Received: 18 August 2022 | Accepted: 5 January 2023

DOI: 10.1111/jdv.18870

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

LETTER TO THE EDITOR

Association between HLA-Cw6 and response to treatment with biologics in patients with psoriasis: A systematic review and meta-analysis

Dear Editor,

A proportion of patients treated with biologics for psoriasis do not respond to therapy.[1,2] Reason for lack of response includes among other clinical[3] and genetic factors[4] of which HLA-Cw6 is the most thoroughly investigated.[5] Several studies have shown an association between HLA-Cw6 and response to ustekinumab, but the magnitude of this association is unknown and smaller studies have shown conflicting results for interleukin-17 inhibitors and TNF-α inhibitors. Therefore, we conducted a systematic review and meta-analysis with the aim of determining the effect of HLA-Cw6 on the effectiveness of treatment with biologics of psoriasis.

Search terms were the individual biologic and HLA-Cw6. Data synthesis was conducted using StatsDirect. Proportion meta-analysis was performed to obtain pooled prevalence. Heterogeneity was assessed with Cochran's *Q*-test, using a significance level of 0.05, and I^2 statistic. Estimates were conducted using random effects model (Der Simonian and Laird). Publication bias was assessed with funnel plots and the Egger test.

Three thousand two hundred seventy records were screened, 57 were full-text screened for eligibility, and 36 were excluded. Twenty-one studies with 4295 patients were included. No publication bias was found.

Twelve studies assessed the association between HLA-Cw6 and IL-12/23 inhibitors (Table 1). The proportion of patients responding after 3 months, 6 months and 12 months was higher among the patients who were HLA-Cw6 positive compared with negative patients for all outcomes. The odds ratio of patients responding was significantly higher for HLA-Cw6-positive patients compared with negative patients for all outcomes (Figure 1).

Seven studies assessed the association between HLA-Cw6 and TNF-α inhibitors (Table 1). Similar proportion of HLA-Cw6-positive and HLA-Cw6-negative patients responding after 3, 6 and 12 months, when assessing response as PASI50 or PASI75, was observed. After 6 and 12 months, the proportion of patients responding was higher for patients who were HLA-Cw6-negative compared with HLA-Cw6-positive patients when assessing response as PASI90. After 12 months, HLA-Cw6-negative patients had significantly higher odds of response compared with positive patients when assessing response as PASI90 (Figure 1).

Four studies assessed the association between HLA-Cw6 and IL-17 inhibitors (Table 1). No association between HLA-Cw6 status and response to IL-17 inhibitors was observed (Figure 1).

One study assessed the association between HLA-Cw6 and response to IL-23p19 inhibitors. A higher proportion of patients who were HLA-Cw6 positive achieved PASI90 after 6 months compared with negative patients (Table 1).

We observed HLA-Cw6 to be associated with response to IL-12/23 inhibitors for all outcomes and time points, indicating HLA-Cw6 to be a biomarker of response. This association was observed in 10 out 12 of the studies, underlining the importance of HLA-Cw6 in regard to response to IL-12/23 inhibitors. HLA-Cw6 did not appear to be associated with response to IL-17 inhibitors. It is important that few studies have been conducted on IL-17 inhibitors and while we found no association, two of four studies on IL-17 inhibitors showed an association between HLA-Cw6 status and response. The results for TNF-α inhibitors were not unambiguous. A significant association between non-response to TNF-α inhibitors and HLA-Cw6 was observed after 12 months and assessing response as PASI90. At other timepoints and using other response criteria, no association among HLA-Cw6-positive patients was observed.

The study is subject to limitations. Differences in the time of assessment of treatment response across studies resulted in some studies not being included in some of the meta-analyses. Furthermore, criteria for selection of drug might differ across nations and populations.

This study highlights the association between HLA-Cw6 status and response to IL-12/23 inhibitors. Response to IL-17 inhibitors appears to be independent of HLA-Cw6 status. HLA-Cw6 might be a potential biomarker to identify patients for whom IL-12/23 inhibitors and TNF-α inhibitors might be beneficial although further studies comparing response and HLA-Cw6 status across treatments need to be conducted.

