IgG1 heavy chain-coding gene polymorphism (G1m allotypes) and development of antibodies-to-infliximab

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Introduction

The antibody response to infliximab (ATI) is associated with an increased risk of infusion reactions and reduced duration of therapeutic response [1]. Because ATI were not detected in all treated patients [1], we looked for factors that could influence infliximab immunogenicity. It probably results from the presence of murine variable domains within this chimaeric anti-TNF-α IgG1κ antibody (HACA, human anti-chimeric antibodies). However, there are also polymorphisms in the constant region of the immunoglobulin gamma chains likely contributing to the immunogenicity of recombinant antibodies. Such polymorphisms are defined as G1m and Km allotypes for human γ 1 heavy chain and κ light chain, respectively (Figure 1).

G1m allotypes	IGHG1 allele names	Amino acid positions[a]		
		CH1[b]	CH3[b]	
		120 (97) *214*	**12** (16) *356*	**14** (18) *358*
G1m1,17	IGHG1*01 IGHG1*02	Lys K a**a**a	Asp D gat	Leu L ctg
G1m3	IGHG1*03	Arg R a**g**a	Glu E gag	Met M atg

[a]Amino acid numbering in bold is according to IMGT unique numbering for C-DOMAIN [2], between parentheses: exon numbering and in italics: EU numbering.
[b]CH1 Lys 120 determines the G1m17 allotype, whereas CH3 Asp 12 and Leu 14 determine the G1m1 allotype (present on G1m1,17 γ 1 chains). CH1 Arg 120 determines the G1m3 allotype (present on G1m3 γ 1 chains). Nucleotides highlighted in bold in codon 120 are those characterized by the IGHG1 CH1 359g/a genotyping method used in this paper

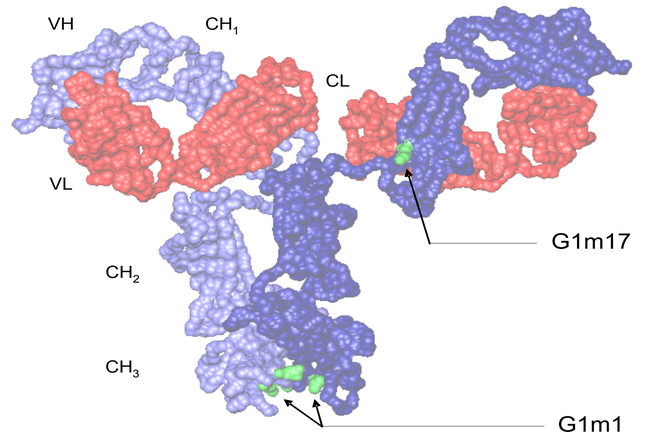

Figure 1: Nomenclature and localisation of G1m allotype system

Results

We determine infliximab allotype (Table 1) as G1m1,17 which are very rare in Caucasian population. We therefore hypothesized that patients homozygous for the G1m3 allotype, who are about 50% of the caucasian population, would have a greater risk to develop ATI due to the allotype incompatibility. We genotype treated patients for IGHG1CH1-359g/a allowing the determination of their γ 1 allotype and analyse these results with ATI production (Prometheus Lab, [1]) (Table 2).

Table 1: Serological G1m allotype determination of therapeutic antibodies by inhibition of hemagglutination

	HP 6027 anti-G1m3	HP 6184 anti-G1m1	HP 6189 anti-G1m17
Therapeutic antibodies			
alemtuzumab	-	+	+
basiliximab	+	-	-
cetuximab	+	-	-
daclizumab	-	+	+
infliximab	-	+	+
rituximab	-	+	+
trastuzumab	-	-	+
Controls			
IgG1m3	+	-	-
IgG1m1, 17	-	+	+

Table 2: IGHG1CH1-359g/a genotyping in 118 Crohn's disease patients treated with infliximab

Πατιεντσ	ΗΩΕ[α]	ΙΓΗΓ1 ΧΗ1– 359 γενοτψπε (Γ1μ πηενοτψπε)				Αλλελεσ φρεθυενχιεσ		
		g/g (3/3)	g/a (3/17)	a/a (17/17)	p[b]	g	a	p[b]
Blood donors (n=245)	NS[c]	127 (51.8%)	95 (38.8%)	23 (9.4%)	0,675	71.2%	28.8%	0,659
Crohn patients (n=118)	NS	60 (50.8%)	44 (37.3%)	14 (11.9%)		69.5%	30.5%	
ATI negative (n=45)	NS	25 (55.5%)	16 (35.5%)	4 (8.9%)	0,416	73.3%	26.7%	0,378
ATI positive (n=73)	NS	35 (47.9%)	28 (38.3%)	10 (13.7%)		67.1%	32.9%	
ATI < 8μγ/μΛ (ν=32)	ΝΣ	16 (50.0%)	12 (37.5%)	4 (12.5%)	0,744	68.8%	31.2%	0,725
ATI > 8 μγ/μΛ (ν=41)	ΝΣ	19 (46.3%)	16 (39%)	6 (14.6%)		65.9%	34.1%	

[a]Exact test for Hardy-Weinberg equilibrium, [b]exact test for populations differentiation, [c]non significant.

Conclusion

We could not be able to find any association between the presence of ATI or their concentrations and G1m allotypes. A first hypothesis to explain this lack of association could be the inability of the ATI double-antigen ELISA to detect anti-allotype antibodies [1]. However control sera containing high titers of anti-allotype antibodies gave positive results in our home-made ATI double-antigen ELISA (data not shown). Another explanation could be that allotypes are minor antigenic determinants when compared to the infliximab murine variable domains or to the idiotype itself which could dominate in the ATI humoral response. The impact of allotype immunogenicity relative to immunogenicity of variable domains could be different in the case of humanized or fully human antibodies. In tis respect, it has to be noted that trastuzumab has been engineered to an unnatural allotype (Table 1), most likely to prevent from any antibody response to the G1m allotype. Whether IGHG1 polymorphism a genetic factor influencing immunogenicity of humanized or fully human antibodies and other therapeutic antibodies therefore remain to be carefully studied.

References : [1] Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. 2003;348:601-8.
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