to the general population. Further, despite the availability of increasingly effective therapies, there remain many unmet needs in these patient populations. While signs and symptoms of the disease are frequently measured using disease activity indices, social and psychological problems are assessed with various QOL questionnaires. Assessment of health-related QOL (HRQOL) allows healthcare providers to better address patients' individual needs and to tailor possible solutions to their specific problems.

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HRQOL OUTCOME MEASURES IN RHEUMATOID ARTHRITIS (RA)

Sensitivity of Generic Instruments in Patients with Rheumatic Diseases

A number of generic and disease-specific instruments are used to assess HRQOL in patients with rheumatic diseases[1,2,3]. Such disease-specific measures have been developed to identify which aspects of a disease are most likely to improve with therapy. Although there is no well established disease-specific QOL instrument for RA, the Health Assessment Questionnaire (HAQ) and modified HAQ (MHAQ) are 2 of the most commonly used functional measures[2,3,4]. More generic measures are essential in assessing and comparing outcomes across different disease states. Generic instruments can also be used to evaluate cost-effectiveness and as such are valuable in policy-related decisions. Concerns have been expressed regarding the sensitivity of

generic measures. For example, the Medical Outcomes Study (MOS) Short-Form 36 (SF-36), a commonly used generic measure, may lack the ability to register changes of clinical relevance in individuals with rheumatic disease[5,6,7]. According to Hurst, *et al*[5], SF-36 is less sensitive to changes in patients with RA than the EuroQOL-5 dimensions (EQ-5D) instrument. Vaile, *et al*[6] found the SF-36 to be insensitive in revealing clinically significant improvement after isolated treatment of carpal tunnel syndrome in patients with RA. Russell, *et al*[7] assessed the variability of the MHAQ, SF-36, and EQ-5D in patients with clinically stable RA, and compared this variability to the changes seen in patients successfully treated with infliximab. The aim was to determine if these measures could readily detect clinically important differences in routine practice. The degrees of responsiveness calculated by the investigators are shown in Table 1. Changes in EQ-5D utilities were about twice as high as those for the SF-36. This may be due to the greater range of scores for the EQ-5D than the SF-36. However, due to the larger variability of scores, the effect size for the EQ-5D is actually smaller despite the greater mean numerical change. Changes in the SF-36 and HAQ scores were more closely related to changes in patient global and patient pain assessments than to changes in swollen and/or tender joint counts.

Spydergrams to Display and Interpret SF-36 Data

Spydergrams are a new and effective tool that allows fast perception of patterns of changes in complex sets of data[8]. Contrary to the current way of displaying SF-36 as 8-column bar graphs, spydergrams allow changes to be seen more easily across all 8 domains. Further, inclusion of baseline values as well as matched norms allows visual comparisons. The thickness of the "rings" is proportional to the degree of change from baseline values and/or as compared to healthy controls. Thus, by examining the changes along individual domain axes, treatment-associated changes in terms of clinically meaningful response can easily be distinguished. The spydergram in Figure 1 provides SF-36 data for adalimumab in patients with RA (PREMIER trial) in comparison to age and sex-matched controls (panel A) and treatment-associated improvement at 1 and 2 years (panel B)[8,9,10].

HRQOL and Patient-Reported Outcomes (PRO) in Clinical Trials with Biologics

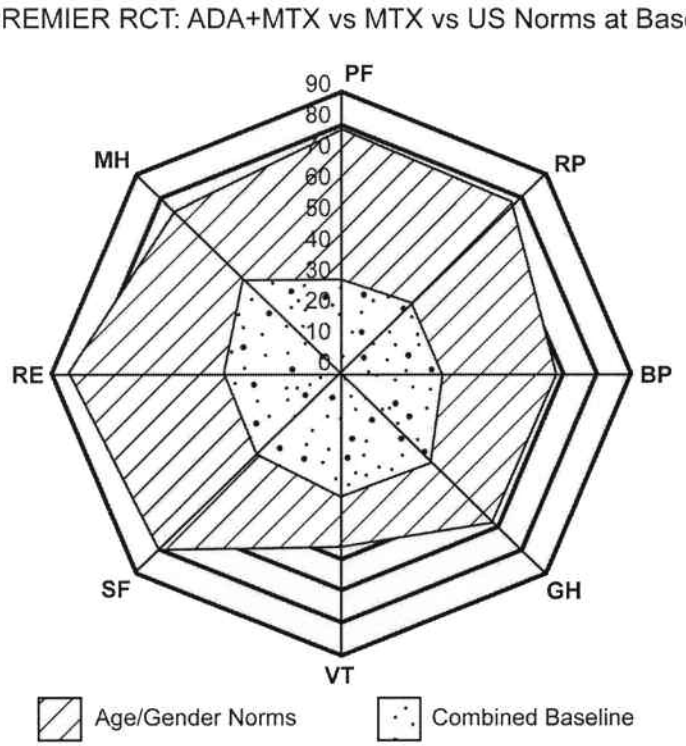
Over the past decade, there has been significant movement toward incorporation of HRQOL and PRO as outcome measures in clinical trials with RA[11,12,13,14,15,16,17,18]. Further, the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) 6 meeting included arthritis patients as workshop participants[11,12,13,14]. These patients provided input as to which RA outcome measures are important from a patient perspective[15]. A global sense of well-being, fatigue, and disturbed sleep were identified as the main patient-related concerns not included in the current core set of RA criteria. As a result, clinical trials with biologics conducted after OMERACT 6 include fatigue and other PRO as key measures[9,16,17,18,19,20]. For example, a clinical trial that evaluated abatacept in patients with RA who have inadequate response to methotrexate (MTX) showed statistically significant improvements across a range of HRQOL measures, including physical function, fatigue, all 8 domains of the SF-36, and the physical and mental component summaries (PCS and MCS) in the abatacept-treated group versus placebo[19]. Similarly, Mittendorf, *et al*[20] demonstrated that patients treated with adalimumab displayed rapid and statistically significant improvements from baseline in both HRQOL measures and fatigue (Figure 2). Patients treated with the B cell depletion therapy rituximab plus MTX also show significant improvement in HAQ and SF-36 PCS scores compared to those receiving MTX alone[21].

