Do Crohn's disease patients benefit from an optimized adalimumab therapy?

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Research Article

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Abstract

Background

Adalimumab induction and maintenance therapy have been applied to patients with Crohn's disease (CD). This study aimed to analyze the efficacy and safety of an optimized dose versus a standard dose of adalimumab in the treatment of CD.

Methods

It was a retrospective study involving 192 CD patients treated with adalimumab. According to the maintenance therapy following an induction therapy, CD patients were assigned to receive a standard dose (subcutaneously injected with 40mg of adalimumab every other week) and an optimized dose (subcutaneously injected with 80mg of adalimumab every other week). The clinical remission rate, inflammatory and nutritional indicators, mucosal healing rate, endoscopic response rate at 12th week, risk of treatment failure and safety were compared between groups.

Results

There were 139 patients in the standard dose group and 53 in the optimized dose group. At 12 weeks, no significant difference was detected in the clinical remission rate (79.1% vs. 81.1%; RR, 0.97; 95% CI, 0.81–1.24; P = 0.842). In infliximab-exposed CD patients, the optimized dose of adalimumab provided a significantly higher clinical remission rate (76.9% vs. 44.4%; RR, 0.58; 95% CI, 0.37–0.88; P = 0.018) and lower risk of treatment failure (HR, 0.36; 95% CI, 0.14–0.97; P = 0.042), but not in infliximab-naïve CD patients. The incidence of adverse events was comparable between groups (32.1% vs. 30.9%, P = 0.864).

Conclusions

An optimized adalimumab dose does not provide additionally clinical benefits to infliximab-naïve CD patients, compared with a standard dose, but can increase the clinical remission rate and lower the risk of treatment failure in infliximab-exposed CD patients at 12 weeks, without increasing the incidence of adverse events.

Introduction

Crohn's disease (CD), a chronic, progressive, and relapsing disease, mainly involves the gastrointestinal tract. Typical clinical symptoms of CD include abdominal pain, diarrhea, weight loss, and fatigue, all seriously affecting the quality of life[1]. About half of CD patients require a surgical treatment within 10 years after onset, due to intestinal strictures, fistulas, and abscesses caused by a progressive course of CD[2]. The goals of induction and maintenance therapies for CD are to alleviate clinical symptoms, improve the quality of life, minimize the use of glucocorticoids, and prevent the development of fistulas and stenosis that need to be surgically treated [3]. Anti-tumor necrosis factor (TNF) agents, including infliximab and adalimumab, can greatly improve the prognosis of CD, and reduce the rates of
complications and hospitalization [4]. At present, anti-TNF agents are still considered as cornerstone drugs for CD, even though biological agents and small-molecule compounds have been burgeoned [3]. Due to the immunogenicity and administrative route, the infliximab therapy easily causes the production of anti-infliximab antibodies that lead to infusion reactions, allergic reactions and secondary unresponsiveness[5]. Adalimumab is a fully human monoclonal antibody approved by the FDA in 2007 for the treatment of moderate-to-severe CD. Adalimumab induction and maintenance therapies provide clinical benefits to either infliximab-exposed or infliximab-naïve CD patients[6]. Based on the data from the CLASSIC II trial, adalimumab 40 mg every other week is recommended as a standard maintenance dosage [7]. Clinical evidences have also demonstrated that the trough concentration of adalimumab is positively correlated with the clinical response and mucosal remission of CD [8–10]. Dose escalation or shortening dosing frequency is a promising strategy to require the secondary unresponsiveness to adalimumab, which may be attributed to the increased concentration of adalimumab[11]. The immunogenicity and production of anti-drug antibodies contribute to the unresponsiveness to anti-TNF agents [12]. An insufficient exposure to anti-TNF agents is more likely to produce anti-drug antibodies[13], and patients who develop anti-infliximab antibodies are more likely to develop anti-adalimumab antibodies[14]. Therefore, it is necessary to optimize the adalimumab therapy to provide CD patients with more clinical benefits, especially those experience infliximab treatment failure.

This study aimed to assess the efficacy and safety of an optimized dose versus a standard dose of adalimumab in the treatment of CD, especially for CD patients experiencing treatment failure of infliximab.

