# Predicting response to anti-TNF agents for the treatment of Crohn's disease

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***Abstract*:** The arrival of anti-tumor necrosis factor (TNF) agents has led to a dramatic improvement in the care of patients with Crohn's disease. Since these medications do not work in everyone, and are associated with rare, but serious side effects, we want to selectively treat patients who have the highest chance of responding. A number of variables have been studied to determine their association with response to anti-TNF agents. Clinical parameters include patient characteristics, smoking status and disease phenotype, and biologic markers include C-reactive protein, serum TNF levels and immune responses to microbial antigens. More recently, research has focused on genetics to identify polymorphisms associated with treatment response. Results from individual studies of these factors have not yet allowed for solid clinical applicability. However, further work in this area along with multivariate clinical prediction modeling may soon allow us to deliver 'personalized medicine' by predicting individualized treatment response in patients with Crohn's disease.

## Introduction

Over the past ten years there have been remarkable strides for the treatment of patients with Crohn's disease. Specifically, the Food and Drug Administration (FDA) approval of infliximab in 1998, and more recently adalimumab in 2005 and certolizumab pegol in 2008 have led to a better quality of life in many patients with Crohn's disease. The mechanism of action of these anti-tumor necrosis factor (TNF) agents is likely multi factorial. The antibody may bind and clear soluble TNF, and also bind to cell-bound TNF that can induce apoptosis of cells expressing membrane TNF. Despite different formulations and some difference in mechanism of action (certolizumab pegol does not appear to induce apoptosis as do infliximab and adalimumab), the efficacy of these three medications appears to be remarkably similar. Across agents, in the pivotal clinical trials for Crohn's disease the initial response rate was approximately 60%, with about 30% of these responders maintaining remission out to one year [Hanauer *et al*. 2002; Colombel *et al*. 2007; Schreiber *et al*. 2007a].

Although those who do respond can enjoy a dramatic improvement in their disease status, there are still many patients who respond sub optimally or not at all. This may be due to the fact that they do not have active inflammatory Crohn's disease (e.g., they have fibrotic disease or irritable bowel syndrome), have received suboptimal dosing, or that the mechanism of their disease is less dependent on TNF and therefore is less responsive to anti-TNF agents. Since these medications have multiple reported potential side effects, the benefit to risk ratio is narrow [Siegel *et al*. 2006]. Therefore, to optimize this ratio we want to use these medications in those who have the highest chance of responding. Recently, there have been exciting developments in finding factors that can help predict who is more likely to respond to anti-TNF agents. We hope that in the near future this will allow us to be more elegant in targeted patient selection.

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## Factors contributing to predicting a response to anti-TNF agents

### *Clinical parameters*

There have been a number of individual patient characteristics evaluated for an association with a response to anti-TNF agents. Disease duration has been evaluated with the hypothesis that patients with shorter disease duration will have a better response to early treatment. This was demonstrated in *post-hoc* analyses from large

clinical trials where those with a disease duration shorter than two years had a higher chance of responding to anti-TNFs than those with more long-standing disease [Sandborn *et al.* 2006; Schreiber *et al.* 2007b]. This was also demonstrated in pediatric populations [Lionetti *et al.* 2003], and the significantly higher response rates in the REACH trial of infliximab in children [Hyams *et al.* 2007] (as compared to adult response rates) may also be a result of earlier intervention or a younger age of treatment [Vermeire *et al.* 2002a]. There was no association seen in other studies evaluating disease duration and age [Parsi *et al.* 2002; Arnott *et al.* 2003; Fefferman *et al.* 2004]. New treatment algorithms suggest that early combination anti-TNF and immunomodulator therapy will yield better outcomes than waiting until immunomodulator monotherapy failure [D'haens *et al.* 2008]. With some conflicting results, it is still not clear if patients with a shorter duration of disease will have a more favorable response to anti-TNFs. Intuitively though, treating patients earlier when inflammatory disease predominates over fibrosis is appealing.

