Journal Club 2023.6.20 by Dr. 大村

Clinical and immunological effects of hydroxychloroquine in patients with active rheumatoid arthritis despite antirheumatic treatment

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背景

b/ts DMARDsはすべての人に用いることができるわけではない。
HCQの有効性と安全性はよく知られている。
ただ、世界中で使われているHCQが日本では保険適応ではない。
日本人RAでの有効性、安全性データはない。

学会からの公知申請を検討するため、RAにおけるヒドロキシクロロキン(HCQ)調査小委員会が発足されました。
（中略） 今後、医療上の必要性の高い未承認薬・適応外薬検討会議への要望を準備しています。
（中略） 会員の皆様におかれましてはアンケートによる調査へご協力くださいますようお願い申し上げます。
回答期限　6月26日

2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Liana Fraenkel,[1] Joan M. Bathon,[2] Bryant R. England,[3] E. William St. Clair,[4] Thurayya Arayssi,[5] Kristine Carandang,[6] Kevin D. Deane,[7] Mark Genovese,[8] Kent Kwas Huston,[9] Gail Kerr,[10] Joel Kremer,[11] Mary C. Nakamura,[12] Linda A. Russell,[13] Jasvinder A. Singh,[14] Benjamin J. Smith,[15] Jeffrey A. Sparks,[16] Shilpa Venkatachalam,[17] Michael E. Weinblatt,[16] Mounir Al-Gibbawi,[18] Joshua F. Baker,[19] Kamil E. Barbour,[20] Jennifer L. Barton,[21] Laura Cappelli,[22] Fatimah Chamseddine,[18] Michael George,[23] Sindhu R. Johnson,[24] Lara Kahale,[18] Basil S. Karam,[18] Assem M. Khamis,[18] Iris Navarro-Millán,[25] Reza Mirza,[26] Pascale Schwab,[21] Namrata Singh,[27] Marat Turgunbaev,[28] Amy S. Turner,[28] Sally Yaacoub,[18] and Elie A. Akl[18]

ACRガイドラインでは
HCQをLDAのRAであれば、
イニシャル治療として使用してもよい
という立場

Initiation of treatment in DMARD-naive patients with low disease activity

Hydroxychloroquine is **conditionally** recommended over other csDMARDs. Certainty of evidence: Very low

Sulfasalazine is **conditionally** recommended over methotrexate. Certainty of evidence: Very low

Methotrexate is **conditionally** recommended over leflunomide. Certainty of evidence: Very low

Treatment modification

Addition of a bDMARD or tsDMARD is conditionally recommended over **triple therapy** for patients taking maximally tolerated doses of methotrexate who are not at target.

Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Josef S Smolen ,[1] Robert B M Landewé ,[2] Sytske Anne Bergstra ,[3]

Recommendationsの条文中にHCQの文字はない

Eular recommendationsでは
HCQをあまり評価しておらず、
Low/High DAにかかわらずイニシャル治療は
MTX（禁忌でない限り）

4. *MTX should be part of the first treatment strategy.* In the context of this and the subsequent recommendation (to prescribe leflunomide or sulfasalazine when MTX is contraindicated) the question regarding the application of **hydroxychloroquine** arose, just as during previous task forces' deliberations. However, reference was made to an RCT published more than 30 years ago, which very clearly showed a substantial difference in progression of joint damage between sulfasalazine and **hydroxychloroquine**, suggesting that the latter may only be a very weak DMARD. Thus, **hydroxychloroquine** may be used in patients with early, mild disease (ie, without poor prognostic factors) in whom the other three csDMARDs are contraindicated or not tolerated. Of note, **hydroxychloroquine** is widely used in other diseases, especially SLE, but not for the purpose of inhibiting joint damage progression. Consequently, this drug is not mentioned among the recommendations, because the task force did not wish to suggest that MTX could be replaced by **hydroxychloroquine**.

（続き）

Hydroxychloroquine is also frequently used when csDMARD combinations are applied, such as **triple therapy** with MTX plus sulfasalazine and **hydroxychloroquine**. This strategy has been shown in some previous studies and SLRs to not provide any added benefit but rather convey more adverse events, leading to low persistence rates. Since some rheumatologists continue to use triple therapy as an initial treatment modality, the term ‘part of ’ was kept in the recommendation, even though the preference of the current and previous Task Forces is on MTX monotherapy in combination with short-term GCs (see below); however, MTX should be used in any case, unless not tolerated or contraindicated, such as in patients with significant renal impairment.

（参考）本論文でHCQ efficacyを報告したとするreview論文(ref. #16)より

Table 1. Characteristics of the patients included in the studies comparing HCQ in monotherapy to other csDMARDs*

Study author, year (ref.)	Type of study	Study duration (wk)	Group (no. patients)	Mean dose	Age (yrs)	Disease duration (yrs)	csDMARD-IR patients, no. (%)
Dixon et al, 1988 (5)	RCT	24	HCQ (13)	400 mg/day	NR	NR	NR
			SSZ (15)	1.5–3 gm/day	NR	NR	NR
Nuver-Zwart et al, 1989 (7)	RCT	48	HCQ (30)	200–400 mg/day	53.0 (22–72)†	1.2 (0.2–13.7)‡	0 (0)
			SSZ (30)	2 gm/day	53.5 (22–75)†	0.9 (0.2–10)‡	0 (0)
Van der Heijde et al, 1989 (8)	RCT	48	HCQ (28)	200–400 mg/day	53.1 (22–72)†	1.3	0 (0)
			SSZ (22)	2 gm/day	53.5 (22–75)†	1.1	0 (0)
Faarvang et al, 1993 (6)	RCT	24	HCQ (31)	250 mg/day	NR	6.3 (0–37)‡	NR
			SSZ (29)	2 gm/day	NR	6.3 (0–37)‡	NR
Alam et al, 2012 (3)	RCT	24	HCQ (30)	200–400 mg/day	42.9 ± 9.2§	1.8 ± 0.3§	0 (0)
			MTX (30)	7.5–17.5 mg/wk	41.7 ± 12.2§	2.3 ± 0.4§	0 (0)
Gossen et al, 2016 (4)	Cohort	260	HCQ (16,796)	NR	57.8 ± 15.0§	NR	NR
			MTX (85,082)	NR	57.8 ± 15.0§	NR	NR

* HCQ = hydroxychloroquine; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; ref. = reference; IR = inadequate response; RCT = randomized controlled trial; SSZ = sulfasalazine; NR = not reported; MTX = methotrexate.
† Values are the years of age (minimum–maximum range).
‡ Values are the years of disease duration (minimum–maximum range).
§ Values are the mean ± SD.

プラセボとの比較がない

Rempenault C et al., Arthritis Care & Research Vol. 72, No. 1, January 2020, pp 36–40

A Randomized Trial of Hydroxychloroqui Rheumatoid Arthritis: The HERA Study

The HERA Study Group*

156 February 1995 The American Journal of Medicine® Volume 98

TABLE I
Characteristics of Patients With Early Rheumatoid Arthritis at Randomization, by Treatment Group

Characteristic	Hydroxychloroquine (n = 59)	Placebo (n = 60)	P Valu
Age (y)	53 ± 13.5	53 ± 14.8	0.85
Female (%)	45 (76)	45 (75)	0.87
Education (y)	11.2 ± 2.9	10.5 ± 3.2	0.23
Duration of rheumatoid arthritis (m)	8.8 ± 5.8	9.3 ± 5.8	0.63
ARA criteria	4.6 ± 0.67	4.6 ± 0.74	0.94
Patients with extra-articular features (%)	6 (10)	7 (11)	0.80
Tender joint count	25.3 ± 13.4	26.2 ± 14.4	0.72
Swollen joint count	13.4 ± 7.8	12.2 ± 7.7	0.39
Grip strength (mm Hg)	179 ± 78	175 ± 81	0.79
Morning stiffness (min)	143 ± 124	146 ± 141	0.91
Arthritis Impact Measurement Scales[17]			
Physical disability (0–10)	2.52 ± 1.47	2.59 ± 1.56	0.79
Psychological disability (0–10)	3.21 ± 1.61	3.47 ± 1.92	0.42
Pain (0–10)	6.53 ± 1.67	6.47 ± 1.78	0.83
Health Assessment Questionnaire[16]			
Physical disability (0–3)	1.06 ± 0.60	1.00 ± 0.61	0.60
Pain (0-3)	1.46 ± 0.75	1.36 ± 0.78	0.51
Rheumatoid factor positive (%)	24 (41)	32 (53)	0.17
Hematocrit (%)	0.391 ± 0.038	0.381 ± 0.038	0.18
Erythrocyte sedimentation rate (mm/h)	32.8 ± 14.5	33.5 ± 16.7	0.80

Values are given as mean ± one standard deviation.
ARA = American Rheumatism Association.