**Methods**

**Study design and patient recruitment**

It was a retrospective observational study that assessed the efficacy and safety of an optimized dose versus a standard dose of adalimumab in the treatment of CD. CD patients admitted in the Inflammatory Bowel Disease Center, the Sixth Affiliated Hospital, Sun Yat-sen University and treated with adalimumab from January 2020 to July 2022 were retrospectively recruited. Experimental protocols were approved by the Ethic committee, the Sixth Affiliated Hospital, Sun Yat-sen University (E2022071), which were in accordance with the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Inclusion criteria: (1) male or female patients aged 18–70 years; (2) CD was diagnosed based on clinical, endoscopic and histological findings according to the European Crohn's disease and Colitis Organization (ECCO) 2021 Congress; (3) patient with involvement into the terminal ileum or colorectum; (4) patients with active CD determined by a minimum Crohn's disease activity index (CDAI) of 150 points.

Exclusion criteria: (1) the patient was managed by two or more biological agents; (2) the patient received an adalimumab therapy for preventing postoperative relapse of CD; (3) the patient had insufficient
clinical data; (4) the patient was engaged in other clinical trials during the same period; (5) the duration from adalimumab therapy to the last follow-up visit was less than 12 weeks of; (6) the patient was managed by an adalimumab therapy at different dosages, rather than 40 mg (optimized dose regimen) or 80 mg (standard dose regimen) adalimumab every other week; (7) the patients was accompanied with central nervous diseases; (8) severe cardiopulmonary, liver or kidney dysfunction; (9) malignancies; (10) active tuberculosis, hepatitis B, severe immune deficiency, post-organ transplantation, or severe infection.

**Primary outcome**

The clinical remission rate at 12 weeks was considered as the primary outcome, either for the optimized or the standard dose of adalimumab. The clinical remission was defined as a CDAI of < 150. The clinical remission rate was defined as the proportion of patients in clinical remission to enrolled patients.

**Secondary outcomes**

Secondary outcomes: (1) mucosal healing rate and endoscopic response rate at 12 weeks; (2) nutritional indexes like hemoglobin (Hb), albumin (ALB) and body mass index (BMI) at 12 weeks of treatment; inflammatory indexes like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) at 12 weeks; (4) risk of treatment failure during the maintenance therapy; (5) safety during the whole treatment.

Mucosal healing was determined by the Simple Endoscopic Score for Crohn's Disease (SES-CD) of 0 point. Endoscopic response was defined as the SES-CD score decreased by ≥ 50% from baseline. Mucosal healing rate and endoscopic response rate were calculated by the number of CD patients achieving mucosal healing and endoscopic response to the total case number, respectively.

Treatment failure was defined as (1) recurrent clinical symptoms accompanied by increased inflammatory indexes or endoscopic recurrence that required for changing the adalimumab dosage or regimen, or (2) additional use of glucocorticoids or immunosuppressants, or (3) adverse events that required withdrawal or surgical procedures.

Any adverse events occurred from the first use of adalimumab to the last follow-up visit were recorded. Severe adverse events were defined as those that caused hospitalization, prolonged length of stay, or severe disability, or fatal, life-threatening events.

**Data collection**

Eligible CD patients were divided into the standard dose group (subcutaneously injected with 40 mg adalimumab every other day) and the optimized dose group (subcutaneously injected with 40 mg adalimumab every other day). The following data were recorded: (1) demographic data, including sex, age, height, body weight, etc.; (2) baseline characteristics, including the course of disease, involved site and behaviors of according to the Montreal classification, presence of perianal diseases, medication
history, history of CD-associated perianal and abdominal surgery, CDAI, SES-CD, and baseline CRP, ESR, ALB, Hb and BMI; (3) adverse events from the first dose of adalimumab to the treatment failure, last follow-up visit or the end of the observation period, whichever occurred first.

**Statistical analysis**

Statistical analysis was performed using SPSS 20.0. Measurement data were expressed as mean ± standard deviation. Unpaired data and paired data normally distributed were compared by the Student’s *t*-test and paired sample *t*-test, respectively, otherwise by the Wilcoxon rank sum test. Enumeration data were expressed as the absolute value and percentage, and unpaired data were compared by the Fisher’s exact test. The grouping variable and previous infliximab treatment were considered as interaction terms. If an interaction effect existed, a stratified analysis was performed according to previous infliximab treatment in both groups. Meanwhile, the logistic regression analysis adjusted for sex, age and behaviors of CD was performed. The Kaplan-Meier curve was plotted to analyze the survival. Two-sided *p* < 0.05 was considered as statistically significant.

