Substitution of Aspartic Acid at Position 57 of the DQβ1 Affects Relapse of Autoimmune Pancreatitis

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See editorial on page 625.

Background & Aims: **Although autoimmune pancreatitis (AIP) responds well to corticosteroid therapy, relapse during maintenance corticosteroid therapy or after the withdrawal of corticosteroid treatment is not uncommon. To date, the factors related to relapse of AIP have not been fully explored.** ***Methods:*** **To determine the clinical and genetic predictors relating to the relapse of AIP, we evaluated clinical factors, HLA polymorphisms, and the amino acid sequences in 40 patients with AIP.** ***Results:*** **At a median follow-up period of 40 months (range, 12–67 months), relapse developed in 13 of 40 patients with AIP (33%), in whom complete remission was achieved with oral corticosteroid therapy. Among demographics, clinical characteristics in the initial diagnosis of AIP, we could not find any clinical predictor for relapse of AIP; however, in amino acid sequence analysis for relapse of AIP, the substitution of aspartic acid to nonaspartic acid at residue 57 of DQβ1 showed a significant association with relapse of AIP (nonrelapse group, 29.6%; relapse group, 100%; $P = .00003$; odds ratio, 3.38; 95% confidence interval, 1.9–6.0). There was a significant difference in the timing of relapse of AIP, according to density of the nonaspartic acid residue at DQβ1 57 (nonaspartic acid homozygosity: mean ± SD, 6.7 ± 4.2 months; nonaspartic acid heterozygosity: mean ± SD, 33 ± 11 months; $P < .001$).** ***Conclusions:*** **Substitution of aspartic acid to nonaspartic acid at DQβ1 57 appears to represent a key genetic factor for relapse of AIP (ClinicalTrials.gov number, NCT00444444).**

Autoimmune pancreatitis (AIP) is a type of chronic pancreatitis characterized by an autoimmune inflammatory process in which prominent lymphoplasmacytic infiltration and fibrosis of the pancreas cause organ dysfunction.[1–4] The dramatic response to corticosteroid therapy is a well-known phenomenon in AIP, which has been shown to improve symptoms, reverse the inflammatory process, and resolve radiographic and laboratory abnormalities.[1,2,5,6] Long-term follow-up studies have shown, however, that relapses of AIP after remission with corticosteroids can occur in up to 30%–40%.[7–15] Furthermore, a previous report showed that more than half of patients experiencing a relapse had pancreatic calcifications and/or pancreaticolith.[13] These results suggest that AIP is essentially a progressive condition, resulting in irreversible damage with intense fibrosis in a similar development to that of ordinary chronic pancreatitis.[13,16–18] It is likely that this late stage of AIP with a destroyed basement membrane may not show corticosteroid responsiveness.[6,7,16,18,19] The identification of clinical and/or genetic factors that are predictive of relapse, therefore, may be crucial to the prognosis and clinical outcome of the disease.

According to recent studies on autoimmune hepatitis,[20–22] HLA alleles and genetically encoded amino acid sequences at the antigen presentation site of the HLA molecule may act as primary determinants of susceptibility or relapse of autoimmune hepatitis. Therefore, to determine whether there is a clinical or genetic factor predictive of relapse in the initial diagnosis of AIP, clinical assessment and HLA high-resolution genotyping using polymerase chain reaction/sequence-based typing (PCR/SBT) were performed. The allele or haplotype associated with AIP was also evaluated in our study.

Materials and Methods

Study Population

Between February 2002 and May 2006, 46 consecutive patients were diagnosed with AIP. Patients treated surgically because pancreatic cancer could not be excluded in the initial diagnosis (n = 4) and patients who had an inadequate dose of corticosteroid due to poor compliance (n = 2) were excluded from

Abbreviations used in this paper: AIP, autoimmune pancreatitis; PCR/SBT, polymerase chain reaction/sequence-based typing.

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the study. The remaining 40 patients (32 men and 8 women) ages 33–78 years (median age, 58.5 years) were enrolled in the study.

