Patients with Crohn's disease on anti-tumor necrosis factor therapy are at significant risk of inadequate response to the 23-valent pneumococcal polysaccharide vaccine☆

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Abbreviations: PPSV23, 23-valent pneumococcal polysaccharide vaccine; anti-TNF, anti-Tumor Necrosis Factor; IM, Immunomodulator; HBI, Harvey-Bradshaw Index; GMT, Geometric Mean Titer; IBD, Inflammatory Bowel Disease; CD, Crohn's disease; UC, Ulcerative Colitis.
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1. Introduction

Crohn’s disease (CD) is a long-standing inflammatory bowel disease (IBD) that often requires long-term use of immunosuppressants including immunomodulators (IMs) (such as azathioprine, 6-mercaptopurine and methotrexate) and anti-tumor necrosis factor (anti-TNF) agents (such as infliximab and adalimumab). Because recent research has demonstrated that early immunosuppressive therapies can improve the clinical outcomes of patients with CD, a growing number of patients are currently treated with a variety of immunosuppressants—including anti-TNF agents, IMs or their combination—in clinical practice. Introduction of immunosuppressive therapies, however, involves the risk of host susceptibility to various infectious illnesses. Therefore, adequate immunization for vaccine-preventable infectious diseases is currently recommended for all patients with IBD and is emerging as an important target for quality improvements in IBD care. However, ongoing issues regarding underuse of immunization and impaired efficacy of vaccines in patients with IBD remain.

Pneumococcal disease due to Streptococcus pneumoniae is a major health problem in the general population and an important cause of serious illness in patients with CD. The current preventive strategy consists of vaccination with the standard 23-valent pneumococcal polysaccharide vaccine (PPSV23) before starting IMs and a single revaccination after 3–5 years if the patient is immunosuppressed, but data regarding the immune response to pneumococcal vaccine in patients with IBD are lacking. Recently, several small studies addressed this issue and suggested that anti-TNF therapy (alone or in combination with IM) may cause diminished serological response to the PPSV23 in patients with IBD, including CD and ulcerative colitis (UC). However, the results remain inconclusive and no prospective trial that focuses on the patients with CD, who are a major target for anti-TNF therapy in IBD, has been conducted.

Thus, we prospectively evaluated the effect of immunosuppressants on the serological response to PPSV23 in a large cohort of adult patients with CD.

2. Materials and methods

2.1. Study population and design

This was a multi-center, prospective observational study of invited outpatients with CD who were recruited from 15 academic teaching hospitals in Korea over a 12-month period. The study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Boards of all participating hospitals. The study was registered at www.clinicaltrials.gov (NCT01505855). Adult outpatients (over 18 years of age) who had a definitive diagnosis of CD for at least 6 months and received ongoing medical treatment for more than 3 months were eligible for this study. The CD diagnosis was based on the current guidelines, which include clinical, radiological, endoscopic and histological findings. Medical records of eligible patients were reviewed to obtain their demographics and baseline disease characteristics, including disease duration, phenotype by the Montreal classification, clinical disease...
activity by the Harvey–Bradshaw index (HBI) and current medications at enrollment. Exclusion criteria were (1) hypersensitivity or allergy to any component of the pneumococcal vaccine, (2) patients who were treated with glucocorticoids (prednisolone ≥ 20 mg/day equivalent for 2 weeks or more and were within 3 months of ending treatment), (3) receiving another vaccine in the past 4 weeks (including influenza vaccination), (4) pregnancy, (5) history of invasive pneumococcal disease, and (6) any conditions considered to be inappropriate by the investigators. Written informed consent for this study was obtained from all enrolled patients.

The study population was classified into four treatment groups according to their current treatment for CD, as follows: (1) patients treated with 5-aminosalicylate (5-ASA) alone (5-ASA group as a control), (2) patients treated with IM alone (IM group), (3) patients treated with anti-TNF agent alone (anti-TNF group), and (4) patients treated with both IM and anti-TNF (combination group). IMs included azathioprine or 6-mercaptopurine of the weight-adjusted effective dose (azathioprine 2.0–2.5 mg/kg/day or 6-mercaptopurine 1.0–1.5 mg/kg/day) for more than 3 months before vaccination, but an adjusted lower dose was permitted in patients with drug-induced side effects, such as leukenopia. Anti-TNF therapies included at least one dose of infliximab or adalimumab within 3 months before vaccination.

2.2. Vaccination and measurements of anti-pneumococcal antibody titers

Enrolled patients received one intramuscular injection of 0.5-ml PPSV23 (Prodxia-Zyme™, MSD Korea, Seoul, Korea) in the deltoid muscle. The PPSV23 included 25-μg purified capsular polysaccharide antigens of the following S. pneumoniae serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F.