TABLE 1 All results Sorted by drug class, PASI and month. For each group, the number of studies, the number of patients, the number of HLA-Cw6-positive and HLA-Cw6-negative patients were recorded.

Response and evaluation month	Studies (*n*)	Patients (*n*)	HLA-Cw6-positive patients (*n*)	HLA-Cw6-negative patients (*n*)	HLA-Cw6-positive patient with response % (95% CI)	HLA-Cw6-negative patients with response % (95% CI)	OR (95% CI), *p*-value, I^2
IL-12/23 inhibitors							
PASI50							
3 months	5	935	406	529	75.6 (53.3–92.3)	60.8 (37.1–82.1)	2.60 (1.12–6.02), 0.03, 66.2%
6 months	3	844	368	476	94.8 (91.7–97.2)	72.2 (49.3–90.3)	5.29 (2.59–10.83), <0.0001, 33.5%
12 months	1	255	127	128	96.1[a]	85.2[a]	3.93[a]
PASI75							
3 months	11	1804	847	957	78.6 (72.0–84.5)	57.5 (50.0–64.8)	2.79 (2.13–3.65), <0.0001, 22.9%
6 months	9	1793	849	944	88.9 (83.0–93.7)	64.1 (53.9–73.7)	4.54 (2.53–8.14), <0.0001, 73.9%
12 months	7	1177	597	580	85.1 (78.4–90.7)	66.1 (57.5–74.1)	2.68 (1.73–4.15), <0.0001, 49.4%
PASI90							
3 months	8	1451	671	780	54.5 (43.4–65.4)	40.3 (27.6–53.6)	2.34 (1.51–3.61), 0.0001, 62.8%
6 months	5	1427	665	762	61.7 (51.7–71.2)	39.8 (29.1–51.1)	2.09 (1.68–2.6), <0.0001, 51%
12 months	5	885	446	439	72.7 (59.0–84.5)	53.3 (41.5–64.9)	2.22 (1.6–3.08), <0.0001, 17%
PASI100							
3 months	4	1281	617	664	25.7 (17.1–35.4)	15.2 (12.1–18.7)	1.90 (1.43–2.52), <0.0001, 0%
6 months	4	1361	657	704	34.9 (26.4–44.0)	23.6 (15.6–32.8)	1.72 (1.35–2.19), <0.0001, 0%
12 months	3	811	413	398	39.5 (25.2–54.8)	25.5 (20.7–30.6)	1.93 (1.3–2.87), 0.0011, 40.7%
TNF-α inhibitors							
PASI50							
3 months	2	238	95	143	80.6 (72.2–87.9)	76.2 (65.0–85.9)	1.32 (0.69–2.53), 0.4, 0%
6 months	2	238	95	143	73.5 (64.2–81.8)	72.4 (64.8–79.3)	1.06 (0.59–1.91), 0.84, 0%
12 months	1	122	46	76	69.6[a]	72.4[a]	0.87[a]
PASI75							
3 months	4	735	343	392	66.3 (58.6–73.6)	66.3 (61.4–70.8)	1.05 (0.77–1.44), 0.74, 0%
6 months	7	1192	687	505	76.9 (71.4–82.0)	67.4 (57.2–76.7)	1.32 (0.81–2.13), 0.09, 41%
12 months	2	636	317	319	69.0 (50.4–84.8)	71.4 (50.3–88.6)	0.82 (0.57–1.19), 0.3, 0%
PASI90							
3 months	3	564	264	300	58.8 (37.3–78.6)	60.4 (33.3–84.4)	1.12 (0.79–1.59), 0.51, 0%
6 months	2	708	367	341	44.9 (36.7–53.3)	56.4 (50.6–62.1)	0.68 (0.36–1.29), 0.24, 62.5%
12 months	3	677	329	348	45.6 (40.3–51.0)	55.5 (48.7–62.3)	0.69 (0.51–0.93), 0.02, 0%