The diagnostic criteria[23–26] of AIP in the present study were as follows: (1) pancreatic imaging showing enlargement of the pancreas on computed tomography and diffuse or segmental irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography, (2) laboratory findings of elevated level of immunoglobulin (Ig) G or IgG4 or autoantibodies detected, (3) histopathologic findings of fibrosis and lymphoplasmacytic infiltration, (4) response to a corticosteroid, and (5) extrapancreatic organ involvement. As a result, patients diagnosed with AIP by us also met the diagnostic criteria of AIP proposed by the Mayo Clinic[27] or the revised criteria by the Japan Pancreas Society.[28]

Follow-up and Strategy of Treatment

From February 2002 to June 2003, a prospectively collected database was analyzed retrospectively because the first case of AIP relapse was seen in June 2003, and the remaining cases were prospectively followed up for at least 12 months (mean, 38.9 months; median, 40 months; range, 12–67 months) in this study.

All enrolled patients were treated with prednisolone. Our regimen for corticosteroid therapy was as follows: the induction dosage of prednisolone was initially administered at 0.5 mg/kg per day for 1–2 months and gradually reduced by 5–10 mg per month to the maintenance dosage. The maintenance dosage (2.5–7.5 mg/day) of corticosteroid started after confirmation of complete remission. Maintenance corticosteroid therapy was continued for an average of 6 months and then completely stopped. In this study, complete remission or response to corticosteroids was defined by a disappearance of clinical symptoms, negative conversion of detected autoantibodies, normalization of elevated levels of serum IgG or IgG4, and resolution in pancreatic and/or extrapancreatic manifestations on imaging studies. For follow-up after complete remission, the laboratory tests were performed every 2–3 months, and imaging studies such as computed tomographic scans or magnetic resonance imaging/magnetic resonance cholangiopancreatography every 6 months, or at the time of relapse, until May 2007. We defined relapse of AIP as a recurrence of symptoms with the development or reappearance of pancreatic and/or extrapancreatic (bile duct, salivary gland, retroperitoneum, and so on) abnormalities on imaging studies and elevation of serum IgG or IgG4 level. Event of relapse was prospectively determined by physicians (M.-H.K., S.-K.L., D.-W.S., and S.-S.L.) in charge of each patient. For patients who experienced a relapse, a second trial of corticosteroid therapy was prescribed again as the regimen mentioned previously.

Collection of Samples and Clinical Assessment

We obtained blood samples from the patients, and HLA high-resolution PCR/SBT for class I and class II allelic genotypes was performed. Based on results of the HLA genotyping with amino acid sequencing, and clinical data for both the relapse and nonrelapse groups, allelic or clinical markers relevant to relapses of AIP were evaluated. Before this analysis (May 2007), clinical and genetic data for relapse and nonrelapse groups were concealed from the evaluator (D.H.P.), so that early knowledge of these preliminary results did not affect the schedule of corticosteroid therapy for enrolled patients.

To determine alleles associated with autoimmune pancreatitis in the Korean population, HLA class I and II genotypes from 154 ethnically matched healthy subjects (76 women) were identified and used as a control. The controls did not have any chronic illness and were not affected by any acute medical problems. The amino acid sequences, determined from known HLA class II second exon nucleotide sequences, were also analyzed for common shared determinants in both patients and controls. All participants provided informed written consent for the tests, and serum samples were obtained after receiving informed consent from both the patients and the healthy subjects. This study protocol was approved by the institutional review board of our hospital.

HLA Class I and Class II High-Resolution Genotyping

High-resolution HLA genotyping was performed. Alleles of the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci were genotyped using the PCR/SBT kit (Biosewoom, Inc, Seoul, Korea). The genes of HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 were amplified by PCR. For SBT, exon 2 and exon 3 of HLA-A, HLA-B, and HLA-C and exon 2 of HLA-DRB1 and HLA-DQB1 were sequenced directly. Sequencing was performed using the BigDye Terminator v3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA) and purified by the Wizard MagneSil Sequencing Reaction Clean-Up System (Promega, CA). The purified products were electrophoresed on an ABI PRISM 3730xl Genetic Analyzer (Applied Biosystems). Sequences were analyzed with an HLA analysis program (Biosewoom, Inc). The first domain's amino acid sequences of HLA-DRβ1 and HLA-DQβ1 polypeptides were determined from the IMGT database for all patients and controls.[29]

