

Improvement of psychological status after infliximab treatment in patients with newly diagnosed Crohn's disease

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Background: Patients with newly diagnosed Crohn's disease (CD) are associated with impaired physical and psychological well-being. These psychological characteristics are dynamic with the course of disease and could be influenced by medical treatment. Infliximab is effective and widely used in moderate-to-severe CD patients. The aim of this study was to evaluate the improvement of psychological status after infliximab treatment in patients with newly diagnosed CD.

Methods: Newly diagnosed moderate-to-severe CD patients were prospectively enrolled in our study. Infliximab 5 mg/kg was administered at weeks 0, 2, 6, 14, 22, and 30. Outcomes including disease severity, illness perceptions, coping strategies, anxiety, depression, and quality of life (QoL) were measured at baseline, week 14, and week 30.

Results: Eighty-two patients completed our study. The rates of clinical remission at weeks 14 and 30 were 59/82 (72.0%) and 58/82 (70.7%), respectively. Patients who achieved clinical remission at weeks 14 and 30 significantly improved in illness perceptions ($P < 0.001$ and < 0.001), maladaptive coping ($P = 0.005$ and 0.004), anxiety ($P < 0.001$ and < 0.001), depression ($P = 0.004$ and 0.004), and QoL ($P < 0.001$ and < 0.001). However, emotion-focused coping and problem-focused coping remained unchanged. For infliximab nonresponders, no significant changes were seen in illness perceptions, coping strategies, anxiety, depression, or QoL at week 14 or 30.

Conclusion: Effective infliximab treatment not only led to clinical remission in patients with newly diagnosed moderate-to-severe CD but also improved their psychological status including illness perceptions, maladaptive coping, anxiety, depression, and QoL.

Keywords: illness perceptions, coping strategies, anxiety and depression, quality of life, infliximab

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder characterized by discontinuous inflammation that can occur anywhere in gastrointestinal tract, predominantly in the small intestine and the colon. As a chronic disease, CD brings physical, psychological, and social impairments to patients, which would pose negative effects on their lives in all aspects.¹⁻³ It is reported that quality of life (QoL) is reduced in CD patients compared to healthy controls.^{4,5} Moreover, high levels of anxiety and depression are inconvenient truths in CD patients.⁶

It has been shown that psychological distress and QoL are not only associated with the disease severity itself but also associated with factors such as illness perceptions and coping strategies, which is supported by the Common Sense Model (CSM).⁷ Illness perceptions are individual's mental representations of their disease, while

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coping strategies are defined as the ways that an individual manages or deals with stress.⁸ According to the CSM, patients generate cognitive representations based on the disease threat they are faced with. Patients would form illness perceptions in response to disease severity, which in turn may influence coping strategies and finally the illness outcomes such as psychological health and QoL.^{9,10} Therefore, disease severity, illness perceptions, coping strategies, psychological well-being, and QoL are significantly associated with each other.^{8,11,12}

For newly diagnosed CD patients, a complex psychological adaption occurs in a very short time, including emotional responses such as distress and guilt and behavioral responses such as seeking social support, taking new medication, and evaluating the disease's impact on life. This adaption is dynamic with the unpredictable changes of disease progression since patients may experience ongoing physical and psychological challenges.¹³

The treatment target for CD patients is to induce and maintain long-term remission. As a proinflammatory cytokine, tumor necrosis factor- α (TNF- α) plays an important role in the pathogenesis of CD. Infliximab is the human-murine chimera anti-TNF- α monoclonal antibody, which can bind to TNF- α with high affinity and neutralize its biological activity. Therefore, infliximab tends to alleviate patient's symptoms quickly due to its prompt anti-inflammatory effect. Moreover, infliximab is by now the only anti-TNF- α agent available for us which is approved by China Food and Drug Administration (CFDA) for CD.^{14,15}

Up till now, there are many cross-sectional studies on psychological well-being in CD patients, but it lacks prospective follow-up studies. Besides, most research focuses on remission rates after infliximab administration, while improvement of psychological status remains little known. This study was aimed to evaluate the changes of illness perceptions, coping strategies, psychological well-being (anxiety and depression), and QoL in patients with newly diagnosed CD after infliximab induction therapy.

Patients and methods

Patients

Newly diagnosed CD patients in Ruijin Hospital from September 1, 2014 to December 31, 2016 were prospectively enrolled. Inclusion criteria were as follows: 1) having Harvey-Bradshaw Index (HBI)^{16,17} score >4 ; 2) receiving infliximab as induction therapy; and 3) willing to answer the questionnaires at baseline, week 14, and week 30 after intervention independently and voluntarily. Exclusion criteria

were as follows: 1) used CD-related medication before; 2) with contraindications of infliximab such as infection and stricture; 3) history of mental disease or psychological intervention before; and 4) with other chronic diseases.