TABLE 1 (Continued)

Response and evaluation month	Studies (*n*)	Patients (*n*)	HLA-Cw6-positive patients (*n*)	HLA-Cw6-negative patients (*n*)	HLA-Cw6-positive patient with response % (95% CI)	HLA-Cw6-negative patients with response % (95% CI)	OR (95% CI), *p*-value, I^2
PASI100							
3 months	1	401	206	195	21.8[a]	22.6[a]	0.96[a]
6 months	1	586	321	265	24.3[a]	36.2[a]	0.57[a]
12 months	1	514	271	243	25.5[a]	36.6[a]	0.59[a]
IL-17 inhibitors							
PASI50							
3 months	2	449	195	254	84.0 (36.7–99.1)	84.4 (41.9–99.7)	1.24 (0.48–3.24), 0.66, 0%
6 months	1	431	185	246	97.2[a]	96.4[a]	0.96[a]
PASI75							
3 months	3	502	228	274	86.1 (67.4–97.5)	81.9 (65.6–93.8)	1.44 (0.49–4.21), 0.51, 37.3%
6 months	2	485	218	267	92.3 (88.4–95.5)	87.1 (69.3–97.8)	1.71 (0.38–7.68), 0.49, 61.7%
12 months	1	50	31	19	88.3[a]	66.9[a]	3.27[a]
PASI90							
3 months	3	486	201	285	69.4 (36.7–93.8)	69.1 (44.4–89.1)	1.04 (0.69–1.57), 0.31, 0%
6 months	1	431	185	246	83.2[a]	81.3[a]	1.14[a]
12 months	1	37	6	31	100[a]	71.0[a]	0.41[a]
PASI100							
3 months	1	431	185	246	49.5[a]	43.9[a]	1.25[a]
6 months	1	431	185	246	62.2[a]	61.0[a]	1.04[a]
IL-23 inhibitors							
PASI90							
6 months	1	519	260	259	83.1[a]	76.8[a]	1.46[a]

Abbreviations: CI, confidence interval; HLA, human leucocyte antigen; IL, interleukin; OR, odds ratio; PASI, Psoriasis Area Severity Index; TNF, tumour necrosis factor.

[a]Not in meta-analysis.