Statistical Analysis

For investigation of clinical factors predictive of relapse between the relapse and nonrelapse groups, continuous data with normal and nonnormal distributions were compared with the use of Student t test and the Mann–Whitney U test, respectively. Differences in categorical variables were analyzed by means of the χ^2 and Fisher exact test. To detect relapse-associated alleles, the frequencies

Table 1. Demographics and Clinical Characteristics in the Initial Diagnosis of AIP in the Nonrelapse and Relapse Groups

	Nonrelapse group (n = 27)	Relapse group (n = 13)	*P* value
Age (*y*), mean ± SD	56.6 ± 10.3	56.2 ± 14.4	.93
Sex (M/F)	21/6	11/2	1.000
Body weight loss (%)[a]	70	77	1.000
Diabetes mellitus (%)/HbA_{1c} (%), mean ± SD	55.6/7.7 ± 0.4	78.6/7.4 ± 0.6	.41/.68
Obstructive jaundice (%)[b]	63	69	1.000
Amylase/lipase level (*U/L*), median (interquartile range)	71 (46–139)/70 (36–269)	74 (59–147)/86 (47–354)	.63/.71
Initial IgG/IgG4 level (*mg/dL*), median (interquartile range)	1695 (1418–2340)/110 (24–660)	1780 (1205–3060)/318 (58–765)	.92/.59
Autoantibodies (%)	37	69	.06
Other organ involvement (%)	26	23	1.000
Follow-up (*mo*), mean ± SD	38.9 ± 16	39 ± 18	.99

[a]Body weight loss was defined as >5% loss of body weight over the past 6 months.
[b]Obstructive jaundice was defined as a condition in which increased levels of biliary enzyme and total bilirubin (>1.5 mg/dL), together with dilatation of the bile duct, were observed.

of HLA class I and class II alleles in the nonrelapse group and the relapse group were compared using χ^2 analysis. Phenotype frequencies were estimated by direct counting for each HLA allele. The Bonferroni correction was applied by multiplying the *P* value by the number of alleles compared (15 for HLA-A alleles, 26 for HLA-B alleles, 17 for HLA-C alleles, 20 for HLA-DRB1 alleles, and 15 for HLA-DQB1 alleles). The strength of association was estimated by calculating the odds ratio. In the amino acid sequence analysis, relapses associated with specific first domain amino acid residues were looked for using χ^2 analysis. Finally, to determine the susceptible alleles for AIP, the frequencies of HLA class I and class II alleles in patients with AIP and the control group were compared using χ^2 analysis. A 2-tailed *P* value of <.05 was accepted as statistically significant.

Results

Clinical Outcome of Long-Term Follow-up for AIP With Corticosteroid Treatment

With corticosteroid therapy, complete remission was achieved in all enrolled patients. During a median follow-up period of 40 months (range, 12–67 months), 13 of 40 patients (33%) experienced relapses of AIP. These relapses occurred during maintenance corticosteroid therapy or after a complete discontinuation of corticosteroids. Seven of the 13 patients experienced a relapse on the maintenance dosage of prednisolone (2.5–7.5 mg/day; median period from initial diagnosis to relapse, 6 months; interquartile range, 4–6 months), and the remaining 6 patients experienced a relapse while off corticosteroids (median period from initial diagnosis to relapse, 37 months; interquartile range, 20.8–41.8 months). On relapse, they all responded again to corticosteroid therapy.

Clinical Characteristics Relevant to the Relapse of AIP

There was no significant difference in the demographics and clinical characteristics in the initial diagnosis of AIP, including body weight loss (>5% loss of body weight over the past 6 months), presence of diabetes mellitus, obstructive jaundice, serum IgG or IgG_4 level, amylase and lipase level, autoantibodies detected, existence of other organ involvement, and duration of follow-up periods between the nonrelapse and relapse groups (Table 1). In the relapse group (n = 13), 6 patients had involvement confined to the pancreas, 4 in the bile duct only, one in both the pancreas and the bile duct, one in the retroperitoneum with fibrosis, and one in the salivary gland.

Genetic Factors to Predict the Relapse of AIP

Among HLA class I (A, B, and C) and class II (DRB1 and DQB1) alleles, only DQB1*0302 showed a significant association with the relapse of AIP (nonrelapse, 18.5% [5/27]; relapse, 76.9% [10/13]; $P = .001$, corrected $P = .015$).