This study was approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and written informed consent was signed by each patient.

Methods

At baseline, disease severity was measured using HBI, and patients were asked to fill a questionnaire measuring psychological characteristics. Then, a dose of 5 mg/kg intravenous infusion with infliximab was applied at weeks 0, 2, 6, 14, 22, and 30. The disease activity was re-evaluated at weeks 14 and 30. Clinical remission was defined as a HBI score of ≤ 4 . Meanwhile, patients were asked to fill out the same questionnaires. All the questionnaires were completed in our hospital, and patients were encouraged to finish the questionnaires within 30 minutes.

Questionnaires

Illness perceptions

The Brief Illness Perceptions Questionnaire¹⁸ is a validated 9-item scale evaluating patient's perceptions of overall effect of the disease, including consequences, timeline, personal control, treatment control, identity, concern, understanding, and emotional response. These items are scored on a continuous 0–10 scale, with higher total scores representing poorer illness perceptions.

Coping strategies

The Brief Coping Operations Preference Enquiry¹⁹ is a validated 28-item questionnaire to assess coping behaviors, which are divided into adaptive problem-focused coping (active coping, planning, and using instrumental support), adaptive emotion-focused coping (positive reframing, acceptance, humor, religion, and using emotional support), and maladaptive coping (self-distraction, denial, venting, substance use, behavioral disengagement, and self-blame).²⁰ Each item is measured with a scale ranging from 0 to 3, with higher scores indicating that particular coping strategies are more adopted.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS)²¹ is a 14-item tool (seven items for a separate anxiety score and seven items for a separate depression score) to measure individual's emotional adjustment. Each item is assessed on

a 4-point scale. Total scores of either anxiety or depression range from 0 to 21, higher scores representing higher levels of anxiety or depression.

QoL

The Inflammatory Bowel Disease Questionnaire²² is a disease-specific, health-related QoL questionnaire, containing 32 items, with a graded response range of 1–7 and a total score range of 32–224, with lower scores indicating poorer QoL.

Statistical analysis

The paired *t*-test was used to calculate changes in the questionnaire measures from baseline to week 14 and from baseline to week 30 after treatment. Statistical significance was considered if the calculated two-tailed *P*-value was <0.05. SPSS 21.0 was used to perform all the data analyses.

Results

A flow diagram of our study is shown in Figure 1. We found that of the 98 participants who met our inclusion criteria and filled out our baseline questionnaires, 87 patients completed questionnaires at week 14. Four patients experienced severe side effects to infliximab (two for allergy and the other two for myelosuppression) that treatment had to be terminated. Seven patients did not return the follow-up questionnaires. At week 30, 82 patients completed our questionnaires. One patient dropped out because of myelosuppression,

and four patients did not complete follow-up assessment. Finally, 82 patients finished our study. The demographic characteristics of the final cohort are shown in Table 1.

Fifty-nine of the 82 (72.0%) patients achieved clinical remission at week 14, with HBI decreasing from 6.24 ± 1.68 to 2.42 ± 1.00 ($P < 0.001$). Changes in psychological parameters of these patients are shown in Table 2. Patients made significant improvement in illness perceptions ($P < 0.001$), maladaptive coping ($P = 0.005$), anxiety ($P < 0.001$), depression ($P = 0.004$), and QoL ($P < 0.001$). At week 30, 58/82 (70.7%) patients were in clinical remission, whose HBI decreased from 6.40 ± 1.70 to 2.26 ± 1.12 ($P < 0.001$). As shown in Table 2, patients made significant improvement in illness perceptions ($P < 0.001$), maladaptive coping ($P = 0.004$), anxiety ($P < 0.001$), depression ($P = 0.004$), and QoL ($P < 0.001$), compared with those at baseline. However, emotion-focused coping and problem-focused coping remained unchanged at week 14 or 30.

Meanwhile, 23/82 (28.0%) and 24/82 (29.3%) patients did not achieve clinical remission at weeks 14 and 30, respectively. For these infliximab nonresponders, their psychological characteristics including illness perceptions, coping strategies, anxiety, depression, and QoL achieved no significant improvement after treatment, which are shown in Table 3.