Serum samples for the determination of serial anti-pneumococcal antibody titers were obtained at day 0, immediately before the vaccination, and 4 weeks after vaccination. All samples were immediately centrifuged and transported to the central laboratory (Seoul Clinical Laboratories, Seoul, Korea). The IgG anti-pneumococcal antibody titers were measured using a commercially available quantitative enzyme-linked immunosorbent assay kit (Vaccine™ anti-pneumococcal capsular polysaccharide kit, Birmingham, United Kingdom), as described previously. Both quality control and specific laboratory protocols were followed according to the manufacturer’s guidelines.

2.3. Adverse events and effect of vaccination on disease activity

All patients were routinely monitored for vaccination-related adverse events up to 4 weeks after vaccination via patient visit and/or phone call. Local reactions included pain, redness, and swelling at the injection site. Systemic reactions included fever ≥ 38 °C, chills, fatigue/malaise, and myalgia/arthritis.

We also evaluated potential detrimental effects of the vaccination on CD activity. At the final visit 4 weeks after vaccination, all patients were assessed for development of any significant changes in CD activity, defined as a total HBI score ≥ 5 points plus an increase (Δ) in HBI of ≥ 3 points and any alteration of CD medication.

2.4. Outcome measurements and statistical analysis

The primary study objective was to compare the serological response rates to PPSV23 among the four study groups. Serological response rate was defined as the percentage of subjects achieving a twofold increase in IgG antibody titer. Secondary outcomes included a change in geometric mean titer (GMT), rate of adverse events, and significant changes in CD activity.

Sample size calculation was based on the results of two previous studies that reported 84.0–89.0% serological response rates in patients on 5-ASA and 45–58% in patients on anti-TNF therapy with or without IM. With an α value of 0.05 and a power of 80%, 34 patients were required to detect a difference of 30% between patients on anti-TNF therapy and patients on 5-ASA. Considering a 20% dropout rate, we aimed to recruit 43 patients per group.

Data are presented as means (standard deviation) or medians (range), as appropriate. Categorical variables were assessed using the χ² test or Fisher’s exact test for small expected frequencies. Student’s t-test was used for continuous variables. The GMTs among the four subgroups were assessed by one-way ANOVA with post hoc Scheffe’s test. A logistic regression analysis was used to identify predictive factors associated with impaired serological response to the vaccine. All data were analyzed using the Statistical Package for the Social Sciences software (version 18.0K for Windows, SPSS Korea Inc., Seoul, Korea); P-values < 0.05 were considered to indicate a statistical significance.

3. Results

3.1. Baseline characteristics

Between January and December 2012, 210 patients were considered eligible and invited to participate. Of these, 197 patients completed the protocol (Fig. 1). The proportion of male patients was 66.5% (131/197) and the mean age was 32.4 years, with a 64.1-month mean disease duration. In terms of disease activity, the mean HBI score was 2.16 points and the mean CRP was 0.42 mg/dL. A total of 172 patients (87.3%) had inactive disease at the time of enrollment (accoring to HBI index). The detailed baseline characteristics are shown in Table 1.

3.2. Serological response to PPSV23

The overall rate of serological response to PPSV23 was 67.5% (133/197). There were significant differences in serological response rates among the four groups (P < 0.004). Both the anti-TNF group and combination group had a significantly lower serological response rate (50.0%; 20/40 and 58.0%; 29/50) than the 5-ASA group (78.4%; 29/37, all P-values vs. 5-ASA group < 0.05, respectively) (Fig. 2). There was no
significant difference between the 5-ASA and IM groups (78.4%; 29/37 vs. 78.6%; 55/70, P > 0.05).

Among patients on anti-TNF therapy (with or without IM), 45.6% (41/90) had a non-serological response to the vaccine; the duration of anti-TNF therapy was not associated with the serological response rate of the vaccine (odds ratio; OR 0.991, 95% confidence interval; CI 0.964–1.018, P = 0.497). In a subgroup analysis of 80 patients treated with infliximab (38 in the anti-TNF group; 42 in the combination group), 64 (80%) patients were vaccinated within 6 weeks after the last dose of infliximab, while 16 (20%) were vaccinated during 7–8 weeks after the last dose of infliximab. In these subsets of patients, there was no significant difference in serological response rate regarding timing of vaccination relative to infliximab infusion cycle: 56.2% (36/64) vs. 43.8% (7/16), P = 0.370.