**Results**

**Baseline characteristics**

A total of 224 CD patients were retrospectively recruited. After excluding 6 patients lost to follow-up, 18 with insufficient clinical data, 6 treated with adalimumab for preventing postoperative recurrence of CD, and 2 with other causes, a total of 192 eligible CD patients were finally enrolled for the following experiments, including 139 in the standard dose group and 53 in the optimized dose group (Fig. 1).

Demographic data and baseline characteristics of CD patients are listed in Table 1. The proportion of CD patients receiving previous infliximab was significantly higher in the optimized dose group than in the standard dose group (49.1% vs. 25.9%, *P* = 0.003), while ALB level was significantly lower (35.8 ± 6.4 g/L vs. 37.9 ± 5.4 g/L, *P* = 0.029). Other demographic data and baseline characteristics were comparable between groups (*P* > 0.05).
<table>
<thead>
<tr>
<th></th>
<th>Standard dose group (n = 139)</th>
<th>Optimized dose group (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
<td>0.239</td>
</tr>
<tr>
<td>Male</td>
<td>93 (66.9%)</td>
<td>30 (56.6%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 (33.1%)</td>
<td>23 (43.4%)</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>26.6 ± 11.1</td>
<td>26.3 ± 9.5</td>
<td>0.874</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>19.4 ± 4.3</td>
<td>19.6 ± 3.0</td>
<td>0.731</td>
</tr>
<tr>
<td>Course of disease (years)</td>
<td>4.2 ± 3.7</td>
<td>3.9 ± 3.5</td>
<td>0.691</td>
</tr>
<tr>
<td>Involved site (n, %)</td>
<td></td>
<td></td>
<td>0.336</td>
</tr>
<tr>
<td>Ileum</td>
<td>10 (7.2%)</td>
<td>6 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>18 (12.9%)</td>
<td>3 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Ileum and colon</td>
<td>111 (79.6%)</td>
<td>44 (83.0%)</td>
<td></td>
</tr>
<tr>
<td>Upper digestive tract</td>
<td>31 (22.3%)</td>
<td>16 (30.2%)</td>
<td></td>
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<tr>
<td>Behaviors of CD (n, %)</td>
<td></td>
<td></td>
<td>0.528</td>
</tr>
<tr>
<td>Non-stricturing/non-penetrating</td>
<td>103 (74.1%)</td>
<td>35 (66.0%)</td>
<td></td>
</tr>
<tr>
<td>Stricturing</td>
<td>23 (7.4%)</td>
<td>12 (22.6%)</td>
<td></td>
</tr>
<tr>
<td>Penetrating</td>
<td>13 (74.1%)</td>
<td>6 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Previous infliximab treatment (n, %)</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>I.A.</td>
<td>36 (25.9%)</td>
<td>26 (49.1%)</td>
<td></td>
</tr>
<tr>
<td>N.A.</td>
<td>103 (74.1%)</td>
<td>27 (50.9%)</td>
<td></td>
</tr>
<tr>
<td>Previous abdominal surgery (n, %)</td>
<td></td>
<td></td>
<td>0.999</td>
</tr>
<tr>
<td>I.A.</td>
<td>29 (20.9%)</td>
<td>11 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>N.A.</td>
<td>110 (79.1%)</td>
<td>42 (79.2%)</td>
<td></td>
</tr>
<tr>
<td>CDAI (points)</td>
<td>219.7 ± 84.1</td>
<td>213.3 ± 70.1</td>
<td>0.621</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>21.1 ± 84.1</td>
<td>23.9 ± 35.6</td>
<td>0.590</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>23.8 ± 23.3</td>
<td>28.0 ± 26.4</td>
<td>0.291</td>
</tr>
</tbody>
</table>

