Genetic predictors of response to anti-tumor necrosis factor drugs in rheumatoid arthritis

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Abstract

The introduction of anti-tumor necrosis factor (anti-TNF) agents has dramatically improved the outlook for many patients with rheumatoid arthritis (RA). However, 30% of patients fail to respond to treatment for unknown reasons. While research has identified clinical markers of response, including baseline disease activity, disability and the concurrent use of disease modifying therapy, these account for only a small proportion of the variation in treatment response. A number of groups, therefore, have started to investigate genetic markers of response to anti-TNF therapies. To date, many of these studies have been small, underpowered and have largely been restricted to the analysis of candidate genes. The only replicated and validated genetic predictor of anti-TNF response is the 308G>A SNP in the TNF promoter region, but the amount of variation in response accounted for by this marker is modest. It is unknown whether variation in treatment response is determined by several genes each with a small effect size or small numbers of genes with large effect sizes but what is certain is the need for a non-hypothesis driven approach in order to identify further genetic markers of anti-TNF response. The identification of genetic predictors of response to anti-TNF therapies would enable clinicians to tailor treatment of these expensive and potentially harmful agents to patients most likely to benefit from them.

Introduction

The introduction of anti-tumor necrosis factor (TNF) drugs revolutionized the treatment of rheumatoid arthritis (RA) particularly for patients who showed little or no response to disease modifying anti-rheumatic drugs (DMARDs). There are currently three anti-TNF drugs licensed for treatment of RA in the UK. They are etanercept (Enbrel®), adalimumab (Humira®) and infliximab (Remicade®). Etanercept is a fusion protein of two p75 TNF receptors that are linked to the Fc component of the human immunoglobulin Ig-G1. It works by binding to soluble TNF and neutralizing it but can also bind lymphotoxin-α (LTA). Adalimumab and infliximab are monoclonal antibodies directed against membrane-bound and soluble TNFα.[1] Whilst DMARDs may slow radiological progression, studies using anti-TNF drugs have shown their superiority in suppressing structural change.[2] However, anti-TNFs are not without their drawbacks. As well as being expensive, studies have shown links with malignancy and serious infections.[3] Furthermore, for unknown reasons, up to 30% of patients fail to respond to treatment with anti-TNFs.[4] In many countries, these concerns limit the wholesale use of these drugs. In the UK, for example, the National Institute for Health and Clinical Excellence (NICE) advises that anti-TNF therapies can be prescribed for RA patients who:

- have a 28-joint count disease activity score (DAS28) of >5.1 on 2 occasions;
- have previously tried two DMARDs which have failed, one being methotrexate.[5]

These guidelines were developed based on the cost-benefit analysis but may mean that patients destined to require anti-TNF therapy experience undue delays in receiving treatment, with the consequent burden of sustained disease activity. If it were possible to identify those patients most, or indeed least, likely to respond to treatment, the altered cost-benefit ratio may allow better targeting of these expensive treatments.

Discussion

There are currently few clinical or biological predictors of response to anti-TNF drugs. Hyrich *et al.* conducted a large study investigating clinical predictors of response in patients receiving either etanercept or infliximab.[6] Patients were recruited from the British Society for Rheumatology (BSR) Biologics Register, an observational cohort study which aims to recruit and follow up 4,000 patients on each of the 3 currently licensed anti-TNF drugs. The study concluded that current use of NSAIDs and methotrexate improved response while poorer response was achieved in smokers and those with higher baseline disability scores.[6] Subsequently, Kristensen *et al.* confirmed that concomitant treatment with methotrexate improved response to anti-TNF therapies. They also concluded that gender was not a predictor of response, but disease activity and poor functional ability at baseline were.[7] However, these clinical factors only explained a minority of the variation in response to therapy.