Discussion

This study aimed to determine the changes of psychological parameters in newly diagnosed CD patients after infliximab

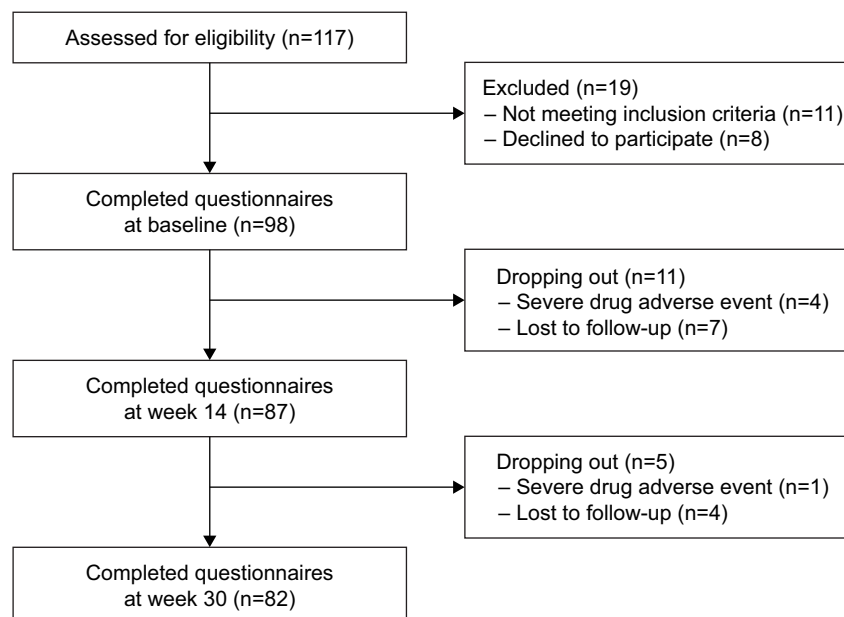


Figure 1 Participant flow diagram.

Table 1 Demographics of participants

Variable	n (%)
Gender	
Male	45 (54.9)
Female	37 (45.1)
Marital status	
Married	57 (69.5)
Single	25 (30.5)
Age at diagnosis (A)	
≤16 years (A1)	0 (0.0)
17–40 years (A2)	60 (73.2)
>40 years (A3)	22 (26.8)
Location (L)	
Terminal ileum (L1)	35 (42.7)
Colon (L2)	17 (20.7)
Ileocolon (L3)	30 (36.6)
Upper gastrointestinal tract (L4)	5 (6.1)
Behavior (B)	
Nonpenetrating nonstenosing (B1)	71 (86.6)
Stenosing (B2)	0 (0.0)
Penetrating (B3)	11 (13.4)
Fistula history	33 (40.2)
Gastrointestinal surgery history	9 (13.1)
Smoking or alcohol history	12 (9.2)
IBD family history	3 (2.3)

Abbreviation: IBD, inflammatory bowel disease.

treatment. We found that patients who achieved clinical remission had significantly improved illness perceptions, decreased adoption of maladaptive coping strategies, lower levels of anxiety and depression, and better QoL. However, no improvement in psychological parameters was seen in infliximab nonresponders.

As a simple tool to evaluate disease activity for CD patients, HBI decreased significantly after induction treatment in our study. Meanwhile, most patients achieved clinical remission, which was similar to previous research.^{23–27} Infliximab is effective in improving symptoms and alleviating disease severity for CD patients.¹⁴

Inflammatory bowel disease (IBD) patients with impaired psychological health and decreased QoL were highly associated with strong belief that IBD would have negative

consequences for their life.⁷ Our study found that with the improvement of disease severity after induction treatment, patient's illness perceptions improved as well, which was consistent with previous research.^{28–31} However, follow-up study of illness perceptions is little known among IBD patients, which still needs further exploring.

In our study, maladaptive coping decreased significantly after effective treatment for patients achieved clinical remission, while no such changes were seen in emotion-focused coping or problem-focused coping. It could be explained by the previous evidence indicating maladaptive coping is significantly associated with individual's physical status and psychological status.^{8,11,13,20,32} As patients become healthier through medical interventions, the need to cope with difficult situations significantly decreases. Nevertheless, a recent longitudinal study evaluating changes of coping strategies in newly diagnosed IBD patients showed different results.²⁰ They found that maladaptive coping did not change with time. In their research, most patients were treated with 5-aminosalicylic acid and immunomodulators, with very few patients treated with corticosteroids and no one used anti-TNF- α agents. However, in our study, all the participants were treated with infliximab, which was thought to be a rapid and effective medication in CD treatment. This might explain why our patients acquired better improvement and used fewer maladaptive coping strategies after treatment.

