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Invited Review

The Great Debate With IBD Biosimilars

Con: Biosimilars Should Not Be Routinely Used as a First Line Biologic and Not Switched From Reference Biologics

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The costs associated with biologic therapy in immune-mediated diseases, including inflammatory bowel disease has steadily increased since their introduction over 2 decades ago. The introduction of biosimilars has the promise of cost savings and putting reimbursement pressure on future market entries. However, the interpretation of evidence to support the use of biosimilars either as first line or as part of a nonmedical switch strategy is not straight forward due to low to very low-quality evidence. In particular, switching to a biosimilar is associated with both clinical, ethical, and possibly medicolegal issues. Due to these factors, solutions to address cost efficiency should involve an open, transparent, and collaborative dialogue among the various stakeholders and if at all possible involve strategies that allow patients to remain on originator biologics.

Lay Summary

Biosimilars are not generic versions of originator biologics, but they can be affordable alternatives in patients requiring biologics. However, switching from an originator to a biosimilar should only be performed if it does not adversely affect patients' health.

Key Words: biosimilars, inflammatory bowel disease, nocebo effect, patient preference

Introduction

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis and Crohn's disease (CD), is a chronic relapsing condition that primarily affects the gastrointestinal tract.[1,2] IBD is a potentially debilitating disease associated with impaired quality of life, need for hospitalizations, and surgeries in patients who do not respond to medical therapy.[3] The medical management of IBD was revolutionized with the introduction of biologic therapy—the first being the tumor necrosis factor (TNF) antagonist, infliximab (Remicade), with Food and Drug Administration (FDA) approval for CD in 1998. Since that time, other TNF antagonists including adalimumab (Humira) and golimumab (Simponi) have been approved. These agents along with newer biologics have become cornerstones of IBD treatment. In addition to improving patients symptoms and quality of life, data demonstrate that the rates of hospitalizations and surgeries for CD and ulcerative colitis have steadily decreased across many jurisdictions.[4] For example, a population-based study from Canada demonstrated that over a 10-year period, surgical resections fell significantly by 3.5% per year, accompanied by a substantial 10.1% annual decrease in emergency operations for patients with CD, much of which is attributable to the introduction of TNF antagonists.[5] Preventing hospitalization and surgery in IBD has economic benefits; for decades these were the major drivers of direct medical coast. Furthermore, preventing emergency surgery is vitally important as a meta-analysis has shown that postoperative mortality for CD and ulcerative colitis is 3.6% and 5.3%, respectively, in this setting.[6]

The initial hope that introduction of biologics would reduce direct medical costs through the reduction of hospitalization and surgical rates was soon met with the reality of an overall increase in direct medical costs. Biologic therapy quickly became the major drive of direct medical costs due to their high cost and the need for ongoing maintenance therapy. In a 2018 report, infliximab was reported to be the drug with the highest spend over a 5-year period, costing $3.8 billion.[7] Although, arguments remain that estimating the precise cost of IBD is complex and biologics in fact hold their value when indirect medical costs are considered. Despite these arguments, it is difficult to ignore the price tags associated with chronic biologic therapy. Costs have only continued to rise with the approval and introduction of additional biologic therapies coupled with the increased uptake by both patients and physicians.

One approach to reducing drug costs of IBD is the introduction of biosimilars. According to the FDA, a biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product (RP).[8] The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the RP or originator biologic, *not to independently establish the safety and effectiveness of the proposed product*.[8]

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Initially, this concept of biosimilarity came under scrutiny because of the fact that the production of biologics requires replication in living cells, resulting in variability of these complex proteins and rendering the products biosimilar but not bioidentical. Further arguments contest that at an individual patient-level subtle differences in molecular structure may lead to differences in either efficacy, safety, or tolerability. A candidate biosimilar product is granted biosimilarity following the review and approval of the totality of evidence presented to the regulators, which comprises preclinical molecular, structural, and functional characterization data, as well as clinical pharmacokinetic, pharmacodynamic, and efficacy, safety, and immunogenicity data. Based on proving bioequivalence on the grounds of these data and in a clinical population sensitive enough to detect any significant differences, biosimilarity of the candidate product can be extrapolated to all indications for which the RP has been approved. In addition, there has been some concern surrounding extrapolation across disease states, whereby a biosimilar may be approved for an indication without having direct data for that indication.

