Landscape of immunoglobulin heavy chain γ gene class switch recombination in patients with adult T-cell leukemia–lymphoma

We are currently conducting the multicenter prospective study "Monitoring of immune responses following mogamulizumab-containing treatment in patients with adult T-cell leukemia–lymphoma (ATL)" (MIMOGA), (*Trial registration number: UMIN000008696*).[1-4] We previously reported the importance of humoral immune measures, such as the proportion of CD2-CD19+ B cells in peripheral blood mononuclear cells (PBMC), for the outcome of ATL patients.[5] Subsequently, we demonstrated that lower immunoglobulin G (IgG) B-cell diversity in PBMC was a significant unfavorable prognostic factor for overall survival (OS) in patients.[6] In that study, we had focused on the diversity-generating mechanism for the IgG variable regions. Therefore, here we focused on the diversity-generating mechanism in the IgG constant region, namely class switch recombination (CSR),[7-9] and explored its detailed status in ATL patients. The present investigation was affiliated with the MIMOGA study, and 81 ATL patients were enrolled according to the criteria used in that previous study.[5,6] Unbiased amplification and high-throughput sequencing of the immunoglobulin heavy chain γ (*IGHG*) genes was conducted using PBMC at enrollment in the MIMOGA study.[6,10] The sequence reads whose immunoglobulin heavy chain constant (*IGHC*) region was determined to be assigned to immunoglobulin heavy constant γ P were excluded from the analysis. *IGHG* unique reads, with identical *IGHV* (variable), *IGHD* (diversity) and IGHJ (joining) gene usage and identical deduced amino acid sequences of the *CDR3* complementarity determining region 3 (*CDR3*), were designated "*VDJ/CDR3* identical unique reads". Among *IGHG* unique reads in PBMC, the percentage of *VDJ/CDR3* identical reads which were shared between two or more different subclass genes was designated "the percentage of CSR of *IGHG* unique reads in PBMC", abbreviated to "%CSR of *IGHG*". In practice, the %CSR of *IGHG* was calculated as follows: the total number of *VDJ/CDR3* identical unique reads which were shared between two subclass genes (*IGHG3-IGHG1*, *IGHG3-IGHG2*, *IGHG3-IGHG4*, *IGHG1-IGHG2*, *IGHG1-IGHG4*, or *IGHG2-IGHG4*), or three subclass genes (*IGHG3-IGHG1-IGHG2*, *IGHG3-IGHG1-IGHG4*, *IGHG3-IGHG2-IGHG4*, or *IGHG1-IGHG2-IGHG4*), or four subclass genes (*IGHG3-IGHG1-IGHG2-IGHG4*) was divided by the total number of *IGHG* unique reads.

We first analyzed *VDJ/CDR3* identical unique reads according to the type of subclass genes in PBMC of ATL patients, compared to those of 12 healthy individuals, who had also participated in our previous study.[6,10] The percentage of *IGHG* unique reads which had a single subclass gene of *IGHG1* tended to be higher in ATL patients than in healthy individuals. Among *IGHG* unique reads, the percentages of *VDJ/CDR3* identical reads which were shared between two different functional subclass genes, namely, *IGHG3-IGHG1*, *IGHG3-IGHG2*, *IGHG3-IGHG4*, or *IGHG1-IGHG2* were significantly lower in ATL patients. The remaining two pairs consisting of two different subclasses, such as *IGHG1-IGHG4* and *IGHG2-IGHG4*, tended to be lower in ATL patients. Additionally, those shared between three different functional subclass genes, in all four available pairs, i.e., *IGHG3-IGHG1-IGHG2*, *IGHG3-IGHG1-IGHG4*, *IGHG3-IGHG2-IGHG4*, or *IGHG1-IGHG2-IGHG4*, were significantly lower in ATL patients. Accordingly, the %CSR of *IGHG* was significantly lower in ATL patients than in healthy controls (Table 1). These data indicate that the CSR of *IGHG* unique reads occurs significantly less frequently in ATL patients. These differences in the frequency of CSR among *IGHG* are likely to reflect the degree of impairment of the humoral immune system.