Table 1. A comparison of responsiveness indices for outcome measures for patients successfully treated with infliximab (n = 60). Reproduced with permission from Russell AS, *et al*. J Rheumatol 2003;30:941-7.

Measures	Mean Change*	Effect Size	Standardized Response Mean	Improved by > 2 SEM, %	Improved 95%, Bland-Altman Limits of Agreement, %
Pain	24.39**	1.08	0.93	52	35
MHAQ	0.40**	0.62	0.74	58	48
EQ-5D	0.20**	0.67	0.64	43	27
SF-6D	0.10**	1.40	0.87	35	25
Standard gamble***	0.12**	0.49	0.43	33	21
EQ VAS	17.38**	0.99	0.90	37	25
SF-36 PCS	8.62**	1.07	0.94	48	37
SF-36 MCS	4.69**	0.42	0.42	18	10

* Absolute mean changes with results of paired t tests; ** $p < 0.001$. All mean changes are in expected direction (improved), *** Only 24 of the 60 patients completed the standard gamble. SEM: standard error of mean; MHAQ: Modified Health Assessment Questionnaire; EQ-5D: EuroQoL (quality of life)-5 dimensions; SF-36: Medical Outcome Study Short-Form 36 survey; VAS: visual analog scale; PCS: physical component summary scale; MCS: mental component summary scale.

A



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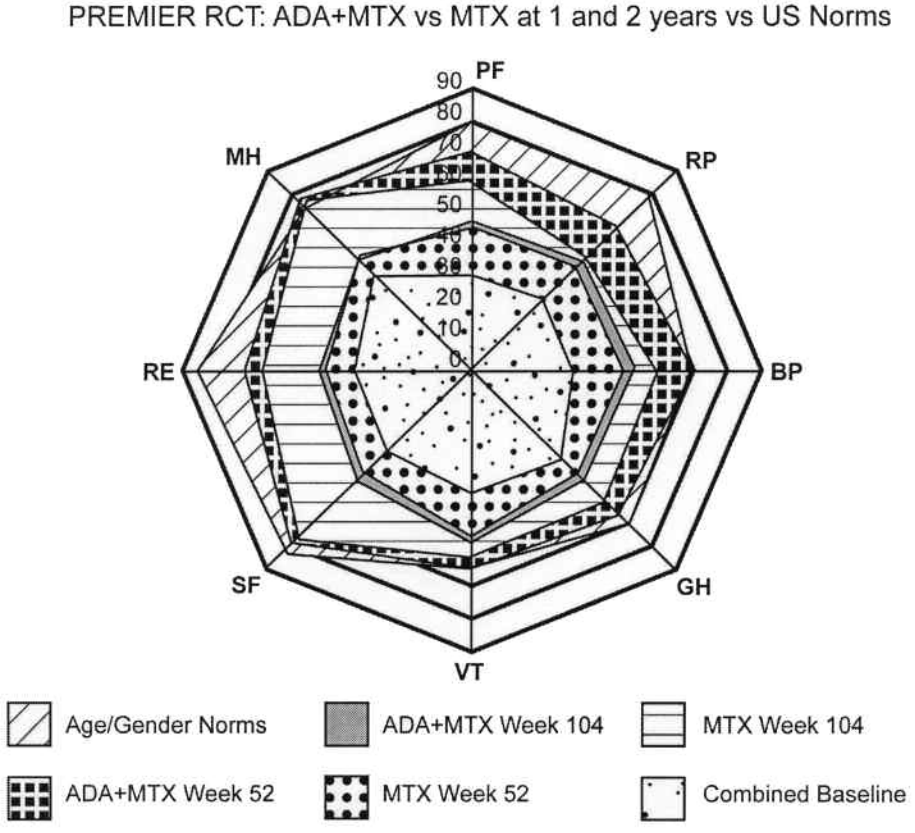

Figure 1. Spydergram presentation of data from the PREMIER trial: Adalimumab plus methotrexate (ADA+MTX) versus methotrexate (MTX) in MTX-naïve patients with RA duration of 7–9 months. A. Baseline scores from the PREMIER trial (inner polygon, stippled) versus age- and gender-matched healthy subjects (outer polygon, cross-hatched). B. Treatment-associated improvements at 1 and 2 years with MTX monotherapy (solid circles and horizontal hatching) or ADA+MTX (solid squares and grey) as concentric rings, compared with baseline and age/gender-matched healthy subjects. Reproduced with permission from Strand V, *et al*. Ann Rheum Dis 2009;68:1800-4. Copyright© 2009, BMJ Publishing Group Ltd., and the European League Against Rheumatism.