FDA first approved biosimilar infliximab (infliximab-dyyb) in April 2016. Presently, there are 4 approved biosimilars to infliximab and 6 approved biosimilars to adalimumab.[9] These approvals have been accompanied by FDA's Biosimilars Action Plan published in 2018 which was established to aid the development of the biosimilar market and to increase competition for biologic drugs.[10] This competition is expected to substantially impact the pharmaceutical industry and national health systems. Goals of the plan include streamlining the approval process, improving regulatory clarity, increasing educational efforts to improve understanding among stakeholders, and collaborating with the Federal Trade Commission to address anticompetitive behaviors.

Globally, biosimilars of TNF antagonists are associated with an approximately 30%–40% decrease in the listed price compared to RPs.[11] Therefore, for healthcare systems and payers this cost savings is extremely attractive (estimated $1.1 billion currently and $54–250 billion over 10 years).[11] As stewards of the healthcare system, healthcare providers should be committed to supporting policies aimed at reducing the cost of care that do not substantially influence effectiveness or safety. Within the European Union, there has been a progressive uptake of biosimilars to TNF antagonists and this has been associated with significant cost savings.[12] In many instances, these cost savings have been reinvested into enhancing the direct care of patients with IBD.[13] Therefore, the question arises if biosimilars are associated with similar efficacy and safety as the RP; what would be the arguments against either initiating a biosimilar as a first line biologic or switching a stable patient away from a an originator biologic to one of its biosimilars. This brief review will look at arguments against these practices.

Evidence for the Use of Biosimilars in Anti-TNF-Naive IBD Patients/First-Line Use

There have been several studies establishing first-line use of biosimilar infliximab in patients with IBD. Recently, the results from a phase III randomized, double-blind parallel group trial, conducted in patients with moderate to severe CD has been reported by Ye et al.[14] The study compared the efficacy of a biosimilar infliximab (CT-P13; infliximab-dyyb) to originator infliximab, with 220 patients from 16 countries. The primary outcome of this study was to compare the efficacy between 2 groups based on clinical (ΔCDAI-70) response rates (defined as a reduction from the baseline CDAI score by at least 70 points) at week 6. In a per protocol analysis, CDAI-70 response rate was quite similar (CT-P13 69.4% vs originator 74.3%: difference, 4.9%; 95% CI, 16.9–7.3). Similarly, there were no differences in the more robust (ΔCDAI-100) clinical response (CDAI-100 response, decrease in CDAI score of at least 100 points from baseline), between originator infliximab and the biosimilar (CT-P13 60.4% vs originator 64.2%: difference, 3.9%; 95% CI, 16.7–9.6). Data from week 30 also revealed similar results between the 2 groups based on CDAI-70 response rate, CT-P13 76.6% versus originator 75.2%; CDAI-100 response rate, CT-P13 72.1% versus originator 73.4%; and clinical remission (CDAI score of less than 150 points) rate, CT-P13 55.0% versus originator 56.9%. In this randomized study, CT-P13 was well tolerated and displayed a safety profile comparable to that of originator up to 30 weeks. This study suggests in naive patients that the infliximab biosimilar can be used as a first line biologic. However, although there were measures of biomarkers such as C-reactive protein and fecal calprotectin there was no endoscopic evaluation. A further limitation of the study is that it was not powered to show statistically significant differences between groups for important secondary or tertiary endpoints, including those after week 30, limiting the extent to which data obtained at week 54 can be interpreted. Furthermore, the duration of follow-up (22 weeks) after continuation or switch at week 30 might not be sufficient for differences to be observed.

