

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Reversal of Immunogenicity in Inflammatory Bowel Disease



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### **G&H** Why does immunogenicity occur in patients with inflammatory bowel disease?

**SB-H** This is a complex issue. Immunogenicity refers to the propensity of biologic drugs to elicit immune reactions against them in the recipient. Essentially, most protein drugs administered for inflammatory bowel disease (IBD) or for other disorders are considered by the immune system to be foreign bodies or nonself proteins, even when the proteins are fully humanized. The way that the human immune system is constructed, any foreign or nonself proteins are treated as potential threats and elicit reactions against them by an array of antibodies (also known as antidrug antibodies). However, some proteins are more immunogenic, or considered to be more nonself, than other proteins.

### **G&H** Which patient, product, and prescribing factors have been associated with immunogenicity?

**SB-H** Little is known about the impact of patient factors on immunogenicity because there has not been a very well-documented examination of which characteristics of an individual patient will induce immunogenicity. A few studies have examined the genetic background of patients, but most of the research involving anti-tumor necrosis factor agents has not shown an association between specific genetic backgrounds and immunogenicity. A small study on human leukocyte antigen (HLA), which differs in each person, did suggest that 1 HLA gene set was associated with a greater likelihood of developing antibodies to infliximab (Remicade, Janssen); however, these findings have not been reproduced.

In terms of product factors, chimeric biologic agents (ie, agents that are composed of both a mouse-derived part and a human-derived part) are known to be more immunogenic than biologic agents that are fully humanized. However, even agents that are fully humanized (ie, completely composed of human sequences of the protein) are still immunogenic to a certain extent. Another product factor that impacts immunogenicity is glycosylation; every protein has attached glucose or glycosylated chains, which cause immunogenicity. A further parameter is the tendency of proteins to aggregate, whether in the body or before they are administered, so instead of 1 molecule, 2 or 3 molecules are attached together. Aggregation activates and enhances the immune system's recognition of the protein and its reaction against it.

The 2 main prescribing factors that impact immunogenicity are the scheduling of therapy and the use of concomitant medications. Administering a drug on a set schedule for maintenance therapy is associated with less immunogenicity than episodic treatment (ie, administering the drug once or twice, stopping for some time, and then administering another episode of treatment). Episodic treatment tends to boost the immune system further. In addition, concomitant use of immunomodulators such as azathioprine or methotrexate reduces immunogenicity of a biologic agent.

### **G&H** How do the immunogenicity rates of different biologic agents compare?

**SB-H** Although all biologic agents induce immunogenicity, they appear to do so at different rates. However, it is not clear how much of the difference in rates can be attributed to how immunogenicity is assessed in

different studies. There has not been a good head-to-head comparison of biologic agents using the same methodology in terms of sampling times. Sampling once or twice compared to long-term sampling (eg, for 52 weeks) may show a lower rate of immunogenicity. In addition, there has not been a good head-to-head comparison using the same assays. Different assays with different techniques may vary in their sensitivity to detect antibodies. Finally, findings may slightly differ in different patient populations (eg, patients with rheumatoid arthritis vs patients with IBD).

### **G&H** Can adding an immunomodulator reverse immunogenicity in patients with IBD?

**SB-H** There has only been a little research on this issue, so caution is advised when evaluating it. My colleagues and I published our first experience in this area in 2013. A group of 5 patients had lost clinical response to infliximab with no drug levels and high antibody levels. However, there were no other biologic treatment options for these patients, so we tried adding an immunomodulator to their therapeutic regimen. In all 5 patients, this addition slowly eliminated antibodies to the drug, caused a gradual increase in drug level, and eventually restored clinical response.

In collaboration with a French center, our group recently published a series of over 20 patients with antibodies to adalimumab (Humira, AbbVie) who had lost clinical response to the drug and had low drug levels and high antibody levels. The addition of an immunomodulator resulted in a 50% success rate in the reversal of immunogenicity and restored clinical response.

Over the past few years, several other research groups have shown similar results in small groups of patients; approximately 50% to 60% of patients who develop immunogenic loss of response gradually reverse immunogenicity with the addition of an immunomodulator.