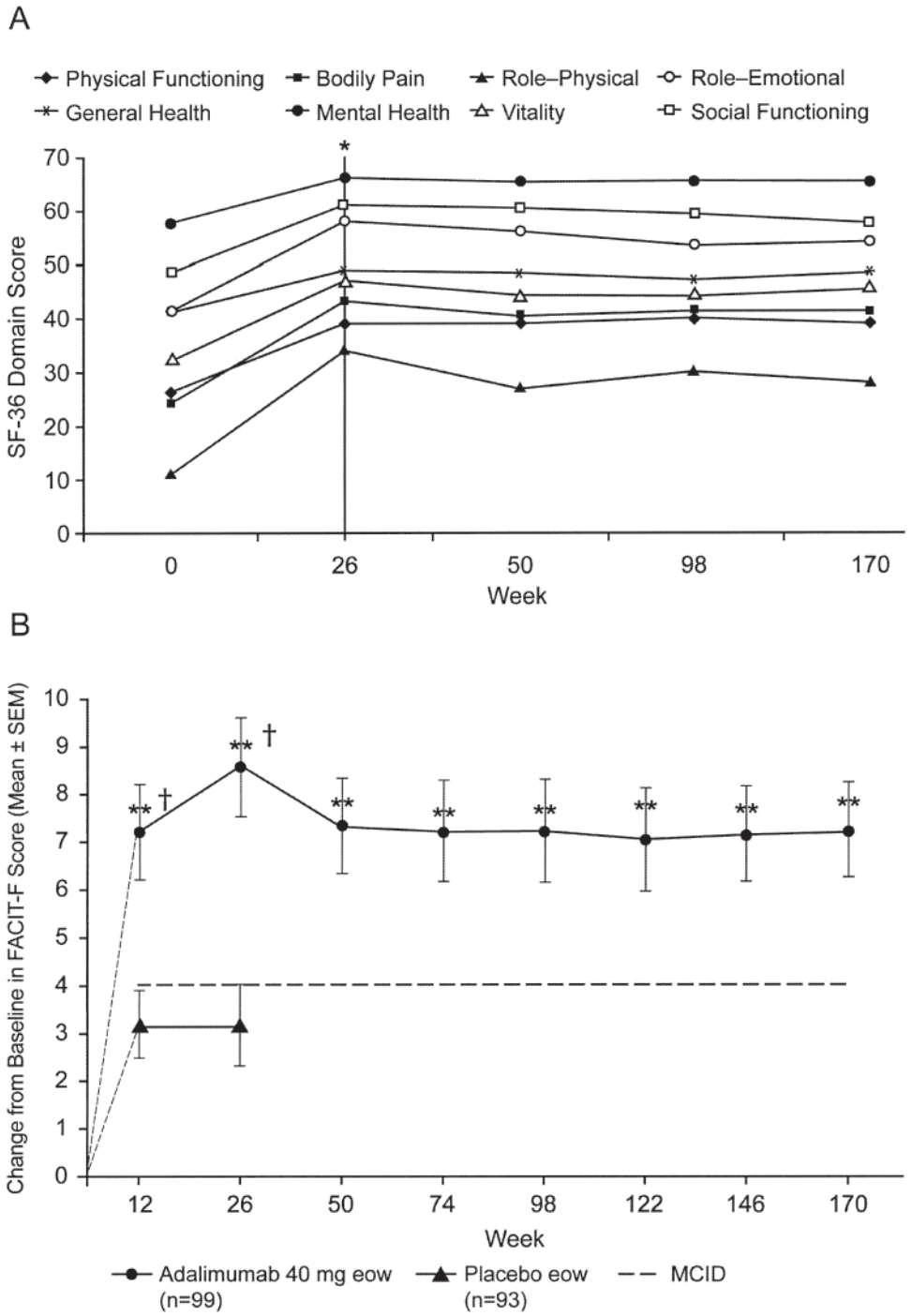

Figure 2. Improvement and longterm maintenance of QOL during treatment with adalimumab in patients with severe rheumatoid arthritis (RA). A. SF-36 health profile scores. *Significant difference ($p < 0.02$) adalimumab versus baseline for all domains except role-physical, which was $p < 0.05$, on and after Week 26. B. Changes from baseline in FACIT-Fatigue scores. N = 99; FACIT: Functional Assessment of Chronic Illness Therapy. **Significant difference ($p < 0.001$) versus baseline. †Significant difference ($p < 0.01$) versus placebo. MCID: minimum clinically important difference; SEM: standard error of the mean. Reproduced with permission from Mittendorf T, *et al*. J Rheumatol 2007;34:2343-50. Copyright© 2007, The Journal of Rheumatology Publishing Company Limited.

In regard to the effectiveness and the improvement in HRQOL, Kievit, *et al*[22] demonstrated that all 3 commonly used tumor necrosis factor-α (TNF-α) agents — adalimumab, etanercept, and infliximab — reduce Disease Activity

Score in 28 joints (DAS28) and improve SF-36 PCS (Figure 3). However, the change was larger for adalimumab and etanercept in comparison to infliximab ($p < 0.001$). The analyses of the HAQ and the EQ-5D scores showed a similar but nonsignificant trend.

Fatigue as an Outcome Variable in RA: Correlation Between Fatigue and DAS28

Fatigue is an important symptom in patients with RA, associated with illness severity, psychological distress, and reduced QOL[23]. In fact, fatigue has been identified by the OMERACT consensus effort as one of the most important problems for patients[11]. Using separate clinical settings, Bergman, *et al*[24] investigated whether fatigue levels and correlates differ between different disease states. Patients with RA, osteoarthritis (OA), and fibromyalgia (FM) were compared to determine whether the fatigue levels were higher in an inflammatory disorder such as RA compared to a noninflammatory disorder like OA. The contribution of RA activity to fatigue scores was also investigated. The authors concluded that patients with OA and RA displayed similar levels of fatigue. Further, inflammatory components of the DAS28 contributed minimally to fatigue (Table 2). Thus, the authors concluded that fatigue is not an inflammatory variable and as such has no unique association with either OA or RA treatment.

QOL and Utility Assessments

Utility assessments and cost-utility analyses such as quality-adjusted life-years (QALY) are often used to demonstrate the value of new therapeutic options in various diseases including RA. To that end, several studies assessed the value and contribution of HRQOL measures to cost-utility analyses in rheumatic diseases[25,26,27]. By comparing EQ-5D and SF-36 QOL measures in 1316 patients with systemic lupus erythematosus (SLE), 13,722 with RA, 3623 with noninflammatory rheumatic disorders, and 2733 with FM, Wolfe, *et al*[25] concluded that, although SF-36 scores are widely