A French equivalence study by Meyer et al[15] compared the effectiveness and safety of originator infliximab with CT-P13 in patients with infliximab-naive CD. This large trial comprised approximately 2500 patients in each arm and was designed as a real-life, comparative, equivalence cohort study. Using a nationwide health administrative database, the researchers included all patients with CD who had received 1 or more doses of infliximab between March 1, 2015 and November 30, 2016. The primary outcome of the study was a composite endpoint of death, all-cause hospitalization, CD-related surgery, and documented use of second-line biologic therapy. Patients were followed until the onset of a predefined outcome or censoring. Patients were censored at the study's end (June 30, 2017), at switch from originator to CT-P13 (or vice versa) plus 30 days, or at the discontinuation of infliximab. The equivalence margin was set as 10%. The primary outcome did not differ between originator infliximab and CT-P13 groups (log-rank test, $P > .20$). The 6-, 12-, and 18-month cumulative incidence rates of the primary outcome were 29.6% (95% CI, 27.8–31.4), 43.1% (95% CI, 41.2–45.1), and 51.5% (95% CI, 49.6–53.4), respectively, in the originator group, and 28.6% (95% CI, 26.9–30.4), 41.6% (95% CI, 39.7–43.6), and 50.1% (95% CI, 48.1–52.0), respectively, in the CT-P13 group. In the multivariate analysis of the primary outcome, CT-P13 was equivalent to the originator (hazard ratio, 0.92; 95% CI, 0.85–0.99). In terms of safety, the multivariable analysis did not demonstrate any significant differences between originator infliximab and CT-P13.

Therefore, evidence exists from both randomized controlled trials and a large real world cohort that biosimilar infliximab can be used as first-line therapy. This would support a policy in which patients starting on an anti-TNF could be offered the lowest cost alternative within the anti-TNF class including an infliximab or adalimumab biosimilar. However, there are a variety of clinical scenarios in which healthcare providers and patients may choose a biologic with an alternative mechanisms of action to which a biosimilar does not exist. These choices may be based on comorbidities, coexisting conditions, or safety concerns. Therefore, mandating first-line anti-TNF biosimilar would therefore only be based on cost considerations. Additionally, requiring patients to fail anti-TNF therapy may be associated with decreased efficacy of other agents as second line as has been demonstrated in numerous randomized controlled trials. Therefore, it is imperative that healthcare provider and patient choice be maintained even in the era of anti-TNF biosimilars.

Evidence for Nonmedical Biosimilar Switching

The current state of evidence evaluating the efficacy and safety of switching between an originator biologics and subsequent entry biosimilar is summarized elsewhere.[16–18] It should be noted that many of the published studies are often hampered by small numbers, retrospective analyses, lack of defined endpoints, or short duration of follow-up. While most of the available data have not identified significant risks associated with a single switch between originator and biosimilar infliximab others have identified high discontinuation rates, need to return to the originator molecule, or issues with tolerability.[19] Therefore, the data are very inconsistent. While some of this has been attributable to the nocebo effect, this is difficult to demonstrate conclusively.

Some of these issues were addressed in the Joint Canadian Association of Gastroenterology (CAG)/Crohn's Colitis Canada (CCC) Position Statement on biosimilars in IBD.[20] The authors reviewed the available literature to evaluate efficacy, safety, and patient acceptance of using biosimilar versus originator biologics in both patients naive to anti-TNF therapy as well as patients undergoing a nonmedical switch. In contrast to other position statements, the CAG/CCC recommendations were based on a systematic review of the literature with formal evaluation of the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The authors involved were experts in GRADE methodology and reported no apparent conflicts of interest. The conclusions were that the overall quality of evidence was low to very low.

Recognizing the overall conclusions from the CAG/CCC position statement, there are several important considerations when evaluating the evidence for and against nonmedical switching. First and foremost, there is a paucity of high-quality randomized controlled trials evaluating this question. Existing studies are underpowered to determine noninferiority in IBD patients, much less equivalence. Second, existing studies have primarily been randomized transition studies, where patients are randomized to switch to the biosimilar or continue the originator biologic; the requisite crossover and interchangeability studies necessary to answer critical questions regarding the risk of immunogenicity postswitching have not yet been performed. Third, while several jurisdictions have implemented nonmedical switch policies, appropriate postswitch pharmacovigilance and surveillance studies have not been rigorously conducted and often fail to include adequate follow-up time or evaluation of meaningful endpoints. Determining the degree of attributable excessive risk in uncontrolled studies is difficult given that the annual risk of loss of response to anti-TNF therapy can be as high as 10%–20% per patient-year, which may be underestimated when other biologic therapies are not available,[21] and there may be a nocebo effect in patients switching to biosimilar therapy.[22] Finally, extrapolating results from biosimilar switch experiences for rheumatologic or dermatologic indications to patients with IBD may not be valid. There are differential effects of biologic treatments across disease states and the consequences of loss of response in IBD are arguably more significant related to the lack of advanced therapeutic options and the reality that surgical intervention carries a high risk of morbidity and unacceptable mortality rate.[6,23]

