Single nucleotide polymorphisms in genes for IL-2, IL-6, and TNF-alfa influence on osteolysis and survival of total hip arthroplasty

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INTRODUCTION

Periprosthetic osteolysis (OL) is the major long-term complication of total hip arthroplasty (THA). The pathogenesis of OL is complex involving both biological and mechanical mechanisms. The former is orchestrated by cytokines (TNF-alfa, IL-1, M-CSF, RANKL, etc.) and chemokines (MCP-1, IL-8, etc.). However, substantial interindividual variability in OL severity and rate of failure has been found even in cases of comparable rates of wear and identical prostheses. The explanation for this may lie in genetic susceptibility to OL underlined by particular variants of the genes for key signal molecules/ pathways.

HYPOTHESIS

There is an association between the variants of cytokine genes and severity of periprosthetic OL leading to premature failure of THA.

PATIENTS AND METHODS

205 patients after THA and 150 healthy subjects without THA (genetic background). Case-control study (Fig.1): a candidate gene approach; 22 selected cytokine / cytokine receptor gene polymorphisms; genotyping by PCR- SSP; statistics for genetic association study.

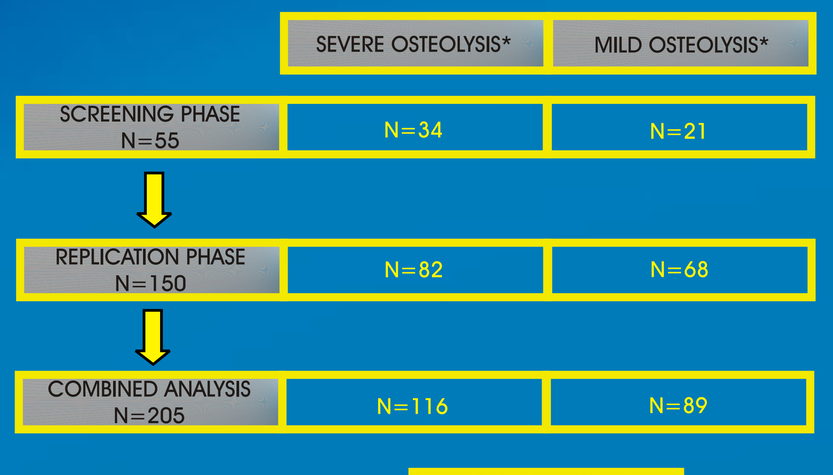

Fig. 1. Flow diagram showing design of the study.
**Severe (types III-V) and mild (I+II) osteolysis according to Saleh et al classification, J Bone Joint Surg Am, 83: 1040, 2001.*

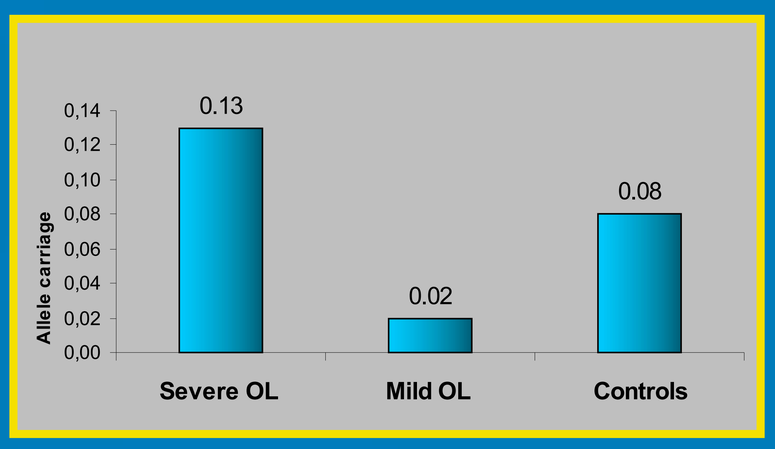

Fig. 2. TNF-238*A allele carriers in patients with severe / mild OL - combined analysis. OR (odds ratio) = 6.6, p = 0.005, PAR% (*population attributable risk percentage*) = 5.2. Controls - healthy subjects without THA.

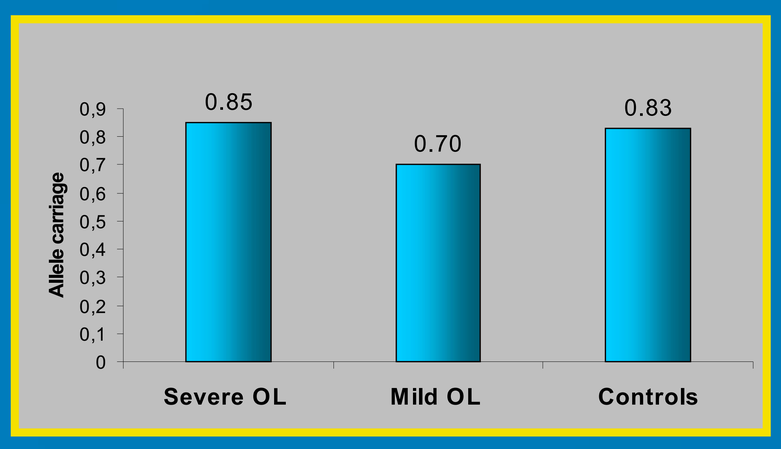

Fig. 3. IL-6-174*G allele carriers in patients with severe / mild OL - combined analysis. OR = 2.5, p = 0.007, PAR% = 31.5.