Second, we sought correlations between the %CSR of *IGHG*, and the Shannon–Weaver diversity index (SWDI) for the *IGHG* repertoire in PBMC.[6,10] We found a significant positive correlation of the %CSR of *IGHG* with the SWDI (Spearman rank correlation coefficients [Rs]=0.860; $P<0.001$) in ATL patients. This was also the case in healthy controls (Rs=0.846; $P=0.001$), likely because both CSR and somatic hypermutation (SHM) leading to the diversification of antibody variable regions are mediated by activation-induced cytidine deaminase (AID).[12-14]

Third, we analyzed the clinical characteristics of ATL patients according to the %CSR of *IGHG*. Clinically meaningful cut-off values of the %CSR of *IGHG* had not been determined. Hence, we divided the patients into two groups according to the %CSR. Subsequently, univariate analysis for survival was performed using a Cox proportional hazards regression model at each of the six cut-off points. In the present study, the cut-off point yielding the minimum *P* value was selected as the most meaningful cut-off value, as previously described.[5,11] As a result, the cut-off value of the %CSR of *IGHG* was set at 9.363% (*Online Supplementary Table S1*). In this context, the median age was 67 years (range, 41–86) and 70 years (range, 58–83) in patients with a lower and higher %CSR, respectively (not significantly different; $P=0.119$). There were also no

Table 1. *VDJ/CDR3* identical unique reads according to the types of shared subclass genes in adult T-cell leukemia–lymphoma patients and healthy individuals.

Subclass gene				Healthy (N=12) mean/median (%)	ATL (N=81) mean/median (%)	*P*
IGHG3	*IGHG1*	*IGHG2*	*IGHG4*			
■				3.66/3.25	7.94/3.51	0.766
	■			27.52/26.61	41.25/37.99	0.009
		■		31.72/31.60	39.05/40.15	0.242
			■	1.06/0.93	2.81/0.47	0.449
■	■			**1.29/0.97**	0.58/0.44	**0.003**
■		■		**1.56/1.49**	0.65/0.52	**< 0.001**
■			■	**0.10/0.09**	0.05/0	**0.003**
	■	■		**19.00/19.15**	4.06/3.46	**< 0.001**
	■		■	0.22/0.23	0.18/0.01	0.005
		■	■	0.17/0.15	0.12/0.01	0.023
■	■	■		**10.58/10.55**	1.94/1.58	**< 0.001**
■	■		■	**0.15/0.16**	0.072/0	**< 0.001**
■		■	■	**0.09/0.06**	0.0306/0	**0.001**
	■	■	■	**0.99/0.78**	0.20/0.03	**< 0.001**
■	■	■	■	1.88/1.42	1.06/0.72	0.059
%CSR of *IGHG*				**36.04/37.38**	8.95/8.38	**< 0.001**

The *IGHG* unique reads which have a single subclass gene (*IGHG3, IGHG1, IGHG2*, or *IGHG4*), and the *VDJ/CDR3* identical unique reads according to the types of shared subclass genes in peripheral blood mononuclear cells (PBMC) of adult T-cell leukemia–lymphoma (ATL) patients and healthy individuals are shown. Subclass genes employed by the *VDJ/CDR3* identical unique reads are represented by the filled gray cells. The mean and median values (percentages) of each type of subclass gene are indicated before and after the / symbol, respectively. Significant differences in the proportions between ATL patients and healthy individuals are indicated as *P* values. *P*<0.050/15 was considered statistically significant after Bonferroni correction. Significantly higher values are indicated in bold. The total proportions of all types of subclass genes employed by the *VDJ/CDR3* identical unique reads are 100% in each healthy individual or ATL patient. *IGHG* unique reads, with identical *IGHV* (immunoglobulin heavy chain variable), *IGHD* (diversity), and *IGHJ* (joining), gene usage and identical deduced amino acid sequences of the *CDR3* (complementarity determining region 3), were designated as "*VDJ/CDR3* identical unique reads". Among *IGHG* unique reads, the percentage of *VDJ/CDR3* identical reads which were shared between two or more different subclass genes (*IGHG3, IGHG1, IGHG2,* or *IGHG4*) was designated as "the percentage of CSR of *IGHG* unique reads", abbreviated to "%CSR of *IGHG*". CSR: class switch recombination; *IGHG*: immunoglobulin heavy chain γ gene; *IGHG3*: immunoglobulin heavy constant γ3 gene.