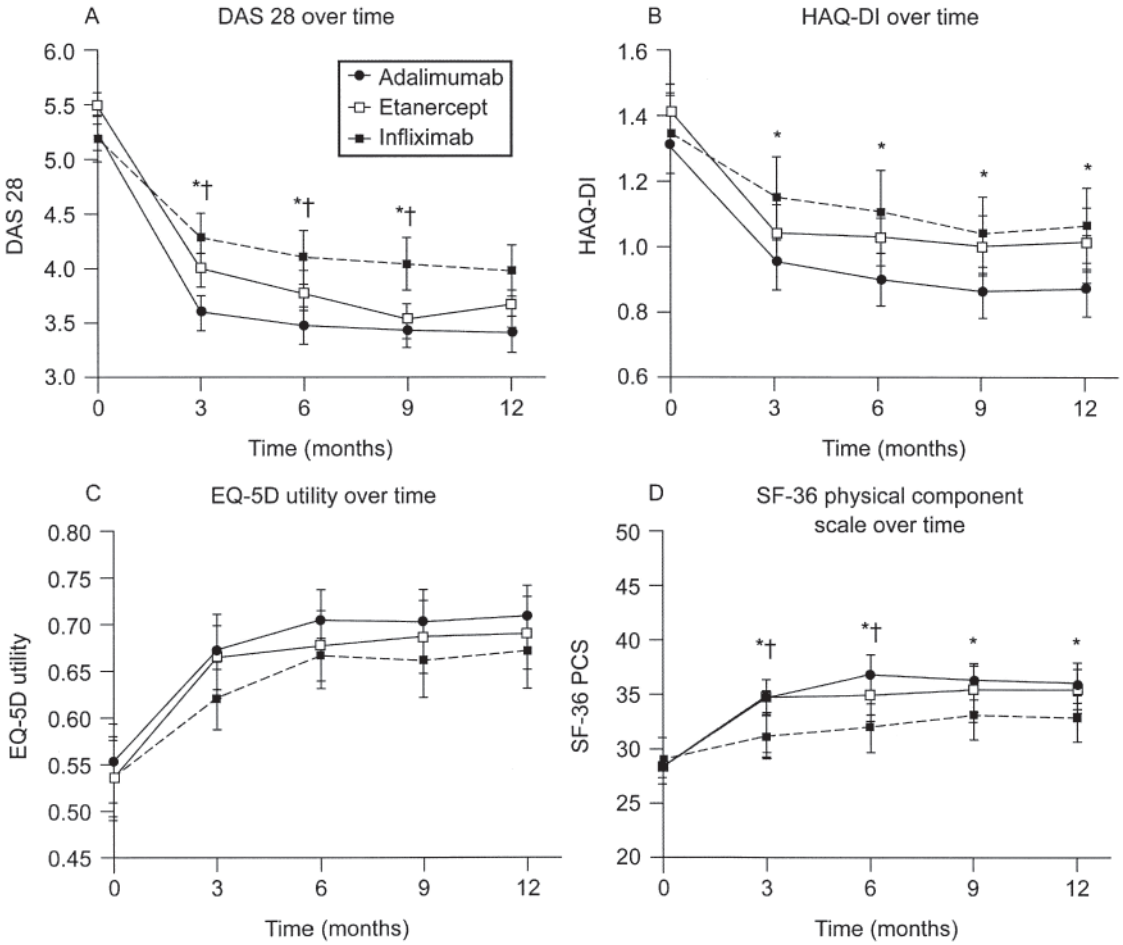

Figure 3. The effectiveness and HRQOL data with 3 anti-tumor necrosis factor-α agents in the treatment of RA from prospective clinical practice data. DAS28: Disease Activity Score in 28 joints; HAQ-DI: Health Assessment Questionnaire Disease Index. *Significant difference ($p < 0.05$) versus infliximab patients. †Significant difference ($p < 0.05$) versus infliximab patients. Reproduced from Kievit W, *et al*. Ann Rheum Dis 2008;67:1229-34; with permission from BMJ Publishing Group Ltd.

Table 2. Correlation analysis of fatigue and Disease Activity Score-28 (DAS28) and clinical variables in patients with RA. Reproduced with permission from Bergman MJ, *et al*. J Rheumatol 2009;36:2788-94.

Variable	Fatigue	DAS28
Fatigue	1.000	0.399
Pain	0.668	0.503
Patient global severity	0.657	0.587
HAQ2	0.588	0.491
CDAI	0.446	0.828
DAS28 score	0.399	1.000
MD global activity	0.384	0.701
Tender joint count	0.294	0.760
Swollen joint count	0.112	0.614
ESR	0.071	0.399

ESR: erythrocyte sedimentation rate; HAQ2: Health Assessment Questionnaire II; CDAI: Clinical Disease Activity Scale.

reported, the numbers have no clear relevance to clinicians. SF-36 scores provide numerical measures of health status but do not include preferences for health states and therefore cannot be directly used in cost-effectiveness analyses. Similarly, using a sample size of over 12,000 patients with RA, Wolfe, *et al*[26] compared the American and British EQ-5D with the Medical Outcomes Study Short-Form Survey 6-Dimension (SF-6D) scales at all levels of the HAQ, as well as at important levels of RA outcomes. The differences between the scales at different levels of RA and HAQ severity were also described. As shown in Figure 4, the SF-6D aligns closely with the UK EQ-5D at HAQ values up to 1.0, at which point the curves diverge. Further, at any level of clinical severity, the US EQ-5D had a higher utility score than the UK EQ-5D. Thus, as pointed out by Beresniak, *et al*[27], when interpreting and using HRQOL measures as part of utility assessments and cost utility analysis in RA by health-technology agencies, the medical community should take into consideration the restrictions and significant uncertainty of these approaches. Further, cost-effectiveness analyses based on observed clinical outcomes seem to be more robust and reliable to support the decision-making process, particularly in patients with RA.

QOL DATA IN PSORIASIS AND PSORIATIC ARTHRITIS (PsA)

Impact of Psoriasis and PsA on Patient QOL and Emotional Well-being

Psoriasis, a chronic, inflammatory immune-mediated skin condition, affects about 2% of the world's population[28]. The disease usually begins early in life, with 60% of cases occurring before the age of 30[29,30]. Thus, changes in appearance and resulting psychosocial effects influence patients' emotional development and present long-lasting hardship. Psoriasis and its related condition PsA, which affects about 10%–20% of psoriatic patients[29], have been shown to have a negative effect on HRQOL. This is not surprising, as the evident signs and symptoms of the disease often leave affected individuals with a distorted self-image as well as a feeling of awkwardness about their appearance[29].