Disease phenotype may offer some predictive value in who will respond to anti-TNF medications. Patients with isolated Crohn's colitis may respond better [Vermeire *et al.* 2002a; Arnott *et al.* 2003], and those with intestinal strictures and prior surgery have been shown to have a lower response rate [Vermeire *et al.* 2002a; Weinberg *et al.* 2002]. Others have not found an association between phenotype and response [Parsi *et al.* 2002; Orlando *et al.* 2005], which may be due to a true lack of an association, underpowered evaluations or different study designs.

Smoking is known to negatively influence disease course, and patients who are smokers have been shown to have lower response rates than nonsmoking Crohn's patients. Parsi *et al.* assessed 100 patients with Crohn's disease [Parsi *et al.* 2002]. They were evaluated based on smoking status and the presence of either inflammatory or fistulizing disease. Smokers (>5 cigarettes per day for >6 months) with inflammatory disease were less likely to respond to infliximab [OR = 0.09 (0.02–0.38)], but this was not seen in those with fistulizing disease. Another study also found a negative association with smoking, with a 1 year relapse rate after receiving infliximab of 100% in smokers compared to 40% in nonsmokers ($p = 0.0026$) [Arnott *et al.* 2003]! Others did not find the same relationship [Vermeire *et al.* 2002a; Fefferman *et al.* 2004; Orlando *et al.* 2005]. Encouraging Crohn's disease patients to stop smoking is always a good idea, but based on these data the role of smoking as a predictor of response in Crohn's disease is unclear. Table 1 summarizes these results, in addition to data regarding biochemical, serologic and genetic markers associated with anti-TNF response.

### Biologic markers

Biologic markers such as cytokine levels, C-reactive protein (CRP) and anti microbial antigens have been studied. In a small study of 36 patients with fistulizing Crohn's disease, TNF, IL-1$\beta$ and IL-6 levels were measured before and after treatment with infliximab. In this 10 week study, patients who did not respond to infliximab had higher baseline TNF levels [Martinez-Borra *et al.* 2002]. A larger study of 226 patients did not find a relationship between treatment response and TNF levels [Louis *et al.* 2002]. In this same study, elevated CRP levels were shown to predict response to infliximab [(76% of patients with a baseline CRP >5 mg/L responded to infliximab compared to only 46% of normal CRP patients ($p = 0.004$)]. This was also observed in an early study of certolizumab pegol where patients with an elevated CRP responded more effectively to anti-TNF agents than those with lower baseline levels [Schreiber *et al.* 2005]. Whether an elevated CRP is truly predictive of response to anti-TNF or simply a marker that symptoms are truly due to active inflammatory disease remain to be proven.

There has been enthusiasm to study antineutrophil cytoplasmic antibody (ANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) as predictors of response to anti-TNFs. In a study of 269 Crohn's disease patients, using a combination of a positive perinuclear (*p*)ANCA and a negative ASCA there was a nonstatistically significant trend ($p = 0.067$) towards prediction of a negative response to infliximab [Esters *et al.* 2002]. Another study did show a statistically significant association between speckled ANCA (sANCA) and a better anti-TNF response when compared to patients with other ANCA staining patterns [pANCA or cytoplasmic (cANCA)] ($p = 0.003$ at 4 weeks) [Taylor *et al.* 2001]. In ulcerative colitis these markers may also be helpful, with a poorer infliximab response in patients with a positive *p*ANCA and negative

ASCA [Ferrante *et al.* 2007]. Although these data suggest that a positive *p*ANCA and negative ASCA could predict nonresponse to anti-TNF, we have not yet seen data convincing enough to use this routinely in clinical practice.

### *Genetics*

With the rapid progression of the understanding of the association of genetics and Crohn's disease, searching for genetic markers to predict response to therapy is appealing.

