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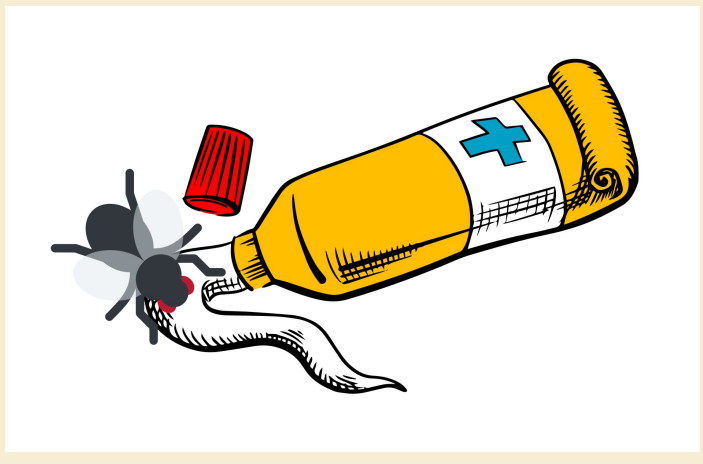
Are Biologics a Practical Choice for Treating IBDs?

Conventional drugs are basically formulated from synthetic chemicals, using typical laboratory techniques. By comparison, biologic drugs are produced by using live animal, plant, or microorganism cells to generate large quantities of monoclonal antibodies (MAbs) that have been specifically selected, because after purification, they're capable of binding to a specific pro-inflammatory protein, and deactivating it. In essence, this is how a biologic treatment suppresses an inflammatory response. First developed several decades ago, the technology appears to be so promising that it has spawned a huge industry as researchers attempt to use it to find novel ways to resolve difficult health issues.

But there's a fly in the ointment.



Alas, despite its many potential possibilities, therapeutic remedies that are developed by using this technology are often challenged by the production of anti-drug antibodies (ADAs) by the human immune system. The mechanisms by which this occurs are undoubtedly complex, but considering that these drugs are attempting to hijack a basic function of the immune system, it's not surprising that the immune system might object to this behavior.

Of course, this can create problems, and not only can it significantly

limit a drug's usefulness, but it may eventually lead to a severe immune system reaction. And similar to corticosteroids, whenever a treatment with a biologic product is stopped, and subsequently restarted again, efficacy tends to be reduced. Additionally, the odds of a serious allergic reaction are increased with reintroduced treatments.

Once thought to have the potential of the Holy Grail for medicine, the technology hasn't been able to live up to its initial expectations. Nevertheless, despite the challenges, according to the FDA, by November 18, 2020, there were 621 FDA licensed Biologics products (U.S. Food and Drug Administration, 2021, November).[1]

But IBD patients aren't interested in the complexities of the technology – they're interested in results. From an inflammatory bowel disease (IBD) patient's perspective, regardless of how favorable advertising claims by pharmaceutical companies may be, and despite the fact that many doctors may be prescribing them, whether or not a medication is a good choice for treating a medical issue depends primarily upon three basic criteria that every patient must consider, namely,

1. **Effectiveness**
2. **Cost**
3. **Safety**

Probably the most important consideration regarding Biologics in this instance is, “How effective are they for treating (IBDs)?

Not very, according to a review of the results of a number of trials using various biologic medications to treat Crohn's disease. If we consider the overall effectiveness, it appears that fewer than one in five patients, on the average, were able to successfully maintain remission using a biologic.

The review, which attempted to identify the actual percentage of patients in each trial who were in remission at the end of the respective trial follow-up, was published in Clinical Gastroenterology and Hepatology (Kayal et al, 2022).[2]

Phase III randomized clinical trials that included at least one year of follow-up data, were included in the study, and trials that involved the use of infliximab (Remicade), adalmumab (Humira), vedolizumab (Entyvio), ustekinumab (Stelara) were included. Note that only subjects who responded to the induction phase were allowed to continue into a maintenance phase.

Patients were very carefully selected for these trials in order to maximize the likelihood of a successful outcome.
Here's how the pharmaceutical companies typically manage (manipulate) patient selection for these trials in order to ensure that the efficacy of their drugs will be maximized in the trial results:

They conduct an induction phase, during which they are able to determine which patients show a response to their drug, and then they choose patients to participate in the actual trial from that group of responsive patients. Interestingly, they fail to report how many patients in the control group show symptom improvement (due to the placebo effect). It's worth noting here that in some drug trials,

the symptom improvement due to the placebo effect has been greater than the drug remission rates reported in these trials. And although these trials typically report “statistically significant" symptom improvement, they don't define what this actually means. Is it truly beneficial improvement, or merely a minor reduction of symptoms? What, exactly, do they consider to be remission? We can only guess.

