method achieving almost 100% eradication rate.

**Conclusion**

Treatment of the peptic ulcers with the potent inhibitors of acid secretion such as PPIs has made great progress in the healing of these ulcers, and there are now considerably fewer intractable ulcers. The recurrence of ulcer was once a major problem which was considered impossible to solve, but recurrence is now nearly completely prevented by *H. pylori* eradication and this is more effective than maintenance therapy using H₂-blockers. Although the Japanese health insurance system does not cover this therapy at present, it is highly likely that diagnosis and eradication of *H. pylori* will be added to the health insurance system by the Ministry of Health and Welfare in the near future. Accordingly, it is anticipated that most peptic ulcers will commonly come to be treated from the viewpoint of an infectious disease.

**References**


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2. Recent Advances in Therapy for Patients with Inflammatory Bowel Disease

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**Key words:** IBD, hGR, leukocyte apheresis

**Introduction**

In Japan, the incidences of ulcerative colitis (UC) and Crohn’s disease (CD) have increased to 50,000 (UC) and 14,000 (CD) patients. The etiologies of these diseases are considered to be multifactorial in both genetic and environmental conditions, although the precise mechanisms of disease development are still unclear. Here, we review the recent strategies for the management of these diseases, including our new results of the molecular mechanism of nonresponsiveness to glucocorticoid administration, and leukocyte apheresis as an alternative therapy in UC patients. We also discuss the problem of postsurgical relapse in CD, and some new trials to decrease the reoperation risk of these patients.

**Glucocorticoid insensitivity in UC patients**

Glucocorticoids (GC) are one of the first-line therapies for active UC patients, as well as optimal doses of salicylate derivatives. However, it is documented that some UC patients do not respond to GC treatment even with a high-dosage protocol, such as intensive intravenous regimen (IIR) of Troulove.
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Primary Transcript of hGR gene

Alternative splicing

mRNA

Protein

hGRα

hGRβ

727 aa

777 aa

50 aa

15 aa

742 aa

Full effect

No effect

: Glucocorticoid Response Element binding site

Figure 1. Two isoforms of human Glucocorticoid Receptor.

For example, the remission-inducing rate of IIR in our institution was 56%, and nonresponders for this protocol required other treatments including total colectomy. But GCs caused some minor or major side effects and an increase in operative risk of these patients, even if the administrated GCs were not effective. Therefore, it is necessary to evaluate the responsiveness to GC prior to its therapy.

It is known that GC receptor (glucocorticoid receptor; GR) is essential for GC action on various effector cells or tissues. Regarding human GRs, there are two isoforms, termed hGRα (human glucocorticoid receptor α) and hGRβ, both of which are derived from a common gene by alternative splicing of the primarily transcripted mRNA (Fig. 1). hGRα is a functional GC receptor, which acts as a transactivator for GRE (glucocorticoid response element) containing gene. In contrast, the physiological role of hGRβ has not been elucidated. Bamberger et al (1) recently reported the possibility that hGRβ is an intrinsic dominant-negative inhibitor for GC action. As hGRβ is reported to be expressed in some tissues or cultured cells to a lesser extent, we tried to investigate the hGR expressions in immune cells of UC patients, particularly peripheral blood mononuclear cells (PBMCs) which are thought to be the target of GC action to suppress inflammation of this disease.

Using RT-PCR method, we found that hGRβ mRNA is expressed in PBMC of some UC patients, but it is not detected in PBMC of healthy control subjects (Table 1). Disease activity of these UC patients was evaluated by the clinical activity index (CAI), which was calculated using the following: frequency of diarrhea, amount of bloody stool, general conditions, degree of anemia and ESR. Responsiveness to GC administration of these hGRβ (+) patients was significantly lower than that of hGRβ (-) patients (Table 2). These results suggest that the expression of hGRβ in PBMC is closely related to GC insensitivity in UC patients. Statistical analysis between GC sensitivity and hGRβ expression or various clinical parameters such as disease activity, disease duration, or total GC amount administrated, showed that hGRβ is the only significant, negative indicator to predict the likelihood of GC sensitivity in UC patients (logistic regression test, Odds ratio 0.008, data not shown). These findings also point to the possibility that GC

| Table 1. Incidence of hGRβ Expression in PBMC of UC Patients |
|-----------------|-----------------|-----------------|-----------------|
|                 | hGRβ mRNA (-)  | hGRβ mRNA (+)  | Statistical     |
| Ulcerative Colitis | 23 (52.2%)     | 12 (47.8%)     | Difference      |
| healthy Volunteers | 8 (100%)       | 8 (0%)         | p = 0.0028*    |

* : Fisher’s Exact test.
insensitivity is predictable by testing hGRβ expression in PBMC of UC patients.

