Leveraging Machine Learning to Characterize Relationships Among Biosimilar Product Quality Attributes and Clinical Performance

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Abstract

Under the Biosimilar User Fee Act (BsUFA) III, a regulatory research pilot program has been established to pursue various research areas of interest. One research priority is to increase reliance on analytical data for a demonstration of biosimilarity to a reference product. Defining and standardizing analytical approaches relevant to clinical performance could help support demonstrations of no clinically meaningful differences using less resources than clinical studies require. However, despite improvements in analytical techniques, there is an incomplete understanding of the relationship between a product's quality attributes and its clinical performance. We employ unsupervised machine learning techniques such as dimensionality reduction and hierarchical clustering to answer questions 1) whether there is any pattern in quality attributes' behaviors in the demonstration of biosimilarity and 2) whether differences in analytical assessments in biosimilars relate to clinical outcomes. The relationship across analytical data, pharmacokinetic data, and clinical efficacy data was explored for 9 approved biosimilar products of adalimumab. Galactosylation and high mannose behave similarly and show the highest variance of all quality attributes. Galactosylation, ADCC activity, high mannose and reverse signaling were found to have high correlation with pharmacokinetic similarity with a reference product.

Introduction

A biologic is a pharmaceutical drug manufactured in, extracted from, or synthesized from biological sources. Unlike their counterparts in chemically synthesized drugs, biologics are complex mixtures whose structure might not be always completely known. Examples include recombinant proteins such as monoclonal antibodies (mAbs) and gene and cell therapy products.

The main goal of this work is to determine whether machine learning can be used to expedite the approval of biosimilar products. Specifically, we aim to use ML methods to characterize the relationships among product quality attributes (QA), clinical pharmacokinetic, and clinical efficacy performance.

A significant body of research has been done suggesting the reduction of reliance on comparative clinical efficacy trials. Bielsky et al.[1] review biosimilar applications in the European Union (EU) and conclude that analytical assessments largely predict bioequivalence in clinical efficacy trials when combined with PK data. They also suggest a new pathway for biosimilar applications to replace the status quo. Guillen et al.[2] also review biosimilar applications in the EU, but instead focus on how disagreements between the biosimilar and reference products are arbitrated. They find that most disputes are able to be resolved by other QA data, without relying on efficacy data. Kirsch-Stefan et al.[3] build on these works by focusing on withdrawn applications and investigate if these withdrawals could be predicted by analytical assessments alone.

Disclaimer

The present study reflects the views of the authors and should not be constructed to represent the views or policies of the US Food and Drug Administration.

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Materials and methods

As of September 30, 2024, there are 40 approved mAbs biosimilars. **In this study, we limit our analysis to biosimilars of adalimumab.**

Adalimumab was the first fully human monoclonal antibody approved by the FDA. Adalimumab binds with specificity to tumor necrosis factor-alpha (TNF-alpha) and inhibits its interaction with the p55 and p75 cell surface TNF receptors. In the US and the EU, adalimumab is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa, and uveitis.

Table 1. List of all biosimilar products we investigate in this report.

Trade Name	Scientific Name	Approval Date	Reference Product
Abrilada*	adalimumab-afzb	11/15/19	Humira
Amjevita	adalimumab-atto	9/23/16	Humira
Cyltezo*	adalimumab-adbm	8/25/17	Humira
Hadlima*	adalimumab-bwwd	7/23/19	Humira
Hulio	adalimumab-fkjp	7/6/20	Humira
Hyrimoz*	adalimumab-adaz	10/30/18	Humira
Idacio	adalimumab-aacf	12/13/22	Humira
Yuflyma	adalimumab-aaty	5/23/23	Humira
Yusimry	adalimumab-aqvh	12/17/21	Humira

*Indicates biosimilar is also 'interchangeable'.

Results

Exploratory Data Analysis

Included in Figure 1 is the raw quality attribute data. The blue color range signifies what percentage of the biosimilar batches fell within the quality range of the reference product. Binary qualitative data was truncated to 1 or 0 as appropriate. Grey boxed indicate the data is missing and was not reported by the manufacturer for that biosimilar. Figure 1 presents overview of data regarding missingness and types of quality attributes.