Sequencing the amino acids from the known HLA class II second exon, it was revealed that a single nucleotide substitution at position 57 of DQβ1 solely affects the relapse of AIP by alignment analysis (Figure 1). Because the peptide binding preference of the DQβ1 57 may be dependent on the presence of aspartic or nonaspartic acid (Ala, Val, or Ser) at this position,[30–32] the amino acid was divided into 2 amino acid groups (nonaspartic vs aspartic acid). In this analysis, the nonaspartic acid residue at DQβ1 57 was significantly associated with relapse of AIP (nonrelapse group [n = 8/27], 29.6%; relapse group [n = 13/13], 100%; $P = .00003$; odds ratio, 3.38; 95% confidence interval, 1.9–6.0) (Table 2). All patients who experienced a relapse during corticosteroid maintenance (n = 7) had a nonaspartic acid homozygosity at codon 57 of DQβ1. By contrast, nonaspartic acid heterozygosity at codon 57 of DQβ1 was identified in all patients who experienced a relapse after corticosteroid treatment was discontinued (n = 6). There was a significant difference in the timing of relapse of AIP, according to density of the nonaspartic acid residue at DQβ1 57

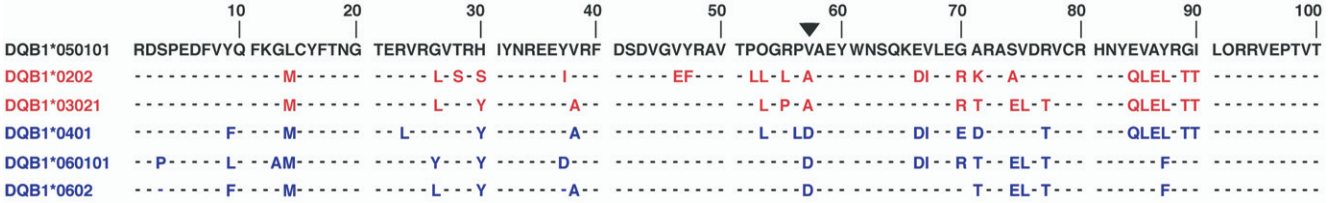

Figure 1. Alignment of amino acid sequence of exon 2 (peptide binding site) at DQB1. DQB1*0202 and DQB1*0302 (*red*) represent the frequent alleles of the relapse group (frequency of 30.8% and 76.9%, respectively). DQB1*0401, DQB1*0601, and DQB1*0602 (*blue*) represent the frequent alleles of the nonrelapse group (frequency of 14.8%, 29.6%, and 22.2%, respectively). The identical sequence with DQB1*050101 (reference sequence) is shown in *dashes*. Numbers above sequence correspond to the amino acid position in mature protein. The *arrowhead* denotes the 57 codon of DQβ1.

(nonaspartic acid homozygosity [mean ± SD], 6.7 ± 4.2 months; nonaspartic acid heterozygosity [mean ± SD], 33 ± 11 months; $P < .001$) (Table 3). In addition, there was no AIP relapse-related amino acid residue or motif in the second exon nucleotide sequences of DRβ1.

HLA Association Study to Detect the Genetic Susceptibility to AIP

Among HLA class I alleles, the frequency of B*1501 was increased in patients with AIP compared with those of healthy subjects ($P = .028$), but this difference was lost after correction. Among HLA class II antigens, the frequency of DR4 was increased in patients with AIP compared with healthy subjects ($P = .017$). This difference was also lost after correction. Among the DR4 subtypes, there was no significant association for AIP. Among the other HLA class II alleles, only DRB1*0701 ($P = .033$) and DQB1*0202 ($P = .023$) had a weak association for AIP in our study. This result was also not significant after correction (Table 4).

With regard to the substitution of aspartic acid to nonaspartic acid at residue 57 of DQβ1, there was no difference in this amino acid substitution between AIP and controls (n = 21/40 [53%] vs n = 98/154 [64%], respectively; $P = .2$).