Using the SF-36 scale to compare QOL impact between different diseases, Rapp, *et al*[31] reported that patients with psoriasis describe reductions in physical functioning and mental health comparable to those seen in patients with cancer, arthritis, hypertension, heart disease, depression, and diabetes (Table 3). Further, the negative effects of psoriasis

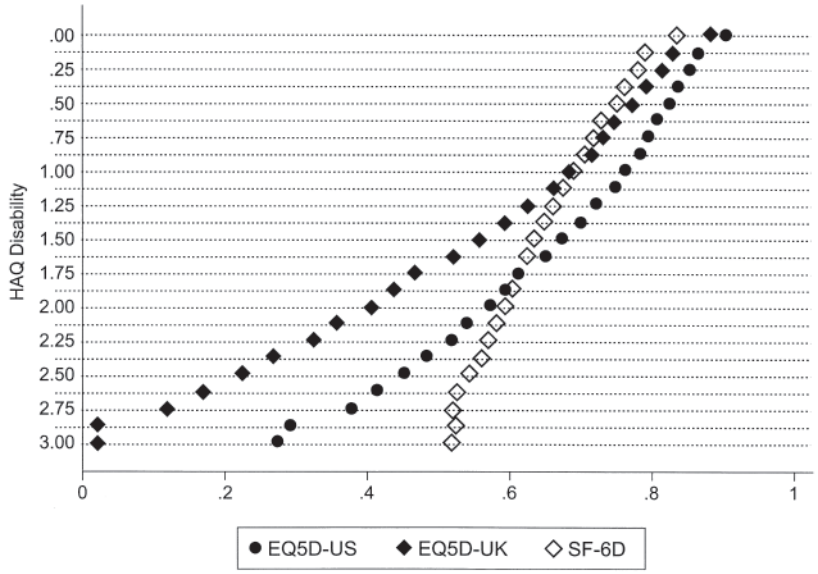

Figure 4. Mean values of US EQ-5D, UK EQ-5D, and SF-6D at all levels of the HAQ-DI scale. Reproduced with permission from Wolfe F, *et al*. J Rheumatol 2010;37:1615-25. Copyright© 2010, The Journal of Rheumatology Publishing Company Limited.

Table 3. Comparison of psoriasis with other chronic conditions in Medical Outcomes Study Short-Form 36 survey PCS and MCS scores (1 = little impact; 11 = great impact). Reprinted from Rapp SR, *et al*. J Am Acad Dermatol 1999;41:407-7; with permission from Elsevier.

	PCS	MCS
Psoriasis	10	9
Healthy adults	1	1
Dermatitis	2	8
Arthritis	6	7
Cancer	3	6
Chronic lung disease	8	10
Hypertension	5	2
Myocardial infarction	7	4
Congestive heart failure	11	5
Type 2 diabetes	9	3
Depression	4	11

PCS: physical component summary scale; MCS: mental component summary scale.

on different aspects of life can be worse than those created by life-threatening illnesses.

In a survey of patients between the age of 18 and 34 (n = 1918), conducted by the National Psoriasis Foundation, 90% felt frustrated with their condition and 88% were fearful of disease exacerbation[32]. Moreover, 81% of the responders reported feeling shame and embarrassment and 75% reported feeling unattractive. A recent online survey that involved about 500 Canadians with psoriasis revealed that the condition takes a significant emotional toll on patient lives[33]. While 66% of participants reported self-consciousness, 56% felt embarrassed, 53% frustrated, and 52% unattractive. Further, moderate or severe effects on QOL [Dermatology Life Quality Index (DLQI) score ≥ 6] was reported by 39% of responders[34]. Approximately 30% of participants reported symptoms of depression and anxiety, which correlated with psoriasis severity and the female sex[33,35]. Depression was reported by 20% of women versus 11% of men ($p < 0.01$)[35]. Similarly, participants in the European Federation of Psoriasis Patient Associations survey indicated that psoriasis had a marked impact on their activities of daily living, especially affecting clothing choice, bathing routine, and sporting activities[36]. Overall, 77% of responders reported that psoriasis was a problem or a significant problem. The mean Psoriasis Disability Index (PDI) score among the survey participants was 12.2 (25% of the maximum score). However, this score increased to 21 (44% of the maximum score) in patients with greater than 10% body surface area (BSA) involvement.

Although the BSA is often used to define severity of the disease, Krueger, *et al*[37] pointed out that such a definition may not be applicable when evaluating individual differences between psoriasis sufferers. Depending on which area of the body the psoriasis affects, a low BSA (i.e., face, dominant hand) can lead to severe functional impairment, whereas a higher BSA (i.e., back) may have very little influence on an individual's day-to-day activities.

It is also important to bear in mind that the impaired emotional well-being in patients with psoriasis can have detrimental effects on treatment outcomes. For example, in a study involving 122 psoriatic patients, high-level or pathological worry was the only significant predictor of time to clearance of psoriasis with psoralens and ultraviolet A light therapy (Table 4)[38].

Measuring Patient Experience of Psoriasis: Qualitative versus Quantitative Approach

Qualitative (ethnographic) approach. The qualitative approach involves medical ethnographers shadowing patients at home, audio- and videotaping, and taking photographs and field notes[39]. As a detailed method of recording daily events in the context in which they occur, ethnography can help healthcare professionals deal with issues on an individual basis. However, the approach is too cumbersome for extensive use in clinical trials and/or clinical practice.

Quantitative approach. The quantitative approach to measuring HRQOL in the psoriatic population involves generic [i.e., SF-36 and visual analog scale (VAS)] and disease-specific instruments[29]. Similar to rheumatologic diseases, there have been reports of limitations of the SF-36 in psoriasis[29,40,41]. For example, while emphasizing impairment and physical disability, the SF-36 does not give equal significance to stigmatism and embarrassment, which are often more relevant to patients with psoriasis[29,40]. In patients with PsA, the SF-36 correlated only modestly with clinical indicators of pain, function, and disease activity[29,41].

Developed by Finlay and Khan[42], the DLQI is the most utilized and validated measurement of HRQOL in psoriasis. It consists of 10 items divided into 6 domains (symptoms and feelings, daily activities, leisure, work/school, relationships, and treatment). Responders answer questions on a 0–3 Likert scale based on their experience during the previous week. The scores are expressed as a number from 0 to

Table 4. Pathological/high-level worry predicts non-clearance with psoralen-ultraviolet A light. Reprinted with permission from Fortune DG, *et al*. Arch Dermatol 2003;139:752-6. Copyright© 2003 American Medical Association.

Variable	Statistic Score	p
Pathological/high-level worry	6.34	0.01
Anxiety	2.53	0.11
Duration of psoriasis, yrs	2.13	0.14
Clinical severity of psoriasis	1.48	0.22
Skin types	1.16	0.76
Alcohol intake per week	0.93	0.33
Family history of psoriasis	0.71	0.31
Depression	0.49	0.48
Sex	0.02	0.88
Age	0.01	0.90

30, with higher values indicating worse outcomes. Improvement by 5 points indicates a clinically relevant change[43].