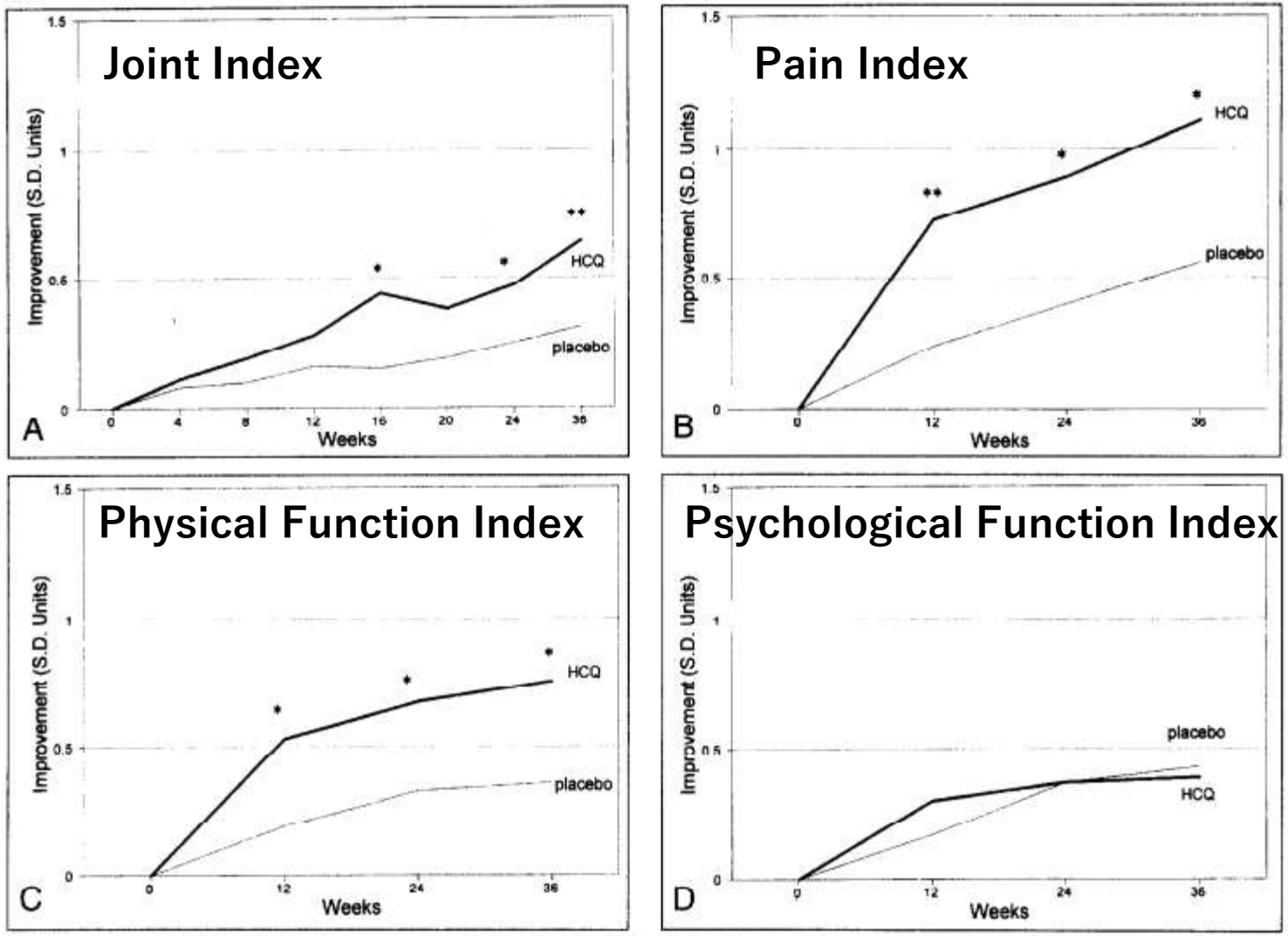


Figure. Improvement in primary outcomes, given in standard deviation (SD) units, over the course of a 36-week, double-blind study of 119 patients with early rheumatoid arthritis. Patients were given hydroxychloroquine (HCQ) or placebo at a dose of 3.5 mg/kg per day for the first 2 weeks. If there were no side effects, doseage was increased to 7 mg/kg per day (maximum dose = 400 mg/d) for the remaining 34 weeks. Data were evaluated by analysis of variance with repeated measures. **A.** Change in joint index ($P = 0.034$). The joint index combined the tender joint count, the swollen joint count, the grip strength, and the duration of morning stiffness. **B.** Change in pain index ($P = 0.001$). The pain index included the pain dimension of the Arthritis Impact Measurement Scales (AIMS)[17] and the visual analog scale of the Health Assessment Questionnaire (HAQ).[16] **C.** Change in physical function index ($P = 0.011$). The physical function index combined the physical disability scores from the AIMS, the HAQ, and the McMaster-Toronto Arthritis Patient Preference Disability Questionnaire.[15] **D.** Change in psychological function as measured by the psychological subscale of the AIMS ($P = 0.89$). The asterisks denote significant benefit of HCQ compared to placebo at a specific visit (*$P < 0.05$; **$P < 0.01$).

＃14の引用論文より

placebo-controlled RCTでHCQの有効性を示している

PECO（I）

Patients:

・1987 ACR or 2010 ACR/EULAR criteriaを満たすRA
・MTXもしくは2つ以上のcsDMARDを3ヶ月以上使用し
　DAS28-ESR ≧ 2.6
・4週以上治療薬の変更なし
・poor prognostic factorをもっている（HDA, RF(+), CCP(+),
　erosion (+), 1つ以上の関節腫脹(+), 1つ以上の圧痛関節(+)
・3ヶ月以上あければb/tsDMARDs使用歴OK

Historical Control group

・慶応大学リウマチコホートにおいて同じinclusion,
　exclusion criteriaの患者
・HCQ groupとpropensity score matchingにて背景を合わせた
　患者

PECO（2）

Exposure:　enrolment時の治療にHCQをadd on（理想体重別のSLE投与量）

Comparison: HCQ投与のない患者（historical control）

Outcome:　1°endpoint: 24週後のACR20達成率

2°endpoints:

- 4, 8, 12, 24週における1段以上のDAS-ESRカテゴリーの改善率
- LDA (DAS28-ESR)達成率
- 臨床的寛解率（4, 8, 12, 24wk）
- HAQ寛解率（4, 8, 12, 24wk）
- X線寛解率（ΔmTSS≦0.5）（24wk）
- ACR20/50/70達成率（4, 8, 12, 24wk）
- 有害事象