Results have thus far been mixed, but there is promise for future clinical utility. TNF-$\alpha$ gene polymorphisms have been a focus of work on this topic. Taylor *et al.* showed that patients homozygous for a TNF-$\alpha$ polymorphism (LTA NcoI-TNFc-aa13L-aa26 1-1-1-1 haplotype) were not responsive to infliximab [Taylor *et al.* 2001] and Pierik and colleagues saw a lower response to infliximab in patients TNFR-1 + 36 [Pierik *et al.* 2004]. Subsequent studies have not corroborated the relationship between TNF gene polymorphisms and impaired infliximab response in Crohn's patients [Mascheretti *et al.* 2002b; Louis *et al.* 2004]. Based on the association of the NOD2 gene and Crohn's disease efforts have been made to identify a relationship between NOD2 response to anti-TNFs. Thus far, a relationship has not been established [Mascheretti *et al.* 2002a; Vermeire *et al.* 2002b]. However, the IBD5 gene (5q31) is associated with a negative response to infliximab [Urcelay *et al.* 2005] and the IgG Fc receptor IIIa (Fc$\gamma$RIIIa) gene (V or F, expressed on macrophages and natural killer cells and triggers cell activation of cytotoxic immune cells) showed an increased response, with homozygous V/V patients having a 100% biologic response compared to 70% of others [Louis *et al.* 2004].

Some very interesting work from Belgium focuses on polymorphisms in apoptosis genes to predict response to infliximab (as above, both infliximab and adalimumab have been shown to induce cellular apoptosis) [Hlavaty *et al.* 2005]. They developed an apoptosis pharmacogenetic index (API) based on three single nucleotide polypmorphisms (SNPs): Fas ligand-843 C/T; Fas-670 G/A; Caspase9 93 C/T [Hlavaty *et al.* 2007]. Points were given for an individual patients' profile to calculate their API ranging from 0–3. Clear differences were seen with higher API scores leading to improved response and remission rates in both luminal ($p = 0.005$, response, $p = 0.02$, remission) and fistulizing ($p = 0.054$, response; remission, $p = 0.045$) disease. Subsequently, they used these results in