With the disappointing results from studies investigating clinical factors, research is moving towards identifying other markers that may predict response to anti-TNF therapy. Positivity for either rheumatoid factor or anti-CCP antibody tests have been reported to be associated with a poorer response to therapy but, even combined with clinical predictors, only 17% in the variation of treatment response was explained in one study.[8]

A number of investigators have hypothesized that genetic variation may affect response to anti-TNF therapies. Support for this theory comes from studies of response to other drugs in which genetic variation has been shown to play an important role. For example, up to 50% of the variation in warfarin dose required between individuals can be explained by single nucleotide polymorphisms (SNPs) within 2 genes, cytochrome P450 C29 (*CYP2C9*) and *VKORC1*.[9]

A number of genetic studies have been undertaken using different study designs. In designing studies to investigate genetic predictors of response to anti-TNF therapies, there has been debate as to whether studies should investigate the anti-TNF agents individually or as a class. Evidence that infliximab is effective in Crohn's disease while etanercept and adalimumab are not fuels the argument that the different anti-TNFs work via different pathways.[10,11] Similarly, patients who have failed to respond to one anti-TNF drug may benefit from a second supporting the idea that response to each of the anti-TNF drugs should be analyzed separately. However, a large study showed that the reason for stopping the second anti-TNF was often the same as for the first, reinforcing the argument that anti-TNFs work in a similar manner and, therefore, that there may be a class effect in treatment response.[12] Table 1 lists the studies in which response to anti-TNF drugs has been analyzed as a class effect for a number of can-

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didate genes.

Many authors, however, have analyzed response to the anti-TNF drugs separately, as outlined in Tables 2-4, in order to reduce heterogeneity in the patient population. It should be noted that only one study to date has investigated polymorphisms associated with response to adalimumab therapy alone (Table 4). This most likely reflects the fact that this drug was the one most recently licensed and, therefore, there will be fewer patients receiving this therapy at the current time.

These studies raise a number of points for discussion. Firstly, the sample sizes included to date are small in comparison with those tested when investigating susceptibility genes. Plenge *et al.* highlighted in a recent review that to detect a SNP with an odds ratio (OR) of 3 (equivalent to the effect of the shared epitope) recruitment of several hundred participants would be required.[33] Therefore, investigation of SNPs with much smaller OR may require studies with thousands of participants to give statistical power to the results. It is not clear at the moment whether a small number of genes with large effect sizes or a large number of genes with small effect sizes will determine response to these therapies but, even so, the majority of reported studies have been underpowered to detect even large effects making it difficult to interpret statistically insignificant results. Where positive associations have been reported, there are few examples where the findings have been subsequently validated in independent cohorts. One notable exception is the TNF-308G>A SNP (rs1800629), association with which has been replicated in independent studies and been shown to be a weak predictor of anti-TNF treatment response. Previous functional studies have suggested that patients carrying -308 A allele express higher levels of TNF.[24,26,27]

Secondly, the response criteria vary between the different studies conducted. Some studies have used American College of Rheumatology

Table 1. Studies investigating association between genes and response to combinations of anti-TNFs. The table below summarises the studies to date investigating genes and response to anti-TNF therapies in which the studies did not separate the three anti-TNF drugs but investigated a class effect of treatment response.

Study	Anti-TNF	N. recruited	Response criteria	Genes investigated	Conclusion	Ref.
Toonen *et al.* 2008	Infliximab Adalimumab	234	DAS28	*TNFS1b*	Not significant	(13)
Seitz *et al.* 2007	Etanercept Infliximab Adalimumab	54	DAS28	*TNFA*	-308 GG associated with improved response	(14)
Fabris *et al.* 2002	Etanercept Infliximab	66	Not stated	*TNFR2*	+676 G allele associated with reduced response	(15)
Tutunca *et al.* 2005	Etanercept Infliximab Adalimumab	30	Physician decided according to criteria	Fc γ-receptor type IIIA	F/F genotype associated with improved response	(16)
Kastbom *et al.* 2007	Etanercept Infliximab	282	ACR20 ACR50 ACR70 DAS28	Fc γ-receptor type IIIA	No association found	(17)
Potter *et al.* 2008	Etanercept Infliximab Adalimumab	642	DAS28	Shared Epitope *PTPN22*	No association found	(8)

Table 2. Studies investigating predictors of etanercept response.