Propensity score matching

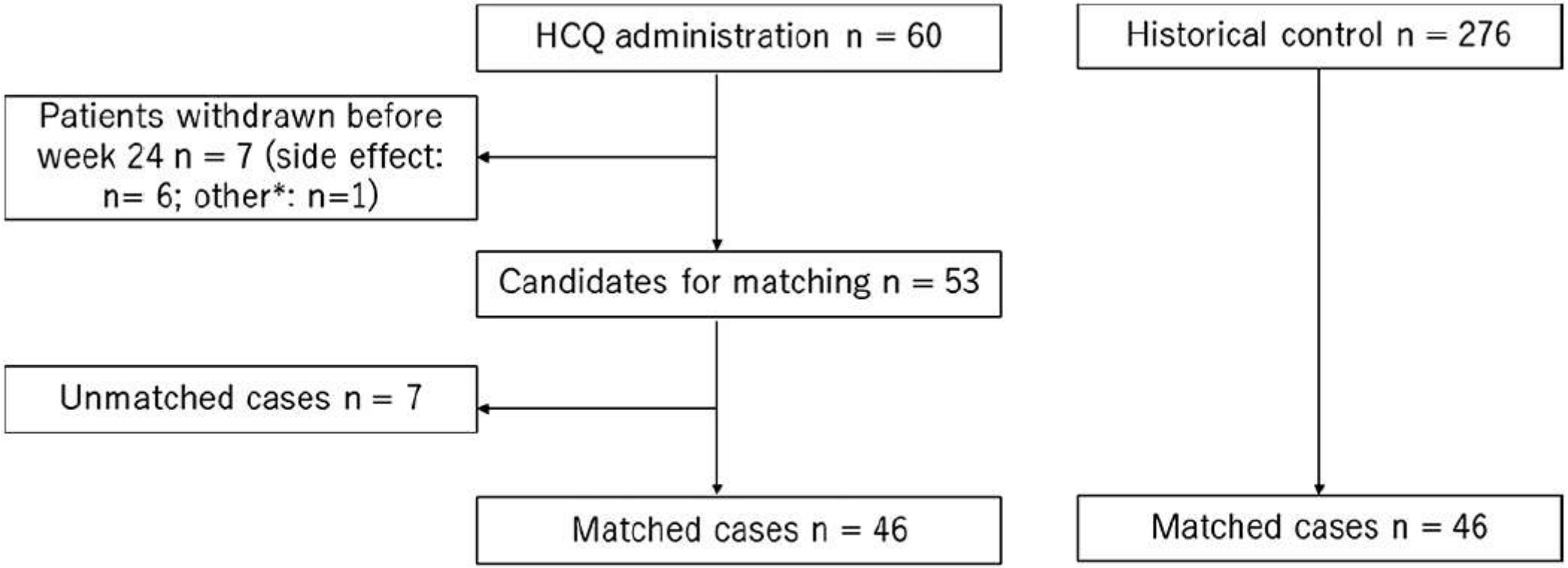
慶応リウマチコホートで2011年12月時点において、276名がinclusion/exclusion criteriaに合致し、24週間治療変更をされていない患者がいた。
11の共変量（年齢、性別、罹病期間、GC use、DAS-ESR、patient global assessment、evaluator global assessment、CRP level、bDMARD use、current MTX use、RF or CCP positivity）を用いてpropensity scoreをマッチさせた

統計解析

sample size estimation:
　　HCQのACR20達成率 60%, Ctr 30%として80%のpowerで優越性を示すには49人。
　　脱落率10%として各グループ60人が必要。
Baseline characteristics
　　Fisher’s exact test（比率）とtwo-sample t-test（平均値）で検定
24wkでのendpoint
　　McNemar’s test (比率）とtwo-sample t-test (平均値)
Cytokine levelと免疫細胞比率
　　Wilcoxon’s signed-rank test

Figure 1

患者フロー



*The visit at week 24 was cancelled due to pandemic of COVID-19 infection

患者背景

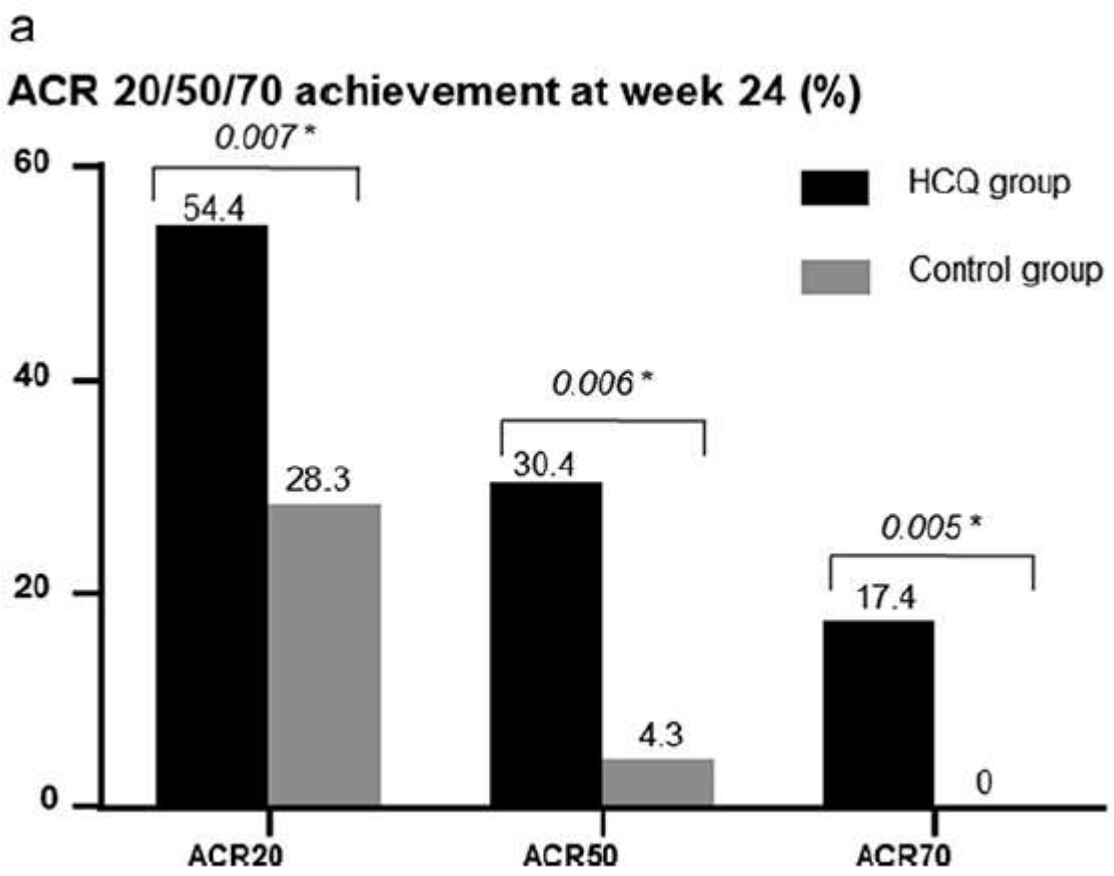
Table 1. Baseline characteristics of propensity score–matched patients.

