Reviewer #1:

1. The results of another study not included in the reference list of the article (Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, Golovics PA, Kristóf T, Lakatos L, Csontos ÁA, Juhász M, Nagy F, Palatka K, Papp M, Patai Á, Lakner L, Salamon Á, Szamosi T, Szepes Z, Tóth GT, Vincze Á, Szalay B, Molnár T, Lakatos PL. Efficacy and Safety of the Biosimilar Infliximab CT-P13 Treatment in Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort. J Crohns Colitis. 2016 ;10:133-40. doi: 10.1093/ecco-jcc/jjv220. Epub 2015 Dec 10), should be added

The following was added:
A prospective study of 210 patients also found that CT-P13 is effective in inducing clinical remission in Crohn's disease and ulcerative colitis but noted decreased response to treatment and increased risk of allergic reactions in those previously treated with reference infliximab.

2. The way of switching from an original biological agent to a biosimilar should be noted in the discussion section bearing in mind the following references (Schmitz EMH, Boekema PJ, Straathof JWA, van Renswouw DC, Brunsveld L, Scharnhorst V, van de Poll MEC, Broeren MAC, Derijks LJJ. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study. Aliment Pharmacol Ther. 2018;47:356-363. doi: 10.1111/apt.14453. Epub 2017 Dec 5). (Switching from Innovator to Biosimilar (Subsequent Entry) Infliximab: An Updated Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jan.).

The following were added:
While the Canadian Agency for Drugs and Technologies in Health (CADTH) has reported equivalent safety and efficacy in switching from reference biologic to biosimilar in treatment of rheumatologic diseases, the one cohort study examining interchangeability in treatment of Crohn's disease and ulcerative colitis had a sample size of eight patients at week 48 following the change to biosimilar infliximab.

A prospective study of 133 patients with inflammatory bowel disease measured antibodies to infliximab as well as C-reactive protein and erythrocyte sedimentation rate in context of disease activity scores to obtain numerical measurements of interchangeability. It found no differences between reference infliximab and biosimilar infliximab, but it also did not directly compare to continuing patients on reference infliximab.

3. The Nocebo effect should be mentioned in the discussion section using the following reference (Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther. 2017 Dec;4(2):209-218. doi: 10.1007/s40744-017-0085-z. Epub 2017 Oct 14).

The following was added:

The reluctance of physicians also may affect clinical trials and even patient outcomes through the nocebo effect, which has been documented as causing generalized side effects despite a lack of plausible pharmacological mechanism based on the drug itself or side effects more severe than observed when medication use is blinded. The way in which a physician discusses the effects of a drug with a patient influence the possibility of a nocebo effect.

Reviewer #2:

1. Abstract - "While they are still created within living systems, they may differ slightly in manufacturing process to decrease costs" - Th cost reduction is surely not mainly due to different manufacturing process by rather the reduced need of clinical trials

The following was added:
Although the manufacturing process still involves production within living cells, biosimilars undergo fewer clinical trials than do their reference biologics. This ultimately reduces the cost of production and the cost of the biosimilar drug compared to its reference biologic.

2. Introduction - "Therapeutic proteins, also known as biologics, are pharmaceutical agents created in a laboratory setting to mimic the effects ...." It is not just mimicking but also as the case of anti TNF to antagonize proteins or block receptors.

The following was added:
They may either mimic the natural protein's function or antagonize the function of the natural protein.

3. Introduction - "To address this growing issue, biosimilar drugs were developed." Indeed biosimilars are developed because of originator patent's expire.

The following was added:
As patents on biologic drugs expired, biosimilar drugs were developed and are helping to address this growing issue.

4. Chapter on IBD - rather that the experience of 25 gastroenterolosist in Germany I would mention the ECCO survey J Crohns Colitis. 2014 Nov;8(11):1548-50 and J Crohns Colitis. 2016 Nov;10(11):1362-1365

The following was added:
A 2016 study examined survey responses of inflammatory bowel disease specialists regarding biosimilars. Out of 118 responses, only 19.5% were not confident with using biosimilars, and 44.4% believed the biosimilar to be interchangeable with the reference biologic. The primary perceived benefit reported was cost reduction, and the main concern was immunogenicity.

5. Chapter Limitations - I would add that one of the main concern of the physicians is the possible occurrence of multiple switches (from originator to biosimilar and back and more importantly among different biosimilars of the same originators). The possible consequence of these scenarios are completely unknown.

The following was added:
Additional studies will also be needed to further examine interchangeability of biologics and biosimilars. The case of switching from a biosimilar to a biologic if the biosimilar does not produce significant clinical improvement should also be explored, especially considering the number of biologic-naïve patients who may be started on a biosimilar rather than biologic therapy.

Reviewer #3:

1. In the abstract there is sentence "Currently, five biosimilars have been approved by the FDA ….." in the discussion section and the Table – "Currently there are seven biosimilars approved…." – please correct appropriately

The number in the abstract was corrected from five to seven.

2. Table 1 – legend: please explain what means N/A in the Table 1

Added clarification in table 1 that N/A stands for Not Available.

Reviewer #4:

All necessary changes were made.