Discussion

During the genetic analysis, we found that substitution of aspartic acid to nonaspartic acid at the 57 residue of DQβ1 may relate to relapse of AIP (Figure 1). The onset of relapse of AIP was determined, moreover, according to the density of nonaspartic acid at DQβ1 57. Patients who experienced a relapse with homozygosity of nonaspartic acid had a significant tendency toward the early onset of relapse (mean, 6.7 months), whereas those with heterozygosity of nonaspartic acid had a delayed onset of relapse after being off corticosteroids (mean, 33 months). There was no difference in the substitution of aspartic acid to nonaspartic acid at residue 57 of DQβ1 between AIP and controls (n = 21/40 [53%] vs n = 98/154 [64%], respectively; $P = .2$). In our study, there was also no significant difference in the dosage and duration of corticosteroid treatment required for complete remission between patients with the substitution of aspartic acid to nonaspartic acid at residue 57 of DQβ1 and without it. The role of this amino acid substitution in AIP may therefore determine relapse rather than susceptibility or corticosteroid responsiveness.

A plausible explanation regarding the pathogenetic role of substitution of aspartic acid at DQβ1 57 on relapse of AIP is as follows. First, DQβ1 residue 57 is located near one end of the peptide-binding groove of class II molecules, where it functions as a molecular gatekeeper for the peptide side chain at the peptide binding pockets termed P9. When DQβ1 residue 57 is a small noncharged residue, such as alanine, large peptide side chains are able to occupy P9. There is a positively charged arginine residue at position 76 of the DQ

Table 2. Analysis of the Associations With Amino Acid at the 57 Residue of DQβ1 in the Relapse and Nonrelapse Groups

Amino acid residue	Position	Encoding alleles	Relapse group (n = 13)	Nonrelapse group (n = 27)	*P* value	Odds ratio (95% confidence interval)
Nonaspartic acid (V, S, A)[a]	B1 57	DQB1*0201 DQB1*0202 DQB1*0302 DQB1*0501 DQB1*0502 DQB1*0604 DQB1*0609	13 (100%)	8 (29.6%)	.00003	3.38 (1.9–6.0)

V, valine; S, serine; A, alanine.
[a]DQB1*0301, DQB1*0303, DQB1*0401, DQB1*0402, DQB1*0503, DQB1*0601, DQB1*0602, and DQB1*0603 are encoded by aspartic acid at DQβ1 57.

Table 3. Clinical Characteristics and HLA DRB1-DQB1 Haplotype of the 13 Patients Who Had a Relapse

Patient no.	Age/sex	Initial serum IgG/IgG4 level[a]	Period to relapse (*mo*)	Follow-up (*mo*)	HLA haplotype DRB1/DQB
1	53/M	1990/150	40/A	67	0405,0302/0406,0401
2	58/M	4100/780	41/A	63	0403,0302/1301,0603
3	61/M	1500/190	44/A	47	0802,0302/1501,0602
4	63/M	1780/658	6/D	35	0701,0202/1302,0604
5[b]	49/F	2000/445	22/A	37	0405,0302/0406,0401
6	59/M	1230/ND	16/D	60	0406,0202/0701,0302
7[c]	68/M	3550/136	5/D	47	0101,0302/0406,0501
8	36/M	1060/50	4/D	32	0406,0302/0802,0302
9	78/M	4570/158	34/A	36	0701,0202/0803,0601
10	34/F	1070/11	6/D	40	0406,0202/0701,0302
11[d]	67/M	1670/81	4/D	12	0404,0302/1302,0609
12	34/M	966/10	17/A	19	0701,0202/1101,0301
13	71/M	2570/72	6/D	12	0403,0202/0701,0302

NOTE. Underlined text denote nonaspartic acid at DQβ1 57.

A, relapse after the withdrawal of corticosteroid therapy; D, relapse during maintenance corticosteroid therapy; ND, not done.

[a]An IgG level >1800 mg/dL and IgG4 level >135 mg/dL were considered to be a cut-off value for diagnostic criteria of AIP.

[b]Pancreatic parenchymal calcifications with stone formation were noted during follow-up periods.

[c]Although the patient responded again to the induction dose of corticosteroid, he had a third recurrent attack of AIP during each maintenance corticosteroid therapy period.

[d]Although the patient responded again to the induction dose of corticosteroid, he had a second recurrent attack of AIP during each maintenance corticosteroid therapy period.