Variables	Control ($n = 46$)	HCQ ($n = 46$)	P value
Female	44 (95.7)	43 (93.5)	1.00
Age	63.2 (15.1)	63.6 (13.3)	.74
Seropositive for RF or anti-CCP	37 (80.4)	38 (82.6)	1.00
Disease duration, years	12.4 (10.8)	12.1 (11.9)	.75
History of biological agent use	10 (21.7)	8 (17.4)	.79
Concomitant methotrexate use	40 (87.0)	40 (87.0)	1.00
Methotrexate dose, mg	9.8 (2.9)	8.7 (2.4)	.06
Concomitant glucocorticoid use	3 (6.5)	4 (8.7)	1.00
Glucocorticoid dose, mg	5 (1.0)	4 (2.2)	.50
CRP, mg/dl	0.8 (1.3)	0.7 (1.6)	.74
Erythrocyte sedimentation rate, mm/h	36.2 (24.4)	32.1 (29.0)	.46
DAS28-ESR	4.4 (1.1)	4.4 (0.9)	.78
DAS28-CRP	3.5 (1.1)	3.6 (0.8)	.56
SDAI	16.2 (11.9)	17.3 (7.0)	.60
CDAI	15.4 (11.1)	16.6 (6.4)	.53
HAQ-DI	0.8 (0.7)	0.6 (0.6)	.22
Swollen joint count 0–28	4.8 (5.6)	5.4 (2.8)	.54
Tender joint count 0–28	4.0 (4.4)	4.4 (2.5)	.64
Swollen joint count 0–66	6.4 (7.2)	7.0 (4.0)	.58
Tender joint count 0–68	5.0 (5.9)	5.7 (3.5)	.51
Patient global assessment, mm	33.2 (24.3)	32.9 (23.1)	.93
Evaluator global assessment, mm	32.2 (18.4)	34.3 (19.1)	.42
Pain VAS, mm	33.8 (24.6)	32.8 (23.2)	.84
Concomitant sulphasalazine use	8 (17.4)	8 (17.4)	1.00
Sulphasalazine dose, mg	1187.5	968.8	.24
Concomitant bucillamine use	1 (2.2)	5 (10.9)	.20
Bucillamine dose, mg	300	220	.18
Concomitant iguratimod use	1 (2.2)	5 (10.9)	.20
Iguratimod dose, mg	50	40	.54
Concomitant tacrolimus use	4 (8.7)	1 (2.2)	.36
Tacrolimus dose, mg	1.6	1.5	.69

Data are presented as n (%) or mean (SD). RF, rheumatoid factor; CCP, cyclic citrullinated peptide; VAS, visual analogue scale.