Despite the multitude of concerns, many refer to the NOR-SWITCH randomized controlled trial that was designed in an attempt to answer this question. It does provide some insights into the potential risks and benefits associated with biosimilar switching, but the question remains whether it truly has answered the pivotal questions as the trial included a mixed populations and was underpowered to detect meaningful differences both in the total population and in the IBD subpopulation. The NOR-SWITCH study was a phase IV randomized, double-blind, noninferiority transition trial including adult patients with CD, ulcerative colitis, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, and psoriasis in Norway.[24] The noninferiority margin was set at 15%. Patients on originator infliximab at stable doses for a period of at least 6 months were randomized 1:1 to continue the originator or switch to biosimilar CT-P13. Patients were observed for 52 weeks with no allowance for a change in dosing regimen. A total of 482 patients were randomized, including 155 patients with CD and 93 patients with ulcerative colitis. While there was overall noninferiority with switching to biosimilar CT-P13 for disease worsening (overall adjusted treatment difference –4.4% [95% CI: –12.7%, 3.9%]) or occurrence of adverse events, the data in CD patients were far less reassuring with a treatment difference of –14.3% [95% CI: –29.3%, 0.7%], favoring continuation of reference infliximab. A second, double-blind, prospective randomized controlled trial in 200 IBD patients has been reported from a single center in Munich, Germany.[25] In this trial, 111 patients were switched to CT-P13 and 89 patients were continued on infliximab originator. While this study was also underpowered to detect either noninferiority or equivalence, there was an 11% nominal difference (62.2% vs 73.0%, P = .104) in patients achieving the primary endpoint (clinical remission and continuation of study drug at 52 weeks), again, favoring reference infliximab. When results from these 2 randomized control trials are pooled, the relative risk of loss of response or worsening disease was 0.64 (95% CI: 0.44, 0.94; P = .02), favoring continuation of originator infliximab. The resulting calculated number needed to harm is 11 (95% CI: 6, 50). Ultimately, this would suggest that healthcare providers and patients would need to be comfortable with 1 in 10 patients having an unfavorable course postswitch.

Further, uncontrolled cohort studies that compared patients continuing originator infliximab versus switching to biosimilar CT-P13 have been published and summarized.[26,27] These have also been underpowered to detect a clinically relevant difference and suffer from the risk of bias which accompanies open-label designs where the decision to switch is made by the patient and clinician and confounded by a variety of factors. However, accounting for these limitations nonsignificant signals for worsening disease activity were detected: In a cohort study of 219 adults with IBD, patients who continued on infliximab originator had lower risks of disease worsening (RR: 0.66 [95% CI: 0.28, 1.57]), and biologic dose increase/treatment discontinuation (RR: 0.69 [95% CI: 0.38, 1.25]), mirroring observations from randomized controlled trials. Furthermore, a larger cohort of 1388 patients continuing on infliximab originator therapy across all indications compared to 136 patients switching to CT-P13 demonstrated a greater than 5-fold increased hazard of discontinuing treatment at 12 months (HR: 5.53 [95% CI: 4.01, 7.63]).[28]