CD, Crohn's disease; BMI, body mass index; I.A., applicable; N.A., not applicable; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; ALB, albumin; Hb, hemoglobin; SES-CD, simple endoscopic score for Crohn's disease.
<table>
<thead>
<tr>
<th></th>
<th>Standard dose group (n = 139)</th>
<th>Optimized dose group (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB (g/L)</td>
<td>37.9 ± 5.4</td>
<td>35.8 ± 6.4</td>
<td>0.029</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>120.6 ± 22.1</td>
<td>117.7 ± 22.4</td>
<td>0.430</td>
</tr>
<tr>
<td>SES-CD (points)</td>
<td>9.9 ± 7.5</td>
<td>10.1 ± 8.1</td>
<td>0.886</td>
</tr>
</tbody>
</table>

CD, Crohn's disease; BMI, body mass index; I.A., applicable; N.A., not applicable; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; ALB, albumin; Hb, hemoglobin; SES-CD, simple endoscopic score for Crohn's disease.

**Efficacy**

**Clinical remission**

Compared with that at baseline, CDAI at 12 weeks was significantly reduced in either the standard dose group (219.7 ± 84.1 points vs. 107.8 ± 69.5 points, \( P < 0.001 \)) or the optimized dose group (213.3 ± 70.1 points vs. 101.5 ± 7.5 points, \( P < 0.001 \)) (Fig. 2). It is suggested that the disease activity in CD patients was effectively inhibited by the adalimumab at either a standard or an optimized dose.

There was no significant difference in the clinical remission rate at 12 weeks between the optimized dose group and standard dose group (81.1% vs. 79.1%; OR, 1.13; 95% CI, 0.53–2.46; \( P = 0.842 \)). An interaction term between the optimized/standard dose of adalimumab and previous infliximab treatment was created, and a significant difference (\( P = 0.002 \)) suggested that dose regimen of adalimumab might have produced a difference in the clinical remission rate at 12 weeks in either infliximab-exposed or infliximab-naïve CD patients. We thereafter performed a stratified analysis based on previous infliximab treatment or not. Our data revealed that there was no significant difference in the clinical remission rate at 12 weeks in infliximab-naïve CD patients between the optimized dose group and the standard dose group (91.3% vs. 85.2%; OR, 0.55; 95% CI, 0.17–1.74; \( P = 0.469 \)). Nevertheless, a significantly higher clinical remission rate at 12 weeks was detected in infliximab-exposed CD patients of the optimized dose group than that of the standard dose group (76.9% vs. 44.4%; OR, 4.17; 95% CI, 1.28–13.7; \( P = 0.018 \)) (Fig. 3). After adjusting sex, age and behaviors of CD, the clinical remission rate at 12 weeks was still found significantly higher in the optimized dose group than in the standard dose group (OR, 3.469; 95% CI: 1.12–11.89, \( P = 0.032 \)).

**Inflammatory indexes**
After 12 weeks of adalimumab therapy, the CRP levels in CD patients of both groups were significantly reduced compared with those at baseline (standard dose regimen group, 21.1 ± 29.5 mg/L vs. 8.4 ± 19.1 mg/L, \( P < 0.001 \); optimized dose regimen group, 23.9 ± 35.6 mg/L vs. 6.0 ± 12.3 mg/L, \( P < 0.001 \)). Stratified by previous infliximab treatment or not, the decreases in CRP at 12 weeks were comparable between infliximab-naïve CD patients of the standard dose group and the optimized dose group (15.4 ± 34.1 mg/L vs. 15.8 ± 34.9 mg/L, \( P = 0.968 \)). The decrease was significantly larger in infliximab-exposed CD patients of the optimized dose group than that of the standard dose group (8.2 ± 18.8 mg/L vs. 21.4 ± 31.4 mg/L, \( P = 0.044 \)) (Fig. 4). The ESR levels in CD patients of both groups were significantly reduced at 12 weeks compared with those at baseline (standard dose group, 23.8 ± 23.3 mm/h vs. 12.1 ± 13.5 mm/h, \( P < 0.001 \); optimized dose group, 28.0 ± 26.4 mm/h vs. 12.7 ± 17.9 mm/h, \( P < 0.001 \)). Stratified by previous infliximab treatment or not, the decrease in ESR was slightly smaller at 12 weeks in either the infliximab-naïve (13.2 ± 23.2 mm/h vs. 17.9 ± 23.2 mm/h, \( P = 0.385 \)) or the infliximab-exposed CD patients (6.1 ± 17.7 mm/h vs. 12.6 ± 23.4 mm/h, \( P = 0.214 \)) of standard dose group than that of the optimized dose group, although a significant difference was not detected (Fig. 4).