The PDI, another commonly used disease-specific instrument, is a 15-item questionnaire that evaluates daily activities, work or school matters, personal relationships, leisure, and treatment[44]. Each question is graded from 0 to 6 on a VAS (maximum score 90) or 0 to 3 on a tick-box scoring system (maximum score 45).

Improving QOL: Treatment of Psoriasis and Psoriatic Arthritis with Biologics

It has been almost a decade since biologic agents emerged as a therapeutic option for patients with moderate to severe psoriasis. Anti-TNF agents have been proven to reduce signs and symptoms of psoriasis[45,46,47,48] as well as PsA[49,50,51]. All 3 commonly used anti-TNF agents (adalimumab, etanercept, and infliximab) as well as anti-interleukin 12/23 monoclonal antibody ustekinumab have also been shown to significantly improve the DLQI from baseline values (Figure 5)[45,52,53,54]. At Week 10 in the EXPRESS trial[52], patients with chronic plaque psoriasis treated with infliximab had a significantly greater improvement in DLQI scores as well as SF-36 PCS and MCS scores than those receiving placebo. These improvements persisted with maintenance infliximab treatment at Week 24.

At Week 2, the mean percentage improvement from baseline in the DLQI was also significant in patients with psoriasis treated with different etanercept doses: a low dose (25 mg once weekly), a medium dose (25 mg twice weekly), or a high dose (50 mg twice weekly)[45]. By Week 12, the mean improvement was 47.2% in patients receiving low dose, 50.8% in those receiving medium dose, and 61.0% in the high-dose group, as compared with 10.9% in the placebo group ($p < 0.001$ for all 3 comparisons with the placebo group)[45].

After 16 weeks, patients treated with adalimumab also reported significantly greater improvements in DLQI total score ($p < 0.001$), SF-36 PCS score ($p < 0.001$), and MCS score ($p < 0.001$) compared with those treated with placebo[53]. According to a recent study by Menter, *et al*[55], adalimumab was also associated with a reduction of depression, measured by the Zung Self-rating Depression Scale. Depression improvement was correlated with improvement in the Psoriasis Area and Severity Index and the DLQI.

In addition to biologic agents, other therapeutic approaches such as phototherapy[56], immunosuppressants[57], and topical creams[58] that are effective in reducing symptoms of skin disease have also been shown to be effective in improving patient QOL.

HRQOL OUTCOME MEASURES IN INFLAMMATORY BOWEL DISEASE (IBD)

HRQOL Instruments Used in IBD

Several disease-specific QOL tools have been developed and validated in IBD, including the Inflammatory Bowel Disease Questionnaire (IBDQ)[59] and the Rating Form of IBD Patient Concerns (RFIPC)[60]. The IBDQ is currently considered a reference standard for measuring disease-specific QOL in patients with IBD, as the experience with the RFIPC is still limited. The IBDQ is a self-administered, 32-item questionnaire that includes 4 domains: bowel function, emotional status, systemic symptoms, and social functioning[59,61,62]. Each item is rated on a 7-point Likert scale and the total IBDQ score ranges from 32 to 224, with lower scores indicating a worse QOL. A proposed cutoff value for remission is ≥ 170 points and a proposed clinically important change in score for clinical response is ≥ 32 points[62]. The IBDQ is commonly used as a secondary endpoint in many clinical trials in IBD to ensure that the QOL is improved in medically treated patients with IBD[63]. Several shortened versions of the IBDQ have also been developed[64,65], but the original[64] appears to be robust. More than 40 translations are available for multinational trials. As in other IMID, commonly used generic tools include the SF-36

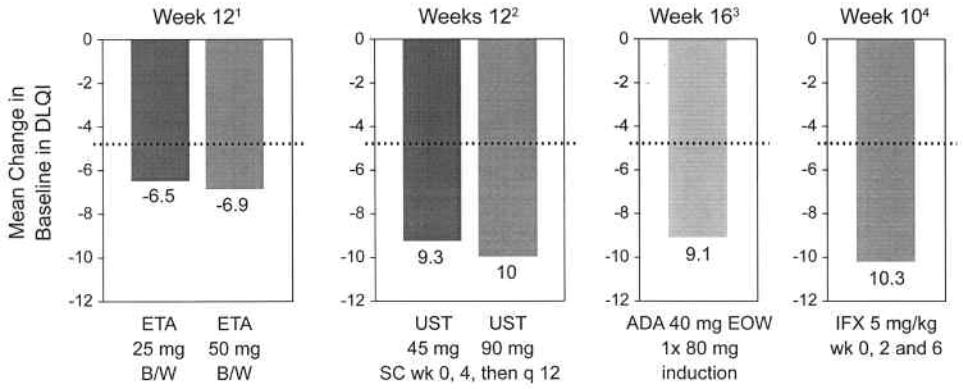

Figure 5. Efficacy of biologics by improvement of mean DLQI[45,52,53,54]. ADA: adalimumab; B/W: twice weekly; EOW: every other week; ETA: etanercept; IFX: infliximab; SC: subcutaneous; UST: ustekinumab.

and EQ-5D. More recently, the work productivity activity index has been tested, as have utility indices (i.e., standard gamble, time trade-off, feeling thermometer, VAS, and Likert scale).

Factors Shown to Affect HRQOL in IBD

The unique characteristics of IBD indicate that HRQOL analysis has an important role in understanding the true influence of the disease on patient well-being as well as in guiding therapeutic decisions. The chronicity, with recurrent flares of the disease, accompanied by an early age of onset, implies that patients will be faced with the disease and its consequences throughout most of their adult life, and will need to balance its impact with other lifestyle features[66,67]. Factors affecting HRQOL in IBD can be divided into those that are directly related to the disease and those that are disease-unrelated[67,68,69]. Disease-related factors include disease severity, frequency of relapse, complications, the presence of fistulizing disease or extraintestinal manifestations, the efficacy of medical and surgical therapy, and adverse effects of treatment. Disease-unrelated factors involve gender (females appear to be more affected than males), early age of onset, current age, smoking status, body mass index, country of residence and health coverage, satisfaction with healthcare, and comorbidities (physical and psychological).