Regarding GMT, there were no significant differences in the pre-vaccination GMT among the four groups (P = 0.099) (Table 2). The post-vaccination GMT was significantly lower in patients on immunosuppressants (IM, anti-TNF, and combination of both) than in those on 5-ASA (P < 0.001). However, the post-/pre-GMT ratios were not significantly different among the 5-ASA, IM, and anti-TNF groups.

On univariate analysis, several factors were associated with a non-serological response to the vaccine, including patient gender, type of therapy, and age at diagnosis. A logistic regression analysis showed that female gender and use of anti-TNF therapy were significant predictors of a non-serological response to the vaccine after adjustment for age, baseline disease activity (CRP and HBI score), disease duration, and duration of immunosuppressive therapy (OR 2.316, 95% CI 1.178–4.552, P = 0.015; OR 2.582, 95% CI 1.007–6.619, P = 0.048, respectively) (Table 3).

3.3. Safety and effect of vaccination on disease activity

There were 16 mild self-limited adverse events associated with PPSV23 (8.13%), including 13 local and 3 systemic reactions (Table 4). Pain at the injection site was the most common adverse event (12/197). All adverse events resolved spontaneously without specific medical treatment within 24 h after vaccination. The rates of adverse events did not differ significantly among the subgroups. There were no serious adverse events in the study.

At the final visit (4 weeks after vaccination), only one patient in the combination group had a significant change in the disease activity index. In that patient, the CRP level was within normal range during the study period, and the follow-up colonoscopy showed endoscopic remission of CD. None of the study participants required any alteration of their medications for CD during the study period.

4. Discussion

The effect of immunosuppressants on the efficacy of a variety of vaccines, such as HBV, influenza, and pneumococcal vaccine, is an ongoing issue in patients with IBD. While several risk factors have been suggested for an inadequate serologic response to vaccines in patients with IBD, this issue has remained controversial to date. Currently, few studies have addressed the efficacy of pneumococcal vaccination in patients with IBD. In a prospective controlled trial involving 45 patients with IBD (30 with CD, 14 with UC, and 1 with indeterminate colitis) and 19 healthy controls, Melmed et al. reported that overall serological response to PPSV23 in patients treated with a combination of an anti-TNF agent and IM was lower than in healthy controls and patients on 5-ASA (45% vs. 84%, P = 0.01; 45% vs. 80%, P = 0.07, respectively). However, the investigators did not demonstrate whether the suboptimal response to the vaccine was derived from the anti-TNF drug, the IM or the combination of both. Fiorino and colleagues addressed this question in their study by evaluating the overall serological response rate of 96 patients with IBD (54 with CD and 42 with UC) to PPSV23; the enrolled patients were divided into four treatment groups, 5-ASA, IM, anti-TNF agent, and combination of anti-TNF agent with IM. Patients treated with anti-TNF agent alone or in combination with IM had significantly lower serological response rates to the vaccine (57.6% and 62.5%, respectively), compared to patients on 5-ASA alone (88.6%; P < 0.05 for both comparisons). However, these two studies had several limitations, such as small sample size, and more importantly the heterogeneity of the population evaluated (including CD and UC), which might be a potential confounding factor, as stated by the authors themselves.

To overcome these limitations, we evaluated the effect of PPSV23 in patients with CD in a large multicenter trial. To our knowledge, this was the largest prospective study of the effect of immunosuppressants on the serological response to the standard PPSV23 in patients with CD. The results showed that serological response rates in patients treated with anti-TNF agent alone or in combination with IM (50.0% and...
58.0%, respectively) were significantly lower than in those on 5-ASA (78.4%; all \( P \)-values \(<0.05 \) for both comparisons). Approximately half of the patients (45.6%; 41/90) on anti-TNF therapy (with or without IM) were not protected by PPSV23. In addition, we found that anti-TNF therapy was a significant predictor associated with non-serological response to PPSV23 in patients with CD (OR 2.582, 95% CI 1.007–6.619, \( P = 0.048 \), respectively). However, both the duration of anti-TNF therapy and the timing of vaccination in relation to infliximab infusion cycle were not associated with the vaccine efficacy. Our results are in agreement with previous studies that examined the efficacy of PPSV23 in patients with IBD including CD and UC, \(^{18,19} \) and ultimately suggest that pneumococcal vaccination strategy should be optimized for patients with CD on anti-TNF therapy, such as dose intensification or booster immunization. Booster immunization can be an attractive solution for patients who do not respond to the first dose of PPSV23. To date, however, there are no data regarding whether the second booster dose of PPSV23 is beneficial to patients with non-serological response to the vaccine. The cost effectiveness of this second booster strategy is an additional consideration because routine serological examination is not currently recommended by professional guidelines. \(^{9,11} \) In addition, there is no standard protective antibody titer; future studies should address this issue. Additionally, further specific recommendations provided by professional IBD societies are expected. We believe that timely vaccination before initiation of anti-TNF therapy can be a practical solution for maximizing the efficacy of PPSV23 at this point. Clinicians also should be aware that