**Nutritional indexes**

Nutritional indexes, including ALB (standard dose group, 120.6 ± 22.1 g/L vs. 127.9 ± 20.7 g/L, \( P < 0.001 \); optimized dose group, 117.7 ± 22.4 g/L vs. 127.0 ± 22.3 g/L, \( P < 0.001 \) and Hb (standard dose group, 37.9 ± 5.4 g/L vs. 40.7 ± 8.4 g/L, \( P = 0.002 \); optimized dose group, 35.8 ± 6.4 g/L vs. 40.0 ± 4.2 g/L, \( P < 0.001 \) were significantly reduced in CD patients of both groups at 12 weeks compared with those at baseline. Stratified by the previous infliximab treatment or not, the increases in ALB and Hb at 12 weeks were both smaller in either the infliximab-naïve (Hb, 1.9 ± 33.9 g/L vs. 9.63 ± 19.9 g/L, \( P = 0.262 \); ALB, 1.47 ± 13.5 g/L vs. 3.8 ± 4.4 g/L, \( P = 0.339 \)) or the infliximab-exposed CD patients (Hb, 4.1 ± 22.5 g/L vs. 7.5 ± 11.5 g/L, \( P = 0.512 \); ALB, 1.9 ± 9.2 g/L vs. 4.8 ± 9.2 g/L, \( P = 0.299 \)) of the standard dose regimen group than that of the optimized dose group, although significant differences were not detected (Fig. 5).

**Mucosal healing and endoscopic response**

SES-CD scores were significantly lowered in CD patients of both groups at 12 weeks compared with those at baseline (standard dose group, 9.9 ± 7.5 points vs. 4.7 ± 5.6 points, \( P < 0.001 \); optimized dose group, 10.1 ± 8.1 points vs. 4.4 ± 5.0 points, \( P < 0.01 \)). The stratified analysis revealed higher mucosal healing rate (44.4% vs. 33.9%, \( P = 0.370 \)) and endoscopic response rate (70.4% vs. 56.3%, \( P = 0.271 \)) in infliximab-naïve CD patients of the optimized dose group than those of the standard dose group, although no significant differences were detected. Similarly, higher mucosal healing rate (26.9% vs. 16.7%, \( P = 0.359 \)) and endoscopic response rate (46.2% vs. 38.9%, \( P = 0.610 \)) were detected in infliximab-exposed CD patients of the optimized dose group than those of the standard dose group, while no significant differences were detected (Fig. 6).
Risk of treatment failure

The median follow-up periods of infliximab-exposed CD patients of the standard dose group and the optimized dose group were 48 (IQR: 12, 122) weeks and 69 (IQR: 12, 130) weeks, respectively. The risk of adalimumab treatment failure was significantly lower in infliximab-exposed CD patients of the optimized dose group than that in the standard dose group (HR, 0.36; 95% CI, 0.14–0.97; \( P = 0.042 \)). The median follow-up periods of infliximab-naïve CD patients of standard dose group and optimized dose group were 53 (IQR: 12, 125) weeks and 63 (12, 112) weeks, respectively. The risk of adalimumab treatment failure was slightly lower in infliximab-naïve CD patients of the optimized dose group than that in the standard dose group, although a significant difference was not detected (HR, 0.77; 95% CI, 0.39–1.51; \( P = 0.449 \)) (Table 2).

<table>
<thead>
<tr>
<th>Hazard ratios of an optimized dose to the risk of adalimumab treatment failure.</th>
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<tbody>
<tr>
<td>IFX-naïve CD patients (n = 130)</td>
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<td>---------------------------------</td>
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<tr>
<td>Hazard ratio (95% CI)</td>
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<td>( P ) value</td>
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</table>

CD, Crohn's disease; IFX, infliximab.

