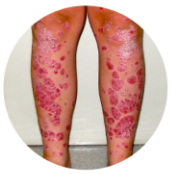
HLA polymorphism and methotrexate response in Slovenian patients with psoriasis

Jasna Grželj [1], Tanja Gmeiner [2], Pij B. Marko [3], Irena Mlinarič-Raščan [2], Sabina Kunilo Jamnik [4], Blanka Vidan-Jeras [4]



Facts about plaque psoriasis

- Systemic skin disease orchestrated by different immune cells.
- Affects approximately 2-3% of the world population [1].
- HLA-Cw*06:02 is the major susceptibility allele affecting disease onset, phenotype and severity.

Treatment

- Moderate to severe plaque psoriasis requires systemic treatment.
- Several biologics now available as second line treatment.
- Methotrexate still remains the gold standard, but is associated with a relatively low response rate and a high rate of adverse effects [1, 3].
- Limited data is available on metotrexate pharmacogenomics in psoriasis.

Aim of the study

- HLA-B and HLA-C genotypization in Slovenian psoriasis patients.
- Correlation of HLA-Cw*06:02 with the response to methotrexate treatment.

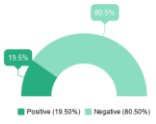
Methods

- Case control study including 131 patients with plaque psoriasis and 164 healthy controls. The study was approved by the National Ethics Committee (KME86/06/15).
- HLA-B and HLA-C typing performed using reverse sequence-specific oligonucleotide probe hybridization with PCR product (PCR-rSSO).
- Retrospective analysis of patient charts to identify response to methotrexate treatment.
- Statistical analysis using two-tailed Fischer exact test (in-house computer program).

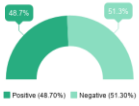
Results

HLA-C*06:02 status

- Reported frequency in Slovenian patient population in line with previously reported data [2].
- HLA-C*06:02 is significantly more common in patients as in controls ($p=7.00\times10^{-9}$).

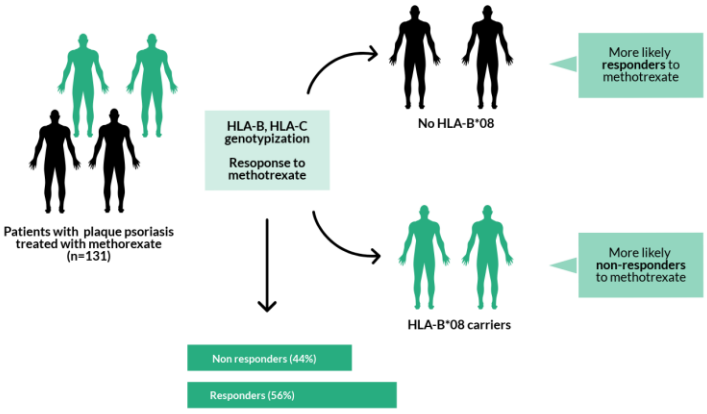


HLA-C*06:02 status - Controls



HLA-C*06:02 status - Patients

Correlation of HLA genotype and response to methotrexate



- No significant difference in C*06:02 frequency between responders and non-responders.
- C*06:02 more frequent in both patient groups compared to healthy controls ($p=2.01\times10^{-4}$ for responders and and $p=2.19\times10^{-8}$ for non-responders).
- **B*08 significantly less frequent in responders (4%) compared to non-responders (23%), $p=2.11\times10^{-4}$.**
- Although C*06:02 and B*08 are not in linkage disequilibrium, stratification by C*06:02 was performed. Consequently a lower number of patients was included, resulting in a lower significance for B*08 (p=0.09).

Conclusions

- HLA-B*08 could be used to predict response to methotrexate in psoriasis patients.
- Further investigation is required to confirm the effects of HLA on the response to methotrexate and to establish the predictive value of this finding.

References

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(3) Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. Clin Exp Dermatol. 2013;38(6):573-88

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Psoriasis is a systemic skin disease orchestrated by different immune cells such as T lymphocytes, dendritic cells and inflammatory cytokines. Despite the availability of several new systemic agents, methotrexate remains the gold standard for the treatment of moderate to severe psoriasis. The HLA-C*06:02 is a major susceptibility allele, which affects disease onset, clinical phenotype and severity of psoriasis. The frequency of this allele in patients varies from 10 to 77%, as reported in different populations. Despite the known role of C*06:02, little is known on its effect on methotrexate treatment. To our knowledge, two clinical studies so far reported a better response in patients carrying C*06. We examined the association between C*06:02 and response to methotrexate in a case-control study including 131 patients with plaque psoriasis and 164 healthy controls typed for HLA-B and C alleles. While 56% out of all patients responded to the treatment with methotrexate (RMTX), 44% were non-responders (NRMTX). Our own computer program based on two tailed Fisher exact test was used for statistical analysis. As expected, C*06:02 was significantly more frequent (f=49%) in patients with psoriasis compared to controls ($p=7.00\times10^{-9}$). Surprisingly, the same allele C*06:02 was overrepresented in both groups of patients NRMTX ($p=2{,}19\times10^{-8}$) and RMTX ($p=2.01\times10^{-4}$) compared to controls, respectively. However, no significant difference in HLA-C*06:02 frequencies was observed between RMTX and NRMTX. On the other hand, the B*08 was significantly less frequent in the RMTX than in NRMTX ($p=2.11\times10^{-3}$). Although C*06 and B*08 are not in linkage disequilibrium, we performed stratification by C*06:02, resulting in lower number of patients included in the analysis and the lower significance for B*08 (p=0.09). We conclude that further investigation is required to confirm the effects of HLA on the response to methotrexate and to establish the predictive value of this finding.