significant differences between patients with a lower or higher %CSR regarding previous systemic chemotherapy (yes or no; *P*=0.579), sex (*P*=1.000), or Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0, 1 *vs.* 2, 3, 4; *P*=0.207). In addition, there were also no significant differences between patients with a lower or higher %CSR for clinical subtype (chronic, smoldering *vs.* acute, lymphoma; *P*=1.000), or in serum soluble interleukin-2 receptor (sIL-2R) (mean and median, 17,971, and 8,600, *vs.* 13,879 and 4,590; *P*= 0.127). Accordingly, this makes it hard to estimate the status of *IGHG* CSR based on clinical characteristics.

Fourth, we analyzed the immunological characteristics of ATL patients according to the %CSR of *IGHG*. The percentages of CD2-CD19+ B cells were significantly higher in the patients with a higher %CSR of *IGHG* compared to those with a lower %CSR. This suggests that as more B cells, including IgG B cells, are present in PBMC, more CSR of *IGHG* can occur. On the other hand, there was no significant difference in the percentage of CD3+CD8+ or CD3+CD4+ T cells in the patients with a higher or lower %CSR. With respect to CD16+CD56+ natural killer (NK) cells, or CD11c+ monocytes, the former were significantly higher, and the latter tended to be higher in the patients with a higher %CSR. These NK cells or monocytes might assist CSR for IgG, but no responsible mechanisms have been clearly identified. Serum IgG and IgA titers were significantly higher in patients with a higher %CSR than in those with a lower %CSR, but the difference in serum IgM was not significant (Table 2). These results likely reflect the gene order in the *IGHC* locus on chromosome 14q32, such as *IGHM* (immunoglobulin heavy constant μ)-*IGHD* (immunoglobulin heavy constant δ)-*IGHG3*-*IGHG1*-*IGHA1* (immunoglobulin heavy constant α1)-*IGHG2*-*IGHG4*-*IGHE*

Table 2. Immunological characteristics of T-cell leukemia–lymphoma patients according to the percentage of class switch recombination of *IGHG* unique reads of *IGHG* in peripheral blood mononuclear cells.

Characteristics	%CSR of *IGHG* in PBMC		*P*
	lower (<9.363%)	higher (>9.363%)	
N (%)	50 (62)	31 (38)	
CD2-CD19+ cells (%)* mean median range	 1.16 0.39 0.00-8.17	 4.89 1.25 0.03-32.91	0.009
CD3+CD8+ cells (%)* mean median range	 14.07 7.45 0.10-71.73	 13.41 9.86 0.74-52.33	0.620
CD16+CD56+ cells (%)* mean median range	 6.74 3.62 0.07-31.57	 11.97 8.22 0.43-39.42	0.016
CD11c+ monocytes (%)** mean median range	 50.50 53.05 0.50-97.18	 68.88 78.60 0.34-95.76	0.059
CD3+CD4+ cells (%)* mean median range	 65.64 69.34 11.16-98.14	 57.31 61.62 14.60-97.48	0.108
Serum IgG (mg/dL) mean median range	 908 941 303-1,663	 1,142 1,177 512-2,310	0.002
Serum IgA (mg/dL) mean median range	 168 139 5-522	 274 216 93-1,076	0.002
Serum IgM (mg/dL) mean median range	 41 38 5-112	 48 35 15-99	0.270
SWDI for IgG heavy-chain repertoire in PBMC mean median range	 3.643 3.487 1.004-6.516	 6.385 6.355 3.233-10.096	<0.001