Safety

The optimized dose of adalimumab increased neither the incidence of adverse events during the treatment period (32.1% vs. 30.9%, \( P = 0.864 \)), nor the incidence of severe adverse events (5.7% vs. 4.3%, \( P = 0.718 \)). Injection site reactions were the most-common adverse events, but they barely caused withdrawal. The incidences of infections and allergies were comparable between groups (Table 3).
Table 3
Adverse events of adalimumab therapy (n = 192).

<table>
<thead>
<tr>
<th></th>
<th>Standard dose regimen group (n = 139)</th>
<th>Optimized dose regimen group (n = 53)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adverse events (n, %)</td>
<td>43 (30.9%)</td>
<td>17 (32.1%)</td>
<td>0.864</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>39 (28.1%)</td>
<td>14 (26.4%)</td>
<td>0.859</td>
</tr>
<tr>
<td>Infections</td>
<td>3 (2.2%)</td>
<td>2 (3.8%)</td>
<td>0.617</td>
</tr>
<tr>
<td>Others</td>
<td>2 (1.4%)</td>
<td>1 (1.9%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Severe adverse events (n, %)</td>
<td>6 (4.3%)</td>
<td>3 (5.7%)</td>
<td>0.718</td>
</tr>
</tbody>
</table>

Discussion

Due to the intimate involvement of TNF-\( \alpha \) in the pathogenesis of CD, the anti-TNF monoclonal antibody biologics have been globally recommended as the first-line treatment of CD [15, 16]. Infliximab and adalimumab are approved anti-TNF agents in China's mainland for the treatment of CD. The maintenance dose of adalimumab is recommended as 40 mg every other week[17]. However, some CD patients do not achieve a clinical response to a standard dose of adalimumab, with the primary and secondary unresponsiveness rates of 10–30% and 23–46%, respectively[18]. An optimized dose of adalimumab is believed to reconstruct the clinical response in CD patients due to higher concentrations of drugs. The objective of this study is to explore whether the optimized dose of initial adalimumab therapy provide more clinical benefits for CD patients.

Our data revealed that the clinical remission rate at 12 weeks was significantly increased by either a standard or an optimized dose of adalimumab, but no significant difference between the two groups (81.1% vs 79.1%; OR, 1.13; 95%CI, 0.53–2.46; \( p = 0.842 \)). A stratified analysis further identified that the optimized dose of adalimumab provided a significantly higher clinical remission rate at 12 weeks in infliximab-exposed CD patients than that in the standard dose group (76.9% vs 44.4%; OR = 4.17; 95%CI, 1.28–13.7; \( p = 0.018 \)), but this effect was not observed in infliximab-naïve CD patients (91.3% vs 85.2%; OR, 0.55; 95%CI, 0.17–1.74; \( p = 0.469 \)). We further compared nutritional and inflammatory indexes, mucosal healing and endoscopic response at 12 weeks of adalimumab therapy. A significantly pronounced decrease in CRP level was found in the infliximab-exposed CD patients of the optimized dose group than in the standard dose group. However, we did not detect significant differences in nutritional indexes and mucosal healing between groups, which may be attributed a small sample size.

A previous study has reported a lower clinical remission rate in CD with loss of response to infliximab transferred to adalimumab therapy, compared with without previous infliximab treatment[19]. Consistently, our data revealed a higher clinical remission rate at 12 weeks of an optimized dose than
that of a standard dose in CD with previous infliximab treatment, which may be attributed to the production of anti-adalimumab antibody in infliximab-exposed CD patients that required a higher dose [14]. It is reported that CD patients carrying the HLA-DQA1*0.5 allele are prone to produce anti-TNF antibody. Thus, a combination treatment based on genetic variants of CD patients may provide a stronger clinical remission [20]. We speculated that unresponsiveness to infliximab may be correlated with mutations in human leukocyte antigen (HLA). It is unclear whether an optimal dose regimen can be used as a treatment strategy in loss of response patients with this genotype. In the absence of genetic testing, an optimized dose of adalimumab seems to be associated with a higher rate of clinical remission in infliximab-exposed CD patients.