### Table 1 Baseline characteristics of enrolled patients (\( n = 197 \)).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5-ASA group (( n = 37 ))</th>
<th>IM group (( n = 70 ))</th>
<th>Anti-TNF group (( n = 40 ))</th>
<th>Combination (^a) group (( n = 50 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>21 (56.8)</td>
<td>48 (68.6)</td>
<td>26 (65.0)</td>
<td>36 (72.0)</td>
</tr>
<tr>
<td>Age, years</td>
<td>36.0 (19.0–65.0)</td>
<td>26.5 (24.0–48.0)</td>
<td>32.0 (18.0–48.0)</td>
<td>30.5 (16.0–57.0)</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>23.0 (9.0–68.0)</td>
<td>30.0 (11.0–69.2)</td>
<td>87.5 (14.0–228.0)</td>
<td>59.5 (29.7–98.7)</td>
</tr>
<tr>
<td>Disease phenotype (^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, n (%)</td>
<td>0 (0)/27 (73.0)/10 (27.0)</td>
<td>4 (5.7)/56 (80.0)/10 (14.3)</td>
<td>4 (10.0)/34 (85.0)/2 (5.0)</td>
<td>3 (6.0)/43 (86.0)/4 (8.0)</td>
</tr>
<tr>
<td>Disease location, n (%)</td>
<td>15 (40.5)/6 (16.2)/16 (43.2)</td>
<td>14 (20.0)/5 (7.1)/51 (72.9)</td>
<td>6 (15.0)/3 (7.5)/31 (77.5)</td>
<td>5 (10.0)/5 (10.0)/40 (80.0)</td>
</tr>
<tr>
<td>Disease behavior, n (%)</td>
<td>24 (64.9)/11 (29.7)/2 (5.4)</td>
<td>38 (54.3)/26 (37.1)/6 (8.6)</td>
<td>15 (37.5)/5 (12.5)/20 (50.0)</td>
<td>17 (34.0)/20 (40.0)/13 (26.0)</td>
</tr>
<tr>
<td>Baseline HBI (^c) score</td>
<td>2.34 (1.99)</td>
<td>1.60 (1.76)</td>
<td>2.45 (2.61)</td>
<td>2.58 (2.86)</td>
</tr>
<tr>
<td>Baseline CRP, mg/dL</td>
<td>0.38 (0.59)</td>
<td>0.31 (0.45)</td>
<td>0.64 (0.86)</td>
<td>0.43 (0.61)</td>
</tr>
<tr>
<td>Immunosuppressive therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment duration with IM, months</td>
<td>15.0 (4–180)</td>
<td>23.0 (3–90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine/6-mercaptopurine, n (%)</td>
<td>69 (98.6)/1 (1.4)</td>
<td>47 (94.0)/3 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine dose, mg/day</td>
<td>75.5 (34.6)</td>
<td>71.2 (41.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration with anti-TNF, months</td>
<td>24.0 (3.0–65.0)</td>
<td>16.0 (3.0–85.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab/adalimumab, n (%)</td>
<td>38 (95.0)/2 (5.0)</td>
<td>42 (84.0)/8 (16.0)</td>
<td></td>
<td></td>
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<tr>
<td>Treatment duration with combination therapy, months</td>
<td>14.0 (3.0–49.0)</td>
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</tbody>
</table>

Data are expressed as means (standard deviation) or numbers (%).

\(^a\) Anti-TNF agent plus immunomodulator.

\(^b\) Classified according to the Montreal classification. \(^23\)

\(^c\) Harvey–Bradshaw index. \(^24\) 5-ASA, 5-aminosalicylate; IM, immunomodulator; Anti-TNF, anti-tumor necrosis factor; CRP, C-reactive protein.