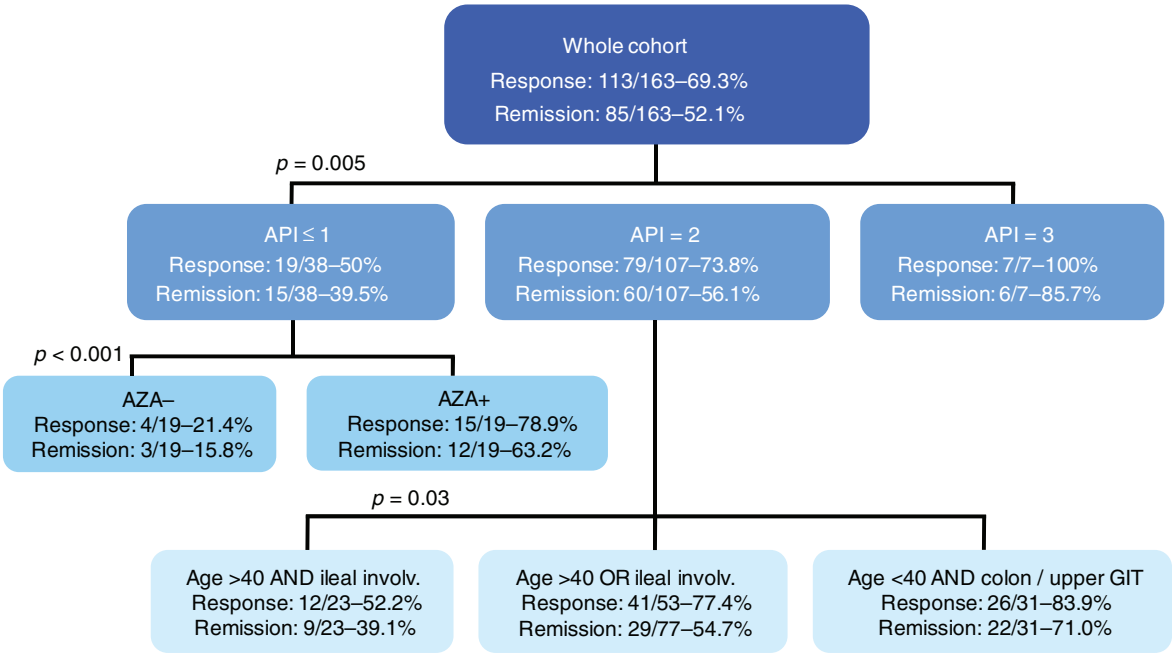


**Figure 1.** Proposed treatment algorithm for luminal Crohn's disease based on the apoptosis pharmacogenetic index [Hlavaty *et al.* 2007]. Reproduced with permission from Wiley Interscience. API, apoptosis pharmacogenetic index; AZA, azathioprine; GIT, gastrointestinal tract.

**Table 1.** Summary of studies investigating factors predicting infliximab response.

| | Parameter | Study author (cohort size) | Association in terms of response to infliximab |
|---|---|---|---|
| Clinical/patient characteristics | Duration of disease | Lionetti *et al.* [Lionetti *et al.* 2003] (22 paediatric) | Positive association with short disease duration |
| | | Parsi *et al.* [Parsi *et al.* 2002] (100) | No association |
| | | Arnott *et al.* [Arnott *et al.* 2003] (74) | No association |
| | | Fefferman *et al.* (200) | No association |
| | Young age | Vermeire *et al.* [Vermeire *et al.* 2002a] (240) | Positive association |
| | | Orlando *et al.* [Orlando *et al.* 2005] (573) | No association |
| | | Fefferman *et al.* (200) | No association |
| | Disease site | Arnott *et al.* [Arnott *et al.* 2003] (74) | Positive association with colonic disease |
| | | Vermeire *et al.* [Vermeire *et al.* 2002a] (240) | Positive association with isolated colitis and negative with isolated ileitis |
| | | Parsi *et al.* [Parsi *et al.* 2002] (100) | No association |
| | | Orlando *et al.* [Orlando *et al.* 2005] (573) | No association |
| | Intestinal stricture | Weinberg *et al.* [Weinberg *et al.* 2002] (127) | Negative association |
| | Previous surgery | Vermeire *et al.* [Vermeire *et al.* 2002a] (240) | Negative association |
| | | Arnott *et al.* [Arnott *et al.* 2003] (74) | No association |
| | | Orlando *et al.* [Orlando *et al.* 2005] (573) | Negative association |
| | Smoking | Parsi *et al.* [Parsi *et al.* 2002] (100) | Negative impact on response rate and duration |
| | | Arnott *et al.* [Arnott *et al.* 2003] (74) | Negative association |
| | | Vermeire *et al.* [Vermeire *et al.* 2002a] (240) | No association |
| | | Orlando *et al.* [Orlando *et al.* 2005] (573) | No association |
| | | Fefferman *et al.* (200) | No association |
| Biochemical and immunological parameters | C-reactive protein | Louis *et al.* [Louis *et al.* 2002] (153) | Positive association |
| | pANCA/ASCA/sANCA | Esters *et al.* [Esters *et al.* 2002] (279) | No association (+pANCA, −ASCA: trend towards negative response, $p = 0.07$) |
| | | Taylor *et al.* [Taylor *et al.* 2001] (59) | sANCA positive association |
| | | Arnott *et al.* [Arnott *et al.* 2003] (74) | No association |
| Pharmacogenomics | TNF and TNFR polymorphism | Mascheretti *et al.* [Mascheretti *et al.* 2002b] (90/444) | No association |
| | | Pierik *et al.* [Pierik *et al.* 2004] (166) | No association |
| | NOD2 | Mascheretti *et al.* [Mascheretti *et al.* 2002a] (534) | No association |
| | | Vermeire *et al.* [Vermeire *et al.* 2002b] (245) | No association |
| | IBD5 (5q31) | Urcelay *et al.* [Urcelay *et al.* 2005] | Negative association |
| | Fc$\gamma$RIIIa genotype | Louis *et al.* [Louis *et al.* 2004] (200) | Positive (V/V genotype) association |
| | Apoptosis genes (Fas ligand–843CC/CT, caspase-9 93 TT) | Hlavaty *et al.* [Hlavaty *et al.* 2005] (247) | Positive association |
| | Apoptosis genes (Fas ligand–843 TT) | Hlavaty *et al.* [Hlavaty *et al.* 2007] (247) | Negative association (overcome by 6MP/AZA) |