The SERENE CD trial demonstrated that the clinical benefits are comparable in CD patients treated with a standard dose or a higher dose of adalimumab [21]. We considered that the enrollment of biologics-naïve CD patients in the SERENE CD trial, and an absence of a stratified analysis based on previous infliximab treatment or not caused the controversy. So the results cannot be extrapolated to patients who have previously failed anti-infliximab therapy. Inconsistently, a lower risk of adalimumab treatment failure was yielded in infliximab-exposed CD patients of the optimized dose group than that of the standard dose group (HR 0.36; 95% CI [0.14, 0.97]; p = 0.042) in our study. However, this effect was not detected in infliximab-naïve CD patients (HR 0.77; 95% CI [0.39, 1.51]; p = 0.449). It is suggested that an optimized dose of adalimumab provided more clinical benefits to infliximab-exposed CD patients.

The safety analysis showed that the optimized dose did not additionally increase the incidence of adverse events (32.1% vs 30.9%, p = 0.864). In detail, injection site reactions were the most common adverse events of adalimumab therapy, but none of CD patients experienced withdrawal. The most concerned adverse effect of anti-TNF-α was infection, but the incidence of infection was similar between the two dosing regimens in our study (5.7% vs 4.3%, P = 0.718). Therefore, the optimized dose of adalimumab was relatively safe.

Collectively, we compared the efficacy and safety of optimized and standard doses of adalimumab in infliximab-exposed and infliximab-naïve CD patients. Our findings provided references for the first-line and second-line adalimumab treatment of CD. Some limitations in the present study should be concerned. First of all, it was a retrospective analysis with a small sample size. The selection of an optimized or standard dose regimen of adalimumab was determined by experts experienced in the clinical management of inflammatory bowel diseases (IBD), which may cause potential biases. Third, we were unable to analyze the potential cause of infliximab treatment failure due to the small sample, and we did not analyze the correlation between the concentration of adalimumab and clinical benefits to CD patients. Further prospective, randomized, controlled studies may provide more theoretical basis for adalimumab dose decision.

**Conclusion**
Adalimumab induction and maintenance therapies can be applied to CD patients. An optimized adalimumab dose does not provide additionally clinical benefits to infliximab-naïve CD patients, compared with the standard dose, but may provide more clinical benefits to infliximab-exposed CD patients without increasing the incidence of adverse events.

**Declarations**

**Author contributions**

Peng Xiang and Min Zhi were involved in study conception and design; Xiang Peng and Zhao-yuan Xu performed literature search and data collection; Xiang Peng and Min Zhang performed data analysis; Peng Xiang, Jia-yin Yao were involved in the draft of the manuscript; Peng Xiang, Zhao-yuan Xu, Min Zhang, Jia Yin Yao, Min Zhi were involved in critical revision of the manuscript for important intellectual content; All authors have approved the final version of the manuscript.

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**Availability of Data and Material**

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflict of Interest**

No potential conflict of interest was reported by the authors.

**Ethical Statement and consent to participate**

The study was conducted in compliance with all national and international ethical standards for research with humans. This clinical trial was approved by the Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University (E2022071). Informed consent was exempted because it was a retrospective study.

**Consent to publish**

All authors consent to publish

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Figures
CD patients with Adalimumab (N=224)

Excluded
- Lack of clinical follow-up (N=6)
- Insufficient clinical data (N=18)
- Postoperative prevention of recurrence (N=6)
- Other reason (N=2)

Standard dose (N=139)

Optimize dose (N=53)

Figure 1

The flow diagram of follow-up and analysis

Figure 2

CDAI at baseline and 12 weeks of adalimumab therapy in the standard dose group (a) and optimized dose group (b).
Figure 3

Clinical remission rate at 12 weeks in CD patients of the standard dose group versus the optimized dose group.

Figure 4

(a) CRP change (mg/L) and (b) ESR (mm/h) in IFX-naive and IFX-exposed patients.
CRP (a) and ESR decreases (b) at 12 weeks in infliximab-naïve and infliximab-exposed CD patients of the standard dose group versus the optimized dose group.

Figure 5

ALB (a) and Hb levels (b) at 12 weeks in infliximab-naïve and infliximab-exposed CD patients of the standard dose group versus the optimized dose group.

Figure 6

Mucosal healing rate (a) and endoscopic response rate (b) at 12 weeks in infliximab-naïve and infliximab-exposed CD patients of standard dose group versus the optimized dose group.