α-chain adjacent to P9, and if the peptide side chain carries a negative charge, such as aspartic acid, there is a strong attractive interaction as a native "salt bridge," which leads to a stable, high-avidity binding interaction at this site. This salt bridge forms a structural constraint on the peptide residues, which can be accommodated in P9. Peptides with an aspartic acid at P9 do not bind; however, small aliphatic residues are sufficient to stabilize the binding interactions.[33] It is therefore clear that minimal differences in residues within these key peptide binding regions can have a profound effect on the immune response.[30,31] Second, pemphigus vulgaris, bullous pemphigoid, and atopic dermatitis are known to be associated with high serum IgG4 concentrations, as in AIP, and substitution of amino acid at residue 57 of DQβ1 may have a critical role in the susceptibility of their diseases.[34–38] IgG4 may behave as a pathogenetic antibody in pemphigus vulgaris and as a suppressive antibody via the generation of regulatory T cells in allergic disease.[39] In AIP, the immune reactions mediated by Th_2 cells and regulatory T cells also may be predominant.[39] Because the HLA-DQ molecule may act as a restriction element for both proliferative and suppressor cells,[40] an epitope of DQβ1 57 may have a role of T-cell regulator for relapse of AIP.

Table 4. Statistical Analysis of HLA-DRB1 and HLA-DQB1 Subtypes Among Patients With AIP and Healthy Subjects

HLA	Patients with AIP (%) (n = 40)	Healthy subjects (%) (n = 154)	Standard *P* value (odds ratio)	Corrected *P* value
DRB1*04	55	34.4	.017 (2.329)	NS
DRB1*0405	15	13.6	NS	
DRB1*0406	20	11.7	NS	
DRB1*0701	25	11.7	.033 (2.519)	NS
DQB1*02				
DQB1*0202	25	11	.023 (2.68)	NS
DQB1*03	72.7	65.6	NS	
DQB1*0302	38	22.7	NS	
DQB1*04	17.5	20.1	NS	
DQB1*05	20	29.9	NS	
DQB1*06	62.5	57.1	NS	

NS, not significant.

Corticosteroid therapy can reconstitute regulatory T-cell function and attenuate the cell-mediated cytotoxic response.[41] Furthermore, corticosteroids may inhibit the production of IgG4 antibody.[42] In our study, interestingly, relapse of AIP only occurred during maintenance corticosteroid therapy or after a complete discontinuation of corticosteroids, and all the patients with relapses responded again to the induction dose of corticosteroid. These observations, therefore, may implicate the dose-dependent effect of corticosteroid for regulatory T-cell function.

In attempting to evaluate risk factors for relapse of AIP, as previous studies showed,[10,13] among the demographics of serum level of IgG or IgG4, presence of obstructive jaundice, and existence of other organ involvement in the initial diagnosis of AIP, we could not find any clinical predictor for relapse of AIP (Table 1).

To date, the pathogenesis of AIP is still unclear. Kawa et al reported that the DRB1*0405-DQB1*0401 haplotype may be associated with AIP in the Japanese population.[43] The same investigators have reported an association between polymorphisms in the Fc-receptor–like 3 gene and AIP.[44] There was, however, no correlation between the

Fc-receptor–like 3 gene polymorphisms and the DRB1*0405-DQB1*0401 haplotype, which suggests that although both are related to susceptibility for AIP, they are part of different mechanisms that underlie the development of the disease.[5] In our study, among HLA class I and class II antigens, there was no significant susceptible allele associated with AIP (Table 4). Although this result may be because of ethnic differences and the small number of subjects enrolled, non-HLA genes may also have a role in the development of this autoimmune disease.[45]

In summary, we found that substitution of aspartic acid to nonaspartic acid at DQβ1 57 may be a predictive factor for relapse of AIP. Although AIP as a cause of relapsing pancreatitis in the West is really quite rare,[46] HLA high-resolution genotyping with amino acid sequence analysis may be useful in identifying the subgroup of individuals who are at a potentially greater risk for relapse of AIP. For patients with AIP identified as having this genetic factor predictive of relapse, the treatment strategy may need to be adjusted by including higher dosages or lifelong administration of maintenance corticosteroid therapy or additional treatment with an immunosuppressive agent.

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