Divide and Conquer: Using Patient Stratification to Optimize Therapeutic Drug Development in Inflammatory Bowel Disease

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ABSTRACT

Inflammatory Bowel Disease (IBD) is a complex and heterogeneous disorder. Clinical symptoms can vary widely among patients and etiology of the disease is likely influenced by numerous factors including genetic predisposition and environmental factors, as well as social behaviors such as smoking and diet. It is likely that IBD comprises several disorders that share clinical features with the two most well accepted classifications of IBD, Crohn’s Disease (CD) and Ulcerative Colitis (UC), being two extremes of a continuum. Such complexity has hampered the effectiveness of current treatment and has slowed the development of successful therapeutics. In this review, we discuss a personalized medicine approach that may promote both faster and more efficient development of new therapies and potentially increase the efficacy of existing drugs.

ABBREVIATIONS

IBD: Inflammatory Bowel Disease; CD: Crohn’s Disease; UC: Ulcerative Colitis; MRUC: Medically Refractory Ulcerative Colitis; EIM: Extra-Intestinal Manifestations; FDA: Food and Drug Administration; GWAS: Genome-Wide Association Studies; pANCA: perinuclear-staining Anti-Neutrophil Cytoplasmic Antibodies; ASCA: Anti-Saccharomyces Cerevisiae Antibodies; OmpC: Outer membrane Porin C.

INTRODUCTION

In the world of computer science, divide-and-conquer algorithms break down a complex problem into multiple ‘sub-problems’ of the same or similar type until these problems become simple enough to be solved directly. Thus the technique of simplification is a powerful tool for solving complexity.

The complexity and heterogeneity of Inflammatory Bowel Disease (IBD) is widely accepted. Etiology of the disease is likely influenced by numerous factors including genetic predisposition and environmental factors such as the microbiota, as well as social behaviors such as smoking and diet. Moreover, the presentation of IBD varies in terms of clinical symptoms including location of disease involvement, disease severity, associated complications, presence of extra-intestinal manifestations (EIMs), and age at diagnosis. Thus it is likely that IBD comprises several disorders that share clinical features and, currently, the two most well accepted classifications of IBD, Crohn’s Disease (CD) and Ulcerative Colitis (UC), are two extremes of a continuum.

Such complexity has contributed to the frustration of successful drug development and new innovative therapies in recent years. The last novel class of biologics (non-anti-TNF derivatives) approved for IBD was in 2008 with the approval of Natalizumab [1]. The failure of new therapies to come to market is not due to lack of effort. Many novel classes of therapeutics have been in clinical trials for IBD in recent years [2] but none, other than Natalizumab, have made it to approval as of December, 2013. However, the FDA advisory committee has recently recommended approval for Vedolizumab, a monoclonal antibody specific for the α4β7 integrin, for the treatment of moderate to severe UC and CD.

Although current therapeutic trials are hampered by the need for large subject numbers to overcome high placebo rates and the limitations of traditional endpoint measurements to detect low response rates [3], the slow rate of drug development in IBD may be due to a more fundamental issue related to
disease complexity. Arguably, the most surprising drug failure for IBD in recent years has been the anti-IL-17A monoclonal antibody, Secukinumab. Trial data showed no therapeutic effect in CD patients and indeed, some patients demonstrated acute exacerbation of disease following treatment [4]. These data were unexpected since anti-IL17A treatment is efficacious for Psoriasis [5] and more recently, Ankylosing Spondylitis [6], both of which are inflammatory diseases that demonstrate significant overlap with IBD in terms of biological pathways and genetic susceptibility associations [7]. Such results highlight the fact that investigators still lack a fundamental understanding of how the multifactorial components that contribute to the development of IBD pathobiology can influence our ability to modify the disease course.

It is clear then, that a path to simplification of this complex disease is a necessary step toward the advancement of successful therapeutics. In order to reduce the complexity of this disease it may be necessary to embrace the approach of patient stratification to enrich for patient sub-groups that have similar phenotypes irrespective of whether these are defined using clinical, serological, genetic, histopathological, biological, microbiomial or by other parameters.

Clinical phenotype classifications, such as the Montreal classification [8], have helped to stratify patient groups with similar manifestation of disease. However, given the broad etiology of the disease, additional stratification through serology, genetics and biological process is expected to further contribute to the identification of increasingly homogenous patient groups. There is evidence, for example, that serological markers not only differentiate CD from UC, but also define subgroups within either disease group. Anti-neutrophil cytoplasmic antibodies (ANCA), for example, define subgroups of patients with colonic disease both in UC and CD. Moreover, in the absence of perinuclear-staining ANCA (pANCA), the expression of both IgG and IgA of a second autoantibody, anti-saccharomyces cerevisiae (ASCA), has been associated with fibrostenotic and perforating disease [9]. A panel of these antibodies that recognize bacterial proteins have been developed to help phenotypically classify IBD (reviewed in [10] and summarized in Table 1). Importantly, the association of serologies with different IBD phenotypes implies that patients with a particular disease phenotype respond to bacterial antigens differently. This suggests that different biological pathways may be more prominent in certain disease phenotypes than others and that many factors may influence these biological pathways including the local microbiota and/or host genetic background.