### **G&H** Is it known why some patients experienced reversal of immunogenicity in these studies, while other patients did not?

**SB-H** No. One of the difficulties in answering this question is that it requires comparing patients who experienced reversal of immunogenicity with patients who did not, but only small groups of patients have been investigated regarding the effect of adding an immunomodulator. Thus, further dividing these patients into 2 subgroups leads to very small numbers of patients, making it quite difficult to definitively identify the set of characteristics associated with the reversal of immunogenicity.

### **G&H** Are there any other ways to reverse immunogenicity?

**SB-H** In some patients with low-level immunogenicity (ie, antibody and drug levels that are both low), just increasing the dose of the biologic agent may overwhelm the antibodies to the drug and restore effective drug levels. However, this is usually not helpful if there is a high level of antibodies to the drug. In that situation, usually even if the dose is doubled, immunogenicity will not be reversed and the antibodies that the body generates will still clear the drug away.

### **G&H** Instead of reversing immunogenicity that has already occurred, how can it be reduced or prevented?

**SB-H** The goal of reducing immunogenicity starts in the developmental or manufacturing stage of biologic agents. When developing a new biologic agent, manufacturers usually have several candidate proteins that will produce the same effect in terms of binding to the target, and then will screen them using various chemical or biologic assays to identify which of the similar proteins will be less immunogenic. Manufacturers may even introduce mutations into the protein with the sole purpose of reducing its immunogenicity.

As far as reducing immunogenicity in clinical practice, as mentioned above, scheduled therapy rather than episodic therapy has been shown to be associated with less immunogenicity. Episodic therapy boosts the immune system, similar to what occurs when a series of vaccines is administered. A possible simplistic explanation is that if the immune system receives less frequent (or episodic) encounters with an antigen, it will react to the antigen as if it is a foreign invader, whereas if the frequency of encounters is increased (as with scheduled therapy), the immune system might start to think that the foreign protein that it encounters so frequently is actually not an intrusion but part of the self, resulting in tolerance.

In addition, high-risk patients (ie, those with disease that is very likely to progress or cause severe complications) should be treated with combination therapy to make sure that they have the best chance of having effective therapy. Combination therapy may be associated with a higher level of side effects, but it also has a lower risk of immunogenicity and loss of response.

Finally, one study has shown that perfusion corticosteroids can reduce antibodies to infliximab. These study findings have not been replicated, so perfusion corticosteroids are not routinely used in many centers. However, my colleagues and I give perfusion corticosteroids at our center for the first 5 infusions of infliximab, and if there

are no infusion reactions and no detectable antibodies during these infusions, we usually stop giving perfusion corticosteroids in the infusions thereafter.

**G&H** Are there any other special considerations that should be kept in mind when managing IBD patients in terms of immunogenicity?

**SB-H** It is important to measure drug levels and antibodies to the drug because pharmacokinetic and immunogenic measurement will give clues as to why patients flare. Physicians should not only know whether a patient has antibodies to a drug, but also what the drug levels of the patient are. For example, if a patient has a good level of the drug and no antibodies yet the patient flares, this may indicate that the flare or symptoms are being caused by something other than IBD, such as an infection or irritable bowel syndrome. Alternatively, if the flare is ascertained to be IBD activity–related, such a result may indicate the futility of trying to increase the dose even further and the need to consider switching to a drug with another mode of action. Thus, it is important to incorporate testing for drug level and immunogenicity as part of the workup when patients flare.

Having said this, it is also important to keep in mind that the measurement of immunogenicity can be problematic due to differences in assays and interpretation of results. It is possible that similar results should be interpreted differently according to the clinical situation. For example, select groups of patients in complete remission may have zero or low drug levels and high antibodies (ie, the development of immunogenicity) despite still being in remission, indicating that their remission is possibly

now independent of continued therapy. In this scenario, it may be possible to consider stopping therapy in select low-risk patients. In contrast, if the same test result of zero or low drug levels and high antibody levels is seen at the time of loss of response, it should be interpreted as an immunogenic loss of response and a call to switch to another biologic agent within the same class. Thus, interpretation of results can be complex and dependent upon the clinical scenario, and requires expertise.

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### Suggested Reading

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