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**Figure 2** Serological response rate to the vaccine, defined as the percentage of subjects achieving a twofold increase in IgG titer (\( n = 197 \)). 5-ASA, 5-aminosalicylate; IM, immunomodulator; anti-TNF, anti-tumor necrosis factor. Combination indicated anti-TNF agent plus IM.
the use of 13-valent pneumococcal conjugate vaccine is now recommended in patients on immunosuppression, regardless of the efficacy of PPSV23.30

In the present study, treatment with IM alone had a minimal impact on the serological response to the vaccine. In addition, there was no synergistic immunosuppressive effect of anti-TNF agent combined with IM on the serological response to the vaccine. Although the post-vaccination GMT was significantly lower in patients on immunosuppressants (IM, anti-TNF, and combination of both) than in patients on 5-ASA, there were no significant differences in post-/pre-vaccination GMT ratio among the 5-ASA, IM, and anti-TNF groups. Our results are in agreement with the report by Dotan et al.20 Therapeutic doses of thiopurines (azathioprine and 6-mercaptopurine) for IBD showed no significant suppressive effect on the immune responses to the several vaccines evaluated, including pneumococcal, tetanus, and Haemophilus influenzae type B vaccine.20

In our study, female gender was significantly associated with non-serological response (OR 2.316, 95% CI 1.178–4.552, P = 0.015). Although the reason for this finding is unclear, a bias regarding the gender of the patients may have been present because the study was not randomized. Likewise, our study was not powered to detect differences according to the type of anti-TNF drugs or IMs. Further studies are required to evaluate the impact of specific drugs, as opposed to drug class, on the serological response to vaccination. In addition, differences in the immunogenicity of the pneumococcal vaccine according to ethnicity should be considered in future studies. In this regard, our study provides the first data on the immunogenicity of PPSV23 in Asian patients with CD.

Vaccination was generally safe and tolerated by all patients. The overall rate of adverse events in the present study was slightly higher than in other reports, but all local and systemic adverse events were mild and self-limited.18–20 In addition, the impact of the vaccine on CD activity appeared to be negligible.

This study had several limitations. First, we did not perform serotype-specific assays of the individual antibody responses to the 23 serotypes included in the vaccine evaluated. Our data, therefore, indicate only the overall response to PPSV23. Second, the mean dose of azathioprine was relatively low (75.5 mg/day in the IM group; 71.2 mg/day in the combination group), given the therapeutic doses recommended by current guidelines (2–2.5 mg/kg/day of azathioprine).1,25 Although we did not evaluate the specific cause of this finding, we assumed that it was due to azathioprine dose adjustment because of drug-induced toxicity. As mentioned earlier, we recommended a weight-adjusted effective thiopurine dose but allowed an adjusted low thiopurine dose in patients with drug-induced side effects. Thiopurine-induced leukopenia is a common phenomenon among Korean patients with IBD, with an incidence of 31.2% to 56.4%.25,31,32 Nevertheless, we could not perform thiopurine testing (thiopurine methyltransferase phenotype/genotype or thiopurine metabolites) because the

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.316 (1.178–4.552)</td>
<td>0.015</td>
</tr>
<tr>
<td>Type of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-aminosalicylate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Immunomodulator</td>
<td>0.864 (0.313–2.385)</td>
<td>0.777</td>
</tr>
<tr>
<td>Anti-tumor necrosis factor</td>
<td>2.582 (1.007–6.619)</td>
<td>0.048</td>
</tr>
<tr>
<td>Age at diagnosis a</td>
<td></td>
<td></td>
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<tr>
<td>A1 (&lt;16 years)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>A2 (16–40 years)</td>
<td>0.912 (0.215–3.868)</td>
<td>0.900</td>
</tr>
<tr>
<td>A3 (40 years)</td>
<td>0.462 (0.040–5.277)</td>
<td>0.534</td>
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</tbody>
</table>

* a Classified according to the Montreal classification.23
availability of these tests in Korea is limited. Third, we did not demonstrate that vaccination reduced the occurrence of invasive pneumococcal disease. Further long-term studies of a clinically meaningful endpoint are needed to verify the clinical relevance of pneumococcal vaccination in patients with CD. Finally, we did not perform functional assays of immunological changes that could develop in patients receiving immunosuppressants; we aim to resolve this issue in our future research.

In conclusion, this was the largest study to date of the effect of immunosuppressants on the immunogenicity of the pneumococcal vaccine in patients with CD. A substantial number of patients who were treated with anti-TNF therapy exhibited an impaired response to PPSV23. Anti-TNF therapy was a predictor of non-serological response to the vaccine. Our data indicate that optimal strategies for pneumococcal vaccination should be developed for patients with CD receiving anti-TNF therapy.

Conflict of interests
The authors declare no conflict of interests.

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CL and HK: study concept and design, drafting of the manuscript, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. BY, KL, and YK: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. SR: concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. All authors read and approved the final manuscript.

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