Using the RFIPC, Drossman, *et al*[60] identified top concerns and worries among 991 members of the Crohn's and Colitis Foundation of America [320 patients with ulcerative colitis (UC) and 671 with Crohn's disease (CD)]. The most prevalent concerns were uncertainty regarding disease progression, the effects of medication, energy levels, having surgery and/or a colostomy bag, being a burden on others, loss of bowel control, and developing cancer. As for the clinically consistent differences between CD and UC, those with UC were more concerned with developing cancer, while CD patients worried about their energy levels, pain, and being a burden on others. Almost 20 years later, Stjernman, *et al*[70] reported similar findings.

In a population-based study conducted in Sweden, Nordin, *et al*[71] found that the SF-36 scores in IBD patients were significantly lower than those in the general population. While UC patients had a similar mean PCS score as the matched controls, CD patients had lower PCS and MCS scores compared to the Swedish population. Further, UC patients' scores for physical function and bodily pain were similar to those observed in the general population, but their scores for the other 6 domains were lower. On the other hand, CD patients scored significantly lower in all of the subscales compared to the matched controls. Using data from the population-based Manitoba IBD Cohort Study, Graff, *et al*[72] demonstrated the effect of disease activity on HRQOL. Patients who had inactive disease over an extended period (i.e., 6 months) reported psychological functioning and QOL outcomes similar to those in the general community. In contrast, those with active disease over the previous 6 months were more likely to have impaired QOL (Figure 6). Data from Lix, *et al*[73] support these findings as they also demonstrate a difference in IBD-related QOL over a longitudinal profile of disease activity (Figure 7). Despite the higher QOL reported by patients with low disease activity, this study also demonstrated that certain measures of psychological functioning, including pain, anxiety, and catastrophizing, were not influenced by patients' disease activity pattern, suggesting that IBD may have an effect even in the absence of symptoms.

Differences between UC and CD patients were also assessed in 239 CD and 122 UC patients attending a tertiary care center[74]. Although a majority of patients reported pain and discomfort, this number was significantly higher among CD than UC patients (70% vs 60%, respectively; $p < 0.05$). Surprisingly, 24% of CD patients reported trouble walking versus 12.5% of UC patients ($p < 0.05$). Over 40% of patients in both the CD and UC groups reported anxiety or depression. Reported rates of problem with usual care and daily activities were also similar between the 2 groups (Table 5)[74].

Benefits of Anti-TNF Agents Beyond Response and Remission

Although early studies have shown 5-aminosalicylic acid and azathioprine as key therapies for IBD, well designed clinical trials measuring QOL outcomes with these agents are generally lacking. This is likely because these drugs were tested prior to recognition of the importance of QOL outcomes, and their consequent inclusion in clinical trials. It is worth noting that a recent study by Irvine, *et al*[75] demonstrated that oral mesalazine does result in a clinically and statistically significant improvement in QOL in patients with mildly and moderately active UC.

Many recent clinical trials in IBD have included HRQOL as a secondary outcome, often utilizing the IBDQ[76,77,78,79,80]. In all of these trials, anti-TNF agents showed benefits beyond improvement in signs and symptoms of the disease. Both adalimumab and infliximab are effective in treating fistulizing disease[81]. They also showed steroid-sparing properties, reduction in hospitalization, and improvement in QOL[81]. In fact, the improvement in HRQOL scores paralleled the reduction in disease activity achieved with anti-TNF[76,77,78,79,80,81].

After 4 weeks of treatment with infliximab, CD patients were found to have a significantly larger improvement in overall IBDQ score as well as in all IBDQ dimensions compared to those receiving placebo[76]. Patients treated with infliximab also significantly differed from placebo in responses regarding anger, frustration, fatigue, ability to work, general well-being, depression, and anxiety. The HRQOL benefits achieved with infliximab were maintained over 2 years[77].

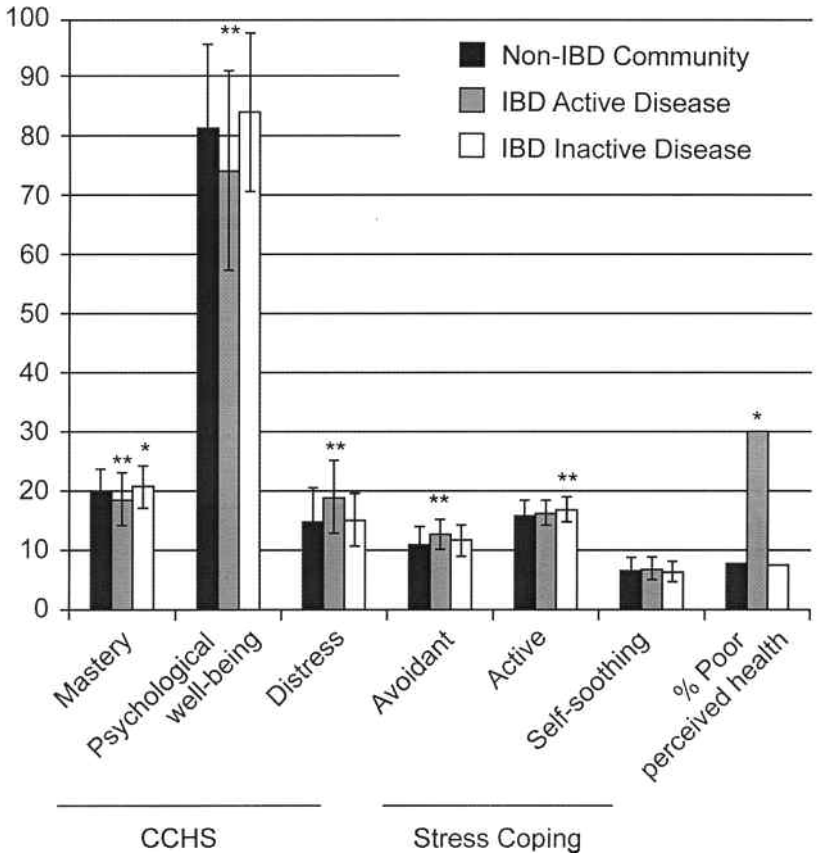

Figure 6. Psychological functioning and health perceptions comparing non-IBD community controls with an IBD community sample[72]. CCHS: Canadian Community Health Survey. Statistical comparisons are with community sample as the reference category (*p ≤ 0.02; **p ≤ 0.001). Data are mean ± standard deviation unless otherwise indicated.