Unsupervised Learning

Unsupervised learning can discover hidden patterns and relationships in QA data. We use Principal Components Analysis (PCA) to plot the data according to the first two principal components. The first two principal components explain a large portion of the variance. The results of the PCA is shown in Figure 2. Next, we employed hierarchical clustering on the quality attribute data. The results are shown in Figure 4. Galactosylation and high mannose behave similarly. We note that the analytical methods used to assess galactosylation and high mannsose were not exactly same across products. Also, the way of galactosylation and high mannose QAs being presented was not exactly same for all biosimilars. Nevertheless, the similarity of QAs among biosimilars presented here is consistent with previous report on comparability of analytical characterization and consistent and controlled manufacturing profile across biosimilars [7, 8]

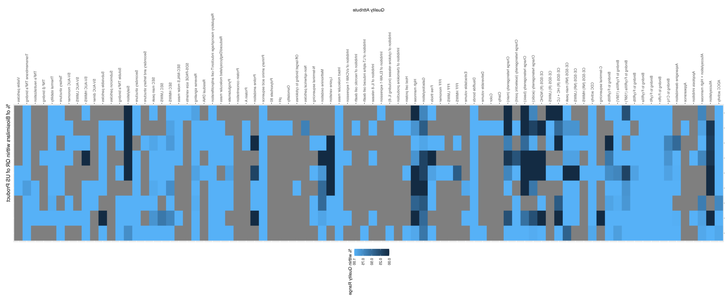

Figure 1. Raw quality attribute data

Supervised Learning

Supervised learning allows us to make predictions by analyzing the relationships between similarity in QA and PK similarity. We point out limitations of our data which is in a high dimensional setting. We assess the strength and direction of the linear relationships between QA agreement and summary statistics of PK similarity (e.g., geometric mean ratio for Cmax, AUC0-inf, and AUC0-t). Similarity in galactosylation is highly correlated with geometric mean ratio of AUC0-inf and AUC0-t (e.g., p-value 0.023 and 0.041 respectively). It is found that similarity in ADCC activity to have moderate correlation with the geometric mean ratio of AUC0-inf. Figure 3 shows that similarity in galactosylation and ADCC activity is positively related to the PK similarity. High mannose and Reverse signaling show negative correlation to the PK similarity

Galactosylation had been reported to impact pharmacokinetics of mAbs and the impact seemed to depend on the overall glycosylation profile [4]. In addition, galactosylation was found to influence ADCC activity in natural killer cell assays of both manufacturing batches mAbs and enzymatic hypergalactosylation [5]. In addition, effect of high mannose on pharmacokinetics of adalimumab and biosimilars, as well as other mAbs, had been collectively documented [6]. Again, we are cautious with data interpretation as analytical methods and data presentation for galactosylation, high mannose and other QAs might not be exactly the same,

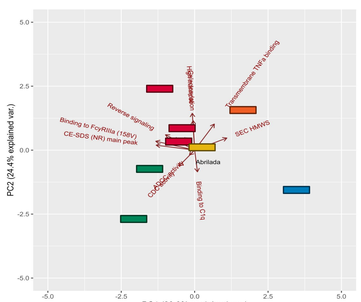

Figure 2. Principal Components Analysis (PCA) of adalimumab. The first two principal components, which explain the most variance in the data, are plotted on the x and y axis. Additionally, the red arrows show the projection of each feature onto the lower dimensional space. Product brand names are covered.

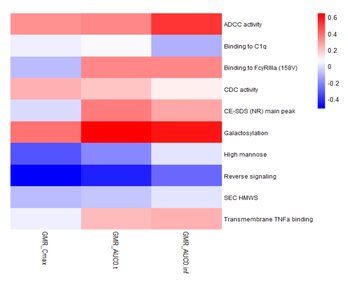

Figure 3. Correlation matrix for adalimumab between QA and Geometric mean ratio of PK parameters. Red color indicates a positive linear relationship, while blue indicates a negative linear relationship.

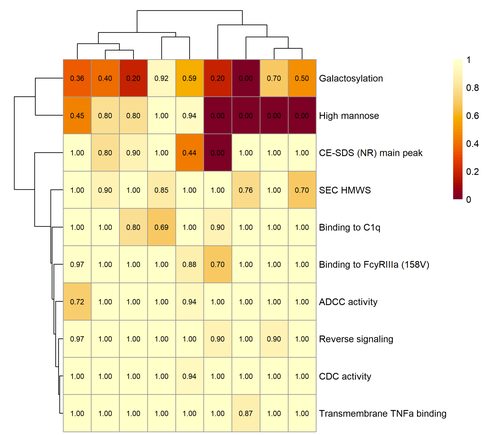

Figure 4. Hierarchical clustering and heatmap for adalimumab.

Discussion

This is the first AI/machine learning application using quality attribute data in biosimilars. Furthermore, this study highlights the need for standardization of which data is collected from sponsors, as well as how this data can be stored and communicated with FDA reviewers. We look forward to more efforts on systematic harmonized naming, which will allow for more streamlined analysis. Further analysis will be conducted.

References

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