ATL: adult T-cell leukemia-lymphoma; CSR: class switch recombination; *IGHG*: immunoglobulin heavy chain γ gene; PBMC: peripheral blood mononuclear cells; SWDI: Shannon-Weaver diversity index. *Percentage among whole lymphocytes in PBMC. **Percentage among whole monocytes in PBMC.

(immunoglobulin heavy constant ε)-*IGHA2* (*Online Supplementary Figure S1*).[8] That is to say, the *IGHG* gene region overlaps *IGHA* on chromosome 14q32. Therefore, the frequent CSR of *IGHG* would be likely associated with frequent CSR of *IGHA*, thus leading to higher serum IgG and IgA, but not IgM, titers. The significantly higher SWDI for the *IGHG* repertoire in patients with a higher %CSR of *IGHG* would be expected, due to AID,[12-14] and SHM and CSR might both reflect the degree of impairment of the humoral immune system.

Finally, we analyzed the prognostic impact of %CSR of *IGHG*. The OS of patients with a higher %CSR of *IGHG* was significantly longer than of those with a lower %CSR (median OS, 30.9 *vs*. 13.2 months; *P*=0.043) (*Online Supplementary Figure S2A*). Multivariate analysis of OS in the 81 ATL patients was performed using the following six variables: sex, age, clinical subtype, ECOG PS, sIL-2R, and %CSR of *IGHG*. Of these, two variables significantly af-

Table 3. Multivariate analysis including the percentage of class switch recombination of *IGHG* unique reads in peripheral blood mononuclear cells for overall survival of patients with T-cell leukemia–lymphoma.

Variables	N	Hazard Ratio	95% CI	*P*
Sex				
Male	50	1.000	-	Reference
Female	31	1.057	0.560-1.993	0.865
Age in years				
≤70	52	1.000	-	Reference
>70	29	1.272	0.659-2.456	0.474
Clinical subtype				
chronic, smoldering	13	1.000	-	Reference
acute, lymphoma	68	2.287	0.755-6.925	0.143
ECOG PS				
0,1	58	1.000	-	Reference
2,3,4	23	1.214	0.611-2.413	0.580
sIL-2R (U/mL)				
<20,000	64	1.000	-	Reference
>20,000	17	4.924	2.303-10.527	<0.001
% CSR of *IGHG* unique reads in PBMC				
<9.363	50	1.000	-	Reference
>9.363	31	0.439	0.229-0.839	0.013

CSR: class switch recombination; *IGHG*: immunoglobulin heavy chain γ gene; PBMC: peripheral blood mononuclear cells; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; sIL-2R: soluble interleukin-2 receptor.

fected OS, namely a higher serum sIL-2R, and a higher %CSR of *IGHG* (HR, 0.439; 95% confidence interval [CI]: 0.229–0.839) (Table 3). CSR is a process resulting in improved ability of antibodies to eliminate pathogens.[8,9,14] Thus, a higher frequency of efficient CSR possibly implies better humoral immune status, leading to a more favorable prognosis. Considering the previously identified prognostic factor, the frequency of CD2-CD19+ B cells within lymphocytes,[5] the OS of patients with both a lower %CSR and a lower CD2-CD19+ B cells was significantly worse than of the other patients (median OS 7.2 *vs*. 18.8 months; *P*=0.004) (*Online Supplementary Figure S2B*). Based on the present observations of host immune status of the patients, together with an assessment of somatic alterations in the tumor cells,[15] the establishment of precision medicine for patients with ATL is imminent.