Figure 2

ACR20/50/70による臨床効果の評価



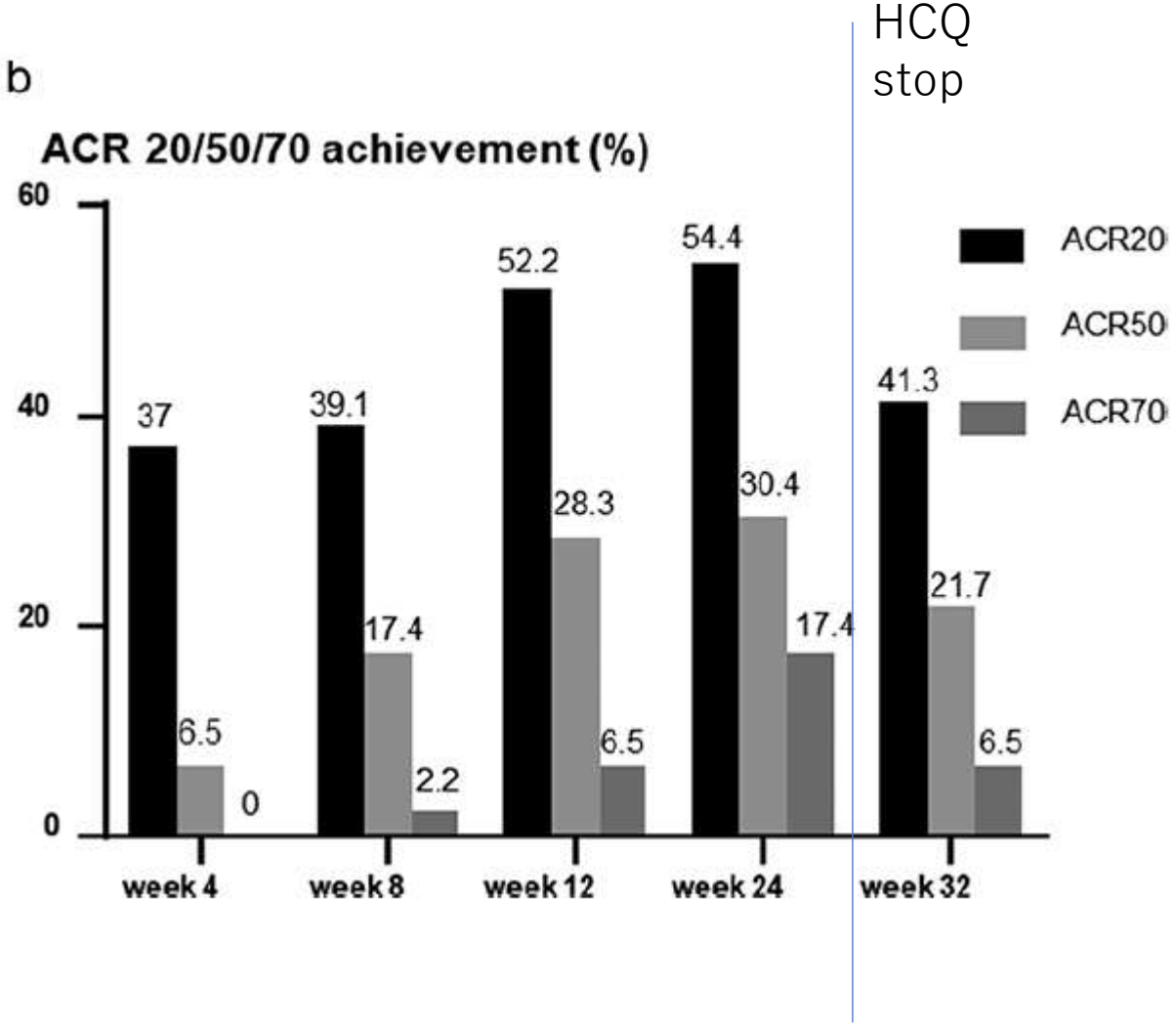


Figure 3

DAS28-ESRによる臨床効果の評価（１）

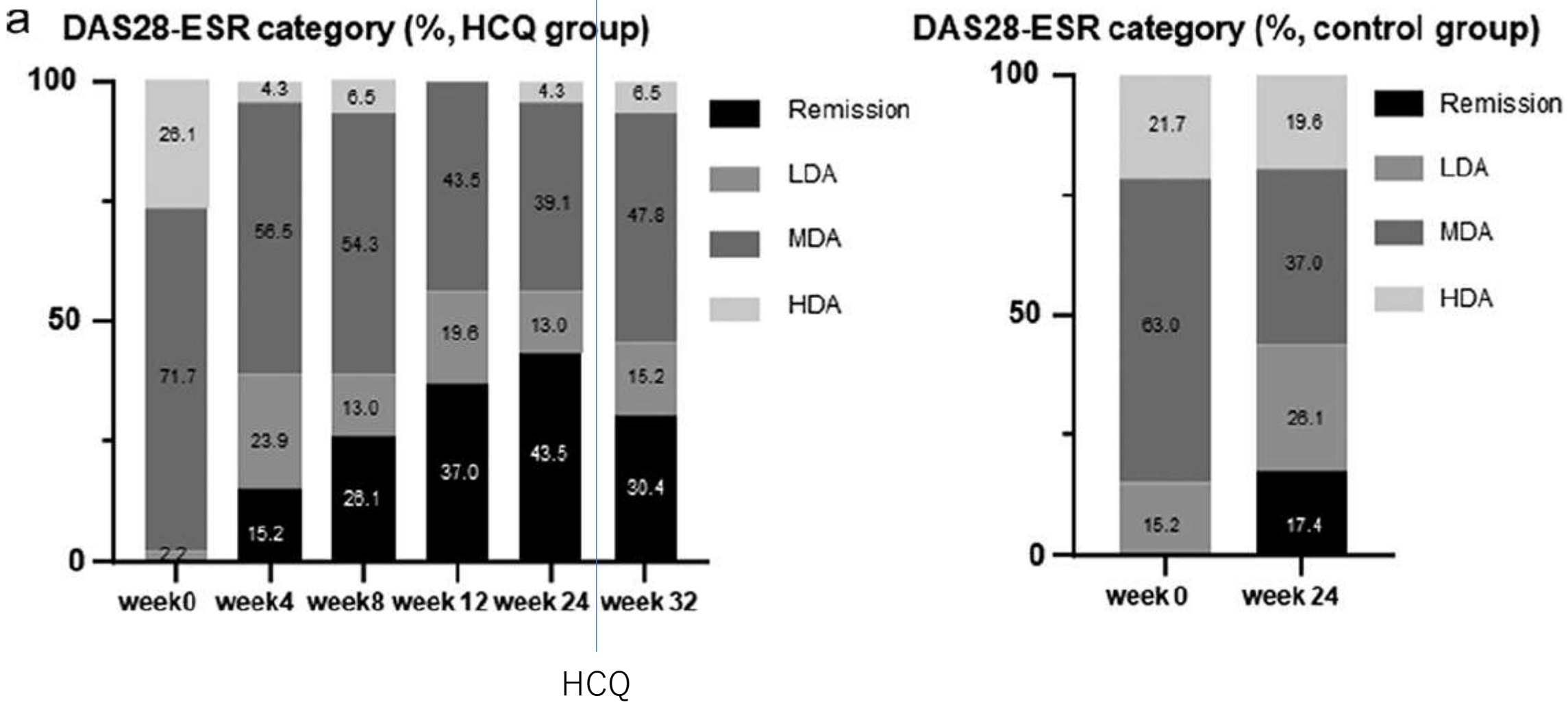


Figure 3

DAS28-ESRによる臨床効果の評価（2）

b

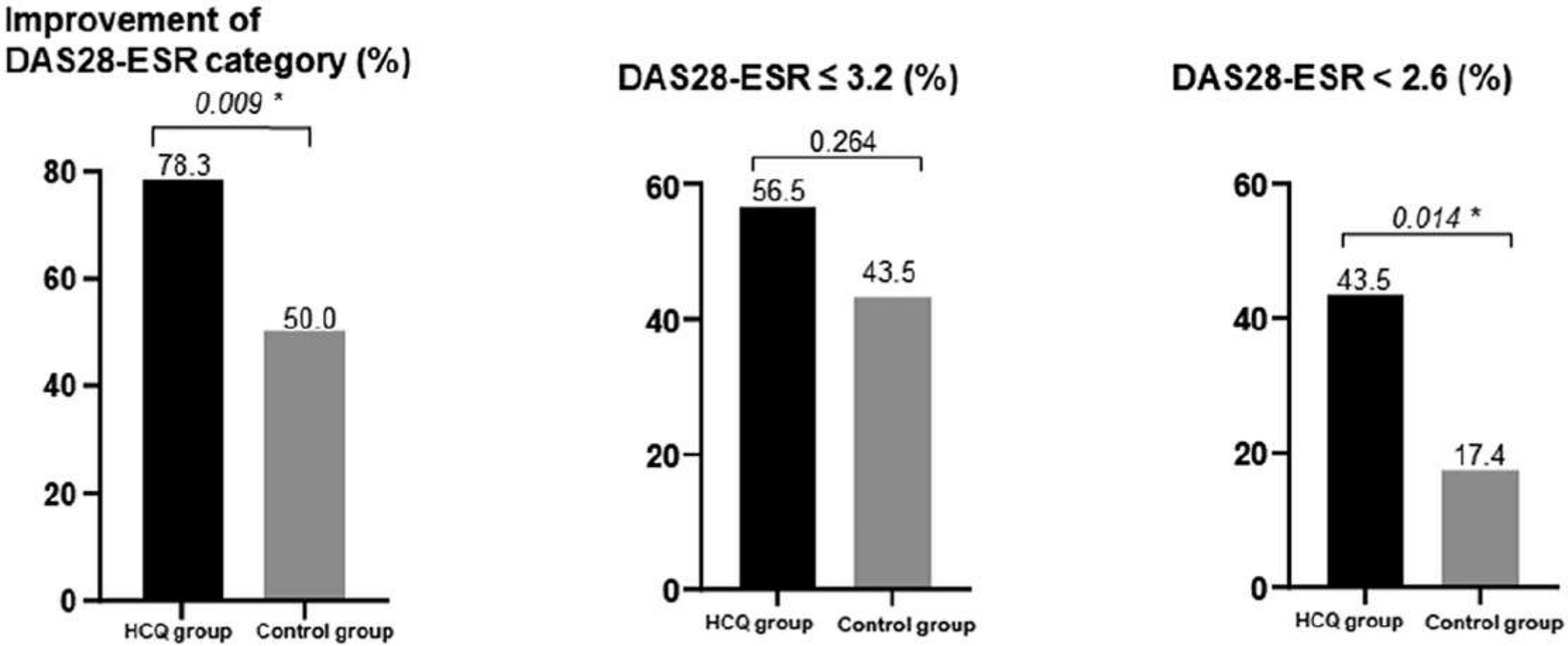


Figure 3

DAS28-ESRによる臨床効果の評価（3）

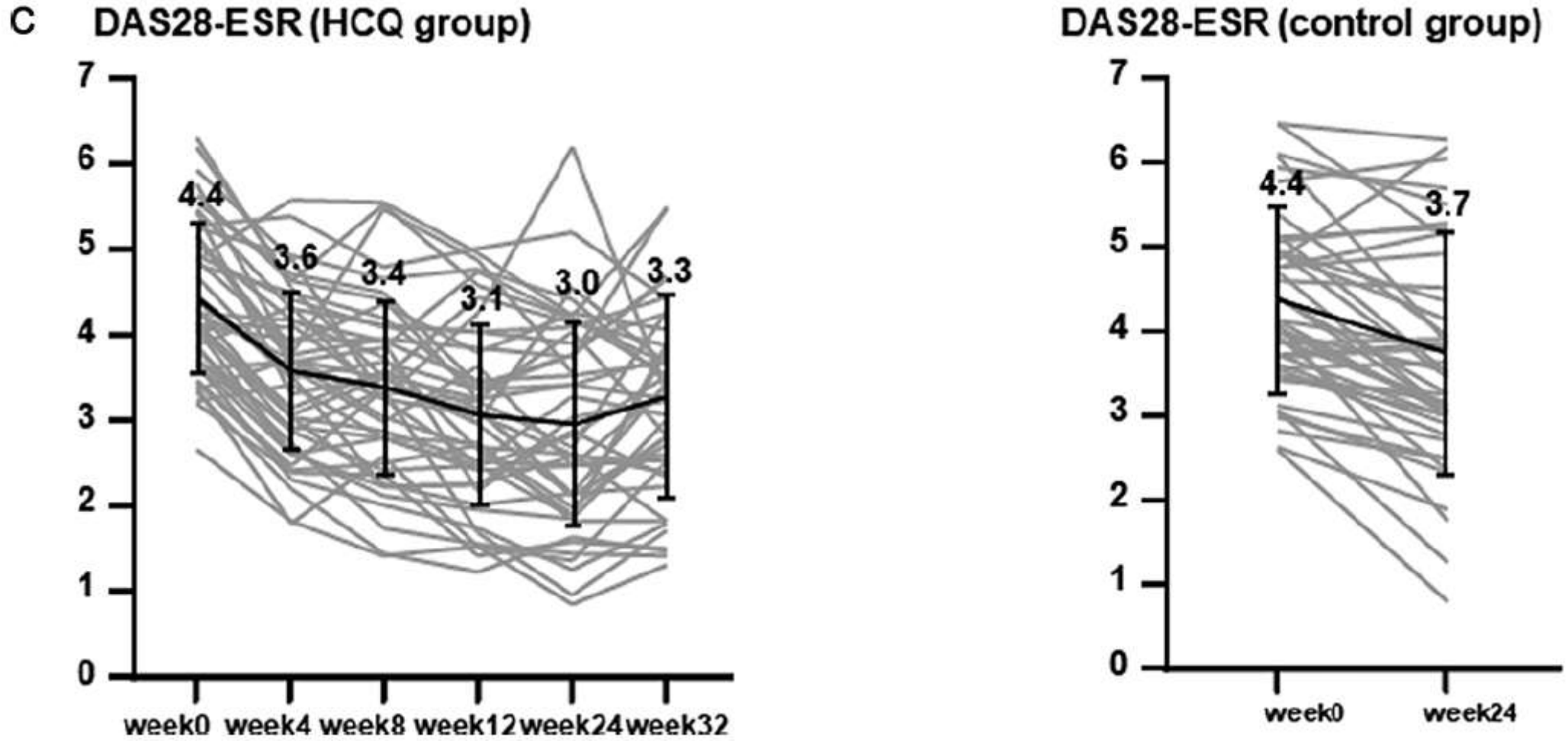


Figure 4

HAQによる機能的評価（1）

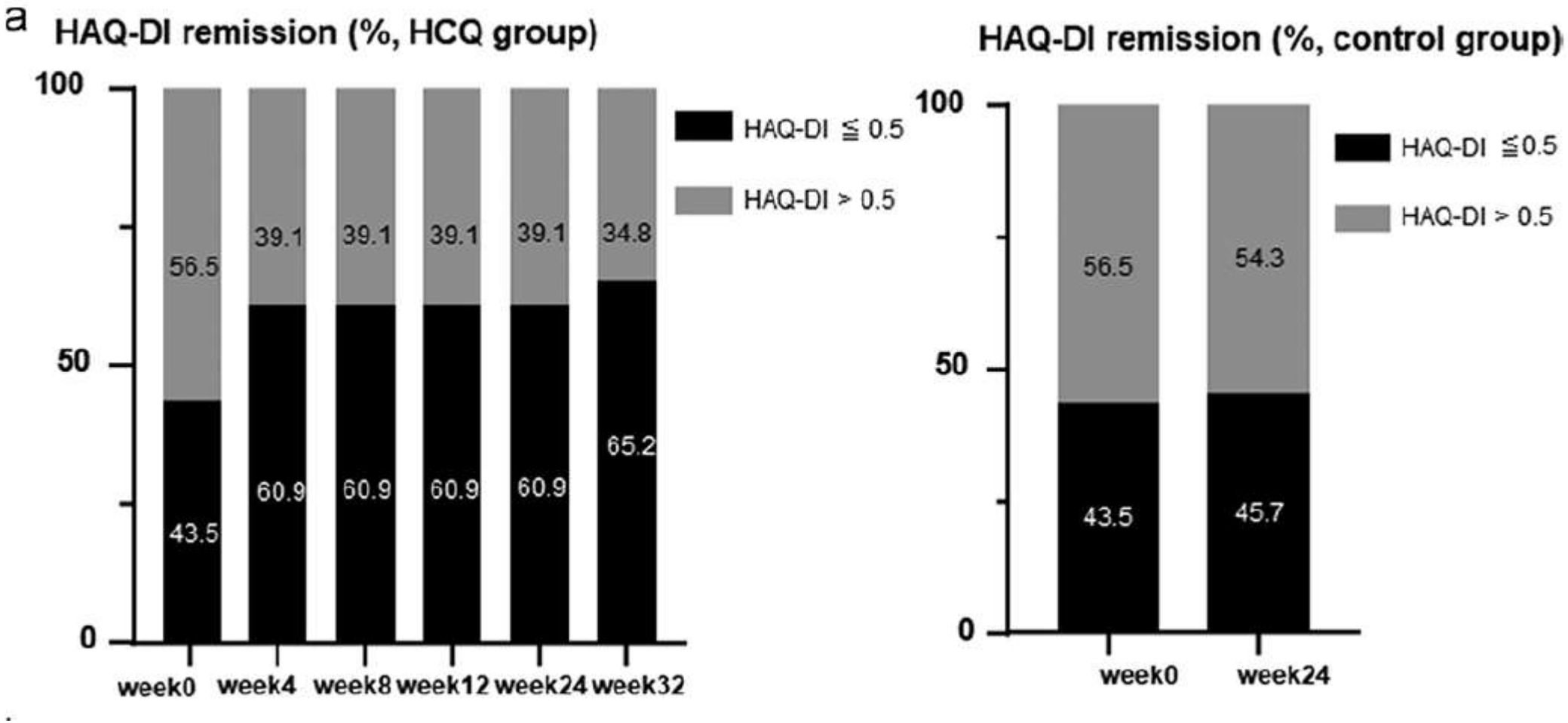


Figure 4

HAQによる機能的評価（2）

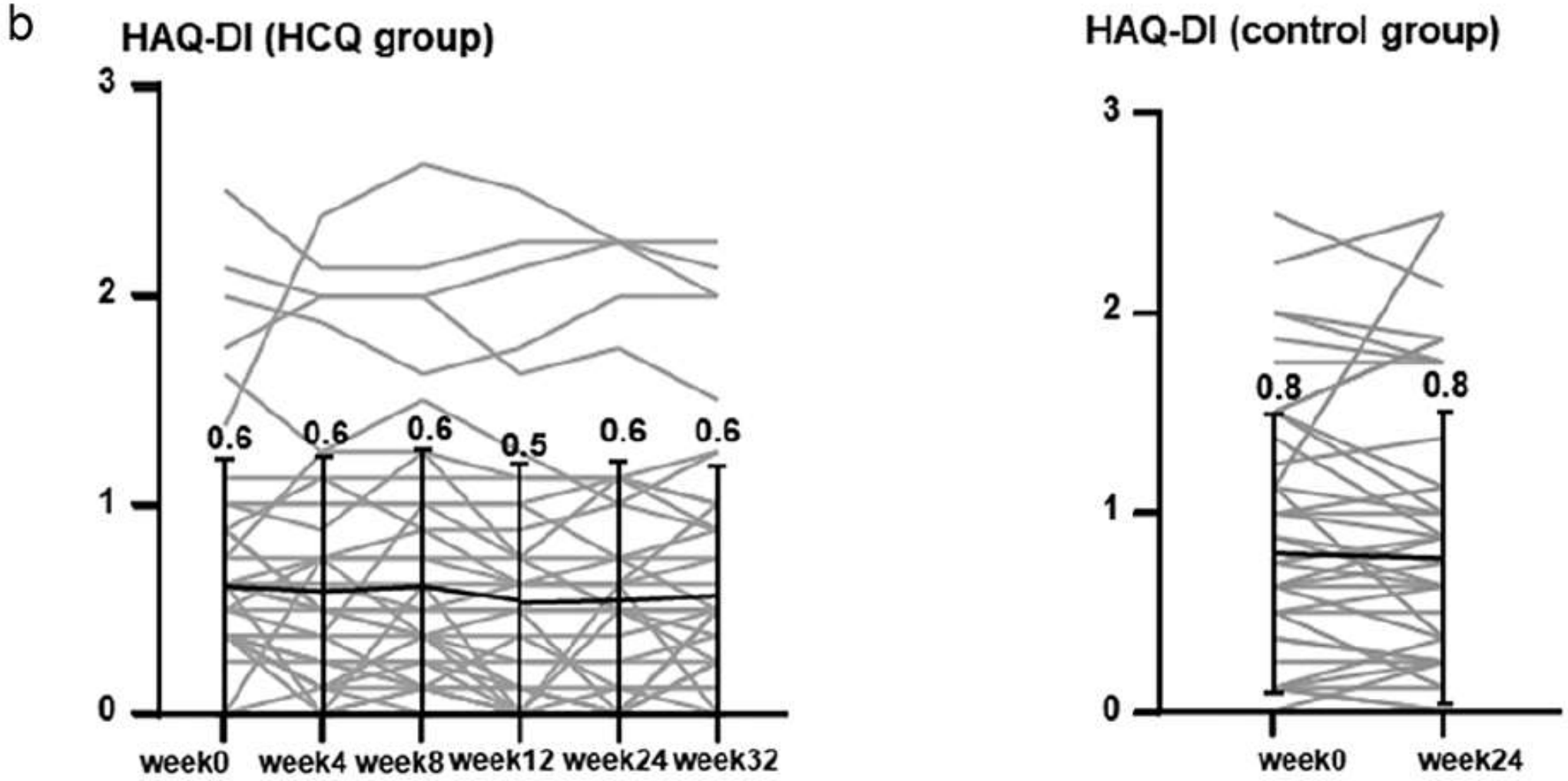
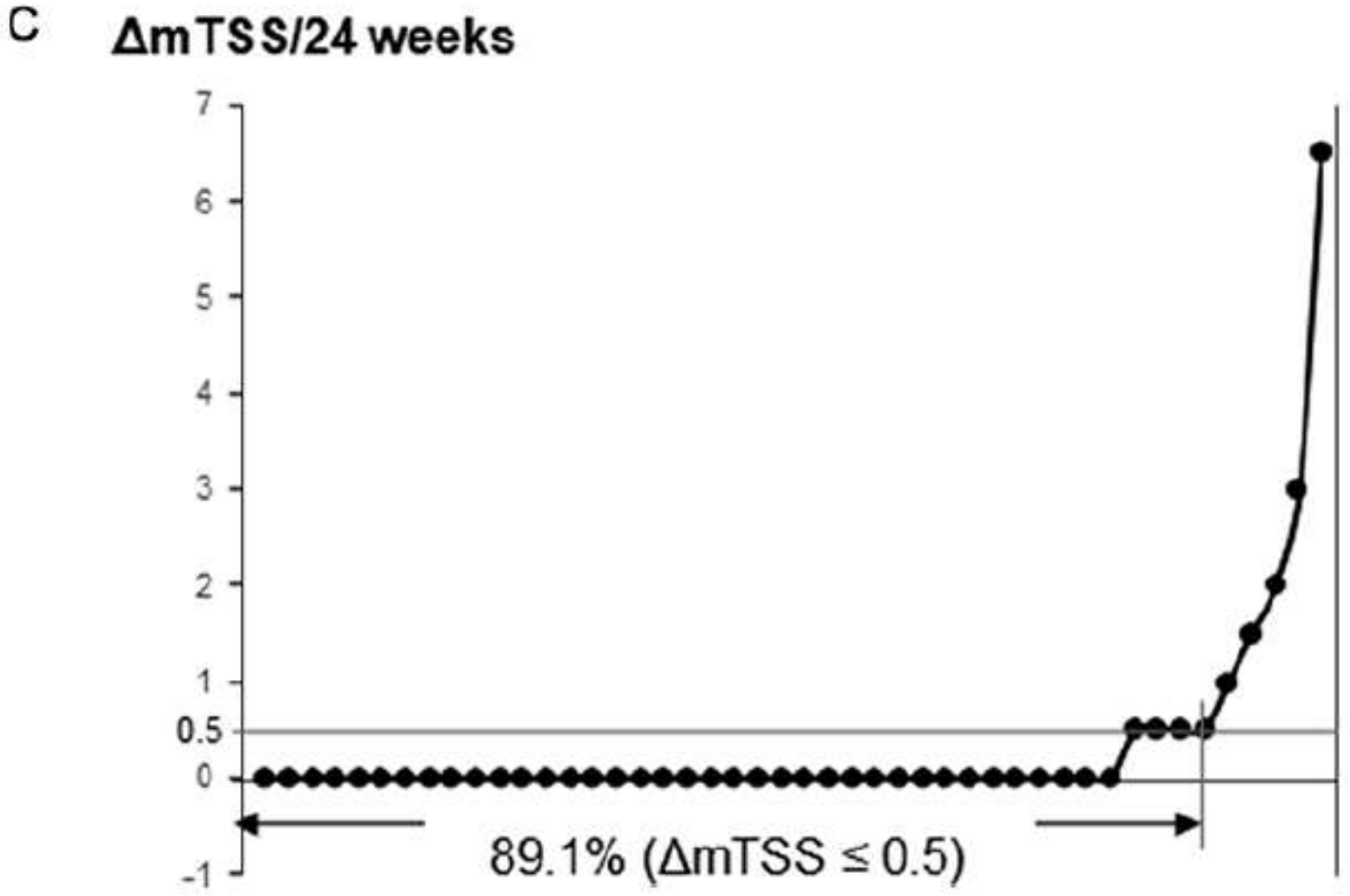


Figure 4

構造的評価



HCQを1度でも内服した60人の患者の安全性に関する結果

Table 2. Safety results of all 60 patients who received at least one dose of HCQ during 32 weeks.

All patients treated with HCQ ($n = 60$)				