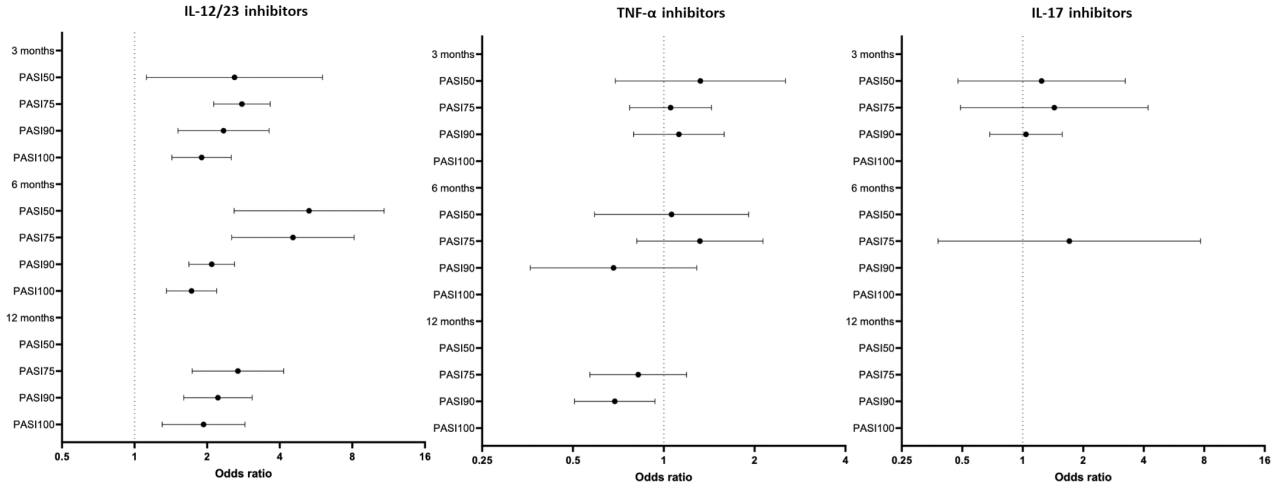

FIGURE 1 Odds ratio for Psoriasis Area Severity Index (PASI)50, PASI75, PASI90 and PASI100 at 3 months, 6 months and 12 months for interleukin (IL)-12/23 inhibitors, tumour necrosis factor (TNF)-α inhibitors and IL-17 inhibitors with 95% confidence interval.

FUNDING INFORMATION

Mie Siewertsen received research stipend from Herlev and Gentofte Hospital. The study is part of the PSOBIO initiative, which has received funding from the Aage Bang Foundation, Ebba Celinders Legat, the Danish Psoriasis Foundation, the Kong Christian X foundation, the LEO Foundation and the AP Møller foundation.

CONFLICT OF INTEREST

LS has received honoraria as a consultant and/or speaker from AbbVie, Pfizer, Janssen, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall, Bristol-Myers Squibb and Sanofi. She has served as an investigator for AbbVie, Sanofi, Janssen, Boehringer Ingelheim, Almirall, AstraZeneca, Eli Lilly, Novartis, Regeneron and LEO Pharma, and has received research grants from Novartis, Sanofi, Bristol-Myers Squibb, Janssen and LEO Pharma. CZ has received honoraria as a consultant and/or speaker from AbbVie, Janssen, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall and CSL. He has served as an investigator for AbbVie, Sanofi, Janssen, Boehringer Ingelheim, Almirall, AstraZeneca, Eli Lilly, Novartis, Regeneron, CSL and LEO Pharma. NL has been an honorary speaker for Eli Lilly and Janssen Cilag. MS, RS, HD and GA have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at ResearchGate at http://doi.org/10.13140/RG.2.2.27572.12163, reference number DOI: http://doi.org/10.13140/RG.2.2.27572.12163.

Mie Siewertsen[1,2]
Rownaq Al-Sofi[1,2]
Hajer Dridi[1,2]
Gayathri D. Ajenthen[1,2]
Claus Zachariae[1,2]
Lone Skov[1,2]
Nikolai Loft[1,2]

[1]*Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark*
[2]*Copenhagen Research Group for Inflammatory Skin, Herlev and Gentofte Hospital, Hellerup, Denmark*

Correspondence
Nikolai Loft, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark.
Email: nikolai.nguyen.loft@regionh.dk

ORCID

Mie Siewertsen https://orcid.org/0000-0002-8913-9644
Lone Skov https://orcid.org/0000-0002-4784-9680
Nikolai Loft https://orcid.org/0000-0002-2950-3280

REFERENCES

1. Loft N, Egeberg A, Rasmussen MK, Bryld LE, Nissen CV, Dam TN, et al. Prevalence and characterization of treatment-refractory psoriasis and super-responders to biologic treatment: a nationwide study. J Eur Acad Dermatology Venereol. 2022;36:1284–91. https://doi.org/10.1111/jdv.18126
2. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172:244–52.
3. Schwarz CW, Loft N, Rasmussen MK, Nissen CV, Dam TN, Ajgeiy KK, et al. Predictors of response to biologics in patients with moderate-to-severe psoriasis: a Danish Nationwide cohort study. Acta Derm Venereol. 2021;101:adv00579.
4. Loft ND, Skov L, Iversen L, Gniadecki R, Dam TN, Brandslund I, et al. Associations between functional polymorphisms and response to biological treatment in Danish patients with psoriasis. Pharmacogenomics J. 2018;18:494–500.
5. Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018;178:854–62.