Net clinical remission rates (a measure of effectiveness) in these trials, reported by the study, are disappointing.
By looking past the induction phase, so that they could base their results on the number of patients who initially enrolled in the trials, and also the placebo effect, the study found that the final net clinical remission rates at the end of the follow-up periods were 16.7% for Remicade, 28.5% for Humira, 18.7% for Entyvio, and 13.9% for Stelara (Long, 2022, March 16).[3]

And it's interesting to note that patients in the study who were subject to prior biologic anti-tumor necrosis factor treatments, typically had lower response rates (clinical remission rates) to all of the treatment trials in the study. Although this wasn't mentioned in the study report, those lower response rates suggest that response rates to Biologics in general, may decline with continued, or repeated use, a problem shared by many medications. Overall, the effectiveness of Biologics in general, apparently leaves a lot to be desired.

There don't appear to be any similar studies that involve ulcerative colitis or microscopic colitis patients, so we can only guess at the effectiveness of Biologics for treating these syndromes. But these diseases are quite similar to Crohn's in many ways, so it's not likely that they would have a significantly better or worse response to treatments with biologic medications, although this is obviously unverified speculation.

And here's the really bad news:
A recently published Japanese study has found that compared with younger IBD patients, older IBD patients have significantly lower response rates to this class of medications.[4] The retrospective study, which analyzed the records of patients who were aged 60 or over at the time of diagnosis, who were hospitalized for IBD, and who were treated with biologic therapy, found that when compared with younger patients, the older age group of patients showed remission rates that were approximately 60% of those experienced by younger patients. Interestingly older IBD patients who were diagnosed before the age of 60, experienced clinical remission rates similar to younger patients.[5] Furthermore, severe adverse events (allergic reactions) were significantly more likely for patients who were diagnosed after the age of 60, when treated with Biologics.

Nor is the cost of these drugs a redeeming factor.
As is typical of most medications approved by the FDA in recent decades, treatments using Biologics are quite expensive. Typical annual treatment costs for some of these drugs may make them unaffordable for many patients, even if they have insurance. For example:

1. 100 mg treatment with Remicade costs $31,602 to $46,415.
2. 40 mg treatment with Humira costs $22,211.
3. 300 mg treatment with Entyvio costs $26,320.

And as is always the case with medical procedures, there's no guarantee that any patient will derive any benefit from any treatment, regardless of how much money they, or their insurance company spends.

High treatment costs have led to the development of biosimilar products.

A biosimilar product is one that has been developed to be a replacement for a previously FDA approved biologic, known as the reference product, with no clinically significant differences from the reference product (Public Policy Resources, 2018, July 27).[6] Note that biosimilar drugs are not generic drugs, although the differences are rather subtle, and hardly worth noting. To date, the FDA has approved 33 biosimilar drugs that correspond to 11 different reference products (U.S. Food and Drug Administration, 2021, November).

Internet sites rarely mention potential safety issues of Biologics.

There are plenty of definitions of biologic medications on the Internet, including one by the FDA. But while most sites typically describe in detail all the perceived advantages of this class of medications, they rarely mention the disadvantages, despite the fact that the biggest disadvantage (of all Biologics) is the elephant in the room, namely, immune system suppression, and the dangerous consequences that can sometimes result from that attribute. Hopefully, everyone's doctor will take the time to describe the risks involved before prescribing a biologic for any treatment purpose.

Henrickson, Ruffner, & Kwan, (2016),[7] for example, report:

The use of biologics is not without hazard; however, as these agents block immune pathways adapted to protect the host. This has been borne out by increased rates of infections as well as induction of new autoimmune and hematologic adverse effects. As new drugs for the treatment of autoimmune conditions are entering the pipeline, it is incumbent on the practicing immunologist to understand the mechanism of these biologics and the implications of clinical use.

While it's true that other medications used to treat IBD's, such as corticosteroids, tend to suppress the immune system, this problem has been greatly diminished by the use of corticosteroids that target the intestines rather than the entire body. These days, doctors typically prescribe budesonide to treat IBD's, and the treatments are usually limited to a few months, which helps to eliminate (or at least significantly diminish) any major immune system suppression effects, in most cases.

So an evaluation of the relative safety of this class of medications reveals an elevated risk of adverse effects, including the possibility

of a fatal outcome, when compared with most other conventional medications that are used to treat IBD's. Yes, biologics can offer seemingly miraculous symptom relief to those lucky few who are able to use them successfully. But to many of us, the risks of living in a cancer filled world, where infection opportunities may lie right around the next corner, the prospect of attempting to live every day without the protection of our immune system may be an unacceptable safety risk.

Summary

If we listen to the pharmaceutical companies, and presumably many doctors, Biologics are the greatest invention since sliced bread. And they may be, for certain autoimmune diseases. But if we carefully examine the results of typical IBD treatment trials, Biologics don't appear to be a particularly good choice for treating IBD's. Their efficacy is relatively low, they're expensive enough to be unaffordable for many patients, and although many patients are able to use them without any safety problems, for many of us, they impose an unacceptable degree of risk. Therefore, as is usually the case, before choosing a treatment, every patient must weigh the facts, and make their own decision.

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