If one reflects on the totality of these data sources and discounts the multiple limitations, it is easy to conclude that there were no significant differences observed in either the randomized control trials or the observational studies with respect to clinical remission or adverse events in patients continuing originator infliximab or biosimilar CT-P13. However, healthcare providers need to further interpret these results with caution. First, the overall proportion of patients who are in remission at 1 year is biased if dropout of nonresponders is not adjusted for. Second, worsening of IBD is the most relevant adverse event in biologic trials, which has typically been considered separately in biosimilar noninferiority studies. Third, the existing data in IBD have predominantly evaluated switching to biosimilar CT-P13 but there are no data specifically evaluating outcomes after switching to other biosimilars in this population which may be relevant in jurisdictions where multiple biosimilars to infliximab and adalimumab will be available. Given the overall data suggesting that nonmedical biosimilar switching leads to an increased risk of disease worsening, dose escalation, and/or switching to an alternative therapy, the CAG/CCC Joint Position statement provides caution against nonmedical switching from reference infliximab to biosimilar in IBD patients with stable disease.[20] Perhaps more simply, the question needs to be asked is that in clinical practice in a patient with stable IBD (especially in those with significant risk factors) what is the risk that healthcare providers and/or patients would be willing to take of losing remission. The answer in the authors opinion should not be 10% or 15%; the answer should be zero.

Ethical and Logistical Implications of Biosimilar Switching

A comprehensive review on the legal and ethical implications of switching has been authored by Murdoch and Caulfield.[29] The authors are quoted: "At a minimum, the controversy surrounding the switch will necessitate, as part of the consent process, a robust and thorough disclosure of relevant risks, benefits and reasonable alternatives." Consequently, healthcare providers have an ethical duty to explain to their patients the rationale and implications of switching patients from a RP to a biosimilar. In the absence of this discussion and understanding of the inherent risks associated with such a strategy, medicolegal action could be taken forward by the patients in the case of loss of response. As mentioned, with limited therapies available to patients with IBD, the potential downstream consequences of loss of response in a patient previously stable must be considered. Therefore, gastroenterologists are obligated to properly consent patients to a treatment switch. These clinic visits are also necessary to address the fear and anxiety that many patients feel about switching their biologic.[30] Also, patients treated with infliximab have a high propensity for immunogenicity: antibodies form in the environment of low drug levels.[31] Consequently, any logistical delays in transitioning from a reference biologic to biosimilar will lead to decreasing levels and increase the likelihood of antibody formation. Downstream effects include subsequent need to increase doses and, more importantly, clinically meaningful loss of response. This increased cost has been shown in other autoimmune conditions.[32–34] This pathway of harm will not only drive costs up but also put patients at risk as they will need to transition to second-line biologic therapy, which is often not associated with any appreciable cost savings and has reduced efficacy when used second line. The Crohn's Colitis Foundation of America (CCFA) is the foremost advocacy group for those who suffer from IBD. The foundation is not opposed to 1 time transitions but is opposed to multiple transitions. More importantly, they advocate for discussions at the pharmacy, patient, and healthcare provider level.[35]

Biosimilar Switching in Vulnerable Populations

Special populations with IBD may be more vulnerable to an adverse outcome related to a biosimilar switch including children, pregnant women, and the elderly where data on switching are limited.[36–39] The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition released an updated position statement in January 2019, stating that a biosimilar switch may be considered in children with IBD in clinical remission, following at least 3 induction infusions.[37] Given the lack of published data, it may be prudent to delay switching in individuals who are in the process of transitioning from pediatric to adult care,[39] as many other changes are already occurring, including change in physician, hospital, clinic, and insurance. Minimizing additional changes during this crucial time may improve the success of pediatric to adult transition. Similarly, although there are no published data on the effect of biosimilar switch during pregnancy on maternofetal outcomes, pregnancy constitutes a defined time period and delaying a mandated switch to the postpartum period may result in less mental and physical stress.[38] Finally, data on switching in seniors with IBD are lacking. In the elderly population, age and increased comorbidities reduce the physiological reserve available to recover from the consequences of an IBD flare.

High-risk patients with IBD who are stabilized on a reference biologic are at significant risk for surgery if they develop secondary loss of response. This includes those patients with acute severe disease at presentation, hospitalization at presentation, are in the midst of induction therapy, have perianal disease or extraintestinal manifestations, are obese, or are active smokers.[40] When these patients flare, options for medical rescue are limited. Stratified analyses documenting safety of switching in these populations are exceedingly limited.

Consequently, exemptions for switching should be offered to vulnerable and high-risk populations with IBD.