Indeed, one study investigating genetic polymorphisms within a gene encoding a C-type lectin critical for protection against fungal infection in mice, found a single nucleotide polymorphism within that gene associated with medically refractory UC (MRUC) in humans [11]. Furthermore, the observation that murine norovirus is crucial for the development of CD-like features in the ATG16L1 hypomorphic mouse potentially implicates a viral trigger in IBD pathogenesis [12]. These findings support the concept that genetic factors influence the host response to microbiota and potentially drive distinct clinical phenotypes.

Genetic studies in IBD have also confirmed the complexity of IBD, with a recent study extending the number of IBD susceptibility loci to 163 [7]. However, subsequent clinical sub-phenotype analysis has demonstrated that genetic variation is also associated with particular disease phenotypes and natural history. Examples in adult individual loci associated with a clinical phenotype such as the TNFSF15 association with fibrostenosing and/or stricturing disease [13] or NOD2 and complicated disease [14]. Composite genetic modalities, including altered gene expression profiles, are also associated with natural history and response to therapy [15,16]. Furthermore, combining genetic, serological, and clinical phenotypes can aid in decisions on treatment by predicting which patients are unlikely to respond to a particular therapeutic [17], or identify patients that are likely to progress to surgery faster, allowing for more aggressive approaches to therapeutic intervention in both CD and UC [18,19].

Through an understanding of these complexities related to IBD, clinical and translation researchers at the Cedars Sinai Medical Center, Los Angeles, have developed a repository of over 11,000 pediatric and adult-onset IBD patient specimens, collected over the last 26 years, including clinical metadata, serological, genetic and biological information (Figure 1). Clinical information not only includes data on clinical subtype but also includes natural history as well as information on medication and response to therapies. IBD-associated serological markers including ANCA, ASCA, anti-I2, anti-OMPC and anti-CBir1 are available as well as genetic data including sequencing data and data generated using genome-wide, exome and immunochip platforms. In addition, we have access to biological information that is generated through various gene expression platforms (i.e. RNA-Seq, Microarray) or...
Table 1: Antibody Panel for IBD Classification.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Predominant Disease Location</th>
<th>Disease Behavior</th>
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<tbody>
<tr>
<td>pANCA</td>
<td>Nuclear envelop protein of neutrophils</td>
<td>Colon</td>
<td>Distal colitis</td>
</tr>
<tr>
<td>ASCA</td>
<td>Saccharomyces cerevisiae cell wall</td>
<td>Small Bowel</td>
<td>Fibrostenosing, Internal Penetration</td>
</tr>
<tr>
<td>OmpC</td>
<td>Omp-C transport protein of Escherichia coli</td>
<td>Small Bowel</td>
<td>Fibrostenosing, Internal Penetration</td>
</tr>
<tr>
<td>I2</td>
<td>Pseudomonas-associated sequence I2</td>
<td>Small Bowel</td>
<td>Fibrostenosing, Internal Penetration</td>
</tr>
<tr>
<td>Chb1</td>
<td>Bacterial flagellin Cb1r1</td>
<td>Small Bowel</td>
<td>Fibrostenosing, Internal Penetration</td>
</tr>
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Abbreviations: pANCA: perinuclear-staining anti-neutrophil cytoplasmic antibodies; ASCA: anti-saccharomyces cerevisiae antibodies; OmpC: Outer membrane Porin C

through in vitro and ex vivo cellular assays from patient samples as well as microbiomal, metaproteomic and metabolomics data from gut specimens [20]. One goal that precipitated the development of this resource is to facilitate the discovery of novel therapeutics that are designed to be most effective in a pre-selected patient populations. Consequently, clinical trial design for therapeutics arising from these investigational studies will, by definition, be better informed through the use of biomarkers and genotypic information. Given these pre-screened populations would be selected based on their likelihood of response to the therapy, clinical trial sizes would be expected to be greatly reduced, saving both time and resources.

The focus of our work is to improve on the success and speed with which innovative therapies move through the drug development process. Through the generation of this biorepository and patient database 26 years ago we instigated a “bedside-to-bench” approach for therapeutic target discovery. Now, we are focused on the completion of the equation with the reverse “bench-to-bedsite” focus on personalized medicine that selects a patient population predicted to respond to a particular therapeutic. We envision that this holistic approach to target identification and drug development will be the key to achieving the much needed, novel therapies for treatment of IBD and possibly other similar immune-related conditions.

CONFLICT OF INTEREST

DPM is on the advisory boards of UCB and Lily. SRT is on the advisory boards of Takeda Pharmaceuticals International and Prometheus Laboratories Inc.

REFERENCES