The patients with ≥1 AEs or ≥1 SAEs, (%, 95% CI)	AEs (36), (60.0, 46.5–72.4)		SAEs (2), (3.3, 0.4–11.5)	
	No. of events	No. of patients (%, 95% CI)	No. of events	No. of patients (%, 95% CI)
Infections and infestations	21	15 (25.0, 14.7–37.9)	0	0
Bacterial pneumonia	3	2 (3.3, 0.4–11.5)	0	0
Herpes zoster	1	1 (1.7, 0.0–8.9)	0	0
Gastrointestinal disorders	12	11 (18.3, 9.5–30.4)	0	0
Diarrhoea	4[a]	4 (6.7, 1.8–16.2)	0	0
Musculoskeletal and connective tissue disorders	9	7 (11.7, 4.8–22.6)	0	0
Exacerbation of RA	2[a]	2 (3.3, 0.4–11.5)	0	0
Eye disorders	3	3 (5.0, 1.0–13.9)	1	1 (1.7, 0.0–8.9)
Cataract surgery	1	1 (1.7, 0.0–8.9)	1	1 (1.7, 0.0–8.9)
Skin and subcutaneous tissue disorders	3	2 (3.3, 0.4–11.5)	0	0
Drug eruption	2[a]	2 (3.3, 0.4–11.5)	0	0
Nervous system disorders	2	2 (3.3, 0.4–11.5)	1	1 (1.7, 0.0–8.9)
Cerebral haemorrhage	1	1 (1.7, 0.0–8.9)	1	1 (1.7, 0.0–8.9)
Tremor	1[a]	1 (1.7, 0.0–8.9)	0	0
Respiratory, thoracic, and mediastinal disorders	2	2 (3.3, 0.4–11.5)	0	0
Ear and labyrinth disorders	2	2 (3.3, 0.4–11.5)	0	0
Metabolic and nutritional disorders	2	2 (3.3, 0.4–11.5)	0	0
Renal and urinary disorders	1	1 (1.7, 0.0–8.9)	0	0
Blood and lymphatic system disorders	1	1 (1.7, 0.0–8.9)	0	0
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	1	1 (1.7, 0.0–8.9)	0	0

[a]Six patients withdrew during the 24-week period due to AEs ($N = 6$; diarrhoea in one patient, arthritis exacerbation in two patients, drug eruption in two patients, and tremor in one patient).

