Polymorphisms in Fc gamma RIIIa (CD16) receptor expression are associated with clinical response to Rituximab in Waldenstrom's macroglobulinemia.

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Polymorphisms in position 158 of the Fc gammaRIIIa (CD16) receptor expression have been reported to modulate human immunoglobulin G1 binding, and antibody dependent cell mediated cytotoxicity (ADCC). Genetic dimorphisms at position 158 result in expression of either valine (V), or phenylalanine (F). Recently, Cartron et al (Blood 99:754, 2002) observed higher response rates to rituximab (an IgG1 chimeric antibody) in patients with untreated follicular non-Hodgkin's lymphoma (NHL) who were homozygous for V vs. carriers of F at this locus. In these studies, we used allele specific PCR analysis to determine position 158 polymorphisms for 58 patients with Waldenstrom's macroglobulinemia for whom clinical responses to rituximab therapy were known. PCR amplifications of exon 4, intron 4 and most of intron 5 were performed using primers which specifically amplified Fc gamma RIIIa but not Fc gamma RIIIb. Each end of the PCR product was then sequenced, and sequence information from exon 4 was used to provide genotype information for codon 158, while the sequence information from exon 5 end was used to confirm that the PCR product was specifically from the Fc gamma RIIIa gene. Of the 58 WM patients examined, 10/58 (17%) were homozygous for V (Fc gammaRIIIa-V/V); 26/58 (45%)were heterozygous (Fc gamma RIIIa-V/F); and 22/58 (38%) were homozygous for F (Fc gamma RIIIa-F/F). No significant differences in sex, age, baseline IgM levels, number of prior therapies, and number of rituximab infusions received was seen among the three allotype groups. The overall response rate (major, i.e. >50% decline in IgM and minor, i.e. >25% decline in IgM responses) for the three allotype groups were as follows: 6/10 (60%) Fc gamma RIIIa V/V; 13/26 (50%) Fc gamma RIIIa V/F; and 8/22 (36%) Fc gamma RIIIa F/F (V/V and V/F vs. F/F p=0.28). Comparison of major RR among the V carriers vs. F/F revealed even greater differences: 4/10 (40%) Fc gamma RIIIa V/V; 9/26 (35%) Fc gamma RIIIa V/F (13/36 for V carriers combined), and 2/22 (9.0%) for Fc gamma RIIIa F/F (V/V and V/F vs. F/F p=0.03). The results of these studies support an association between V carrier status and higher response rates (particularly for major responses) to rituximab among patients with Waldenstrom's macroglobulinemia.