Patients' anxiety and depression also decreased significantly after treatment in our cohort. Similar to our results, the study by Calvet et al³³ showed that patient's psychological distress improved greatly and restored to normal levels after 6-month remission, but the research by McCombie et al²⁰ did not find improvement in anxiety or depression after 6-month treatment. Casellas et al³⁴ suggested that the recovery of emotional impairment was delayed compared with the recovery of function on physical and social dimensions. Another interesting finding about psychological issues in our study was that although both anxiety and depression improved significantly after treatment, the extent of improvement in anxiety seemed

Table 2 Infliximab responders: significance of change in questionnaire scores

Variable	Baseline, n=59	Week 14, n=59	P-value	Baseline, n=58	Week 30, n=58	P-value
Illness perceptions	44.59±12.23	36.75±12.01	<0.001	45.22±12.07	35.47±11.30	<0.001
Emotion-focused coping	18.46±5.16	19.42±4.41	0.063	17.95±4.95	18.59±5.19	0.337
Problem-focused coping	14.19±2.75	13.86±3.07	0.346	14.07±2.77	13.60±3.64	0.329
Maladaptive coping	11.95±6.43	9.97±6.25	0.005	11.78±6.59	9.67±6.18	0.004
Anxiety	10.02±2.14	8.44±1.64	<0.001	10.03±2.09	8.16±1.82	<0.001
Depression	9.05±2.46	8.10±2.08	0.004	9.00±2.36	8.02±1.95	0.004
Quality of life	153.66±27.06	187.41±22.54	<0.001	151.38±26.66	192.10±23.11	<0.001

Note: Data shown as mean ± standard deviation or P-value.

Table 3 Infliximab nonresponders: significance of change in questionnaire scores

Variable	Baseline, n=23	Week 14, n=23	P-value	Baseline, n=24	Week 30, n=24	P-value
Illness perceptions	51.13±9.57	49.13±11.93	0.170	49.33±11.06	47.79±10.95	0.391
Emotion-focused coping	19.61±4.73	17.87±4.77	0.053	20.79±4.78	19.54±4.96	0.346
Problem-focused coping	14.61±2.71	13.39±3.31	0.111	14.88±2.61	13.63±3.32	0.121
Maladaptive coping	13.57±5.92	12.39±5.16	0.241	13.92±5.35	12.54±5.70	0.097
Anxiety	10.57±2.11	10.26±2.20	0.573	10.50±2.23	9.83±1.47	0.141
Depression	8.83±2.04	9.13±2.40	0.585	8.96±2.33	9.75±2.31	0.089
Quality of life	137.48±24.24	146.17±23.41	0.104	143.67±28.13	149.42±21.79	0.284

Note: Data shown as mean ± standard deviation or P-value.

to be greater. This is probably because patient's HADS-Anxiety scores were much higher than HADS-Depression scores before treatment in our research, indicating that more CD patients were in anxiety rather than depression.¹¹

One of the primary treatment purposes of chronic diseases is the improvement of patient's QoL. From the perspective of QoL, an ideal result after treatment should be that patients achieved similar scores in QoL compared with general people. In our study, participants achieving clinical remission reported significant improvement in QoL after treatment, which is in good agreement with previous studies.³⁵⁻⁴² Moreover, research demonstrated that the early restoration of the QoL after induction treatment in patients with CD was associated with prolonged remission in the future.⁴³ Unconscious little alterations in QoL often reflect individual's general well-being, sometimes even before the appearance of obvious symptoms. The QoL has shown to be very sensitive to detect early changes of disease activity. Therefore, regular evaluation of QoL is quite meaningful, which can effectively predict the activity of the disease in the long term and discover early signs of disease flares.⁴³⁻⁴⁵

Our study found that patient's physical and psychological features including disease severity, illness perceptions, maladaptive coping, anxiety, depression, and QoL changed with time, which is in accordance with the CSM theory.^{9,10} As the disease activity decreased, patient's disease cognition and management, psychological status, and QoL improved at the same time, suggesting that disease stimuli, illness perceptions, coping strategies, and illness outcomes had complex interrelationships.^{8,11,12}

There were some limitations in our study. First of all, we used HBI to assess our patient's disease severity, which mainly represent their clinical symptoms rather than mucosal healing (MH). Research showed that MH was associated with future hospitalization and surgery; thus, it was an important parameter in evaluating patient's health status.⁴⁶⁻⁴⁸ Therefore, evaluation of both clinical and endoscopic disease severities would be a more accurate way of reflecting patient's disease

status. Second, number of flares, changes in laboratory results, and dosage changes in medication were not recorded in our study. These data may reflect patient's disease status, which could have an influence on patient's psychological characteristics. Third, all the patients in our study received infliximab treatment, while medications such as 5-aminosalicylic acid, steroids, and immunomodulators were not included. Studies on the comparison of patient's psychological changes between different treatments could be made in the future. Finally, we re-evaluated patient's physical and psychological parameters only at weeks 14 and 30. Several studies suggested that effective treatment brought benefits to CD patients both in the short term and up to 1 year, even as long as 4 years.^{23,39,42,43,49,50} We should make more frequent and longer follow-ups in further studies.

Conclusion

Newly diagnosed CD patients achieving clinical remission after effective infliximab treatment reported improved illness perceptions, maladaptive coping, anxiety, depression, and QoL. Interventions that help reduce patient's disease activity might also be beneficial to the improvement of their psychological characteristics.

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Disclosure

The authors report no conflicts of interest in this work.

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