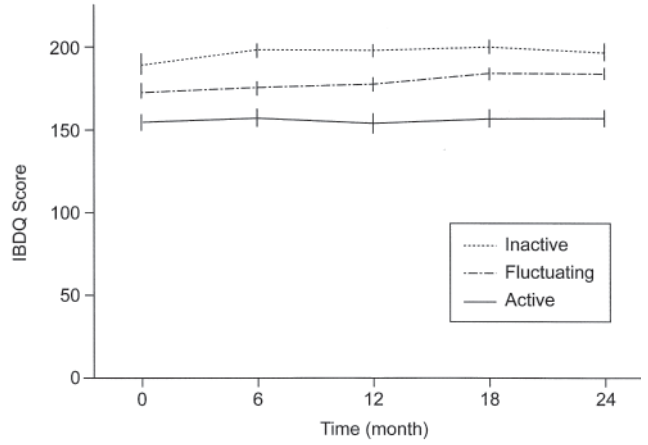

Figure 7. Profile plot of means and 95% confidence intervals for the IBD quality of life measure. Reproduced from Lix LM, *et al*. Inflamm Bowel Dis 2008;14:1575-84; with permission from John Wiley and Sons. Copyright© 2008 Crohn's and Colitis Foundation of America, Inc.

In the Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance (CHARM)[78], after 4 weeks of adalimumab induction therapy, patients with moderate to severe CD experienced statistically significant improvement in all HRQOL measures compared to their baseline values. At 56 weeks, those who continued adalimumab reported less depression, fewer fatigue symptoms, greater improvement in the IBDQ, and less abdominal pain. Similarly, patients receiving certolizumab maintenance therapy reported clinically meaningful improvements in HRQOL relative to baseline and to placebo-treated participants[79]. More patients receiving certolizumab reported a clinically meaningful improvement in IBDQ score (60% vs 43%; p < 0.001), in SF-36 physical (51% vs 34%; p < 0.001)

Table 5. EQ-5D problems in the previous 4 weeks[74].

	CD, % (n = 239)	UC, % (n = 122)
Problems walking	24.3	12.5*
Problems with self-care	2.5	2.1
Problems with usual activities	30.6	39.2
Pain and discomfort	69.9	59.5
Anxious or depressed	42.5	46.2

* p < 0.05 for differences between CD and UC. UC: ulcerative colitis; CD: Crohn's disease.

and mental (44% vs 32%; p = 0.016) component summary responses, and in the EQ-5D VAS (57% vs 38%; p < 0.001) than did those receiving placebo. There was also a significantly greater gain in QALY for patients receiving certolizumab as compared with placebo (mean ± SD: 0.25 ± 0.10 and 0.21 ± 0.11; p = 0.001). Reinisch, *et al*[80] demonstrated that response and remission achieved with infliximab are associated with improved QOL, employment, and productivity in patients with UC (Figure 8).

CONCLUSION

Patients with IMID have a significantly impaired HRQOL, with numerous fears, concerns, and unmet needs. Disease activity, comorbidities, and treatment-related side effects are some of the contributors to significantly impaired physical, emotional, and social functioning. The information provided in this review gives further weight to the importance of HRQOL assessments in these patients. It is necessary to continue the use of HRQOL measures in the clinical trials of agents for the treatment of patients with IMID in order to raise greater awareness on the part of physicians and other healthcare providers as well as policy makers. Utility analyses should further assist in the pharmacoeconomic evaluation of the influence of IMID on society and the potential effects of new therapies, allowing for appropriate allocation of healthcare resources. Although neither generic nor disease-specific HRQOL instruments are perfect, their combination makes it possible to determine the minimum clinically important difference that predicts a relevant improvement upon which clinical and policy-related decisions can be made.

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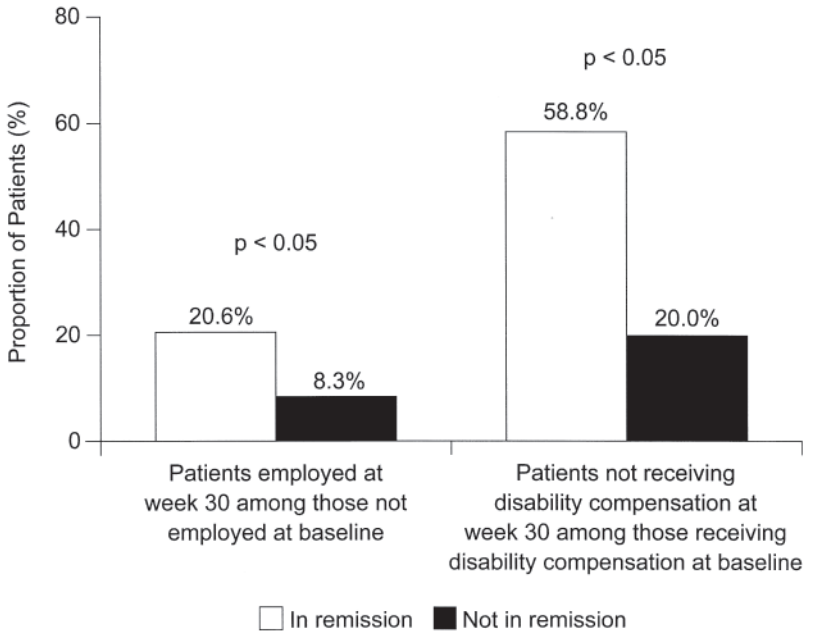

Figure 8. Decreased unemployment and disability after infliximab therapy in ulcerative colitis. Reproduced from Reinisch W, *et al*. Inflamm Bowel Dis 2007;13:1135-40; with permission from John Wiley and Sons. Copyright© 2007 Crohn's and Colitis Foundation of America, Inc.

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