Study	N. recruited	Response criteria	Genes investigated	Conclusion	Ref.
Padyukov *et al.* 2003	123	ACR20 DAS28	*TNFA, IL10, TGFB1, IL1RN*	No allele significant on its own but a combination of TNF-308GG and TNF-1087GG improved response to etanercept ($p<0.05$) as did a combination of alleles at IL1RN and TGFB1($p<0.05$)	(18)
Kang *et al.* 2005	70	ACR20 ACR70	*TNFA* *LTA*	TNF-857 T alleles associated with better response	(9)
Schotte *et al.* 2005	50	EULAR	*IL10.R* *IL10.G*	IL10.R3 allele associated with improved response (OR 5.46, $p= 0.01$) while IL10-G13 allele associated with moderate or no response (OR 0.18, $p=0.01$)	(20)
Guis *et al.* 2007	86	DAS28	*TNFA*	TNF-308 GG associated with improved response	(21)
Criswell *et al.* 2004	457	ACR50	*HLA-DRB1* *TNF* *LTA* *TNFRSF1A* *TNFRSF1B* *FCGR3A* *FCGR3B*	Carriage of *0404 and *0101 shared epitope alleles associated with better response	(22)
Maxwell *et al.* 2008	455	DAS28	*TNF*	TNF-308AA associated with poor response	(23)

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Table 3. Studies investigating predictors of response to infliximab.

Study	N. recruited	Response criteria	Genes investigated	Conclusion	Ref.
Mugnier *et al.* 2003	59	DAS28	*TNFA*	TNF-308 GG associated with improved response	(24)
Martinez *et al.* 2004	78	DAS28	*HLA* *MICA* *TNF* *BAT2*	TNFa11;b4 minihaplotype and D6S273_4/BAT2_2 haplotype associated with improved response.	(25)
Cuchacovich *et al.* 2004	20	ACR20 ACR50	*TNFA*	TNF-308 G>A associated with improved response	(26)
Balog *et al.* 2004	9	DAS28	*TNFA*	Carriage of A allele at TNF-308 associated with decreased response	(27)
Marotte *et al.* 2008	198	ACR20 DAS28	*HLA* *IL1B* *IL1RN* *TNFA*	No association found	(28)
Fonseca et al. 2005	22	DAS28	*TNFA*	TNF-308 GG associated with improved response	(29)
Tolusso *et al.* 2006	49	DAS28	*IL1B* *IL1RN*	Non-responders have higher IL1RN*3 frequency	(30)
Chatzikyriakidou *et al.* 2007	58	DAS28	*TNFR1* *TNFR2* TNFA	No allele significant alone but a combination of TNFR2 TNFR2 676T>G with either TNFA -857C>T or 489 G>A (which are in LD with one another) was associated with improved response	(31)
Maxwell *et al.* 2008	450	DAS28	*TNF*	TNF-308AA associated with poorer response	(23)

Table 4. Study investigating predictors of response to adalimumab.

Study	N. recruited	Response criteria	Genes investigated	Conclusion	Ref.
Cuchacovich *et al.* 2006	70	ACR20DAS28	*TNFA*	TNF-308 GG associated with improved response	(32)

(ACR) response criteria while others have used DAS 28 (Tables 1-4).[13,20,21,23] Although previous work has validated the sensitivity and specificity of these measures, they are somewhat subjective and potentially open to manipulation. For example, it has been shown that the DAS28 is greatly influenced by the tender joint count, which is a very subjective measure.[34] Hence, it may be argued that more objective measures of response, such as the percentage improvement in the erythrocyte sedimentation rate (ESR) or C- reactive protein (CRP) may be more robust.

Thirdly, the different studies have taken different approaches when trying to account for baseline co-variables. Smoking, baseline DAS28, age, concurrent DMARD therapy and disability [as measured by the health assessment questionnaire (HAQ)] influence absolute change in DAS28 but not all studies have adjusted for these potential confounders. This leads to difficulties when trying to conduct a meta-analysis incorporating all available data.

Finally, all of these pharmacogenetic studies have investigated SNPs that map to obvious RA candidate genes such as the *TNF*α gene. However, as has been demonstrated by genome wide association (GWA) studies of RA susceptibility, associated variants often map to loci that had not previously been identified as important in the pathogenesis of RA.[35] This highlights the need for a hypothesis-free approach to pharmacogenetics. At the moment, the availability of large, well-phenotyped cohorts of anti-TNF treated patients and suitable resources for undertaking GWA studies limit progress in this field. However, initiatives to bring together researchers in order to pool resources and samples are underway. Such national and international collaboration will be necessary to advance this clinically important research. Ultimately, the identification of predictors of response, whether they are genetic or otherwise, has the potential to make an enormous impact on clinical practice by helping physicians to target the right therapies to the right patients.

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