Patient Perspective

A substantial gap exists between patients with IBD and policymakers who mandate nonmedical biosimilar switch. A Canadian survey of nearly 800 patients with IBD and their caregivers provides some insights into the thoughts of patients and providers. The survey revealed that over 3 quarters of patients or their caregivers disapproved of a nonmedical switch. Open comments from the survey revealed that opposition for the policy was driven by substantial fear and anxiety.[30]

Mental anguish of patients with IBD who are stable on originator biologic and forced to switch to a biosimilar has far-reaching consequences. A nocebo effect has been proposed in this setting whereby anxiety over a medical decision leads to patient harm that was not caused directly by the intervention.[41,42] Studies have documented that between 20% and 30% of patients with IBD suffer from mental illness, such as depression and anxiety.[43] Consequently, patients with IBD are highly susceptible to a nocebo effect. Moreover, studies indicate that depression can affect intestinal inflammation such that the mental anguish of switching could directly worsen disease activity irrespective of the efficacy of the new medication.[44] These concerns are heightened among high-risk patients who have previously experienced debilitating symptoms, hospitalizations, and surgeries that preceded remission on anti-TNF therapy.

Cost of Biosimilar Switching

In most jurisdictions that implemented nonmedical switching, the rationale is to achieve cost savings. Collaborative efforts exist in which part of the cost savings were reinvested into healthcare resources that directly benefit the patients affected by the switch.[13] In most healthcare systems in the United States it is unlikely that these cost savings will be passed on to patients or those who care for them. If the rationale is purely based on cost than originator biologics should be allowed to compete through various agreements on price in order to allow patients to stay on their originator. However, this is a complex environment and the desire to "carve out" a niche so biosimilars can not only survive but thrive is attractive to payors. Prior economic evaluations in Europe that were favorable toward switching do not account for factors such as increased resource utilization, hospitalization, and potential surgery in patients who loose response. Moreover, in 1 European cohort study, transitioning to biosimilar was associated with 20% higher costs than remaining on originator biologic.[5] Further, a systematic review of nonmedical switching of all types of drugs did not support cost savings while nearly 70% of studies reported cost savings with originator drugs.[45] One must then question the ethics of nonmedical switching when there are no anticipated cost savings to be achieved and real patient harms that are anticipated. Stakeholders should work collaboratively to preserve the health and wellness of patients. Indeed, in the world of multiple biologic options, alternatives to forced nonmedical switching that achieve the goals of patients, physicians, and policymakers do exist. This includes, for example, maximal allowed cost strategies or lowest cost alternatives where payors would allow for a fair market pricing while allowing for patient and physician choice and minimizing the cost to the system. However, to have meaningful discussions around patient-oriented, cost-effective strategies, these conversations need to be conducted transparently and with input from patients at the ground level, not just post hoc after policies have already been unilaterally crafted.

Conclusions

It is important for all stakeholders to be accountable for the costs within a healthcare system. First-line use of biosimilars that offer comparable effective but are less costly makes sense. Switching stable patients from an originator medication to a biosimilar is a completely different proposition; as are mandatory policies which do not allow for patients and physician choice or a competitive market. These policies may actually be counterproductive in the long term. These decisions need to go beyond potential cost savings related to drug acquisition costs but equally the psychosocial cost this may have on patients. This first dictum of the Hippocratic Oath remains "First do no Harm." Despite the evidence switching to a biosimilar will harm at least some patients with IBD.

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Conflicts of Interest

Dr. Panaccione reports consulting from AbbVie, Abbott, Alimentiv (formerly Robarts), Amgen, Arena Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Genentech, Gilead Sciences, Glaxo-Smith Kline, Janssen, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Satisfai Health, Sandoz, Schering-Plough, Shire, Sublimity Therapeutics, Theravance Biopharma, UCB, and Takeda Pharmaceuticals. He has received speaker's fees from AbbVie, Arena Pharmaceuticals, Celgene, Eli Lilly, Ferring, Gilead Sciences, Janssen, Merck, Pfizer, Roche, Sandoz, Shire, and Takeda Pharmaceuticals.

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