Adapted from Chaudhary and Ghosh (2005) [Chaudhary *et al.* 2005] and reproduced with permission from Elsevier.
pANCA, peri-nuclear anti-neutrophil cytoplasmic antibody; ASCA, anti-Saccharomyces cerevisiae antibody; sANCA, speckled anti-neutrophil cytoplasmic antibody; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; IBD, inflammatory bowel disease; 6MP, 6-mercaptopurine; AZA, azathioprine.

combination with clinical parameters to develop an algorithmic predictive model for response to infliximab (Figure 1). Although this was a relatively small retrospective study, promising ideas come from this approach. For example, for patients in the API = 3 group, it may not be necessary to consider use of concomitant immunomodulators as the response rate to infliximab is already so high. In contrast, in the API $\leq 1$ group, patients taking concomitant azathioprine had a 63.2% rate of remission compared to a 15.8% remission rate with infliximab monotherapy.

### *Imaging*

The understanding of apoptosis as a mechanism of action of infliximab has also led to other techniques for predicting response. Van den Brande and colleagues used (99m)Technetium-annexin V single-photon emission computer tomography (SPECT) for real-time visualization of apoptosis in patients with Crohn's disease [Van Den Brande *et al.* 2007]. Increase in uptake could be measured within 24 hours of an infliximab infusion, and those with higher uptake values of technetium had higher response rates compared to nonresponders ($p = 0.03$). This novel approach to quickly determine likelihood of future response can help in both decreasing unnecessary drug exposure and saving costs.

## Modeling complex factors

Making decisions on who should be treated with anti-TNF agents has typically been left up to clinical judgment and an attempt to assimilate all of the above complex data into a gestalt of which patients need these medications. As more information become available and further predictive factors are discovered, help from computer modeling can assist in making good decisions, and just as importantly, clearly communicating our reasoning to patients. System dynamics analysis (SDA) is a methodology that addresses complex interactions and predicts outcomes based on available data and the consequences associated with expected and unexpected associations. This technique, primarily used in fields other than medicine, has the advantage over traditional multiple logistic regression is in its ability to incorporate the inherent dynamic complexity of interactions and graphically convey the outcomes. SDA is being used in Crohn's disease to provide individualized prediction of outcomes of disease and treatment [Siegel *et al.* 2009]. Ultimately, this model, using many of the variables above to developed simple output graphs will be able to be used at the bedside to demonstrate to patients their predicted course of disease severity and how this can be altered with biologic therapy. This is a first step in taking complicated (and oftentimes conflicting) statistical results and helping patients understand how their disease and treatment may affect them over time.

## Conclusion

The anti-TNF agents are the first of what we expect to be many in the class of biologic agents. In addition to natalizumab, an alpha-4-integrin molecule that was approved for Crohn's disease in 2008, multiple others are currently in clinical trials. The above early work with anti-TNFs gives us a vision of the future of 'personalized medicine' that we can strive for over the next few years. These agents work, but not in everyone. To limit toxicity, save cost and more precisely deliver effective treatment, the future of this line of research is critical.

## Conflict of interest statement

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