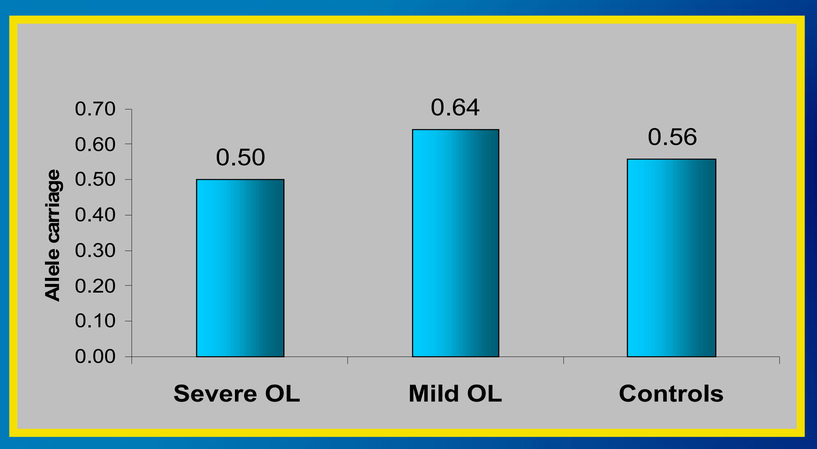

Fig. 4. IL-2-330*G allele carriers in patients with severe / mild OL - combined analysis. OR = 0.55, p = 0.043.

RESULTS

- The proportion of TNF-238*A and IL-6-174*G allele carriers was higher in patients with severe OL than in those with mild OL in both study phases and in combined analysis (Fig. 2, 3). By contrast, combined analysis revealed that the allele IL-2-330*G was protective from severe OL (Fig. 4).
- Carriage of TNF-238*A allele was associated with worse THA survival (Fig. 5). On the other hand, THA survived better in patients carrying IL-2-330*G allele (Fig. 6).
- Similarly, a risk for THA revision was higher in TNF-238*A allele carriers (p = 0.017) and decreased in patients carrying IL-2-330*G allele (p = 0.02).

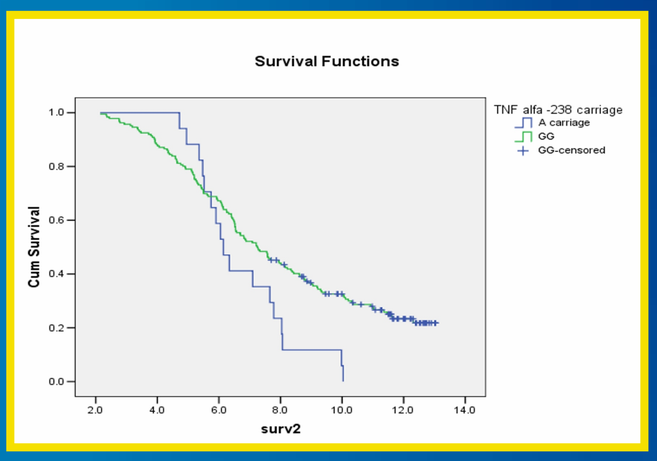

Fig. 5. THA survival among the carriers (blue curve) and non-carriers (green curve) of TNF-238*A allele (log rank test: p = 0.022).

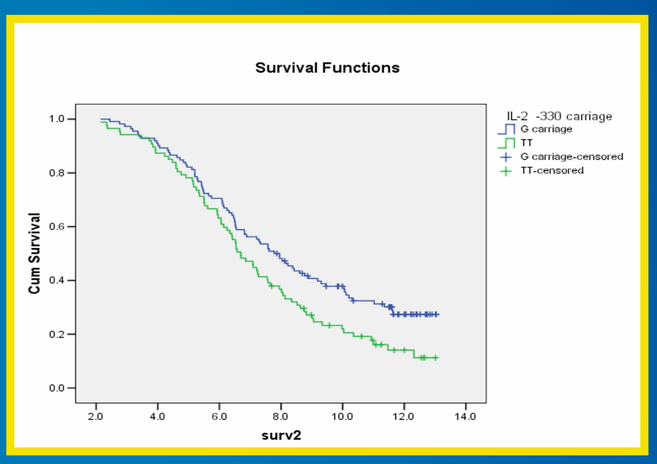

Fig. 6.THA survival among the carriers (blue curve) and non-carriers (green curve) of IL-2-330*G allele (log rank test: p = 0.018).

CONCLUSIONS

The alleles TNF-238*A and IL-6-174*G may predispose patients after THA to the development of severe periprosthetic OL.
By contrast, carriage of IL-2-330*G allele appeared to be protective from severe OL in our group of THA patients.
Furthermore, certain variants of cytokine genes were associated with worse (TNF-238*A) or better (IL-2-330*G) overall THA outcome (THA survival and risk for THA revision).

ACKNOWLEDGMENT
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