The present investigation offers significant observations regarding associations of *IGHG* CSR with clinical outcomes in ATL patients. However, a limitation of the study should be recognized, namely, the possibility that the %CSR of *IGHG* was affected by the absolute B-cell count in the patients' blood used for the *IGHG* sequencing, which cannot be completely excluded. Nonetheless, mitigating against this in the present patient cohort, there was no significant correlation between these two factors (Rs=0.214; *P*=0.056).

In conclusion, the present study demonstrated that *IGHG* CSR occurs less frequently in ATL patients than in healthy individuals. Additionally, the lower frequency of CSR of *IGHG* was a significant independent unfavorable prognostic factor in patients with ATL receiving mogamulizumab-containing treatment. These observations provide novel insights into the mechanism of impaired humoral immunity in ATL patients, the degree of dysfunction of which may be reflected in the status of *IGHG* CSR, which is associated with the clinical outcome. Further investigation of strategies to enhance the quality of humoral immunity is warranted.

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Contributions

HH, RU and TI developed the concept and design of the study; KN, SK, NN, IC, MY, YI, MH, HS, JM, EO, TJ, MO, AI, KY, HT, TK, TK, YS, KI, SI, AU and TI aquired and analyzed data; HH, TM, HN, RU and TI interpreted data. All authors wrote and approved the final version of the manuscript.

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Data-sharing statement

Original data can be made available in response to a reasonable, written request to the corresponding author.

References

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leu-kemia: clinical and hematologic features of 16 cases. Blood. 1977;50(3):481-492.
2. Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res. 2010;16(5):1520-1531.
3. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol. 2012;30(8):837-842.
4. Ishida T, Jo T, Takemoto S, et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol. 2015;169(5):672-682.
5. Yonekura K, Kusumoto S, Choi I, et al. Mogamulizumab for adult T-cell leukemia-lymphoma: a multicenter prospective observational study. Blood Adv. 2020;4(20):5133-5145.
6. Nosaka K, Kusumoto S, Nakano N, et al. Clinical significance of the immunoglobulin G heavy-chain repertoire in peripheral blood mononuclear cells of adult T-cell leukaemia-lymphoma patients receiving mogamulizumab. Br J Haematol. 2022;196(3):629-638.
7. Honjo T, Kataoka T. Organization of immunoglobulin heavy chain genes and allelic deletion model. Proc Natl Acad Sci U S A. 1978;75(5):2140-2144.
8. Xu Z, Zan H, Pone EJ, Mai T, Casali P. Immunoglobulin class-switch DNA recombination: induction, targeting and beyond. Nat Rev Immunol. 2012;12(7):517-531.
9. Westra ER , Sünderhauf D, Landsberger M, Buckling A. Mechanisms and consequences of diversity-generating immune strategies. Nat Rev Immunol. 2017;17(11):719-728.
10. Kitaura K, Yamashita H, Ayabe H, Shini T, Matsutani T, Suzuki R. Different somatic hypermutation levels among antibody subclasses disclosed by a new next-generation sequencing-based antibody repertoire. Analysis. Front Immunol. 2017;8:389.
11. Mazumdar M, Glassman JR. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. Stat Med. 2000;19(1):113-132.
12. Muramatsu M, Sankaranand VS, Anant S, et al. Specific expression of activation-induced cytidine deaminase (AID), a novel member of the RNA editing deaminase family in germinal center B cells. J Biol Chem. 1999;274(26):18470-18476.
13. Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T. Class switch recombination and hypermutation require activation- induced cytidine deaminase (AID), a potential RNA editing enzyme. Cell. 2000;102(5):553-563.
14. Feng Y, Seija N, Di Noia JM, Martin A. AID in antibody diversification: there and back again. Trends Immunol. 2021;42(1):89.
15. Tanaka N, Mori S, Kiyotani K, et al. Genomic determinants impacting clinical outcome of mogamulizumab treatment for adult T-cell leukemia/lymphoma. Haematologica. 2022;107(10):2418-2431.