**Leukocyte apheresis as an alternative therapy for GC-resistant UC patients**

There have been many studies undertaken to improve the medical management of UC patients, especially the patients with insensitivity to conventional GC treatments. Previously, 5-ASA enema, intravenous immunoglobulins, or methotrexate was used to induce remission of the patients refractory to GC therapy. A recent report by Lichtiger et al (2) demonstrated that intravenous cyclosporin has a great benefit to induce remission in 82% of these patients, and further, they established the standard protocol for cyclosporin administrations in UC. Other noninvasive therapies for UC patients were reported by Japanese investigators, that removal of peripheral blood leukocytes from UC patients decreased activity of this disease. Sawada et al (3) reported the effectiveness of leukocyte apheresis with leukocyte removal column (LCAP) in UC and CD patients. Ayabe et al (4) in our department independently reported that leukocyte apheresis with a centrifugal separator (CFLA) effectively induces remission in UC patients refractory to GC treatment. After that trial, we have treated the 40 patients with active UC treated with CFLA. As shown in Fig. 2, a statistically significant decrease of disease activity (assessed with CAI) or endoscopic severity of the disease (assessed with Matts’ criteria) was noted after the fourth CFLA, that was performed once a week. The remission-inducing rate of these patients (CAI≤4) was 67.5% (27/40) at the fourth week. Among these patients, the disease duration, total amount of administrated GC, and history of ineffective steroid therapies were not related to the effectiveness of CFLA treatment. No significant side-effect was noted in those patients. Through these observations, leukocyte apheresis with a centrifugal separator (CFLA) or removal column (LCAP) should be safe, alternative methods for the treatment of GC resistant patients with UC. Multicenter trials for these methods are now on-going in Japan.

**Trials to prolong remission periods of CD patients**

The major purpose of the medical management for CD is to improve QOL (quality of life) of the patient. Drugs such as 5-ASA, GC or other immunosuppressants, and nutritional management with parenteral or enteral hyperalimentation are em-

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**Table 2. Sensitivity for Steroid Administration in hGRβ (-) or hGRβ (+) Patients with UC**

<table>
<thead>
<tr>
<th></th>
<th>hGRβ mRNA (-)</th>
<th>hGRβ mRNA (+)</th>
<th>Statistical Difference</th>
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<tbody>
<tr>
<td>CAI before treatment</td>
<td>8.1 ± 2.9</td>
<td>8.8 ± 3.3</td>
<td>NS*</td>
</tr>
<tr>
<td>CAI 4 weeks after steroid administration</td>
<td>1.8 ± 2.2</td>
<td>8.3 ± 4.2</td>
<td>p = 0.0007*</td>
</tr>
</tbody>
</table>

* : Mann-Whitney U test.

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**Figure 2. Therapeutic effects of centrifugal leukocyte apheresis (CFLA) in patients with UC.**
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Figure 3. Non-relapse curve of postoperative stenosis in CD patients undergoing HEN.

Employed together to achieve clinical remission of the disease. Administration of anti-TNF-α chimelic antibody is one of the new effective induction therapies for CD. However, a flare-up of the CD and high re-operation rate of postsurgical CD are still difficult problems. In Japan, home enteral nutrition therapy (HEN) (nocturnal nutritional supplement with elemental diet) is recommended to maintain remission, although there has been no satisfactory evidence obtained by nationwide randomized control study to support this. Furthermore, the result of our preliminary uncontrolled trials for the prevention of postoperative recurrence in CD patients by long-term HEN showed a high recurrence rate in these postoperative patients (Fig. 3).

In the United States and Europe, it is reported that high-dose 5-ASA slightly but significantly improves the re-operation risk in postsurgical CD patients. Immunosuppressive agents such as azathiopurine or 6-mercaptopurine also decrease the postoperative recurrence. A very recent report demonstrated that oral budesonide is also effective for these patients (6). These newly developed methods should be evaluated with Japanese patients with CD. Endoscopic balloon dilation method, reported by Matsui et al (7) is now widely used in Japan, as a nonoperative treatment for intestinal or colonic stenosis due to the inflammation of CD. Re-stenosis at anastomotic sites in postoperative CD patients should be a good indication for this technique.

Conclusion

The recent progress in the therapies for IBD were reviewed. Especially in the treatment of UC patients, cyclosporin and leukocyte apheresis are available as powerful tools for refractory patients. Moreover, we may select the patients indicated for these new protocols prior to ineffective GC administration by assessing the GRβ expression.

References