胃腸症状、皮疹など過去の報告と同様の結果。6例がAEのために脱落

HCQグループ患者のHCQ治療前後の血清サイトカイン濃度

Table 3. Serum cytokine levels at each time point in the propensity score–matched HCQ group.

Cytokine (pg/ml)	Week 0	Week 4	Week 8	Week 12	Week 24	8 Weeks after treatment with HCQ	*P* value, baseline vs. Week 24
GM-CSF	0 (0–0.14)	0 (0–0.14)	0.01 (0–0.13)	0 (0–0.13)	0.05 (0–0.15)	0 (0–0.07)	.355
IL-12/23p40	97.7 (80.6–127.9)	93.9 (75.9–141.9)	93.9 (73.8–149.3)	107.3 (75.1–162.6)	92.6 (66.1–138.6)	91.4 (70.3–135.4)	.97
IFN-γ	7.3 (3.6–16.2)	5.4 (2.8–10.9)	6.1 (3.0–10.1)	6.4 (2.7–13.3)	5.0 (2.6–8.0)	7.5 (3.4–12.5)	<.001
IL-1β	0.03 (0–0.08)	0.02 (0–0.05)	0.03 (0–0.05)	0.03 (0–0.07)	0.01 (0–0.04)	0.01 (0–0.04)	.013
IL-2	0.6 (0.1–1.6)	0.5 (0.08–1.8)	0.5 (0.1–2.0)	0.5 (0.15–1.7)	0.4 (0.1–1.1)	0.5 (0.05–1.4)	.299
IL-6	1.1 (0.5–4.2)	0.8 (0.4–3.2)	1.1 (0.4–4.0)	1.1 (0.4–2.0)	0.8 (0.3–2.0)	1.1 (0.5–2.4)	.018
IL-8	13.2 (8.5–23.3)	11.4 (7.1–17.9)	10.9 (8.0–24.0)	11.6 (7.6–16.6)	11.3 (7.2–16.8)	10.0 (6.7–16.0)	.253
IL-10	0.25 (0.20–0.36)	0.27 (0.14–0.32)	0.26 (0.18–0.38)	0.23 (0.17–0.37)	0.23 (0.16–0.32)	0.24 (0.15–0.37)	.258
IL-12p70	0.53 (0.13–1.92)	0.43 (0.14–1.80)	0.59 (0.19–1.80)	0.54 (0.16–1.67)	0.52 (0.14–1.85)	0.53 (0.13–1.86)	.013
TNF-α	1.2 (0.7–1.9)	1.2 (0.7–1.7)	1.3 (0.7–1.8)	1.1 (0.6–1.8)	1.1 (0.6–1.6)	1.1 (0.6–1.9)	.043

Values are presented as median (interquartile range). GM-CSF, granulocyte–macrophage colony-stimulating factor

IFNγ, IL-1b, IL-6, IL-12p70, TNFαがHCQ治療後に低下

HCQ stop

HCQグループ患者のHCQ治療前後のリンパ球サブセット変化

Table 4. Proportion of cell subsets at each time point analysed by flow cytometry in propensity score–matched HCQ group.

Cell subset (%)	Week 0	Week 4	Week 8	Week 12	Week 24	8 weeks after treatment with HCQ	*P* value, baseline vs. Week 24
$CD3^+$ T cells/ lymphocytes	62.8 (56.8–68.5)	62.8 (56.9–69.0)	60.6 (55.7–68.2)	61.6 (56.2–67.6)	63.8 (55.3–69.0)	61.5 (53.7–67.4)	.496
$CD4^+$ T cells/ lymphocytes	45.0 (38.7–47.5)	44.3 (40.0–48.2)	43.9 (38.6–47.3)	43.8 (39.3–47.1)	44.5 (38.2–48.1)	42.4 (38.5–45.9)	.48
$CD8^+$ T cells/ lymphocytes	13.6 (9.6–17.7)	13.3 (9.8–18.2)	12.2 (10.0–17.5)	12.9 (9.7–18.3)	11.2 (8.4–15.8)	12.1 (9.4–17.1)	.045
Treg/$CD4^+$ T cells	2.4 (1.7–4.7)	1.5 (0.8–2.6)	1.8 (1.1–2.7)	1.5 (0.9–2.3)	2.2 (1.2–3.6)	4.2 (2.2–5.2)	.107
Th1/$CD4^+$ T cells	9.9 (7.2–13.3)	10.3 (7.9–12.5)	11.2 (8.7–14.5)	10.5 (8.4–13.1)	9.8 (7.7–13.3)	9.7 (7.0–13.1)	.980
Th2/$CD4^+$ T cells	12.7 (9.5–19.0)	13.3 (10.3–19.0)	12.7 (8.8–17.6)	13.8 (10.6–19.0)	12.5 (8.4–19.3)	12.4 (8.4–17.9)	.552
Th17/$CD4^+$ T cells	15.7 (11.8–21.7)	16.8 (14.1–22.0)	15.1 (12.2–19.4)	16.3 (12.3–21.5)	15.2 (12.5–22.2)	14.8 (12.2–20.1)	.297
B cells/ lymphocytes	8.2 (6.3–10.9)	8.6 (5.6–12.6)	10.0 (6.3–13.5)	8.1 (5.7–12.9)	8.3 (6.3–11.9)	8.3 (6.5–12.6)	.843
Classical monocytes/$CD14^+$ monocytes	44.8 (36.2–56.4)	42.2 (29.6–55.1)	32.1 (13.2–47.3)	40.8 (26.2–53.8)	36.3 (29.2–48.0)	50.5 (40.0–59.0)	.032
Intermediate monocytes/$CD14^+$ monocytes	3.7 (2.1–8.1)	3.4 (2.1–6.8)	2.2 (1.6–4.8)	2.4 (1.2–4.6)	3.8 (2.0–5.5)	3.6 (2.3–6.9)	.204
Non-classical monocytes/$CD14^+$ monocytes	2.5 (1.0–3.4)	2.0 (1.0–3.5)	2.8 (1.1–5.9)	2.3 (0.9–4.2)	1.3 (1.0–3.3)	1.9 (1.2–3.2)	.152
NK cells/ lymphocytes	15.0 (11.5–18.8)	15.9 (10.7–21.3)	16.9 (12.5–23.7)	16.7 (13.7–22.3)	18.1 (11.2–25.4)	18.9 (13.0–23.3)	.002

Median (interquartile range). Treg, regulatory T cell; Th, helper T cell.

HCQ stop

CD8+ T cell、classical monocytesが低下、NK cellが上昇

Discussion

- HCQのRCTは存在し、有効性が証明されているが、近代的なcomposite measureで有効性を示したstudyは数えるほどしかない。
- HCQのACR20達成54.4%というのは、一般のbDMARDsのclinical trialでの40-80%、PMSの20-45%と比較すると、わるくない。
- 有害事象はこれまでの報告と変わりなかった。感染症のリスクを上げない。皮疹で中止が2例（3.3%）にあった。日本のSLEにおける皮疹の頻度はPMSでは4.97%で、重症例もあったことから、日本人は重症薬疹を起こしやすい可能性があり注意。
- 過去の報告ではIL-6低下はTregの上昇をきたし、X線進行抑制と関連する
- RAではNK細胞が滑膜組織に移行するために、末梢血では減るとして知られている。NK上昇は炎症の軽減を示すのかも。

Limitation

1. RCTではなく、sample sizeも少ない
2. HCQが盲検ではない。=> ESR (8.6mm/h)やCRP (0.18mg/dL)が改善しているという客観的所見はある（suppl Fig. 3）。
3. APC機能を評価していない。

suppl Fig. 3